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A Mini Review of Node Centrality Metrics in Biological Networks

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Abstract: The diversity of nodes in a complex network causes each node to have varying significance, and the important nodes often have a significant impact on the structure and function of the network. Although the interpretation of the results of biological networks must always depend on the topological study of nodes, there is presently no consensus on how to use these metrics, and most network analyses always result in a basic interpretation of a limited number of metrics. To thoroughly comprehend biological networks, it is necessary to consistently understand the notion of node centrality. Therefore, for 10 typical nodal metrics in biological networks, the study first assesses their current applications, advantages, disadvantages as well as potential applications. Then, a review of previous studies is provided, and suggestions are made correspondingly for the purpose of improving biological topology algorithms. Finally, the following recommendations are made in this study: (1) a comprehensive and accurate assessment of node centrality necessitates the use of multiple metrics, including both the target node and its surroundings, and density of maximum neighbourhood component (DMNC) can be used as a complement to other node centrality metrics; (2) different centrality metrics can be applied to identify nodes with different functions, which in this study are mapped as modular surroundings, bridging roles, and susceptibility; and (3) the following groups of node centrality can often be verified against each other, including degree and maximum neighbourhood component (MNC), eccentricity, closeness and radiality; stress and betweenness.

Keywords: node centrality; biological network; network topology analysis; graph theory; biological interpretation

1. Introduction

Most biological processes are not conducted by single biological individual but depend on the joint efforts of multiple interacting molecules [1]. The uncovering of functional interactions among different molecules is essential because it reveals structure-function connections. In contrast to a mutation in a single trigger specific gene, molecular biological processes are the result of several biological processes interacting within a complex network [2]. There is a growing interest in the study of biology within a network framework [2–7]. The biological network (consisting of nodes that represent biological components and edges) are interactions of node pairs in the aspect of graph theory. The biological network characterises a molecular system along with interconnections which are typically represented as a density graph with millions of vertices. The topological structure of network is the most basic and fundamental information accessible [4]. Understanding the biological mechanisms of organisms can be improved by combining biological data with the topological structure [8].

The connection between topological structure and biological functions has been extensively studied [9–11] under the assumption that real biological systems are non-random and are organised in structure dynamics. It is this assumption that distinguishes biological systems from random networks. Behaviours at subnetwork levels, collective levels and individual levels are utilized to characterise the structural behaviours of biological networks [2].

Typical individual behaviours are topological features of a single node, for instance, the node centralities associated with the systematic primary role [12]. Certain behaviours involve only a subgraph as compared to the whole network, which is known as subnetwork behaviours with modules or motifs [2]. The motif is a subgraph which

appears more frequently than generally expected, whereas the module of a graph is a significant clustering subgraph [13]. Collective behaviours involve all network vertexes, indicating that the nodes play distinct roles in the network structure and functions, including the well-known 'small world' and 'scale-free' phenomena [14]. The small-world phenomenon shows that the average distance among nodes in a network (for connected networks) is short, while the scale-free phenomenon reveals that the degree distribution of vertices follows the power-law distribution [15]. Since complex networks are scale-free, most node degrees are low [16]. A network with a limited number of node degrees has a power-law distribution, and the degrees of nodes are often heterogeneous, with different nodes playing diverse roles in network propagation [17]. In complex networks, the variety of nodes increases the variations of individual significance, and key nodes frequently generate a great deal of impact on the structure network.

A key node is a node that has a stronger impact than other nodes on the network topological properties and the information diffusion [18]. While a network structure consists primarily of the node degree, node distance, network connection and node clustering coefficient, the network function covers, among other factors, the resistance, propagation, and control of networks [19]. In complex network analysis, the following questions are frequently asked. Which node is the most significant? Which node acts as a hub? Which node connects two communities? These problems may be answered using network centralities. Studies show that phenotypes and biological networks are tightly linked, and that fluctuations in certain nodes of biological networks usually cause certain phenotypes [20, 21]. Thus, researching biological networks and discovering key nodes might provide promising information for treatment targets [22, 23]. The difficulty is how to find network key nodes in a reliable and effective way. Finding critical biomolecules for an organism could be understood as identifying key nodes in a network. Researchers have come up with computational methods based on the topology, controllability, where the topology uses the biological knowledge and machine learning method to find the key nodes in biological networks [24]. Approaches based on topological properties, including centrality methods, are the simplest and most suited for undirected and unweighted networks [25]. Over the past years, different approaches carried out to be mining key nodes in a network [7, 25–28]. Examples include using the graph entropy theory, machine learning techniques, and multi-attribute hybrid evaluation methodologies [8, 10, 25, 29]. These investigations have contributed to a better understanding of how node centrality in biological systems is to be understood.

Centrality reflects how network structure influences the significance or status of nodes. Throughout the years, various centrality measurements have been developed [30]. Node centrality as an essential part of biological network analysis has been discussed in several reviews [21, 24, 25, 31−34]. Each of these reviews [21, 24, 25, 31−34] summarizes different common node centrality metrics (e.g., degree, closeness centrality, etc.), but none of them provides an in-depth and systematic generalization of the node centrality analysis in terms of topological functions and biological interpretations. Most studies are also limited to the interpretation of a narrow range of indicators [35−38]. However, there is currently no consensus on how to apply node centrality to the interpretation of biological networks [39]. A mini review was conducted to better obtain clearer analytical ideas between the topological information of nodes and possible biological interpretations. Graphs may capture the connections between enzymes, genomes, metabolites, receptors, diseases, medications, or database information. PPI, metabolic, gene regulatory, and signalling molecule networks are biological networks [21].

In this review, undirected biological networks are the focus. As to the nodal centrality metrics, since they have been frequently discussed in several reviews [21, 24, 25, 31−34] and widely used in several centrality metrics tools [7, 40, 41], only ten of them are selected for in-depth investigation with their biological interprfetation, strengths and weaknesses (in various methodologies), and application directions are clearly investigated. Finally, a summary of existing research is presented, and corresponding recommendations are given for the development of better biological topology algorithms.

2. Categories and Theories of Node Centrality Metrics

The study focuses on a review of ten nodal centrality indicators that have been commonly used in recent years [7, 36], including degree, maximal clique centrality (MCC), maximum neighbourhood component (MNC), density of maximum neighbourhood component (DMNC), betweenness centrality, bottleneck, eccentricity, stress, closeness centrality and radiality (Table 1). Depending on the method used to compute node centrality, algorithms could be categorised as neighbour-based or path-based. Local-based algorithms and global-based algorithms consider different ranges of network nodes within these centrality calculations.

Table 1 Summary of node centrality

Node centrality	Definition
	Local-based method
Degree [16]	$d(v) = \|V\|$ ***N(v)*** is the neighbours direct connect to node ***v***.
Maximal clique centrality (MCC) [45]	$MCC(v) = \sum_{C \in S(v)} (\|C\| - 1)!$ ***S(v)*** is maximum cliques containing ***v***. **(|C|-1)!** are integers smaller than **|C|**. If no edge connects v's neighbours, **MCC(v)** = degree.
Maximum neighbourhood component (MNC)[7]	$MNC(v) = \|V(MC(v))\|$ Node ***v***'s neighbours form ***N(v),*** a subgraph. The score of node ***v***, **MNC(*v*)**, is ***N***'s largest connected component (***v***). ***N(v)*** is the collection of nodes adjacent to ***v*** that does not include ***v***. **G[N(v)]** is the induced subgraph of **G** by **N (*v*)**. **MC(*v*)** is a maximum connected component of **G[N(v)].**
Density of maximum neighbourhood component (DMNC)[7]	$\frac{\|E(MNC(v))\|}{\|V(MNC(v)\|\epsilon}_{1 \le \epsilon \le 2}$ For the ***MNC(v)***, ***N*** is the number of nodes. ***E*** is the number of edges, for a node ***v***. **DMNC(v)** is **E/Nϵ** for some **1≤ϵ≤2** as the score of node ***v***.
	Global-based method
Betweenness centrality [46]	$C_E(v) = \sum_{s \ne t \ne v \in V} \frac{\delta_{st}(v)}{\delta_{st}}$ δ_{st} is shortest paths number connecting nodes ***s*** and ***t***. $\delta_{st}(v)$ is the number of shortest paths taking node ***v*** out δ_{st}.
Bottleneck [47]	$BN(v) = \sum_{S \in V} P_s(V)$ ***Ts*** indicates a shortest path tree through node ***s***. ***Ps(v)*** = 1, if more than **|V(Ts)|/4** paths exist from node ***s*** to other nodes in ***Ts*** to the vertex ***v***, otherwise ***Ps(v)*** = 0. Graph nodes ***v*** are given shortest pathways. Weight of a node equals the number of the shortest routes from ***v*** via this node. A T_V is the bottleneck node weights and contains at least ***n/4*** nodes. BN(v) is T_V bottlenecks ***v***.
Closeness centrality [48]	$C_C(v) = \frac{1}{\sum_{t \in V/\{v\}} dist(v,t)}$ The interchange of the total distance from a node ***v*** to all other nodes in the network. $dist(v,t)$ is the distance of node ***v*** and node ***t***.
Eccentricity [49]	$C_E(v) = \frac{1}{max\{dist(u,v) : u \in v\}}$ Eccentricity is estimated by calculating the shortest path among ***v*** and all other nodes. Then select the longest shortest path ***(v, K)***, where ***K*** is ***v***'s most distant node. Once ***dist(v,K)*** is found, its inverse ***(1/dist(v,K))*** is computed.
Radiality [50]	$C_{rad}(v) = \frac{\sum_{w \in V}(\Delta G + 1 - dist(v,w))}{n-1}$ Radiality of a node ***v*** is the shortest route among it and all other network nodes. The value of each route is subtracted by the diameter ***+1 (G+1)***, then summed. Then, the value is divided by ***n-1***.
Stress [51]	$C_S(v) = \sum_{s \ne t \ne v \in V} \rho_{st}(v)$ $\rho_{st}(v)$ is the number of shortest paths passing through node ***v***.

2.1. Node Centrality Based on Neighbourhood Information (Local-Based Method)

Centralities belonging to this category are focused on the information of node itself and the information of its surrounding neighbouring nodes, where relative relevance is mostly determined by the network nodes' topological position. Furthermore, it is understood that the more nodes are at the core of the network, the more important these nodes are. Centrality algorithms are usually computationally simple and time-saving and are suitable for large and complex networks. This type of centrality can also be seen as the local-based method from the network scope involved, which means only the direct neighbourhood of a vertex is considered.

2.1.1. Algorithm Based on Neighbour Node Information

Centrality based on information about neighbouring nodes evaluates the importance of a node mainly through local information about the node, for example, degree. The importance of a node is often influenced by its own information and that of its neighbouring nodes. This type of centrality algorithm detects the node importance mainly via evaluating the number of neighbours.

2.1.2. Eigenvector Based Algorithms

Neighbourhood node-based ranking algorithms treat surrounding neighbourhood nodes as equally important, whereas the importance of different neighbourhood nodes is generally different. This type of algorithm considers not only the number of neighbours but also the influence of neighbour nodes based on degree [42]. Node centrality based on this theory mainly includes MCC, MNC and DMNC.

2.2. Node Centrality Based on Node Path (Global-Based Method)

Global-based algorithms rank nodes according to shortest pathways or percolated connectivity, considering the nodes' position on the information flow/diffusion path [10]. The idealised propagation is done via the shortest path. However, real-world networks are much more complex, and in addition to the shortest path, other factors such as fault tolerance need to be considered. Another special factor that determines the flow of information is the number of intermediate nodes. The more intermediate nodes there are, the longer the propagation time of the information flow, and the more likely the transmitted information will be distorted or even delayed. It has been shown that if there are more connect edges between any two nodes, the security and reliability of the entire network system will be higher [43]. Nodes globally regulate communication between clusters of nodes with weak connections by serving as a bridge. According to research on both human and animal populations, these "bridges" or "brokers" are essential to the propagation of information and the stability of the entire cluster [26, 44]. Node centrality based on this theory mainly includes Betweenness Centrality, Bottleneck, Eccentricity, Stress, Closeness centrality, and Radiality.

3. Understanding Centrality Measures and Their Applications in Biological Networks

3.1. Indication of Module or Core Nodes

3.1.1. Degree

The degree of a node, as one of the most used metrics, has been linked to numerous dynamical processes and is important for a variety of complex network behaviours, such as controllability [27], synchronization [52, 53], and hub nodes [7], which correspond to high-degree genes associated with diseases [54]. For example, it has been found that the spread influence is positively associated with degree [37]. When compared to long-term effects in the network, degree centrality is a measure of immediate influence. For instance, if a specific percentage of network nodes are infected, any nodes that are directly connected to those infected nodes would also be infected [55, 56]. Even if a network node is only connected to one other node, the likelihood of infection is high if the second node is connected to many others.

In biological networks, several applications have been proposed. For instance, degree enables an immediate assessment of the node regulatory relevance. Proteins having very high degrees of interactions with most signalling proteins in signalling networks suggest a central regulatory role, i.e., the regulatory hubs [57]. Depending on the type of protein, the degree may point to a key role in gene expression (transcription factors) [58, 59], signalling module assembly (docking proteins) [60– 63], amplification (kinases) [64– 67], diversity and turnover (small GTPases) [68–71], etc. Typically, signalling networks have a scale-free architecture [72–75].

Since degree only accounts for the natural neighbourhood of nodes, it may not be a powerful indicator of network topology. Cancer genes have stronger connectedness and centralities of non-cancer genes, implying central functions in the interactome [76, 77]. However, there are some evidence showing that many disease related genes do not typically encode for hub proteins [78]. Nevertheless, a recent study has found that cancer proteins have higher degrees of connectivity than non-cancer proteins [79]. It is a helpful indicator of how closely a vertex is attached to the graph.

3.1.2. Maximal Clique Centrality (MCC)

The size of maximum clique for a node is its largest clique [80]. The "clique" in the network is a subset of nodes with an edge connecting any two. Clique size is the number of nodes. Each graph node may belong to one or more cliques. Complex network community detection focuses on the biggest clique of graph (identified as modular nodes). A group of vertices is a subset of graph vertices with more ties between themselves and less to others [81]. The idea of MCC is that the important proteins tend to stick together in yeast through interactions of proteins in network [7]. It has been found that the Fisher score and the MCC algorithm can be used to find hub genes in HCC [82]. In both high-degree and low-degree proteins top rated rankings, MCC captures more important proteins [7]. Degree-based centrality measures like degree or eigenvector centrality are better linked with maximum clique size than the shortest path-based metrics like closeness centrality or betweenness centrality [83].

3.1.3. Closeness Centrality

The nodes in the graph that are closer to the centre have a lower closeness centrality, which indicates that they are located closer to their neighbouring nodes [84]. It's possible that these nodes will have a more powerful direct influence on other nodes and the information access at those nodes [85]. Typically, the closeness centrality is used to evaluate how effectively the information flows from one node to the others in a network, or in the context of network structure, and also used to evaluate which nodes represent the ideal starting points. The closeness metric evaluates the reciprocal of each node's average network distance that measures the node importance. To ensure evaluation accuracy, the network must be well connected and highly correlated.

The concept of closeness centrality has been utilised to identify which metabolites are particularly important in genome-based, large-scale metabolic networks [86], contrast unicellular and multicellular animals [87, 88], rank pathways [89–91], and gain insight into the evolution of metabolic organisation [35, 92]. The process of evolution has resulted in an increase in the distance between different routes, which has led to a decrease in the closeness and centrality of different components. It has been found that the centrality measure is the most effective measures in terms of locating the network metabolic centre [93–95].

3.2. Indication of Key Bridge Role Nodes

3.2.1. Bottleneck

Each of the nodes within the shortest path trees is identified as "bottlenecks" [96, 97]. There exists a relationship between bottlenecks (high centrality nodes) and essentiality [98–100]. It is crucial to note that the same node can function as a bottleneck for multiple shortest path trees. Most viral and bacterial infections could interact with high-degree proteins, often known as bottleneck proteins, which are essential to many PPI networks [47]. In one system biology research, the genes and mechanisms in childhood obesity are revealed [101], where twelve hub-bottleneck genes are detected that may contribute to childhood obesity [101]. There is a study on rumen microbes including a network, bottlenecks demonstrated the ability to obtain important indicators [28].

3.2.2. Betweenness Centrality

Betweenness centrality is the proportion of shortest routes passing through the node to all other shortest paths connecting it to its neighbours [102]. Betweenness centrality implies that a node centrality is proportional to the number of the shortest pathways across it [103]. It has been found that betweenness centrality may accurately identify network hub nodes that can enhance the transmission efficiency of data [104]. The betweenness of a protein reveals the protein's potential to facilitate communication among a variety of proteins in the protein networks [98]. Proteins have high betweenness centralities are referred to as key connector proteins with crucial functional and dynamic features [105,106], such as metabolites that regulate the flux between two large metabolic modules. In signalling modules, proteins with a high Betweenness likely play an essential role in maintaining the functionality and coherence of signalling pathways [107]. The importance of protein as a structuring regulating molecule increases with its value [108, 109]. The node betweenness in a protein-signalling network might reflect a protein's functional ability to bind communicative proteins together [110].

3.2.3. Stress

A stressed node is one that is crossed by multiple shortest paths [27]. The metric necessitates a network without loops [102]. Stress centrality quantifies the amount of communication an element delivers in an all-to-all situation. Each node transmits as many objects as possible or information units to each other node if there are shortest paths between them, and stress centrality gauges the associated stress [111].

Nodes have both high and low values affecting the average stress value, which is derived by average stress values of all the nodes. A node is stressed when many shortest paths visit it simultaneously. If the high stress rating is not necessary, it indicates that a node is necessary to maintain the connection among nodes to travel through [112]. It's not conceivable for two nodes to be connected via the shortest paths that don't travel through a node.

The importance of a protein as a biologically functional bridge of communication nodes may be reflected in the stress of a node in the biological network [113], for instance, a protein-signalling network [114,115]. The protein's relevance in connecting various regulatory molecules increases with the value. Considering the significance of this relationship, it is conceivable that the stress only identifies a molecule that is deeply involved in cellular functions while has little effect on the stability of protein-protein communication.

3.3. Indication of Node Susceptibility

3.3.1. Eccentricity

Eccentricity quantifies the significance of nodes by calculating the maximum degree of the distance between

them and other nodes [114]. Based on eccentricity centrality indicator, the stronger significance of a node, the closer it is to others. A study demonstrated a negative correlation between the information index and eccentricity [49]. Greater eccentricity values have a positive implication in terms of node connectivity [116]. If a node has high eccentricity, it suggests that all other nodes are close [88]. A low eccentricity, on the other hand, suggests that at least one node (together with all its neighbours) is distant from a particular node [117]. Clearly, this does not exclude the potential that a variety of additional nodes are significantly closer to a particular node. A metric with a high eccentricity is therefore more meaningful. It is noteworthy that extreme values are more meaningful than the average eccentricity of network, which was determined by average the eccentricity levels of each network node [18]. Low eccentricity compared to network average may imply limited functional role [118].

The node eccentricity in the biological network, such as a protein signalling network, can be interpreted as the ease with which all other proteins in the network get functional access to a protein [119]. As a result, the node with a high relative eccentricity compared to the average value will be more susceptible to external influences (the biomolecular is susceptible to a more strict or functional regulation) [35,114]. Consequently, proteins and other bio-objects with a high eccentricity can rapidly detect changes in the concentration of enzymes or chemicals with which they are associated. Compared to proteins with a high eccentricity, those with a low eccentricity typically play a secondary role in the systematic function [112,120]. A robust and stable network connection is necessary for eccentricity to function properly.

3.3.2. Radiality

Because the diameter indicates the largest potential distance of nodes, continually deducting from the diameter of shortest pathways between a node and its neighbours provides high (low) values in case of short (lengthy) paths [121]. Based on its diameter, a large radiality indicates that the node is typically closer to other nodes than it would appear to be, whereas a small radiality indicates that the node is on the periphery of the network [7]. In a similar vein, high or low values are more significant than the mean radiality of the graph, which is derived by averaging the radiality values of all nodes in the graph [36]. High centralities are given to vertices according to the radiality centrality measure when such vertices are near all of the other vertices in their accessible neighbourhood compared to the diameter of the network [122].

The probability of a protein, that is functionally relevant for other proteins, but may be irrelevant for a small percentage of other proteins, is referred to as a node radiality in a biological network, for example a protein-signalling network [123]. Because of this, a protein whose radiality is significantly higher than the network average radiality will play an essential role in the regulating of other proteins, even though the activity of this protein will not have the same effect on other proteins [124].

4. Complementarity and Association of Node Centrality Measures

Some topological indicators were found to have overlapping findings [122]. DMNC and MCC are topological measures respectively based on percolation theory and direct field theory [125]. The high level of consistence between Degree and MNC reveals core nodes that are closely linked to other nodes, and it is likely that dense subgraphs will form around these nodes [28]. A research found that degree centrality had the highest correlation with clique size compared to eigenvector, betweenness, and closeness in ten real-world networks [83].

Additionally, in biological networks, it may also be beneficial to analyse proteins that have low radiality in comparison to the average radiality. Although being less important for that network, these proteins may act as boundaries crossing with other networks [12]. Thus, signaling networks with relatively high radiance are more likely to organize functional units or modules, whereas networks with considerably lower average radiance are more likely to appear as open clusters of proteins connecting multiple regulatory modules [126]. An extensive analysis of eccentricity and closeness should be used to support all these findings [116].

The fact that the hub members of radiality and closeness overlap suggests that these nodes share a regulatory role [115]. Radiality should be integrated as an average tendency towards node closeness or isolation, not as definite information on a node centrality [19, 120]. This must be supported by a proof of eccentricity and closeness. A node with high eccentricity, high closeness, and high radiality suggests a central position in the graph [7].

Betweenness, stress, and bottleneck all rely on the shortest method for determining the distance between two network nodes [106]. Based on previous study of protein networks, high-stress proteins in the protein signal network show that their roles may be relevant in linking regulatory molecules to the protein [115]. Nonetheless, this may also suggest that the protein is involved in other biological processes. The greater a protein's betweenness centrality, the more important it is as a tissue regulator [127–129]. High betweenness may be needed to maintain the functionality of the signalization [107]. More radial proteins have a larger likelihood of forming the network center. Signal networks with a larger mean radiality are more likely to have modules and components that function [112].

Notably, to identify the number of pathways for which a node is critical, one must measure the stress. Consequently, stress and betweenness could be utilized to acquire complementing information. Referring to the Betweenness to node pairings could yield additional information by evaluating the significance of a node for two connected nodes. The high betweenness score indicates that the node is essential for maintaining node connections along particular paths [130]. If a node may be reached by only one path connecting two nodes, and such a path is the only one connecting two nodes, then the stress computation would have a low score (in the betweenness value of node will be high) [121].

DMNC are reported to share the least proteins with the other species. The topological features recovered by DMNC may therefore differ from those extracted by other approaches [7]. A multi-layered network research of the rumen microbiome reveals the same information, and it is the only one that does not include the top metabolite in nine topological rankings [28]. In this sense, it appears that DMNC is more capable at capturing proteins with low node degrees [41]. Different sets of important proteins are captured by DMNC, indicating that it ranks the network differently [7]. It is necessary to apply several approaches for collecting essential proteins because of the heterogeneity of the biological network.

5. Discussion

While the mining of important nodes in complex networks has been relatively mature after more than ten years of development, there are still some problems to be further studied [17,121,126]. Based on the observation derived from social networks, several centrality-based approaches have been proposed to evaluate the relative significance of a node in biological networks and substantial progress has been made. Nevertheless, biological networks' structure is fundamentally different from that of social networks, especially in terms of modularity. [114,119,125]. Another difficulty is the dynamic nature of interactions between biological entities. Even in a network that has been meticulously mapped, not all relationships can exist simultaneously. Consequently, the findings of centrality indices in predicting essential nodes are lacking in several investigations [26]. Key node mining is an important research direction in complex networks. This paper has overviewed the 10 widely used centrality measures and their applications.

There is no basis to assume that network structures and biological functions will be a precise match. As a result, these technologies facilitate "intelligent guessing" [20,23,131]. In consideration of the complexity of biological networks and the difficulty of generating experimental data for different studies, offering clues can already prove to be quite beneficial. Although the neighbour-based algorithm is simple in calculation, it is not suitable for large-scale networks due to the limited information, the algorithm based on global information such as paths has relatively high accuracy, whose computational complexity leads to time complexity [114]. At present, although there are some algorithms that combine the advantages of the two, the advantages (compared with traditional algorithms) are not particularly obvious. For the identification of critical nodes in context-specific biological networks, researchers need to conduct more in-depth analysis and debates to determine which characteristics should be paired with various centrality metrics.

In fact, no single centrality metric reflects the vitality of nodes for all network operations. In many cases, it is more important to find a group of key nodes than a single essential node, or to rank the nodes by how important they are. Combining the most important nodes does not necessarily ensure that the set of essential nodes will be discovered. In fact, such a collection usually comprises of nodes that, when combined with other nodes, have a significant effect despite not being vital on their own [122]. A comprehensive investigation of biological meanings is necessary, which implies that several factors may be at play, and that combination would lead to an increase in biological centrality. For the identification of core functional nodes in biological networks, the recommendation of this study is to first make a judgement on changes or features of the biological network structure based on a specific scenario, such as whether it is a difference in local modules (degree, MCC, closeness centrality) or a change in global bridging (bottleneck, betweenness centrality, stress) or information flow (eccentricity, radiality). Depending on the specific objectives of the study, it may be more important to select several mutually validated node centralities in conjunction with computational approaches that are pointed to by multiple metrics. The following points could be considered in the biological network analysis.(1) It is necessary to employ a variety of measures, including both the target node and its surrounds, to perform a thorough and accurate evaluation of node centrality. With other node centrality metrics, DMNC may be utilised as a supplement. (2) Diverse centrality measures may be used to identify nodes with different functionalities, which in this investigation are represented as modularity, bridging roles, and susceptibility. (3) Degree and MNC; eccentricity, closeness, and radiality; stress and betweenness are the following node centrality groupings that are often cross validated. (4) It is also important to consider the limitations of each node centrality, such as whether the network is directed or has self-loops.

With the availability of more biological data, it is necessary to move beyond pure topological metrics and rein-

terpret the concept of centrality based on the unique characteristics of biological activities. Research driven by biological knowledge would be very informative, for example, by combining the centralities and the evolution of ecological niches from the perspective of microbial mutualism or competition. One of the recommended solutions is to employ functional approaches based on the type of biological networks to be analysed [35]. In the future, the development of measurement metrics is expected to include more applications that fit the centrality of more structures, such as multi-layer networks or multiplexed networks.

Rarely is the entire network assessed simultaneously while measuring centrality. Even the components that have been recognized are subject to measurement errors, false positive or negative connections, and other difficulties. These centrality measurements require a large, noise-free network. Due to computational or measurement limitations, issues with the observed data, or network development over time, we may not be able to derive a complete and accurate graph-based representation for many systems [132]. Local-based centrality will be less affected by network structure uncertainty than path-based centrality. Recent approaches have examined the robustness of centrality measures [133–136] and their calculation in dynamic graphs [137–139]. There are also evidence showing for network functions like synchronization, controllability, communication and spreading information [116]. The research on important node mining algorithms with high precision and low time complexity will still be a popular direction for future research. Moreover, with the surge of data volume and the advancement of machine learning technology, the research of applying machine learning methods to important node mining has received more and more attention [23,131,140]. Fundamentally, the goal of complex network and machine learning is to discover the inherent laws of data and the integration of complex network theory and machine learning technology, and this deserves further investigation. For example, node centrality optimisation based on local or mixed entropy [141–143].

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