

Title: A critical analysis of Network-Based Drug Discovery and Development

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Introduction

The modern pharmaceutical manufacturing organizations are facing numerous challenges in today's world. The ever-increasing expectation of the customers is making things difficult for the healthcare payers. Healthcare providers are seeking advanced, economically and clinically superior alternatives. This desire is laying new cost burdens on the pharmaceutical firms. The need for new developing processes and novel discoveries in order to find new alternatives has also become essential (Barbasi et.al, 2011). The output of pharmaceutical productivity has been stable over the last few years and a sudden increase is debatable. Thus, the new licence applications and molecules approved by the FDA are decreasing in number. Fifty-three fresh molecular units had been approved in the year 1996 and the number has decreased to just nineteen since then. The success rate of the pharmaceutical firms is quite low with respect to candidates suitable for developing advanced drug products (Adams and Brantner, 2006).

Most of the cellular elements interact with other elements located across or within the same cell or organ. The network which is formed from these molecular units is referred to as the interactome in humans which comprises of more than 25,000 genes for coding of proteins, more than 1000 metabolites and innumerable protein types and distinct RNA molecules. Cellular units serving as the interactome nodes exceed the number of 100,000 (Wu et.al, 2013). The intra and intercellular connectivity indicates that the effect generated by a particular genetic defect is not limited to the gene product which carries it and can easily spread to the associated networks. This in turn transforms the activities of the gene products that are healthy. Thus, it is important to have good understanding of the gene networks for assessing the phenotypic effect of the defects affecting it.

A network-based methodology for understanding human diseases helps in making various clinical and biological applications. Development of advanced drugs can take place by understanding the various effects of interconnectivity between cells on progression of diseases. This in turn also helps in identifying the disease pathways and genes in a better way. These developments result in accurate and better biomarkers for monitoring the practical reliability of the networks that get disturbed by various diseases (Sirota et.al, 2011). This study is an overview of the principles that administer cellular networking and the applicability of the principles for

understanding different diseases. The methodologies and tools derived from these principles have led to the evolution of a knowledge pool which is being named as a 'network medicine'.

Biological Network Maps and Interaction Resources

Most of the research work that has been conducted on biological networks in the past has focused largely on *Saccharomyces cerevisiae* and *Escherichia coli*. However, the data found in the Human Genome Project on human cellular networks and model organisms are highly diverse and rich (Arrell and Terzic, 2010). The following discussion will focus on the various network maps along with their limitations.

Protein-Protein Interaction Networks

The attainment of a wide-ranging protein-protein interaction map has been in process since the last five years. Two hybrid maps on high-output yeast were developed for humans by various groups resulting in large number of binary interactions. The application of high-output mass spectrometry and immune-precipitation method is also being practiced on humans for identifying co-complexes (Sirota et.al, 2011). Efforts have also been made for curating the interactions individually certified in existing literature database like Database of Interacting Proteins (DIP), the Protein Interaction Database (IntAct), the Munich Information Centre for Protein Sequence (MIPS), the Molecular Interaction Database (MINT) and the Biomolecular Interaction Network Database (BIND). Additional efforts have also been made to study protein-protein interaction like the Human Protein Reference Database (HPRD) and the Biological General Repository for Interaction Datasets (BioGRID). The database of STRING comprises of both predicted and known protein-protein interactions. In spite of these efforts, existing maps have been considered piecemeal and the data sets found in literature studies are interaction rich but are under investigation (Barbasi et.al, 2011).

Metabolic Networks

Maps that are considered highly comprehensive of various biological networks are the metabolic networks. Databases like the Biochemical Genetic and Genomics knowledge base (BIGG) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) comprise of metabolic networks pertaining to various species. An all-inclusive genome-scale metabolic reform on human metabolism was published recently comprising of 3311 transport and metabolic reactions and 2766 metabolites (Davidov et.al, 2003).

Regulatory Networks

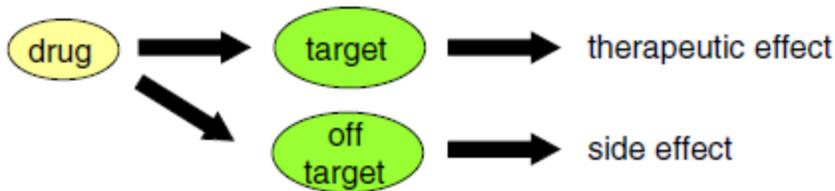
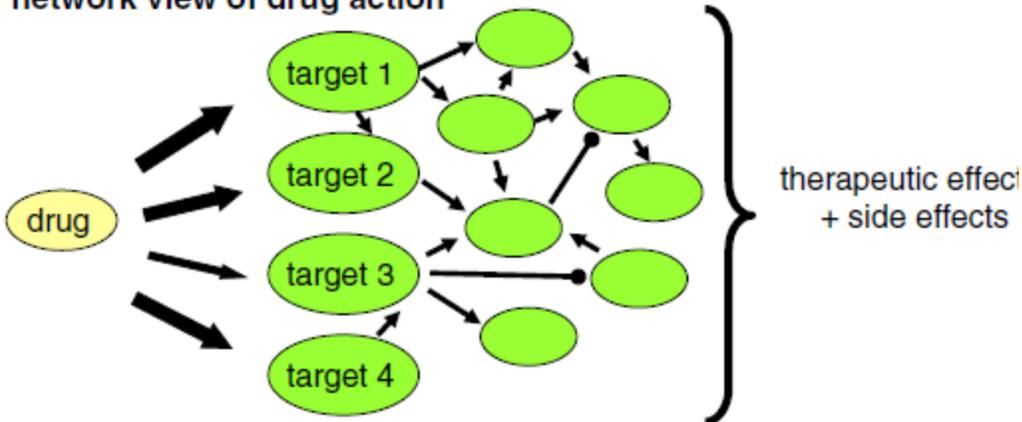
Human regulatory network mapping has not yet been developed completely making it the most unfinished network. Databases like JASPAR and the Universal Protein Binding Microarray Resource for Oligonucleotide Binding Evaluation (UniPROBE) have started accumulating data from experimental approaches like Chromatin immune-precipitation (ChIP) trailed by microarrays (ChIP-chip) and ChIP trailed by sequencing (ChIP-seq). Other databases like B-cell interactome (BCI) and TRANSFAC comprise of DNA-protein and literature-curated interactions. Databases like the CBS prediction database, NetPhorest, Phosphorylation site database (PHOSIDA), PhosphoSite and Phospho.ELM comprise of human post-translational amendments (Harrold et.al, 2013).

RNA Networks

RNA networks are defined as networks that comprise of RNA-DNA or RNA-RNA interactions. The role played by microRNA in different diseases is being understood today which is why microRNA-gene networks are being developed using the anticipated microRNA targets found in databases like miRDB, MiRBase, microRNA, PicTar and TargetScan. There has been a significant rise in the targets that are supported experimentally which are being compiled in the databases like miRecords and TarBase (Harrold et.al, 2013).

Evolution of Network Services in Drug Discovery and Properties of Disease Networks

Developments in network theory have also led to the evolution of network medicine based on the insights on biological network properties. These studies show that networks functioning in social, technological or biological systems are featured by a set of principles and are usually not randomized. It is important to relate diseases with such network principles which help in addressing the basic gene properties associated with diseases.

classic view of drug action**network view of drug action**

Drug Action Network View (Csermely et.al, 2013)

It is believed that 10% of the human genes are associated with some known disease (Leung et.al, 2012). Thus, the main question is if diseased genes have quantifiable and unique features that differentiate them from any other genes. This question can also be put up in another way based on a network view-point. It can be enquired if the placement of diseased genes is random on the interactome or there are identifiable correlations existing between their network topology and location. The need for an answer has resulted in various hypotheses that associate human diseases with an interactome. The rest of the article will focus on the applications and validity of the popular hypotheses.

Location of Disease Genes within Networks

The most surprising feature of biological networks is the evolution of some highly-linked nodes that are referred to as hubs. This suggests that proteins which are signified by these hubs should play a unique biological role. Proof from the various model organisms show that the hub proteins seem to be encoded by the mandatory genes. Also, the genes that encode hubs are quite old and have a slower evolution power when compared to genes that cannot encode the non-hub proteins

(Li et.al, 2012). Deleting the genes that encode hubs generally result in voluminous phenotypic results. However, studies show that a missing hub affects large number of proteins against a missing non-hub protein.

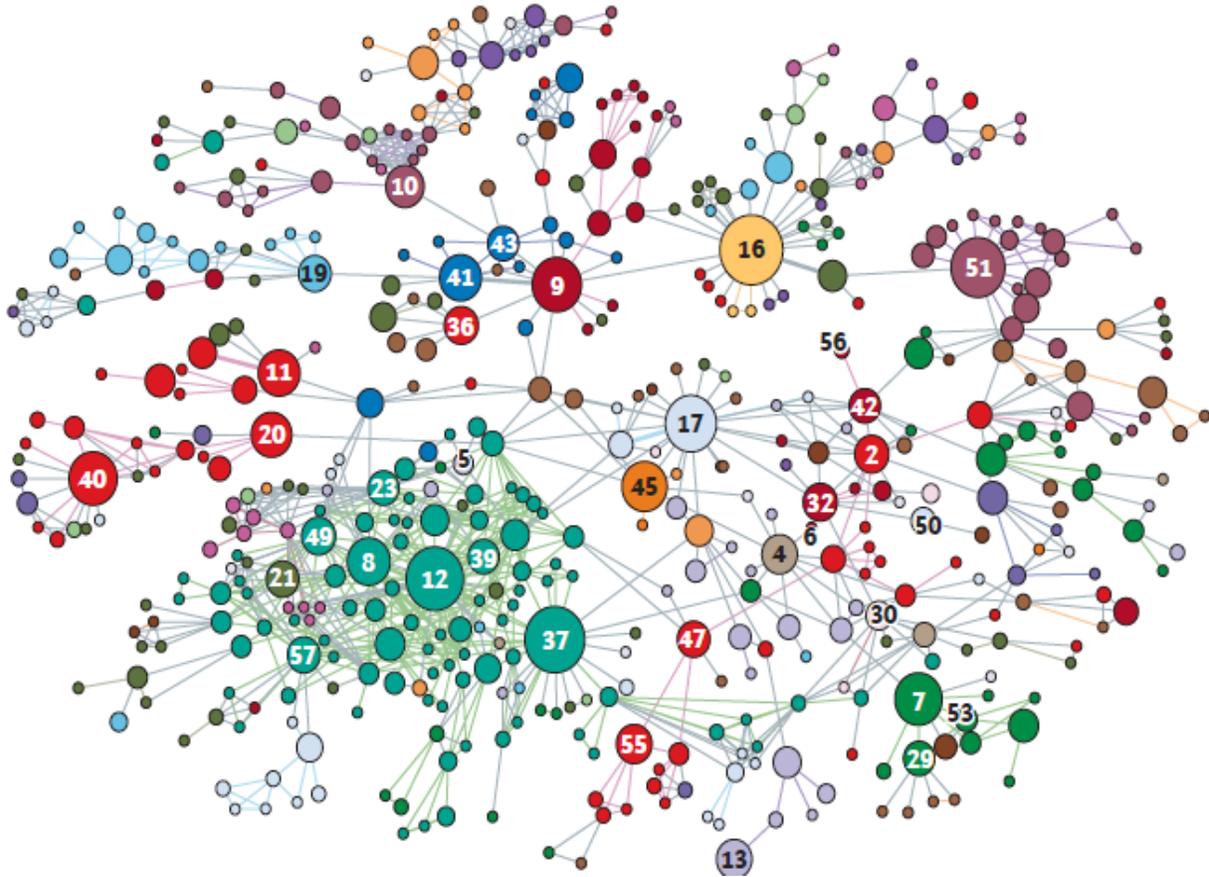
It is important to note that every essential gene in humans is not a disease gene. Genetic mutation which is important in the early development of the foetus fails to spread in the population. Any functional alteration in these genes results in abortion in the first trimester referred to as embryonic lethality. On the other hand, it has been seen that humans are capable of tolerating mutations that cause diseases for a longer period of time even beyond their reproductive age. Thus, it can be proved that disease genes are not necessarily essential genes (Leung et.al, 2012). Now the main question is the association between genes, hubs and essential genes with respect to human diseases. Essential genes which are not linked to any disease exhibit a tendency to be linked with hubs and are found in various tissues located mainly at the interactome's functional core. Nevertheless, non-essential disease genes hardly encode hubs and are found to be specific to tissues and are located at the interactome's functional periphery. Thus, it can be summarized by saying that essential genes in humans encode the hubs.

Network-based Identification of Disease Biomarkers

Network-based identification approaches had been developed in the past few years assisting the analysis of genes that are linked to a specific disease. The methods used for predicting the disease-related genes with the help of networks for making data representations have also been summarized.

There are various network-based approaches that outdo the sequence-based approaches for the identification of disease-related and new genes. The methods that are based on non-localized information on network topology seem to perform much better than the methods that depend on localized network features. It is quite a general notion that greater information results in better predictions (Davidov et.al, 2003). Nevertheless, with increase in the number of datasets, circularity and biases are introduced that result in an overestimated performance. It is a difficult task to differentiate between the contribution and performance of the datasets and predict the methods used. Every dataset requires a distinct approach for optimal analysis. Thus, it was suggested that every data source should be analysed separately and the ranking lists be combined with the help of the rank aggregation algorithms. This approach helps in tracking of the source of

relevant data. GO-term explanations associate functional information to an analysis. Including interactome edge-based disease unrests might enhance the performance of these approaches in the times to come (Harrold et.al, 2013).



Human Disease Network (Barabási & Gulbahce, 2011)

Tools that are designed for network analysis help in selecting the main network positions because options for drug target are associated with a chief dilemma. Network position is of great significance as it influences a diseased body. Also, too much importance must not be associated with a specific network position as its attack might result in toxicity. To find a good solution to this dilemma demands knowledge regarding the dynamics and structure of complicated networks.

Local Topology: Hubs, Motifs and Graphlets

A hub is defined as a minority of the nodes within a set of different networks indicating a node which has a great number of neighbours. These networks exhibit a scale-free degree distribution

which provides an unimportant probability of the hub occurrence. Selective attacks on hubs deteriorate the transfer of information in majority of the real world networks. This has made hubs highly attractive to the drug targets (Hohman et.al, 2009). Nevertheless, few hubs are identified as essential proteins with their attacks resulting in enhanced toxicity. This has narrowed the usage of most of the hubs in the form of drug targets to antibiotics, anticancer treatments and to anti-infectious drugs. Drugs that are FDA approved have targets having greater connectivity with the peripheral nodes and limited connectivity with the hubs. Proteins related to cancer have large number of interaction partners when compared to non-cancer proteins. Thus, the most important strategy of anti-cancer treatments is targeting the cancer-based hubs. Gene Ontology terms and neighbour algorithms have been used to identify the hubs apart from using direct count of interactome. Amino acids serve as hubs for networks of protein structures playing a significant role in transmission of intra-protein data providing good target points to carry out drug interactions (Hopkins, 2008).

There are two contradictory effects that help in summarizing the evolving image of hubs in the form of drug targets. Hubs are well-connected which means that an attack will create a cascading impact compromising the key segment's function within the network. Nodes on the other hand having restricted connections are situated at the network 'ends' with their modulation having restricted effects.

Applying Network-based Knowledge of Disease

A rational approach to drug design requires good understanding of a cellular malfunction triggered by a disease. Such malfunction is restricted to the module of the disease indicating reduced search on therapeutic agents and more on agents that trigger identifiable changes in the module's activity. Network pharmacology also suggests that drugs that had their efficiency predicted by particular target-binding experiments might not create similar impact in vivo. This means that a drug may have multiple binding partners determining its efficiency by multiple interactions resulting in undesired side-effects. Network-based methods exhibit modern trends of drug discovery but the most important aspect of drug developing strategies is network pharmacology as development of drugs are largely affected by the impacts of these intricate networks.

The field of human and bacterial metabolism best illustrates the promises made by the network-based approaches for drug discovery. Metabolic maps are highly accurate and are capable of predicting the flux changes triggered by drug-altered enzymatic activities in bacteria with the help of flux-based and flux balance analysis approaches. Thus, it is possible to explore the metabolic effect of a hypothetical enzyme-blocking drug *in silico*. This makes it possible to test and identify the advanced antibacterial agents and complicated system-based responses that are produced (Iorio et.al, 2010).

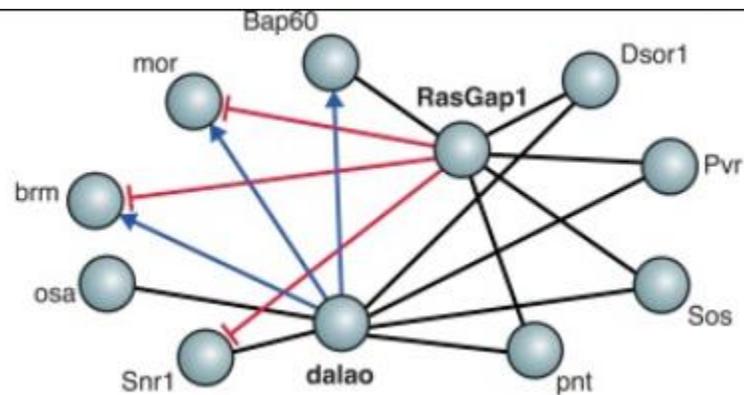
Metabolic fluxes have a coupled nature which enhances the chances of saving a metabolic function that is lost by inhibiting the additional enzymes. This will help in re-routing the metabolic activity in order to reimburse the actual function loss which is an interesting alternative solution to gene therapy.

Single-target drugs are capable of correcting few of the dysfunctional features of a disease module but sometimes they also change the adjoining molecule's activity resulting in side-effects. This is a network-based approach towards drug action which shows that it is a difficult task to reverse a disease phenotype using an intervention which would affect a solo node within the network. Thus, much attention is being paid to therapies that focus on multiple targets and might reverse the disease phenotype. Combinatorial treatments used for depression, cancer and AIDS demonstrate the efficiency of this approach. It results in a question if one can systematically recognize various drug targets having a significant effect on the disease phenotypes (Harrold et.al, 2013). It is a problem of archetypical network type resulting in the development of approaches for identifying drug combinations that start either from a bipartite or metabolic network which associates the compounds with their specific drug-response phenotypes. These research works have resulted in safe multi-target combinations to resolve inflammatory conditions and optimize anticancer drug combinations.

Drug target networks are much more important and associate experimental or approved drugs to specific protein targets assist researchers in visualizing and organizing the existing knowledge pool on interplay between drugs and diseases. An all-inclusive analysis showed that most of the drugs are soothing which means that they do not harm the disease-linked protein but the ones adjoining them.

The use of protein-protein interaction networks in drug design

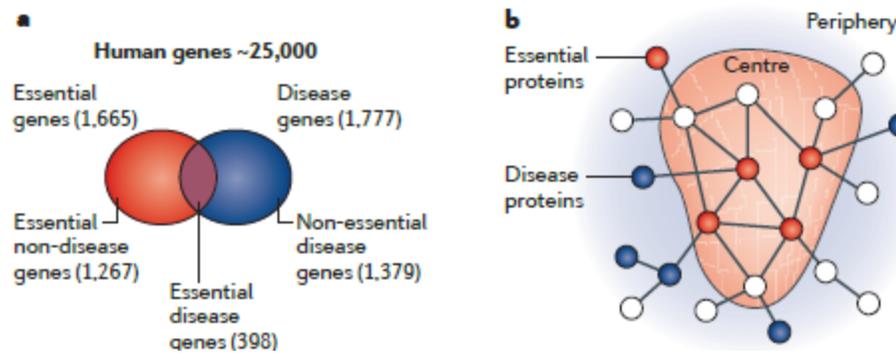
Most of the drug actions focus on proteins which makes it important to describe their dynamics and structure for determining the drug-binding sites and for predicting the effects of the drugs at a sub-molecular level. This section will focus on ways in which a protein structure network helps in characterizing the disease related proteins and in understanding the drug targeting and action mechanisms (Davidov et.al, 2003).



Protein-Protein interaction (Barabási & Gulbahce, 2011)

Representations of a protein structure network are also referred to as protein meta-structures, residue interaction networks and amino acid networks where the amino acid side-chains make up the nodes. These nodes are occasionally referred to as protein atoms but the representation of the side-chains is vindicated by the rigorous movements of these side-chain atoms. The actual distance between the side-chains of the amino acids defines the network edges. The distance is generally measured between the various $C\alpha$ or $C\beta$ atoms but sometimes the mass centre of these side-chains is determined.

The most auspicious network for predicting the drug actions or for identifying the drug-target candidates is protein-protein interaction networks (PPI-networks).



Vital genes in interactome (Barabási & Gulbahce, 2011)

The PPI-networks are usually referred to as interactomes when they comprise of genome data. The nodes that make up these networks are referred to as proteins with network edges being their physical and direct interactions. These networks are referred to as probability-type networks with their edge weights reflecting the chances of actual interactions. Confidence scores represent the edge weights of the interactome. Interaction affinity, co-expression levels, protein abundance and co-localization in the subcellular compartments make up interaction probability (Davidov et.al, 2003).

Detecting the large number of interactions that take place in a human interactome is a significant and on-going process in network-based drug designing efforts. Nevertheless, the complexity of interactome stretches beyond the inventory of binding partners and contacts including the protein domain-dependent, cellular environment-induced like calcium dependent, post-translational modification-induced like phosphorylation-dependent and expression level-induced variations.

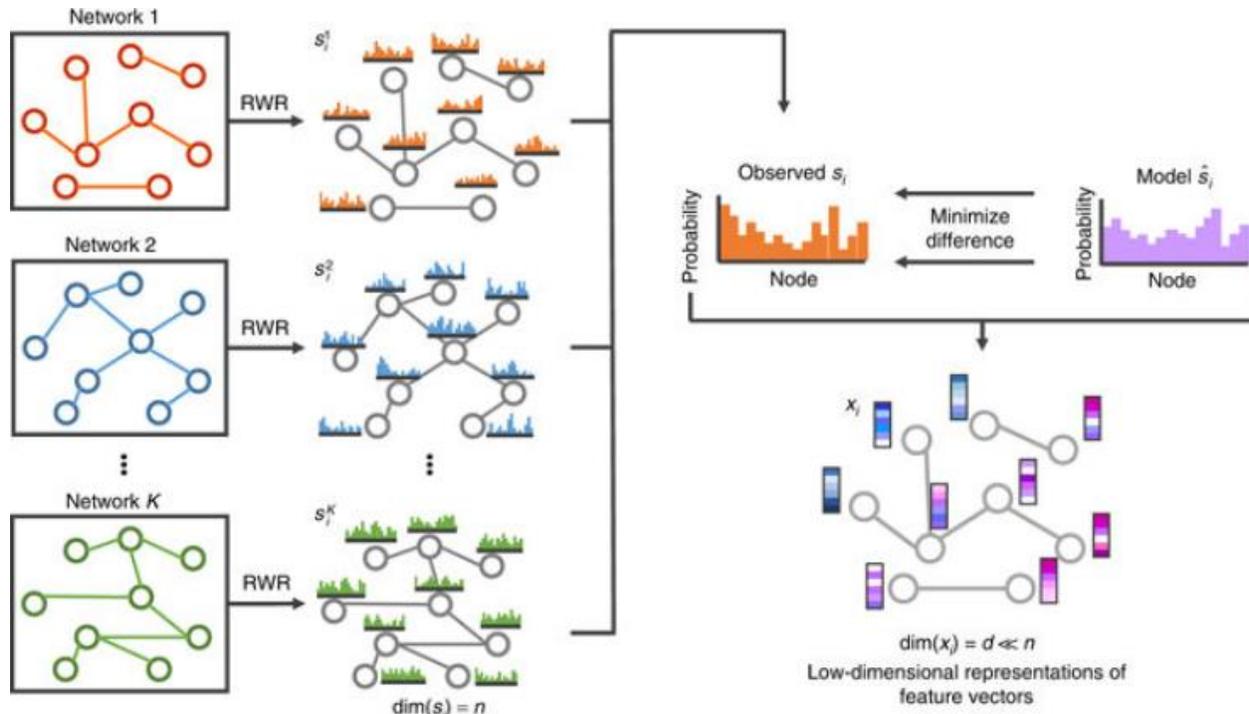
There are a huge number of neighbours associated with drug targets that are found mainly from the middle-degree nodes and not from the hubs. Cancer drug targets are quite an exception having large number of hub structures. Proteins that are targeted by drugs have a low clustering coefficient when compared with other proteins. Drug targets usually have a central position within the human interactome acting as a bridge between multiple modules. Nodes that have a transitional number of neighbours exhibit a wide contact structure. Undesired side-effects can be avoided by targeting such non-hub nodes. These drug target proteins have a controlled impact on the interactome compared to the withdrawn drugs that have a big network impact (Li et.al, 2012).

Interactome topology properties have been used for scoring and predicting new drug target candidates with the help of machine learning methods. Other targets can be predicted based on the similarities between network neighbourhood and test-set of drug targets. This features exhibits the restrictions of machine learning approaches as the existing drug targets are identical to one another. Thus, machine learning methods might not be of use in extending the existing drug target inventory to new hits.

Variation of particular PPI-networks generates greater specificity for restoring the disease pathology to its normal position. Methods used for designing an 'edgetic drug' will be described later. As a result, it is easy to develop protein-protein interaction inhibitors when compared to agents for enhancing binding stability or affinity. The alterations in a yeast interactome were investigated by adding 80 different small molecules. This approach was capable of identifying the new protein-protein interactions disrupted by adding drugs like immunosuppressant named as FK506.

Prominent Methodologies for Network Analysis

Modeling methods have the potential to control and foresee the behaviour of system within new conditions with the help of kinetic parameters, network structures, and experimental data. Network node elimination and drug modulation is involved in identification of drug target. Pharmacological responses is achieved by edges or nodes combination change. Metrics are required that coordinate these subtle elements at the same time to recognize perturbation of optimal network with a high probability of inspiring the coveted restorative reaction and restricting adverse impacts (Meuser et.al, 2016). Graph theory gives a methods for investigation that positions the significance of networked nodes. The node importance is very reliant on how the entire network is organized in respect to the considered results. A networked node may appear to be imperative in a specific region, however have little effect on general result inferable from redundancies of the system. Thusly, varied kinds of significance shall be considered while classifying importance of edges and nodes.



Network integration approach (Iorio et.al, 2010)

The most finest measure of significance, degree centrality, calculates the net aggregate of all nodal joints. This is an enticing metric since it is direct as far as calculation and ease to use is considered. Nodes with multiple hub connection has special significance. Degree centrality ignores the impact of the wider structure of network. From network perspective point of view, more extensive steps for edge or nodal significance are accessible to showcase the importance in signal transduction (Taylor and Derudder, 2015). Genomic and biochemical networks are impacted by normal determination, proposing that transduction of signals through such systems ought to be generally productive.

A transmitting signal will probably select the shortest route through the network. When two such metrics that consider the improved probability of signals taking the shortest route through the network are betweenness centrality and closeness centrality. Closeness centrality, just as name suggests, is a measure of nodes closeness to other. Betweenness centrality positions the quantity of most shortest ways that go through every nodes. The more shortest path that any nodal point is engaged with is thusly utilized as a pointer of significance (Dawson et.al, 2014).

Betweenness centrality is metric destined to recognize vital nodes for arbitrary network. Notwithstanding, evolutionary biological procedures create complex frameworks with semi-self-

sufficient measured units. In this way, measurements that fuse the significance of degree centrality in local mode, closeness centrality in regional way, and global significance of betweenness centrality may give enhanced measures of significance (Taylor and Derudder, 2015). The bridging metric of centrality tries to distinguish network nodes works a bridging component between global network and modular sub network. Information flow is better and loss of structural integrity does not take place where nodes have higher bridging centrality.

Research operations is credited for producing various network optimizing techniques. These variants try to minimize or maximize various efficiency measures by altering the network aspects in a controlled manner. One of the example of this optimization is selection of shortest route between two specified network nodes while following the constraints available in network connectivity.

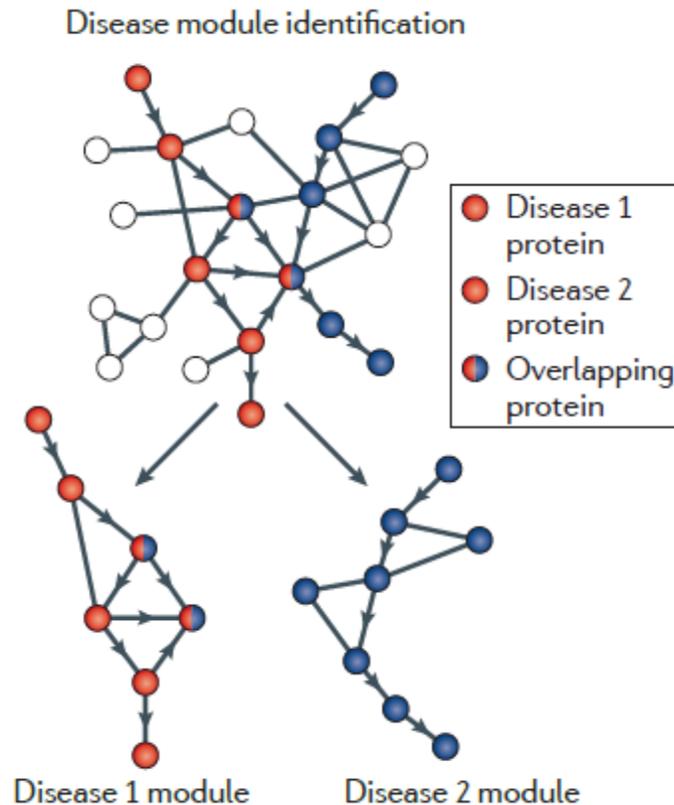
Usage of optimization theory to distinguish between redundancy and connectivity in network can be cited as another application-centered example. What's more, constraints can be infused into the optimized cost function. This produces soft constraint from a hard one (Taylor and Derudder, 2015).

Even though some amount of side-effects may be acceptable, cost functions can be altered. For instance, in type-2-diabetes, objective function reflects adequacy biomarkers, for example, those related with cardiac problems. Imperatives could then be added to stand for the interactomic, genomic, and other networks; indicate the quantity of focuses to distinguish; and incorporate any hard requirements that ought not to be disregarded. The primary test is the huge degrees of opportunity inside the network. But in some cases, techniques of optimization for constraints can really deliver better outcomes with more constraints as every limitation can confine the space and thus the quantity of possible outcomes.

Validation, Identification and Prioritization of drug test

Prioritization of drug target in network and recognizable proof are basically an approach of top-down mode, where impacts of putative-targets are demonstrated to help in the recognition of novel targets. These drug targets are non-clear from a conventional readings expecting to locate the obvious reason for a given illness. Nodal based network drug target forecast may feature non-clear hits, and edge-focusing may make these more focused (Dawson et.al, 2014). It enables us to see the network wide target area and, along with other methods of network, help in

repositioning the drug target. System level integration of drug effects is needed for multiple target design. Non-clear drug targets are distinguished by new idea of allo-arrange drugs, which particularly impact the significant targets causing less side effects as compared with direct targeting technique.



(Barabási & Gulbahce, 2011)

The main necessities needed for discovery of new drugs is the accessibility of protein structures along with its reactions details; the areas where they are found and the cross-talk route path; and how proteins bind with each other in the cell. Displaying interactions of proteins in model format helps to ascertain and foresee the way interaction may happen and which allows the development of cell based network and complete path. The whole system gets affected by protein targeting and these can be easily predicted by PRISM server (Csermely et.al, 2013). It foresees the protein couples and its interaction along with their structural interface. Further, as demonstrated collaborations give additional data on how the proteins communicate with each other, they permit expectation of the outcome that connects through a similar site.

Thus, it can be ascertained that if a specific protein is focused on, this may terminate the binding at site which is shared by each, driving the framework in a specific way, which can be predicted by multiple ways. Such expectations might prove to be powerful for multi-molecule complex, which are inclined to dangerous side reactions. On the off chance that the drug focuses on certain PPIs, the basic network may recommend the other PPI which share comparable motifs may likewise be influenced by the effect (Wu et.al, 2013).

The side-effects associated with multi-target drugs can be explained using networks. Torcetrapib is a popular inhibitor for Cholesteryl Ester Transfer Protein (CETP) whose side-effects were also studied. It was under clinical trials and proposed for treating cardiovascular diseases. All the ligand-binding sites were compared by authors in all the existing protein structures and an off-target binding network was also designed. The study was associated with the biological pathways and the reasons for the impact of torcetrapib were studied with respect to blood pressure.

Dissemination of the drug impacts within the network might be observed for allosteric and orthosteric drugs. Orthosteric drugs function by blocking the active site of the protein impairing and abolishing its function. The modulating impact of the allosteric drugs is disseminated via the protein and across all the pathways via protein-protein interactions (Csermely et.al, 2013).

The effects seem to be the strongest in case of the proteins that share the same complex. The major drawback of a modelled structural network is that it provides only a static view of the proteins and the cells. The cellular network is found to be quite dynamic as proteins dissociate and associate. It is quite a challenging aspect of the model as the interaction affinities are measured typically in solution and do not reflect its in-vivo environment. Allosteric events at varying sites are known to affect the affinities of a binding site like post-translational changes or binding of the other partners (Leung et.al, 2012). They also fail to register the fluctuations and co-factors within the environment. Another challenging issue is protein dynamics with fluctuations in the protein structure and changes in the distribution of conformational bands affecting the conformation of the binding sites along with drug binding. Thus, considering the protein dynamics across the network and pathways is quite a challenging task. The main problem is that it necessitates both computational requirements and experimental data in details. Network scale modelling however has not been capable of addressing these issues till date. Nevertheless, molecular dynamic simulations and Nuclear Magnetic Resonance (NMR) might be of help on a

local scale for particular protein types. In spite of these drawbacks, multi and single drug pharmacology benefit largely from a modelled structural proteome. Hypotheses and leads are provided by predictions that can be justified later by experiments.

Conclusions

Network analysis and description assists in overcoming the ‘one target/one cause and one effect’ paradigm of drug development. It is considered like a magic bullet and is successful sometimes. It is a beneficial step to remove a single hit while designing the drugs based on a ‘central hit strategy’ as they target mainly the network nodes for eliminating malignant cells or pathogens. Nevertheless, unforeseen toxicity or pathogen fighting of anti-cancer drugs may change the outcomes.

It is important to achieve a well-organized rigid network reconfiguration while developing the above stated drug type. It is also essential to reset the network dynamics to normal from a disease affected condition. The old method of discovering a rational drug based on a central and single target under such situations usually fails (Taylor and Derudder, 2015). The scarcity of anti-neurodegenerative drugs that modify drugs calls for the need of new approaches in designing such drugs. Researchers stated that the best idea to discover a novel drug is to begin with the old one.

Network analysis plays a significant role in understanding the huge volume of system-level data that has been accumulated since ages. Nevertheless, network analysis is not enough and must be complemented with insights about existing knowledge pool. One must not overlook the creativity required for predicting the unpredictable within networks. The evolution in the methods associated with network dynamics assist in identifying the main factors of cellular community that are actually concealed masterminds in bringing about cellular changes in disease and health.

Implementation of computational approaches to the rising volume of biomedical data creates new challenges and problems. Advanced network-based models need to deal with huge volumes of data. Biological data has an inherent noisy nature which exhibits the need for advanced algorithms to seek non-evident associations from various data sources. Thus, upcoming research

studies must stress on developing noise-free and large-scale algorithms capable of replacing the one that have been designed previously for dealing with data that is homogenous (Pujol et.al, 2010).

It can be summarized by saying that integrating the computational network-based approaches will minimize the expenses and time of preclinical stages and result in accurate medicines translating into minimized attrition rates of drugs.

Challenges and Opportunities

Apart from achieving adequate drug exposure at the action site, it is important to have good understanding about the biological networks where the drug targets are found. It is important for completely exploiting the network-based approaches for discovery of drugs. An evolutionary procedure results in cellular signalling networks which favour the robustness and redundancy as a response to the environmental issues. These networks are restricted by the inclusion of critical nodes in the data quality and networks. Another issue is that majority of the network models comprise of well-explained edges and significant temporal changes within the nodal connectivity can be overlooked. Multi scale modelling and vertical integration with respect to multi-platform data seem like obstacles in system pharmacology (Csermely et.al, 2013). Thus, improvements are required to select targets using the network-based approaches.

Lack of effectiveness and greater toxicity are key determining factors of the failure of the later stages of drug development. These failures are mainly the result of poor understanding about the biological system's interconnectedness at an organization's multiple scale. It is quite possible to generate precise measurements of the time and intensity of the physiological responses at a macroscopic level but most of the data is largely semi-quantitative, qualitative and static. Analysing the curated data is resulting in advanced insights about the drug targets and biological system's mechanisms. Translational and multi scale systems pharmacology models might be used for further qualifying the targets providing a quantitative basis for designing new drug combinations, attaining individual pharmacotherapy and projecting the inter-individual variability. New innovations are required in computational and experimental systems for realizing the ideal of forecasting the adverse and therapeutic effects of novel chemical bodies from the primary principles.

References

- Adams, C. P., & Brantner, V. V. (2006). Estimating the cost of new drug development: is it really \$802 million?. *Health affairs*, 25(2), 420-428.
- Arrell, D. K., & Terzic, A. (2010). Network systems biology for drug discovery. *Clinical Pharmacology & Therapeutics*, 88(1), 120-125.
- Barabási, A. L., Gulbahce, N., & Loscalzo, J. (2011). Network medicine: a network-based approach to human disease. *Nature reviews genetics*, 12(1), 56.
- Csermely, P., Korcsmáros, T., Kiss, H. J., London, G., & Nussinov, R. (2013). Structure and dynamics of molecular networks: a novel paradigm of drug discovery: a comprehensive review. *Pharmacology & therapeutics*, 138(3), 333-408.
- Davidov, E., Holland, J., Marple, E., & Naylor, S. (2003). Advancing drug discovery through systems biology. *Drug discovery today*, 8(4), 175-183.
- Dawson, S., Gašević, D., Siemens, G., & Joksimovic, S. (2014, March). Current state and future trends: A citation network analysis of the learning analytics field. In *Proceedings of the fourth international conference on learning analytics and knowledge* (pp. 231-240). ACM.
- Harrold, J. M., Ramanathan, M., & Mager, D. E. (2013). Network-based approaches in drug discovery and early development. *Clinical Pharmacology & Therapeutics*, 94(6), 651-658.
- Hohman, M., Gregory, K., Chibale, K., Smith, P. J., Ekins, S., & Bunin, B. (2009). Novel web-based tools combining chemistry informatics, biology and social networks for drug discovery. *Drug discovery today*, 14(5-6), 261-270.

Hopkins, A. L. (2008). Network pharmacology: the next paradigm in drug discovery. *Nature chemical biology*, 4(11), 682.

Iorio, F., Bosotti, R., Scacheri, E., Belcastro, V., Mithbaekar, P., Ferriero, R., ... & di Bernardo, D. (2010). Discovery of drug mode of action and drug repositioning from transcriptional responses. *Proceedings of the National Academy of Sciences*, 107(33), 14621-14626.

Kitano, H. (2002). Systems biology: a brief overview. *Science*, 295(5560), 1662-1664.

Li, J., Lu, C., Jiang, M., Niu, X., Guo, H., Li, L., ... & Lu, A. (2012). Traditional chinese medicine-based network pharmacology could lead to new multicomponent drug discovery. *Evidence-Based Complementary and Alternative Medicine*, 2012.

Leung, E. L., Cao, Z. W., Jiang, Z. H., Zhou, H., & Liu, L. (2012). Network-based drug discovery by integrating systems biology and computational technologies. *Briefings in bioinformatics*, 14(4), 491-505.

Meuser, J. D., Gardner, W. L., Dinh, J. E., Hu, J., Liden, R. C., & Lord, R. G. (2016). A network analysis of leadership theory: The infancy of integration. *Journal of Management*, 42(5), 1374-1403.

Pujol, A., Mosca, R., Farrés, J., & Aloy, P. (2010). Unveiling the role of network and systems biology in drug discovery. *Trends in pharmacological sciences*, 31(3), 115-123.

Sirota, M., Dudley, J. T., Kim, J., Chiang, A. P., Morgan, A. A., Sweet-Cordero, A., ... & Butte, A. J. (2011). Discovery and preclinical validation of drug indications using compendia of public gene expression data. *Science translational medicine*, 3(96), 96ra77-96ra77.

Taylor, P. J., & Derudder, B. (2015). *World city network: a global urban analysis*. Routledge.

Wu, Z., Wang, Y., & Chen, L. (2013). Network-based drug repositioning. *Molecular BioSystems*, 9(6), 1268-1281.