Network Medicine: Methods and Applications

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Aftab Alam, Okan Yildirim, Faizan Siddiqui, Nikhat Imam, and Sadik Bay

Abstract

Network medicine (NM) is a developing field within network science that focuses on molecular and genetic interrelationships, disease network biomarkers, and the discovery of therapeutic targets, and it is a rapidly growing arena for medical science and research, which comes with the possibilities to reform the system of disease diagnosis and its treatment. The NM uses topological and dynamic properties of the biological networks (protein–protein interactions and metabolic pathways) to distinguish the disease patterns (characterizing the behavior of disease genes) and associated drugs. Biomedical data provide a base to develop a significant model and get potential results at the network level. In

Aftab Alam has become affiliated with the United Arab Emirates University, UAE. Okan Yildirim and Sadik Bay are both currently affiliated with the Memorial Sloan Kettering Cancer Center in New York City, USA.

A. Alam
Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi, India

O. Yildirim
Department of Chemical Biology Otto-Hahn-Strasse, Max Planck Institute of Molecular Physiology, Dortmund, Germany

F. Siddiqui
International Medical Faculty, Osh State University, Osh, Kyrgyzstan

N. Imam
Department of Mathematics, Institute of Computer Science and Information Technology, Magadh University, Bodh Gaya, India

S. Bay (✉)
Research Institute for Health Sciences and Technologies (SABITA), Istanbul Medipol University, Istanbul, Turkey

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this chapter, we have discussed the integrative use of emerging tools and the databases of NM, which provide a basic platform to systematically investigate the molecular complexity of diseases, dominant disease genes (modules), drug targets, disease-enriched pathways (altered pathways), and molecular interactions between apparently distinct phenotypes. The field of network medicine and its implications for diagnostics, prognosis, and therapeutics with unprecedented breadth and precision have great potential in the future.

Keywords

Network medicine · System pharmacology · Precision medicine · Disease–gene relationship · Drug repurposing

5.1 Introduction

"Interaction" is a single word that makes communication among the physical body (human beings), and even cellular components activate its functional switches by "interactions" with another component of the cell; overall, these interactions represent the human interactome. Interactome assessment is exclusively a tool-based approach to the theoretical paradigm and methodological tools utilized, describe, investigate, and comprehend structural and relational features of human health and disorders. Network-based research is becoming a crucial technique for identifying disease susceptibility genes and their associations with various diseases (Alam et al. 2022). Additionally, this research has enhanced our comprehension of drug targets and their results and proposed new drug targets, treatments, and therapeutic management strategies for serious disorders (Fig. 5.1).

Network-based approaches to human disease offer a variety of biological and therapeutic uses. Indeed, a better comprehension of the consequences of (1) cellular interconnections failure or (2) rewiring in cellular interconnections on disease progression could lead to the identification and classification of disease-associated genes and pathways which could provide better targets for drug development. Advancement in these fields could also restructure the clinical application and practice, from the development of improved and more precise biomarkers that monitor the functional integrity of the network that is perturbed by the diseases as well as improvements in disease classification and pave the way to personalized therapies and treatment.

In a recent study, Gysi et al. employed network medicine and drug repurposing methods to distinguish the repurposable drugs for COVID-19 (Morselli Gysi et al. 2021). Similarly, a multi-target herb called *Caesalpinia pulcherima* (CP) is used therapeutically to treat breast cancer (Sakle et al. 2020). Furthermore, Azuaje et al. contributed to our understanding of the cardiovascular effects of non-cardiovascular medications by integrating multiple sources of drug and target interaction data. They constructed the myocardial infarction (MI) drug-target interactome network, offering systemic insights into the topic (Azuaje et al. 2011). In a related study, Kim et al. have proposed that examining the network-based drug–disease intimacy can offer a novel perspective on the therapeutic effects of drugs in the context of

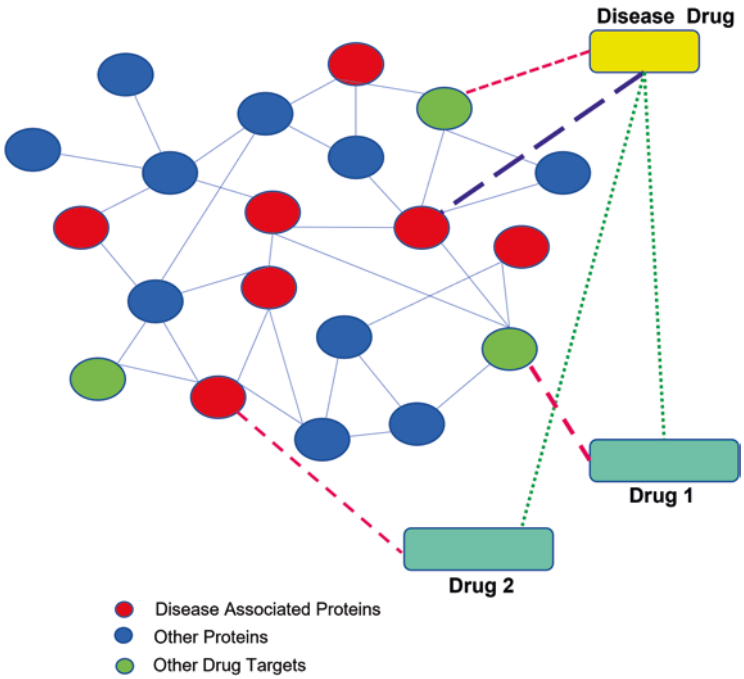

Fig. 5.1 Overview of network medicine approach

Systemic Sclerosis (SSc) disease. This approach may provide insights into drug combinations or drug repositioning strategies (Kim et al. 2020).

In this chapter, we focused on networks and their role in disease, System Pharmacology, Pharmacogenomics in Precision Medicine, Drug–Target Interaction, Drug–Drug Interaction, Drug Repurposing Opportunities, Drug Side Effects, and Integrating Omics data with Networks: Challenges and Ways. We hope this new chapter provides the same platform for scholars from biological science backgrounds to work on interdisciplinary research areas that can be useful for describing the causes of disease and pinpointing potential treatment targets, which will improve preventative healthcare and have a knock-on effect on personalized therapy.

5.2 Basic Principles and Key Components of Network Medicine

5.2.1 Systems Pharmacology

The early understanding of the molecular mechanisms behind pharmacological action was provided by classical investigations, such as the development of the receptor hypothesis that distinguished between competitive and noncompetitive inhibition. The prevalence of medications that target membrane receptors (mostly GPCRs) explains the influence and applicability of receptor theory in contemporary

pharmacology. The majority of the remaining drugs are enzyme inhibitors, which are often analogs based on substrates, analogs based on transition states, or allosteric inhibitors that are designed to bind reversibly or irreversibly based on the substrate and substrate-binding pocket configuration. The genomic, proteomic, network, and other high-throughput investigations have produced a wealth of "systems-level" knowledge over the last 10 years. The number of well-characterized, druggable targets is continuously rising through the use of high-throughput technology, structural and biochemical studies, and human genome research. Targeted therapies and biological medicines have thus emerged as a result of the expansion of the pharmacological pipeline and concentration on complicated, multigenic disorders. In recent studies, regulatory network analysis and structural analysis were used to anticipate the therapeutic benefits of medications for complicated disorders as well as potential off-target consequences (Boran and Iyengar 2010; Black and Leff 1983; Maehle et al. 2002; Colquhoun 2006).

5.2.2 Pharmacogenomics in Precision Medicine

One of the fundamental components of personalized treatment is pharmacogenomics (PGx). In personalized medicine, also known as precision medicine, patients are given prescriptions for drugs that are right for them based on their genetic, environmental, and lifestyle characteristics. Two key functions of pharmacogenomics in precision medicine. It first directs pharmaceutical firms in drug development and discovery. Second, it helps doctors choose the best medication for patients based on their genetic makeup, avoid adverse drug reactions, and maximize drug efficacy by providing the appropriate amount. Based on the understanding of pharmacogenomics, personalized/precision medicine has significant potential benefits. Precision medicine is the future of healthcare, and it will eventually become the standard of care.

5.2.3 Biological Networks and Important Databases

A method of expressing systems as complicated sets of binary interactions or relations between distinct biological components is called a biological network (e.g., genes, proteins, taxa, and metabolites). Now, with the availability of large-scale multi-omics data, the biological system has expanded from basic to advanced levels (like PPI connectivity and functional changes in disease stages, Disease-specific interactome, genetic perturbations, and network dysfunction).

Protein–protein interaction networks (PINs), in which proteins act as nodes and interactions as undirected edges, depict the physical connections between the proteins that are present in a cell. Protein–protein interactions (PPIs) are the most thoroughly studied networks in biology and are crucial to cellular functions. PPIs can be found using a variety of experimental methods, with the yeast two-hybrid system being one of the more popular methods for studying binary interactions. Mass

spectrometry-based high-throughput research have recently uncovered numerous sets of protein interactions.

The databases that catalog experimentally determined protein–protein interactions have been the result of numerous international efforts over the past few decades, such as the Munich Information Center for Protein Sequence (MIPS) protein interaction database (Schoof et al. 2005), Biomolecular Interaction Network Database (BIND) (Bader 2003), Database of Interacting Proteins (DIP) (Xenarios 2000), Molecular Interaction database (MINT) (Chatr-aryamontri et al. 2007), and Protein Interaction database (IntAct) (Hermjakob 2004). These databases are classified into primary and secondary databases based on their interaction prediction method but now one new term introduced "Meta-database" which is a combination of different primary and secondary databases to get new and maximum protein–protein interactions in network (Fig. 5.2). The list of protein interaction databases is given in Table 5.1.

Moreover PPI, the Metabolic networks explain the associations between small biomolecules (metabolites) and the enzymes (proteins) that interact with them to catalyze a biochemical reaction. Genetic interaction networks are valuable for understanding the relationship between genotype and phenotype because they relate to the functional interactions between pairs of genes in an organism.

Similarly, a gene regulatory network (GRN) is a collection of molecular regulators that interact with one another and with other components of the cell to regulate the expression level of mRNA and protein. Further, when different cell signaling pathways interact, cellular signaling networks are built, and they are identified by a combination of experimental and computational techniques.

A complex biological network consists of various nodes (including genes, proteins, and metabolites.) and connections among nodes are represented by joining lines, called "edges." The hubs are nodes that connect with other nodes frequently and play important roles in biological processes. The total number of edges that a node is connected to is referred to as its degree. Finding the node with the top degree can support to distinguish a biological-entity that plays the most important role within the network. For more details about the basic biological network and its

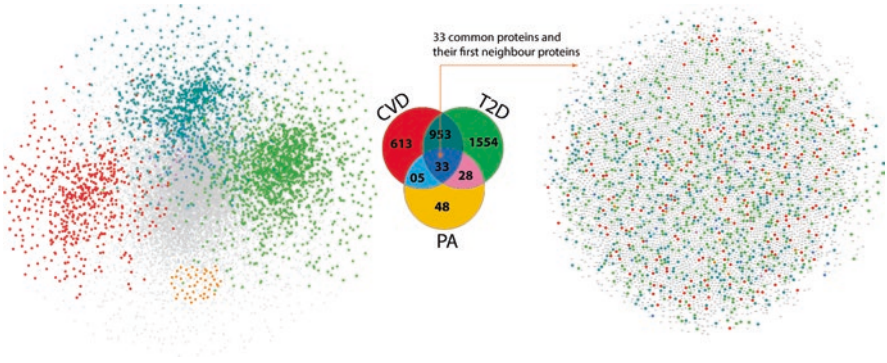

Fig. 5.2 An example of human disease networks

Table 5.1 Protein–protein interaction databases

Primary database			
Databases	URL	Experimental/ Predicted	Reference
BioGrid	https://thebiogrid.org/	Exp.	Oughtred et al. (2019)
HPRD	http://www.hprd.org/	Exp.	Goel et al. (2012)
IntAct	https://www.ebi.ac.uk/intact/home	Exp.	Hermjakob (2004)
MINT	https://mint.bio.uniroma2.it/	Exp.	Chatr-aryamontri et al. (2007)
HuRI	http://www.interactome-atlas.org/	Exp.	Luck et al. (2020)
Secondary database			
STRING	https://string-db.org/	Exp. & Pred.	Szklarczyk et al. (2019)
UniHI	http://www.unihi.org/	Exp. & Pred.	Kalathur et al. (2014)
Mentha	http://mentha.uniroma2.it/	Exp.	Calderone et al. (2013)
APID	http://cicblade.dep.usal.es:8080/APID/init.action	Exp.	Alonso-López et al. (2019)
HIPPIE	http://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/index.php	Exp.	Alanis-Lobato et al. (2017)
HitPredict	http://www.hitpredict.org/	Exp.	Patil et al. (2011)
IID	http://iid.ophid.utoronto.ca/	Exp. & Pred.	Kotlyar et al. (2016)
HINT	http://hint.yulab.org/	Exp.	Das and Yu (2012)
GPS-Prot	http://gpsprot.org/	Exp.	Fahey et al. (2011)

- Primary protein interaction databases containing literature-curated PPIs for human proteins.
- Secondary protein interaction databases containing predicted and curated from primary databases.

topological properties, importance can be read in our previous articles (Alam et al. 2019; Alam et al. 2021).

5.2.4 Human Disease Networks

A disease gene network involves the incorporation of genes linked to specific disease phenotypes into an established human interactome. The hypothesis posits that genes and their corresponding products associated with a given disease have the propensity to interact and form clusters within a localized sub-network, as opposed to being randomly distributed across the entire human interactome (Lee and Loscalzo 2019). The unbiased analysis of pathobiological linkages between various disease processes has also been made possible by disease networks. To construct the human disease network, there are many ways including literature survey to find the disease-associated genes and construct network. Further, there are many good, comprehensive databases available DisGeNet, an extensive and carefully curated database, integrates data from multiple publicly accessible databases, such as "UniProt/

SwissProt," "Cancer Genome Interpreter (CGI)," "Comparative Toxicogenomic DatabaseTM (CTDTM)," "Orphanet," "Mouse Genome Database (MGD)," "PsyGeNET," "Genomics England," "ClinGen," and "Rat Genome Database (RGD)." These databases were utilized to collect information on genes associated with various diseases, which were subsequently compiled and organized within the DisGeNet database (Pinero et al. 2015).

Recently, we analyzed three diseases (including Cardiovascular disease, Diabetes type-2, and Parathyroid adenoma) and found that 33 genes are common in these diseases (Fig. 5.2). Similarly, in our one more previous articles (Alam et al. 2022) where we identified 33 high-scoring significant modules that hub genes that are shared between tuberculosis (TB) and overlapping non-communicable diseases (NCDs) (lung cancer, rheumatoid arthritis, diabetes mellitus, Parkinson's disease, and cardiovascular disease).

5.2.5 Drug–Target Interactions

The conventional "one disease–one target reductionist approach" is not widely applicable since the majority of drugs exert their effects by targeting multiple proteins, resulting in a net pharmacological impact that encompasses both therapeutic and adverse effects. Network techniques provide valuable tools for predicting drug actions in complex biological contexts. In this context, drugs can be mapped onto the human interactome through their identified targets, where the effects of drugs on specific nodes or targets are represented by edges in the biological network. In our previous study, when the common disease genes related to TB and non-communicable disease (NCDs) that include lung cancer, rheumatoid arthritis, diabetes mellitus, Parkinson's disease, and cardiovascular disease; and built a bipartite network (drugs and targets) by mapping the hub genes of the modules to their corresponding drugs using the DGIdb database, the results revealed that a significant portion of the target genes had multiple hits (as shown in Fig. 5.3). This indicates that genes interacting with a greater variety of drugs may be more intricately connected to the underlying mechanisms driving the pathological phenotype associated with these drugs. The presence of multiple drug interactions with a gene suggests its involvement in multiple pathways or biological processes relevant to the disease phenotype, emphasizing its potential significance in the context of therapeutic interventions and understanding disease mechanisms (Alam et al. 2022).

5.2.6 Drug–Drug Interaction

A change in a drug's impact on the body when it is combined with another drug. The absorption of either drug can be sped up, slowed down, or improved by a drug–drug interaction. This could alter the way one or both drugs work, increase or decrease their effects, or have negative consequences. Studies have demonstrated that a substantial proportion, ranging from approximately 37–60%, of hospitalized patients may have one or more potentially interacting drug combinations upon admission

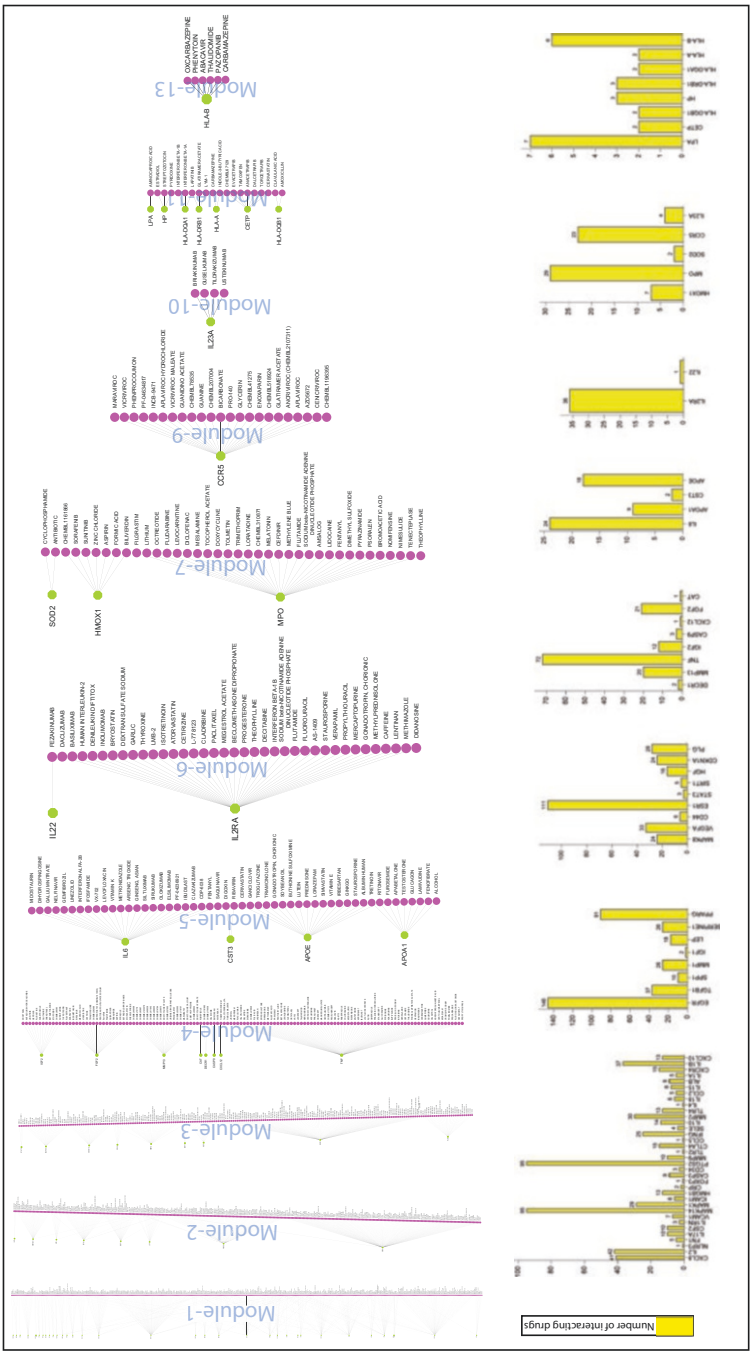

Fig. 5.3 Drug–target interaction network: all the 13 modules' targets (Green) are mapped with their respective drugs (Magenta). The bar graph illustrating the number of interacting drugs with key targets (Ref: doi:10.3389/fphar.2021.770762)

(Costa 1991). Digoxin, beta-blockers, estrogen, oral hypoglycemic medicines, and diuretics were the five drug classes most likely to be involved in possible drug interactions. In this way, Cao et al. have developed a database, e.g., *DDInter* (http://ddinter.scbdd.com) (Xiong et al. 2022), The curated Drug–Drug Interaction (DDI) database offers extensive data, practical medication guidance, an intuitive functional interface, and powerful visualization tools to cater to the needs of the scientific community. The database currently includes approximately 0.24 million DDI associations. Figure 5.3 showcases the Drug–Target Interaction Network, where all 13 modules' targets (in green) are mapped with their respective drugs (in magenta). The illustration on the right demonstrates the number of interacting drugs with key targets, the database connects 1833 approved drugs, encompassing 1972 entities. Each drug in the database is accompanied by essential chemical and pharmacological information, along with its interaction network. This comprehensive annotation allows for a deeper understanding of the drug's characteristics and its interactions with other entities within the network (Fig. 5.4).

5.2.7 Functional Modules in Molecular Networks

Protein clusters or sub-networks that exhibit dense connections are often regarded as potential functional modules within a given network. Another hypothesis proposes that proteins interacting with similar groups of other proteins in the network

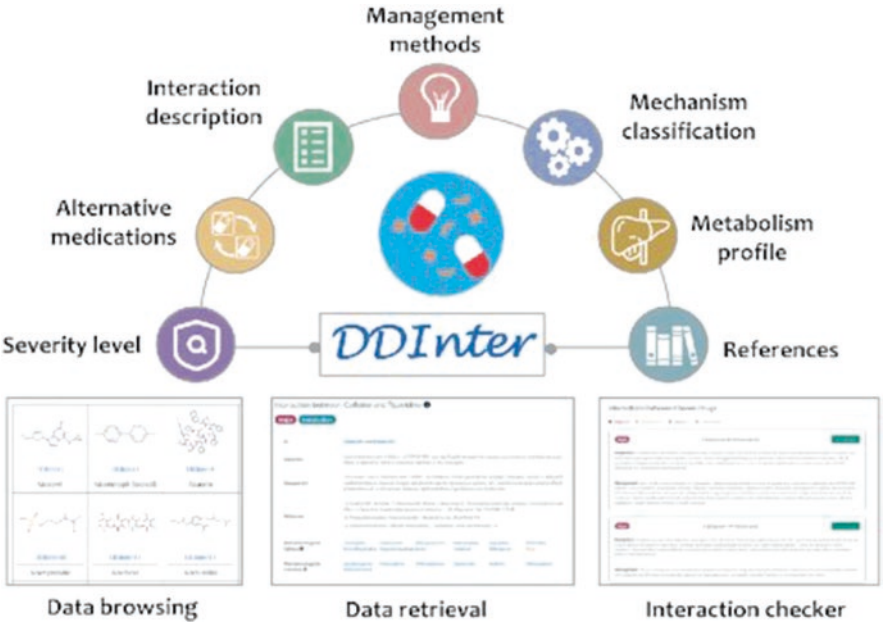

Fig. 5.4 DDInter provides detailed annotations of each DDI association and enables users to conduct data query (image courtesy, please refer: https://doi.org/10.1093/nar/gkab880)

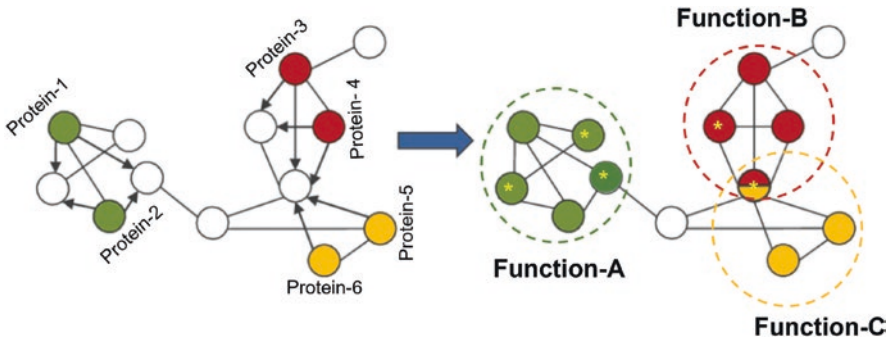

Fig. 5.5 Guilt-by-association approach: different colors are used to denote proteins with known functions, while proteins with unknown functions are left uncolored. Transferring functional annotation from directly interacting proteins allows for the inference of protein function (indicated by arrows)

tend to have comparable functions. Even in cases where direct interactions are absent, these proteins contribute to similar biological functions and should be included in the same modules. However, both definitions of modules rely on a guilt-by-association approach, as illustrated in Fig. 5.5. For instance, if two proteins interact with each other, it is more likely that they share the same cellular functionalities compared to proteins that do not interact (Wang and Qian 2014).

There are many tools for the identification of functional modules within the network, but few are widely used among the researcher including the *LEV* (leading eigenvector) method that detects the communities in network from package "igraph" in R (Newman 2006). Another approach called MCODE (Molecular Complex Detection) focuses on identifying densely connected regions within a network. MCODE aims to identify molecular complexes or clusters characterized by high connectivity and close proximity of nodes (Bader and Hogue 2003).

Another is the *DIAMOnD* (DIseAse MOdule Detection), which we can investigate the local network neighborhood (LNN) near a particular set of known disease proteins, and this helps us identify potential new disease target protein (Ghiassian et al. 2015) and last one which I found very useful and accurate that is MTGO (Module detection via Topological information and Gene Ontology knowledge) is a method that identifies modules within a network using both network topology and the biological role of proteins based on Gene Ontology (GO) terms (Vella et al. 2018).

5.3 Drug–Repurposing Opportunities

Network-based drug repurposing methodologies are based on the premise that drugs capable of interacting with multiple targets can demonstrate efficacy against specific diseases. Furthermore, these methodologies take into account the potential therapeutic implications when two drugs target the same protein. By leveraging the interconnected nature of biological networks, these approaches offer promising

avenues for identifying new therapeutic uses for existing drugs. This approach proves to be effective in the discovery and development of drug molecules with new pharmacological or therapeutic indications. By targeting specific proteins through therapeutic combinations or drug repurposing, it becomes possible to improve clinical conditions in cases of comorbidity, enhance the potency of certain drugs, and achieve synergistic effects for better treatment outcomes (Imam et al. 2023).

5.4 Drug Side Effects

Over a million significant injuries and fatalities are caused annually by adverse drug reactions (ADRs), which are very common. Currently, many machine learning and network-based approaches are used to predict the adverse drug. By leveraging features such as composition, structure, and binding affinity, researchers have employed methods that involve machine learning (ML) and deep learning techniques (Dara et al. 2022). As part of these ongoing efforts, a recent development is the T-ARDIS database (Galletti et al. 2021). T-ARDIS is a carefully curated compilation of relationships between proteins and Adverse Drug Reactions (ADRs). These associations are statistically evaluated and sourced from existing databases of drug–target and drug–ADR associations.

5.5 Integrating Omics Data with Networks: Challenges and Ways

Multi-omics data will soon be regularly used in preclinical and clinical contexts, hence further constraints should apply standardized, rigorous bioinformatics techniques to process, normalize, and analyze the massive datasets from various study modalities. From this perspective, it should soon be possible to build networks of networks to determine how various biological aspects are interconnected. Beyond intracellular molecular networks, we are now combining the connections between various cell-types, organ-systems, hosts and microorganisms, hosts and environmental exposures, as well as other interconnections. It would also be essential to incorporate psychosocial components when defining disease networks in order to link all contributing factors to clinical results. As demonstrated, network controllability analysis continues to be useful for identifying important disease genes and prioritizing potential targets.

The existing human interactome is incomplete, which restricts network analysis of complicated human disorders. The interactome is expected to keep growing as high-throughput technology and bioinformatics continue to progress. The existing interactome is based solely on the binary biophysical interactions between the curated PPIs, with little knowledge of or annotations for protein-binding patterns or domains. There is an ongoing attempt to develop a “domain-specific interactome (DSI)” where commonly shared domains or motifs, such “SH3” and “PDZ domain” are two examples of frequently shared domains or motifs that are being screened

and cloned for their interacting partners. The possibility of modifications to the physical and metabolic characteristics in a physiological context that changes protein binding at these domains is a limitation of this strategy.

In addition, the majority protein–protein interactions (PPIs) within the current interactome are predicted based on the induced protein expression levels observed in experimental yeast cells, which could be very different from the endogenous ecosystem where key targets are normally expressed. An area of active research is the integration of PPIs with gene expression data and further techniques to provide tissue and disease-specific perspective to the existing interactome. Notably, the present interactome only contains one isoform of each gene product and provides scant annotations regarding the splice isoforms that are being considered. It is generally accepted that distinct spliced forms can results in significant changes in phenotypic variations.

Reticulocyte analysis is a recently developed idea in which a patient's unique integrative biological network (reticulome) and a set of molecular-mutants/variants are investigated. Each person has a unique set of biological networks. Biological network environment within an individual unquestionably influences the final result (phenotype) of a certain set of genetic variations (genotype) and therefore, should be an essential element of any patient-specific data assessment. Therefore, customized reticulotype-based network studies have potential to strengthen the current genotype/phenotype correlation attempts and may make the search for customized targeted therapies.

5.6 Case Studies

5.6.1 Case Study: 1

Imam et al. conducted a recent study titled "Network-Medicine Approach for the Identification of Genetic Association of Parathyroid Adenoma with Cardiovascular Disease and Type-2 Diabetes." This study delves into unexplored dimensions of diseases by specifically investigating distantly related protein sets associated with other diseases that have not been previously studied. The aim is to understand their collective physiological impact on the pathological phenotype through network analysis.

The researchers performed a comparative analysis of disease-associated proteins in Parathyroid Adenoma, Cardiovascular Disease, and Type-2 Diabetes with the aim of identifying shared genetic factors. Utilizing network analysis methods, they investigated functional modules within the protein-disease network that exhibited dense internal connections but sparse connections with the rest of the network. As a result, they discovered 13 target proteins that were found to be common to parathyroid adenoma, cardiovascular disease, and type 2 diabetes. These proteins were subsequently organized into hierarchical modules and sub-modules within the Protein–Protein Interaction (PPI) network. In their study, the researchers also employed the concept of drug repurposing and drug combinations. They utilized

target proteins and associated drugs in a drug–target bipartite network, which included experimentally verified drug–target binary connections. They found that 36 drugs were common to both target-associated drugs (TAD) and disease-associated drugs (DAD), supporting the effectiveness of a multi-target drug approach.

This network-based analysis presents promising avenues for personalized treatment and the repurposing of drugs. It allows for the exploration of new targets and combinations of multiple drugs, facilitating a comprehensive understanding of protein–disease associations and disease–disease relationships. By utilizing advanced computational techniques, the study prioritizes drug–target interactions and examines disease–disease connections, thereby enhancing the selection of potential therapeutic targets based on efficacy and safety in complex disease scenarios (For more details, read the full article: https://doi.org/10.1093/bfgp/elac054).

5.6.2 Case Study: 2

A study conducted by Aftab et al. aimed to construct a disease network by investigating the overlap between Tuberculosis (TB) and other Non-Communicable Diseases (NCDs) such as Parkinson's Disease (PD), Cardiovascular Disease (CVD), Diabetes Mellitus (DM), Rheumatoid Arthritis (RA), and Lung Cancer (LC). Through the analysis of this disease network, the researchers identified common genes associated with TB and other NCDs, establishing important gene–disease relationships.

To delve deeper into these diseases, the researchers constructed separate gene interaction networks for each disease by integrating carefully curated and experimentally validated human interactions. Additionally, they generated and analyzed a drug–target interactome network that encompassed clinically relevant drug–drug and drug–target interactions. This comprehensive network offered a more comprehensive understanding of the intricate landscape of drug–target interactions.

The primary objective of this study was to establish a comprehensive workflow that takes into account Tuberculosis (TB) and its overlapping Non-Communicable Diseases (NCDs), emphasizing the significance of reconsidering and redefining therapies and therapeutic management. The findings underscore the potential of exploring uncharted territories in disease research, particularly the shared gene sets that coexist among various diseases. By fostering collaboration, it becomes feasible to collectively impact the pathological phenotype at a physiological level (For more details, read the full article: https://doi.org/10.3389/fphar.2021.770762).

5.7 Conclusion

Multi-omics data will soon be regularly used in preclinical and clinical contexts, hence further constraints should apply standardized, rigorous bioinformatics techniques to process, normalize, and analyze the massive datasets from various study modalities. From this perspective, it should soon be possible to build networks of

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between various cell-_types, organ-systems, hosts and microorganisms, hosts and environmental exposures, as well as other interconnections. It would also be essential to incorporate psychosocial components when defining disease networks in order to link all contributing factors to clinical results. As demonstrated, network controllability analysis continue to be useful for identifying important disease genes and prioritizing potential targets. Reticulocyte analysis is a recently developed idea in which a patient's unique integrative biological network (reticulome) and a set of molecular-mutants/variants are investigated. Each person has a unique set of biological networks. A biological network environment within an individual unquestionably influences the final result (phenotype) of a certain set of genetic variations (genotype) and therefore, should be an essential element of any patient-specific data assessment. Therefore, customized reticulotype-based network studies have the potential to strengthen the current genotype–phenotype correlation attempts and may make the search for customized targeted therapies.

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