

Biological Network Analysis as potential Drug Targets in Systems Pharmacology

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We are constantly, continuously surrounded by complex systems. Networks are integral part of our life, and are the essence of telecommunication networks, biological networks cognitive and even social networks. Network science, is the field which studies complex networks, and integrates fields from mathematics, physics, computer science and sociology. Network medicine is an application of network science, it offers a “platform to explore systematically not only the molecular complexity of a particular disease, leading to the identification of disease modules and pathways, but also the molecular relationships among apparently distinct (patho)phenotypes”¹. Networks play a particularly important role in drug development, which is the focus of this essay.

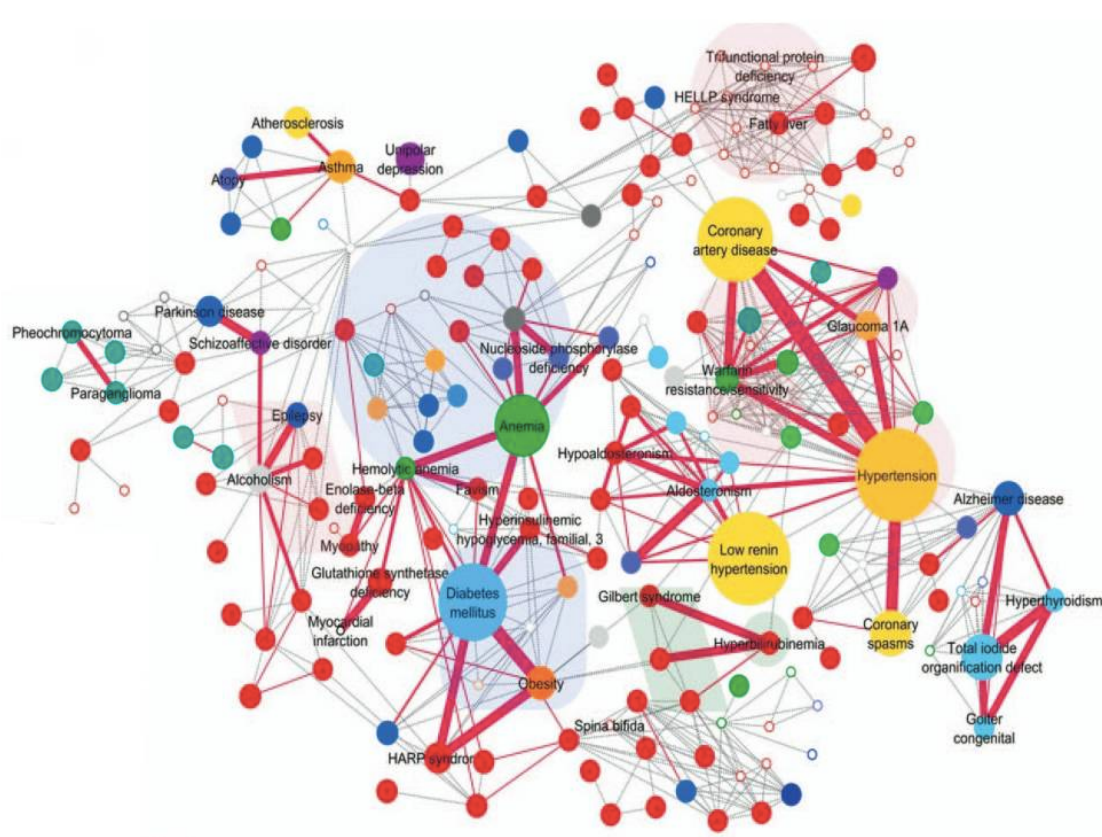
Network description and analysis not only give a systems- level understanding of drug action and disease complexity, but can also help to improve the efficiency of drug design. The aim in drug development, is to find the most therapeutically effective drugs, with the minimal toxicity and adverse effects on the human body. The network- based view of drug action suggests that most diseases cannot be cured through the use of a single “magic- drug”, that affects a single characteristic or abnormality. *Figure 1* illustrates how human diseases are interrelated and interconnected- a pathological abnormality cannot be separated from another; in this example (Metabolic Disease Network), linking two diseases if they are both associated with enzymes and if these enzymes catalyze reactions that share a metabolite.

In this work, a research was performed, aiming to find potential drugs that target disease-network. Networks- based approaches is a rather recent trend, and is predicted to become an essential component of drug development strategies. These drugs aim to improve patients’

¹ Barabási AL, Gulbahce N, Loscalzo J; 2001

quality of life, with the highest possible therapeutic benefit and minimal adverse effects and toxic implications on health

Figure 1: Metabolic Disease Network



Diabetes, a multigenic disease tightly related to central obesity, atherosclerosis and cardiovascular disease, a connection revealed by network representations, can be an example showing the application of network influence strategy, where therapeutic interventions need to push the cell back from the attractor the the disease state to that of the healthy state (Structure and dynamics of molecular networks: A novel paradigm of drug discovery-

A comprehensive review²). Combination of interactome and diabetes- related gene expression data identified the possible molecular basis of several endothelial, cardiovascular and kidney-related complications of diabetes, and identified links to other diseases as well such as

² Peter Csermely, Tamas Korcsmaros, Huba J.M. Kiss, Gabor London, Ruth Nussinov; 2013

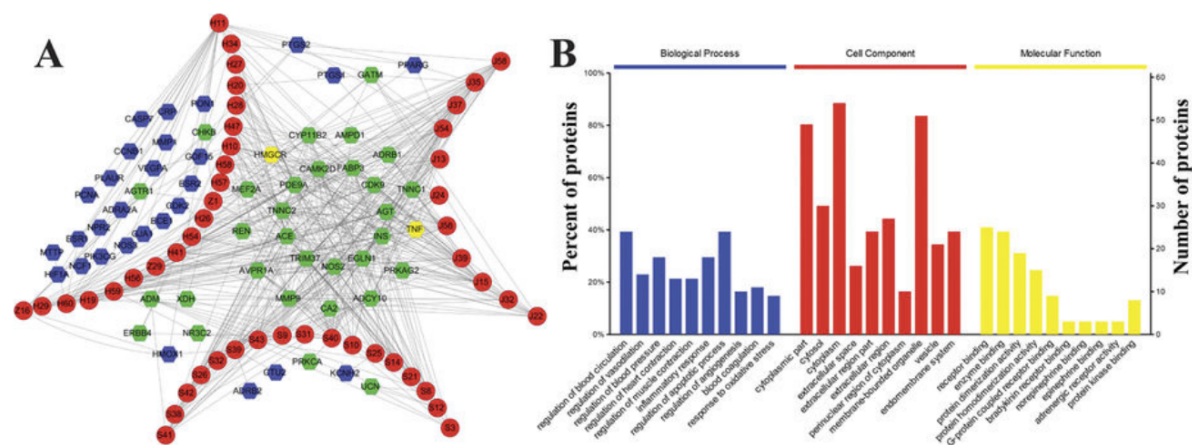
inflammation abnormalities and obesity; according to T2D- db database that provide information for the construction of various diabetes- related networks. Alternatively, studies suggest network interactions between protein- protein bridging insulin signaling and the peroxisome proliferator-activated receptor (PPAR)- related nuclear hormone receptor family. Potentially new metabolic biomarkers were identified by reconstruction changes of the human metabolic network of skeletal muscle in diabetic patients (type II), allowing the construction of diabetes- related transcription factor regulatory network. Such studies will highlight key enzymes of metabolic network, where a drug- induced activity and/ or regulation change may significantly contribute to the rewriting of the metabolic network to its normal state (according to paper). Additionally, reconstruction of the subnetworks of human interactome related to insulin signaling is an ongoing work which will “uncover many important novel targets of therapeutic interventions in the future”. Network influence strategy that rewires the cellular networks from the diseased state to a healthy state can be used as a tool to help drug design. These drugs will target pathway sites specific to disease cells, while avoiding network segments that are important in healthy cells.

Another study that explores drug target identification using network analysis, studies the active components in Sini decoction as an example³. According to the research, there are two fundamentally different approaches to identify molecular targets of bioactive molecules: direct and indirect. Direct approach utilizes affinity chromatography often with compound-immobilized beads. It is only suitable though to identify targets of one drug once and cannot be used to identify many compounds simultaneously. Indirect approach, such as system biology approaches, including proteomics, transcriptomics and metabolomics. In this paper, researchers examined SND (herbal Chinese medicine, used against heart failure) as an example to test the potential of network analysis in target identification. The results aim to investigate the mechanism of action of SND and promote the development of Chinese Drug modernization. *Figure 2* illustrates the Component- Target network (a)- it represents the active components in SND, the gene names of targets of the herbs found by text mining and the targets found by dock,

³ Si Chen, Hailong Jiang, Yan Cao, Yun Wang, Ziheng Hu, Zhenyu Zhu & Yifeng Chai, 2016

or targets found by both; and the enrichment analysis in biological process, cellular component and molecular functions of 61 identified target proteins (b) (for more information, see paper).

Figure 2

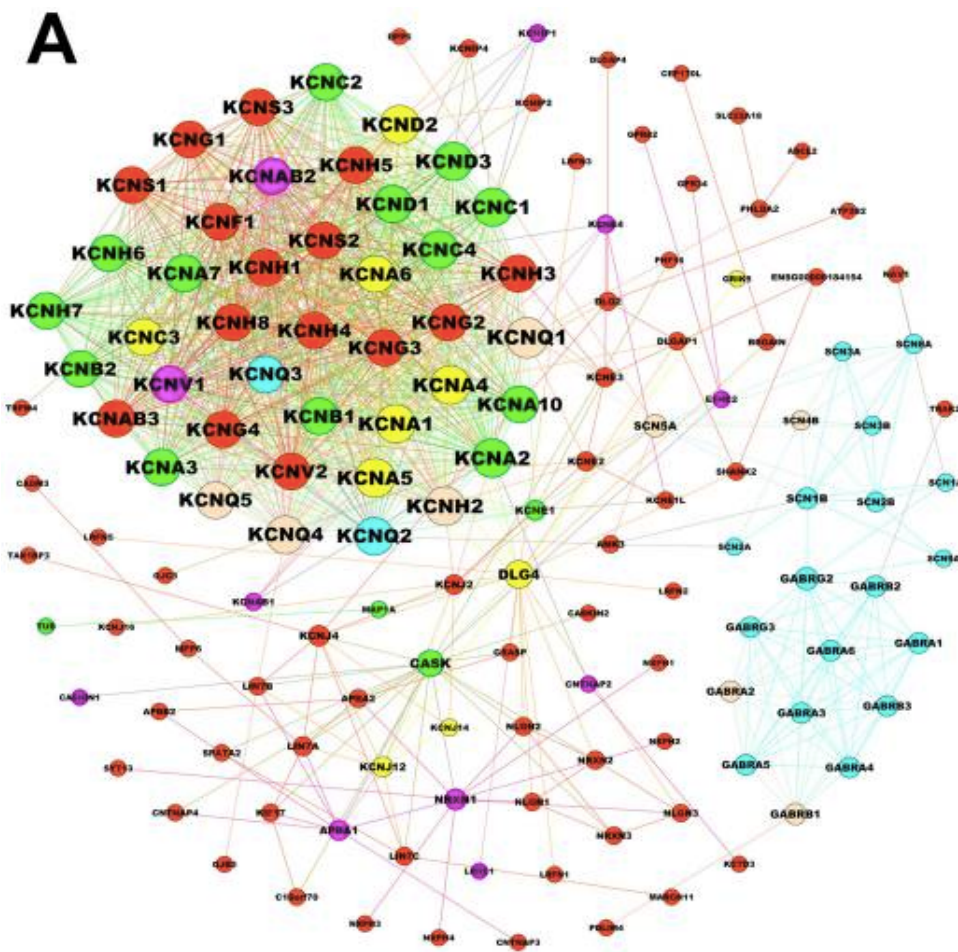


Epilepsy is a complex neurological disorder and a significant health problem. Pathogenesis of epilepsy is still unclear in many patients, and treatment options are not helping in about 30% of patients suffering from the disease, known as refractory epilepsies (RE). In the research: Integrated network analysis reveals potentially novel molecular mechanisms and therapeutic targets of refractory epilepsies⁴, “1876 disease- gene associations of RE were integrated and located those genes to human protein- protein interaction (PPI) network to obtain 42 significant RE- associated disease modules”. The functional analysis of these disease modules showed novel molecular pathological mechanisms of RE; further analysis on the relationships between current drug targets and the RE- related disease genes showed the rational mechanisms of most antiepileptic drugs. A disease module, a “local neighborhood of the interactome whose perturbation is associated with epilepsy”, can be linked to a particular disease presentation. Identifying disease modules can clear molecular mechanisms, discovering new disease genes and related signaling pathways, with the aim to identify targets for drugs. The study discusses the

⁴ Hongwei Chu, Pin Sun, Jiahui Yin, Guangming Liu, Yiwei Wang, Pengyao Zhao, Yizhun Zhu, Xiaohan Yang, Tiezheng Zheng, Xuezhong Zhou, Weilin Jin,⁷ and Changkai Sun

importance of module M155, as it is one of the most important module for drug discovery. The result is illustrated in *Figure 3*; which presents currently known epilepsy drug targets which are not seed genes (*pink*), drug targets not specific for epilepsy which are not seed genes (*green*), currently known drug targets which are also not seed genes (*red*), known epilepsy targets which are seed genes (*blue*), currently known drug targets seed genes (*yellow*), currently known drug targets seed genes (*purple*). The study discusses the requirements that the protein has to fill in order to be considered as a novel target- (1) no known- anti-epilepsy drugs target this protein, (2) the target should exist in the most enriched pathways related to epilepsy.

Figure 3



Finally, this study is another example how network medicine approaches were used to integrate the data from multiple databases to investigate the molecular mechanisms and possible drug targets of RE. Forty two primary disease related gene networks (modules) were constructed and selected based on the interaction information of gene- encoded proteins; these architectures of interaction module indicated the complicated molecular mechanisms of RE and the possible pharmacological targets of RE personalized treatment.

When starting this research and essay writing, I was not aware how much our life is so network-dependent, and specifically how networks plays an integral part of our health and biological system. Finally, it was hard to write such an essay, given that so much research is done at the field. This study truly touched me, as a student in fourth year medical year, where most of my studies focus on pharmacology. The study of drugs, in my opinion, is the climax of our medical studies, as it integrates knowledge from all fields (physiology, biochemistry, pathology etc.), and aims, of course, to heal. My hope is that research on network medicine will continue, in the pharmacological field and related fields, discovering new drug targets and improving current ones, all with the aim of improving patients quality of life and helping us, future doctors, to provide better health care to those in need.

Additional papers used:

- Hongwei Chu, Pin Sun, Jiahui Yin, Guangming Liu, Yiwei Wang, Pengyao Zhao, Yizhun Zhu, Xiaohan Yang, Tiezheng Zheng, Xuezhong Zhou, Weilin Jin,7 and Changkai Sun; “Integrated network analysis reveals potentially novel molecular mechanisms and thepapeutic targets of refractory epilepsies” (2017 Apr 7)
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3140052/>
- Si Chen, Hailong Jiang, Yan Cao, Yun Wang, Ziheng Hu, Zhenyu Zhu & Yifeng Chai; “Drug target identification using network analysis: Taking active components in Sini decoction as an example”. (2016)
 - <https://www.nature.com/articles/srep24245>
- Barabási AL1, Gulbahce N, Loscalzo J; “Network medicine: a network- based approach to human disease” (2011, Jan 12)
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