Integrated Pipeline for Systems Pharmacology in R/Bioconductor

Nan Xiao @road2stat
7th China R Beijing

COMPUTATIONAL BIOLOGY &
DRUG DESIGN GROUP
CENTRAL SOUTH UNIV., CHINA

2009
Vulnerability & Security

2013

Web Scraping with R

2014

Systems Pharmacology

时间都去哪儿了

TIME FLIES... 1994–2009

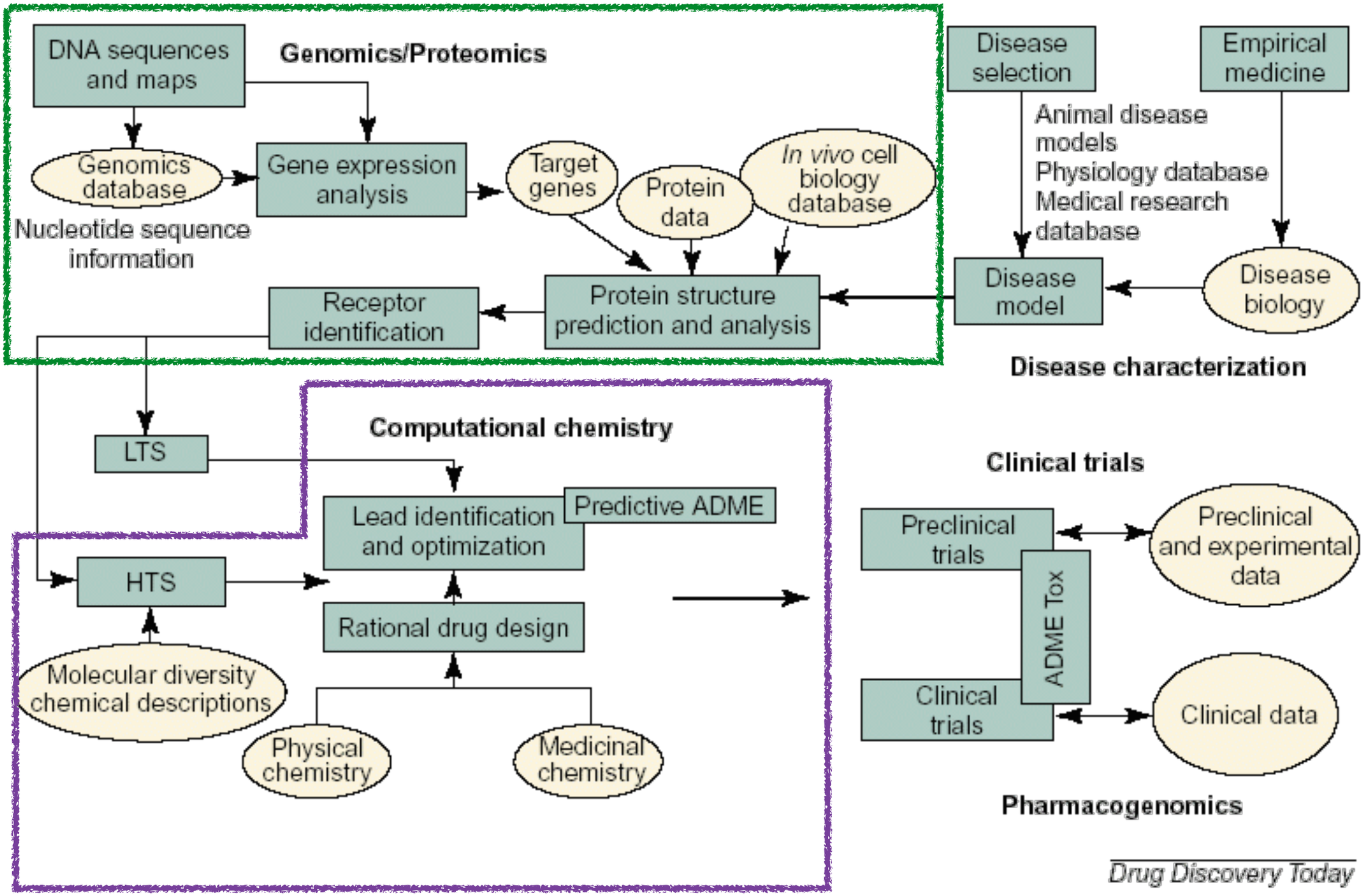
TIME FLIES... 2009–2014

Outline

- Intro: Systems Pharmacology
- Pipeline: Our solution with R
- Case study: Identify novel drug-ADR associations

Part I
Systems Pharmacology

Flow of Information in a Drug Discovery Pipeline



The Evolution of the Innovation

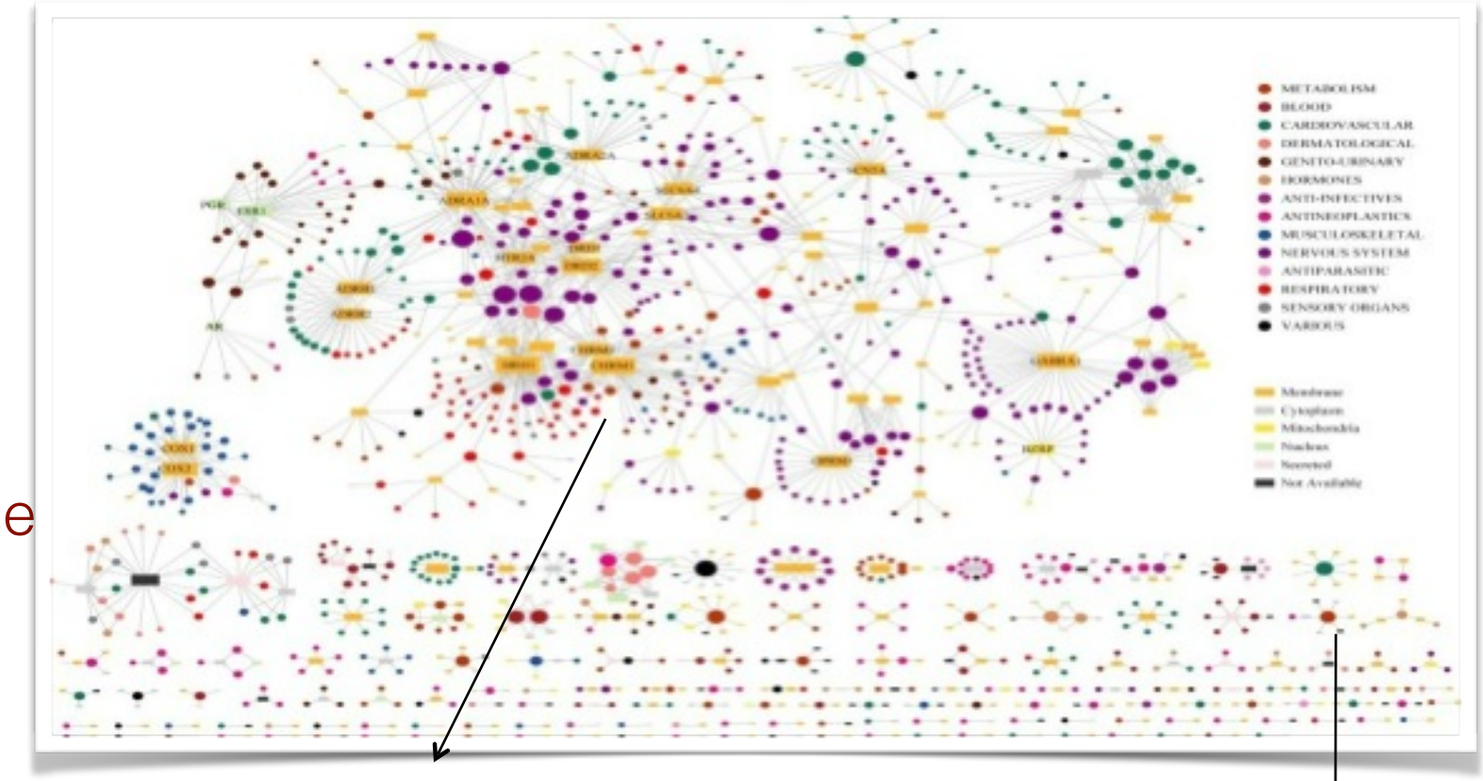
Reductionism

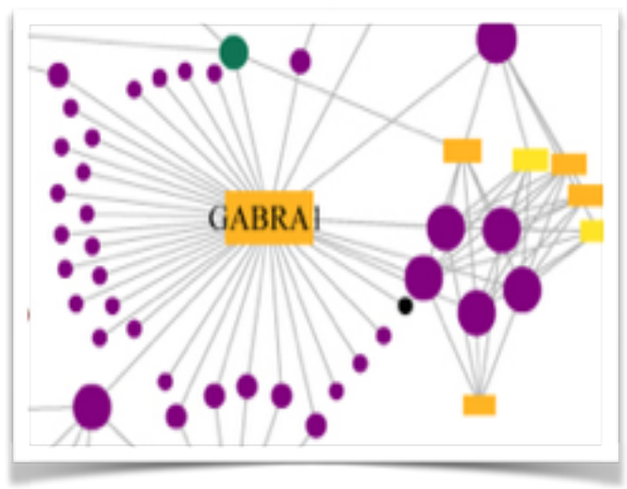
- Key - Lock Model
- Clean Drug
- One drug, one target, one disease

System Theory

- Systems Pharmacology
- Network Pharmacology
- Systems Biology

The Facts





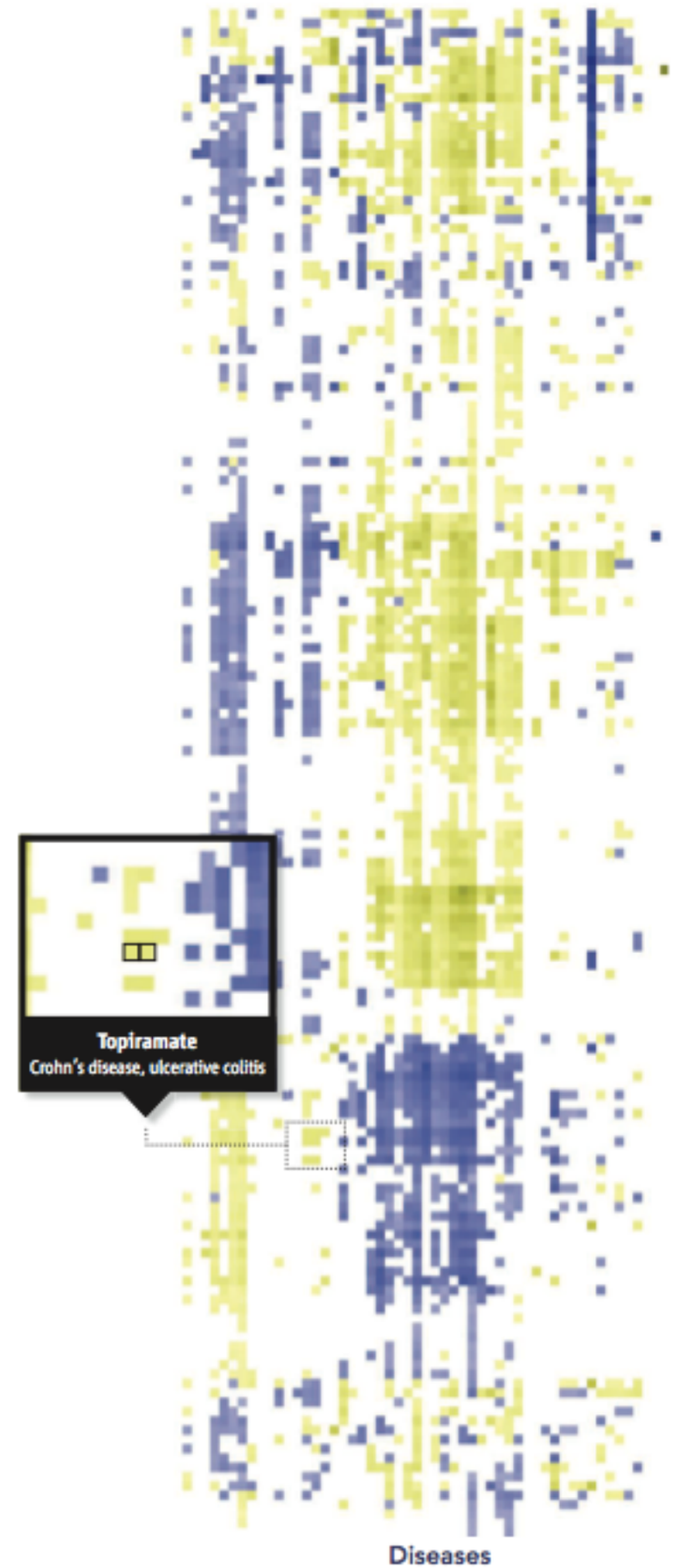
Target *GABRA1* link to ~40 drugs

Drug *Olanzapine* link to ~11 targets

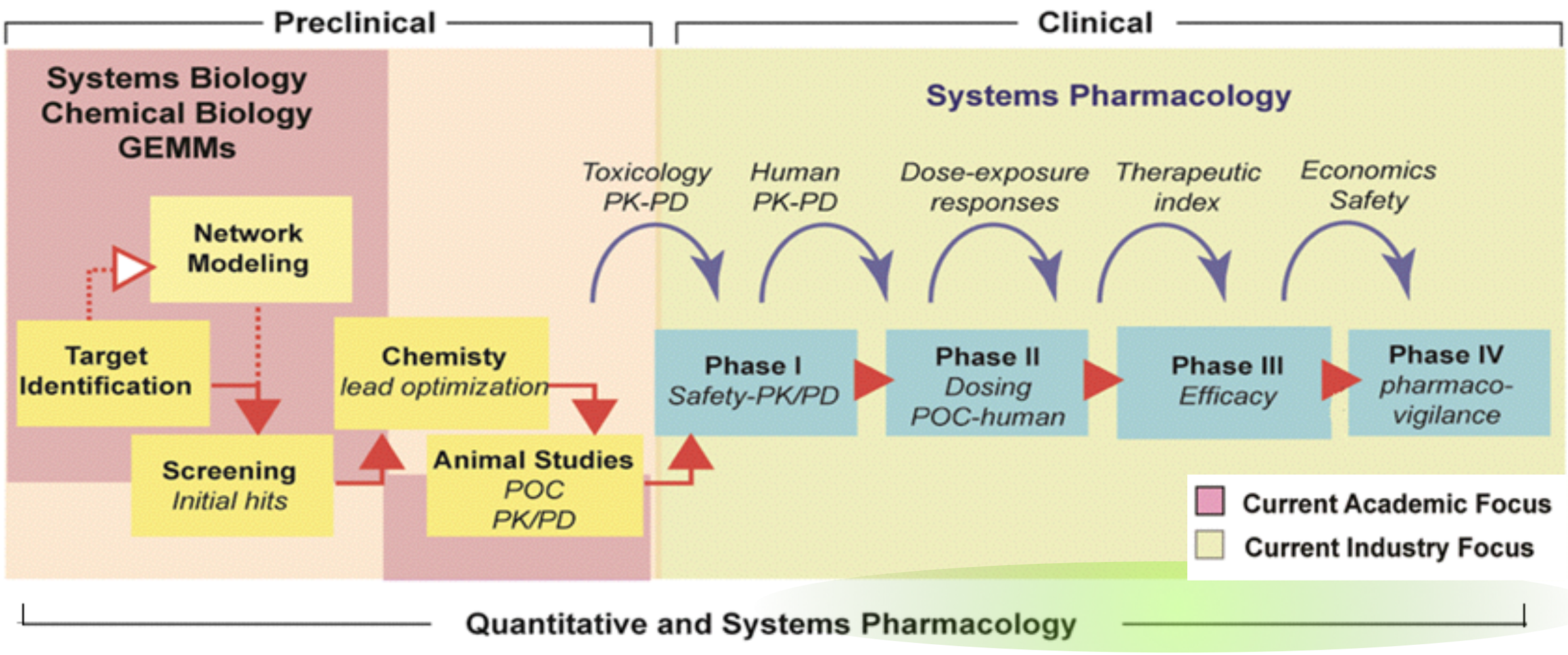
Yildirim,M.A., Goh, k.-I,. Cusick, M.E., Barabasi, A.-l & Vidal, M. (2007) *Nat. Biotech.* 25, 1119-1126.

Big Data, Small Details

M. Sirota et al., Discovery and preclinical validation of drug indications using compendia of public gene expression data. Sci. Transl. Med. 3 (2011).



Pipeline of Systems Pharmacology



Academic

- Application of systems biology approaches
- Combining large-scale experimental studies
- Model-based computational analyses to study drug activities, targets, and effects

Industry

- Using pharmacodynamic (PD) and pharmacokinetic (PK) modelling
- Predicting dose-exposure responses and evaluating market potential

NIH White Paper by the QSP Workshop Group (Oct, 2011)

Biology's Dry Future

The explosion of publicly available databases housing sequences, structures, and images allows life scientists to make fundamental discoveries without ever getting their hands "wet" at the lab bench

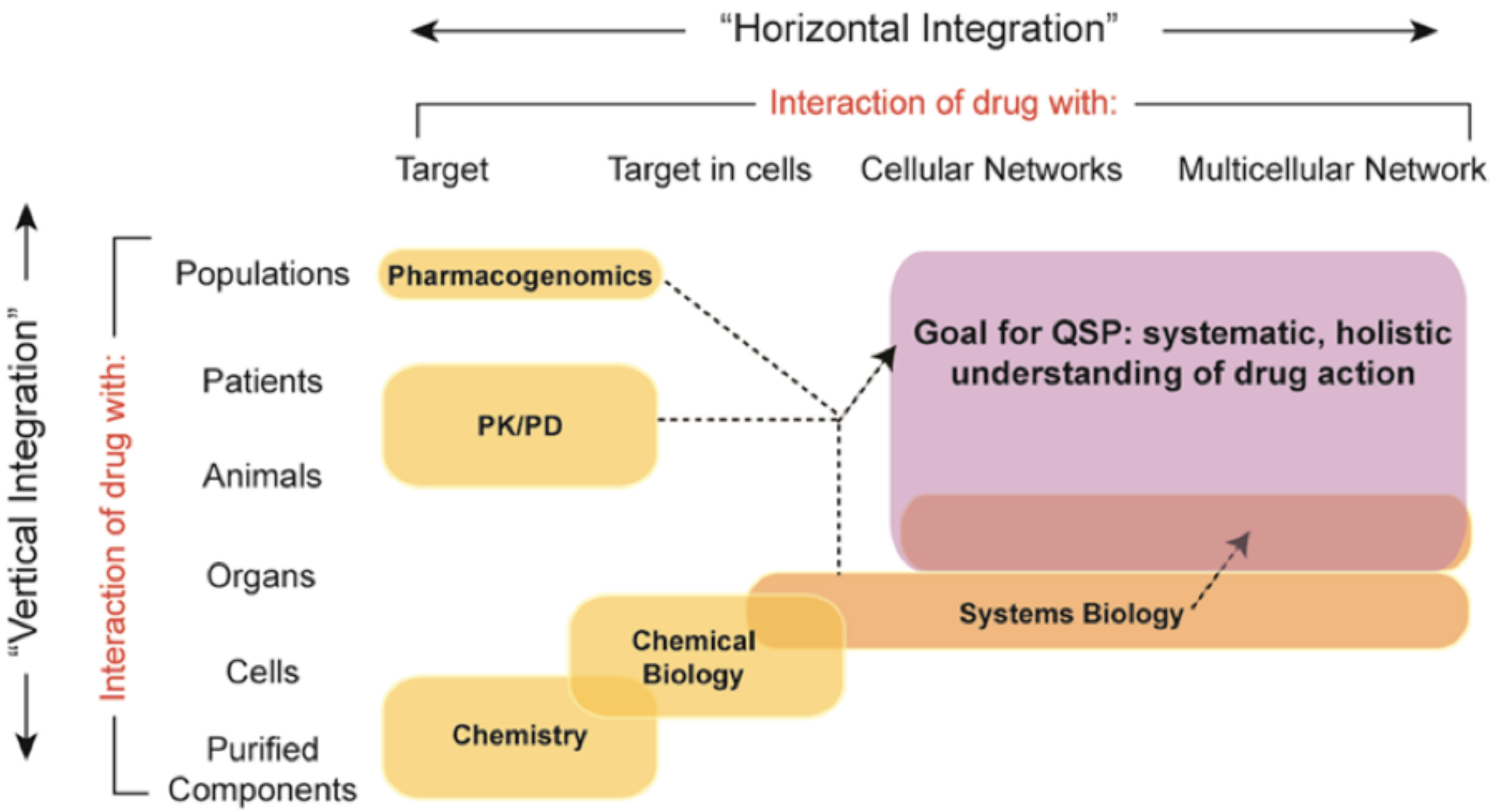
Science (2013) 342, 186-189.

"I'm like a **kid in a candy store**. There is so much we can do."

—Atul Butte, Stanford University School of Medicine

"You basically **don't need a wet lab** to explore biology."

—David Heckerman, Microsoft Research



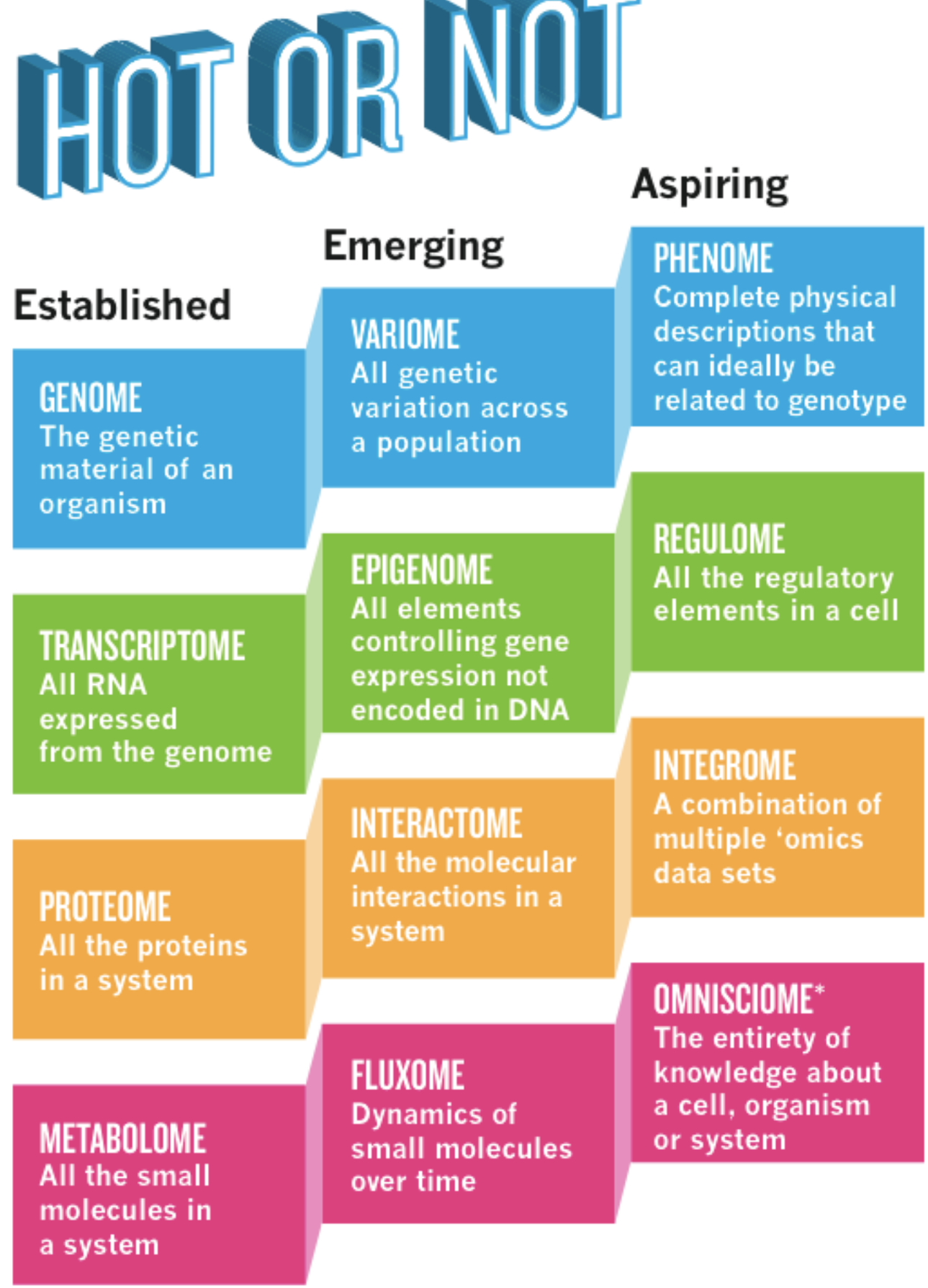
Integration-based systematic thinking, is the core of QSP.

THE 'OMES PUZZLE

Where once there was the genome, now there are thousands of 'omes.

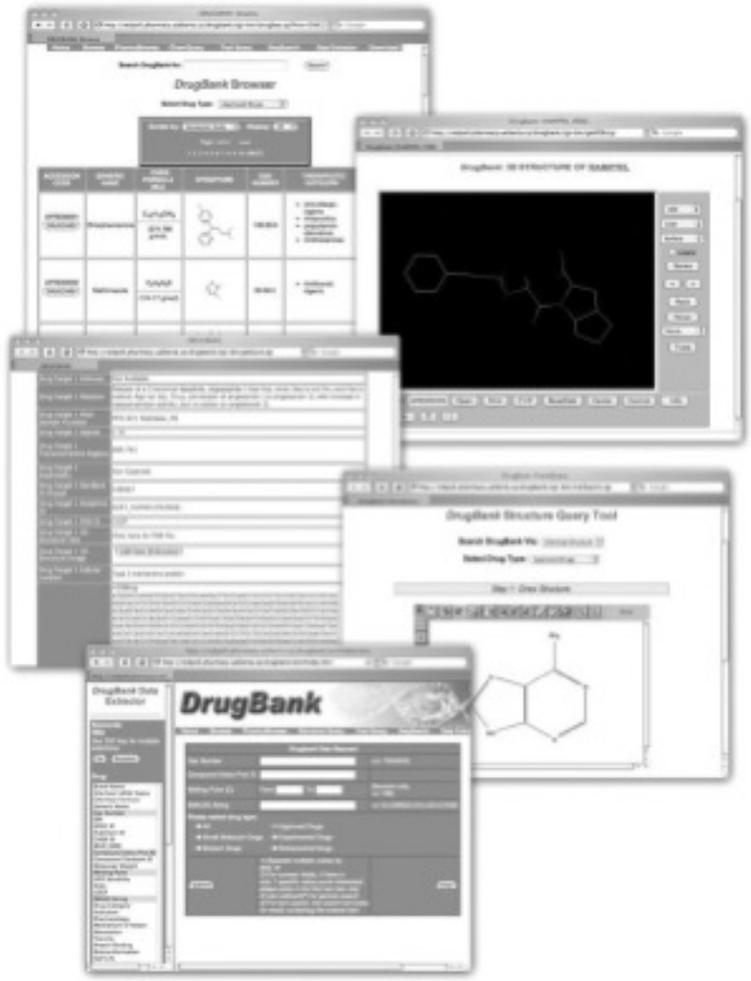
It's a trend to integrate the Omics data, numerical or non-numerical, structural or non-structural, semantic or non-semantic.

Nature (2013) 494, 416-419.



The Dawn of A New Era: Bio Big Data Blossom

Drugbank Database

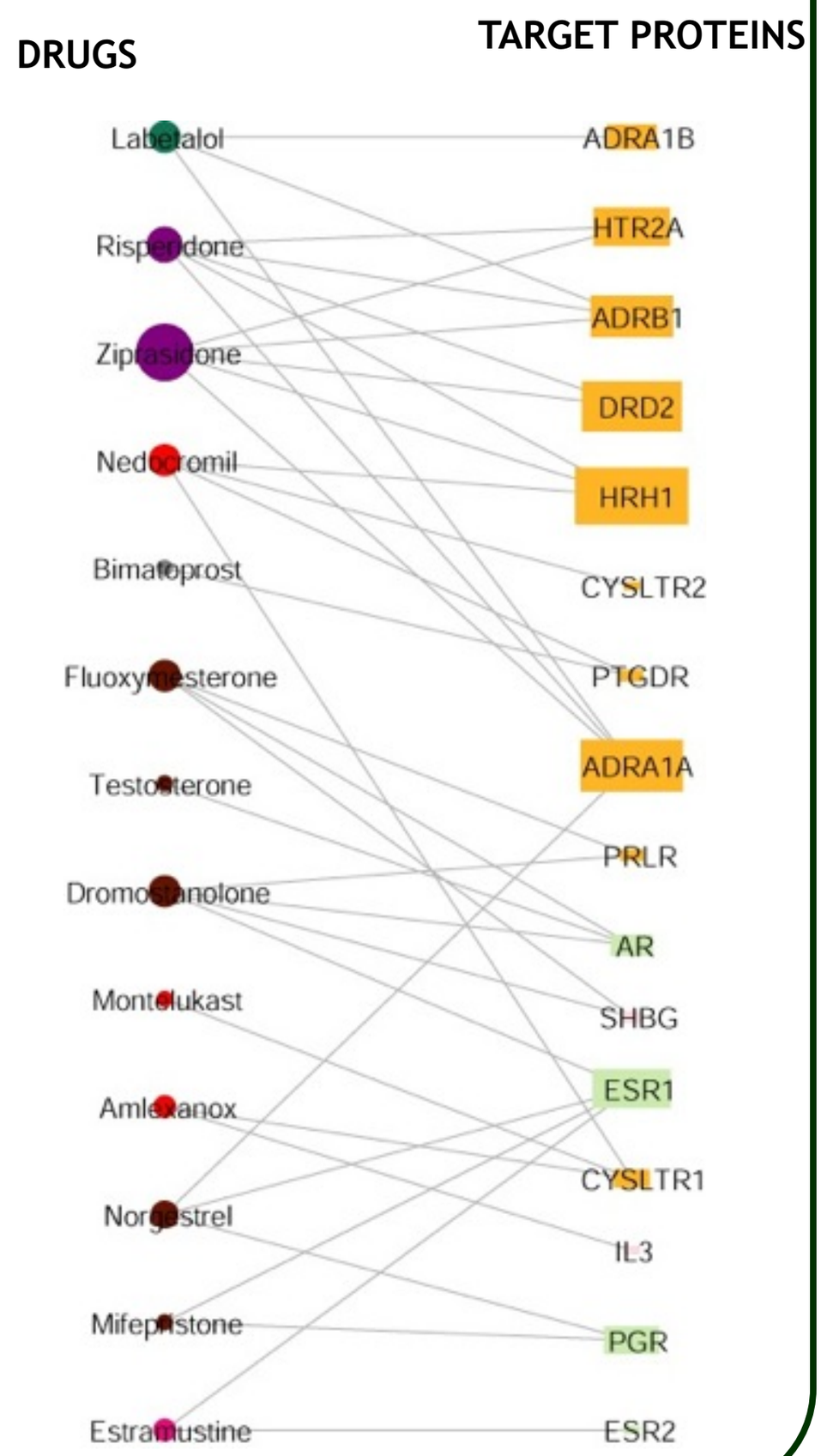


1179 FDA-approved small molecule & biotech drugs (different chemical entities)

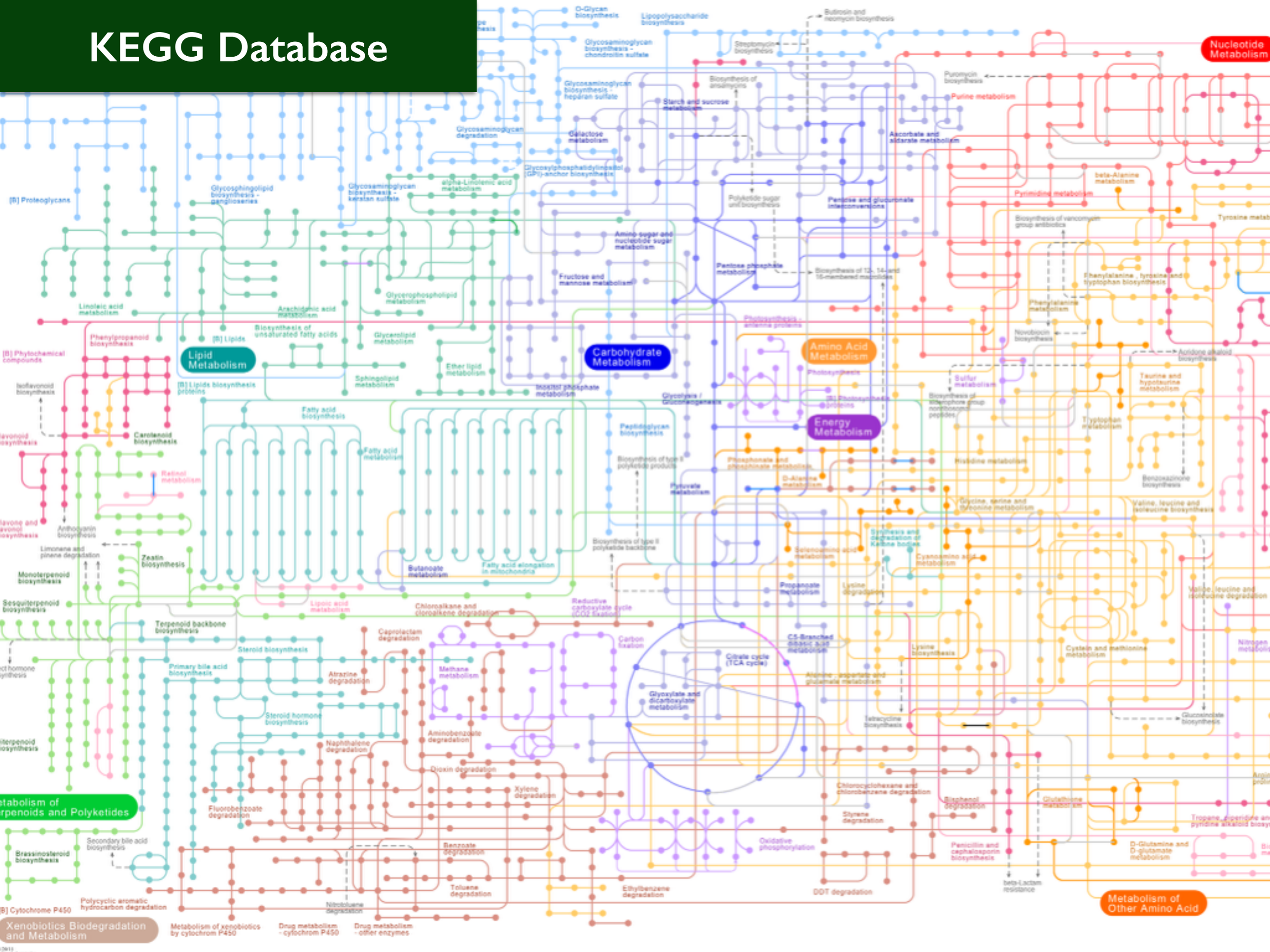
890 / 1179 has human protein targets390 Human Drug Target Proteins for Approved Drugs.

Wishart DS et al., Nucleic Acids Res. 2006 1;3

Drug-Target



KEGG Database

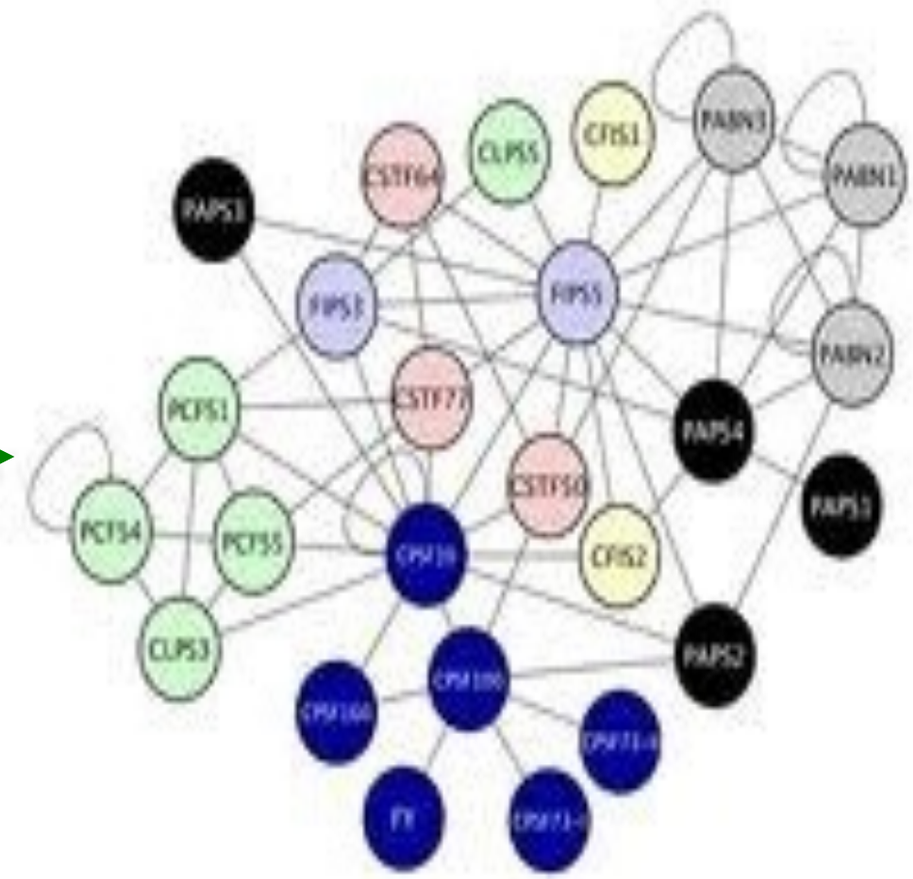


UniProt Database

The mission of UniProt is to provide the scientific community with a comprehensive, high-quality and freely accessible resource of protein sequence and functional information.

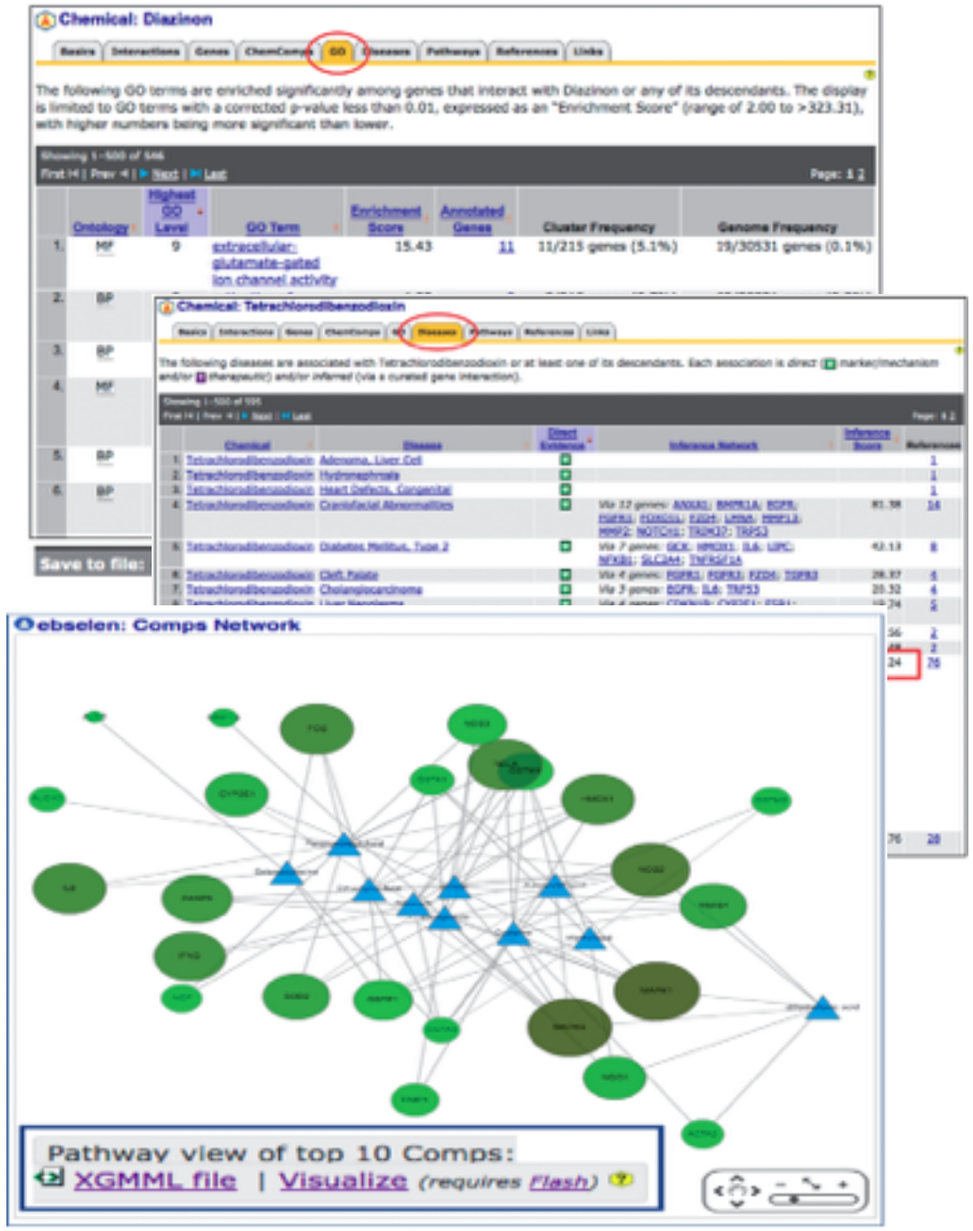
BioGRID Database

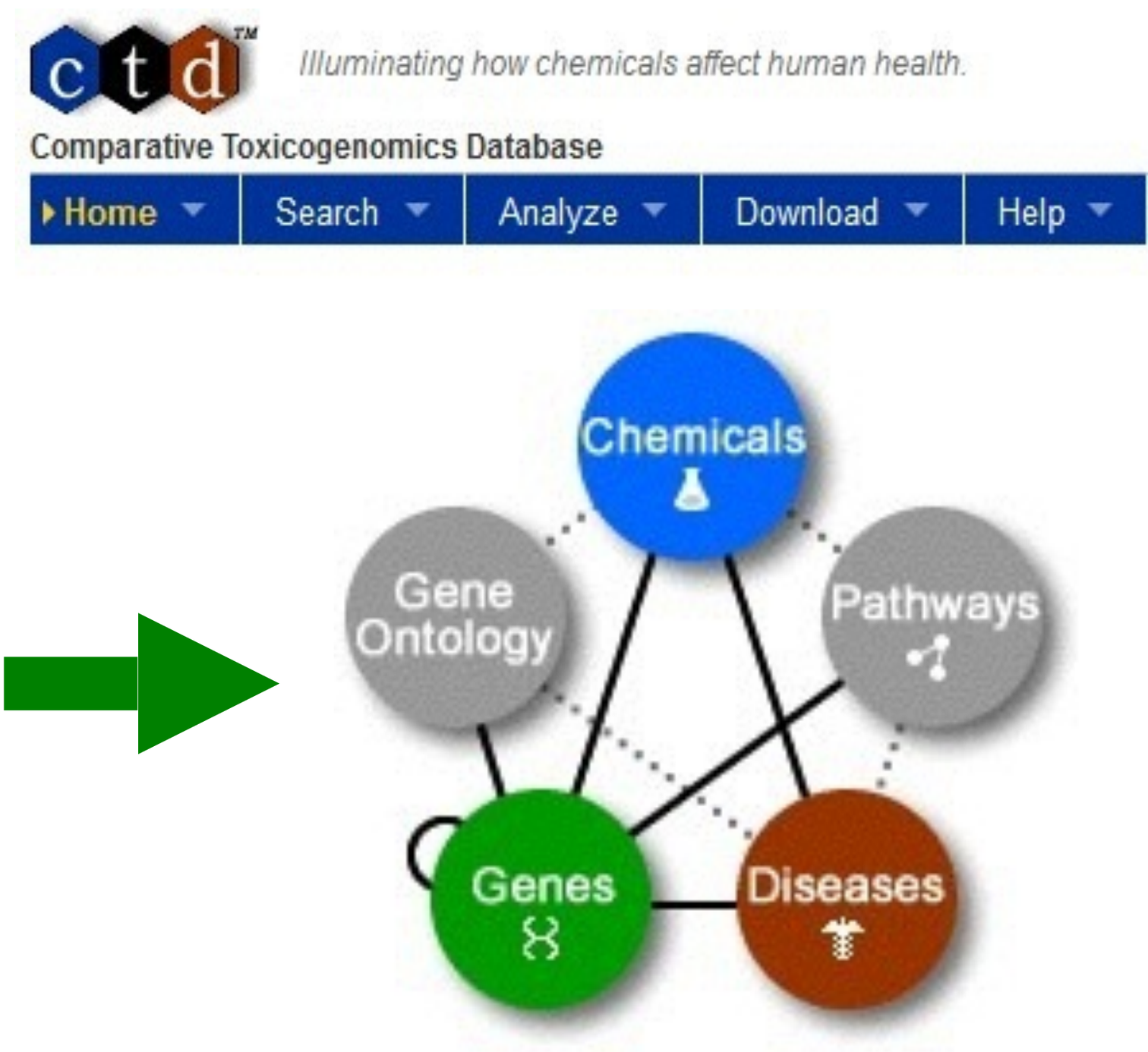
PPI network



BioGRID is an online interaction repository with data compiled through comprehensive curation efforts. The current index searches 41,785 publications for 722,541 raw protein and genetic interactions from major model organism species.

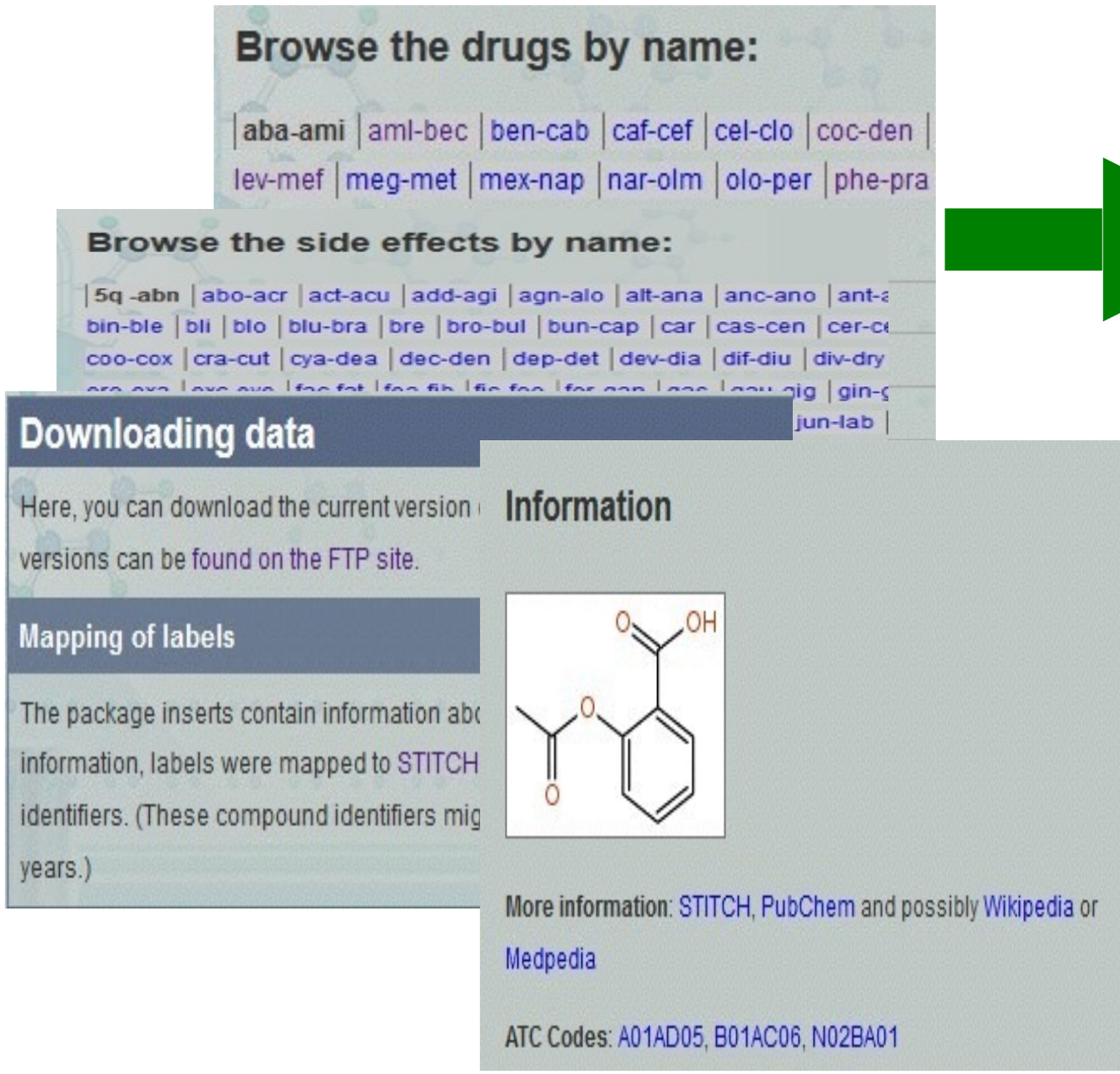
CTD Database

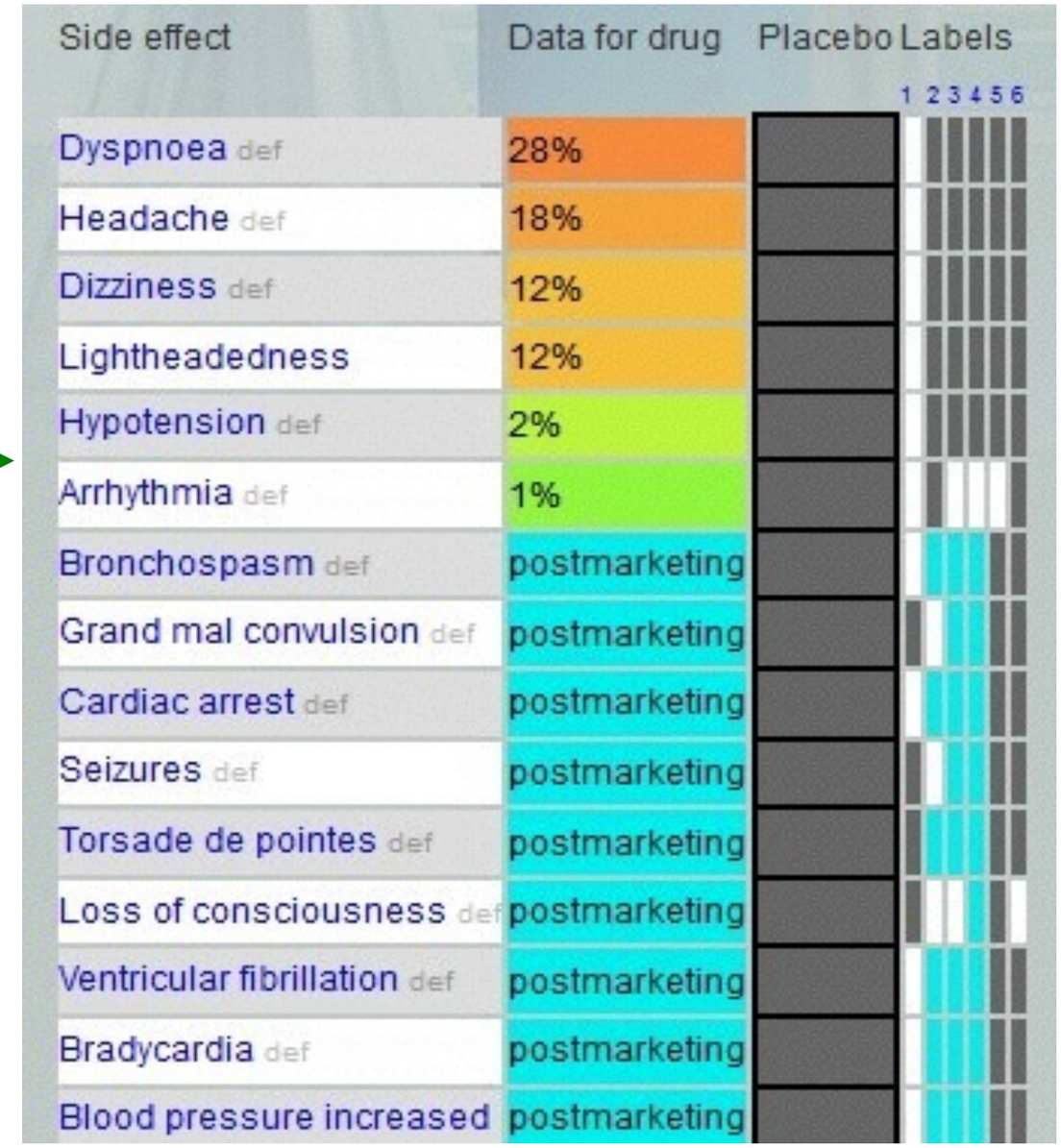




The Comparative Toxicogenomics Database (CTD) provides information about interactions between environmental chemicals and gene products and their relationships to diseases. Chemical-gene, chemical-disease and gene-disease interactions manually curated from the literature are integrated.

SIDER Database





SIDER contains information on marketed medicines and their recorded ADRs. The information is extracted from public documents and package inserts. It contains 99423 drug-ADR pairs associated with 996 drugs and 4192 ADRs.

Michael Kuhn et al., Molecular Systems Biology 2010 (6) 1-6

Database statistics

Number of drugs and side effects

# of SE	# of drugs	# of drug-SE pairs	Pairs with frequency information
4192	996	99423	40.8%

Number of drug–side effect pairs in different frequency ranges

	frequent (with exact data)	infrequent (with exact data)	rare (with exact data)	postmarketing	total
drug	11475 (10316)	9471 (3236)	6650 (2068)	21664	40603
placebo	4330 (4330)	2043 (2043)	1425 (1425)	0	6370

Version Information

The current version has been released on October 17, 2012. This release uses the MedDRA dictionary (version 14.0) and provides access to preferred terms and lower-level terms. The number of drugs has increased from 888 to 996. Compared to the release in March 2012, additional side effects have been retrieved by better processing of the labels. Side effects that are mentioned on the label as either potential or not occurring are removed. SIDER 1 is still available via FTP.

CHALLENGE ACCEPTED

Part II

Packages & Web Servers

What do we need for Systems Pharmacology Modeling?

- Information: Multi-scale Representation
- Methodology: Multi-scale Modeling

What does R need?

- Good at methodology and modeling, state-of-art statistical machine learning methods, Bioconductor
- Lacks of bio/chem data representation
- A good representation is fundamental and critical

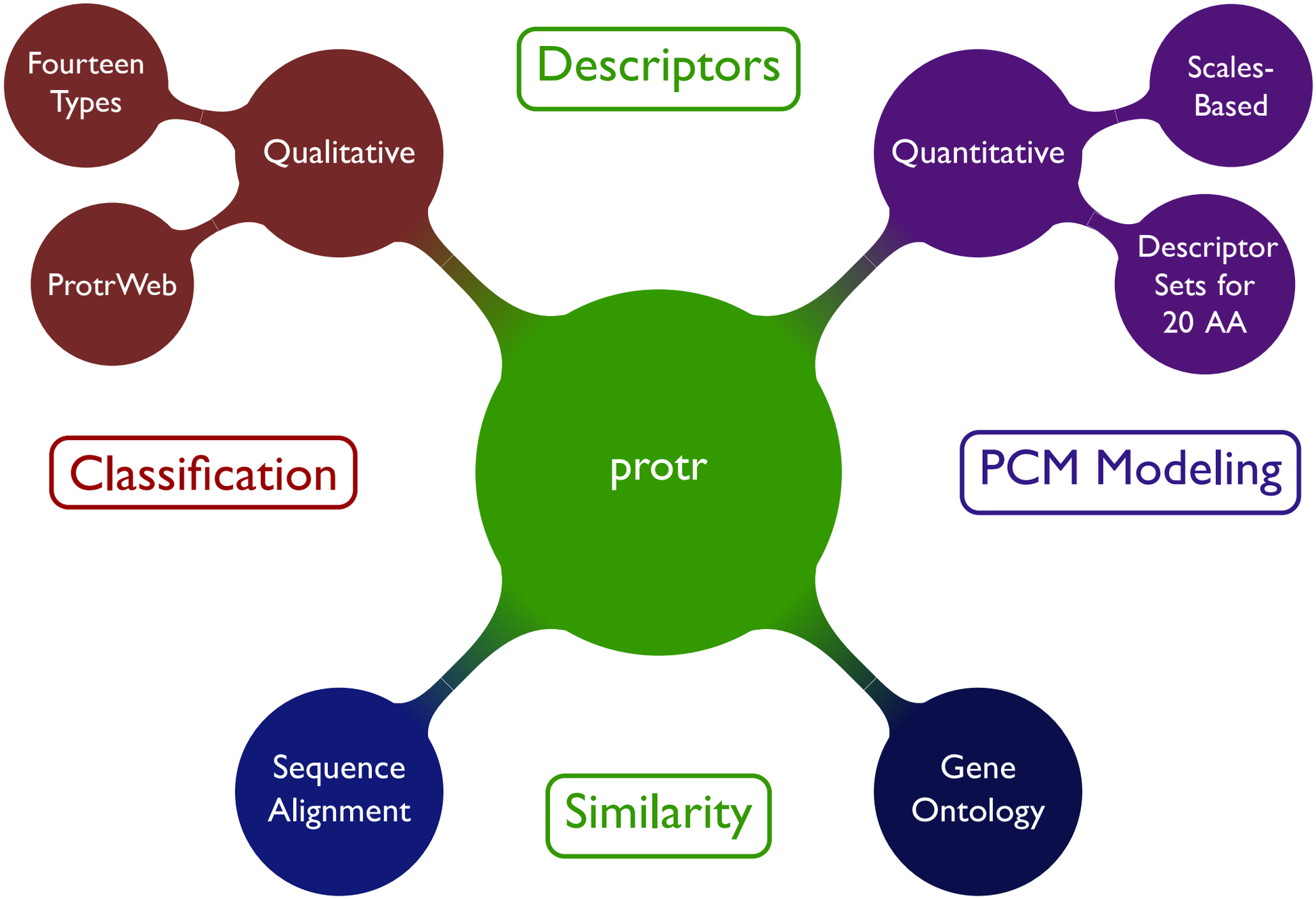
What we did?

R/Bioconductor packages for

multi-scale molecular representation

protr

Protein Sequence Descriptor Calculation
and Similarity Computation with R



Schematic diagram of the protr package.
from Xiao et al., (2014)

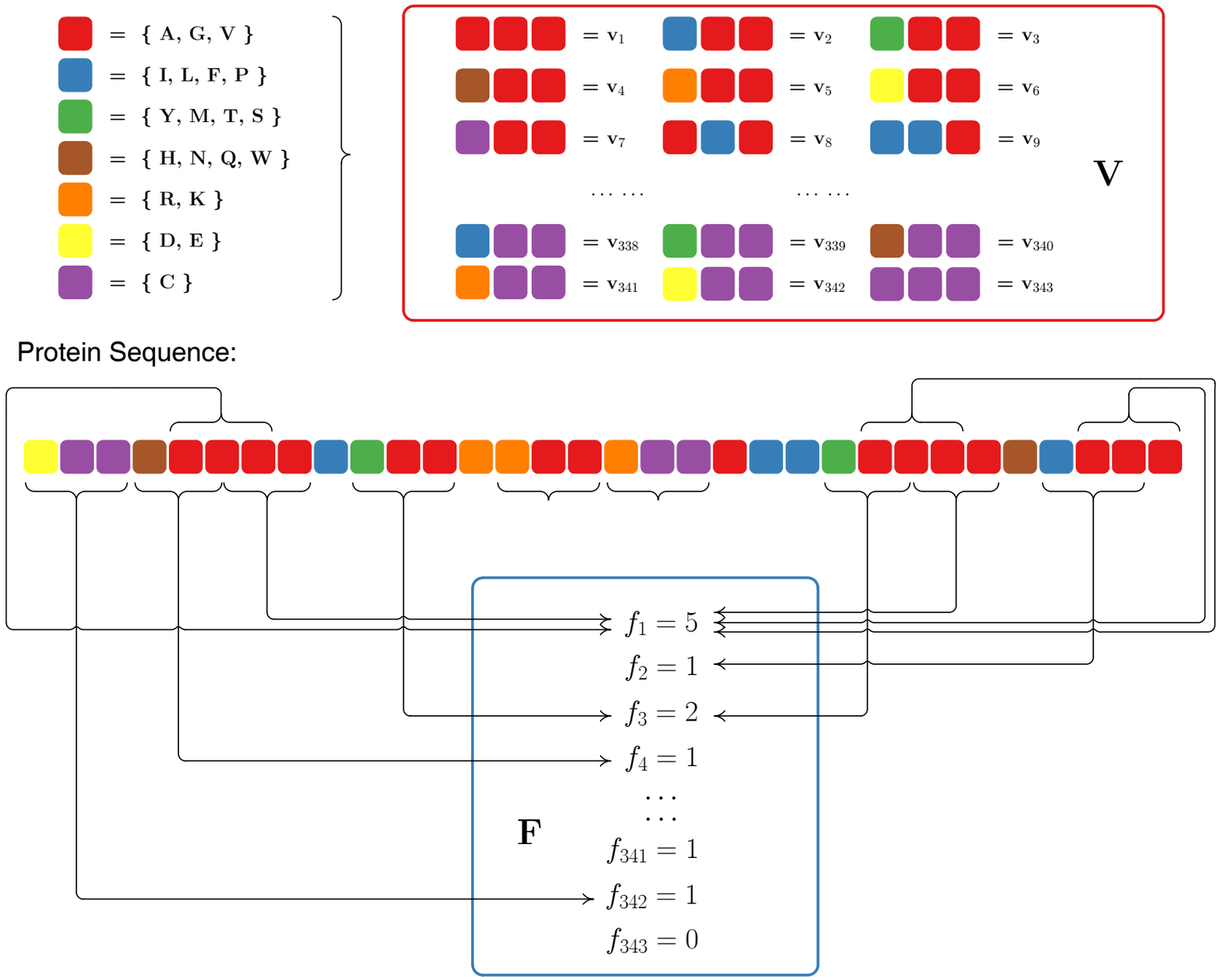
What could protr do?

- For regular predictive modeling
  - 14 types of commonly used descriptors:
    - Bioinformatics (Classification)
  - 6 types of PCM descriptors:
    - Proteochemometrics (Regression)

What could protr do?

- For similarity-based modeling methods
  - Similarity derived by sequence alignment & GO:
    - Similarity-based clustering
    - Kernel methods
    - etc.

Make protein sequence into a numerical vector



- For algorithmic details, see `vignette('protr')`

ProtrWeb

- Shiny-based
- Fast implementation: 1 Day

ProtrWeb

ProtrWeb | Home | Get Started | Example Input | Downloads | CBDD Group

ProtrWeb

Step 1. Upload Protein Sequence

Upload FASTA File:

选取文件 未选择文件

Or Upload Raw Sequence File:

选取文件 未选择文件

Step 2. Select Descriptor(s)

Descriptor Name (Dim):

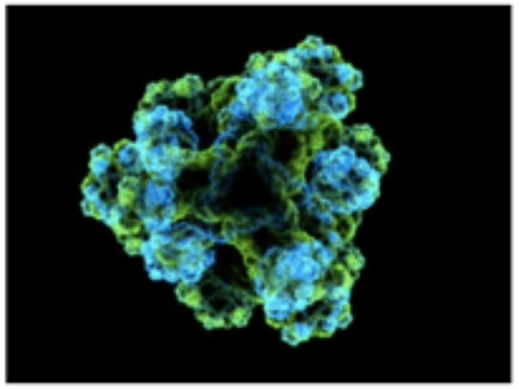
- Amino Acid Composition (20)
- Dipeptide Composition (400)
- Tripeptide Composition (8000)
- Normalized Moreau-Broto Autocorrelation (240)
- Moran Autocorrelation (240)
- Geary Autocorrelation (240)
- C/T/D (21 + 21 + 105)
- Conjoint Triad (343)

Introduction | Data | Results

Protein Sequence Feature Extraction with ProtrWeb

Over the past decade, machine learning methods have been successfully employed in the structural, functional and interaction profiles research of proteins and peptides. The structural and physicochemical descriptors have been intensively applied in the research of protein structure and functionalities, including

- Predicting protein structural and functional classes
- Predicting protein-protein interactions
- Predicting protein-ligand interactions
- Predicting protein subcellular locations
- Identifying protein phosphorylation sites
- Predicting protein crystallization propensity and peptides of specific properties



and many more challenging problems. As the fundamental building blocks, sequence-derived structural and physicochemical descriptors extracted from protein and peptide sequences play a highly critical role in the modeling procedure. Here we present *ProtrWeb*, a web server based on our R package *protr*, dedicated to compute such structural and physicochemical descriptors. Currently, *ProtrWeb* offers the functionality for computing 12 different types of qualitative descriptors presented in the *protr* package. The *protr* package offers more quantitative descriptors, miscellaneous tools and datasets, and more customized descriptors could be crafted by accessing the *protr* package directly.

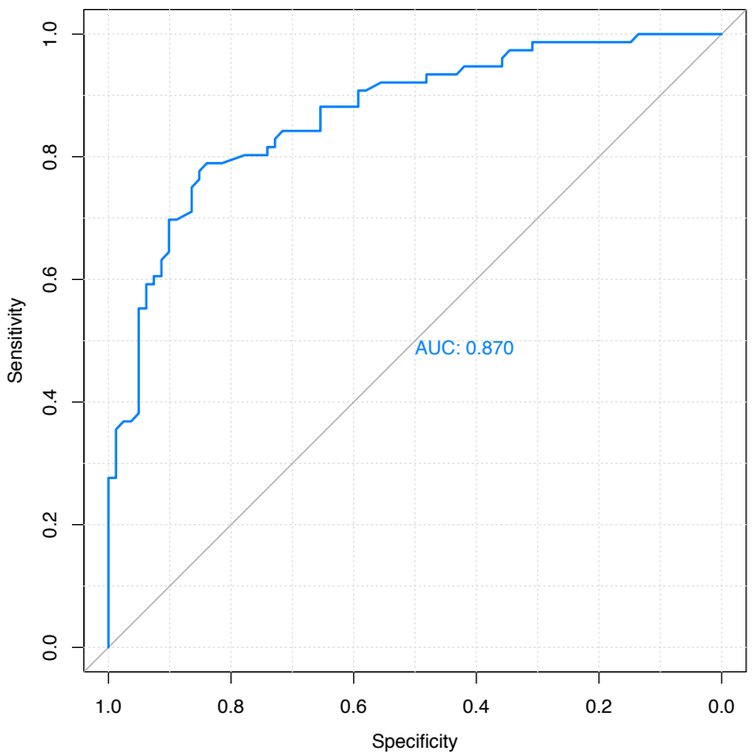
A Screenshot of ProtrWeb

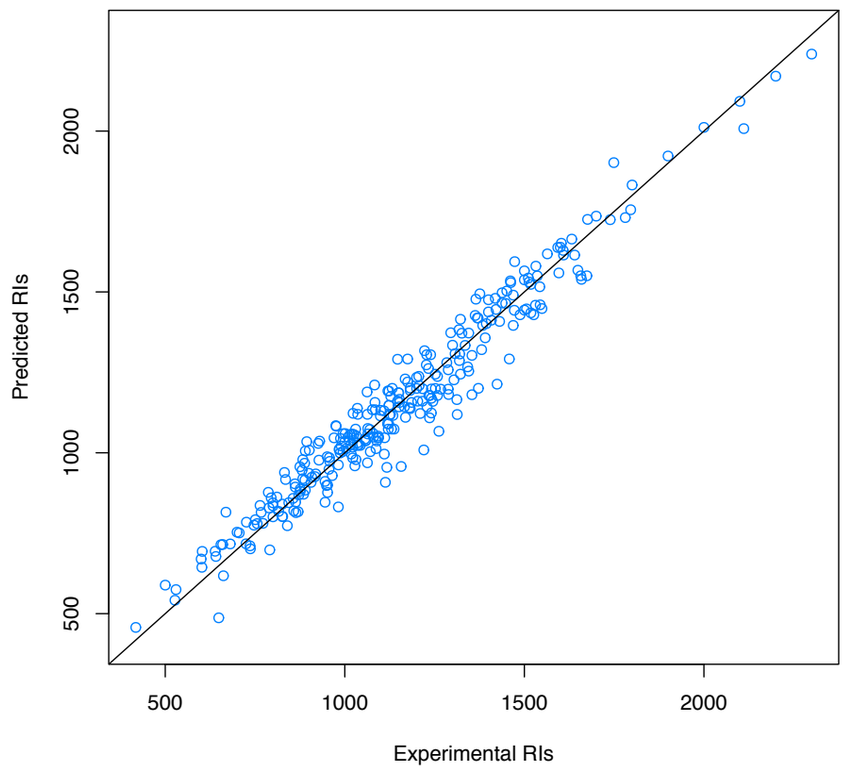
Rcpi

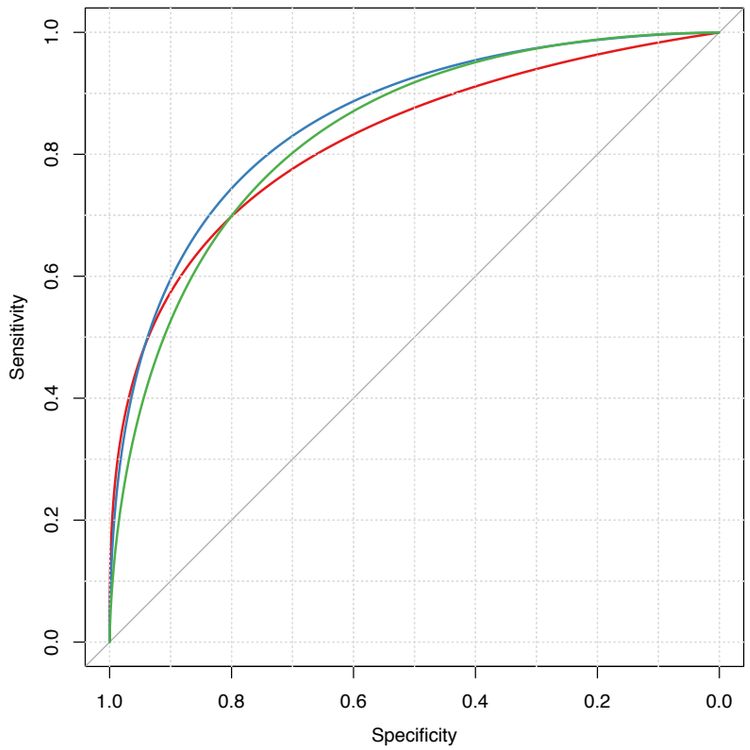
R/Bioconductor Package for Bioinformatics, Chemoinformatics & Chemogenomics Research

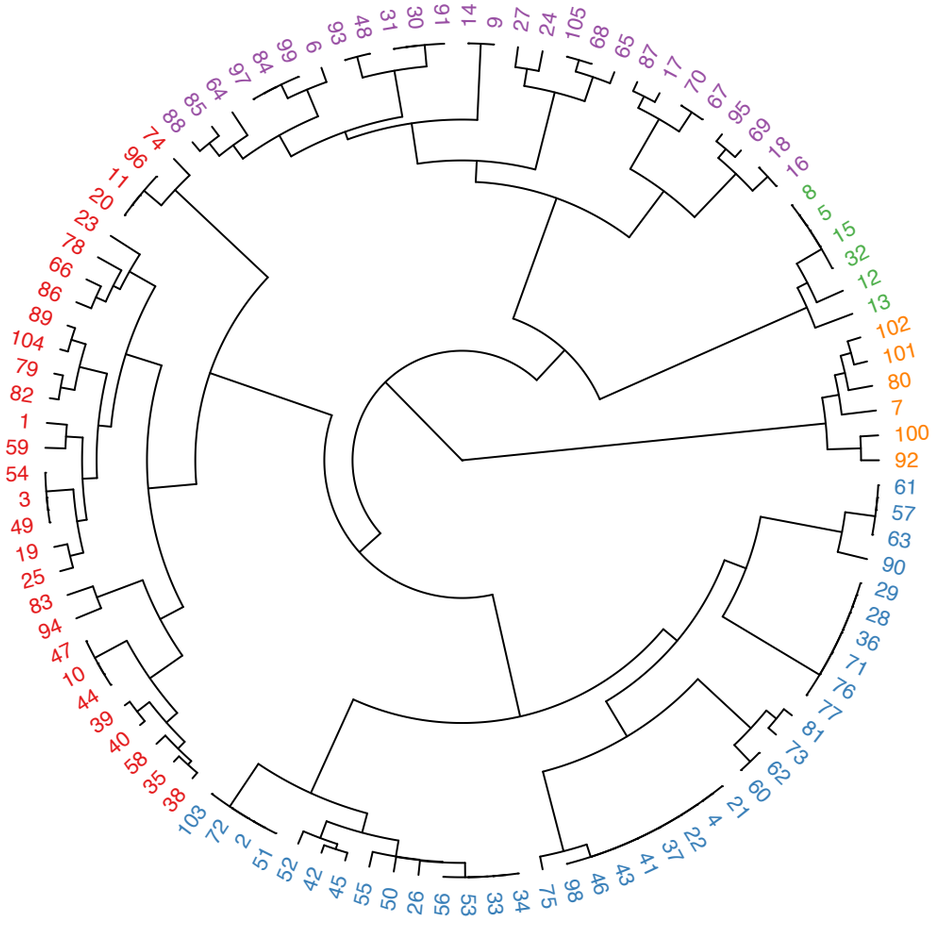
Schematic diagram of the Rcpi package.
from Xiao et al., (2014)

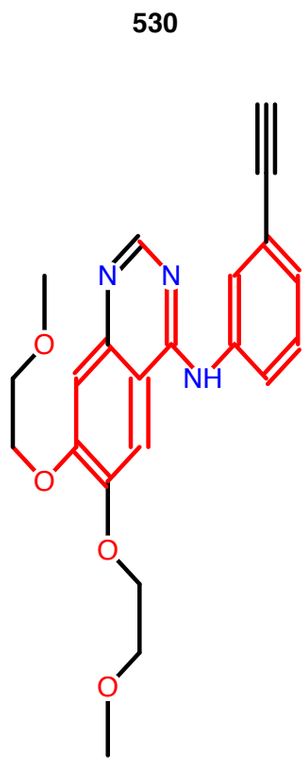
What could Rcpi do?

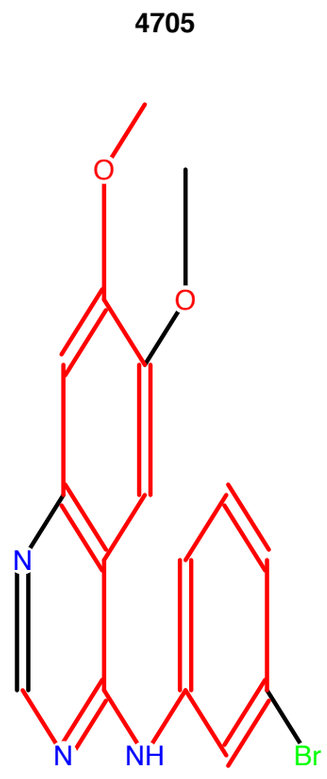

Sensitivity
Specificity
AUC: 0.870
1.0
0.8
0.6
0.4
0.2
0.0

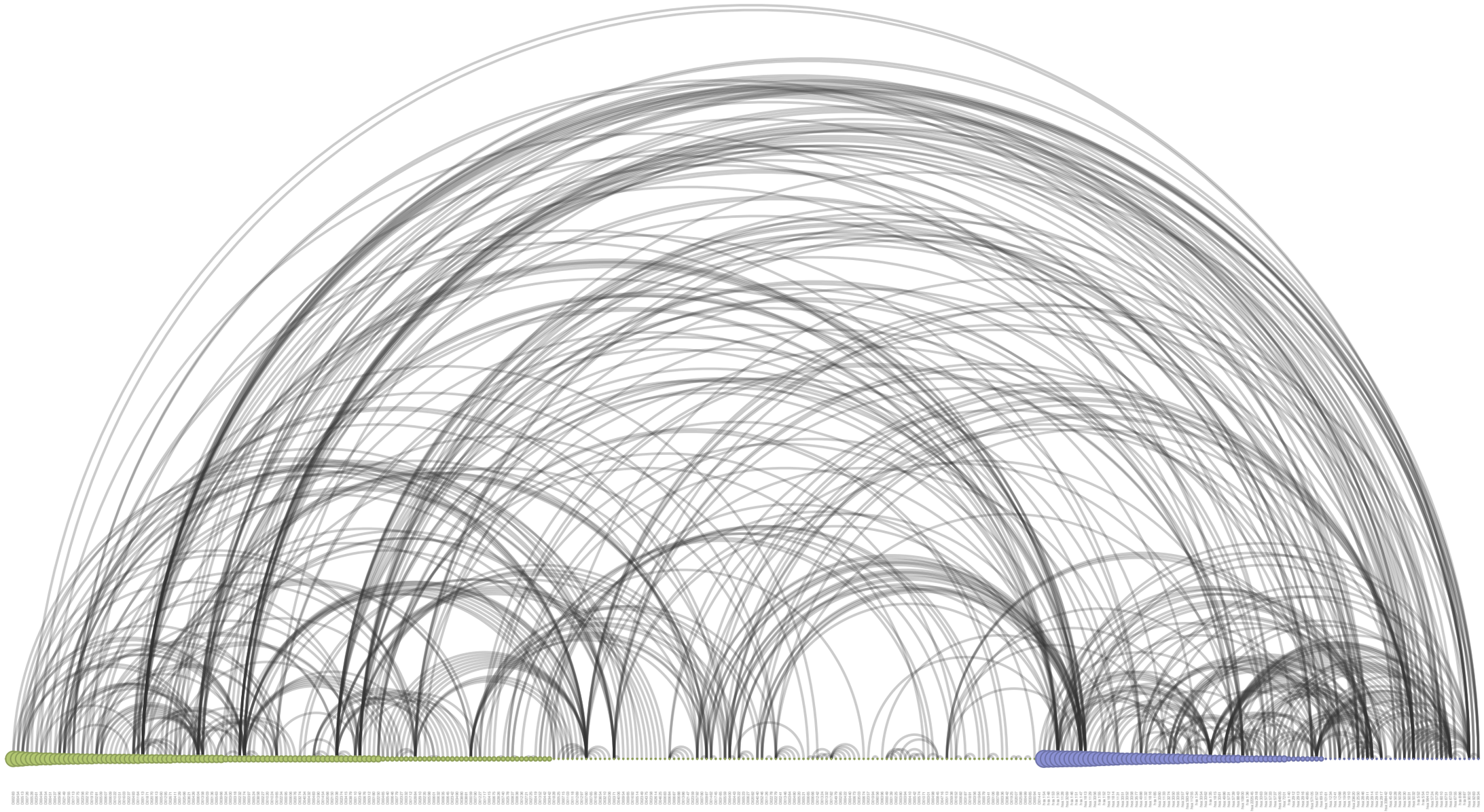

Predicted RIs
Experimental RIs
500
1000
1500
2000


Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0




530
N
N
NH
O
O
O
O


4705
O
O
N
N
NH
Br



Arc diagram of the GPCR drug-target interaction network from Xiao et, al. (2014)

Experience & Pitfalls

Dependency Hell

- foreach / doParallel / doMC
- Biostrings
- GOSemSim
- ChemmineR
- ChemmineOB
- fmcsR
- rcdk
- RCurl

Checking Hell

- R CMD check
- BiocCheck

Experiences

- Use Roxygen2 to generate docs and NAMESPACE
- Cross-platform availability: doParallel / doMC
- Unit Tests

Part III

Drug-ADR Prediction

Identify Novel Drug-ADR Associations

- Integrated multiple evidence from multiple levels
- Collaborative filtering and link prediction
- Mainly done by R, some done by Python

Summary

Summary

- Integrating only in the molecular structure level for now
- With R’s modelling capability, applications promised.

Future Works

- protr: Incorporate protein 3D information
- Rcpi: Integration of RDKit, ChemoPy
- Omics Information (Genome / Proteome / Phenome)
- Network-based representations

Our Vision

- Systematic integration
- Comprehensive pipeline

Resources

- protr

  http://cran.r-project.org/web/packages/protr/

- Rcpi

  http://bioconductor.org/packages/release/bioc/html/Rcpi.html

- ProtrWeb

  http://cbdd.csu.edu.cn:8080/protrweb/

有时，整个地球结盟促进某些幸运的学科发展，而那些学科也随之绽放出新思想的花蕾、取得惊人的进展。而关键在于，哪里有大量累积起来的关于这个领域的有意义的问题，并且总有新技术应用于该领域，使得更加贴近的观察那些过程成为可能。

Efron, B. (2005). Bayesians, frequentists, and scientists. JASA, 100(469).

现在这个星球也许正在联合起来促进统计学的发展。新技术——电子计算技术，打破了曾限制了传统统计理论发展的计算瓶颈。同时，一类重要问题的洪流正奔向我们，其表现形式为大型数据集以及大规模推断问题。我相信，这一代统计学家将投身于一个新的统计创新年代，一个可与 Fisher、Neyman、Hotelling 以及 Wald 的黄金时代相媲美的时代。

Efron, B. (2005). Bayesians, frequentists, and scientists. JASA, 100(469).

Sometimes, not very often, the planets align for some lucky discipline, which then blossoms with new ideas and breath-taking progress. Microbiology is a perfect current example. The key there was a buildup of interesting questions concerning cellular processes, followed by new technology that enabled a much closer look at those processes in action.

Efron, B. (2005). Bayesians, frequentists, and scientists. JASA, 100(469).

Now the planets may be aligning for statistics. New technology, electronic computation, has broken the bottleneck of calculation that limited classical statistical theory. At the same time an onrush of important new questions has come upon us, in the form of huge data sets and large-scale inference problems. I believe that the statisticians of this generation will participate in a new age of statistical innovation that might rival the golden age of Fisher, Neyman, Hotelling, and Wald.

Efron, B. (2005). Bayesians, frequentists, and scientists. JASA, 100(469).

Q & A