Indian Journal of Novel Drug Delivery

IJNDD

Review Article

Network Pharmacology Approaches for Drug Discovery and Repositioning: An Evolving Paradigm

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ARTICLE DETAILS	ABSTRACT
	Network-based on drug discovery and existing drugs is a new method that employs systems biology and computational tools to analyze complicated biological networks. In the case of traditional single-target drug discovery, this aspect concentrates on considering how molecules interconnect within the whole network of proteins, genes, and pathways, taking into account disease mechanisms. It authorizes researchers to recognize original therapeutic uses for developing multi-target treatments for diseases with intricate mechanisms, such as cancer or neurodegenerative disorders, and existing drugs (drug repurposing). By using advancements in data analytics and artificial intelligence, this offer holds high potential for revolutionizing drug discovery and accelerating personalized medicine. However, future challenges, specifically computational complexities and incomplete data, remain to be discovered.

INTRODUCTION

The innovative approaches of network-based drug discovery and drug repurposing emphasize their potential in the pharmaceutical industry. By using the complex interactions within biological systems and these methods give a complete knowledge of drug actions and disease mechanisms. The chapter explores the fundamentals of network biology, which includes biomolecule interactions, pathways, metabolic pathways, and genetic regulatory networks. Then it delves into the computational methodologies such as network pharmacology and biological networks, which highlight their role in identifying new drug targets and understanding some other multi-target drug actions. This methodology also combines several types of 'omics' data, and this data can be utilized in higher-level computational algorithms by researchers to advance fresh employs of existing drugs and, by doing so, it intensifies the drug development and reduces the costs [1]. One of the most common examples of the computational algorithms is the SAveRUNNER algorithm and which advances drug-disease associations by quantifying the interaction between biological targets and disease-specific biomolecules within the human interactome. This approach has been particularly effective in recognizing repurposable drugs for diseases such as COVID-19, cancer, Alzheimer's, and rare conditions, and this also highlights its potential to be used during medical emergencies [2].

Network biology is a multidisciplinary domain that unites computational and life sciences to examine complicated biological systems. This proposal has substantially enhanced the understanding of cellular activities, disease mechanisms, and phylogenetic relationships, especially in regions like cancer research and biological markers. In biological networks, nodes stand for biological entities such as proteins, genes, and metabolites, while edges stand for interactions between them [3].

Types of Biological Networks
Protein-Protein Interaction (PPI) Networks:
Protein-protein interactions (PPI) networks describe the interactions between proteins, which are vital for molecular actions and disease mechanisms. These networks can be created by using several experimental techniques such as two-hybrid networks, mass spectrometry, and protein microarrays [4].

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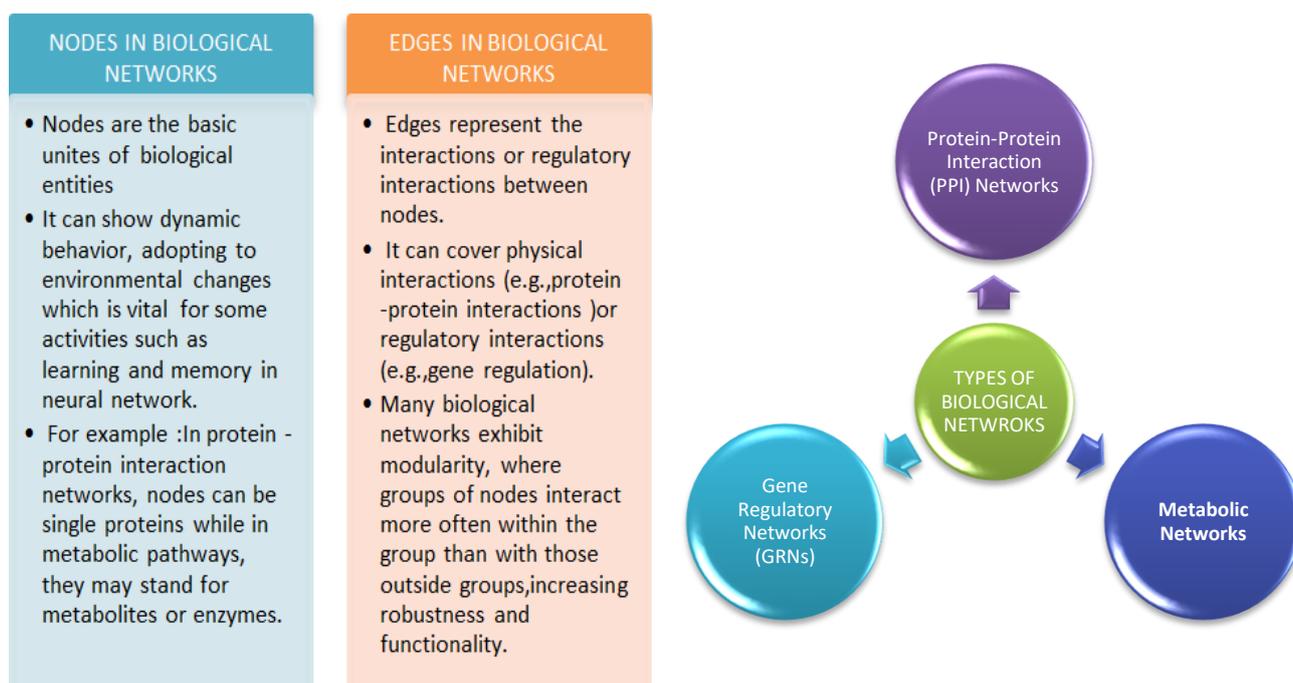*Email:* malavikab@gmail.com

Figure 1: Major Types of Biological Networks in Systems Biology

The study of PPI networks has developed from graph theory-based methods to structure-based methods that offer advantages in drug discovery, repositioning, evolutionary analysis, and prediction of protein activities. Computational techniques for studying PPI networks are topological, statistical, ontology, and data mining-based systems [5].

▪ ***Gene Regulatory Networks (GRNs):***
These networks illustrate the regulatory connections between genes, such as transcription factors that correspond to their genes. They help to understand how genes are turned on or off in response to several stimuli, influencing cellular actions and development. The analysis of these networks can reveal the stability of gene regulation and the ability for dysfunctional in diseases. In plants, the GRN study is achieving momentum due to mapping tools and new high-quality genomes. They are crucial in understanding GRNs for explaining cellular development and evolutionary mechanisms, along with phenotypic outcomes [6].

▪ ***Metabolic Networks:***
Metabolic networks elucidate biochemical reactions and pathways within a cell, revealing how metabolites are interconnected. The study shows that these networks can result in the identification of metabolic blockage and component systems, with the majority of nodes

(80%) attached only within their modules, and different evolutionary pressures on nodes based on their characters [7]. Several systems offer, such as analysis of metabolic flux balance and control tools, have been developed to analyze networks, allowing predictions of gene importance, disease assays, and drug targets. They are essential for comprehending metabolic disorders and the significance of drugs on metabolic mechanisms. They show robust and scale-free characteristics that exhibit similarities across diverse organisms and even non-biological networks [8].

Methods and Logic for Network-Based Drug Discovery
An innovative proposal, such as system biology and network pharmacology, describes network-based drug discovery to upgrade the drug development mechanism. This methodology is transferred from the long-established "one drug, one target" pattern to a more comprehensive "multidrug, multi-targets" framework, enabling the exploration of complex disease mechanisms and drug interactions. Key methodologies used in network-based drug discovery are outlined in the following segments [9].

1. Network Pharmacology
Network pharmacology is a developing field that employs systems biology and network studies to understand drug mechanisms and the discovery of new treatments. The long-established "one

disease, one target, one drug", proposal is challenged by network pharmacology through consideration of the complex interconnections between drug mechanisms and biological networks. Chinese herbal medicine (CHM), which usually involves several components acting on multiple targets, is particularly suitable for analysis using this comprehensive proposal [10].

The mechanisms of CHM formulas can be shown by network pharmacology through the prediction of pharmacokinetics and their effects on the cellular systems. Multi-target proposal: Network pharmacology highlights the importance of targeting multiple proteins for addressing complex diseases. The understanding of drug mechanisms is enhanced by the utilization of multi–omics data sets and computer modeling to predict drug effects and adverse events in data integrations [11].

2. Systems Biology

A novel proposal to drug discovery is offered by systems biology, which involves the integration of complex biological data and networks to understand disease mechanisms and drug actions. The proposal uses high-throughput data and bioinformatics network studies to model disease-corrupted networks and identify drug target interactions [12]. It plays an important role in studying gene, protein, and metabolite data to illustrate molecular determinants and formulate computational tools. Various aspects of drug discovery have been addressed using systems biology methods, including network analysis and dynamical modeling. These include predicting drug-target interactions, investigating adverse effects, drug repositioning, and combination prediction. The development of novel polypharmacology strategies for complex diseases is contributed to by these offers and the translation of research findings into clinical benefits, including biomarkers and drug therapies [13].

Drug repositioning is focused on by the NeDRextool (computational tools) through the analysis of protein-protein and drug-protein interactions, facilitating the identification of potential drug-disease associations. Drugs One is a platform that enhances user interaction through customizable network visualizations, aiding researchers in exploring drug discovery data [14].

Drug target and screening for potential candidates are effectively accomplished by network-based methods, streamlining the discovery mechanism was conducted. Despite their advantages, challenges such as data integration and method selection persist, necessitating careful evaluation of methodologies [15].

Applications of Network–Based Drug Discovery

Significant advancements in several medical fields have been yielded by the application of network studies in drug target identification. How these methodologies have successfully identified new drug targets, enhancing therapeutic strategies for diseases such as COVID-19 and cancer is elucidated by numerous case studies [9].

1. COVID-19 Drug Target Identification

Basic COVID-19-interconnected genes, such as CSF2 and ABL1/2, as potential drug targets, were identified by a neural network utilizing the graph-embedding convolution network (GECN). This proposal promoted the repositioning of existing drugs such as dupilumab and lenzilumab, which target hyper inflammation and viral entry actions [10].

2. Protein-Protein Interaction Networks

The identification of important proteins, vital for drug discovery, was improved by a novel method for detangling protein-protein interaction networks. Prediction accuracy is enhanced by this method, thereby increasing the likelihood of discovering effective drug targets for life-threatening diseases [16].

3. Genetic Evidence and Drug Target Enrichment

Researchers demonstrated that by analyzing genetic associations from the UK Biobank, network propagation of genetic evidence can successfully identify drug targets enriched for clinical success. This method utilizes protein interaction networks to infer novel disease associations [17].

4. Doxorubicin and Cancer Treatment

New drug targets, like Znf428 and Pou5f1b, were identified through a systems biology offer integrating the human interactome with gene expression data from cancer cell lines treated with doxorubicin, which could apply to numerous cancer cell types. These case analyses

highlight the potential of network studies in drug target identification, but challenges remain, which include the need for further empirical validation and the risk of false positives in network predictions [18].

5. Drug Repurposing Using Network Approaches

Drug repurposing is a cutting-edge tool that discovers new therapeutic applications for existing medications. This innovative offer not only saves time but also reduces costs in the drug discovery mechanisms. To accelerate this field, researchers developed an advanced network-based algorithm known as SAveRUNNER. Drug–disease associations are predicted by this new modern tool by analyzing the complicated interconnection between disease-associated genes within the human interactome and drug targets. Connections between disease mechanisms and drug processes that reside in similar network systems are prioritized by SAveRUNNER through the employment of unique network systems [19].

Act by its successful implementation for various syndromes, including viral infections and neurological disorders SAveRUNNER has now been applied by researchers to a diverse panel of 13 cancer types. This study leverages disease-associated genes sourced from well-established databases, coupled with comprehensive gene expression data, to reveal novel therapeutic opportunities in oncology [20].

Advantages of Network-Based Drug Repurposing

The advantages of network-based drug repurposing are multifaceted, leveraging computational methodologies to enhance the identification and validation of existing drugs for new therapeutic uses. This approach integrates diverse biological data, facilitating a more efficient and targeted drug discovery process [21].

1. Enhanced Drug Discovery Efficiency

Reduced Time and Cost: Network-based drug repurposing utilizes existing drugs, significantly shortening the development timeline and lowering costs compared to traditional drug discovery methods.

Rapid Identification of Candidates: By analyzing drug-target interactions and disease modules, researchers can quickly identify potential repurposable drugs, as demonstrated in studies on mpox and schizophrenia [22].

2. Improved Therapeutic Insight

Integration of Multidimensional Data: Network pharmacology combines various data types, such as protein interactions and gene expression, to uncover complex relationships between drugs and diseases. Identification of Drug Synergies: Network approaches can reveal effective drug combinations and pathways, enhancing therapeutic strategies, particularly in complex diseases like cervical cancer

Conversely, while network-based methods offer significant advantages, they may also face challenges such as data integration complexities and the need for extensive validation of predicted drug-disease associations, which can hinder the practical application of findings in clinical settings [23].

1. Challenges and Future Directions

Network-based drug discovery and repurposing encounter several significant challenges especially, in areas such as data integration and validation. These challenges arise from the complexity of bio-systems and the colossal quantity of data generated from several sources [24]. The integration of validation of computational predictions, diverse biological data types, and the influence of progressing technologies like AI and machine learning pose significant challenges and future directions in network-based drug discovery. Addressing these problems is essential for developing the field [25].

Data Complexity:

Challenges in network inference and studies are presented by the increasing volume and diversity of biological data [26].

Interdisciplinary Collaboration:

Collaboration among biologists, data scientists, and medical professionals is required for the effective application of network biology [27].

Data Integration Challenges

Integration of Multidimensional Information:

The integration of genomic, proteomic, and metabolomic data into coherent models is complicated by the varied nature of these datasets. A major hurdle is posed by the integration of diverse data types such as chemical structures, biological mechanisms, and profiles of genomes. For example, the complexity

of combining pharmacological and chemical data is effectively highlighted by the proposal for the integrated drug similarity network (iDSN) [28].

Incomplete Knowledge:

Emerging diseases may complicate the repurposing mechanism due to insufficient information in existing knowledge networks. The COVID-19 pandemic highlighted the necessity for new disease-specific data in order to effectively score drugs [29].

Validation Issues

Experimental Validation:

The accuracy of computational predictions is verified through rigorous experimental validation, which is crucial for the reliability of network-based offers. False positives or negatives are commonly yielded by computational predictions, necessitating rigorous experimental validation to confirm findings [30].

Clinical Importance:

Many computational procedures that translate computational findings to clinical settings are challenging and do not justify the complications of human biology [31].

Future Directions

AI and Machine Learning:

Progress in AI and machine learning is expected to refine network-based drug discovery, enabling better data studies and predictive modeling. A crucial role is played by *in silico* procedures such as machine learning and data mining for a better understanding of drug interactions and emerging clinical applications [32].

Improvement of Models' Prediction:

The prediction of drug strength in new identifications can be improved by the development of a Bayesian network meta-studies system, refining the repurposing mechanism [33].

CONCLUSION

Network-based drug discovery and drug repurposing are revolutionary approaches that leverage systems biology and advanced computational tools to decode complex biological networks. Unlike traditional single-target methods, these strategies focus on the intricate interlinkages among proteins, genes, and pathways involved in disease mechanisms. This holistic view enables researchers to uncover new therapeutic uses for existing drugs and develop multi-target treatments for complex conditions like cancer and neurodegenerative disorders. By integrating cutting-edge data analytics and artificial intelligence, these methods enhance drug discovery and pave the way for personalized medicine. While there are challenges such as computational complexities and incomplete data, to address, embracing this approach could significantly transform drug development and revolutionize healthcare.

CONFLICT OF INTEREST

NONE.

ABBREVIATIONS

NB-DD – Network-Based Drug Discovery
NB-DR – Network-Based Drug Repositioning
PPI – Protein–Protein Interaction
GBA – Guilt-By-Association
DTI – Drug–Target Interaction
MoA – Mechanism of Action
OMICS – Genomics, Transcriptomics, Proteomics, etc.
FDA – Food and Drug Administration
CMap – Connectivity Map
KEGG – Kyoto Encyclopedia of Genes and Genomes

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