ejpmr, 2018,5(2), 228-233

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

COGNITIVE INTRODUCTION TO NETWORK ANALYSIS

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Article Received on 10/12/2017 **Article Revised on 31/12/2017** **Article Accepted on 20/01/2018**

INTRODUCTION

Network analysis of biological systems is useful for elate integration and analysis as it is gaining wide acceptance. Representation of biological system is just the beginning and it provides overview of the system under investigation. As the biological intracellular systems are dynamic, biological outcomes defines the quantitative balances between components. Network models that include more details about the kinetics, localization, and quantities of the molecular components should aid in understanding cellular behavior and cellular regulation at the molecular level from a systems perspective. This overview provide the idea of network analysis to predict interaction of genes and proteins in a biological network of genome to identify the gene or protein as target and aids in the prognosis of disease or malfunction in a biological pathway.

Representation of biological systems as networks

Direct or indirect interaction as links and molecular components within a cell as nodes is deployed as a representation mode of intracellular biological networks (D. Eisenberg et al., 2000). Graphs are the mathematical structures used for representation of different types of intracellular molecular biological networks (A.Ma'ayan et al., 2005). Some examples are (i) metabolic networks, for instance, the EcoCyc database provides access to metabolic networks across many organisms(P. D. Karp et al., 1996) (ii) cell signaling (iii) kinase-substrate networks, such as the one we constructed for developing the tool kinase enrichment analysis (KEA) (A. Lachmann and A. Ma'ayan, 2009) (iv) gene regulatory networks (v) protein-protein interaction networks for instance, the human protein reference database (HPRD), which contains a large manually extracted data set describing mammalian protein-protein interactions (T. S. Keshava Prasad et al., 2009) (vi) epistasis interaction networks, which are networks created by connecting genes if they exhibit a genetic interaction when knocked out or down-regulated (D. Segre et al., 2005) (vii) disease gene interaction networks, which connect diseases to genes that when mutated cause or contribute to the disease (K. I. Goh et al., 2007) and (viii) drug interaction networks in which drugs are linked to their targets.(M. A. Yildrim et. al 2007 and A. Ma'ayan et al., 2007).

Directed or undirected graphs, directed acyclic graphs (DAGS), trees, forests, minimum spanning trees, Boolean networks and Steiner trees (M. T. Dittrich et al., 2008 and A. G. White et al., 2007) are the different types of graphs utilized in representation of networks. The integration of data from many different studies into a single frame work is accomplished with network representation. Tanay et al. showed integration of different types of experimental data of genes as anchors (Tanay et al., 2004). Networks can be generated directly from time-series data of from perturbation data. Reverse engineering of topology of regulatory networks can be done directly from data tables of altered quantities of mRNA expression or protein abundance by time or under different perturbations using Bayesian networks (J. Pearl, 2000 and K. Sachs et al., 2005) which are initiative from advanced statistical learning techniques, or using tools, such as ARCANE, that utilize the notion of mutual information from information theory originally developed by Claude Shannon (A. A. Margolin et al., 2006).

Data visualization is one of the challenging tasks in network analysis. Ball and stick diagram is one of the common methods to visualize networks and several useful software tools exist for creating these: Pajek (http://vlado.fmf.uni-lj.si/pub/networks/ pajek/), GraphViz (http://www. graphviz.org/), Cytoscape (P. Shannon et al., 2003), VisANT (Z. Hu et al ., 2008), SNAVI (A. Ma'ayan et. al 2009), AVIS (S. I. Berger et al., 2007) and yEd (http://www.yworks.com/products/yed/) are a few examples. Biological networks can be based on integration of multiple sources of published information or manipulated directly from the data. Even some biological networks can be connected to diseases or drugs by integrating the different data sets through the abstraction to a network representation.

Breakthrough in Network analysis

Complex systems can be viewed as networks wherein components within a complex system can be represented as nodes and linked through their interactions, which are called edges is a popularized notion propounded by the seminal publications by Watts and Strogatz in 1998 (D. J. Watts, S. H. Strogatz, 1998) and Barabási and Albert in 1999 (A.L. Barabasi, R. Albert, 1999). This approach is attributed in many scientific disciplines, including systems biology and cell signaling research. Analysis of the network's topology is accomplished by representing the complexity of biological regulatory systems as network and it equips insight into the organizational principles of the cell, achieved through evolution.

Network topology encompass information about the general and specific properties of nodes, properties of edges, properties of the entire network (global topological properties) and modules within the network. Properties of nodes embrace connectivity degree, which is the number of links for each node; node betweenness centrality(M. E. Newman, 2001), which is the number of shortest paths that go over a node amidst all shortest paths between all possible pairs of nodes; closeness centrality, which is the mediocre shortest path from one node to all other nodes; eigenvector centrality (J. L. Morrison et al., 2005), which is a more enlightened centrality measure that appraises the closeness to highly connected nodes; and bioinformatic analyses of the molecules depicted by the nodes, for example, their Gene Ontology annotations (M. A. Harris et al., 2004), which exemplify the nodes function, location in the cell and entanglement biological processes.

Edge betweenness centrality (J. Yoon et al., 2006), which is the number of number of shortest paths that go through an edge among all possible shortest paths between all the pairs of nodes; the types of relationship, for example, edges may represent activating or inhibiting relationships between a pair of nodes; and edge directionality, which indicates the upstream and downstream nodes connected by a particular link are the properties of edges supervened in analysis. Phosphorylation, binding, gene regulation, are the type of interactions in which analysis is specified in the Science Signaling Connections Maps in the Database of Cell Signaling (N. R. Gough, 2002), or those proposed by the Edge Ontology (L. J. Lu et al., 2007) can be used to further characterize the network's topology. Global topological characteristics of networks include connectivity distribution (A.L. Barabasi, R. Albert, 1999), which is represented by a histogram showing number of nodes which is to be linked; characteristic path length (D. J. Watts, S. H. Strogatz, 1998), which can be reckoned by using Floyd-Warshall's or Dijkstra's algorithms and represents the average shortest path interpolated all pairs of nodes; clustering coefficient (D. J. Watts, S. H. Strogatz, 1998), which impersonates the local density of interactions by calibrating the connectivity of neighbors for each node averaged over the entire network; grid coefficient, which prolongs the clustering coefficient from only looking at first neighbors to also examining second neighbors; network diameter, which typify the longest shortest path; and assortativity, which assesses whether nodes prefer to attach to other nodes on the basis of common nodal properties (M. E. J. Newman, 2003). Recurring circuits of few nodes and their edges in network are christened as network motifs, which appear in the topology of biological regulatory networks more frequently than in the random or shuffled networks (A. Ma'ayan et al., 2005, R. Milo et al., 2004, S. S. Shen-orr et al., 2002). Particular important motifs directly influence a sysytem's overall dynamics subsumes feedback loops (D. Angeli et al., 2004), feed forward loops (S. Mangan et al., 2003), bifans (A. Lipshtat et al., 2008, P. J. Ingram et al., 2008) and other types of cycles (A. Ma'ayan et al., 2008).

Graphlets (N. Pruzulj et al., 2006) are the network motifs which are identified with directed or oriented graphs or in undirected networks and motifs present in protein-protein interaction network are the biological examples of graphlet. Modularity is a uniquity of network, which embodies the modules, or network clusters, which are dense areas of connectivity separated by regions of low connectivity. Algorithms convened to scare up modules are nearest neighbors clustering, Markov clustering and betweenness centrality– based clustering, which avail nodes with high betweenness centrality and low connectivity to separate clusters (M. E. Newman 2001). Structural organization of biological network and topology analysis relinquish idea to evolutionary processes which develop the observed topology of biological regulatory network. Recreation of realistic topologies by network evolution algorithms is based on simple rules governs the network growth. Network evolution models paved the way to understand the design principles assorted within complex biological regulatory networks. Some of these algorithms comprise rich-get-richer (A.L. Barabasi, R. Albert, 1999), growth by duplication- divergence (S. A. Teichmann, M. M. Babu 2004), exponential growth (A.L. Barabasi, R. Albert, 1999), and geometric growth (D. J. Higham et al., 2008). Alternative models initiated with a random network where network gradually evolves to a realistic topology based on rules of reposition links (D. J. Watts, S. H. Strogatz, 1998). Deviation of topological properties scrutinized in real networks from random connectivity is determined by comparing with Erdos- Renyi random networks (P. Erdos, A. Renyi, 1960) or other types of shuffled networks (S. Maslov, K. Sneppen, 2002), which serve as statistical controls are not beheld by chance. Emanating of general properties of biological regulatory network is accomplished by the application of various topological analyses. Most biological molecular regulatory networks are scale, which imports the connectivity distribution, the distribution of edges per node, fits a power law (A.L. Barabasi, R. Albert, 1999). The scale-free architecture fabricates the networks robust to random failures (R. Cohen et al., 2000).

Biological networks are also heavens above, implied that they are highly clustered with shortcuts that connect the clusters (D. J. Watts, S. H. Strogatz, 1998). "Party" hubs and "date" hubs (J. D. Han et al., 2004) are present in biological networks: Interaction of nodes with many proteins at one cellular compartment at a specific time are party hubs, whereas date hubs are proteins that can be endowed in many places inside the cell and inter react with various partners at different times. Multisite or single-site (P. M. Kim et al., 2006) are the different types of hubs. Some cell signaling networks have receptors which are present in a bow like structure share few downstream adapter proteins (the knot in the bow) (K. Oda, H. Kitano, 2006) and these adapter nodes integrate information from many receptors and then disseminate the information to many effectors in multiple cell signaling pathways. Fewer feedback loops tend to be nested (A. Ma'ayan et al., 2008) which are present in the topology of regulatory biochemical networks than observed in random Erdos-Renyi networks. Bifan motifs are most abundant (R. Milo et al., 2004, A. Lipshtat et al., 2008) in the topology of gene and cell signaling networks, probably due to evolution over duplication and divergence (S. A. Teichmann, M. M. Babu 2004). Feedback loops are depleted in most cycled real networks which are made of source and sink nodes. Such topology bequeath to optimal design for dynamical stability. Network evolution models are developed which starts with a random directed Erdos-Renyi–type network (B. D. MacArthuret al., 2010). Links are reassigned in the network evolution process if they bestowed to a local increase of sources and sinks. Random network becomes dynamically stable and displays a power-law, scale-free, connectivity distribution after several evolutionary steps. In addition of a simple rule, the evolution can endure forever, perpetuating the network scale-free structure, as well as manifesting dynamics that are at the cusp between stability and chaos. The hubs which are highly connected nodes are supplemented in the network; even their rise and fall in their connectivity but the global properties of the network remain constant. Hence, the simple theoretical network model captures dynamical evolutionary features perceived in real complex systems.

Prognosis of network analysis

Different algorithms can be enforced to predict "connections" between lists of "seed" nodes using precedent knowledge of molecular interactions. For example, differentially regulated genes or proteins under control versus treatment conditions could be used as seed nodes for edifice the functional networks using information from antecedent publications (S. I. Berger et al., 2007, K. D. Bromberg et al., 2008). Mean-first-pass-time (MFPT) (J. D. Noh, H. Rieger 2004), nearest neighbor expansion, Steiner trees (M. T. Dittrich et al., 2008, A. G. White, A. Ma'ayan 2007, S. S. Huang, E. Fraenkel, 2009) and the shortest path search algorithm (E. W. Dijkstra, 1959) are the algorithms used to prognosticate the connections between genes, proteins, or both, using information from background networks to form subnetworks.

Huang and Fraenkel intertwine the signaling pathways to transcription factors (S. Huang, E. Fraenkel, 2009) is a basis of Steiner tree approach and it is the similar approach for connecting of commonly expressed genes in stem cells (F. J. Muller et al., 2008). These methods are useful for predicting functional connections of nodes and additional nodes that had not been ascertained experimentally. Utilization of background knowledge is mandatory to predict interactions in network analysis. For example, circuits which appear to have missing links in clusters within the network structure are completed in protein-protein interactions (H. Yu et al., 2008) or by interconnecting the clusters in the network structure with function of nodes in clusters (I. Albert, R. Albert 2004). Instead of predicting the networks or portions of networks, the information about the molecules within the network also be predicted from various properties of the network. For example, protein function is derived from the known protein-protein interactions and the assumption is that proteins which are close in network space are plausibly to share functions (R. Sharan et al., 2007). Gene Set Enrichment Analysis (GSEA) (A. Subramanian et al., 2005) is utilized to derive predictions using network analysis are conceptually related. Gene sets can be indoctrinated to networks and networks can be indoctrinated to gene sets. For example, one can create a network by connecting genes which are targeted by the same micro RNAs, claim many Gene Ontology terms, or found in many pathways together. Gene sets are also created from networks and they encodes proteins of genes serves as a resource gene set library for the gene set enrichment analysis tool Lists2Networks (A. Lachmann, A. Ma'ayan 2010).

Challenges and future perspectives

Pathway and network analysis can adequately unveil biological systems flustered in tumor cells. Despite, the knowledge of pathways and networks both in normal and cancer cells are far complete. Extensive quantitative data, orthogonal data (DNA, RNA and Protein) and comprehensive pathway descriptions and regulatory descriptions are required for the techniques of network-based modeling. Development of pathway databases and regulatory signaling networks is to be constructed for better understanding of biological processes including protein- coding genes which involves many noncoding genomic elements.

A second challenge is the expensive computational modeling needs an extensive weeks of CPU time for permutation-based estimation of statistical significance. As the experimental data sets regarding reference pathways and networks will increase in progressive manner. Fundamental computer science research is needed to recuperate the algorithms to rule thousands of samples (Dittrich, MT., et al., 2008).

A final challenge is the appraisal of pathway and network methods in patient care. Pathway specific therapeutics is to be designed to predict therapies based on network constructed from molecular alterations present in individual tumors. Statistical challenge is embedded to derive the information from adaptive clinical trials. Complex network level alterations happened in patients is to be communicated by clinicians is a difficult method.

Though the understanding of cancer biology through network and pathway analysis is embryonic, but it is the potential path to surmise the disease etiology and treatment.

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