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Review

Exploring the Molecular Terrain: A Survey of Analytical Methods for Biological Network Analysis

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Abstract: Biological systems, characterized by their complex interplay of symmetry and asymmetry, operate through intricate networks of interacting molecules, weaving the elaborate tapestry of life. The exploration of these networks, aptly termed the "molecular terrain", is pivotal for unlocking the mysteries of biological processes and spearheading the development of innovative therapeutic strategies. This review embarks on a comprehensive survey of the analytical methods employed in biological network analysis, focusing on elucidating the roles of symmetry and asymmetry within these networks. By highlighting their strengths, limitations, and potential applications, we delve into methods for network reconstruction, topological analysis with an emphasis on symmetry detection, and the examination of network dynamics, which together reveal the nuanced balance between stable, symmetrical configurations and the dynamic, asymmetrical shifts that underpin biological functionality. This review equips researchers with a multifaceted toolbox designed to navigate and decipher biological networks' intricate, balanced landscape, thereby advancing our understanding and manipulation of complex biological systems. Through this detailed exploration, we aim to foster significant advancements in biological network analysis, paving the way for novel therapeutic interventions and a deeper comprehension of the molecular underpinnings of life.

Keywords: biological networks; network analysis; systems biology; molecular interactions; drug discovery; network medicine

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1. Introduction

Biological networks embody a complex interplay of molecular entities, intricately woven to form life's very fabric and underpin living organisms' functioning [1,2]. These networks, aptly termed the "molecular terrain", are a testament to the delicate balance between symmetry and asymmetry, encompassing diverse biomolecules such as proteins, metabolites, and genes. The molecules interact meticulously, not only to govern various biological processes [3], including signal transduction, gene regulation, and metabolic pathways [4], but also to maintain the equilibrium between symmetrical order and asymmetrical flexibility that is critical for life. Exploring symmetry and asymmetry within these networks offers a deeper understanding of how biological complexity and functionality arise from seemingly simple rules and patterns. Understanding these networks' structure, dynamics, and inherent symmetry/asymmetry has thus become a cornerstone of modern biological research, offering invaluable insights into disease mechanisms, drug discovery, and organismal development [5]. Analytical methods play a pivotal role in unraveling the intricate relationships and the balance between symmetry and asymmetry within these networks. The methods provide critical insights into network structure, dynamics, and functionality [6], enabling researchers to decipher the complex code of biological networks and how their symmetrical and asymmetrical properties drive biological function and adaptation. Figure 1 depicts an example of the significance of investigating biological networks. In Figure 1, images depicting "Decipher the language of life", "Developing personalized medicine", and "Unravel the roots of disease" are sourced from [7], while images illustrating "Synthetic biology solutions" and "Design novel therapies" are sourced from [8]. In this research paper, we embark on a comprehensive exploration of the analytical methods employed in the analysis of biological networks. Our survey aims to provide a holistic view of the diverse tools and techniques available for studying molecular interactions at a network level. By examining the strengths, limitations, and applications of different analytical approaches [9], we seek to enhance the understanding of biological networks and facilitate advancements in molecular biology research.

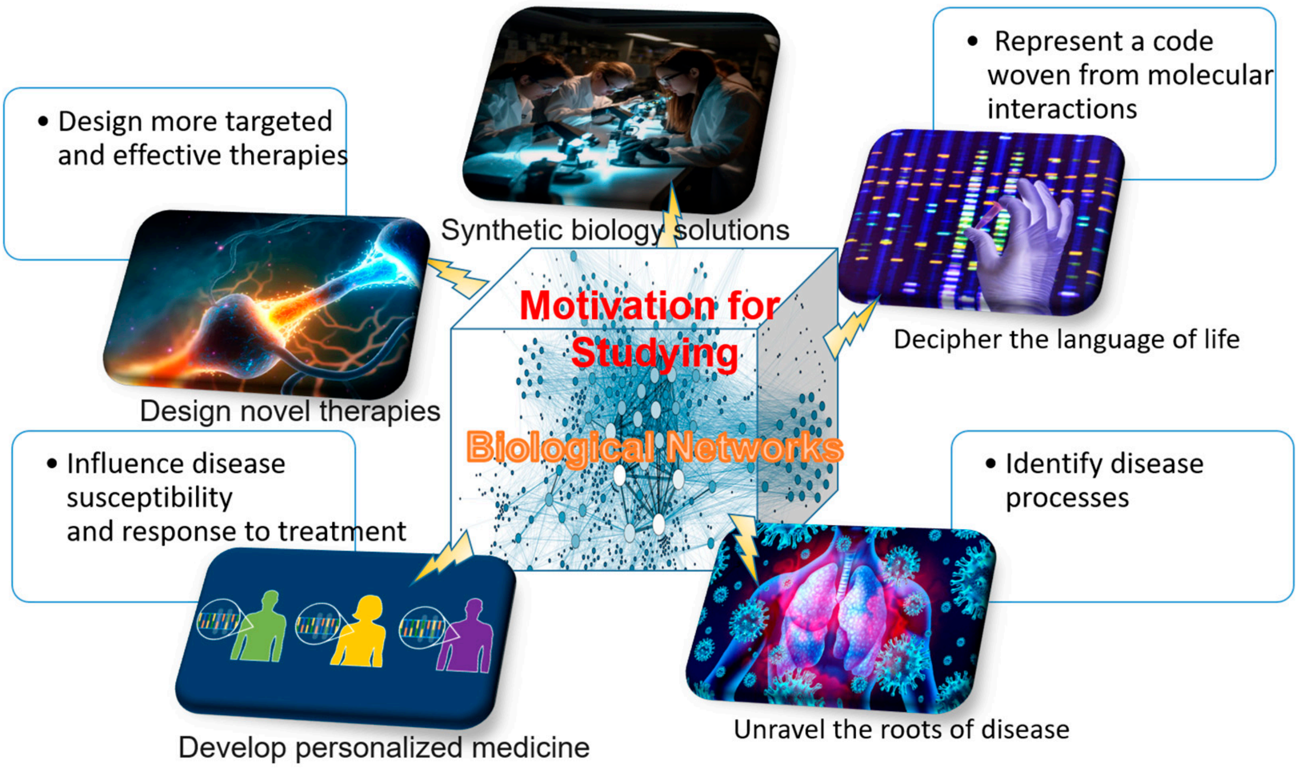

Figure 1. Applications of biological networks.

The study of biological networks is driven by a fundamental desire to understand the underlying mechanisms of life. By unraveling the intricate web of interactions within these networks, we aim to understand the following.

Deciphering the language of life involves understanding biological networks as a code woven from molecular interactions [10]. This understanding enables us to unravel how cells function, communicate, and adapt to changing environments [11].

Unraveling the roots of disease is crucial, as many diseases stem from disruptions in the normal functioning of biological networks [12]. Through the study of these networks, we can pinpoint key players in disease processes, opening avenues for potential therapeutic interventions.

Designing novel therapies is facilitated by comprehending how drugs interact with biological networks. This knowledge empowers us to create more targeted and effective treatments with reduced side effects [13].

Developing personalized medicine is essential, considering that individual variations in network structure can impact disease susceptibility and treatment response [14].

By grasping these variations, we can pave the way for tailored medical approaches for individual patients.

Engineering synthetic biology solutions becomes achievable by leveraging the principles of biological networks [15]. This approach allows us to craft synthetic systems with specific functionalities, potentially driving advancements in fields like bioengineering and bioremediation [16].

This review aims to provide a comprehensive overview of the analytical methods employed for navigating and deciphering the complexities of the molecular terrain. We delve into the diverse tools and techniques used for biological network analysis with the following objectives:

- To provide a holistic view of the various approaches available for studying molecular interactions at a network level.
- To examine the strengths, limitations, and applications of these diverse analytical tools.
- To enhance our understanding of the intricate dance of molecules within the cellular landscape.
- To facilitate advancements in research by equipping researchers with the necessary knowledge and tools to explore the fascinating world of biological networks.

By reaching these goals, we aim to enhance comprehension of the complex realm of life and tap into its extraordinary capacity for creativity and progress.

The remaining parts of this paper are structured as follows. Section 2 delves into conventional methods for network analysis of the various types of biological networks and their diverse applications. Section 3 explores the methodologies for network reconstruction and their experimental validation. Section 4 analyzes and interprets biological networks, highlighting their applications in various domains, such as drug discovery and personalized medicine. Section 5 addresses the challenges and future directions of biological network research. Finally, Section 6 concludes this review by summarizing the key insights and emphasizing the potential of these analytical methods in advancing our comprehension of the intricate world of biological networks.

2. Conventional Methods for Network Analysis

The exploration of the molecular terrain begins with a foundational understanding of network structure and function. Traditional network analysis methods, rooted in graph theory and visualization techniques, provide valuable tools for navigating and deciphering the intricate relationships within biological networks [4,17]. Figure 2 presents a landscape of the conventional approaches to network analysis. In Figure 2, the background images are sourced from [18]. It categorizes and visually represents the different methods based on their key characteristics and functionalities [3]. This allows for easy comparison and understanding of the strengths and weaknesses of each approach, guiding the selection of the most suitable technique for a specific research question or application. The figure typically includes different categories like project management techniques—such as the critical path method (CPM) [19] and the program evaluation and review technique (PERT) [20]; centrality measures—such as degree centrality, betweenness centrality, closeness centrality, and eigenvector centrality [21]; community detection—such as modularity, the Girvan–Newman algorithm [22], and the Louvain modularity algorithm [23]; and flow and diffusion analysis—such as betweenness centrality [24], PageRank, and Katz centrality [25,26].

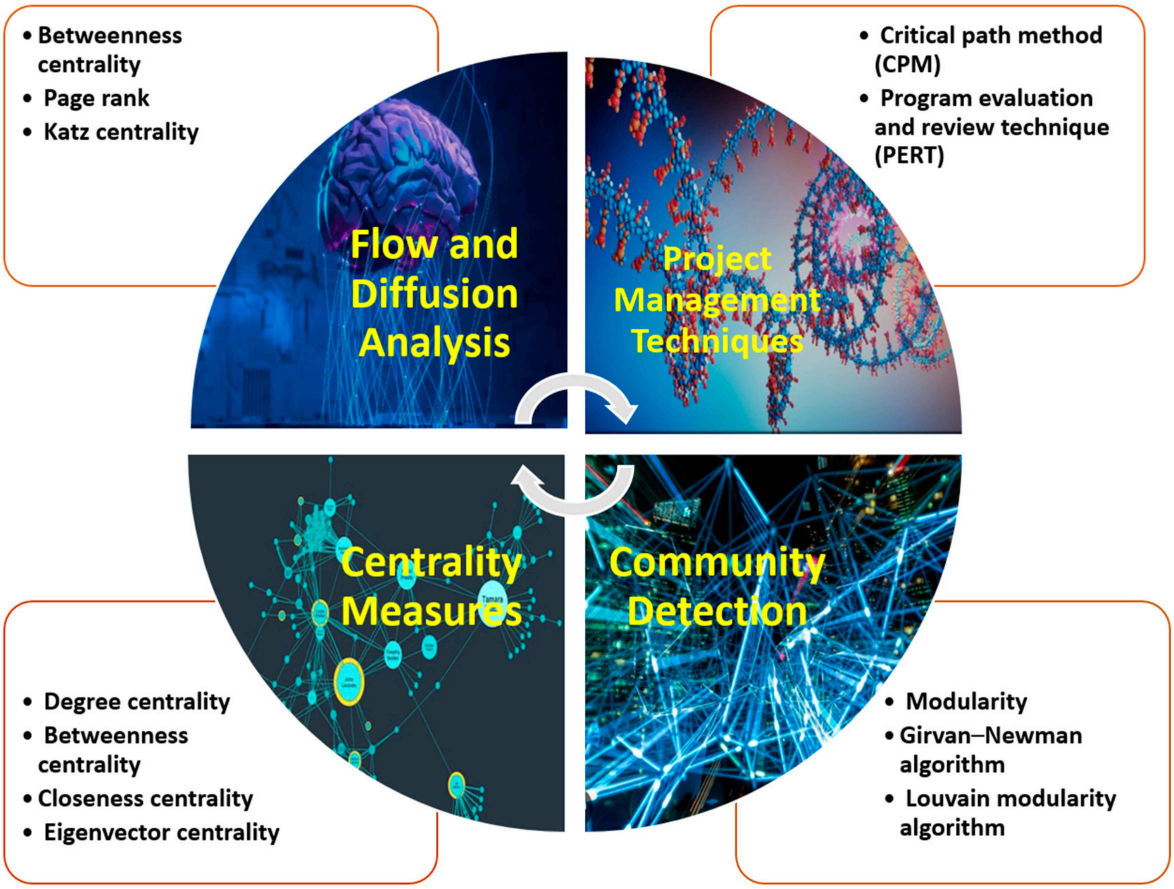

Figure 2. Landscape of conventional network analysis techniques.

2.1. Analytic Perspective on Network Architecture with Graph Theory

Graph theory serves as the cornerstone of traditional network analysis, offering a robust mathematical framework for representing biological networks [27]. In this framework, individual molecules are depicted as nodes, and their interactions are represented as edges [28]. This approach allows researchers to leverage various graph-theoretic tools to quantitatively analyze network structure and identify key network features [29]. Central to this analysis are centrality measures, which quantify the importance of a node within the network. Common centrality measures include the following:

- Degree centrality: this metric simply counts the number of connections a node has, indicating its overall connectivity within the network [17].
- Betweenness centrality: this measure reflects a node's role as a bridge between different network communities, highlighting its potential to influence information flow within the network [30].
- Closeness centrality: this metric signifies how quickly information can propagate from a particular node to all other nodes in the network [31].

By analyzing these centrality measures, researchers can identify crucial nodes that play central roles in network function and communities of interconnected nodes that potentially represent distinct functional modules within the network [32].

2.2. Network Reconstruction

The foundation of biological network analysis is network reconstruction. There are several methods for determining the nodes (molecules) and edges (interactions) in a network, each having advantages and disadvantages [33]. High-throughput experimental techniques include mass spectrometry, yeast two-hybrid experiments, co-immunoprecipitation, and other techniques that allow for the direct identification of molecular interactions [32]. Although these methods provide high-confidence data, they are frequently costly and labor-intensive [34]. Methods based on the literature and text mining are techniques that make use of the large body of scientific literature to extract interaction information from published articles using text-mining algorithms. Although this method is economical, it could be inaccurate because of possible mistakes in the literature [34].

In silico prediction techniques are techniques that use computer algorithms to forecast interactions in light of physical characteristics, sequence homology, and other molecular characteristics [35]. These techniques are scalable and have high throughput, but they need to be carefully validated and might not be as accurate for all kinds of interactions.

Cytoscape is a widely used network analysis and visualization platform [35,36], but it is not the only option. Other popular tools include Gephi version 0.10.1 [37], NetworkX requires Python 3.9 [38], Igraph version 0.10.11 [39], and VisANT version 3.5 [40]. These tools offer a variety of features for network manipulation, analysis, and the creation of high-quality visualizations, making them suitable for rebuilding and exploring networks in various fields. A simple overview of the steps for rebuilding a network with network visualization using the Cytoscape tool [35] is presented in Figure 3.

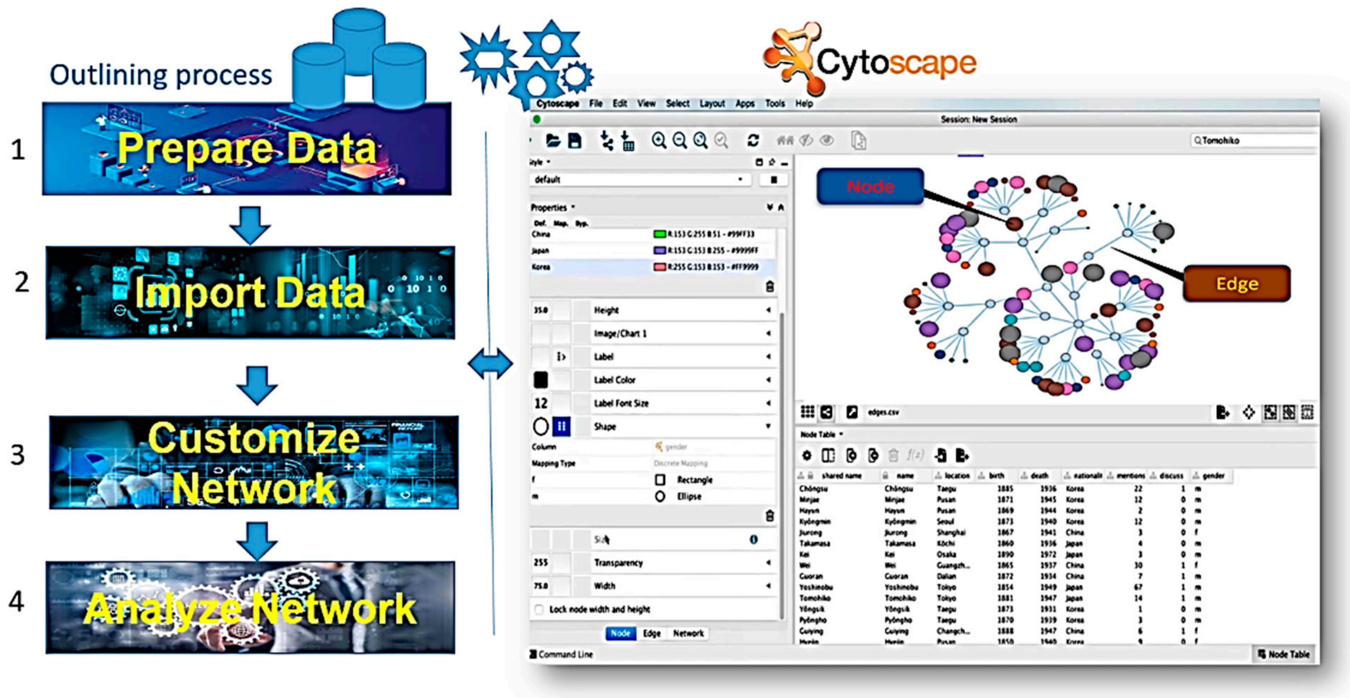

Figure 3. An example of a rebuilding network with network visualization using Cytoscape.

Step 1: The preparation of data involves the creation of two separate tables. The nodes table should contain information about each individual in the network, with each row representing a person and each column representing an attribute about that person. Unique identifiers (IDs) for each individual should be included in the first column [41]. The edges table defines the connections between individuals, typically comprising three columns: "Source", "Target", and potentially an additional column for attributes of the connection (e.g., relationship type). The "Source" and "Target" columns should reference the IDs from the nodes table.

Step 2: The data are imported into Cytoscape. Upon opening Cytoscape, the "Import Network" button is clicked. The nodes table is selected and imported, resulting in the creation of nodes representing each individual. This process is repeated for the edges table, wherein connections between the nodes are established based on the information in the "Source" and "Target" columns.

Step 3: Customization of the network visualization is optional. Various features of Cytoscape can be utilized to customize the appearance of the network. Node shape and color can be adjusted to represent different attributes, such as gender or nationality. Similarly, edge style and color can be modified to reflect the type of connection between individuals. Layout algorithms provided by Cytoscape can be employed to arrange nodes in a clear and informative manner.

Step 4: Exploration and analysis of the network can be conducted. The search bar in Cytoscape enables the identification of specific individuals or groups. Filtering of the network based on node or edge attributes is facilitated by Cytoscape [42]. Additionally, built-in analysis tools can be utilized to calculate network metrics and identify important connections.

2.3. Visualizing Network Patterns

The human brain is wired to excel at processing visual information. Network visualization tools, such as Cytoscape [36], Gephi [37], NetworkX [38], Igraph [39], and VisANT [40], leverage this inherent human capability by transforming complex network data into intuitive graphical representations [43]. These visual representations allow researchers to perform the following actions:

- Explore the overall network structure: by observing the layout and distribution of nodes and edges, researchers can gain a holistic understanding of a network's organization and identify potential patterns or anomalies.
- Identify key network features: visualization tools facilitate the identification of densely connected clusters, isolated nodes, and central hubs, offering valuable insights into potential functional modules and critical players within the network.
- Communicate network insights: visual representations act as powerful communication tools, enabling researchers to effectively share their findings with collaborators and the broader scientific community.

While traditional methods provide a valuable foundation for understanding network structure and function, they are not without limitations. As networks become increasingly complex, limitations in scalability and the lack of dynamic considerations necessitate the exploration of more advanced analytical approaches. The following sections will delve into these cutting-edge approaches, exploring their capabilities and potential to unlock further secrets of the molecular terrain.

Table 1 provides an overview of some conventional approaches used for analyzing biological networks. It categorizes different methods based on their focus and offers a brief description of each approach, along with examples of their applications in biological research. This table serves as a quick reference guide for researchers interested in selecting appropriate network analysis techniques for their specific biological questions and network types.

Table 1. Conventional network analysis tools for biological networks.

Category	Approach	Description	Application Examples
Network Description and Visualization	Degree Centrality	Measures the number of connections a node has.	Identifying important genes, proteins, or metabolites in a network [44].
	Betweenness Centrality	Identifies nodes that act as bridges between different network regions.	Identifying potential bottlenecks, key regulators, or drug targets [17].
	Closeness Centrality	Measures how quickly information can flow from one node to others.	Identifying central players in information dissemination or regulatory processes [17].
	Community Detection	Identifies clusters of nodes with dense connections.	Discovering functional modules, co-regulated genes, or pathways [45].

Table 1. *Cont.*

Category	Approach	Description	Application Examples
Network Function and Dynamics	Shortest Path Analysis	Identifies the most efficient pathway for information/material flow.	Understanding signal transduction, metabolic pathways, or drug action [46].
	Network Motif Analysis	Detects recurring patterns of interactions.	Identifying fundamental regulatory units, signaling modules, or potential drug targets [44].
	Differential Network Analysis	Compares networks under different conditions.	Identifying network alterations in disease, drug treatment, or environmental changes [47].
	Network Diffusion Analysis	Models information/influence propagation through the network.	Simulating drug or signal spread, studying disease progression, or understanding information flow in cellular processes [1].
Integration with Other Data	Gene Co-expression Analysis	Overlaps gene expression data with interaction networks.	Identifying co-expressed genes potentially involved in the same biological process [48].
	Network Enrichment Analysis [49]	Identifies statistically overrepresented pathways/functions within network modules.	Linking network structure to known biological functions or disease mechanisms [50].
	Network-Based Disease Gene Prioritization	Prioritizes candidate genes for disease association based on network connections.	Identifying novel disease genes or therapeutic targets [51].

3. Advanced Network Analysis Techniques

Recent developments have resulted in the creation of sophisticated network analysis tools that go deeper into the intricacies of biological networks, even though traditional methodologies still offer insightful knowledge of the structure and function of networks. These methods provide a deeper comprehension of underlying patterns, predictive powers, and network dynamics.

3.1. Network Inference

The explosion of data from high-throughput technologies like gene expression profiling, protein–protein interaction assays, and metabolic pathway mapping presents both opportunities and challenges. While these datasets offer a wealth of information on molecular interactions, they often lack complete coverage, leading to gaps in our understanding of biological networks. Network inference techniques address this challenge by leveraging existing data to predict missing interactions and reconstruct comprehensive biological networks [52]. Common methods include the following:

- Mutual information: this technique measures the statistical dependence between two variables, helping identify potential interactions between entities based on their co-occurrence patterns in the data.
- Correlation analysis: by calculating the correlation coefficients between different data points, this approach can reveal co-regulations or associations between entities, suggesting potential interactions within the network.

Table 2 shows an overview of methods commonly used for network inference in biological systems. These methods leverage existing data to predict missing interactions and reconstruct comprehensive biological networks, offering valuable insights into molecular interactions and biological systems.

Table 2. Methods for network inference.

Technique	Description	Application	Strengths	Limitations
Mutual information	Measures statistical dependence between variables, suggesting potential interactions.	Identifying co-expressed genes potentially involved in the same biological process. Discovering protein–protein interactions based on co-localization data [53].	Simple and computationally efficient. Less sensitive to noise compared to correlation [54].	May miss weak or non-linear relationships. Requires careful selection of appropriate dependence measures [55].
Correlation analysis	Calculates correlation coefficients to reveal associations between entities, suggesting potential interactions.	Identifying co-regulated genes in gene expression networks. Uncovering potential links between metabolites based on their abundance profiles [56].	Easy to interpret and implement. Suitable for linear relationships [49].	Sensitive to outliers and data scaling. May not capture non-linear dependencies [57].
Boolean networks	Represents biological systems as logical rules governing interactions between entities.	Simulating network dynamics and identifying critical regulatory points. Modeling cellular differentiation or signal transduction pathways [57].	Intuitive and interpretable. Enables qualitative analysis of network behavior.	Limited to discrete states and Boolean logic, potentially oversimplifying complex systems. Can become computationally expensive for large networks.
Bayesian networks	Probabilistic graphical models capture conditional dependencies between variables, allowing for the integration of prior knowledge and reasoning about the likelihood of specific network configurations.	Predicting gene expression levels based on regulatory network structure. Inferring missing links in protein–protein interaction networks [58].	Incorporates prior knowledge and uncertainty. Enables probabilistic reasoning about network interactions.	Computational complexity can increase with network size. Relies on accurate prior knowledge, which may not always be available [59].
Matrix factorization	Decomposes network data matrices into lower-dimensional matrices, revealing hidden patterns and facilitating the identification of potential interactions.	Identifying functionally related genes or proteins based on co-occurrence patterns. Discovering hidden communities within biological networks [60].	Reduces data dimensionality for efficient analysis. Uncovers hidden patterns in complex networks [61].	Can be sensitive to noise and outliers in the data. Interpretation of the decomposed factors can be challenging.

Network inference allows researchers to extract valuable insights from incomplete datasets, providing a more holistic view of the biological system under study.

3.2. Network Dynamics

Biological networks are not static structures but, rather, dynamic entities that exhibit temporal changes throughout various cellular processes. These changes can involve alterations in the strength of interactions, the addition or removal of nodes/edges, and even complete network reconfiguration depending on the cellular context. Network dynamics approaches aim to capture these temporal changes and identify key events in various biological phenomena [62]. Some common techniques include the following:

✓ Differential network analysis is a method that compares networks under different conditions (e.g., healthy vs. diseased state) to identify changes in network topology and connectivity patterns, revealing potential mechanisms underlying biological transitions [63].

✓ Time-series analysis is the approach that analyzes network data collected over time points, allowing researchers to track the evolution of the network and identify dynamic changes in network structure and function [64].

Table 3 presents an analysis of the dynamic behavior within biological networks, shedding light on how interactions evolve and influence the overall system dynamics. The table explores critical aspects of network dynamics, providing insights into the temporal changes, strengths, limitations, and regulatory mechanisms that govern biological processes.

Table 3. Dynamics of biological networks.

Technique	Description	Application	Strengths	Limitations
Differential network analysis	Compares networks under different conditions to identify changes in connectivity patterns.	Identifying differentially expressed genes and their interactions in disease vs. control samples. Unveiling alterations in protein–protein interaction networks upon drug treatment [65].	Reveals changes in network structure and function under different conditions. Helps identify potential disease drivers or drug targets [66].	Requires comparable network data from different conditions. Statistical significance testing can be complex for large networks.
Time-series analysis	Analyzes network data collected over time points to track network evolution.	Studying the dynamic reconfiguration of metabolic networks during cellular processes. Monitoring the temporal changes in gene regulatory networks during cell cycle progression [67].	Captures dynamic network changes at a high resolution. Provides insights into network remodeling and adaptation.	Requires extensive time-series network data, which can be expensive and time-consuming to collect. Data analysis can be computationally intensive [68].

The dynamics of networks record time variations and pinpoint important occurrences in biological networks. Comparing the tissue networks in healthy and sick states is necessary to understand how a disease progresses—this method examines how gene regulatory networks have changed over time; simulates how stimuli affect signal transduction pathways dynamically [69]; offers perceptions of the long-term functioning of networks; and captures momentary alterations and essential occasions. However, it needs time-series network data, which can be challenging to find, and is sensitive to problems with data quality and noise. By studying network dynamics, researchers can gain a deeper understanding of how biological systems adapt and respond to internal and external stimuli.

3.3. Machine Learning in Network Analysis

The field of machine learning (ML) has significantly impacted network analysis by providing powerful tools for extracting hidden patterns, classifying different network types, and predicting missing interactions [70]. Popular ML techniques employed in network analysis include Support vector machines (SVMs) [71], Random forests [72], Nearest neighbors [73], and Naive Bayes [74] techniques. Support vector machines (SVMs) can be used to classify network modules based on specific features, enabling researchers to identify functionally distinct groups of nodes within the network [71]. Random forests are used by constructing multiple decision trees; random forests can predict missing interactions within a network with high accuracy, further refining the understanding of network structure [72].

Table 4 showcases the diverse applications of machine learning techniques in network analysis. By leveraging advanced algorithms and computational methods, machine learning is crucial in extracting meaningful patterns, predicting interactions, and uncovering hidden relationships within complex biological networks. This table highlights the intersection of machine learning and network analysis, illustrating how these approaches enhance our understanding of biological systems. Figure 4 illustrates the transformative impact of deep learning in biological network analysis. In Figure 4, the background images are sourced from [18]. By harnessing the power of deep neural networks, researchers can uncover hidden patterns, predict interactions, classify network types, and model temporal dynamics within complex biological systems.

Table 4. Machine learning applications in network analysis.

Technique	Description	Application	Strengths	Limitations
Support vector machines (SVMs)	Classify network modules based on specific features to identify functionally distinct groups.	Clustering genes into co-expressed modules based on their network interactions. Classifying protein complexes based on their network topology [75].	Effective for high-dimensional data and non-linear relationships. Relatively robust to noise and outliers [71].	May require careful parameter tuning to achieve optimal performance. Can be computationally expensive for large datasets [76].
Random Forests	Predict missing interactions within a network with high accuracy.	Filling gaps in protein–protein interaction networks to improve their coverage. Predicting missing metabolic reactions to complete pathway maps [77].	Handles data heterogeneity well. Provides ensemble learning for improved accuracy and stability [78].	Less interpretable compared to some other techniques. Feature selection and parameter tuning can be crucial.
Nearest neighbors	Classify data points based on their similarity to their nearest neighbors.	Link prediction, node classification [73].	Simple to implement, interpretable results.	Sensitive to noise, suffers from the curse of dimensionality.
Naive Bayes	Probabilistic classifier based on Bayes' theorem.	Spam filtering, social network analysis [74].	Efficient for large datasets, handles categorical data well	Assumes independence of features, may not be suitable for complex relationships.
Deep learning	Utilizes deep neural network architectures to learn complex relationships from network data.	Identifying potential drug targets by analyzing protein–protein interaction networks. Classifying different disease subtypes based on their gene regulatory network properties [44]. Predicting the temporal evolution of biological networks.	Capable of capturing intricate non-linear relationships and hidden features. Can handle high-dimensional and complex network data.	Requires large amounts of data for training, which may not always be available [79]. Interpretability and explainability can be challenging.
Graph neural networks (GNNs)	Specialized deep learning models designed specifically for analyzing graph-structured data, like networks.	Identifying communities of functionally related genes within co-expression networks. Predicting drug–target interactions based on protein–protein interaction networks. Classifying different cell types based on their gene regulatory network features [44].	Tailored for network data, incorporating node features and network topology. Can capture complex dependencies and relationships within networks [80].	Relatively new area with ongoing development. May require specialized hardware and software for training and implementation.

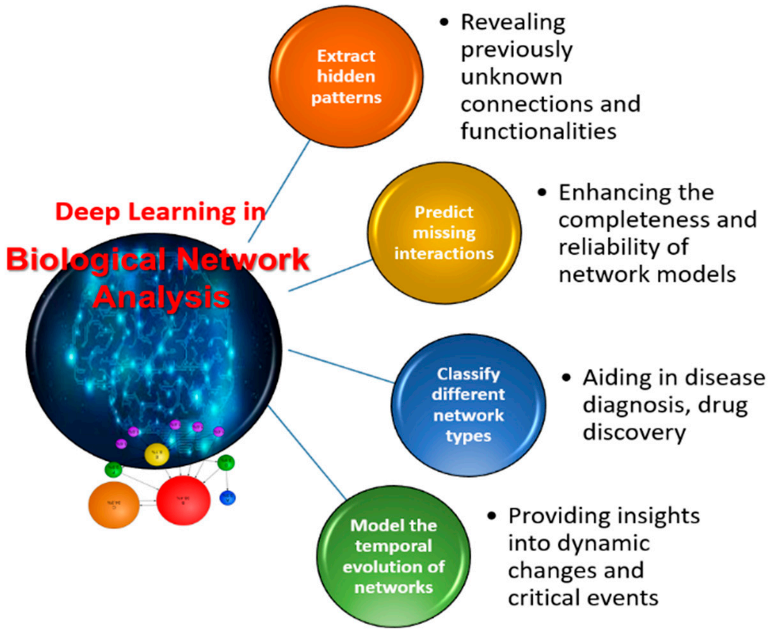

Figure 4. Advancing biological network analysis through deep learning.

Deep learning has emerged as a powerful tool in biological network analysis, offering exciting possibilities for understanding complex biological processes [50]. By leveraging deep neural networks with their ability to learn intricate non-linear relationships from vast datasets, researchers can extract hidden patterns within biological networks, revealing previously unknown connections and functionalities. They can also predict missing interactions with high accuracy, enhancing the completeness and reliability of network models [49]. Furthermore, deep learning enables the classification of different network types based on their structure and function, aiding in disease diagnosis, drug discovery, and understanding cellular processes. Additionally, it allows researchers to model the temporal evolution of networks, providing insights into dynamic changes and critical events within biological systems. While deep learning offers immense potential, challenges remain, including the need for large datasets, the "black-box" nature of some models hindering interpretability, and the requirement for specialized expertise and computational resources. As research in this field advances, deep learning holds significant promise for further revolutionizing our ability to analyze and understand the intricate world of biological networks.

Graph neural networks (GNNs) are a specialized type of deep learning model designed specifically for analyzing graph-structured data, like biological networks [81]. Unlike traditional deep learning models that struggle with the non-linear relationships and complex structures inherent in networks, GNNs excel in this domain due to their unique capabilities. GNNs can incorporate node features and network topology, allowing them to learn from both the features associated with individual nodes (e.g., gene expression levels) and the connections between those nodes within the network [82]. By considering the network structure, GNNs can effectively capture intricate interactions and dependencies between nodes, leading to more accurate and informative insights. This tailored approach allows GNNs to be particularly valuable in biological network analysis, enabling researchers to leverage the strengths of deep learning to extract meaningful patterns, predict interactions, classify network types, and model dynamic changes within biological systems.

Figure 5 showcases the diverse applications of GNNs in biological network analysis. In Figure 5, the background images are sourced from [18]. By leveraging the unique capabilities of GNNs, researchers can identify communities of functionally related genes within co-expression networks, predict drug–target interactions in protein–protein interaction networks, and classify different cell types based on gene regulatory network features. These applications demonstrate how GNNs play a crucial role in uncovering hidden relationships, making predictions, and enhancing our understanding of complex biological systems. Despite being a relatively new and quickly developing discipline, GNNs have the potential to significantly advance our understanding of biological networks and spur discoveries in a variety of biological and medical fields. The integration of ML into network analysis opens exciting avenues for exploring complex biological questions and making data-driven predictions about network behavior.

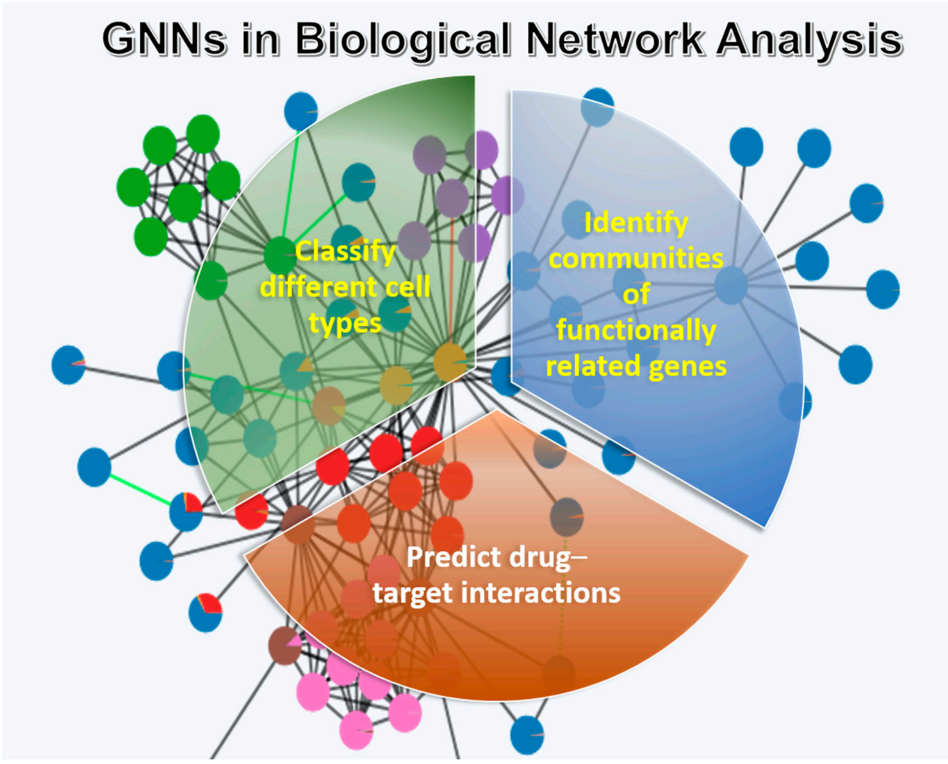

Figure 5. Graph neural networks (GNNs) in biological network analysis.

3.4. Topological Analysis

Once a network is reconstructed, various topological features can be analyzed to gain insights into its organization and function. Key metrics include degree distribution, the clustering coefficient, and shortest paths. Degree distribution reveals the distribution of connections among nodes, shedding light on the network's connectivity patterns [83]. The clustering coefficient measures the degree to which nodes tend to cluster together, indicating the network's tendency for local interconnectedness. Shortest paths represent the minimum number of steps between two nodes, offering valuable insights into information flow dynamics and identifying potential bottlenecks within the network [84]. Topological analysis is delved into in Figure 6, and is a powerful tool for dissecting the intricate organization of networks. In Figure 6, the background images are sourced from [18]. Following the construction of a network, various features are examined by this approach that shed light on its inner workings and functionality. Through the analysis of these topological properties, a deeper understanding is gained of how nodes within the network interact with and influence each other.

The figure highlights several key metrics used in topological analysis: Degree distribution is a metric which unveils the connectivity patterns within the network, revealing how many connections each node possesses. By analyzing these distribution patterns, researchers can identify central hubs—highly connected nodes critical for network function—and peripheral nodes with specialized roles. The clustering coefficient is a metric that quantifies the tendency of nodes to form tightly knit communities within the network. A high clustering coefficient indicates a network with well-defined modules, suggesting a high degree of interconnectedness within these specific groups.

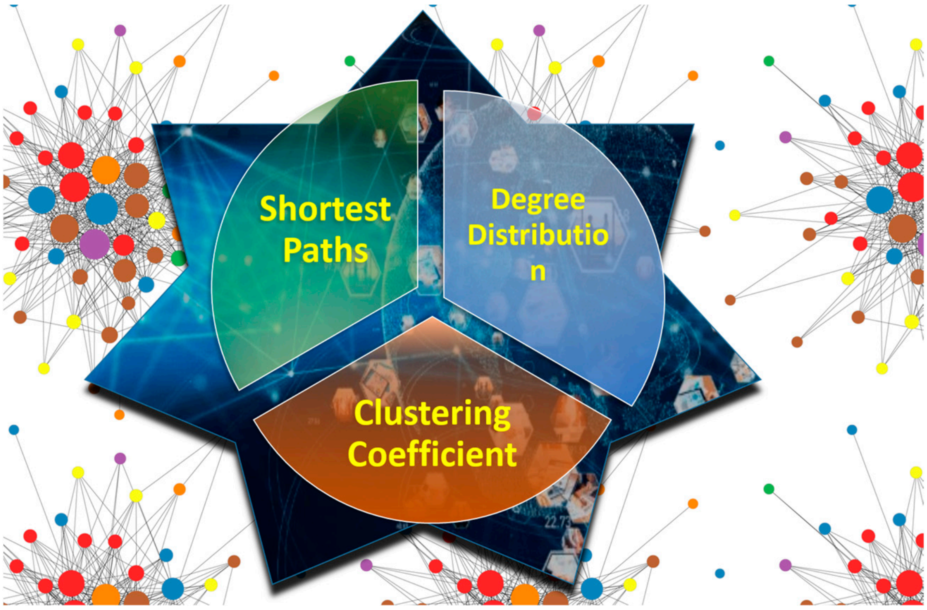

Figure 6. Exploring network topology in intricate organizations.

Shortest paths represent the most efficient routes for information flow between any two nodes within the network. By identifying the shortest paths, researchers can pinpoint potential bottlenecks that hinder communication and information exchange [84].

By examining these topological features, researchers can better understand the structural characteristics and functional properties of biological networks. These topological features can be used to identify key players, predict functional associations, and classify different network types.

4. Applications of Biological Network Analysis

Network analysis has become an indispensable tool across various areas of biological research, offering valuable insights into complex biological systems. In this section, we explore some key applications.

4.1. Understanding Disease Mechanisms

Network analysis plays a crucial role in deciphering the intricate mechanisms underlying disease progression. It is a potent tool for figuring out the complex processes that underlie the development of disease [85]. Researchers can learn a great deal about the important players, interrelated processes, and dynamic changes that contribute to the onset and progression of different diseases by studying disease-associated networks. This section looks at how researchers can be empowered by network analysis.

Figure 7 provides a visual representation of how network analysis techniques can be utilized to understand disease mechanisms at a molecular level. By examining the interactions between genes, proteins, and other biological entities within intricate networks, researchers can identify the key players, pathways, and dysregulations associated with various diseases. This figure highlights the power of network analysis in elucidating the underlying mechanisms of diseases, offering valuable insights for precision medicine, drug discovery, and therapeutic interventions [86]. Researchers can find illness modules, investigate network dynamics, and identify important drivers by examining disease-associated networks.

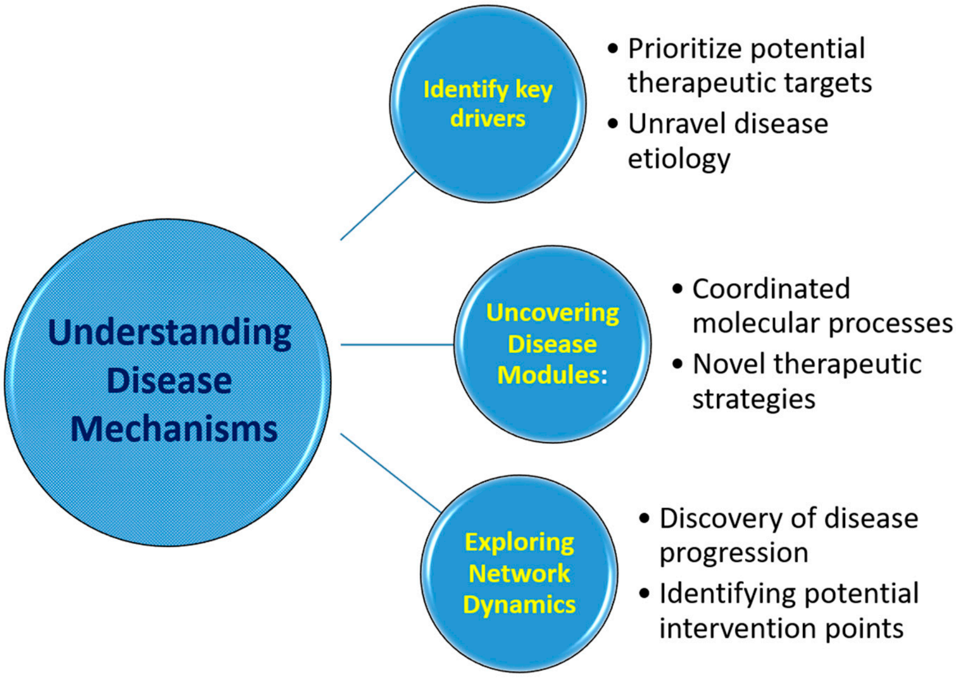

Figure 7. Unraveling disease mechanisms through network analysis.

- Identify key drivers: One crucial application of network analysis lies in pinpointing key drivers of disease progression. These drivers are often highly connected nodes or critical pathways within the network that exert a significant influence on the disease state. By identifying these key drivers, researchers can prioritize potential therapeutic targets. Molecules or pathways identified as key drivers become prime candidates for therapeutic interventions. Disrupting their function or targeting them with specific drugs could potentially halt or reverse disease progression. Moreover, unraveling disease etiology is another critical outcome of identifying key drivers [87]. Understanding the identity and role of key drivers sheds light on the root causes of the disease, providing valuable insights into disease development and progression. This deeper understanding can inform future research directions, personalized treatment strategies, and ultimately contribute to improved patient outcomes.
- Uncover disease modules: Network analysis allows researchers to identify disease modules, which are clusters of interconnected nodes (e.g., genes, proteins) within the network that are functionally associated with the disease [88]. Studying these modules provides valuable insights into coordinated molecular processes: By analyzing the interactions and functions within a disease module, researchers can understand how different molecules within the module work together to contribute to the disease phenotype. This reveals the coordinated molecular processes underlying the disease state. Novel therapeutic strategies: Identifying the components and functions of disease modules opens avenues for the development of novel therapeutic strategies. Instead of targeting individual molecules, these strategies could potentially disrupt entire pathways or processes orchestrated within the disease module, leading to more effective therapeutic interventions. Furthermore, studying disease modules can lead to the discovery of novel therapeutic strategies. Identifying the components and functions of disease modules can pave the way for the development of novel therapeutic strategies that target not just individual molecules but entire pathways or processes contributing to the disease [89]. This holistic approach to targeting disease modules can potentially lead to more effective treatments with fewer side effects and improved outcomes for patients.
- Explore network dynamics: Diseases are rarely static entities but, rather, evolve over time. Network analysis allows researchers to study the dynamics of disease-associated

networks, revealing how the network structure and function change throughout disease progression [90]. This information can be crucial for understanding disease progression. By tracking changes in network connections and properties over time, researchers can gain a deeper understanding of how the disease progresses from its early stages to more advanced forms. Moreover, analyzing network dynamics can help pinpoint critical junctures in disease progression where targeted interventions might be most effective in halting or reversing the course of the disease. By analyzing changes in network structure and function over time, researchers can gain a deeper understanding of how the disease progresses and identify potential points for intervention.

4.2. Drug Discovery

Network analysis has become an indispensable tool throughout the entire drug discovery pipeline, offering valuable insights for identifying potential targets, predicting interactions, and repurposing existing drugs [90]. Figure 8 shows a biological network analysis in drug discovery. In Figure 8, the background images are sourced from [8]. Biological networks represent interactions among various biological molecules, such as proteins, genes, and metabolites.

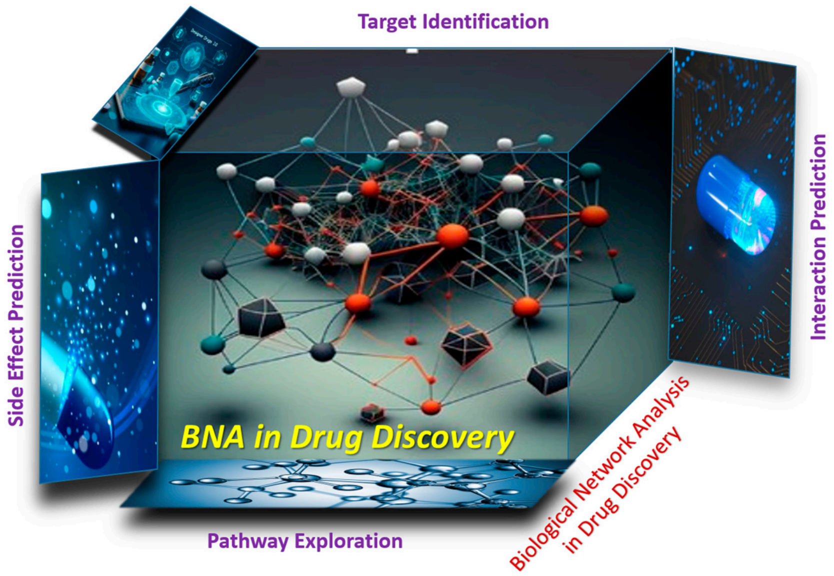

Figure 8. A biological network analysis in drug discovery.

By constructing these networks, researchers gain insights into the complex web of cellular processes. This aids in identifying potential drug targets by analyzing protein–protein interaction networks, allowing researchers to pinpoint crucial proteins associated with diseases. These proteins become promising candidates for drug development. Predictive algorithms analyze network topology to forecast novel interactions. For example, integrating drug-related data and protein networks allows researchers to predict which drugs might bind to specific protein targets, helping avoid adverse effects or enhance therapeutic efficacy. Networks also guide the exploration of biological pathways, enabling researchers to identify critical pathways influenced by drug targets for targeted interventions. Additionally, by examining drug–protein interaction networks, scientists anticipate potential side effects, which informs drug safety assessments [91].

The power of network analysis extends throughout the entire drug discovery pipeline. For instance, it can be used to identify potential drug targets by uncovering network modules or pathways associated with the disease of interest, allowing researchers to prioritize molecules with high potential for therapeutic intervention. Moreover, network-based approaches can predict potential interactions between a drug candidate and various molecules within the biological network, helping identify potential targets for the drug and predict potential side effects. Furthermore, by analyzing existing drug–target networks and disease networks, researchers can identify existing drugs that may be effective in treating new diseases, offering a more efficient and potentially cost-effective approach to drug discovery.

4.3. Personalized Medicine

The burgeoning field of personalized medicine, focusing on individual-specific data, finds network analysis instrumental in its approach. By analyzing patient-specific molecular networks, researchers can gain deeper insights into individual disease etiology and tailor therapeutic interventions based on the unique network profile of each patient [92]. Figure 9 illustrates the concept of dynamic tailoring in personalized medicine and showcases how real-time network data can empower clinicians to customize treatment plans based on individual responses and emerging resistance patterns. In Figure 9, the background images are sourced from [18]. The ability to make prompt adjustments in treatment strategies is crucial to enhancing the efficacy of personalized medicine approaches.

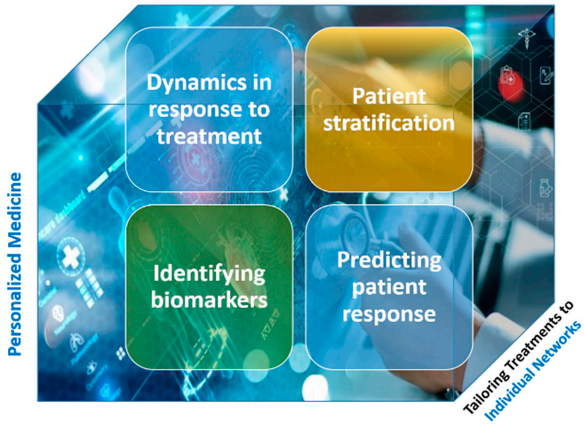

Figure 9. Dynamic tailoring in personalized medicine.

Individual-specific data are utilized by the expanding field of customized medicine, and network analysis is essential in following areas:

Patient stratification: By analyzing individual patient's molecular networks (e.g., gene expression networks), researchers can identify unique network patterns associated with disease progression or drug response. This allows for the stratification of patients into subgroups with similar network profiles, enabling tailored therapeutic interventions [93].

Predicting patient response: Network analysis can be used to predict a patient's response to a specific treatment based on their individual network profile. This information can guide personalized treatment decisions and improve clinical outcomes [94].

Identifying biomarkers: Network analysis can help identify potential biomarkers associated with disease or treatment response by analyzing the network properties of specific nodes or pathways. These biomarkers can be used for early diagnosis, disease monitoring, and personalized treatment strategies [95].

Analyzing network dynamics: Efficacy assessments allow us to observe how a treatment impacts disease-related pathways. If the network stabilizes or shifts toward a healthier state, treatment is deemed effective.

Early warning signs can reveal potential drug resistance mechanisms by dynamic changes. For instance, resistance might be indicated by altered protein interactions [96]. Personalized adjustments as treatment plans can be tailored by clinicians armed with real-time network data. If resistance emerges, adjustments can be made promptly.

4.4. Additional Applications

Network analysis extends its reach beyond disease and drug discovery, contributing to various other areas of biological research:

- ✓ Evolutionary biology: Understanding the evolution of biological systems by analyzing changes in network structure and function across different species [97].
- ✓ Systems biology: Integrating diverse biological datasets (e.g., genomics, proteomics) into network models to gain a holistic understanding of complex biological processes [98].
- ✓ Ecology and environmental biology: Analyzing the interactions between species and their environment using network approaches to understand ecosystem dynamics and environmental impacts [96,98].

These examples showcase the diverse and impactful applications of network analysis in various domains of biology and medicine. As the field continues to evolve, network analysis holds immense potential for driving discoveries, advancing our understanding of complex biological systems, and ultimately improving human health.

Table 5 presents a comprehensive overview of the varied applications of biological network analysis. From understanding complex biological systems to identifying fundamental biomolecular interactions, this table highlights how network analysis is utilized in biology. By showcasing these applications, researchers and practitioners can gain insights into the broad impact and potential of leveraging network analysis techniques in biological research.

Table 5. Diverse applications of biological network analysis.

Application	Description	Examples
Understanding Disease Mechanisms	Identify key drivers and pathways. Uncover disease modules. Explore network dynamics.	Identifying key genes involved in cancer progression by analyzing cancer gene networks. Discovering co-expressed genes potentially contributing to Alzheimer's disease. Studying the temporal changes in protein–protein interaction networks during viral infection [99].
drug discovery	Identify potential drug targets. Predict drug–target interactions. Repurpose existing drugs.	Prioritizing candidate drug targets based on their network connectivity in disease networks [2]. Predicting the potential side effects of a drug candidate by analyzing its interactions within the network. Identifying existing drugs that may be effective for treating a new disease based on network analysis.
personalized medicine	Stratify patients based on network profiles. Predict patient response to treatment. Identify biomarkers.	Grouping patients with similar network patterns associated with a specific disease for targeted therapy [100]. Predicting an individual's response to chemotherapy based on their tumor gene expression network. Identifying potential biomarkers for early diagnosis of a disease by analyzing the network properties of relevant genes.
Additional Applications	Evolutionary biology: Studying network evolution across species. Systems biology: Integrating diverse data into network models. Ecology and environmental biology: analyzing species interactions using networks.	Understanding the evolution of protein–protein interaction networks in different primates [101]. Building a network model integrating gene expression, protein–protein interaction, and metabolic data to study cellular processes. Analyzing the network of interactions between predator and prey species to understand ecosystem dynamics.

5. Future Directions

Biological network analysis stands at the forefront of scientific inquiry, constantly evolving to meet the challenges and opportunities presented by emerging technologies and data intricacies. Figure 10 serves as a guide to navigating the ever-changing terrain of network analysis. In Figure 10, the background images are sourced from [18]. With the field constantly evolving and expanding, it is crucial to stay informed about new trends, methods, and uses. The figure provides a sneak peek into the upcoming directions of network analysis, highlighting essential areas of growth and potential paths for exploration [1]. By following this map, researchers and professionals can more effectively navigate the intricacies of network analysis and leverage its full capabilities to tackle diverse real-world problems.

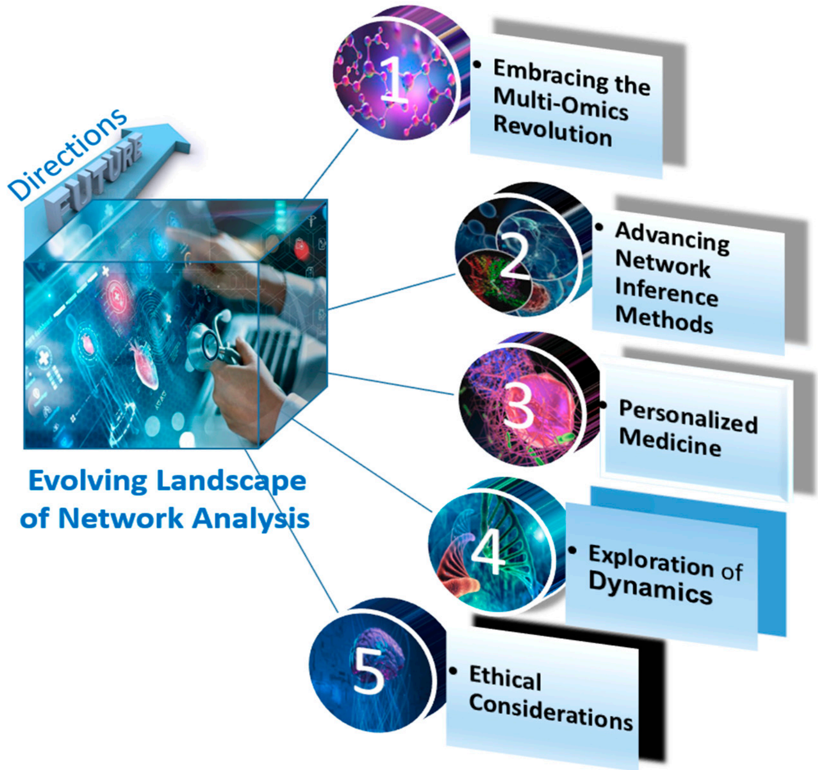

Figure 10. Mapping the way forward: exploring the future of network analysis.

As we navigate the future landscape, several key directions hold immense potential to unlock the full potential of this powerful approach:

5.1. Embracing the Multi-Omics Revolution

The field is poised to experience a significant paradigm shift fueled by the integration of multi-omics data [5]. By incorporating diverse datasets encompassing genomics, transcriptomics, proteomics, metabolomics, and beyond, researchers can create richer network models that capture the intricate interplay between various biological entities [21]. This comprehensive approach promises to the following:

✓ Unveil hidden connections: by bridging the gap between different data layers, multi-omics network analysis can reveal previously unseen connections and dependencies, offering a holistic understanding of biological processes.

✓ Enhance disease understanding: integrating data from multiple omics sources can provide deeper insights into disease mechanisms, identifying key drivers and potential therapeutic targets with greater accuracy and specificity.

5.2. Advancing Network Inference Methods

The ever-growing volume and complexity of biological data necessitate the development of sophisticated network inference methods [2]. Existing techniques may struggle to handle the intricacies of large-scale, high-dimensional datasets. Future advancements lie in the following:

- Machine learning and deep learning algorithms are used by leveraging the power of these techniques; they can enable the development of more robust and accurate methods for inferring network structures and dynamics, especially in the context of multi-omics integration.
- Network dynamics and temporal modeling are applied by developing methods that capture the temporal evolution of networks; they will be crucial for understanding how biological systems change over time, offering insights into disease progression and cellular response to stimuli.

5.3. Personalized Medicine: A Network-Based Approach

Personalized medicine represents a transformative approach to healthcare, aiming to tailor treatments to individual patient profiles. Network analysis, with its ability to capture individual network variations, offers a powerful tool in this domain [14]. By analyzing patient-specific molecular networks, researchers can perform the following:

✓ Predict individual responses: understanding the unique network characteristics of each patient can enable the prediction of their response to specific treatments, guiding personalized therapeutic decisions and improving clinical outcomes.

✓ Identify novel biomarkers: network analysis can help identify potential biomarkers associated with disease progression or drug response, facilitating early diagnosis, personalized treatment strategies, and improved patient monitoring.

5.4. Exploration of Dynamic and Spatial Aspects of Biological Networks

Biological networks are dynamic and spatially organized entities that undergo constant changes in response to internal and external stimuli. Future research directions will focus on exploring the dynamic and spatial aspects of biological networks, including the regulation of gene expression, protein–protein interactions, and signaling pathways in both temporal and spatial dimensions [62]. By developing innovative experimental techniques, imaging technologies, and computational models, researchers can gain insights into the spatiotemporal dynamics of biological networks, unraveling the complex interplay between molecular components and cellular processes in health and disease.

5.5. Ethical Considerations

As the field of network analysis continues to evolve, it is crucial to acknowledge and address the associated ethical considerations [102]. These include the following:

Data privacy and security: ensuring the privacy and security of the individual-specific data used in network analysis is paramount. Robust data protection measures and responsible data sharing practices are essential.

Algorithmic bias: mitigating the potential for bias in network inference algorithms that could lead to inaccurate or discriminatory outcomes is crucial. Careful development and validation of these algorithms are essential to ensure fairness and inclusivity.

Table 6 highlights the emerging trends and potential advancements in the field of biological network analysis.

The table provides insights into the evolving techniques, tools, and methodologies that are shaping the future of network analysis in biological research. By exploring these future directions, researchers can gain a better understanding of the innovative approaches that hold promise for unraveling complex biological networks and driving new discoveries in the field [103].

Table 6. Future directions in biological network analysis.

Direction	Description	Potential Impact
Embracing the Multi-Omics Revolution	Integrate data from various sources (genomics, transcriptomics, proteomics, etc.) into network models.	Unveil hidden connections and dependencies. Enhance disease understanding and identify novel therapeutic targets [104].
Advancing Network Inference Methods	Develop sophisticated methods (machine learning, deep learning) to handle large and complex datasets.	Infer network structures and dynamics more accurately, especially for multi-omics data [105]. Capture the temporal evolution of networks to understand dynamic biological processes [106].
Personalized Medicine: A Network-Based Approach	Analyze patient-specific molecular networks to guide personalized treatment strategies.	Predict individual responses to treatments and improve clinical outcomes [107]. Identify novel biomarkers for early diagnosis, treatment selection, and patient monitoring.
Exploration of Dynamics	Organized entities that undergo constant changes in response to internal and external stimuli.	Developing innovative experimental techniques, imaging technologies, and computational models [108]. Gain insights into the spatiotemporal dynamics of biological networks, unraveling the complex interplay between molecular components.
Ethical Considerations	Address data privacy, security, and algorithmic bias concerns.	Ensure responsible data practices and mitigate potential biases in network analysis [109]. Promote fairness and inclusivity in the application of network analysis.

By embracing these future directions and addressing the associated ethical considerations, network analysis can continue to revolutionize our understanding of biological systems, contributing to advancements in disease diagnosis, drug discovery, and, ultimately, personalized medicine [110]. The journey forward promises to be one of exploration, innovation, and ethical responsibility, leading to a future where the power of networks unlocks unparalleled insights into the complexities of life.

6. Conclusions

The intricate tapestry of biological systems is woven from a network of interactions, and network analysis has emerged as a powerful tool for unraveling its hidden language. This survey has delved into the diverse analytical methods employed in this field, highlighting their strengths, limitations, and potential for advancing our understanding of life. From deciphering disease mechanisms to identifying potential drug targets and paving the way for personalized medicine, network analysis has demonstrably impacted various domains of biological research. As the field continues to evolve, embracing the opportunities presented by multi-omics data integration, developing novel and robust network inference methods, and prioritizing ethical considerations will be crucial for unlocking the full potential of this approach. Continuing to explore the molecular terrain through the lens of network analysis holds the promise of groundbreaking discoveries in the years to come. This journey is poised to unveil novel therapeutic strategies, refine our understanding of complex biological processes, and ultimately contribute to a future where healthcare is tailored to the unique molecular language of each individual.

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visualization, D.-T.P.; supervision, T.-H.D.; project administration, D.-T.P.; funding acquisition, D.-T.P. and T.-K.D. All authors have read and agreed to the published version of the manuscript.

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References

1. Salem, M.S.Z. Biological networks: An introductory review. *J. Proteom. Genom. Res.* **2018**, *2*, 41–111. [CrossRef]
2. Ji, X.; Freudenberg, J.M.; Agarwal, P. Integrating biological networks for drug target prediction and prioritization. *Comput. Methods Drug Repurposing* **2019**, 203–218.
3. Junker, B.H.; Schreiber, F. *Analysis of Biological Networks*; Wiley Online Library: Hoboken, NJ, USA, 2008; Volume 2, ISBN 0470253460.
4. Serban, M. Exploring modularity in biological networks. *Philos. Trans. R. Soc. B* **2020**, *375*, 20190316. [CrossRef] [PubMed]
5. Wuchty, S.; Ravasz, E.; Barabási, A.-L. The architecture of biological networks. In *Complex Systems Science in Biomedicine*; Springer: Boston, MA, USA, 2006; pp. 165–181.
6. Zhu, X.; Gerstein, M.; Snyder, M. Getting connected: Analysis and principles of biological networks. *Genes Dev.* **2007**, *21*, 1010–1024. [CrossRef]
7. Kenhub Human Anatomy Diagram with Illustration of Human Anatomy. Available online: https://www.kenhub.com/ (accessed on 14 March 2024).
8. NIH Graphic Explaining Health Information. Available online: https://newsinhealth.nih.gov/2023/12 (accessed on 14 March 2024).
9. Kepes, F. *Biological Networks*; World Scientific: Singapore, 2007; Volume 3, ISBN 9812772367.
10. Somvanshi, P.R.; Venkatesh, K.V. A conceptual review on systems biology in health and diseases: From biological networks to modern therapeutics. *Syst. Synth. Biol.* **2014**, *8*, 99–116. [CrossRef]
11. Bertamini, M.; Makin, A.D.J. Brain activity in response to visual symmetry. *Symmetry* **2014**, *6*, 975–996. [CrossRef]
12. Beisser, D.; Klau, G.W.; Dandekar, T.; Müller, T.; Dittrich, M.T. BioNet: An R-Package for the functional analysis of biological networks. *Bioinformatics* **2010**, *26*, 1129–1130. [CrossRef]
13. Geppert, T.; Koeppen, H. Biological networks and drug discovery—Where do we stand? *Drug Dev. Res.* **2014**, *75*, 271–282. [CrossRef]
14. Gonzalez-Angulo, A.M.; Hennessy, B.T.J.; Mills, G.B. Future of personalized medicine in oncology: A systems biology approach. *J. Clin. Oncol.* **2010**, *28*, 2777. [CrossRef]
15. Stephanopoulos, G. Synthetic biology and metabolic engineering. *ACS Synth. Biol.* **2012**, *1*, 514–525. [CrossRef]
16. McCarty, N.S.; Ledesma-Amaro, R. Synthetic biology tools to engineer microbial communities for biotechnology. *Trends Biotechnol.* **2019**, *37*, 181–197. [CrossRef] [PubMed]
17. Wang, M.; Wang, H.; Zheng, H. A mini review of node centrality metrics in biological networks. *Int. J. Netw. Dyn. Intell.* **2022**, *1*, 99–110. [CrossRef]
18. Artwork, C. A Piece of Creative Artwork. Available online: https://in.pinterest.com/pin (accessed on 14 March 2024).
19. Shankar, N.R.; Rao, P.P.B.; Siresha, S.; Madhuri, K.U. Critical path method in a project network using ant colony optimization. *Int. J. Comput. Intell. Res.* **2011**, *7*, 7–16.
20. Cottrell, W.D. Simplified program evaluation and review technique (PERT). *J. Constr. Eng. Manag.* **1999**, *125*, 16–22. [CrossRef]
21. Bansal, S.; Khandelwal, S.; Meyers, L.A. Exploring biological network structure with clustered random networks. *BMC Bioinform.* **2009**, *10*, 405. [CrossRef]
22. Despalatović, L.; Vojković, T.; Vukicević, D. Community structure in networks: Girvan-Newman algorithm improvement. In Proceedings of the 2014 37th International Convention on Information and Communication Technology, Electronics and Microelectronics (MIPRO), Opatija, Croatia, 26–30 May 2014; pp. 997–1002.
23. Yao, B.; Zhu, J.; Ma, P.; Gao, K.; Ren, X. A Constrained Louvain Algorithm with a Novel Modularity. *Appl. Sci.* **2023**, *13*, 4045. [CrossRef]
24. Ghosh, S.; Halappanavar, M.; Tumeo, A.; Kalyanaraman, A.; Lu, H.; Chavarria-Miranda, D.; Khan, A.; Gebremedhin, A. Distributed louvain algorithm for graph community detection. In Proceedings of the 2018 IEEE International Parallel and Distributed Processing Symposium (IPDPS), Vancouver, BC, Canada, 21–25 May 2018; pp. 885–895.
25. Zhang, P.; Wang, T.; Yan, J. PageRank centrality and algorithms for weighted, directed networks. *Phys. A Stat. Mech. Its Appl.* **2022**, *586*, 126438. [CrossRef]
26. Zhan, J.; Gurung, S.; Parsa, S.P.K. Identification of top-K nodes in large networks using Katz centrality. *J. Big Data* **2017**, *4*, 16. [CrossRef]
27. Barnes, J.A.; Harary, F. Graph theory in network analysis. *Soc. Netw.* **1983**, *5*, 235–244. [CrossRef]

28. Pavlopoulos, G.A.; Secrier, M.; Moschopoulos, C.N.; Soldatos, T.G.; Kossida, S.; Aerts, J.; Schneider, R.; Bagos, P.G. Using graph theory to analyze biological networks. *BioData Min.* **2011**, *4*, 10–27. [CrossRef]
29. Bullmore, E.; Sporns, O. Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* **2009**, *10*, 186–198. [CrossRef]
30. Dolev, S.; Elovici, Y.; Puzis, R. Routing betweenness centrality. *J. ACM* **2010**, *57*, 1–27. [CrossRef]
31. Veremyev, A.; Prokopyev, O.A.; Pasiliao, E.L. Finding critical links for closeness centrality. *INFORMS J. Comput.* **2019**, *31*, 367–389. [CrossRef]
32. Mohyedinbonab, E.; Jamshidi, M.; Jin, Y.-F. A review on applications of graph theory in network analysis of biological processes. *Int. J. Intell. Comput. Med. Sci. Image Process.* **2014**, *6*, 27–43. [CrossRef]
33. Rice, J.J.; Tu, Y.; Stolovitzky, G. Reconstructing biological networks using conditional correlation analysis. *Bioinformatics* **2005**, *21*, 765–773. [CrossRef]
34. Chen, N.; del Val, I.J.; Kyriakopoulos, S.; Polizzi, K.M.; Kontoravdi, C. Metabolic network reconstruction: Advances in in silico interpretation of analytical information. *Curr. Opin. Biotechnol.* **2012**, *23*, 77–82. [CrossRef]
35. Fang, X.; Lloyd, C.J.; Palsson, B.O. Reconstructing organisms in silico: Genome-scale models and their emerging applications. *Nat. Rev. Microbiol.* **2020**, *18*, 731–743. [CrossRef]
36. Su, G.; Morris, J.H.; Demchak, B.; Bader, G.D. Biological network exploration with Cytoscape 3. *Curr. Protoc. Bioinform.* **2014**, *47*, 8–13. [CrossRef]
37. Bruns, A.; Snee, H. *How to Visually Analyse Networks Using Gephi*; SAGE Publications, Limited: London, UK, 2022; ISBN 1529609755.
38. Papadopoulou, O.; Makedas, T.; Apostolidis, L.; Poldi, F.; Papadopoulos, S.; Kompatsiaris, I. MeVer NetworkX: Network analysis and visualization for tracing disinformation. *Future Internet* **2022**, *14*, 147. [CrossRef]
39. Horvát, S.; Podkalicki, J.; Csárdi, G.; Nepusz, T.; Traag, V.; Zanini, F.; Noom, D. IGraph/M: Graph theory and network analysis for Mathematica. *J. Open Source Softw.* **2023**, *8*, 4899. [CrossRef]
40. Hu, Z.; Snitkin, E.S.; DeLisi, C. VisANT: An integrative framework for networks in systems biology. *Brief. Bioinform.* **2008**, *9*, 317–325. [CrossRef]
41. Gustavsen, J.A.; Pai, S.; Isserlin, R.; Demchak, B.; Pico, A.R. RCy3: Network biology using Cytoscape from within R. *F1000Research* **2019**, *8*, 1774. [CrossRef]
42. Kohl, M.; Wiese, S.; Warscheid, B. Cytoscape: Software for visualization and analysis of biological networks. *Data Min. Proteom. Stand. Appl.* **2011**, *696*, 291–303.
43. Zhang, W.; Thill, J.-C. Detecting and visualizing cohesive activity-travel patterns: A network analysis approach. *Comput. Environ. Urban Syst.* **2017**, *66*, 117–129. [CrossRef]
44. Panditrao, G.; Bhowmick, R.; Meena, C.; Sarkar, R.R. Emerging landscape of molecular interaction networks: Opportunities, challenges and prospects. *J. Biosci.* **2022**, *47*, 24. [CrossRef] [PubMed]
45. Javed, M.A.; Younis, M.S.; Latif, S.; Qadir, J.; Baig, A. Community detection in networks: A multidisciplinary review. *J. Netw. Comput. Appl.* **2018**, *108*, 87–111. [CrossRef]
46. Tandon, G.; Yadav, S.; Kaur, S. Pathway modeling and simulation analysis. In *Bioinformatics*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 409–423.
47. Liu, C.; Ma, Y.; Zhao, J.; Nussinov, R.; Zhang, Y.-C.; Cheng, F.; Zhang, Z.-K. Computational network biology: Data, models, and applications. *Phys. Rep.* **2020**, *846*, 1–66. [CrossRef]
48. Ovens, K.; Eames, B.F.; McQuillan, I. Comparative analyses of gene co-expression networks: Implementations and applications in the study of evolution. *Front. Genet.* **2021**, *12*, 695399. [CrossRef] [PubMed]
49. Perez De Souza, L.; Alseekh, S.; Brotman, Y.; Fernie, A.R. Network-based strategies in metabolomics data analysis and interpretation: From molecular networking to biological interpretation. *Expert Rev. Proteom.* **2020**, *17*, 243–255. [CrossRef] [PubMed]
50. Muzio, G.; O'Bray, L.; Borgwardt, K. Biological network analysis with deep learning. *Brief. Bioinform.* **2021**, *22*, 1515–1530. [CrossRef]
51. Silverman, E.K.; Schmidt, H.H.H.W.; Anastasiadou, E.; Altucci, L.; Angelini, M.; Badimon, L.; Balligand, J.; Benincasa, G.; Capasso, G.; Conte, F. Molecular networks in Network Medicine: Development and applications. *Wiley Interdiscip. Rev. Syst. Biol. Med.* **2020**, *12*, e1489. [CrossRef]
52. Saint-Antoine, M.M.; Singh, A. Network inference in systems biology: Recent developments, challenges, and applications. *Curr. Opin. Biotechnol.* **2020**, *63*, 89–98. [CrossRef] [PubMed]
53. Cantó-Pastor, A.; Mason, G.A.; Brady, S.M.; Provart, N.J. Arabidopsis bioinformatics: Tools and strategies. *Plant J.* **2021**, *108*, 1585–1596. [CrossRef]
54. Novelli, L.; Lizier, J.T. Inferring network properties from time series using transfer entropy and mutual information: Validation of multivariate versus bivariate approaches. *Netw. Neurosci.* **2021**, *5*, 373–404. [CrossRef] [PubMed]
55. Käser, S.; Vazquez-Salazar, L.I.; Meuwly, M.; Töpfer, K. Neural network potentials for chemistry: Concepts, applications and prospects. *Digit. Discov.* **2023**, *2*, 28–58. [CrossRef] [PubMed]
56. Dautle, M.; Zhang, S.; Chen, Y. scTIGER: A Deep-Learning Method for Inferring Gene Regulatory Networks from Case versus Control scRNA-seq Datasets. *Int. J. Mol. Sci.* **2023**, *24*, 13339. [CrossRef]

57. Zhang, T.; Wong, G. Gene expression data analysis using Hellinger correlation in weighted gene co-expression networks (WGCNA). *Comput. Struct. Biotechnol. J.* **2022**, *20*, 3851–3863. [CrossRef]
58. Mercatelli, D.; Scalambra, L.; Triboli, L.; Ray, F.; Giorgi, F.M. Gene regulatory network inference resources: A practical overview. *Biochim. Biophys. Acta BBA Gene Regul. Mech.* **2020**, *1863*, 194430. [CrossRef]
59. Scutari, M.; Graafland, C.E.; Gutiérrez, J.M. Who learns better Bayesian network structures: Accuracy and speed of structure learning algorithms. *Int. J. Approx. Reason.* **2019**, *115*, 235–253. [CrossRef]
60. Han, X.; Wang, B.; Situ, C.; Qi, Y.; Zhu, H.; Li, Y.; Guo, X. scapGNN: A graph neural network–based framework for active pathway and gene module inference from single-cell multi-omics data. *PLoS Biol.* **2023**, *21*, e3002369. [CrossRef]
61. Ramezani, M.; Ahadinia, A.; Ziaei Bideh, A.; Rabiee, H.R. Joint Inference of Diffusion and Structure in Partially Observed Social Networks Using Coupled Matrix Factorization. *ACM Trans. Knowl. Discov. Data* **2023**, *17*, 1–28. [CrossRef]
62. Powell, W.W.; White, D.R.; Koput, K.W.; Owen-Smith, J. Network dynamics and field evolution: The growth of interorganizational collaboration in the life sciences. *Am. J. Sociol.* **2005**, *110*, 1132–1205. [CrossRef]
63. Cornelius, S.P.; Kath, W.L.; Motter, A.E. Realistic control of network dynamics. *Nat. Commun.* **2013**, *4*, 1942. [CrossRef] [PubMed]
64. Zou, Y.; Donner, R.V.; Marwan, N.; Donges, J.F.; Kurths, J. Complex network approaches to nonlinear time series analysis. *Phys. Rep.* **2019**, *787*, 1–97. [CrossRef]
65. Karakurt, H.U.; Pir, P. Integration of transcriptomic profile of SARS-CoV-2 infected normal human bronchial epithelial cells with metabolic and protein-protein interaction networks. *Turk. J. Biol.* **2020**, *44*, 168–177. [CrossRef] [PubMed]
66. Galindez, G.; Sadegh, S.; Baumbach, J.; Kacprowski, T.; List, M. Network-based approaches for modeling disease regulation and progression. *Comput. Struct. Biotechnol. J.* **2023**, *21*, 780–795. [CrossRef]
67. Karabekmez, M.E.; Taymaz-Nikerel, H.; Eraslan, S.; Kirdar, B. Time-dependent re-organization of biological processes by the analysis of the dynamic transcriptional response of yeast cells to doxorubicin. *Mol. Omics* **2021**, *17*, 572–582. [CrossRef] [PubMed]
68. Wu, Y.; Judge, M.T.; Edison, A.S.; Arnold, J. Uncovering in vivo biochemical patterns from time-series metabolic dynamics. *PLoS ONE* **2022**, *17*, e0268394. [CrossRef] [PubMed]
69. Snijders, T.A.B. *Network Dynamics*; Sage: Thousand Oaks, CA, USA, 2011.
70. Xu, X.; Wang, W.; Hong, T.; Chen, J. Incorporating machine learning with building network analysis to predict multi-building energy use. *Energy Build.* **2019**, *186*, 80–97. [CrossRef]
71. Asquith, W.H. The use of support vectors from support vector machines for hydrometeorologic monitoring network analyses. *J. Hydrol.* **2020**, *583*, 124522. [CrossRef]
72. Biau, G. Analysis of a random forests model. *J. Mach. Learn. Res.* **2012**, *13*, 1063–1095.
73. Dong, Y.; Huang, W.; Liu, Z.; Guan, S. Network analysis of time series under the constraint of fixed nearest neighbors. *Phys. A Stat. Mech. Its Appl.* **2013**, *392*, 967–973. [CrossRef]
74. Kanakia, H.; Raundale, P.; Britto, R.; Sawardekar, R. Analysis of Social Networks using Naive Bayes. In Proceedings of the 2019 International Conference on Intelligent Computing and Control Systems (ICCS), Madurai, India, 15–17 May 2019; pp. 88–91.
75. Charles, S.; Natarajan, J. Identification of Key Gene Modules and Novel Transcription Factors in Tetralogy of Fallot Using Machine Learning and Network Topological Features. *Medinformatics* **2023**, *1*, 27–34. [CrossRef]
76. Bansal, M.; Goyal, A.; Choudhary, A. A comparative analysis of K-nearest neighbor, genetic, support vector machine, decision tree, and long short term memory algorithms in machine learning. *Decis. Anal. J.* **2022**, *3*, 100071. [CrossRef]
77. Sebek, M.; Menichetti, G. Network Science and Machine Learning for Precision Nutrition. In *Precision Nutrition*; Elsevier: Amsterdam, The Netherlands, 2024; pp. 367–402.
78. Ganaie, M.A.; Hu, M.; Malik, A.K.; Tanveer, M.; Suganthan, P.N. Ensemble deep learning: A review. *Eng. Appl. Artif. Intell.* **2022**, *115*, 105151. [CrossRef]
79. Kufel, J.; Bargieł-Łączek, K.; Kocot, S.; Koźlik, M.; Bartnikowska, W.; Janik, M.; Czogalik, Ł.; Dudek, P.; Magiera, M.; Lis, A. What is machine learning, artificial neural networks and deep learning?—Examples of practical applications in medicine. *Diagnostics* **2023**, *13*, 2582. [CrossRef] [PubMed]
80. Khemani, B.; Patil, S.; Kotecha, K.; Tanwar, S. A review of graph neural networks: Concepts, architectures, techniques, challenges, datasets, applications, and future directions. *J. Big Data* **2024**, *11*, 18. [CrossRef]
81. Zhao, X.; Wu, J.; Peng, H.; Beheshti, A.; Monaghan, J.J.M.; McAlpine, D.; Hernandez-Perez, H.; Dras, M.; Dai, Q.; Li, Y. Deep reinforcement learning guided graph neural networks for brain network analysis. *Neural Netw.* **2022**, *154*, 56–67. [CrossRef]
82. Veličković, P. Everything is connected: Graph neural networks. *Curr. Opin. Struct. Biol.* **2023**, *79*, 102538. [CrossRef]
83. Hensel, F.; Moor, M.; Rieck, B. A survey of topological machine learning methods. *Front. Artif. Intell.* **2021**, *4*, 681108. [CrossRef]
84. Rieck, B.; Sadlo, F.; Leitte, H. Topological machine learning with persistence indicator functions. In *Topological Methods in Data Analysis and Visualization V: Theory, Algorithms, and Applications*; Springer: Cham, Switzerland, 2020; pp. 87–101.
85. Horvath, S. *Weighted Network Analysis: Applications in Genomics and Systems Biology*; Springer Science & Business Media: Berlin/Heidelberg, Germany, 2011; ISBN 144198819X.
86. Andrejevic, N.; Andrejevic, J.; Bernevig, B.A.; Regnault, N.; Han, F.; Fabbris, G.; Nguyen, T.; Drucker, N.C.; Rycroft, C.H.; Li, M. Machine-learning spectral indicators of topology. *Adv. Mater.* **2022**, *34*, 2204113. [CrossRef] [PubMed]
87. Deng, Y.; Ye, X.; Du, X. Predictive modeling and analysis of key drivers of groundwater nitrate pollution based on machine learning. *J. Hydrol.* **2023**, *624*, 129934. [CrossRef]

88. Zheng, P.-F.; Chen, L.-Z.; Guan, Y.-Z.; Liu, P. Weighted gene co-expression network analysis identifies specific modules and hub genes related to coronary artery disease. *Sci. Rep.* **2021**, *11*, 6711. [CrossRef] [PubMed]
89. Jin, S.; Zeng, X.; Xia, F.; Huang, W.; Liu, X. Application of deep learning methods in biological networks. *Brief. Bioinform.* **2021**, *22*, 1902–1917. [CrossRef] [PubMed]
90. Guerreiro, L.; Silva, F.N.; Amancio, D.R. Recovering network topology and dynamics from sequences: A machine learning approach. *Phys. A Stat. Mech. Its Appl.* **2024**, *638*, 129618. [CrossRef]
91. Lavecchia, A. Machine-learning approaches in drug discovery: Methods and applications. *Drug Discov. Today* **2015**, *20*, 318–331. [CrossRef] [PubMed]
92. Infante, T.; Del Viscovo, L.; De Rimini, M.L.; Padula, S.; Caso, P.; Napoli, C. Network medicine: A clinical approach for precision medicine and personalized therapy in coronary heart disease. *J. Atheroscler. Thromb.* **2020**, *27*, 279–302. [CrossRef] [PubMed]
93. Glaab, E.; Rauschenberger, A.; Banzi, R.; Gerardi, C.; Garcia, P.; Demotes, J. Biomarker discovery studies for patient stratification using machine learning analysis of omics data: A scoping review. *BMJ Open* **2021**, *11*, e053674. [CrossRef] [PubMed]
94. Vougas, K.; Krochmal, M.; Jackson, T.; Polyzos, A.; Aggelopoulos, A.; Pateras, I.S.; Liontos, M.; Varvarigou, A.; Johnson, E.O.; Georgoulias, V. Deep learning and association rule mining for predicting drug response in cancer. A personalised medicine approach. *BioRxiv* **2016**, 70490. [CrossRef]
95. Hammad, A.; Elshaer, M.; Tang, X. Identification of potential biomarkers with colorectal cancer based on bioinformatics analysis and machine learning. *Math. Biosci. Eng.* **2021**, *18*, 8997–9015. [CrossRef]
96. Kurz, F.T.; Kembro, J.M.; Flesia, A.G.; Armoundas, A.A.; Cortassa, S.; Aon, M.A.; Lloyd, D. Network dynamics: Quantitative analysis of complex behavior in metabolism, organelles, and cells, from experiments to models and back. *Wiley Interdiscip. Rev. Syst. Biol. Med.* **2017**, *9*, e1352. [CrossRef] [PubMed]
97. Redhu, N.; Thakur, Z. Network biology and applications. In *Bioinformatics*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 381–407.
98. Barabasi, A.-L.; Oltvai, Z.N. Network biology: Understanding the cell's functional organization. *Nat. Rev. Genet.* **2004**, *5*, 101–113. [CrossRef] [PubMed]
99. Guo, P.; Meng, C.; Zhang, S.; Cai, Y.; Huang, J.; Shu, J.; Wang, J.; Cai, C. Network-based analysis on the genes and their interactions reveals link between schizophrenia and Alzheimer's disease. *Neuropharmacology* **2024**, *244*, 109802. [CrossRef]
100. Wang, R.C.; Wang, Z. Precision medicine: Disease subtyping and tailored treatment. *Cancers* **2023**, *15*, 3837. [CrossRef] [PubMed]
101. Yamada, T.; Bork, P. Evolution of biomolecular networks—Lessons from metabolic and protein interactions. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 791–803. [CrossRef]
102. Ekici, A.; Ekici, S.O. A Bayesian network analysis of ethical behavior. *J. Macromark.* **2016**, *36*, 96–115. [CrossRef]
103. Tyson, J.J.; Laomettachit, T.; Kraikivski, P. Modeling the dynamic behavior of biochemical regulatory networks. *J. Theor. Biol.* **2019**, *462*, 514–527. [CrossRef] [PubMed]
104. Ali, A.M.; Mohammed, M.A. A Comprehensive Review of Artificial Intelligence Approaches in Omics Data Processing: Evaluating Progress and Challenges. *Int. J. Math. Stat. Comput. Sci.* **2024**, *2*, 114–167. [CrossRef]
105. Luo, M.; Zhu, J.; Jia, J.; Zhang, H.; Zhao, J. Progress on network modeling and analysis of gut microecology: A review. *Appl. Environ. Microbiol.* **2024**, *90*, e00092-24. [CrossRef]
106. Dao, T.-K.; Ngo, T.-G.; Pan, J.-S.; Nguyen, T.-T.-T.; Nguyen, T.-T. Enhancing Path Planning Capabilities of Automated Guided Vehicles in Dynamic Environments: Multi-Objective PSO and Dynamic-Window Approach. *Biomimetics* **2024**, *9*, 35. [CrossRef]
107. Ayar, E.S.; Dadmand, S.; Tuncbag, N. Network medicine: From conceptual frameworks to applications and future trends. *IEEE Trans. Mol. Biol. Multi-Scale Commun.* **2023**, *9*, 374–381. [CrossRef]
108. Panayides, A.S.; Amini, A.; Filipovic, N.D.; Sharma, A.; Tsaftaris, S.A.; Young, A.; Foran, D.; Do, N.; Golemati, S.; Kurc, T. AI in medical imaging informatics: Current challenges and future directions. *IEEE J. Biomed. Health Inform.* **2020**, *24*, 1837–1857. [CrossRef] [PubMed]
109. Sohail, S.S.; Farhat, F.; Himeur, Y.; Nadeem, M.; Madsen, D.Q.; Singh, Y.; Atalla, S.; Mansoor, W. Decoding ChatGPT: A taxonomy of existing research, current challenges, and possible future directions. *J. King Saud Univ. Comput. Inf. Sci.* **2023**, *35*, 101675. [CrossRef]
110. Green, S.; Şerban, M.; Scholl, R.; Jones, N.; Brigandt, I.; Bechtel, W. Network analyses in systems biology: New strategies for dealing with biological complexity. *Synthese* **2018**, *195*, 1751–1777. [CrossRef]