STM JOURNALS

International Journal of
Bioinformatics and Computational Biology

Volume 2, Issue 1, 2024
January—June
DOI (Journal): 10.37591/IJBCB

https://journals.stmjournals.com/ijbcb

Research IJBCB

Introduction to Biological Networks and Their Contributions to Systems Biology

Khushboo[1], Pulkit Singh[2], Shazia Haider[3,*]

Abstract

Biological networks provide a conceptual framework to represent and analyze the intricate interconnections among the numerous components that make up living systems. This review paper elucidates the foundational principles of networks and their diverse applications in systems biology, highlighting their crucial role in understanding the inherent complexity of biological processes. Utilizing graph theory, these networks represent entities like genes, proteins, and metabolites as nodes, with their interactions depicted as edges. The review explores core graph theory elements such as nodes, edges, hubs, and motifs, essential for network analysis. It delves into topological parameters like degree, centrality measures, and clustering coefficients, quantifying structural properties and connectivity patterns, and offering insights into network organization and dynamics. Additionally, the review comprehensively examines various biological networks, including protein-protein interaction networks, gene regulatory networks, metabolic networks, cell signaling networks, and ecological networks, highlighting their distinct characteristics and applications. Network visualization techniques, such as force-directed layouts and circular representations, are also explored, facilitating effective communication of complex network structures. The integration of omics technologies with network analysis is addressed, emphasizing the importance of mathematical modeling in deciphering disease mechanisms across multiple scales. The review also underscores the application of network-based approaches in identifying potential drug targets and understanding complex diseases like cancer and diabetes. Overall, this comprehensive review provides an exhaustive introduction to biological networks, their theoretical foundations, analytical tools, and applications in systems biology, accentuating their pivotal role in unraveling the intricacies of living systems and paving the way for future advancements in biomedical research and personalized medicine.

Keywords: Biological network, graph theory, topological parameters, network biology, therapeutics

INTRODUCTION TO NETWORKS

The term ‘network’ originally pertains to everyday language and includes various recognizable and concrete systems. These systems encompass human-made networks, such as railways, roads, airlines, electrical grids, and the Internet. Additionally, biological networks, including metabolic pathways, neural connections, blood circulation, and food webs, also encompass tree-like networks such as hydrographic systems with simpler characteristics. In biology, a network refers to a complex interconnected system of biological elements such as genes, proteins, molecules, or cells, which interact with each other to perform various functions within an organism [1].

***Author for Correspondence**
Shazia Haider
E-mail: shaider1@jmi.ac.in

[1,2]Student, Department of Biosciences, Jamia Millia Islamia, New Delhi, India
[3]Assistant Professor, Department of Biosciences, Jamia Millia Islamia, New Delhi, India

Received Date: April 19, 2024
Accepted Date: May 02, 2024
Published Date: May 28, 2024

Citation: Khushboo, Pulkit Singh, Shazia Haider. Introduction to Biological Networks and Their Contributions to Systems Biology. International Journal of Bioinformatics and Computational Biology. 2024; 2(1): 53–70p.

Understanding Networks Using Graph Theory

Graph theory is a branch of mathematics that studies graphs, which are mathematical structures

© STM Journals 2024. All Rights Reserved

used to represent relationships between objects. These objects are called vertices or nodes, and they are connected by lines or arcs called edges. A mathematical formula for the graph is depicted in Equation (1). Graph theory finds numerous applications in various fields, including computer science, social sciences, and operations research [2].

$$G = (N, E) \tag{1}$$

A graph, denoted as *G = (N, E)*, conceptually comprises nodes *(N)* and edges *(E)*, where nodes represent individual entities and edges depict the connections between them [3].

Components of Graph Theory

Nodes

Nodes are foundational components in graphs, symbolizing individual entities within a network, and are depicted as points or circles in graphical representations, as shown in Figure 1. The mathematical formula for a node is depicted in Equation (2). Each node represents an individual entity [4].

$$N = (1, 2, 3, \ldots .6) \tag{2}$$

To represent a simple network with six nodes/vertices mathematically, we can write this as *N = (1,2,3, ... 6)* [5].

In biological networks, nodes are fundamental components that represent diverse biological entities, such as genes, proteins, molecules, or cells, each signifying a distinct entity within the network. For example, glucose yields glucose-6-phosphate during glycolysis through phosphorylation, where glucose and glucose-6-phosphate are represented by nodes, as shown in Figure 2 [6].

Edges

Edges represent the connections or links between nodes within a graph and delineate the interconnections among nodes [7]. The mathematical formula for the edges is as follows:

These connections are depicted as lines or curves, which indicate the presence of relationships or interactions between them [8].

$$E \subseteq \{\{X, Y\} \mid X, Y \in V \text{ and } X \neq Y\} \tag{3}$$

Mathematically, a set of edges (commonly referred to as links or interactions) comprises unordered pairs of nodes, indicating that each edge is associated with two distinct nodes [9].

For a more general example of edges in networks, consider a simple glycolysis reaction, where nodes represent glucose, Hexokinase, and glucose-6-phosphate, while edges represent the interaction between them through phosphorylation, as shown in Figure 3 [10].

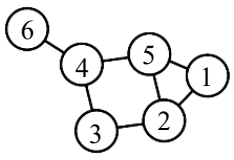

Figure 1. A simple network has 6 nodes/vertices marked as nodes 1, 2, 3, 4, 5, and 6 [5].

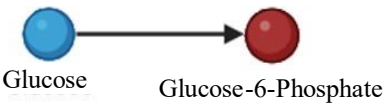

Figure 2. Glucose (blue) and glucose-6-phosphate (red) are represented as biological entities, while the interaction between them is represented by an arrow-headed line (edge) [11].

© STM Journals 2024. All Rights Reserved

There are two types of edges: directed and undirected. These types are illustrated in Figure 4. In an undirected graph, edges lack a specific direction, representing mutual or bidirectional relationships between the connected nodes. In a directed graph, edges have distinct directions, indicating unidirectional relationships between nodes. Directed networks specify the connection direction, whereas undirected networks lack directional information [12].

Hubs and Motifs in Networks

Examining hubs and motifs in biological networks is crucial for revealing organizational principles, identifying key players in cellular processes, and understanding network responses to perturbations [13].

Hubs

Hubs are nodes within a network that have a high number of interactions with other nodes. They are characterized by many more connections than the average node in the network. The hubs are shown in Figure 5. In biological networks, hubs represent vital proteins, genes, or molecules involved in various cellular processes [14].

Motifs

Motifs are recurring, compact patterns within networks, representing configurations of nodes and edges that occur more frequently than randomly. These motifs are shown in Figure 6. Motifs reveal network properties and organization, which are essential for analyzing organizational principles in network analysis [15].

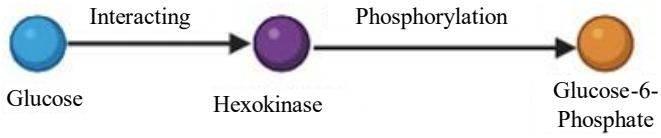

Figure 3. Glucose (blue) interacts with Hexokinase (purple) to yield glucose-6-phosphate (orange) through phosphorylation. Edges (arrow-headed lines) represent interaction and phosphorylation [10].

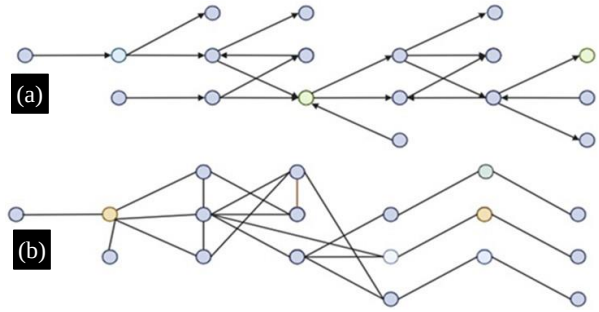

Figure 4. In graph theory, networks have two types of edges: (a) Directed networks have edges with specified directions, and (b) Undirected networks have bidirectional edges [16].

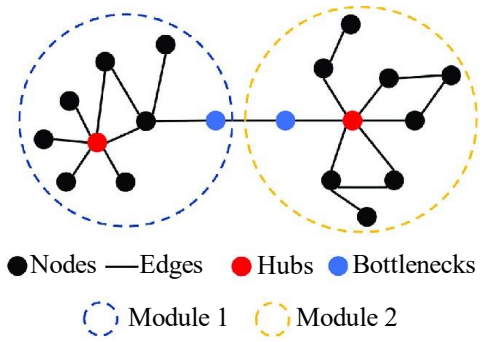

Figure 5. Hubs are nodes with many interactions, modules are clusters where nodes predominantly interact within the cluster, and bottlenecks are nodes that serve as connectors between two ends [17].

© STM Journals 2024. All Rights Reserved

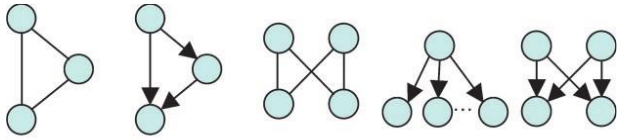

Figure 6. Common motifs in biological networks represent cellular components like genes or proteins, connected by associations such as binding (undirected edges) or influence (directed edges) [18].

Topological Parameters of Networks

Network topological parameters quantify the structural properties and connectivity patterns of networks. These metrics are crucial for analyzing diverse systems, such as social networks, biological networks, and IT infrastructures, providing insights into their organization and functional dynamics [19].

Degree

The degree of a node represents the number of connections between a particular node and other nodes in the graph. The degree of a node represents its number of connections. The mathematical formula for the degree is given in Equation (4). Nodes with a high degree are referred to as 'hubs.' A hub in a network is a highly connected node that serves as a central point for communication and interaction with other nodes [20].

$$deg_{avg} = deg_u^{in} + deg_u^{out} \tag{4}$$

Degree *(deg_{avg})* is the average total connection of a node *(u)*, calculated as the sum of the number of incoming edges *(deg_u^{in})* and outgoing edges *(deg_u^{out})* [21].

Eccentricity

Eccentricity is a measure that evaluates the importance of nodes by determining the maximum distance between them and other nodes. A mathematical formula for eccentricity is given in Equation (5). In a network analysis, nodes with high eccentricity are closer to others, thereby fostering connectivity. High eccentricity indicates proximity to all nodes, whereas low eccentricity suggests that some nodes are distant [22].

$$ECC(v) = \frac{1}{max\{dist\ (v,u):u \in V} \tag{5}$$

The eccentricity *ECC(v)* of a node *(v)* is calculated as *(1)* divided by the maximum shortest path distance from *(v)* to any other node *(u)* in the node set *(V)* of the graph [23].

Closeness centrality

The closeness centrality of a node measures its proximity to other nodes in the network. The mathematical formula for closeness centrality is shown in Equation (6). Nodes closer to others in a graph have higher closeness centrality, indicating their proximity to the center and suggesting higher influence and efficient information flow among closely connected nodes. It is crucial to identify key nodes, and it is the reciprocal of the average network distance for each node, which measures node importance [24].

$$CC\ (v) = \frac{(N-1)}{\sum d(v,u):u \in V} \tag{6}$$

The *CC(v)* of a node *(v)* is calculated as *(1)* divided by the maximum of the shortest path distances from *(v)* to all other nodes *(u)* in the node set *(V)* [25].

Betweenness Centrality

The betweenness centrality, also known as the shortest path betweenness centrality, measures a node's ability to facilitate communication between other nodes. A mathematical formula for

© STM Journals 2024. All Rights Reserved

betweenness centrality is shown in Equation (7). If a node lies on the shortest path between two other nodes or hubs, it controls communication flow. A node's betweenness depends on its ability to control communications, making it central if it controls many nodes [26].

$$C_{bet(u)} = \frac{\delta_{xy}(u)}{\delta_{xy}} \tag{7}$$

The betweenness centrality $C_{bet}(u)$ is calculated as the ratio of the shortest paths between all pairs of nodes *(x and y)* that pass-through node *(u)* denoted as *δxy (u)* divided by the total number of shortest paths between all pairs of nodes, denoted as *(δxy)* [27].

Average Path Length

The average path length or the average shortest path length is the average number of steps along the shortest paths for all pairs of network nodes. The mathematical formula for the average path length is given in Equation (8). It quantifies the average number of steps that connect all possible pairs of nodes, indicating network efficiency and interconnectedness. It offers insights into signal transmission between nodes and network structure characterization [28].

$$l = \frac{1}{n(n-1)}[\sum_j^i d(vi, vj)] \tag{8}$$

The average path length *(l)* is calculated by summing the shortest distances between all pairs of nodes (v_i) and (v_j) in the graph and dividing by the total number of possible node pairs $n(n-1)$, where *(n)* represents the total number of nodes in the graph [29].

Clustering Coefficient

The clustering coefficient measures network clustering by comparing the actual and potential connections. The mathematical formula for the clustering coefficient is shown in Equation (9). It is crucial in biological and computer network analyses to reveal tightly connected communities and functional modularity. High clustering suggests module presence, particularly cooperative interactions among biological entities in biological networks [30].

$$C_u = \frac{2_e}{k(k-1)} \tag{9}$$

The clustering coefficient *(Cu)* of a node *(u)* is calculated by dividing twice the number of edges *(e)* between the neighbors of node *(u)* by the product of the degree *(k)* of node *(u)* and one edge less than its degree [31].

Eigenvector Centrality

The eigenvector centrality measures a node's importance in a network, considering both its connections and the importance of those to which it is connected. A mathematical formula for eigenvector centrality is given by Equation (10). Centrality is calculated by analyzing the centrality of neighboring nodes, with higher values indicating greater influence. The eigenvector of the largest eigenvalue represents the centrality of each node in the network [32].

$$x = \frac{1}{\lambda}Ax \tag{10}$$

The eigenvector centrality *(x)* of the nodes in a network is estimated by multiplying the adjacency matrix *(A)* by *(x)* and scaling the result by the corresponding eigenvalue *(λ)* [33].

Maximum Neighborhood Connectivity

The maximum neighborhood connectivity measures a node's interconnectedness with its immediate neighbors, indicating the density of connections in its local neighborhood. The mathematical formula for the maximum neighborhood connectivity is shown in Equation (10). Higher values suggest stronger connectivity and cooperation among neighboring nodes, often reflecting a central or influential role within the local network structure [34].

© STM Journals 2024. All Rights Reserved

$$MNC\ (V)\ =\ |\ V\ [MC(v)]\ |\tag{11}$$

The maximum neighborhood connectivity *MNC(v)* for a set of nodes *(V)* is calculated for node *(v)* by identifying the largest connected node within the induced subgraph *(G/Nv/)* formed by the neighbors of *(v)* in the network [35].

Subgraph Centrality

The Subgraph Centrality assesses a node's network importance by analyzing its involvement in various subgraphs and evaluating the frequency and lengths of closed walks. A mathematical formula for subgraph centrality is given in Equation (12). It analyzes closed walks of varying lengths, with shorter paths focused on decreasing weights. Each closed walk corresponds to connected subgraphs, highlighting their importance in assessing the node centrality [36].

$$SC(u)\ =\sum_{j=1}^{N}(v)\ \text{^}2.e\tag{12}$$

The subgraph centrality *SC(u)* of a node *(u)* is calculated by summing the squares of the eigenvalues *(v)* of the adjacency matrix, *(e)* assessing the importance of node *(u)* within network subgraphs, with higher eigenvalues *(v)* indicating greater centrality [37].

Stress Centrality

Stress centrality quantifies a node's importance by assessing its role as a bridge or intermediary, connecting nodes through shortest paths, and facilitating communication pathways within the network. A mathematical formula for stress centrality is given in Equation (13). Nodes with high-stress centrality maintain efficient flow and connectivity, offering insights into network structures and functions in communication, transportation, and social networks [38].

$$S(i)\ =\sum i\neq j\neq k\frac{\sigma jk(i)}{\sigma jk}\tag{13}$$

The stress centrality *S(i)* of node *(i)* is calculated by summing the fraction of the shortest paths from all node pairs *(j* and *k)* that pass-through *(i)*, normalized by the total number of shortest paths between *(j)* and *(k)* in the network [39].

NETWORK ORGANIZATION

Network organization in biological networks refers to the structural arrangement and interconnections among biological entities such as genes, proteins, or metabolites. This organization offers insights into biological processes. These networks can be categorized as small-scale, scale-free, and hierarchical networks. Small-scale networks have a limited number of nodes and edges that represent direct interactions. Scale-free networks have a 'hub' structure, with a few highly connected nodes. Hierarchical networks organize nodes into levels based on their functions. Understanding network organization is crucial for unraveling biological complexity, showing how components interact, information flows, and perturbations lead to outcomes, and understanding their functions and behavior [40].

Small-scale Networks

Small-scale biological networks represent localized interactions within cells, biological processes, or limited components, as shown in Figure 7. These are focused networks depicting specific pathways or modules, such as gene regulatory networks that control cellular processes or metabolic pathways. Their localized nature provides insights into molecular and cellular phenomena. Examples include the gene regulatory networks governing specific cellular processes or metabolic pathways [41].

Scale-free Networks

Scale-free biological networks exhibit a power-law degree distribution, where few nodes in the network have a very high number of connections (hubs), whereas most nodes have relatively few connections, as shown in Figure 8. Scale-free topologies in diverse biological networks offer insight

© STM Journals 2024. All Rights Reserved

into their organizational principles and inherent robustness. Examples include protein-protein interactions and gene co-expression networks, which influence the organization and robustness of biological systems [42].

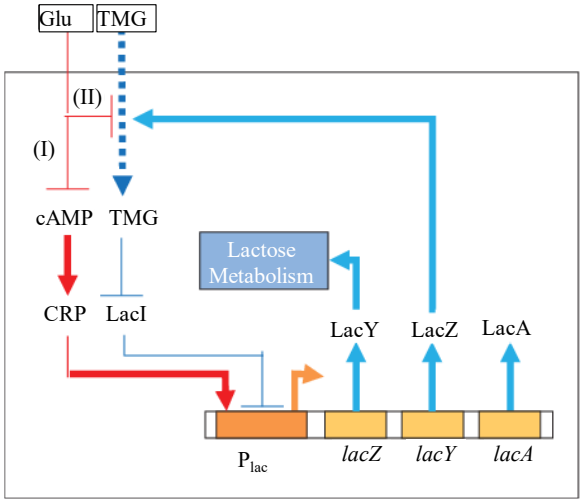

Figure 7. A Lac Operon Model is a small-scale biological network dealing with a limited number of components [43].

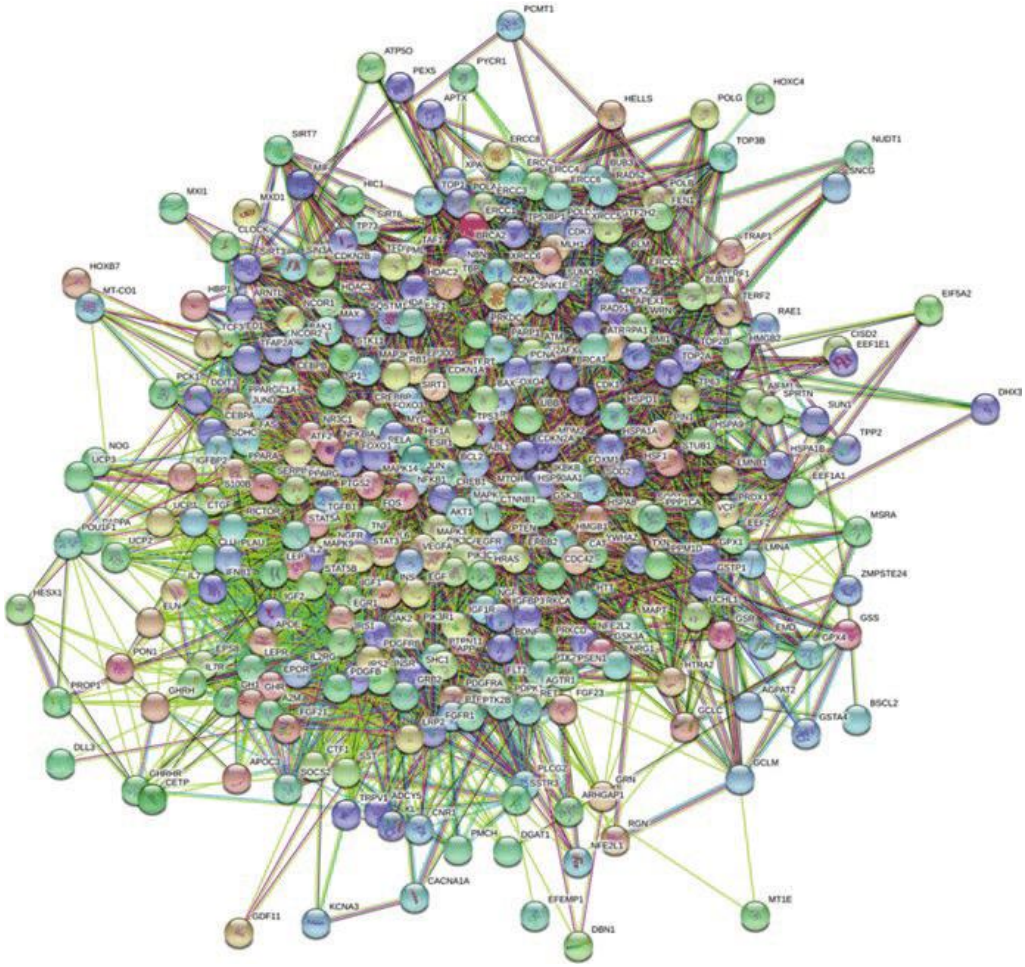

Figure 8. A protein-protein interaction network of genes linked to human aging processing is a scale-free biological network comprising 306 genes sourced from the GenAge Human Database [44].

© STM Journals 2024. All Rights Reserved

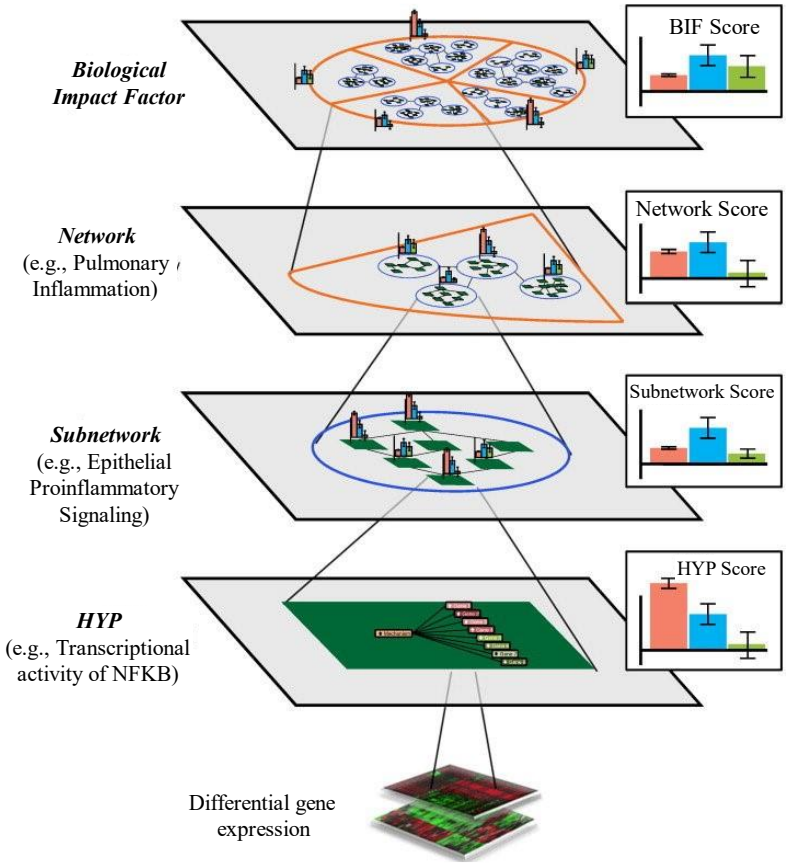

Figure 9. The network hierarchy includes HYPs, subnetworks, and networks, with the scoring hierarchy adding the biological impact factor (BIF) level aggregating across multiple networks [45].

Hierarchal Network

A hierarchical network is a network structure that exhibits hierarchical organization, with nodes arranged in multiple levels or layers, as shown in Figure 9. Higher-level nodes exert control over lower-level nodes in a tree-like manner. Biological systems are hierarchically organized across scales from molecules to organisms. This model captures multiscale organizations, with nodes representing organizational units such as genes, proteins, pathways, and cells. Examples include signaling and regulatory networks spanning biological scales, which facilitate cross-scale analysis in biology [46].

NETWORK BIOLOGY

Network biology integrates diverse omics data, including genomic, transcriptomic, proteomic, and metabolomic information, along with interactome data, such as protein-protein interactions and gene-gene associations, to reveal informative patterns within complex biological systems. By employing statistical methods, graph theory, mathematical modeling, and visualization tools, as outlined in the flowchart in Figure 10, this field enhances the understanding of biological mechanisms and disease causes and aids in discovering therapeutic interventions [47]. The development and use of biological networks can fulfill multiple objectives for exploring network biology. These include identifying and prioritizing candidate genes that may contribute to disease causation [48], uncovering disease-associated subnetworks and systematic perturbations underlying disease states [49], and capturing therapeutic responses to aid in the identification of potential drug targets and discovery of new therapeutic agents [50].

Types of Biological Networks

Biological networks encompass various forms, each portraying unique aspects of biological systems [51]. These include protein-protein interaction networks, interactions between proteins that elucidate

© STM Journals 2024. All Rights Reserved

cellular processes [52], Sequence Similarity Networks that highlight evolutionary relationships [53], KEGG Metabolic Pathways that illuminate biochemical reactions [54], Reactome Signal Transduction Networks that delineate cellular signaling cascades [55], Food Webs that capture ecological interactions [56], and Gene Expression Networks that unravel the coordination of gene activities [57], as depicted in Figure 11. Various network types explore biological complexity at the cellular, molecular, and ecological levels. These networks are categorized based on interacting entities [58].

Protein-protein Interaction Networks

PINs visually depict physical protein connections within cells. Proteins are nodes and interactions are edges that are either undirected or directed. PPIs, As depicted in Figure 11(a) are crucial in cellular processes and have been widely studied. Experimental techniques, such as the yeast two-hybrid system, are commonly used to identify binary interactions [59]. International efforts have led to the cataloging of experimentally determined PPIs [60]. Examples include the Human Protein Reference Database [61], Database of Interacting Proteins (DIP) [62], Molecular Interaction Database (MINT) [63], Intact Act [64], and BioGRID [65]. FunCoup [66] and STRING [67], as depicted in Figure 11(i), compiled PPIs from various sources for public use.

DNA-protein Interaction Networks

The genome produces vital mRNAs and proteins essential for cell functions, such as differentiation, survival, and metabolism. Gene products result from transcription and are governed by transcription factors (TFs). Nearly 1,500 DNA-binding TFs in humans regulate the expression of over 20,000 genes expression [68]. Gene products interact to form gene regulatory networks (GRNs) and control cellular processes by regulating gene product levels PINs visually depict physical protein connections within cells. Proteins are nodes and interactions are edges that are either undirected or directed. PPIs are crucial for cellular processes and have been widely studied. An example of this is a gene expression network, as depicted in Figure 11(f). Experimental techniques, such as the yeast two-hybrid system, are commonly used to identify binary interactions [59]. International efforts have led to the cataloging of experimentally determined PPIs [60].

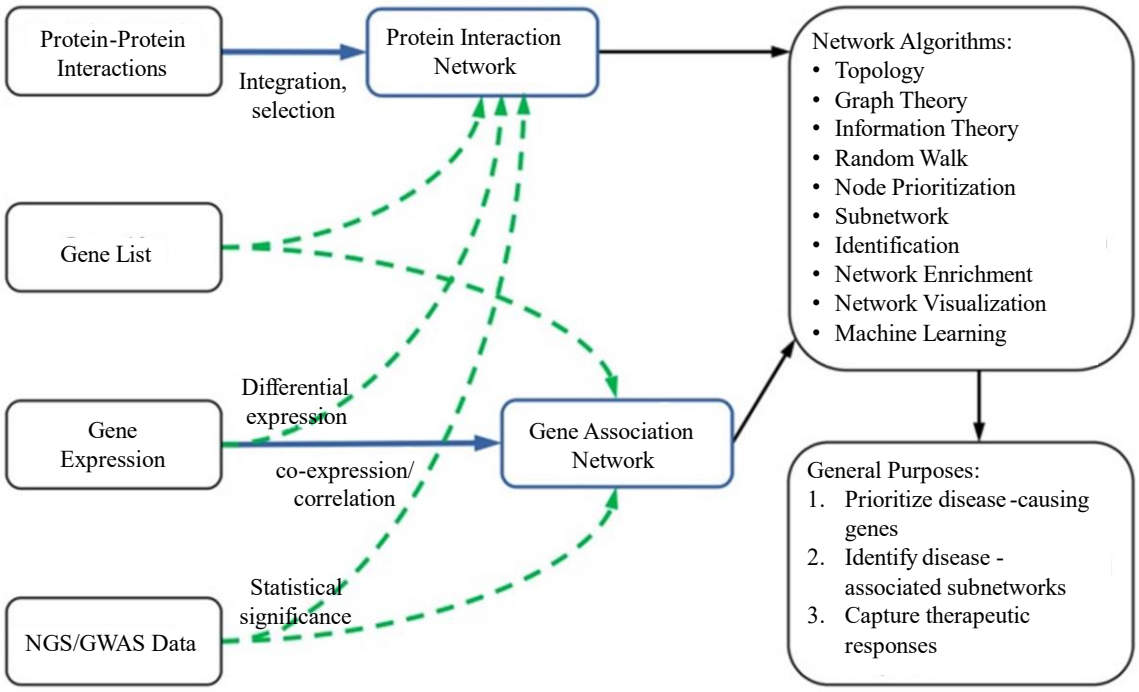

Figure 10. The flowchart illustrates network construction (blue) and mapping of biological data onto networks (green) in biological network studies [69].

© STM Journals 2024. All Rights Reserved

Examples include the Human Protein Reference Database [61], Database of Interacting Proteins (DIP) [62], Molecular Interaction Database (MINT) [63], Intact Act [64], and BioGRID [65]. FunCoup [66], Tagged PubMed abstract as depicted in Figure 11(h), and STRING as depicted in Figure 11(i) [67] compile PPIs from various sources for public use. GRNs depict regulatory connections between genes and TFs as nodes and edges, revealing the promotion and inhibition of gene regulation [70]. GRNs are often built using gene regulation data from databases such as Reactome [71], as depicted in Figure 11(d), and KEGG [72], as depicted in Figure 11(c). High-throughput technologies such as microarrays, RNA-Seq, ChIP-chip, and ChIP-seq have revealed complex gene regulation patterns, advancing our understanding of GRNs [73].

Metabolic Networks

Metabolic networks control metabolite synthesis, degradation, and transport. Metabolites are small compounds that exhibit dynamic changes in tissues and cells. Biochemical reactions, facilitated by gene-encoded enzymes, irreversibly convert substrates to products. These networks are crucial for cellular processes and focus on unraveling relationships through metabolic reconstruction [74]. Historically, mass spectrometry, NMR spectroscopy, and chromatography have been used to identify and quantify metabolites. KEGG (The Kyoto Encyclopaedia of Genes and Genomes) plays a vital role in biological data, particularly metabolic pathways, as depicted in Figure 11(c) [75].

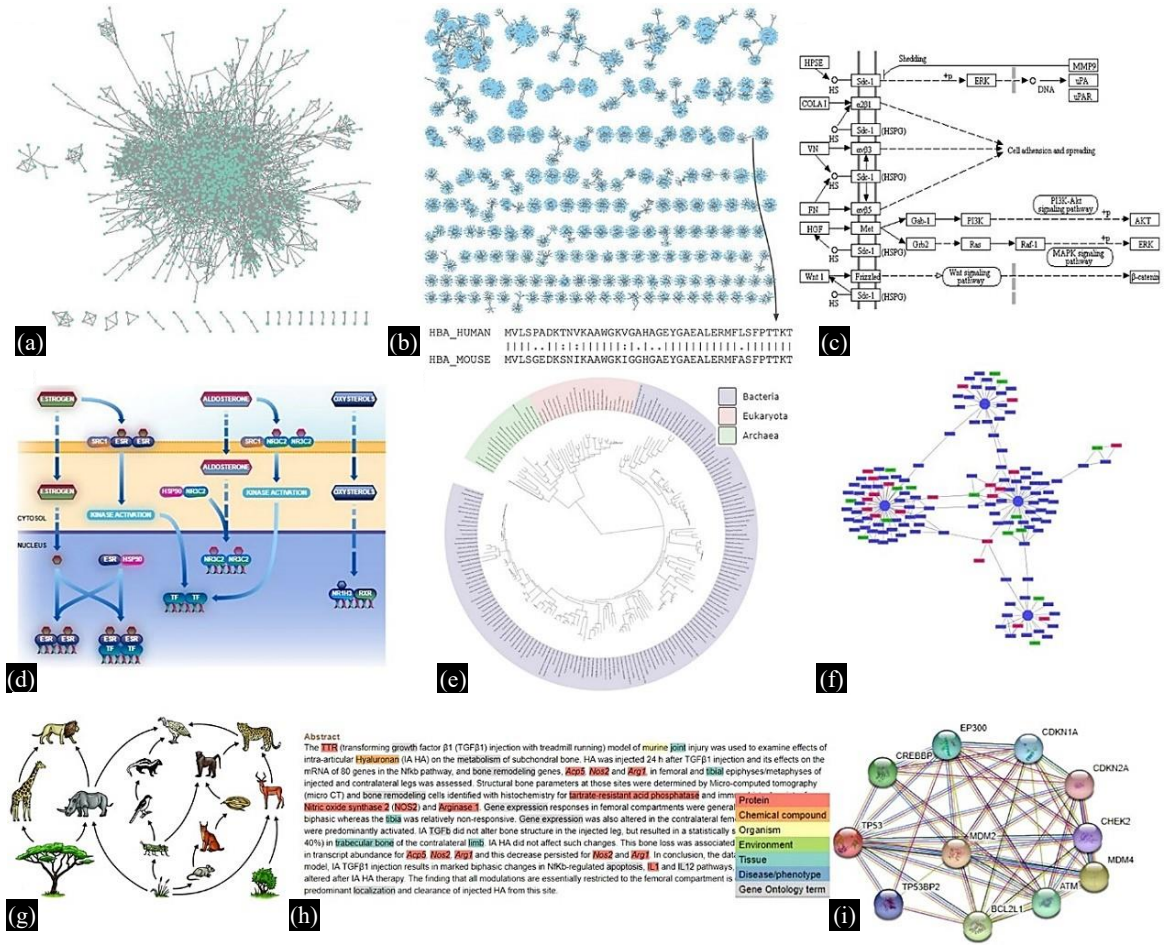

Figure 11. Biological networks include: (a) Protein-protein interaction (PPI) network, (b) Sequence similarity network, (c) KEGG metabolic pathway, (d) Reactome signal transduction network, (e) Tree of life in iTOL, (f) Gene expression network, (g) Savanna food web, (h) Tagged PubMed abstract, and (i) STRING multi-edge PPI knowledge network [76].

© STM Journals 2024. All Rights Reserved

Cell Signaling Networks

Cell signaling networks are intricate molecular systems that enable cell communication and response to the environment, involving signaling molecules, receptors, and pathways that regulate processes such as gene expression and cell growth. For example, reactome signal transduction networks depict cellular signaling through protein interactions, as depicted in Figure 11(d). These networks coordinate cellular activities, respond to stimuli, and maintain an organism's function. They resemble sensory machines, with sensors and processors leading to diverse cellular responses, including gene transcription and cytoskeletal dynamics [77]. Cell signaling networks illustrate molecular interactions in cellular communication, whereas sequence similarity networks, as depicted in Figure 11(b), reveal relationships between biological sequences, such as DNA, RNA, or proteins, based on their alignment scores [76]. Modern cell biology aims to unravel the mechanisms of molecular signaling pathways and their physiological roles, to engineer synthetic signaling circuits [78].

Ecological Networks

Ecological networks depict species interactions in ecosystems, highlighting interdependencies among plants, animals, and microorganisms. They reveal a web of relationships that shape ecological processes within a specific environment [79]. For example, the Savanna food web focuses on feeding relationships between organisms in an ecosystem, as depicted in Figure 11(g), and the Tree of Life in iTOL, focuses on evolutionary relationships between species, as depicted in Figure 11(e). Ecological networks depict intricate interactions among species within ecosystems, including food webs and mutualistic relationships, thereby revealing the complex interconnectedness of ecological systems. Ecological networks display intricate complexity, where each species is intricately linked to others, either directly or indirectly [80]. These links tend to be nested, which is also known as nested links. Nested links in network theory describe a hierarchy of connections between entities, as seen in ecological, social, and biological networks [81].

Implications of Biological Networks

Progress in molecular biology, neurobiology, genetics, and imaging offers insights into neurological diseases, but their pathogenesis remains incompletely understood. Reductionism identifies organism components but fails to explain complex interactions, enabling fitness, robustness, and evolution [82]. Systems biology integrates molecular, physiological, and clinical data into quantitative frameworks, akin to engineering. It uses tools from physics and mathematics, such as nonlinear dynamics and control theory, to understand complex living systems, such as the brain. Studies of gene networks linked to hereditary ataxias have revealed RNA splicing pathways that expose new disease mechanisms [83]. Systems biology will aid in personalized therapeutic strategies and make personalized medicine feasible. By studying component interactions in biological networks, systems biology enhances disease comprehension and fosters personalized treatment development [84].

Network Visualization

Biological network visualization shows genes, proteins, and metabolites as nodes connected by interactions (edges). Network visualization techniques range from matrix representation, as depicted in Figure 12(g), to 2D/3D layouts, as depicted in Figure 12(d) with multi-layered graph visuals, as depicted in Figure 12(b), and are ideal for multi-omics networks. Tools such as STRING graphs, as depicted in Figure 12(e), illustrate the diverse connections between biological entities through multiple relationship types [85]. Force-directed, as depicted in Figure 12(a), and hierarchical layouts struggle with the dense networks 'hairball' effect. Circos and Hive plots using circular or radial linear axes address this issue. Hive plots, as depicted in Figure 12(c), show diverse networks such as cancer and gene regulation, while Circos, as shown in Figure 12(h), depict genomic variation relationships and are challenging to represent linearly. Arc diagrams, Circos, and hive plots using circular or radial linear axes address this, as depicted in Figure 12(f), showing nodes on a single axis with arced links. Specialized visualizations for bipartite graphs, as depicted in Figure 12(i), in epidemiology and gene-disease networks, illustrate the mutual relationships between the two sets. Although other methods exist for hierarchical graphs and biochemical networks, the basic visualization concepts are depicted schematically [86].

© STM Journals 2024. All Rights Reserved

DISEASES AND OMICS TECHNOLOGY

OMIC-based disease modeling, encompassing genomics, proteomics, and metabolomics, mathematically represents disease mechanisms at molecular and physiological levels. This aids computational analysis by translating biological data into quantifiable terms. Kinetic equations are formulated using principles such as the law of mass action and Michaelis-Menten and Hill equations, tailored to the specific reactions and interactions in the pathways. Stochastic modeling methods such as Monte Carlo simulations, Fokker-Planck formulations, and rule-based approaches have been used to study the dynamic behavior of disease pathways owing to their stochastic nature [87].

Mathematical Modeling of Diseases and Their Integration in Networks

Utilizing network development and graph-based analyses can aid in understanding disease interconnections and identifying potential candidates. However, understanding the dynamic nature of these networks presents a challenge. Networks provide static representations of systems and are unable to capture temporal changes caused by variations in conditions, such as mutations and environmental factors. Simulating interactions and mechanisms are crucial to unveiling the dynamic nature of networks that define disease characteristics [88]. Disease modeling mathematically represents disease mechanisms from the molecular to physiological levels, facilitating computational analysis by quantifying biological data. Feedback mechanisms in mathematical models aid in understanding the dynamics and predicting outcomes under various conditions or perturbations using defined parameters [89].

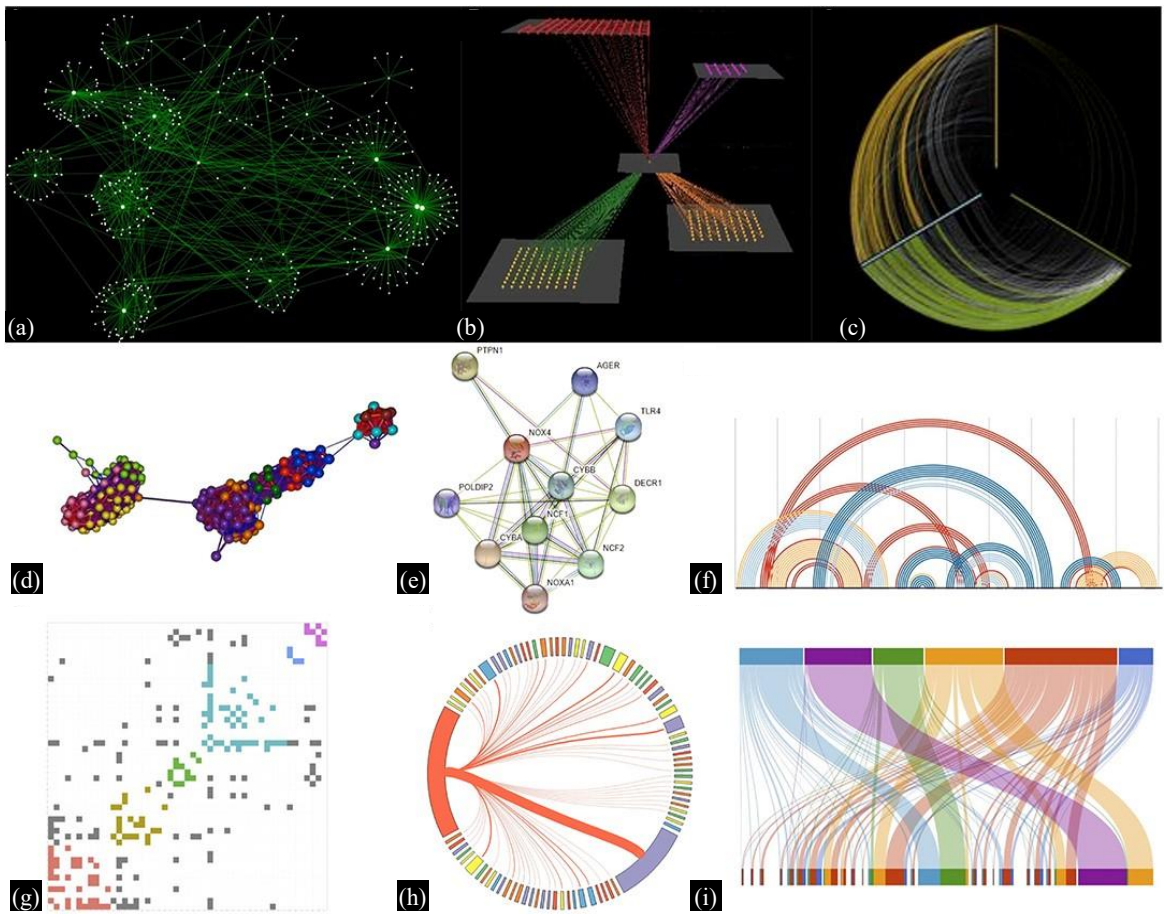

Figure 12. Network visualization techniques include (a) force-directed network layouts, (b) multi-layered graph views, (c) Hive plot representations, (d) 3D network visualizations, (e) STRING Multi-edge network displays, (f) Arc-based network visualizations, (g) Adjacency matrix representations, (h) Circular Circos visualization, and (i) Bipartite graph visualizations [76].

© STM Journals 2024. All Rights Reserved

Networks as Drug Targets

The disease network comprises interacting biomolecules that influence network function toward a disease phenotype. Perturbing essential components within this complexity can alter the phenotypic response and contribute to disease manifestation [90]. Complex diseases such as cancer and metabolic syndrome arise from the contributions of multiple components impacting multigenic functional modules rather than a single target, leading to disease phenotypes [91]. The ineffective use of conventional therapies has prompted a network-based approach targeting subcircuits instead of individual nodes to mitigate disease effects. Both multiple and single targets contribute to network dynamics. Targeting hub genes and proteins affected in complex diseases, while effective, can lead to potential side effects [92]. Yildirim et al. (2007) created a Drug Target network linking FDA-approved drugs to their specific protein targets [93]. Topological analysis identifies drug targets in different network regions than essential proteins, with peripheral disease genes as promising targets with low side effects [94].

Network Modeling in Diabetes and Cancer

Network analysis, modeling, and target identification are crucial for understanding complex diseases such as diabetes and cancer, involving hormones, growth factors, and inflammatory molecules [95]. Mathematical models describe molecular interactions as networks, aid target identification, and quantify disease states through data generation [96].

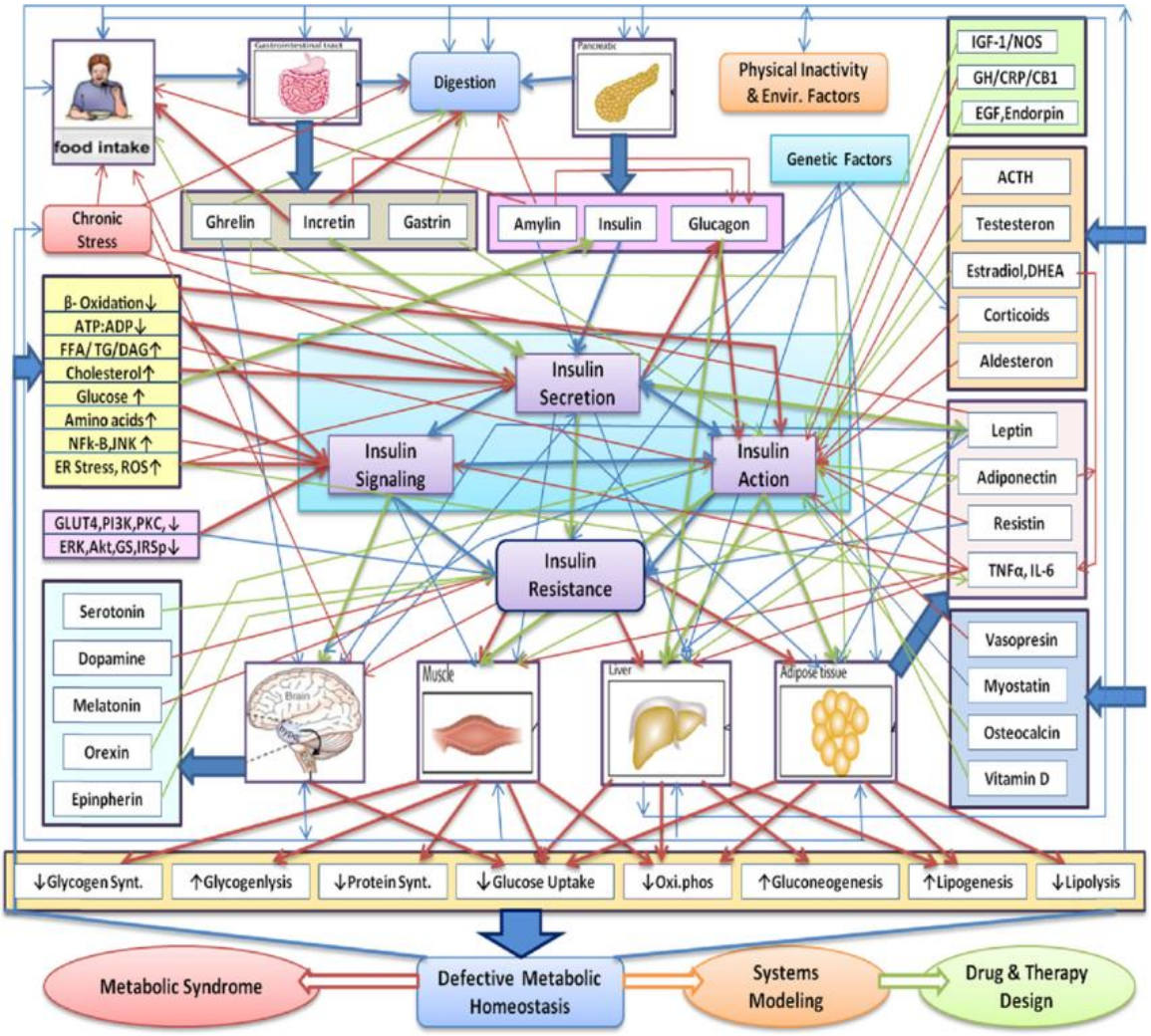

Figure 13. A map illustrates insulin resistance's complexity, showing modeled interactions among factors influencing insulin secretion, signaling, and action in the liver, muscle, adipose, and brain [97].

© STM Journals 2024. All Rights Reserved

In diabetes, network models have revealed interactions between insulin signaling, glucose metabolism, and transcription, thereby identifying therapeutic targets and biomarkers [98]. Network approaches to cancer have uncovered wired signaling, GRNs, and protein interactions driving tumorigenesis, metastasis, and drug resistance, enabling personalized therapies [99]. As illustrated in Figure 13, minimal and pharmacokinetic-pharmacodynamic (PK-PD) models physiologically illustrate glucose and insulin dynamics [100].

CONCLUSION

In conclusion, biological networks provide a powerful framework for understanding complex living systems. This review has explored network analysis principles, from graph theory to topological parameters, and their applications across various biological domains. The integration of omics technologies and mathematical modeling has advanced our understanding of disease mechanisms and drug target identification. As the field progresses, network-based approaches will remain crucial in deciphering biological intricacies, driving innovations in biomedical research and personalized medicine. Future developments in this interdisciplinary field promise to further unravel the complexities of living systems, contributing to improved human health and scientific knowledge.

Acknowledgment

I start by giving thanks to *God* for helping someone as weak as me to complete this review paper, despite the many painful and indescribable hurdles. Yet insignificant and small, it is a little step ahead. I had a little dream to do a PhD, and most probably, I will never get it. However, God is the strongest. If he wants, he will make this happen. I do not know what the future holds for me, but as a believer in this divine universe, I know that if I have God with me, he will help me. All my life, I have been alone. I have dealt with all my pain myself. I never met anyone who understood me or my world. I have a universe inside me. I believe that I am a child of God. I have no one except God.

I want to thank my friend *Pulkit Singh*, who I think is the boy sent to me by God to save me. Without him, this review would not have been possible. His selfless help for me is not something you will find in this materialistic world. Thank you for the sacrifices he made to help me. I am blessed with what he does for me and wish to do it forever and beyond. I wish him all that he wanted.

REFERENCES

1. Lesne A. Complex networks: from graph theory to biology. Lett Math Phys. 2006;78(3):235–62.
2. Pavlopoulos GA, Secrier M, Moschopoulos CN, Soldatos TG, Kossida S, Aerts J, et al. Using graph theory to analyze biological networks. BioData Min. 2011;4:10.
3. Brandes U, Robins G, McCranie A, Wasserman S. What is network science?. Network science. 2013 Apr;1(1):1-5.
4. Erciyes K. Graph-theoretical analysis of biological networks: a survey. Computation. 2023;11(10).
5. Wilson RJ. Introduction to graph theory. John Wiley & Sons, Inc.; 1986.
6. Arul SM, Senthil G, Jayasudha S, Alkhayyat A, Azam K, Elangovan R. Graph theory and algorithms for network analysis. E3S Web Conf. 2023;399:08002.
7. 7BioRender. Create professional science figures in minutes. 2023. Available from: https://www.biorender.com/.
8. Lüschow A. Application of graph theory in the library domain—Building a faceted framework based on a literature review. Journal of Librarianship and Information Science. 2022 Dec;54(4):558-77.
9. Samanta S, Akram M, Pal M. m-Step fuzzy competition graphs. Journal of Applied Mathematics and Computing. 2015 Feb;47(1):461-72.
10. Fuller GG, Kim JK. Compartmentalization and metabolic regulation of glycolysis. J Cell Sci. 2021;134(20).
11. Kloska SM, Pałczyński K, Marciniak T, Talaśka T, Wysocki BJ, Davis P, Wysocki TA. Integrating glycolysis, citric acid cycle, pentose phosphate pathway, and fatty acid beta-oxidation into a single computational model. Sci Rep. 2023;13(1):14484.

© STM Journals 2024. All Rights Reserved

12. Dehmer M, Chen Z, Emmert-Streib F, Tripathi S, Mowshowitz A, Levitchi A, et al. Measuring the complexity of directed graphs: a polynomial-based approach. PLoS One. 2019;14(11).
13. He X, Zhang J. Why do hubs tend to be essential in protein networks? PLoS Genet. 2006;2(6).
14. Goymer P. Network biology: why do we need hubs? Nat Rev Genet. 2008;9(9):650.
15. Amaral LA, Scala A, Barthelemy M, Stanley HE. Classes of small-world networks. Proc Natl Acad Sci U S A. 2000;97(21):11149–52.
16. Newman M. Networks: an introduction. Oxford University Press; 2010.
17. Thomas JP, Modos D, Korcsmaros T, Brooks-Warburton J. Network biology approaches to achieve precision medicine in inflammatory bowel disease. Front Genet. 2021;12:760501.
18. Rice J, Kershenbaum A, Stolovitzky G. Lasting impressions: motifs in protein-protein maps may provide footprints of evolutionary events. Proc Natl Acad Sci U S A. 2005;102:3173–4.
19. Brede M. Networks—an introduction. Mark E. J. Newman. (2010, Oxford University Press.). Artif Life. 2012;18:241–2.
20. Opsahl T, Agneessens F, Skvoretz J. Node centrality in weighted networks: generalizing degree and shortest paths. Soc Networks. 2010;32:245–51.
21. Mengyuan W, Wang H, Zheng H. A mini review of node centrality metrics in biological networks. Int J Netw Dyn Intell. 2022:99–110.
22. Telesford QK, Joyce KE, Hayasaka S, Burdette JH, Laurienti PJ. The ubiquity of small-world networks. Brain Connect. 2011;1(5):367–75.
23. Imran M, Iqbal M, Liu Y, Baig AQ, Khalid W, Zaighum M. Computing eccentricity-based topological indices of 2-power interconnection networks. J Chem. 2020;2020.
24. Evans T, Chen B. Linking the network centrality measures closeness and degree. Commun Phys. 2022;5.
25. Okamoto K, Chen W, Li XY, editors. Ranking of closeness centrality for large-scale social networks. In: Frontiers in Algorithmics. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008.
26. Freeman L. A set of measures of centrality based on betweenness. Sociometry. 1977;40:35–41.
27. Newman MEJ. A measure of betweenness centrality based on random walks. Soc Networks. 2005;27(1):39–54.
28. Chen F, Wang X, Yuan Z. The average path length of scale free networks. Commun Nonlinear Sci Numer Simul. 2008;13:1405–10.
29. Smith RD. Average path length in complex networks: Patterns and predictions. arXiv preprint arXiv:0710.2947. 2007 Oct 16.
30. Lu P, Yu J. A mixed clustering coefficient centrality for identifying essential proteins. Int J Mod Phys B. 2020;34(10):2050090.
31. Arrigo F, Higham D, Tudisco F. A framework for second-order eigenvector centralities and clustering coefficients. Proc R Soc A Math Phys Eng Sci. 2020;476:20190724.
32. Bihari A, Pandia MK. Eigenvector centrality and its application in research professionals' relationship network. In2015 International Conference on Futuristic Trends on Computational Analysis and Knowledge Management (ABLAZE) 2015 Feb 25 (pp. 510-514). IEEE.
33. Ilyas MU, Radha H. A KLT-inspired node centrality for identifying influential neighborhoods in graphs. In2010 44th Annual Conference on Information Sciences and Systems (CISS) 2010 Mar 17 (pp. 1-7). IEEE.
34. Bliss CA, Danforth CM, Dodds PS. Estimation of global network statistics from incomplete data. PLoS One. 2014;9(10).
35. Chin C-H, Chen S-H, Wu H-H, Ho C-W, Ko M-T, Lin C-Y. cytoHubba: Identifying hub objects and sub-networks from complex interactome. BMC Syst Biol. 2014;8.
36. Giscard PL, Wilson RC. A centrality measure for cycles and subgraphs II. Appl Netw Sci. 2018;3(1):9.
37. Estrada E, Rodriguez-Velazquez JA. Subgraph centrality in complex networks. Phys Rev E Stat Nonlin Soft Matter Phys. 2005;71:056103.
38. Viacava Follis A. Centrality of drug targets in protein networks. BMC Bioinformatics. 2021;22(1):527.

© STM Journals 2024. All Rights Reserved

39. Borgatti S. Centrality and network flow. Soc Networks. 2005;27:55–71.
40. Alm E, Arkin AP. Biological networks. Curr Opin Struct Biol. 2003;13(2):193–202.
41. Schmidt H, Cho KH, Jacobsen EW. Identification of small scale biochemical networks based on general type system perturbations. FEBS J. 2005;272(9):2141–51.
42. Albert R, Jeong H, Barabasi AL. Error and attack tolerance of complex networks. Nature. 2000;406(6794):378–82.
43. Avcu N, Demir G, Pekergin F, Alyuruk H, Cavas L, Güzeliş C. Discriminant based bistability analysis of a TMG induced lac operon model supported with boundedness and local stability results. Turk J Electr Eng Comput Sci. 2016;24:719–32.
44. Chand A, Chettiyankandy P, Moharana M, Sahu S, Pradhan S, Pattanayak S, et al. Computational methods for developing novel antiaging interventions. 2018. p. 175–93.
45. Thomson T, Sewer A, Calvino-Martin F, Belcastro V, Frushour B, Gebel S, et al. Quantitative assessment of biological impact using transcriptomic data and mechanistic network models. Toxicol Appl Pharmacol. 2013;272.
46. Favela LH. Review of Networks: an introduction by M. E. J. Newman. Dynamical Systems Mag. 2014.
47. Barabási AL, Oltvai ZN. Network biology: understanding the cell's functional organization. Nat Rev Genet. 2004;5(2):101–13.
48. Magger O, Waldman YY, Ruppin E, Sharan R. Enhancing the prioritization of disease-causing genes through tissue specific protein interaction networks. PLoS Comput Biol. 2012;8(9).
49. Jia P, Zheng S, Long J, Zheng W, Zhao Z. dmGWAS: dense module searching for genome-wide association studies in protein-protein interaction networks. Bioinformatics. 2011;27(1):95–102.
50. Li Q, Lai L. Prediction of potential drug targets based on simple sequence properties. BMC Bioinformatics. 2007;8:353.
51. Bhat B, Singh G, Sharma R, Yaseen M, Ganai N. Biological networks: tools, methods, and analysis. 2019. p. 255–86.
52. Koh GC, Porras P, Aranda B, Hermjakob H, Orchard SE. Analyzing protein-protein interaction networks. J Proteome Res. 2012;11(4):2014–31.
53. Atkinson HJ, Morris JH, Ferrin TE, Babbitt PC. Using sequence similarity networks for visualization of relationships across diverse protein superfamilies. PLoS One. 2009;4(2).
54. Kanehisa M, Furumichi M, Tanabe M, Sato Y, Morishima K. KEGG: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res. 2017;45(D1):D353–61.
55. Croft D, O'Kelly G, Wu G, Haw R, Gillespie M, Matthews L, et al. Reactome: a database of reactions, pathways and biological processes. Nucleic Acids Res. 2011;39(Database issue):D691–7.
56. Dunne JA, Williams RJ, Martinez ND. Food-web structure and network theory: The role of connectance and size. Proc Natl Acad Sci U S A. 2002;99(20):12917–22.
57. Friedman N, Linial M, Nachman I, Pe'er D. Using Bayesian networks to analyze expression data. J Comput Biol. 2000;7(3-4):601–20.
58. Sneppen K, Krishna S, Semsey S. Simplified models of biological networks. Annu Rev Biophys. 2010;39:43–59.
59. Mashaghi AR, Ramezanpour A, Karimipour V. Investigation of a protein complex network. Eur Phys J B. 2004;41(1):113–21.
60. Nooren IMA, Thornton JM. Diversity of protein–protein interactions. EMBO J. 2003;22(14): 3486–92.
61. Peri S, Navarro JD, Kristiansen TZ, Amanchy R, Surendranath V, Muthusamy B, et al. Human protein reference database as a discovery resource for proteomics. Nucleic Acids Res. 2004;32(Database issue):D497–501.
62. Xenarios I, Rice DW, Salwinski L, Baron MK, Marcotte EM, Eisenberg D. DIP: the database of interacting proteins. Nucleic Acids Res. 2000;28(1):289–91.
63. Chatr-aryamontri A, Ceol A, Palazzi LM, Nardelli G, Schneider MV, Castagnoli L, Cesareni G. MINT: the Molecular INTeraction database. Nucleic Acids Res. 2007;35(Database issue):D572–4.
64. Kerrien S, Aranda B, Breuza L, Bridge A, Broackes-Carter F, Chen C, et al. The IntAct molecular interaction database in 2012. Nucleic Acids Res. 2012;40(Database issue):D841–6.

© STM Journals 2024. All Rights Reserved

65. Oughtred R, Rust J, Chang C, Breitkreutz BJ, Stark C, Willems A, et al. The BioGRID database: A comprehensive biomedical resource of curated protein, genetic, and chemical interactions. Protein Sci. 2021;30(1):187–200.
66. Persson E, Castresana-Aguirre M, Buzzao D, Guala D, Sonnhammer ELL. FunCoup 5: Functional association networks in all domains of life, supporting directed links and tissue-specificity. J Mol Biol. 2021;433(11):166835.
67. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019;47(D1):D607–13.
68. Vaquerizas JM, Kummerfeld SK, Teichmann SA, Luscombe NM. A census of human transcription factors: function, expression and evolution. Nat Rev Genet. 2009;10(4):252–63.
69. Zhang P, Itan Y. Biological network approaches and applications in rare disease studies. Genes (Basel). 2019;10(10).
70. Ma S, Kemmeren P, Gresham D, Statnikov A. De-novo learning of genome-scale regulatory networks in S. cerevisiae. PLoS One. 2014;9(9).
71. Kanehisa M, Furumichi M, Sato Y, Kawashima M, Ishiguro-Watanabe M. KEGG for taxonomy-based analysis of pathways and genomes. Nucleic Acids Res. 2023;51(D1):D353–92.
72. Kanehisa M, Goto S. KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res. 2000;28(1):27–30.
73. Angelini C, Costa V. Understanding gene regulatory mechanisms by integrating ChIP-seq and RNA-seq data: statistical solutions to biological problems. Front Cell Dev Biol. 2014;2:51.
74. Amara A, Frainay C, Jourdan F, Naake T, Neumann S, Novoa-Del-Toro EM, et al. Networks and graphs discovery in metabolomics data analysis and interpretation. Front Mol Biosci. 2022;9:841373.
75. Kanehisa M. The KEGG database. Novartis Found Symp. 2002;247:91–101; discussion 103, 119–28, 244–52.
76. Koutrouli M, Karatzas E, Paez-Espino D, Pavlopoulos GA. A guide to conquer the biological network era using graph theory. Front Bioeng Biotechnol. 2020;8:34.
77. Kabir MH, Patrick R, Ho JWK, O'Connor MD. Identification of active signaling pathways by integrating gene expression and protein interaction data. BMC Syst Biol. 2018;12(Suppl 9):120.
78. Kiel C, Yus E, Serrano L. Engineering signal transduction pathways. Cell. 2010;140(1):33–47.
79. Montoya JM, Pimm SL, Solé RV. Ecological networks and their fragility. Nature. 2006;442(7100):259–64.
80. Ulanowicz RE. Quantitative methods for ecological network analysis. Comput Biol Chem. 2004;28(5):321–39.
81. Bascompte J, Jordano P, Melián CJ, Olesen JM. The nested assembly of plant-animal mutualistic networks. Proc Natl Acad Sci U S A. 2003;100(16):9383–7.
82. Yu D, Kim M, Xiao G, Hwang TH. Review of biological network data and its applications. Genomics Inform. 2013;11(4):200–10.
83. Altaf-Ul-Amin M, Afendi FM, Kiboi SK, Kanaya S. Systems biology in the context of big data and networks. Biomed Res Int. 2014;2014:428570.
84. Villoslada P, Steinman L, Baranzini SE. Systems biology and its application to the understanding of neurological diseases. Ann Neurol. 2009;65(2):124–39.
85. Alzahrani H, Fernstad S. An investigation into various visualization tools for complex biological networks. Inf Vis. 2023;22(4):323–39.
86. Pavlopoulos GA, Kontou PI, Pavlopoulou A, Bouyioukos C, Markou E, Bagos PG. Bipartite graphs in systems biology and medicine: a survey of methods and applications. Gigascience. 2018;7(4): 1–31.
87. Ullah M, Wolkenhauer O. Stochastic approaches in systems biology. Wiley Interdiscip Rev Syst Biol Med. 2010;2(4):385–97.
88. Tegnér JN, Compte A, Auffray C, An G, Cedersund G, Clermont G, et al. Computational disease modeling - fact or fiction? BMC Syst Biol. 2009;3:56.

© STM Journals 2024. All Rights Reserved

89. Kiesewetter A, Schmiemann P. Understanding homeostatic regulation: The role of relationships and conditions in feedback loop reasoning. CBE Life Sci Educ. 2022;21(3).
90. Zanzoni A, Soler-López M, Aloy P. A network medicine approach to human disease. FEBS Lett. 2009;583(11):1759–65.
91. Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56–68.
92. Mardinoglu A, Nielsen J. Systems medicine and metabolic modelling. J Intern Med. 2012;271(2):142–54.
93. Yildirim MA, Goh KI, Cusick ME, Barabási AL, Vidal M. Drug-target network. Nat Biotechnol. 2007;25(10):1119–26.
94. Lee CW, Kim SM, Sa S, Hong M, Nam SM, Han HW. Relationship between drug targets and drug-signature networks: a network-based genome-wide landscape. BMC Med Genomics. 2023;16(1):17.
95. Przytycka TM, Kim Y-A. Network integration meets network dynamics. BMC Biol. 2010;8(1):48.
96. Somvanshi PR, Venkatesh KV. A conceptual review on systems biology in health and diseases: from biological networks to modern therapeutics. Syst Synth Biol. 2014;8(1):99–116.
97. R S P, Venkatesh K. A conceptual review on systems biology in health and diseases: from biological networks to modern therapeutics. Syst Synth Biol. 2014;8:99–116.
98. Sengupta U, Ukil S, Dimitrova N, Agrawal S. Expression-based network biology identifies alteration in key regulatory pathways of type 2 diabetes and associated risk/complications. PLoS One. 2009;4(12).
99. Pidò S, Ceddia G, Masseroli M. Computational analysis of fused co-expression networks for the identification of candidate cancer gene biomarkers. npj Systems Biology and Applications. 2021 Mar 12;7(1):17.
100. Lee EK, Wei X, Wright MD, Baker-Witt F. New PK/PD model directly links diabetes drug dose to blood glucose level for personalized care. AMIA Annu Symp Proc. 2022;2022:672–81.

© STM Journals 2024. All Rights Reserved