Enriching Students' Learning through Big Data Analysis using Biological Networks

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Presented by

Phalguni Ghosh and Michael Ansonoff
Natural Sciences Department, Middlesex County College
Edison, NJ

Why Research?

Benefits

- Improve STEM success
  - Enhance student/faculty interaction
  - Reinforce classroom theory with ‘hands-on’ activity
- Improve STEM retention
  - Allows students to ‘tryout’ science as a career
  - Encourages students to develop a scientific identity
  - Introduces students to the scientific community

Challenges

- Cost
  - Requires expensive equipment/consumables
  - Requires highly engaged faculty
- Safety
  - Substantial training
  - Constant oversight
  - Injury risk
  - Hazardous waste

Opportunity
(Bioinformatics)

- Inexpensive
  - Free powerful web based resources
  - Minimal equipment required
    - Computer access
    - Internet connection
- Powerful
  - Hot STEM research field
    - Substantial crossover appeal
  - A project for anyone

What can your students study?

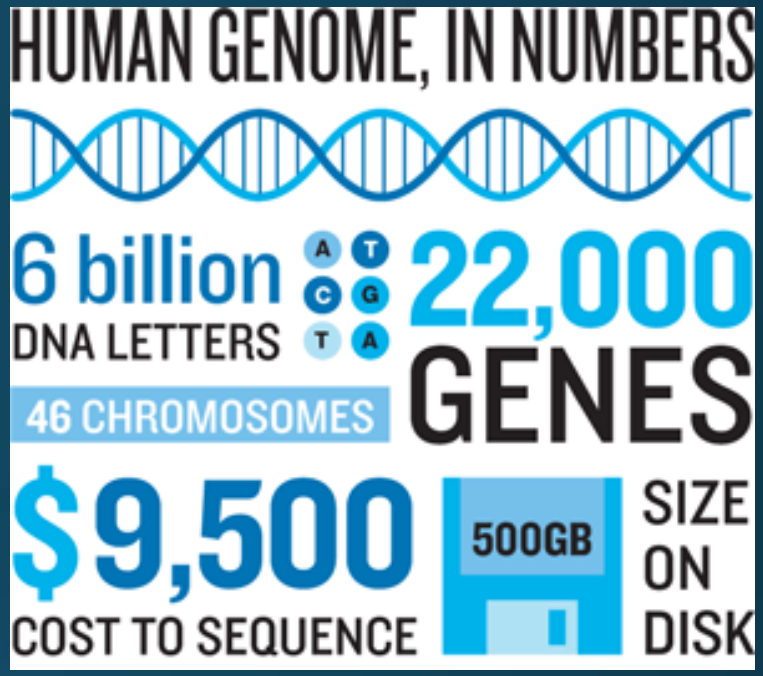
Possible areas of research

- Protein-protein interactions
- Gene regulation
- Drug interactions
- Cell signaling
- Disease pathways
- Environmental impact

Sample Research Projects

Big Data

Big data is an evolving term that describes a **large** volume of structured, semi-structured and unstructured **data** that has the potential **to be mined** for information and used with advanced analytics applications



The mapping of the human genome has generated a vast amount of life science data that is stored in several biological databases

Table 1 Human-related biological databases*

Name	Link	Brief description	Refs.	Category#
1000 Genomes	http://www.1000genomes.org	A deep catalog of human genetic variation	[17]	DNA
AFND	http://www.allelefrequencies.net	Allele Frequency Net Database	[37]	
dbSNP	http://www.ncbi.nlm.nih.gov/snp	Database of single nucleotide polymorphisms	[13]	
DEG	http://www.essentialgene.org	Database of Essential Genes	[38]	
EGA	http://www.ebi.ac.uk/ega	European Genome-phenome Archive	[14]	
Ensembl	http://www.ensembl.org	Ensembl genome browser	[39]	
euGenes	http://eugenes.org	Genomic information for eukaryotic organisms	[40]	
GeneCards	http://www.genecards.org	Integrated database of human genes	[41]	
IMG/HMP	https://img.jgi.doe.gov/imgm_hmp	Human Microbiome MetaGenomes	[15]	
JASPAR	http://jaspar.genereg.net	Transcription factor binding profile database	[42]	
JGA	http://trace.ddbj.nig.ac.jp/jga	Japanese Genotype-phenotype Archive	[43]	
KEGG	http://www.genome.jp/kegg	Kyoto Encyclopedia of Genes and Genomes	[44]	
MITOMAP	http://www.mitomap.org	Human mitochondrial genome database	[45]	
NCBI RefSeq	http://www.ncbi.nlm.nih.gov/refseq	NCBI Reference Sequence Database	[8]	
PolymiRTS	http://compbio.uthsc.edu/miRSNP	Polymorphism in miRNAs and their Target Sites	[46]	
UCSC Genome Browser	http://genome.ucsc.edu	UCSC Genome Browser database	[47]	
ChIPBase	http://deepbase.sysu.edu.cn/chipbase	Database of transcriptional regulation of lncRNA and miRNA genes	[48]	RNA
DARNED	http://darned.ucc.ie	DAtabase of RNa EDiting in humans	[49]	
DIANA-LncBase	http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=lncBase/index	miRNA targets on lncRNAs	[50]	
GENCODE	http://www.gencodegenes.org	Encyclopedia of genes and gene variants	[17]	
H-DBAS	http://www.h-invitational.jp/h-dbas	Human-transcriptome DataBase for Alternative Splicing	[51]	
HEXEvent	http://hexevent.mmg.uci.edu	Database of Human EXon splicing Events	[52]	
LNCipedia	http://www.lncipedia.org	Annotated human lncRNA sequences	[53]	
LncRNA2Target	http://www.lncrna2target.org	Database of differentially-expressed genes after lncRNA knockdown or overexpression	[54]	
lncRNAdb	http://www.lncrnadb.org	lncRNA Database	[20]	
lncRNASNP	http://bioinfo.life.hust.edu.cn/lncRNASNP	Database of SNPs in lncRNAs	[55]	
LncRNAWiki	http://lncrna.big.ac.cn	Human lncRNA Wiki	[10]	
miRBase	http://www.mirbase.org	miRNA Database	[21]	
miRTarBase	http://mirtarbase.mbc.nctu.edu.tw	Experimentally-validated miRNA–target interactions	[56]	
miRWalk	http://mirwalk.uni-hd.de	Database of miRNA–target interactions	[57]	
NONCODE	http://www.noncode.org	Database of ncRNA genes	[58]	
NPInter	http://www.bioinfo.org/NPInter	Database of ncRNA interactions	[59]	
RADAR	http://RNAedit.com	Rigorously Annotated Database of A-to-I RNA editing	[60]	
piRNABank	http://pirnabank.ibab.ac.in	Database of piwi-interacting RNAs	[61]	
RBPDB	http://rbpdb.cebr.utoronto.ca	Database of RNA-binding specificities	[62]	
RDB	http://ndbserver.rutgers.edu	The nucleic acid database	[63]	
Rfam	http://rfam.xfam.org	Database of ncRNA families	[19]	
RNAcentral	http://rnacentral.org	International database of ncRNA sequences	[18]	
snoRNABase	https://www-snorna.biotoul.fr	Database of human H/ACA and C/D box snoRNAs	[64]	
starBase	http://starbase.sysu.edu.cn	Database of ncRNA interaction networks	[65]	
TarBase	http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index	Experimentally-validated miRNA:gene interactions	[66]	
TargetScan	http://www.targetscan.org	Predicted miRNA targets in mammals	[67]	
CATH	http://cath.biochem.ucl.ac.uk	Protein structure classification	[68]	Protein
CPLM	http://cplm.biocuckoo.org	Compendium of Protein Lysine Modifications	[69]	
DIP	http://dip.doe-mbi.ucla.edu	Database of Interacting Proteins	[70]	
EKPD	http://ekpd.biocuckoo.org	Eukaryotic Kinase and Phosphatase Database	[71]	
HPRD	http://www.hprd.org	Human Protein Reference Database	[72]	
hUbiquitome	http://bioinfo.bjmu.edu.cn/hubi/	Ubiquitination sites and cascades	[73]	
InterPro	http://www.ebi.ac.uk/interpro	Protein sequence analysis and classification	[74]	
MEROPS	http://merops.sanger.ac.uk	Database of proteolytic enzymes, their substrates, and inhibitors	[75]	
MINT	http://mint.bio.uniroma2.it/mint	Molecular INTeraction Database	[76]	

(continued)

Table 1 (continued)

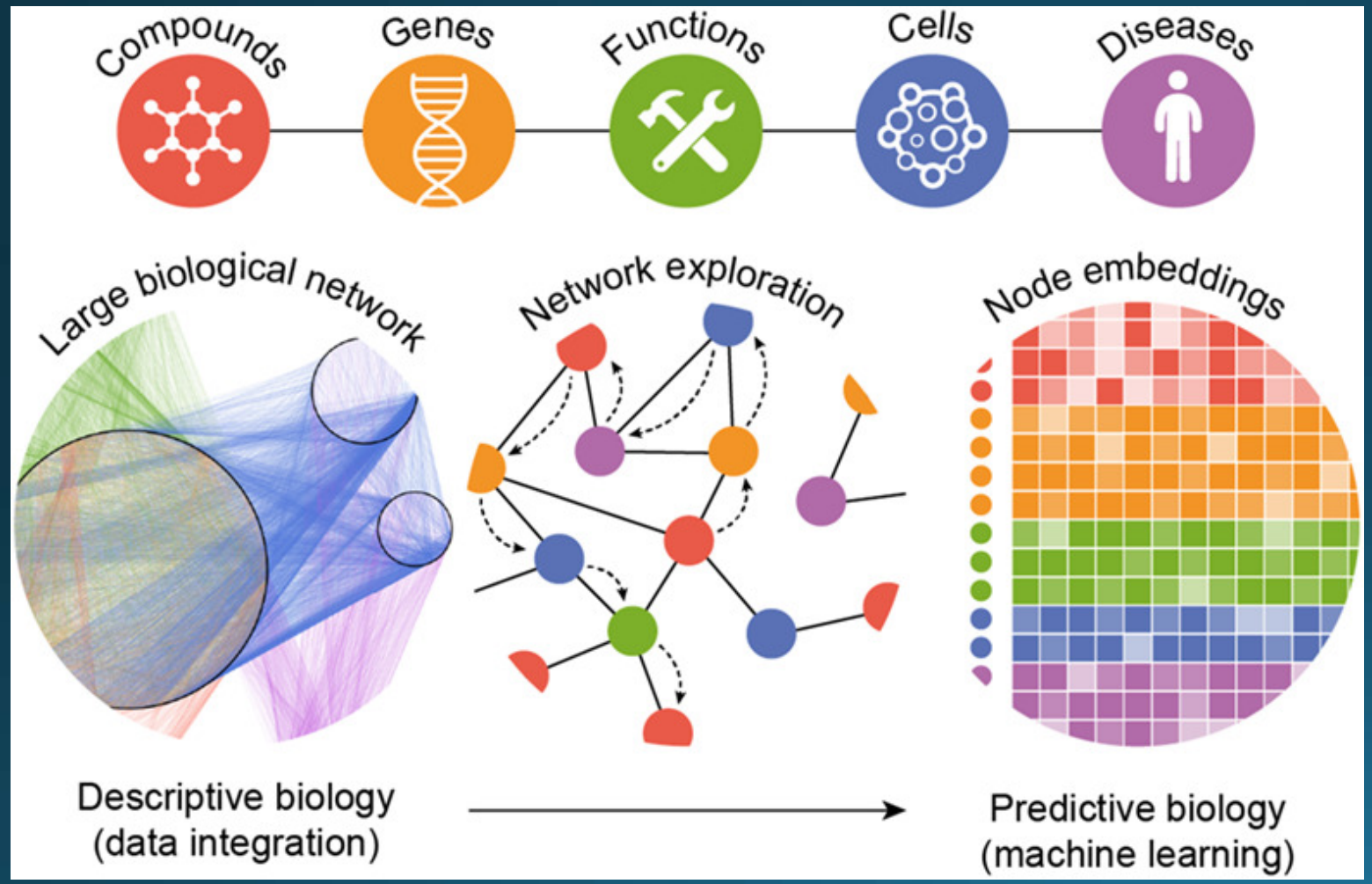
Name	Link	Brief description	Refs.	Category#
ModBase	http://salilab.org/modbase	Database of comparative protein structure models	[77]	
mUbiSiDa	http://reprod.njmu.edu.cn/mUbiSiDa	Mammalian Ubiquitination Site Database	[78]	
PANTHER	http://www.pantherdb.org	Protein ANalysis THrough Evolutionary Relationships	[79]	
PDB	http://www.resb.org/pdb	Protein Data Bank for 3D structures of biological macromolecules	[25]	
PDBe	http://www.ebi.ac.uk/pdbe	Protein Data Bank in Europe	[80]	
Pfam	http://pfam.xfam.org	Database of conserved protein families and domains	[23]	
PhosSNP	http://phossnp.biocuckoo.org	Genetic polymorphisms that influence protein phosphorylation	[81]	
PIR	http://pir.georgetown.edu	Protein Information Resource	[82]	
PROSITE	http://www.expasy.org/prosite	Database of protein domains, families and functional sites	[83]	
SysPTM	http://lifecenter.sgst.cn/SysPTM	Post-translational modifications	[84]	
TreeFam	http://www.treefam.org	Database of phylogenetic trees of animal species	[24]	
UniPROBE	http://thebrain.bwh.harvard.edu/uniprobe	Universal PBM Resource for Oligonucleotide Binding Evaluation	[85]	
UniProt	http://www.uniprot.org	Universal protein resource	[22]	
UUCD	http://uucd.biocuckoo.org	Ubiquitin and Ubiquitin-like Conjugation Database	[86]	
ArrayExpress	http://www.ebi.ac.uk/arrayexpress	Database of functional genomics experiments	[87]	Expression
BioGPS	http://biogps.org	Portal for querying and organizing gene annotation resources	[88]	
Expression Atlas	http://www.ebi.ac.uk/gxa	Differential and baseline expression	[27]	
Human Protein Atlas	http://www.proteinatlas.org	Tissue-based map of the human proteome	[29]	
MOPED	https://www.proteinspire.org	Multi-Omics Profiling Expression Database	[89]	
NCBI GEO	http://www.ncbi.nlm.nih.gov/geo	Gene Expression Omnibus	[26]	
NRED	http://nred.matticklab.com	Database of lncRNA expression	[90]	
ONCOMINE	https://www.oncomine.org	Cancer microarray database	[91]	
PrimerBank	http://pga.mgh.harvard.edu/primerbank	Public resource for PCR primers	[92]	
PRIDE	http://www.ebi.ac.uk/pride	PRoteomics IDEntifications	[93]	
TiGER	http://bioinfo.wilmer.jhu.edu/tiger	Tissue-specific Gene Expression and Regulation	[28]	
WikiCell	http://www.wikicell.org	Unified resource for Human transcriptomics research	[94]	
CPDB	http://consensuspathdb.org	Database of human interaction networks	[95]	Pathway
HMDB	http://www.hmdb.ca	Human Metabolome Database	[96]	
KEGG PATHWAY	http://www.genome.jp/kegg/pathway.html	KEGG pathway maps	[30]	
MetaCyc	http://metacyc.org	Metabolic pathway database	[97]	
Pathway Commons	http://www.pathwaycommons.org	Pathway commons	[98]	
PID	http://pid.nci.nih.gov	Pathway Interaction Database	[99]	
Reactome	http://www.reactome.org	Curated and peer-reviewed pathway database	[100]	
UniPathway	http://www.grenoble.prabi.fr/obiwarehouse/unipathway	Universal Pathway	[101]	
AlzBase	http://alz.big.ac.cn/alzBase	Database for gene dysregulation in Alzheimer's disease	[102]	Disease
CADgene	http://www.bioguo.org/CADgene	Coronary Artery Disease gene database	[103]	
COSMIC	http://cancer.sanger.ac.uk	Catalog Of Somatic Mutations In Cancer	[104]	
DiseaseMeth	http://bioinfo.hrbmu.edu.cn/diseasemeth	Human disease methylation database	[105]	
DisGeNET	http://www.disgenet.org/web/DisGeNET/v2.1	Gene–disease associations	[106]	
GOBO	http://co.bmc.lu.se/gobo	Gene expression-based Outcome for Breast cancer Online	[107]	
GWAS Central	http://www.gwascentral.org	A comprehensive resource for the comparison and interrogation of genome-wide association studies	[108]	
GWASdb	http://jjwanglab.org/gwasdb	Human genetic variants identified by genome-wide association studies	[109]	
HbVar	http://globin.cse.psu.edu/hbvar	Hemoglobin variants and thalassemias	[110]	
HGMD	http://www.hgmd.org	Human Gene Mutation Database	[111]	

Human – related Biological databases

The Application of Big Data Analysis or Data Mining from Biological databases is to improve human Health and Cure diseases. Example are:

Diagnostics	Data mining and analysis to identify causes of illness
Preventative medicine	Predictive analytics and data analysis of genetic, lifestyle, and social circumstances to prevent disease
Disease mitigation	DNA modification to eliminate genetic disorders and rare diseases
Personalized medicine	Development of custom, genome-specific drugs to maximize health outcome
Medical research	Data-driven medical and pharmacological research to cure disease and discover new treatments and medicines
Reduction of adverse medical events	Harnessing of big data to spot medication errors and flag potential adverse reactions
Cost reduction	Identification of value that drives better patient outcomes for long term savings
Population health	Monitor big data to identify disease trends and health strategies based on demographics, geography and socio-economics to improve public health programs.

Network Biology



- Biological networks provide a conceptual framework to understand complex interactions of different components in a biological system
- A biological network hence represents the molecular "wiring" diagram of the interactions within a cell.
- Such analysis enables the prediction of Gene regulation, disease pathway, drug interactions and many more.

How?

Network Biology: 3 Components

a. Biological Databases….1552 and growing…these are libraries of life science information

Data Type	Description	Example
Sequence DB	Protein, nucleotide sequence	Uniprot
Bibliographic DB	Published literature	Pubmed
Structure DB	3D structures of DNA, RNA, Protein, Virus	PDB
Disease DB	Disease data	OMIN
Chemical DB	Biological activity of small molecules	CTD
Enzyme DB	Function, pathways of enzymes	BRENDA

UniProt

PubMed

ctd

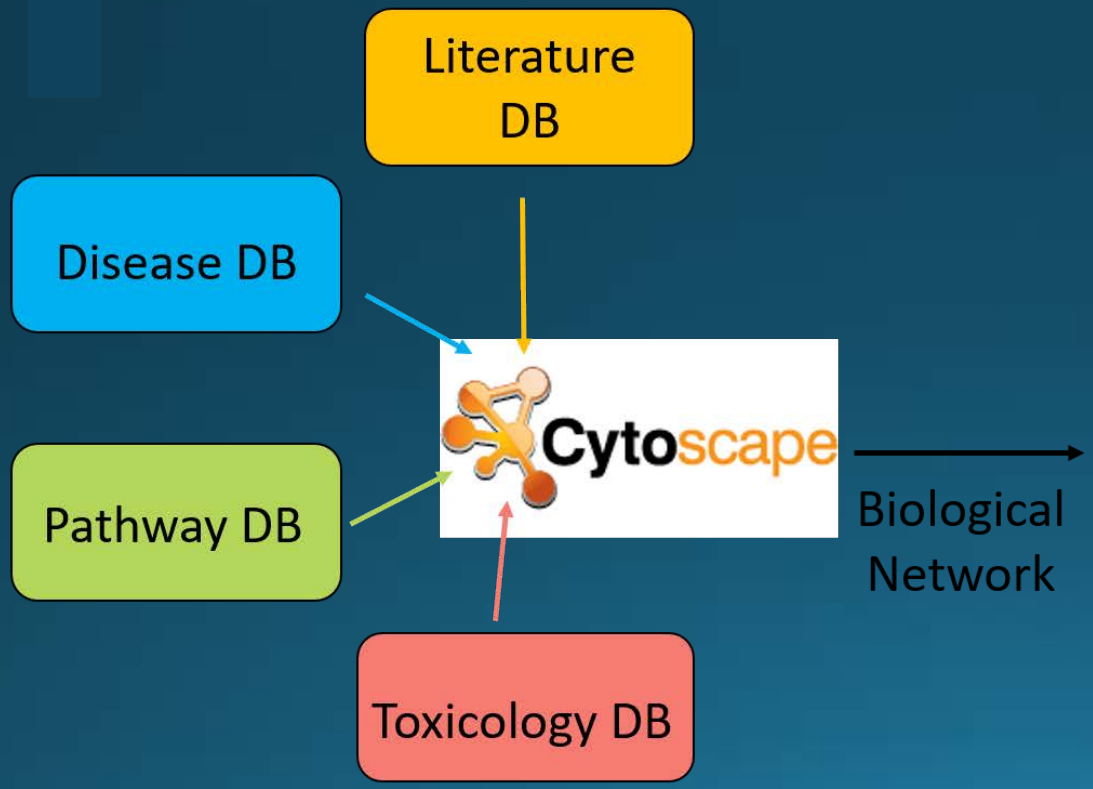
RCSB PDB PROTEIN DATA BANK

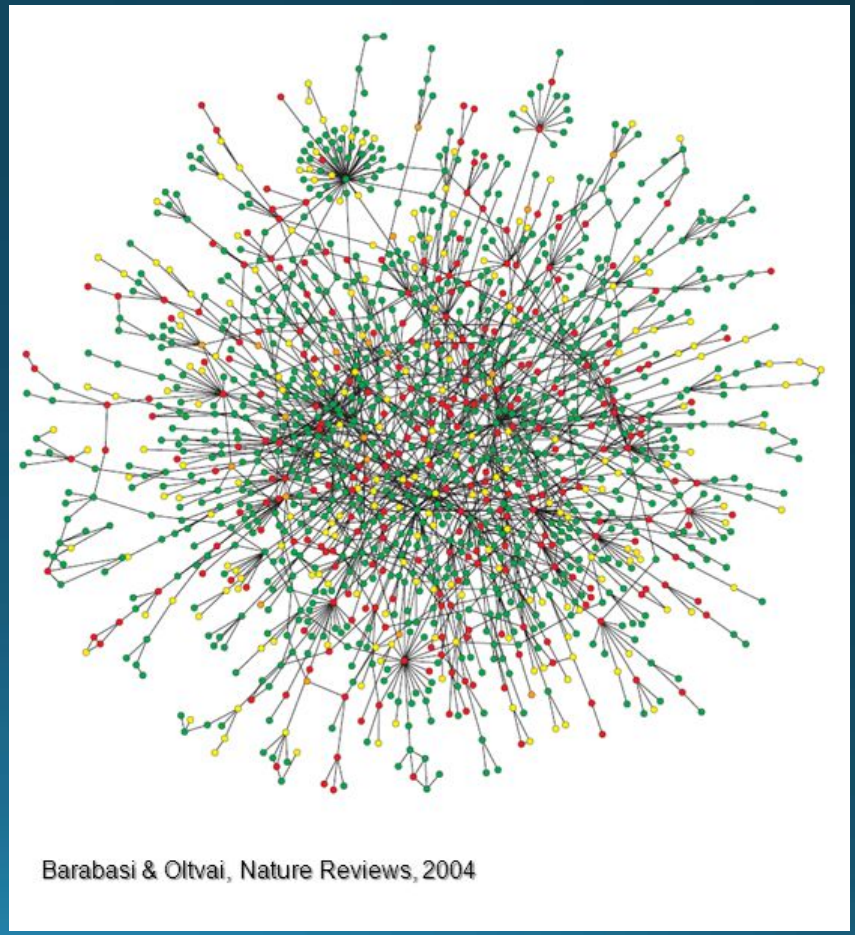
1987 2019 BRENDA The Comprehensive Enzyme Information System

Network Biology

b. Generate Biological Network

Biological networks provide a conceptual framework to understand complex interactions of different components in a biological system…..hence represents the molecular "wiring" diagram of the interactions within a cell

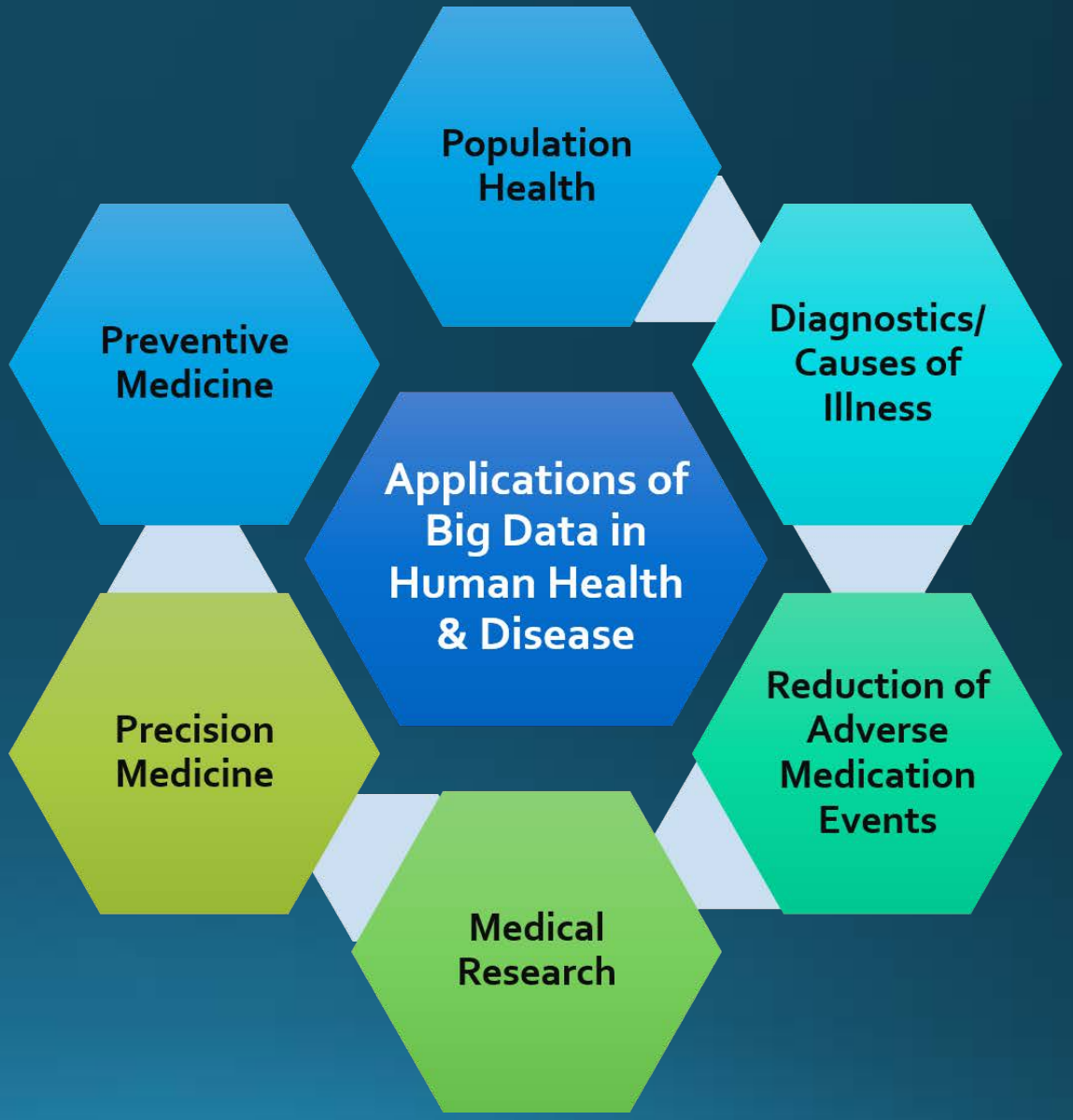




Network Biology

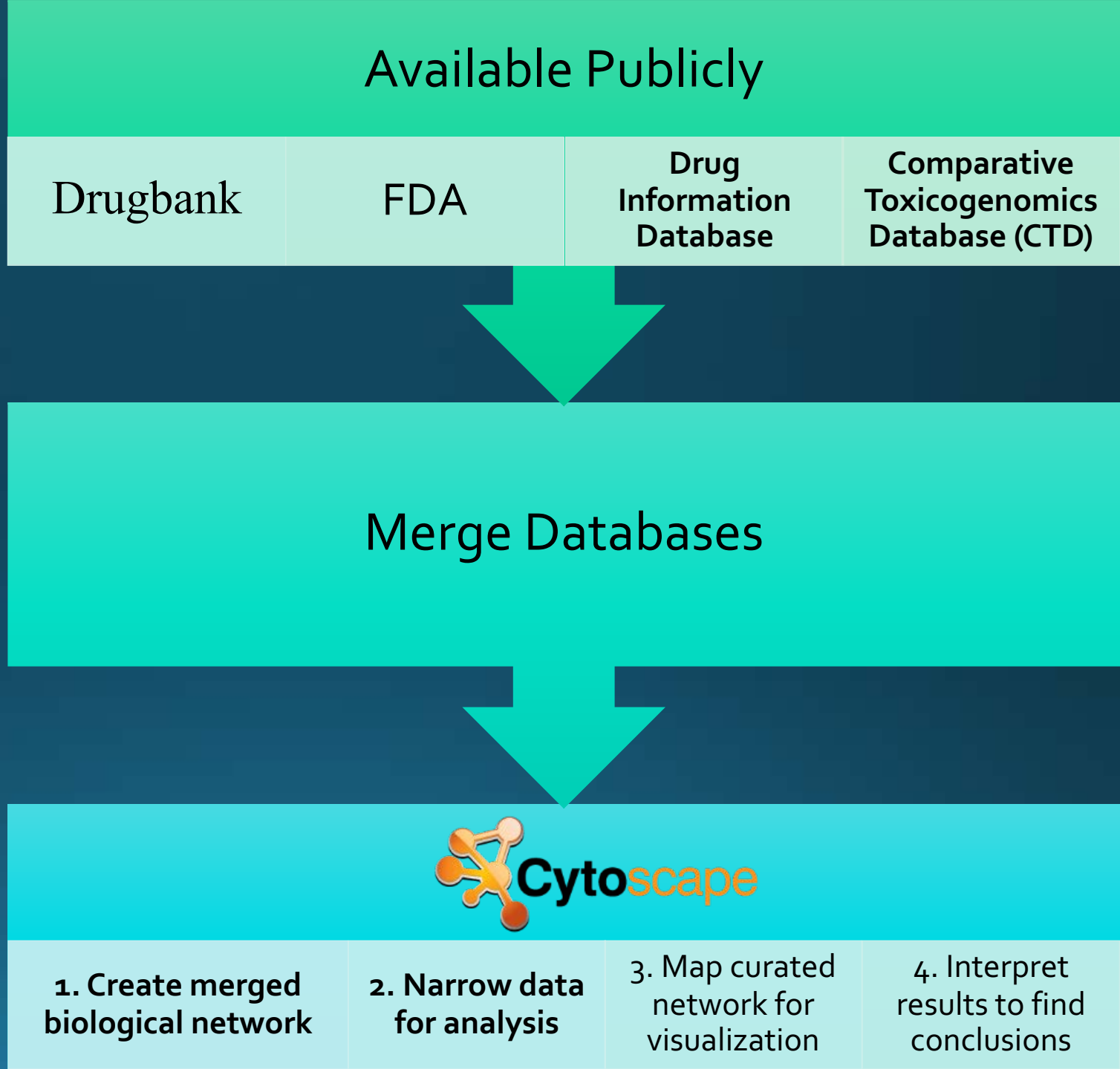
c. Predictive Biology

- Network analysis enables the prediction of gene regulation, disease pathway, drug interactions and many more
- Has multiple applications in human health and disease



Methodology

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 new dataset to create a network
4. Curate network to remove unnecessary or unwanted data.
5. Apply layouts, styles and filters for visual analysis.
6. Interpret results to find conclusions



Network A: Drug-Protein Interaction

- Understanding methods for analyzing big data
- Single protein molecule being targeted by different classes of drugs
- Single drug interactions 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

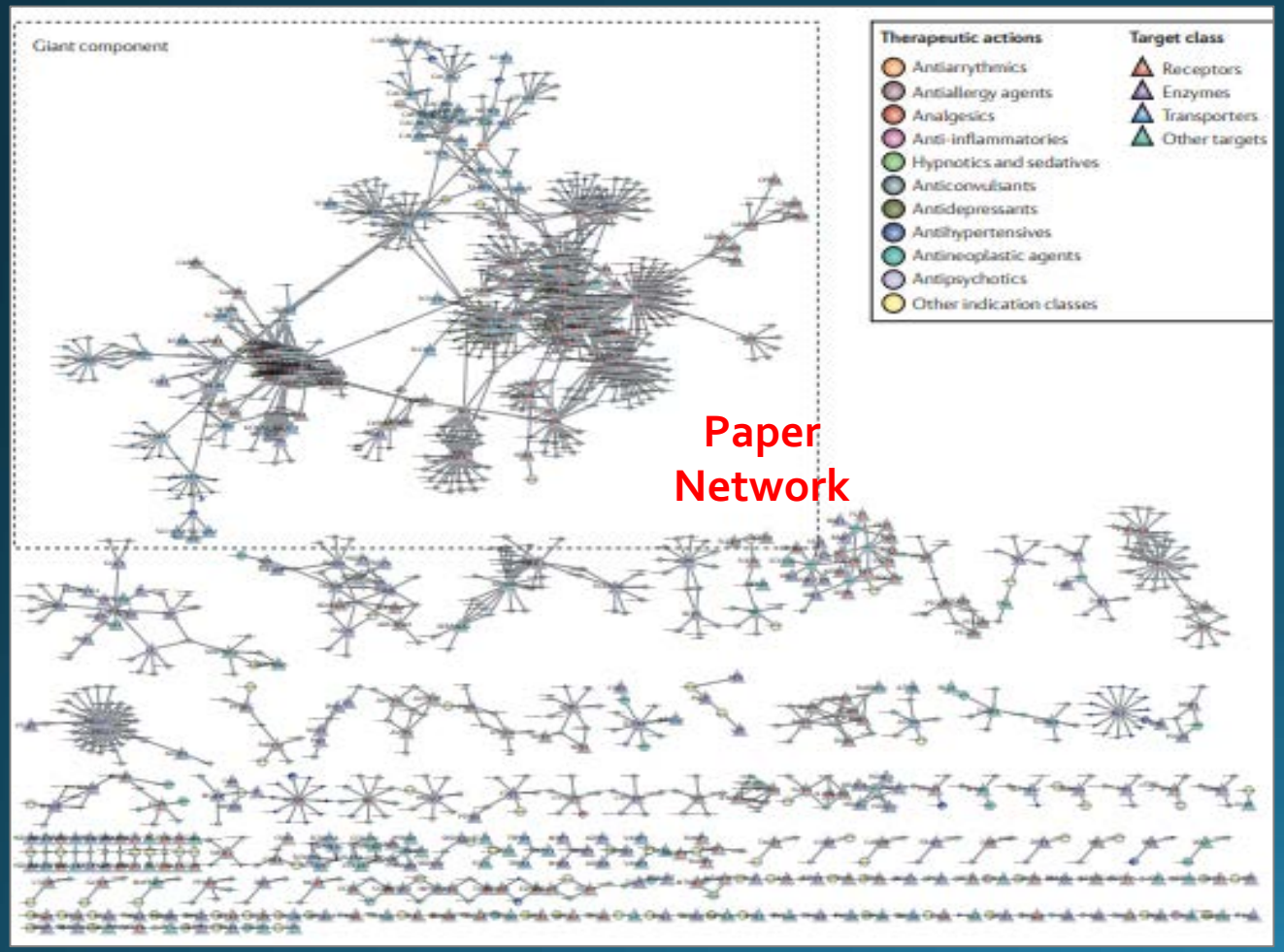
Network D: Adverse-Drug Interaction

- Midazolam

Big Data analysis using biological networks: results on drug, chemical, and disease association

Published Paper: Understand & Reproduce Results

NATURE REVIEW | DRUG DISCOVERY
VOLUME 10 | AUGUST 2011 | 579



ANALYSIS

Trends in the exploitation of novel drug targets

Mathias Rask-Andersen, Markus Sällman Almén* and Helgi B. Schiöth*‡*

Abstract | The discovery and exploitation of new drug targets is a key focus for both the pharmaceutical industry and academic biomedical research. To provide an insight into trends in the exploitation of new drug targets, we have analysed the drugs that were approved by the US Food and Drug Administration during the past three decades and examined the interactions of these drugs with therapeutic targets that are encoded by the human genome, using the DrugBank database and extensive manual curation. We have identified 435 effect-mediating drug targets in the human genome, which are modulated by 989 unique drugs, through 2,242 drug–target interactions. We also analyse trends in the introduction of drugs that modulate previously unexploited targets, and discuss the network pharmacology of the drugs in our data set.

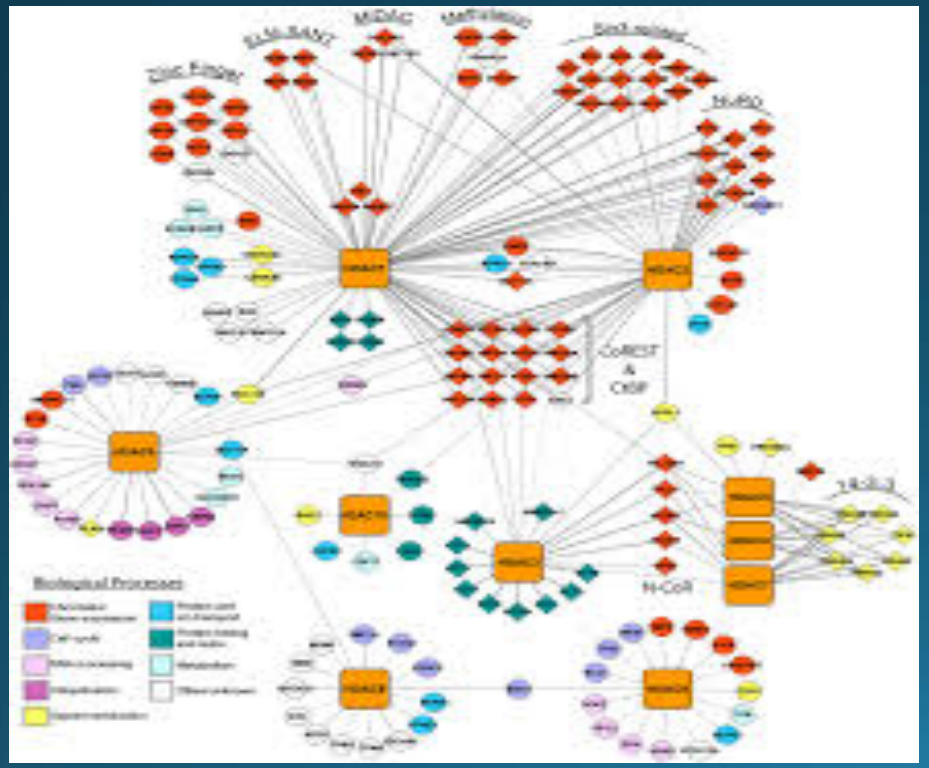
Understanding the identity of drug targets that are encoded by the human genome is of great importance for the development of new pharmaceutical products and the allocation of resources within academic and industrial biomedical research. Currently marketed drugs mediate their effects through only a small number of the potential human target proteins. Previously

estimated to contain ~30,000 genes and, of these, ~3,000 genes were suggested to be linked to disease based on the extrapolation of data from the number of antifungal targets in the yeast genome. The overlap between the two sets of genes — estimated to be ~600–1,500 genes in total[1] — was suggested to represent the number of pharmacologically exploitable targets.

Graphical representation of all of the interactions between drugs (989) and therapeutic drug targets (2,242) in the curated data set. Nodes (Target Class) represent targets (shown as triangles) and drugs (shown as circles).

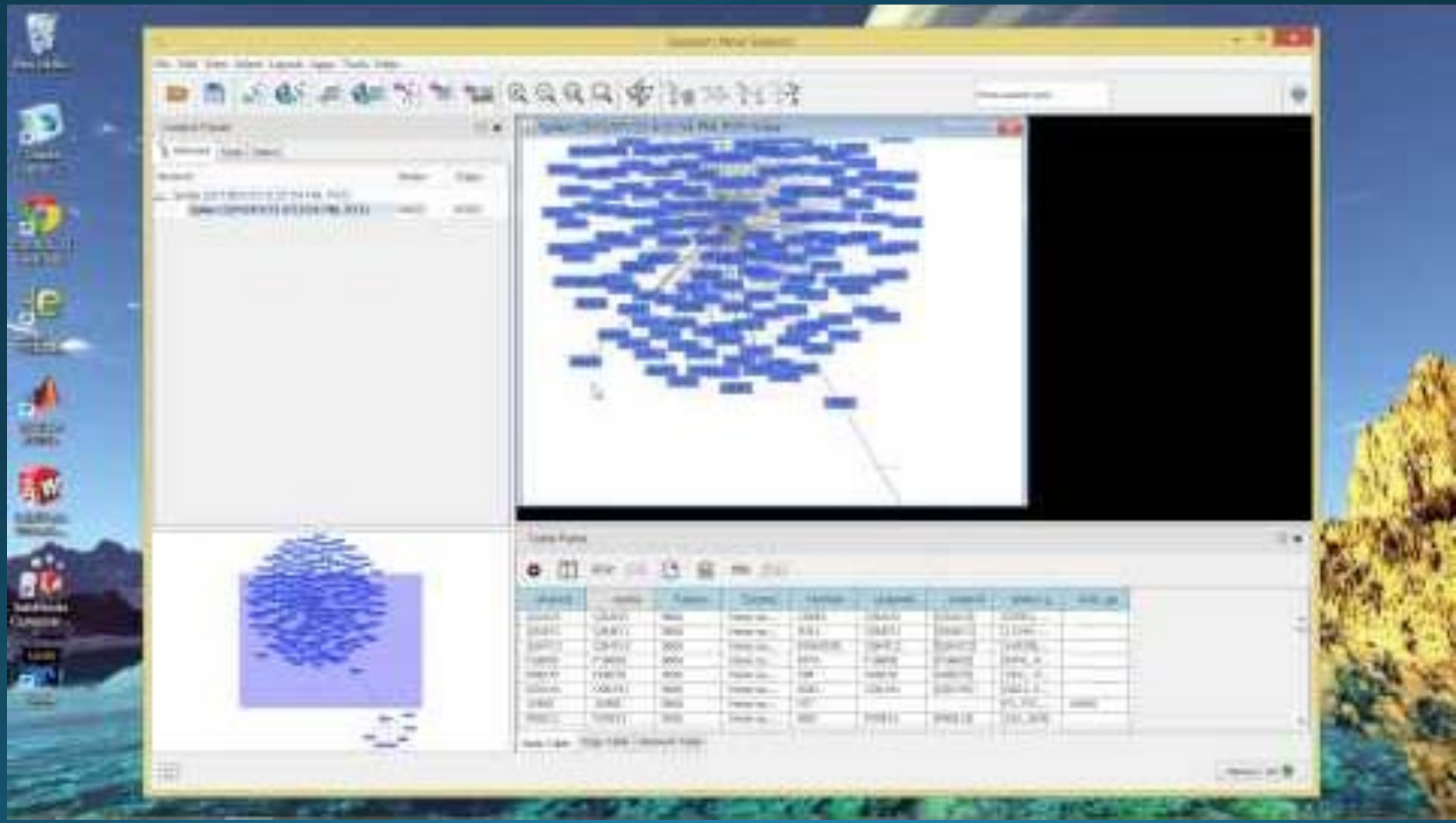
Tutorial Cites:

- https://www.youtube.com/watch?v=wjuVCF9_D-Y (approximately 1.0 hr tutorial, May 18, 2018; Bioinformatics DotCa; Network Visualization and Analysis with Cytoscape) **University of Toronto**.
- https://www.youtube.com/watch?v=lcfrqe3gvr4 (1hr and 42 min.; Introduction to Pathway and Network Analysis of Gene Lists)
- https://www.youtube.com/watch?v=ZwaTTCcA-fo **University of Toronto**. approximately 50 minutes tutorial, June 27, 2018
- https://www.youtube.com/watch?v=lA1-lHms0I0 (Approx. 21 min., May14, 2019; Cytoscope Tutorial – Beginners Guide in Jupyter
- https://www.youtube.com/watch?v=IuH5QT_loHM (Approx. 22 min. Tutorial)



Cytoscape is a free software platform that allows the investigation and visualization of integrated diverse networks.
Our students used 3.4.1 version made available in May 2016.

Cytoscape Tutorial



Published Paper: Understand & Reproduce Results

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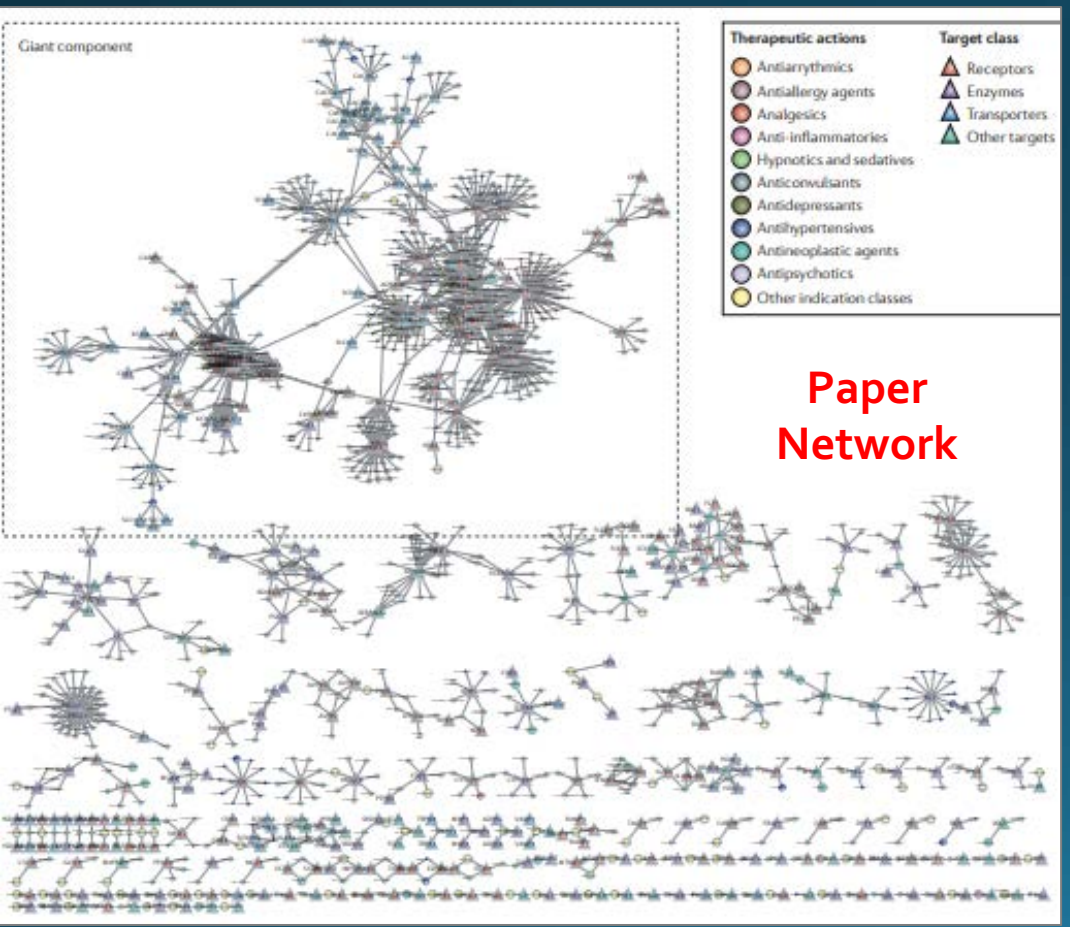
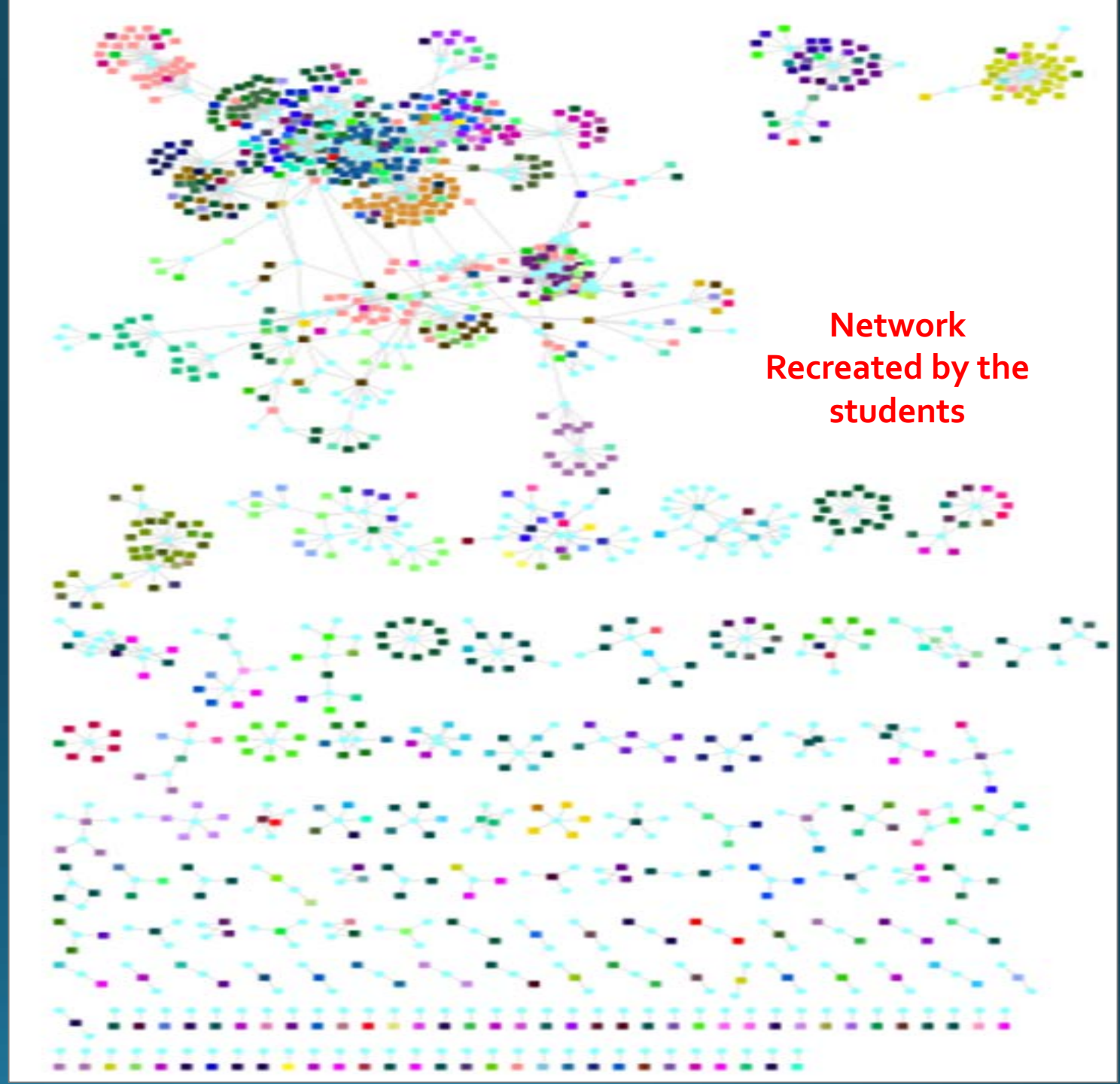


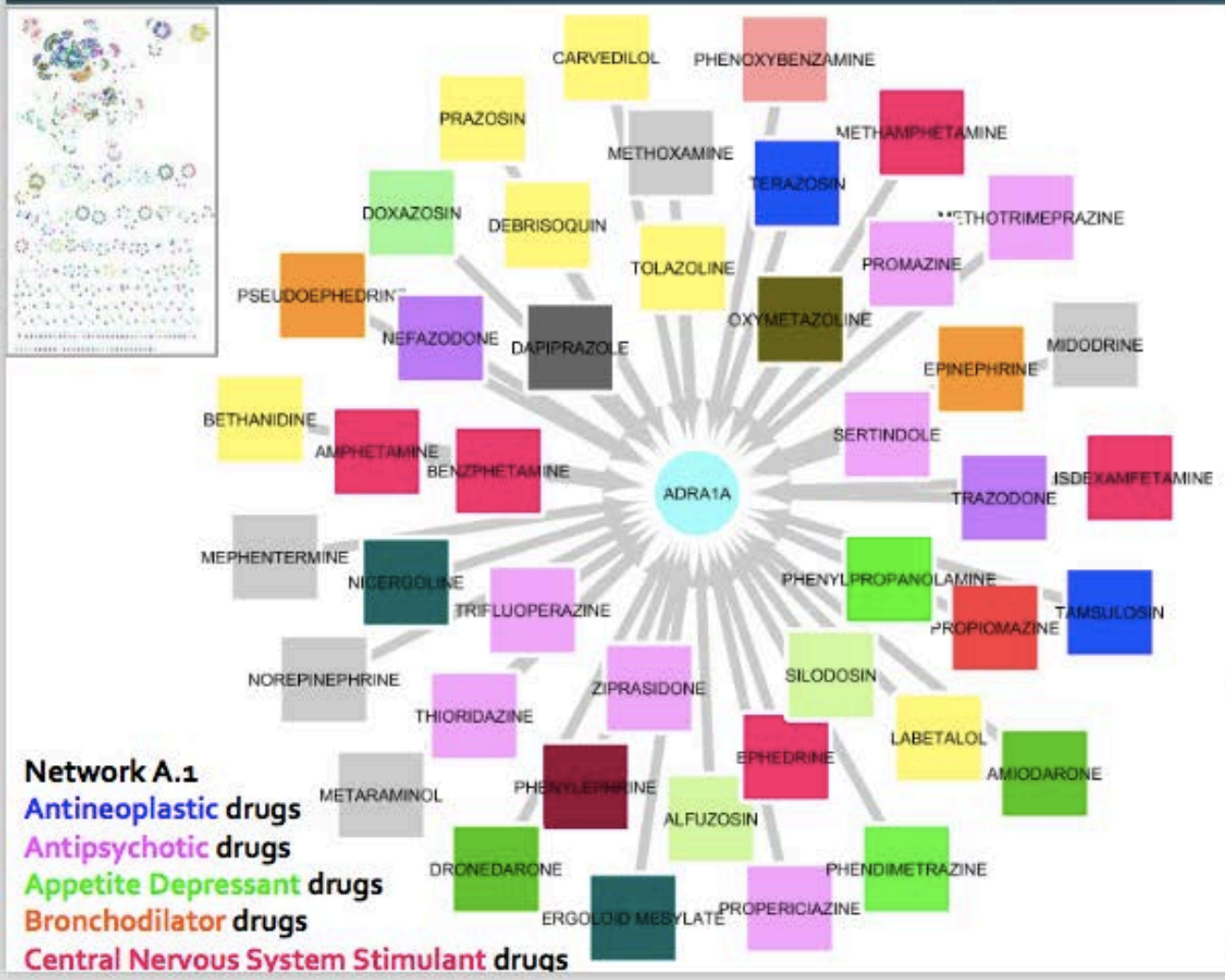
Paper Network

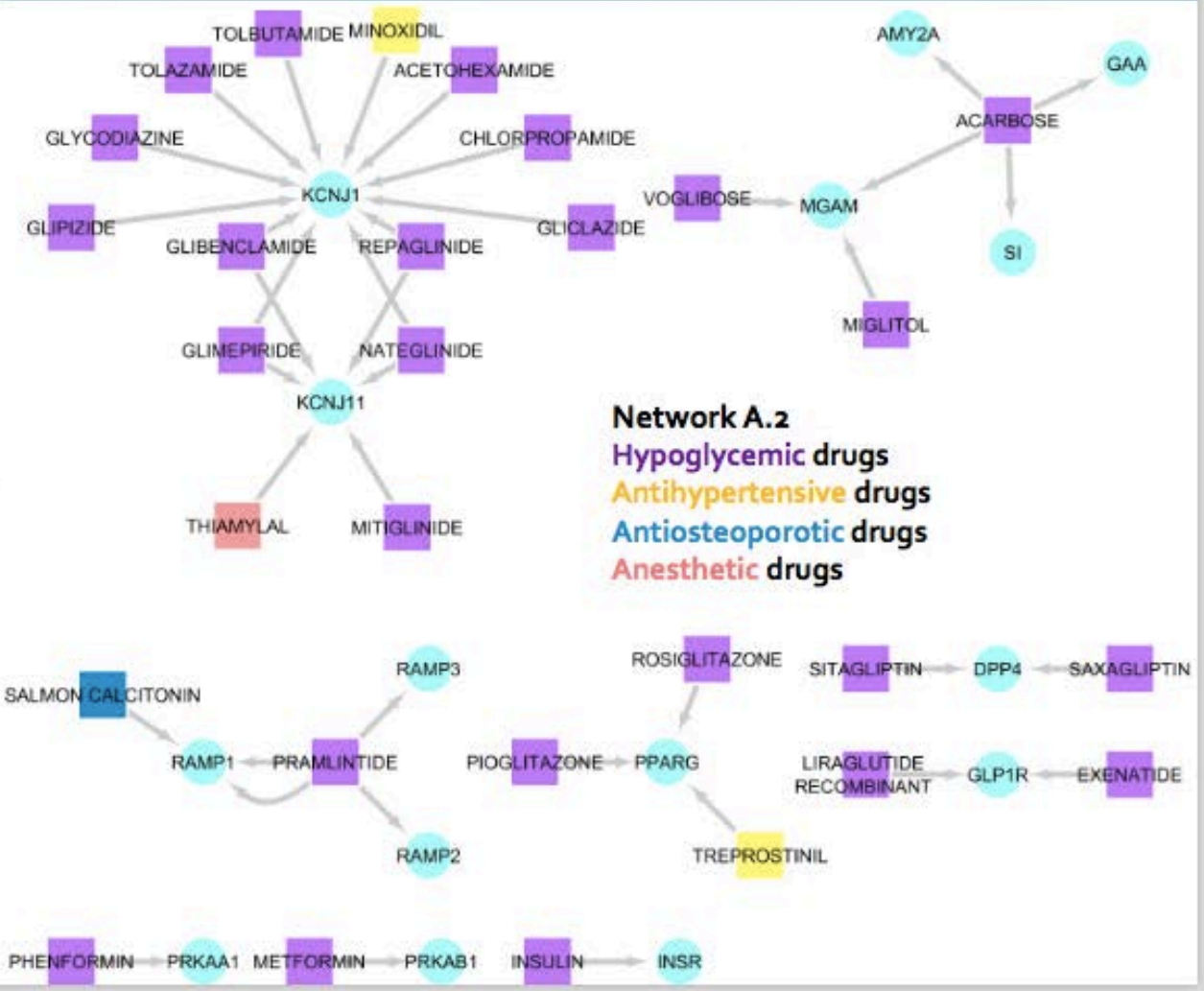


Network Recreated by the students

Network A: Drug-Protein Interaction

Starting from a complex drug-target network, identified Alpha-1A Adrenergic Receptor being targeted by 18 different classes of drugs (Network A.1). This is a multi-functional protein and this network image shows the role of this protein in various biological processes. This network (Network A.2) shows multi-target pharmacology for various drugs, with an focus on hyperglycemic drugs. Multi-target drugs have advantages for treating complex diseases and prospective drug reposition to avoid drug resistant problems.



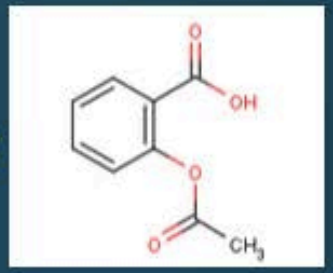


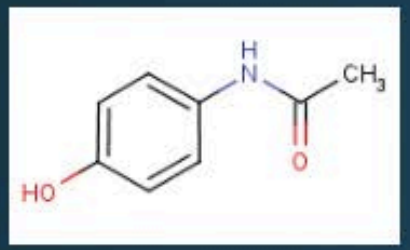
Network B1: Drug - Disease Association

Examining the increased chance of disease association with each drug as an adverse side effect. The disease that are associated as mechanism based not therapeutic.

Aspirin (224)

Type: blood thinner & NSAID

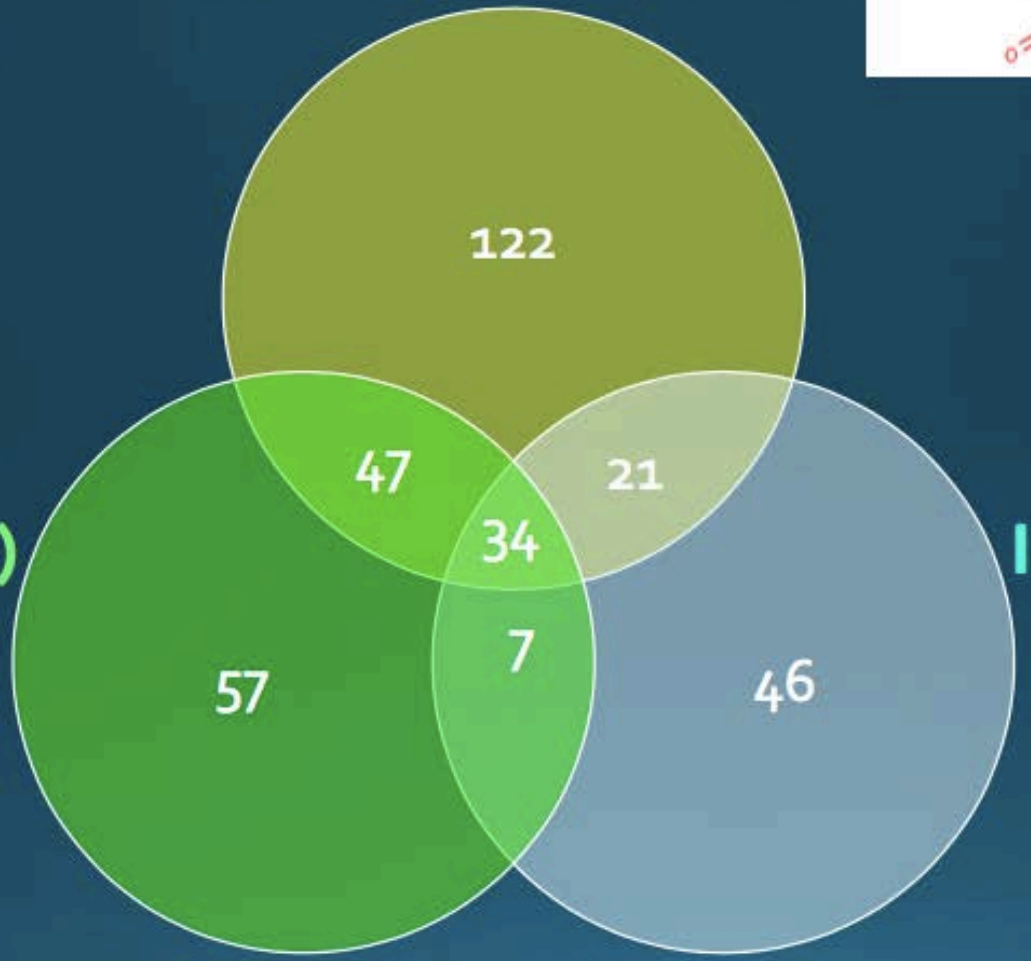




Acetaminophen (145)

Brand: Tylenol

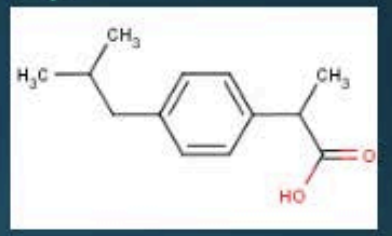
Type: Analgesic



Ibuprofen (108)

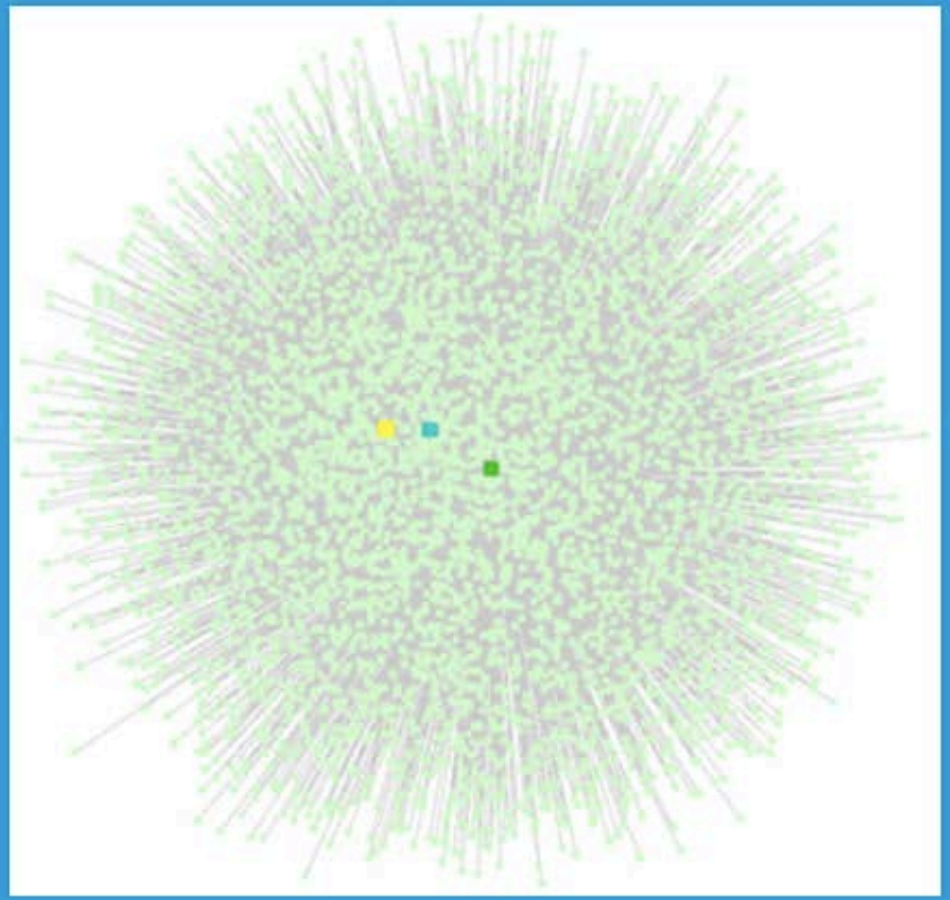
Brand: Advil

Type: NSAID



Network B1: Disease Association for 3 Pain Drugs

3 Pain Drugs: Combined Network and Individual Networks



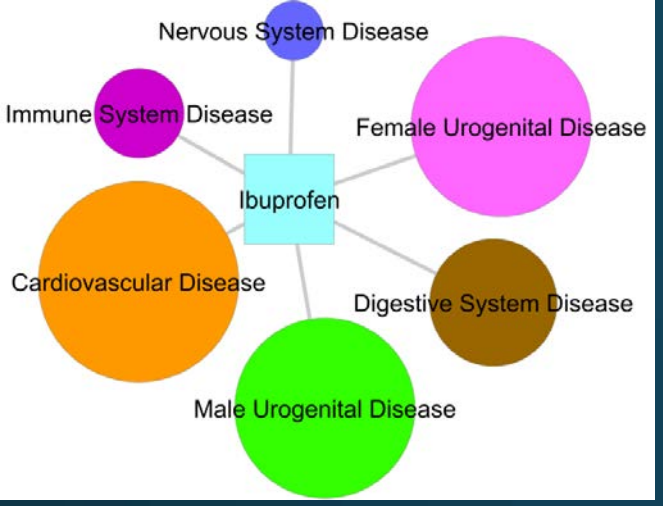
Network of Drug-Disease Association for 3 Common Pain Drugs

a) Ibuprofen

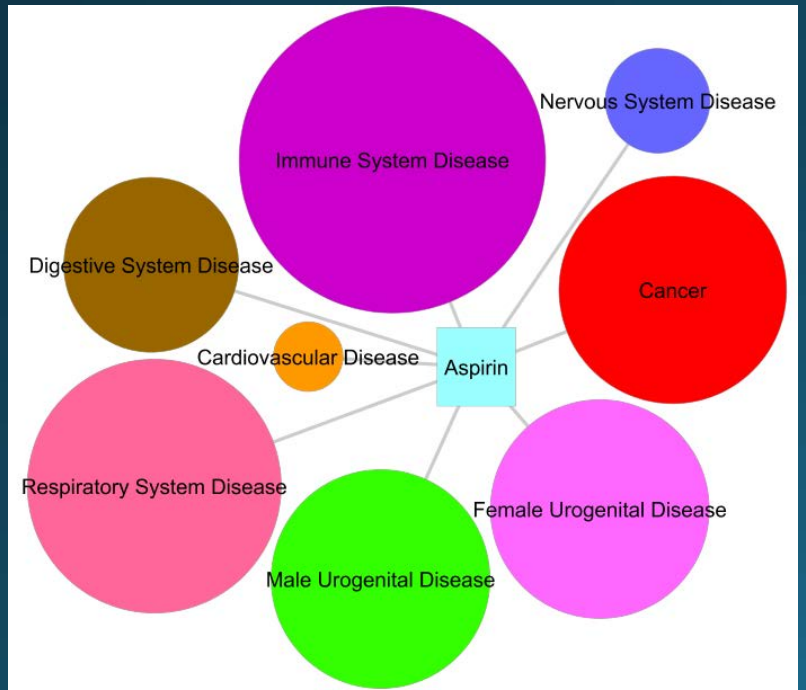
b) Aspirin

c) Acetaminophen

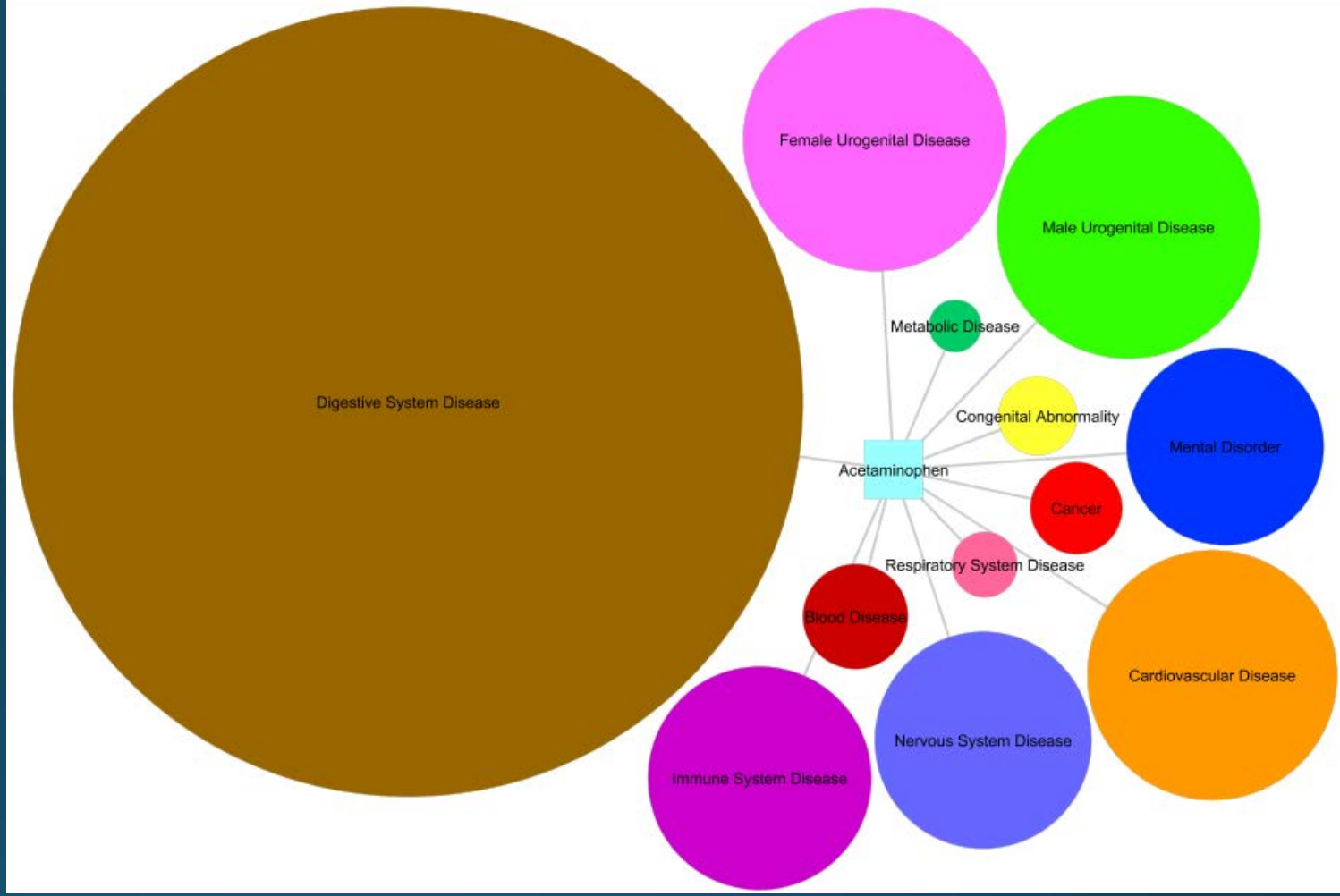
Grouped Network: 3 Pain Drugs



a) Ibuprofen (Advil) has the highest association with cardiovascular disease



b) Aspirin has highest association with immune disease, respiratory disease, and cancer

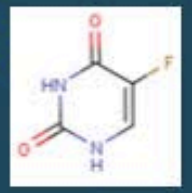


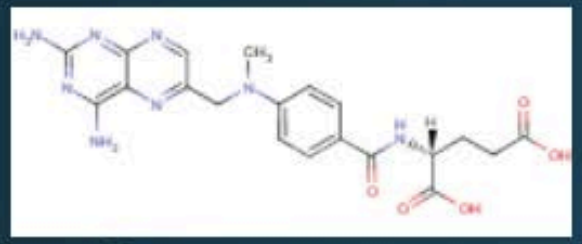
c) Acetaminophen (Tylenol) has the highest association with digestive & urogenital disease

Examining the increased chance of disease association with each drug as an adverse side effect. The disease that are associated as mechanism based not therapeutic.

Fluorouracil (196)

Type: Chemotherapy



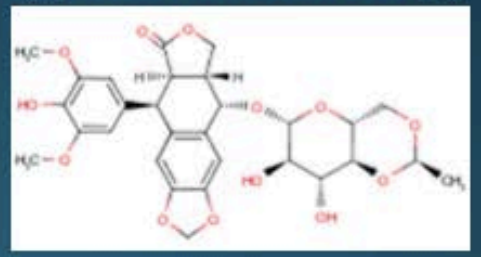


Methotrexate (309)

Type: Immunosuppressive & chemotherapy

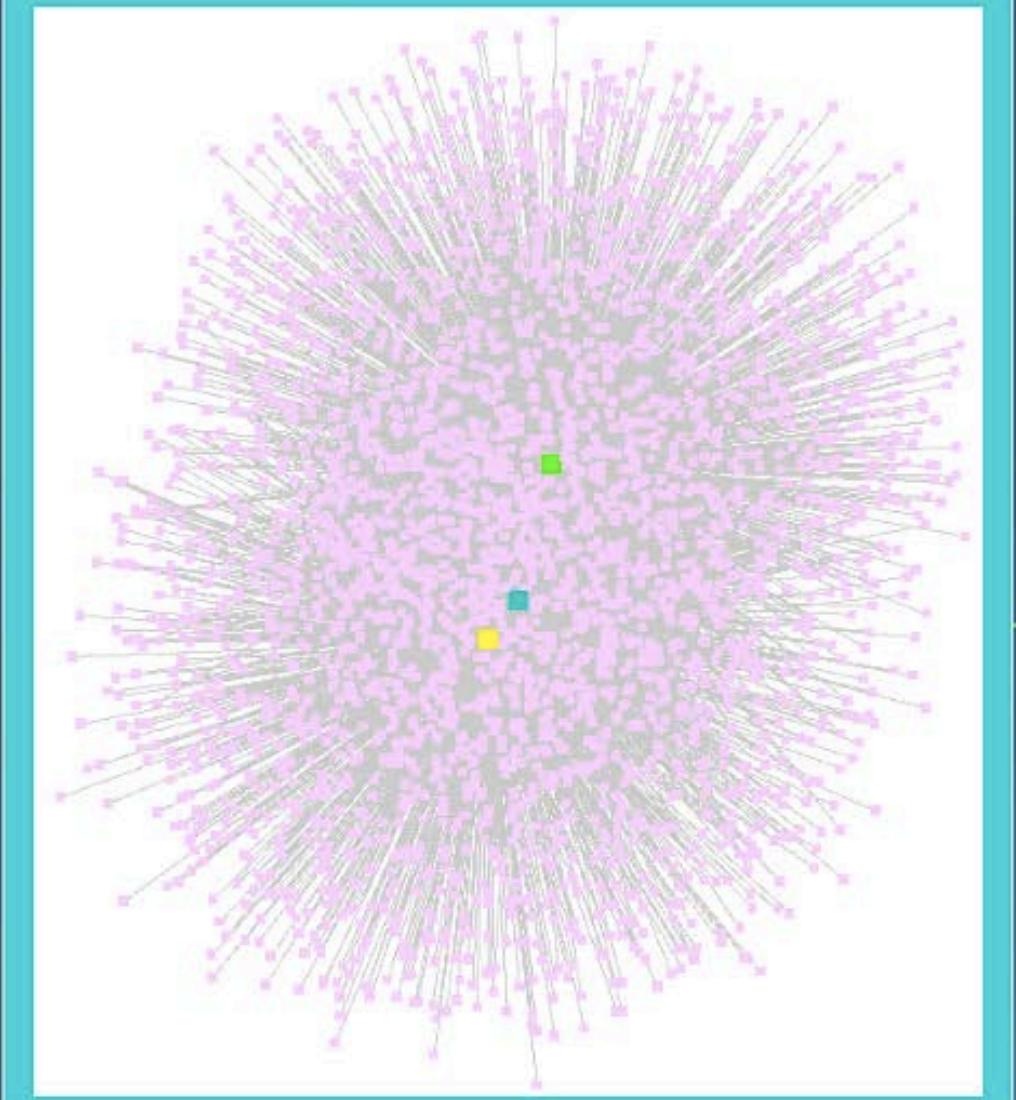
Etoposide (89)

Type: Chemotherapy



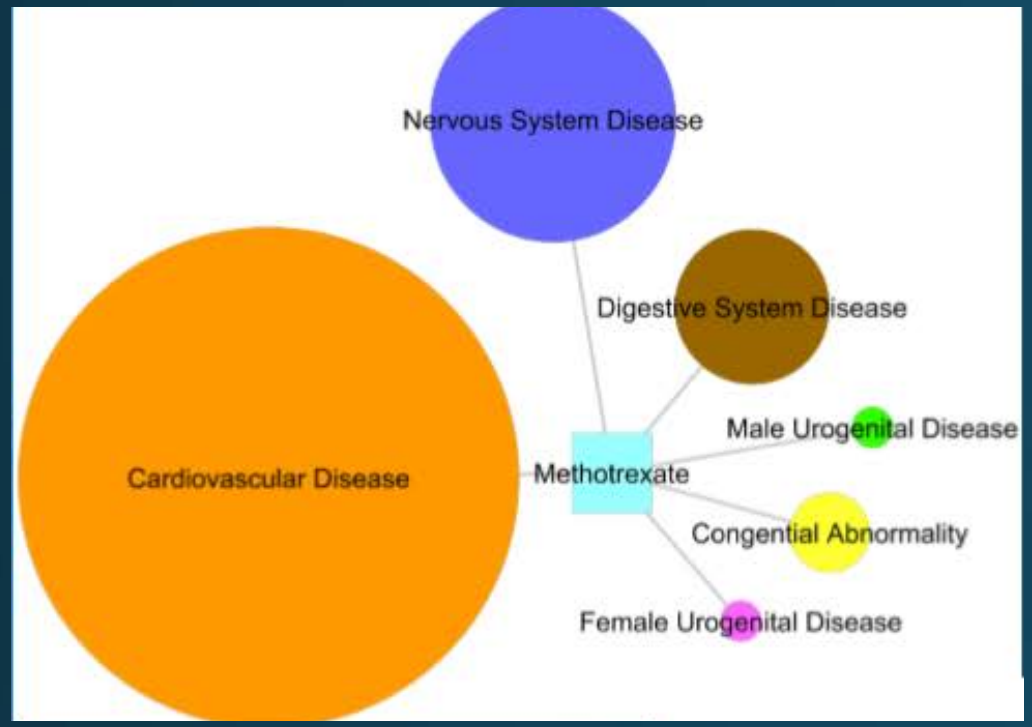
Network B2: Disease Association for 3 Cancer Drugs

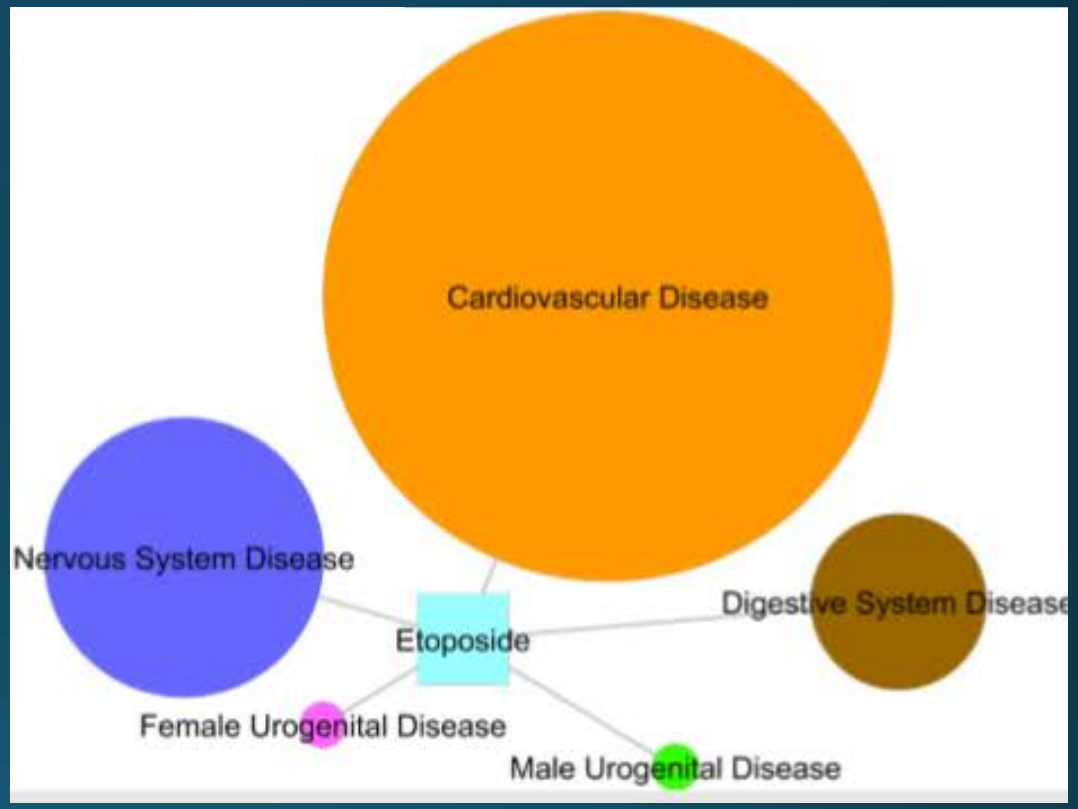
3 Cancer Drugs: Combined Network and Individual Networks

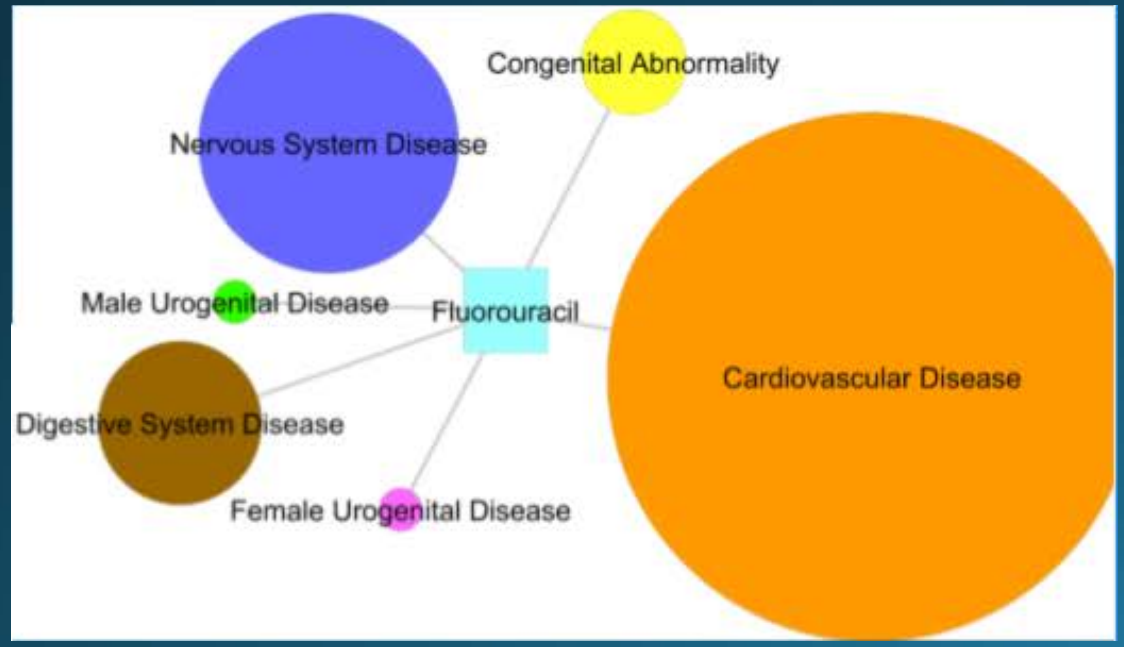


Network of Drug-Disease Association for 3 Cancer Drugs

Grouped Network: 3 Cancer Drugs





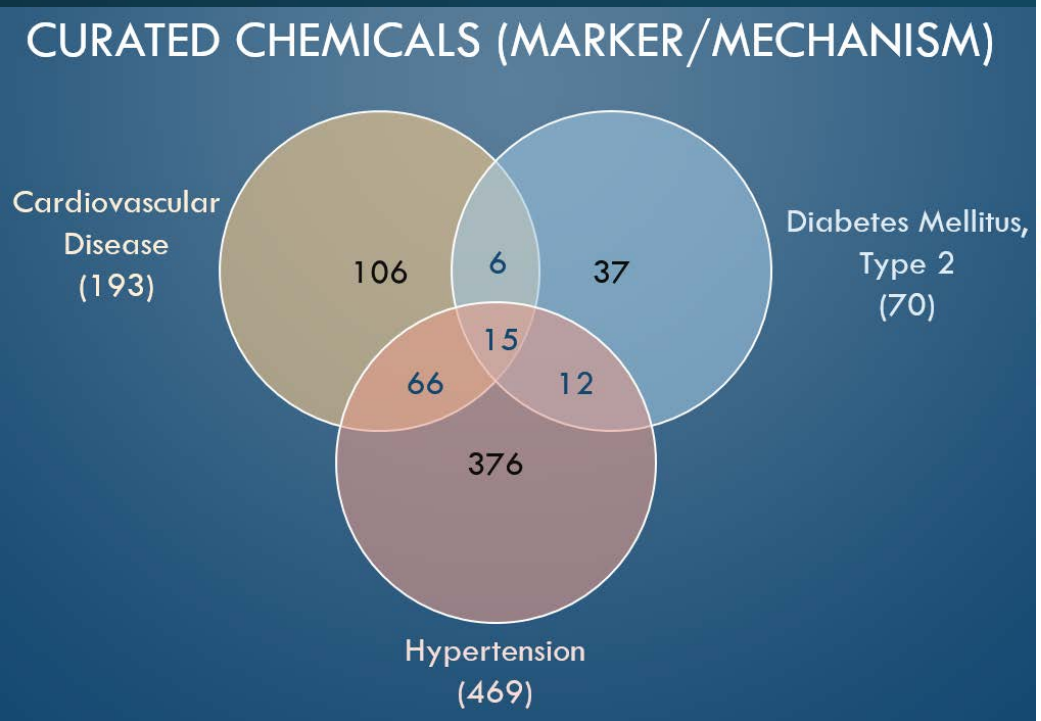


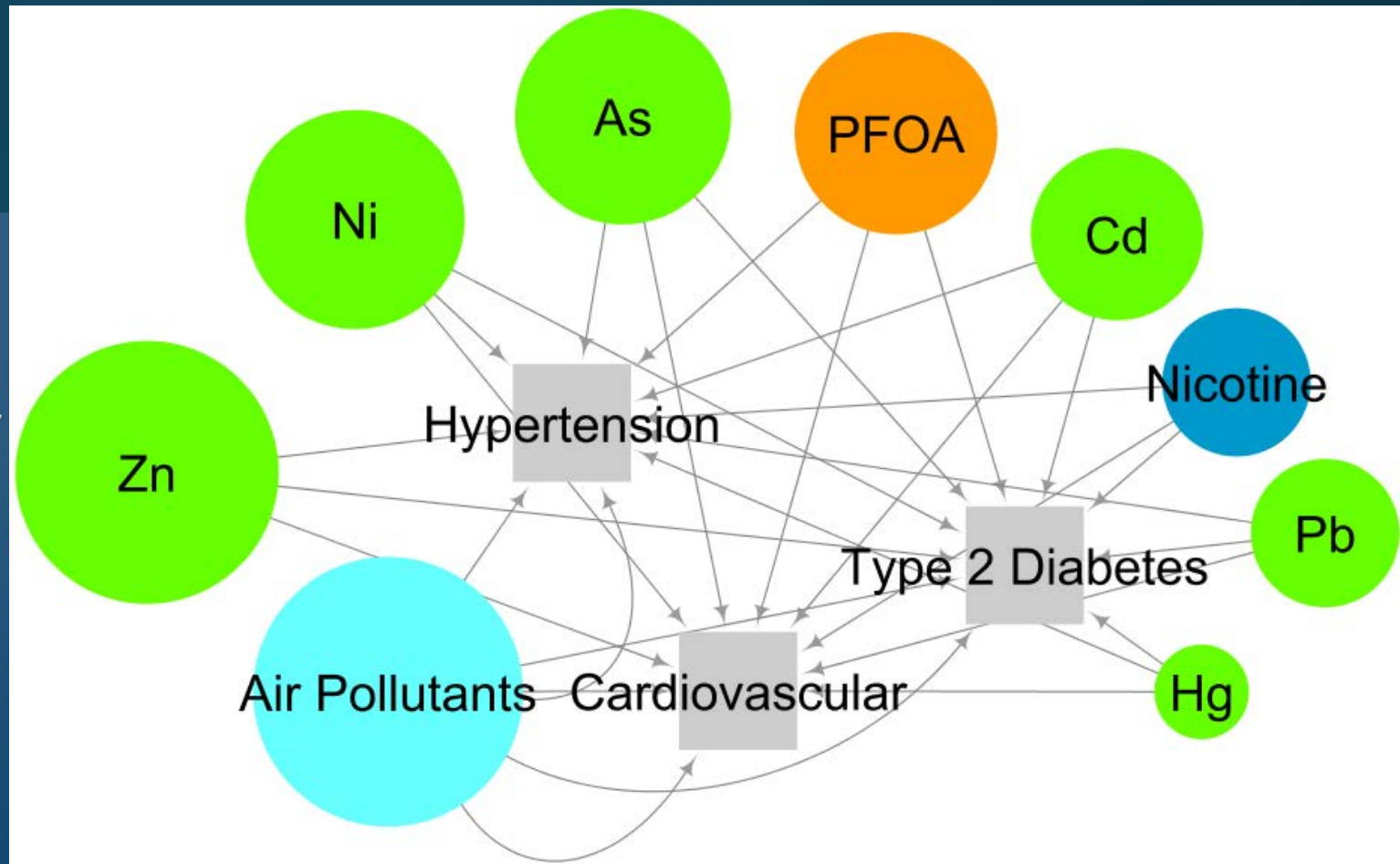
Methotrexate, Etoposide, Flurouracil all have the highest association with cardiovascular & nervous system diseases

Network C: Chemical-Disease Association

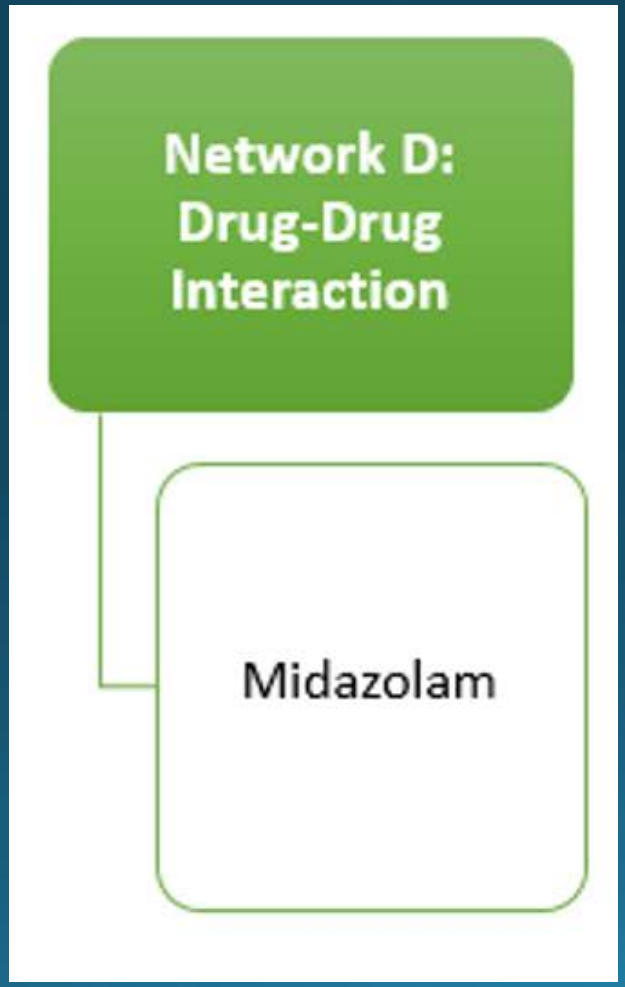
Cardiovascular disease, hypertension, and type 2 diabetes have 15 chemical associations in common.

Of these chemicals 6 are metals but the highest disease association for the three diseases is air pollutants.





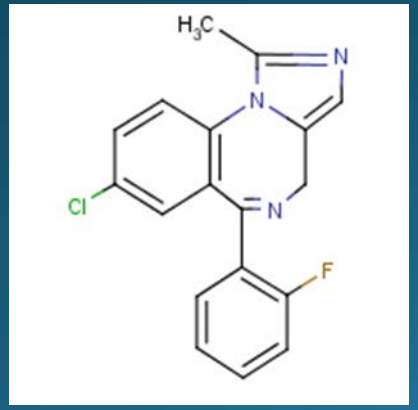
Network D: Adverse Drug-Interactions

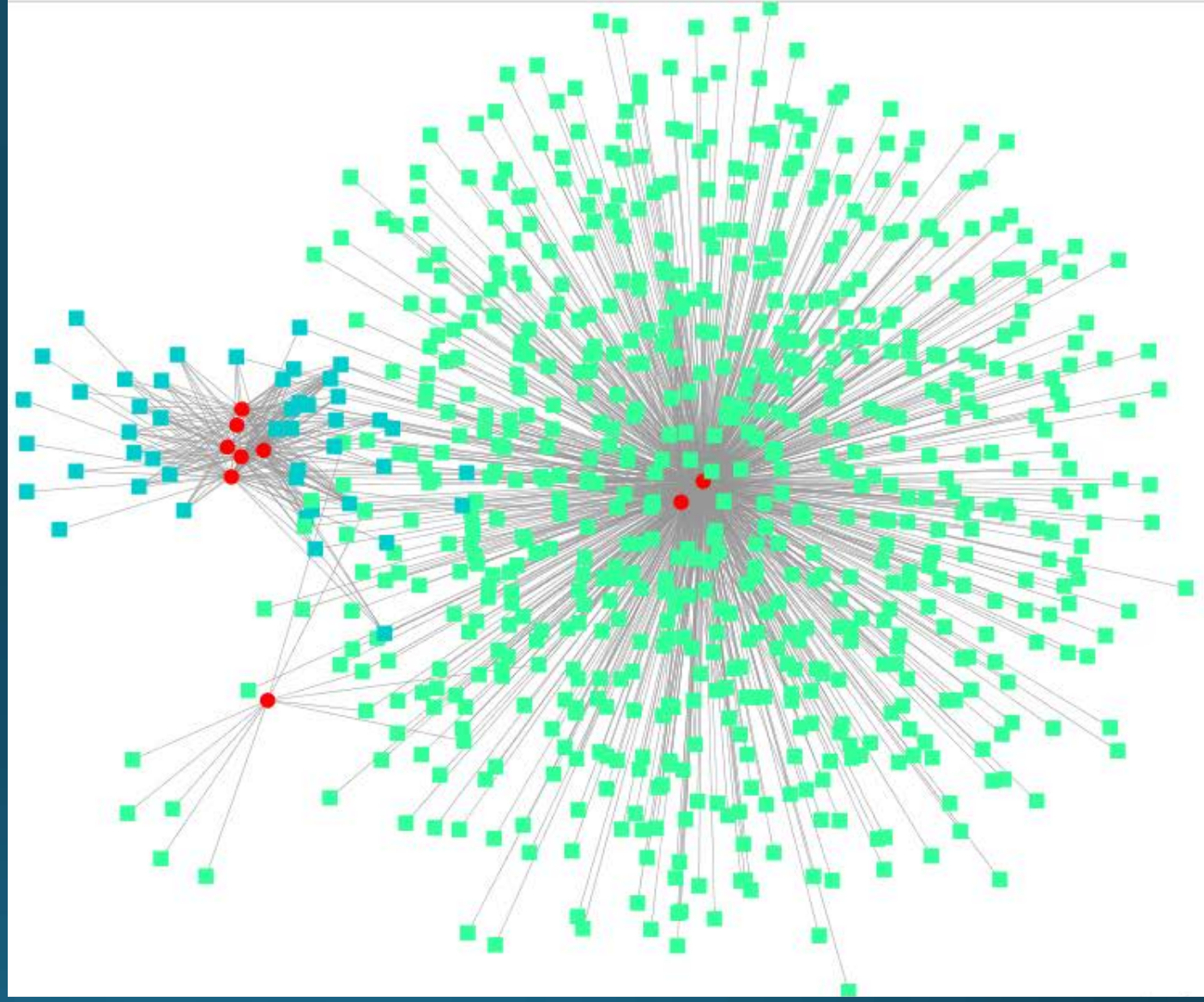


Network D: Midazolam Adverse Interactions

- A short-acting hypnotic-sedative drug with anxiolytic and amnestic properties.
- Used in dentistry, cardiac surgery, endoscopic procedures, as pre-anesthetic medication, and as an adjunct to local anesthesia.
- The short duration of action and cardiorespiratory stability makes it useful in poor-risk, elderly, and cardiac patients.

Data extracted from CTD, **Drug.com**; **Drug-Bank,** and **FDA database**





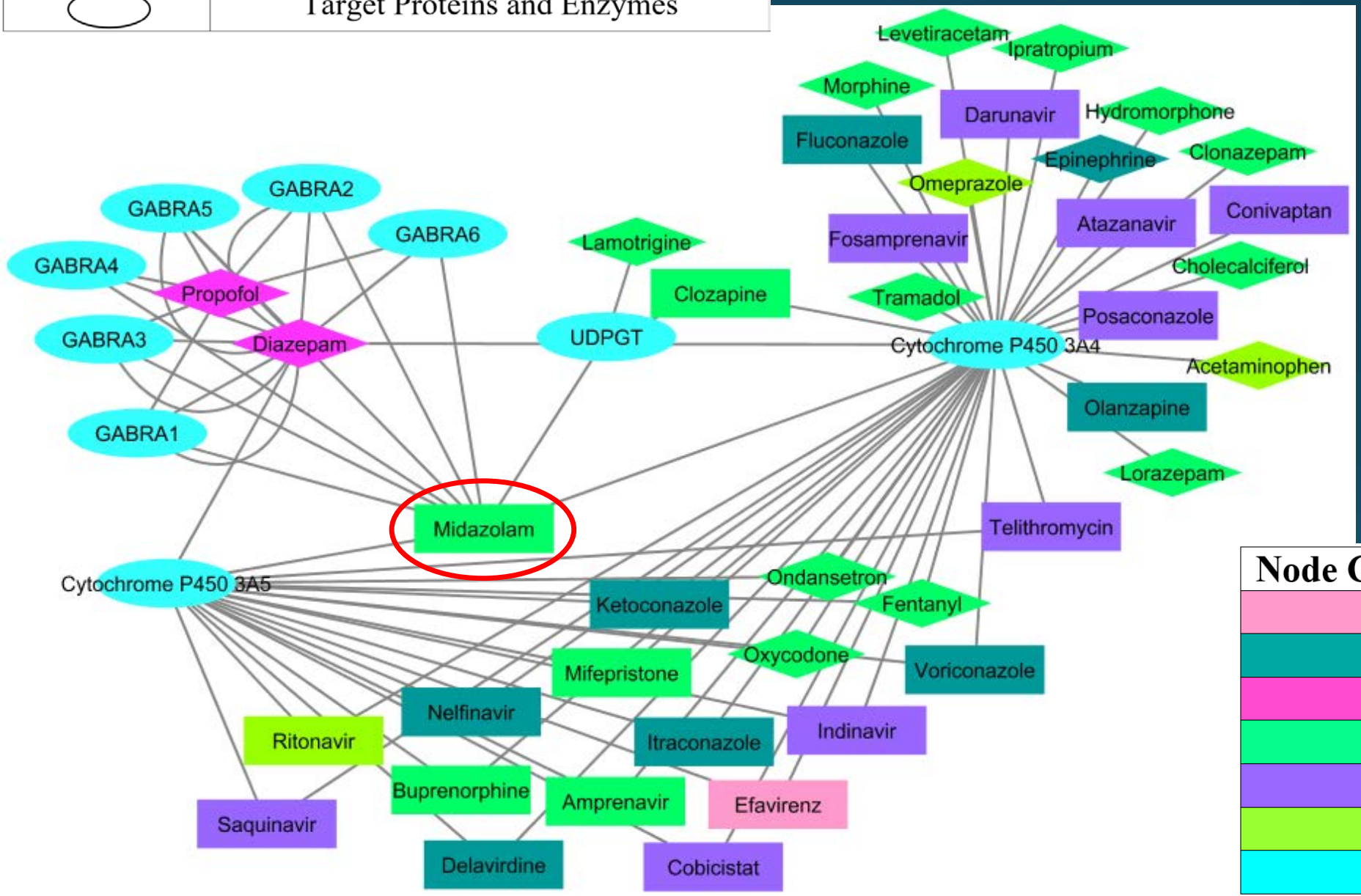
Green Squares = Drugs → Enzymes

Blue Squares = Drugs →Target Proteins

Red Circles = Targets

Curated Network for targets of Midazolam with Major and Common Drug Interactions

Node Shape	Identifies
◇	Common Drugs to Check for Interactions
▭	Major Drug Interactions
⬭	Target Proteins and Enzymes



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.

Node Color	Actions
	Inducer
	Inhibitor
	Positive Allosteric Modulator
	Substrate
	Substrate/Inhibitor
	Substrate/Inhibitor/Inducer
	Target Proteins/Enzymes

Cytoscape Usage

Total Publications

2,729 Analyze

h-index

85

Average citations per item

22.66

Sum of Times Cited

61,832

Without self citations

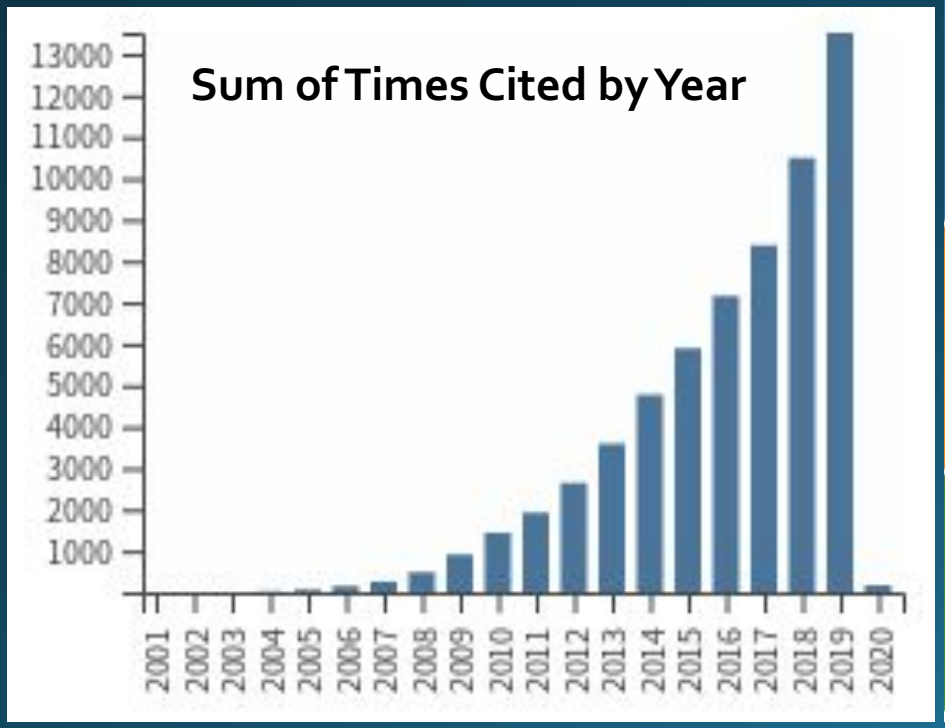
55,657

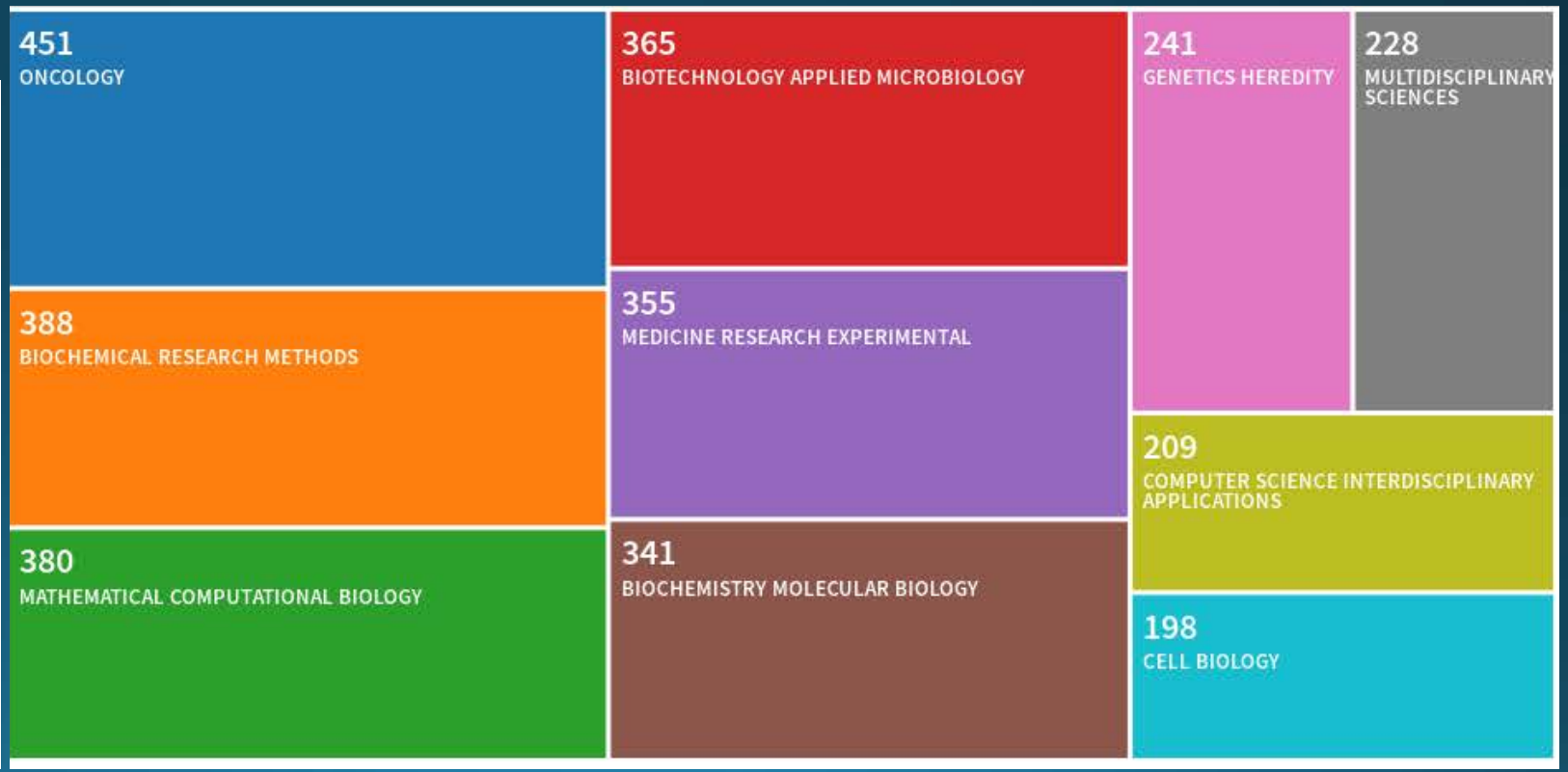
Citing articles

46,518 Analyze

Without self citations

44,143 Analyze





CTD Usage

Total Publications

795 Analyze

h-index

76

Average citations per item

30.77

Sum of Times Cited

24,463

Without self citations

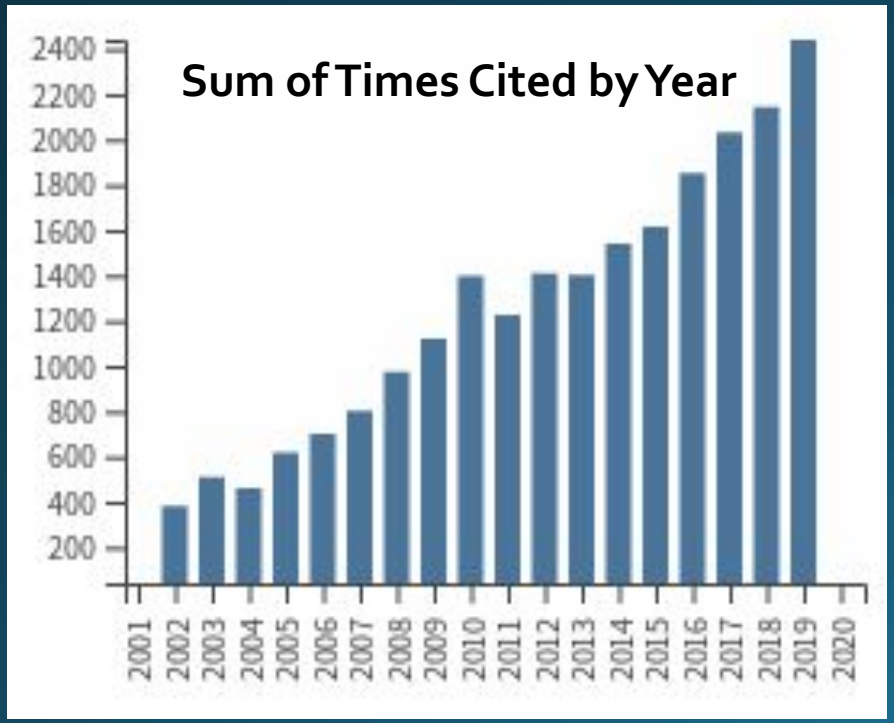
23,051

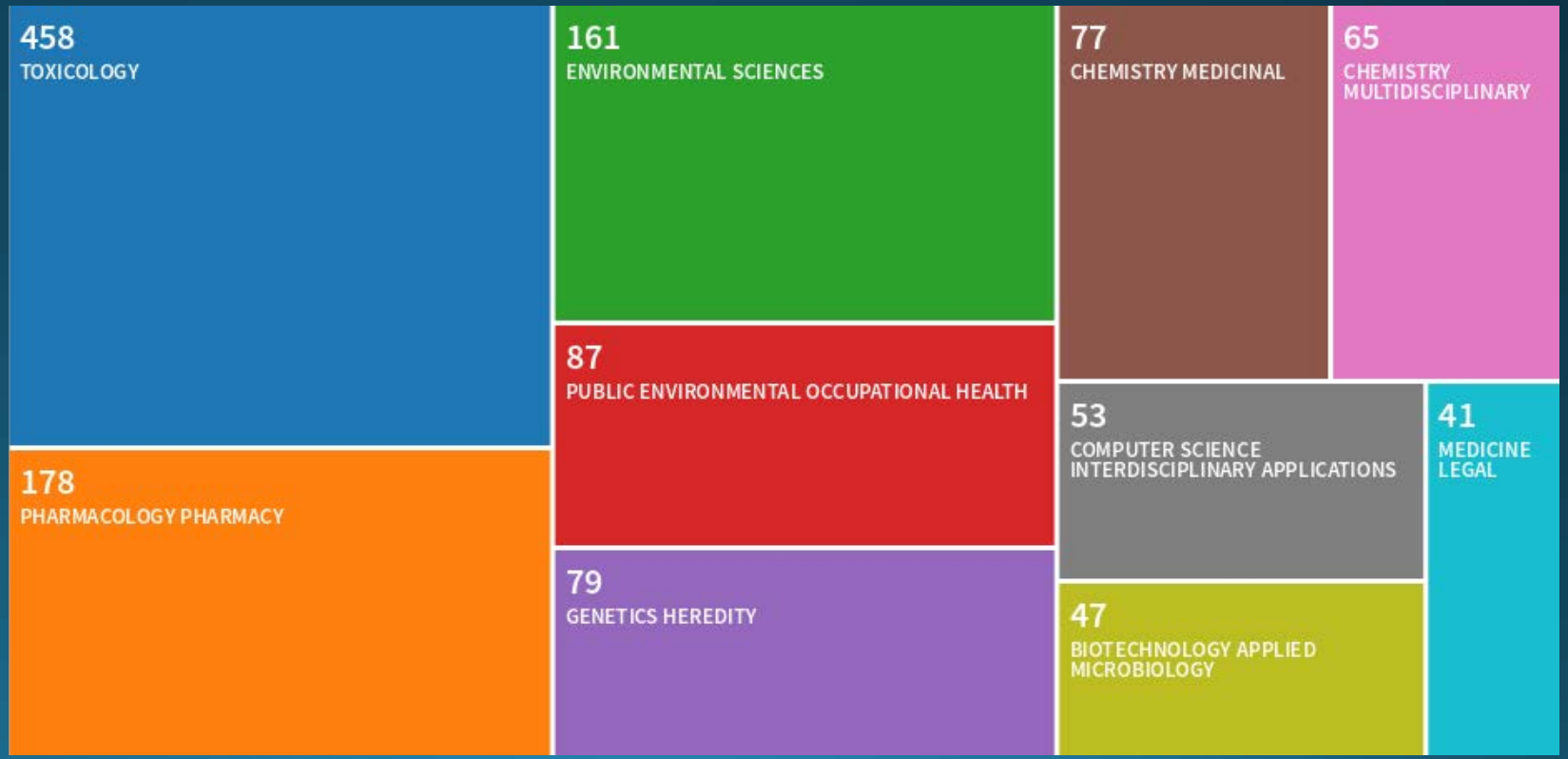
Citing articles

18,220 Analyze

Without self citations

17,799 Analyze





DrugBank Usage

Total Publications

470 Analyze

h-index

47

Average citations per item

31.56

Sum of Times Cited

14,834

Without self citations

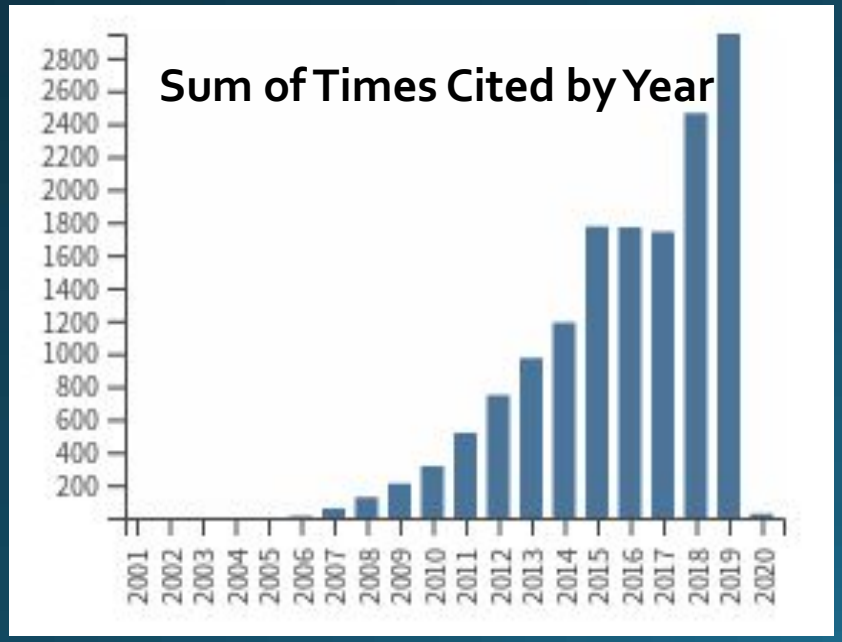
14,056

Citing articles

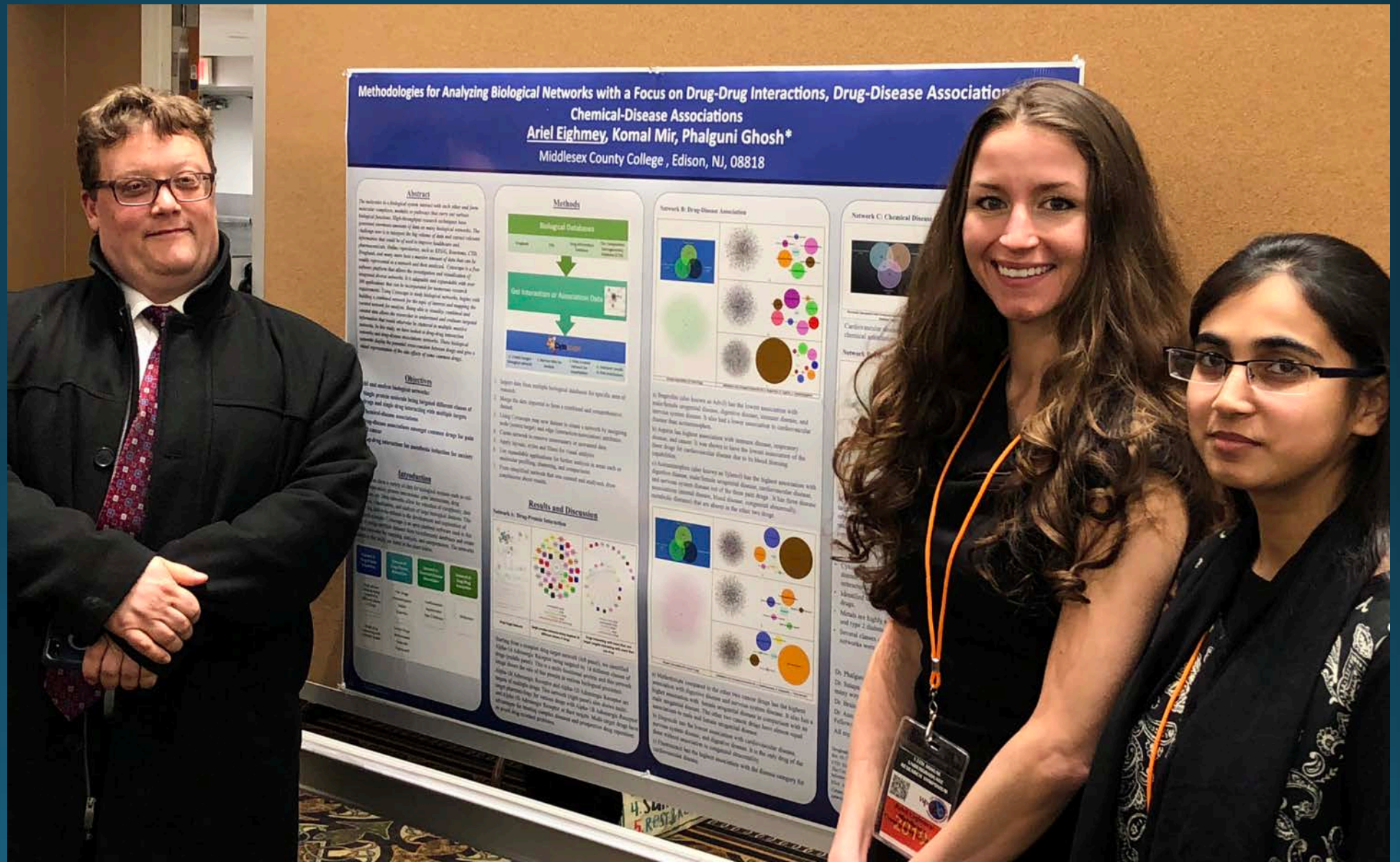
11,715 Analyze

Without self citations

11,330 Analyze



Ariel & Komal


Methodologies for Analyzing Biological Networks with a Focus on Drug-Drug Interactions, Drug-Disease Associatio
Chemical-Disease Associations
Ariel Eighmey, Komal Mir, Phalguni Ghosh*
Middlesex County College , Edison, NJ, 08818
Abstract
Methods
Biological Databases
Objectives
Introduction
Results and Discussion

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Thank you for your kind Attention.