Methodologies for Analyzing Biological Networks with a Focus on Drug-Drug Interactions, Drug-Disease Associations, and Chemical-Disease Associations

Ariel Eighmey and Dr. Phalguni Ghosh*

Middlesex County College, Edison, NJ, 08818

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***** Majoring in Chemistry and Biology (MCC)
******Research Advisor, Dr. Phalguni Ghosh (Faculty, MCC)

Abstract

The molecules in a biological system interact with each other to form molecular complexes, modules or pathways that carry out various biological functions. High-throughput research techniques have generated enormous amounts of data on many biological networks. The challenge now is to interpret the large volume of data and extract relevant information that could be used to improve healthcare and pharmaceuticals. Online repositories, such as KEGG, Reactome, CTD, Drugbank, and many more host a massive amount of data that can be readily represented as a network and then analyzed.

Cytoscape is a free software platform that allows the investigation and visualization of integrated diverse networks. It is adaptable and expandable with over 300 applications that can be incorporated for numerous research requirements. Using Cytoscape to study biological networks, begins with building a combined network for the topic of interest and mapping the curated network for analysis. Being able to visualize combined and curated data allows the researcher to understand and evaluate targeted information that would otherwise be cluttered in multiple massive networks. In this study, we have looked at drug-drug interaction networks and drug-disease associations networks. These biological networks display the potential cross-reaction between drugs and give a visual representation of the side effects of some common drugs.

Objectives

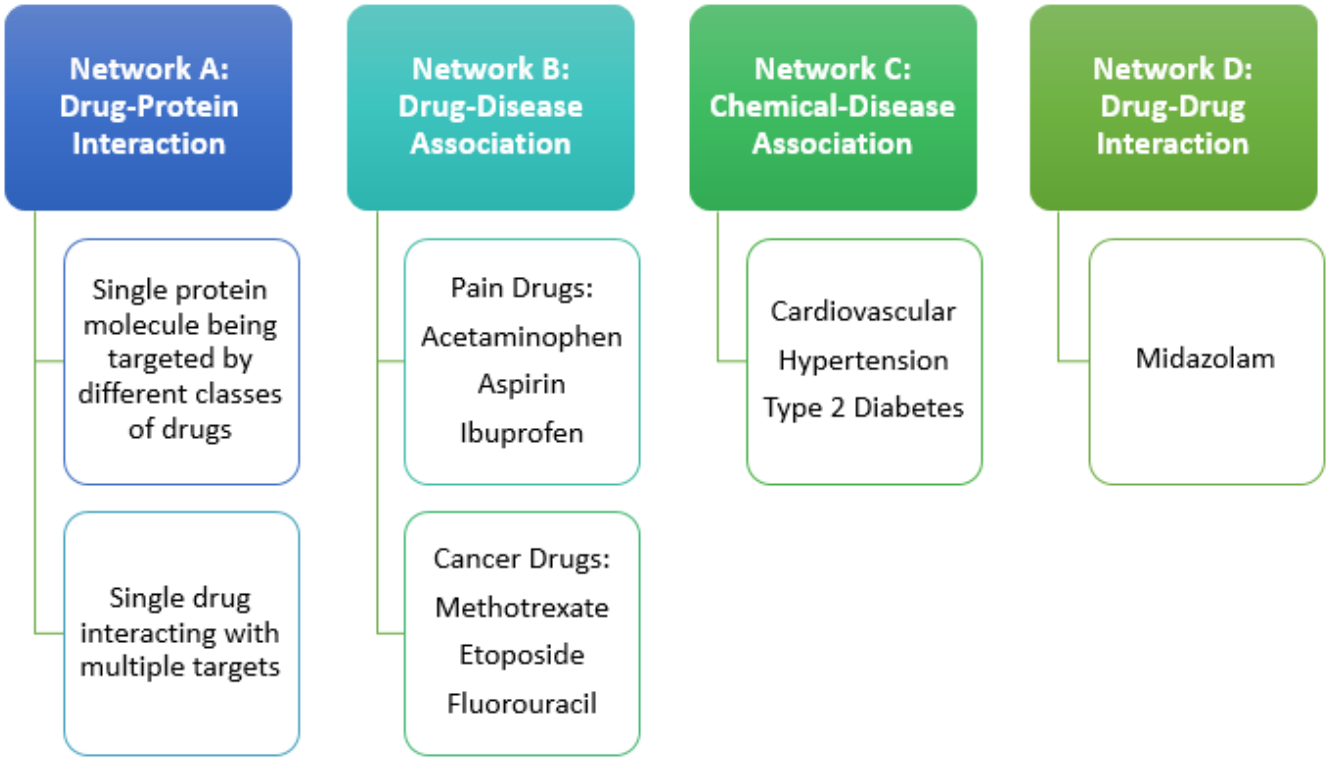
Build and analyze biological networks of:

- **Single protein molecule being targeted by different classes of drugs and single drug interacting with multiple targets.**
- **Chemical-disease associations**

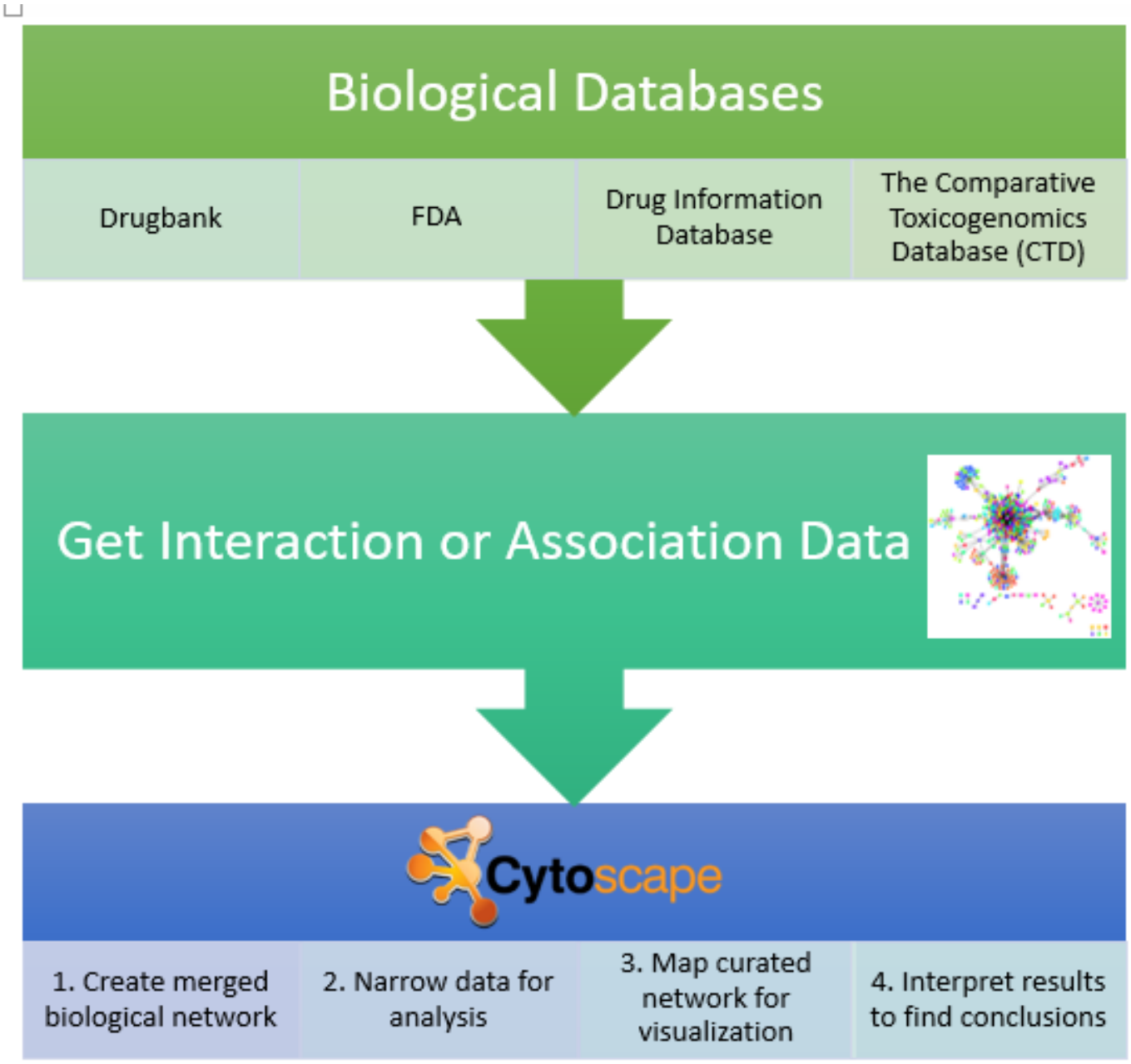
- **Drug-disease associations amongst common drugs for pain and cancer**
- **Drug-drug interaction for anesthesia induction for anxiety drug**

Introduction

Networks can show a variety of data for biological systems such as cell-cell communication, protein interactions, gene interactions, drug interactions, etc. Data networks allow for reduction of complexity, data integration, visualization, and analysis of large biological datasets. This enables big data to be utilized in the development and exploration of biological sciences. Cytoscape is an open platform software that is used in this paper to merge multiple datasets from bioinformatic databases and create curated networks for mapping, analysis, and interpretation. The networks created in this study are listed in the chart below.


Network A: Drug-Protein Interaction
Single protein molecule being targeted by different classes of drugs
Single drug interacting with multiple targets
Network B: Drug-Disease Association
Pain Drugs:
Acetaminophen
Aspirin
Ibuprofen
Cancer Drugs:
Methotrexate
Etoposide
Fluorouracil
Network C: Chemical-Disease Association
Cardiovascular
Hypertension
Type 2 Diabetes
Network D: Drug-Drug Interaction
Midazolam

Methods

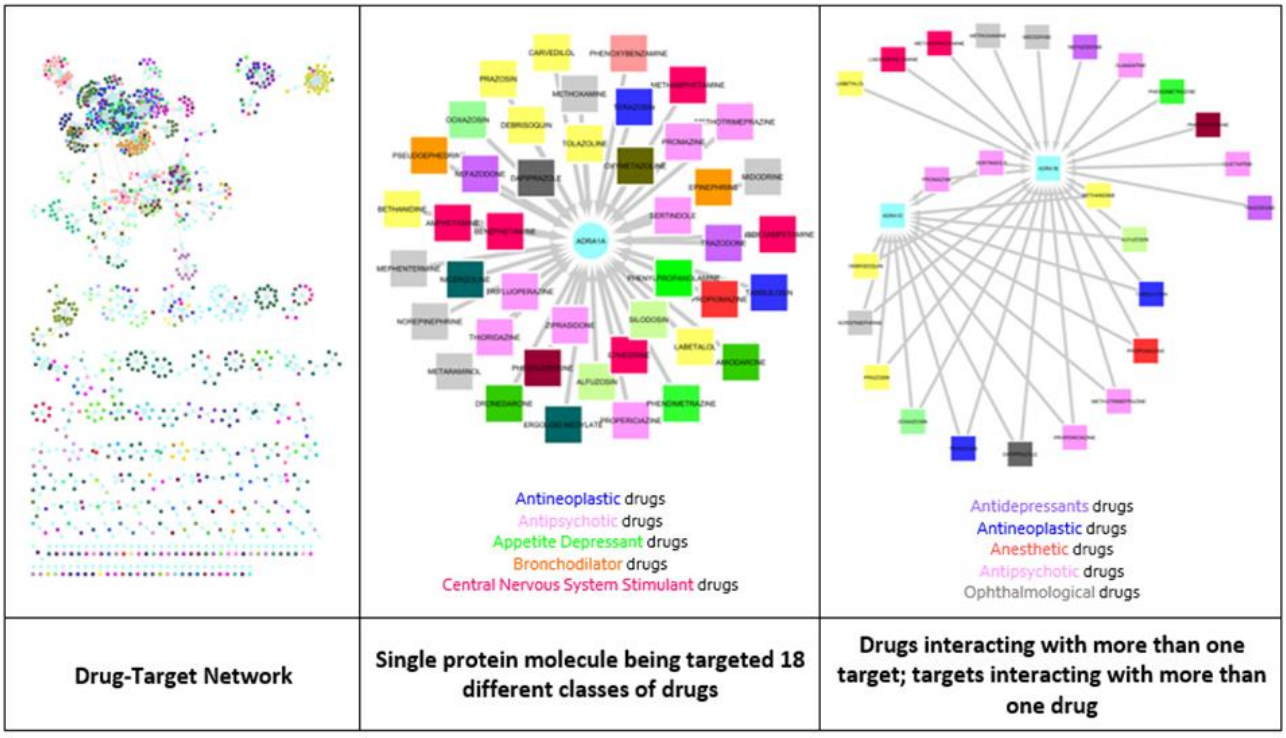


1. Import data from multiple biological databases for specific area of research.
2. Merge the data imported to form a combined and comprehensive dataset.

3. Using Cytoscape, map a new dataset to create a network by assigning node (source/target) and edge (interaction/association) attributes.
4. Curate the network to remove unnecessary or unwanted data.
5. Apply layouts, styles and filters for visual analysis.
6. Use expandable applications for further analysis in areas such as molecular profiling, clustering, and comparisons.
7. From the simplified network that was curated and analyzed, draw conclusions about results.

Results and Discussion

Network A: Drug-Protein Interaction



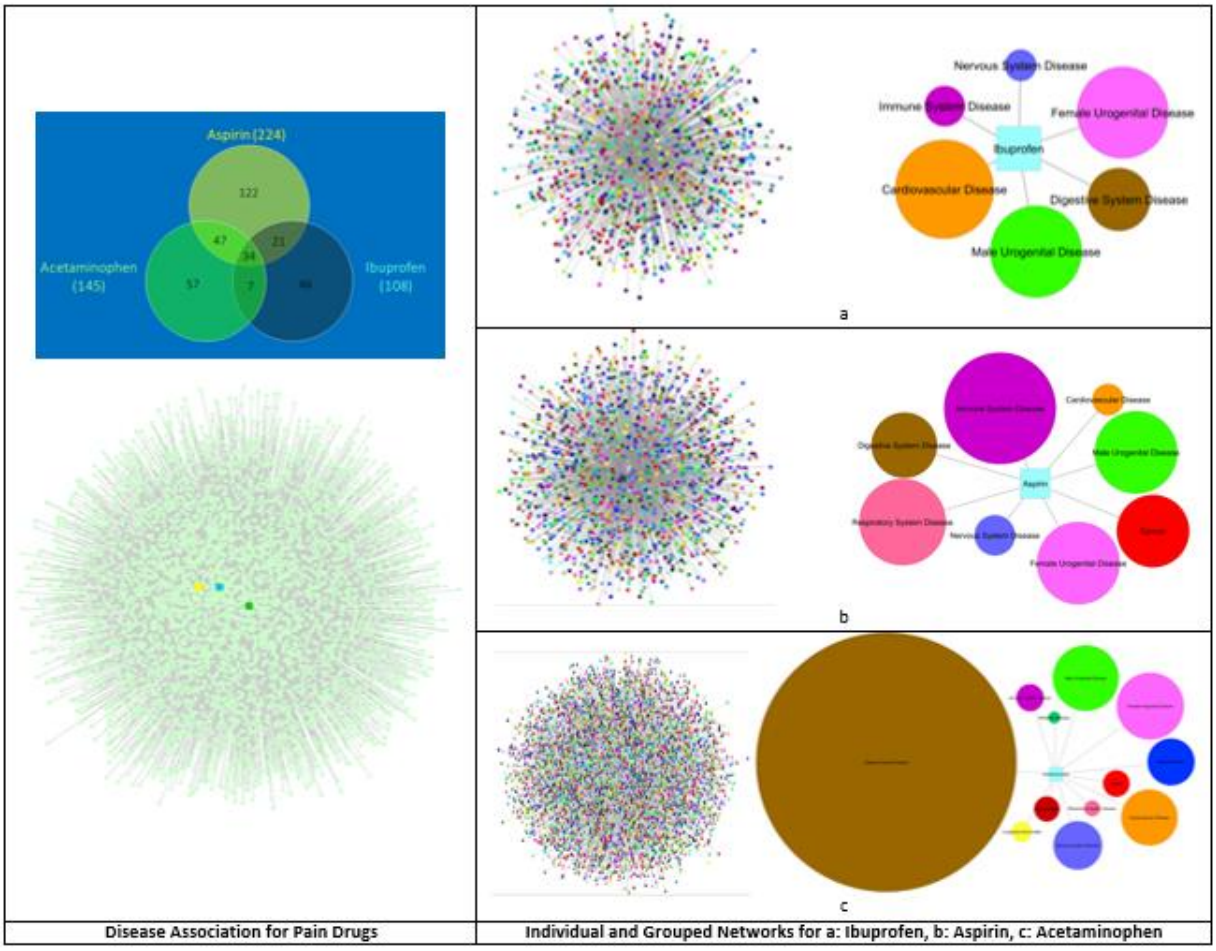
Drug-Target Network	Single protein molecule being targeted 18 different classes of drugs	Drugs interacting with more than one target; targets interacting with more than one drug

Starting from a complex drug-target network (left panel), we identified the Alpha-1A Adrenergic Receptor being targeted by 18 different classes of drugs (middle panel). This is a multi-functional protein and this network image shows the role of this protein in various biological processes.

Alpha-1B Adrenergic Receptor and Alpha-1D Adrenergic Receptor are targets of multiple drugs. This network (right panel) also shows multi-target pharmacology for various drugs with Alpha-1B Adrenergic Receptor and Alpha-1D Adrenergic Receptor as their targets. Multi-target drugs have advantages for treating complex diseases and

prospective drug reposition to avoid drug resistant problems.

Network B: Drug-Disease Association



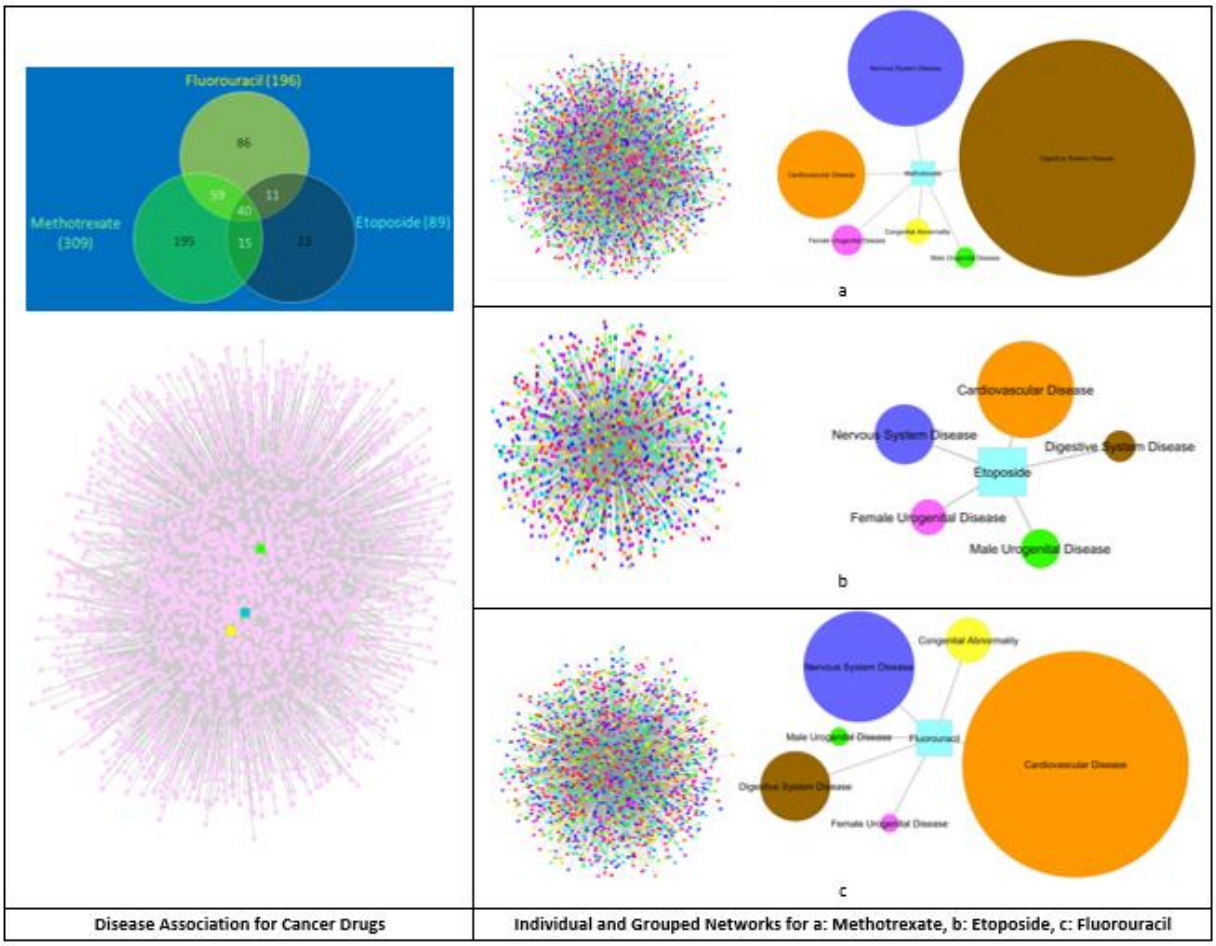
Disease Association for Pain Drugs | Individual and Grouped Networks for a: Ibuprofen, b: Aspirin, c: Acetaminophen

a) Ibuprofen (also known as Advil) has the lowest association with male/female urogenital disease, digestive disease, immune disease, and nervous system disease. It also had a lower association to cardiovascular disease than acetaminophen.

b) Aspirin has highest association with immune disease, respiratory disease, and cancer. It was shown

to have the lowest association of the three drugs for cardiovascular disease due to its blood thinning capabilities.

c) Acetaminophen (also known as Tylenol) has the highest association with digestive disease, male/female urogenital disease, cardiovascular disease, and nervous system disease out of the three pain drugs. It has three disease associations (mental disease, blood disease, congenital abnormally, metabolic diseases) that are absent in the other two drugs.



Disease Association for Cancer Drugs

Individual and Grouped Networks for a: Methotrexate, b: Etoposide, c: Fluorouracil

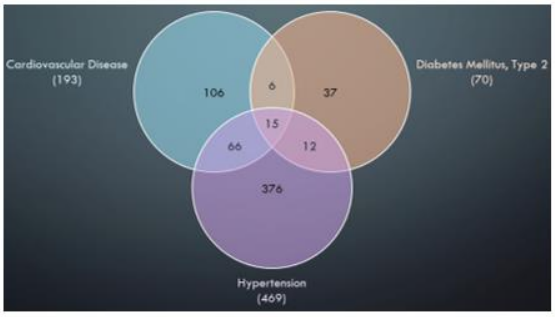
a) Methotrexate compared to the other two cancer drugs has the highest association with digestive disease and nervous system disease. It also has a higher association with female urogenital disease in comparison with its male urogenital disease. The other two cancer drugs have almost equal associations to male and female urogenital disease.

b) Etoposide has the lowest association with cardiovascular disease, nervous system disease, and

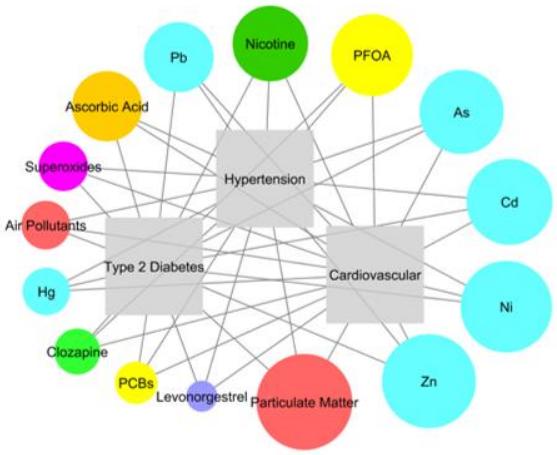
digestive disease. It is the only drug of the three without association to congenital abnormality.

c) Fluorouracil has the highest association with the disease category for cardiovascular disease.

Network C: Chemical Disease Association



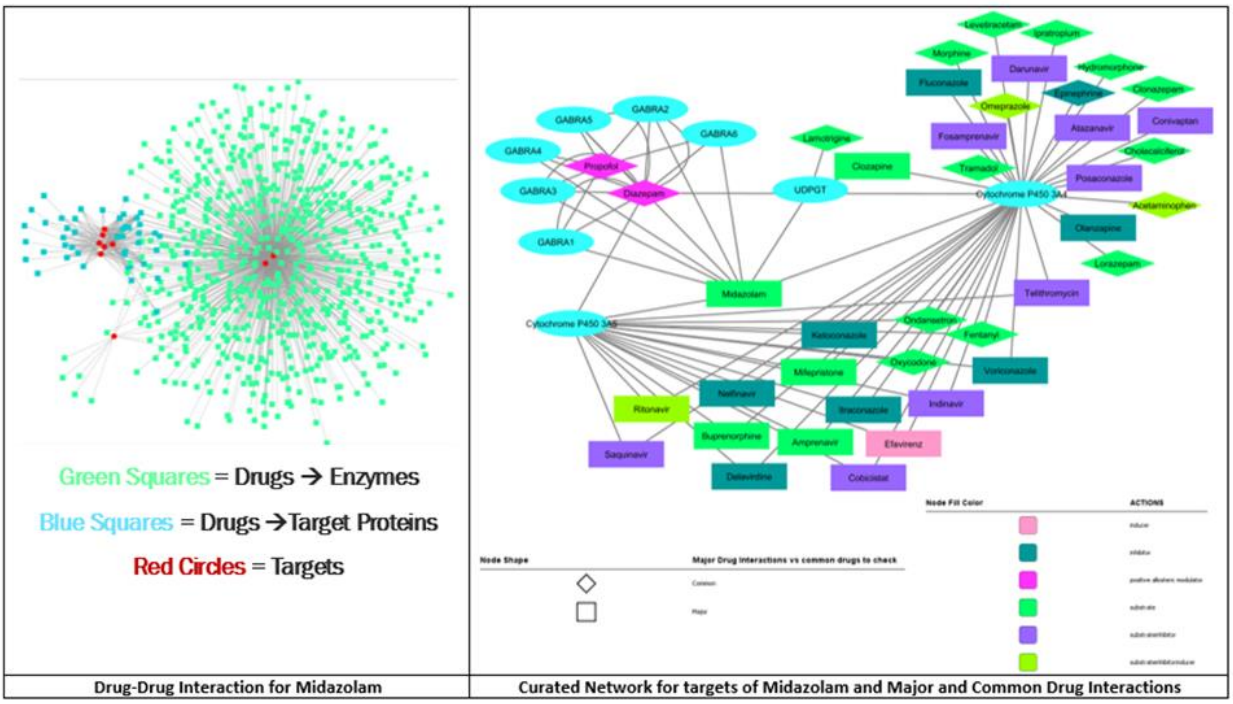
Chemicals Associated with Cardiovascular Disease, Hypertension, and Diabetes Type 2



Network for 15 Chemicals in Common for Cardiovascular Disease, Hypertension, and Diabetes Type 2

Cardiovascular disease, hypertension, and type 2 diabetes have 15 chemical associations in common. Of these chemicals 6 are metals

Network D: Drug-Drug Interaction



Drug-Drug Interaction for Midazolam | Curated Network for targets of Midazolam and Major and Common Drug Interactions

Midazolam has 6 Gamma-Aminobutyric Acid Receptor Subunit Alpha targets and 3 enzyme interactions. These 9 proteins interact with many other drugs as shown in mapping left above. This depicts the complexity of midazolam's cross reactions. The major drug interactions and the commonly check drug interactions do not overlap (right panel).

Conclusions

- Cytoscape was used to map and analyze drug-target interactions, drug-disease associations, chemical-disease associations, and drug-drug interactions.

- Identified the major disease associations with 3 studied pain and cancer drugs.
- Metals are highly associated with cardiovascular disease, hypertension, and type 2 diabetes.
- Several classes of drug-target interaction and drug-drug interaction networks were successfully examined to highlight cross-reactions.

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