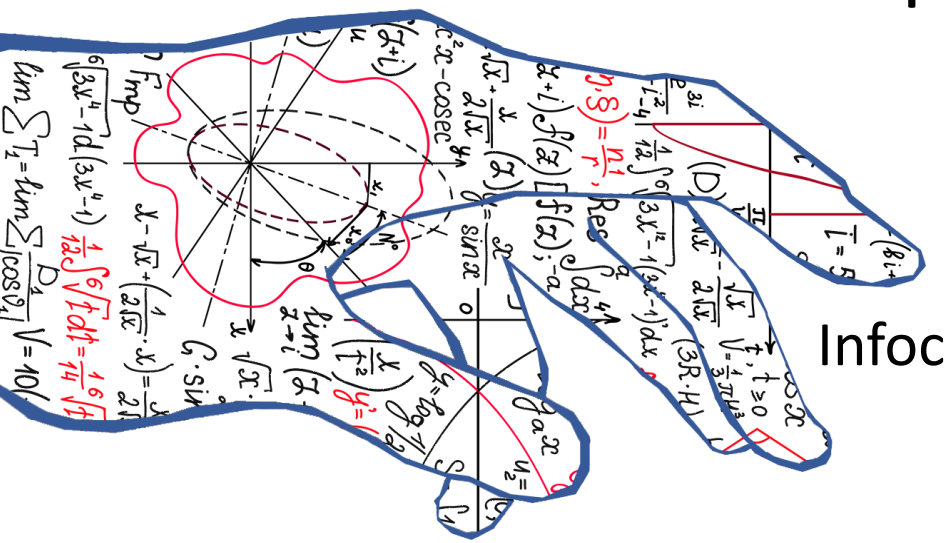
ITMO UNIVERSITY

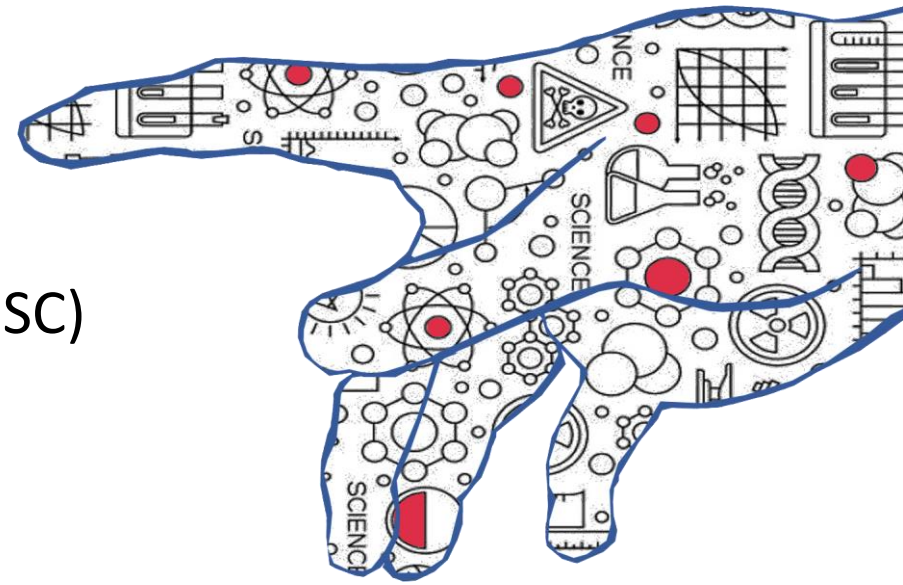
INFOCHEMISTRY SCIENTIFIC CENTER

From Cheminformatics to Systems/Synthetic Biology

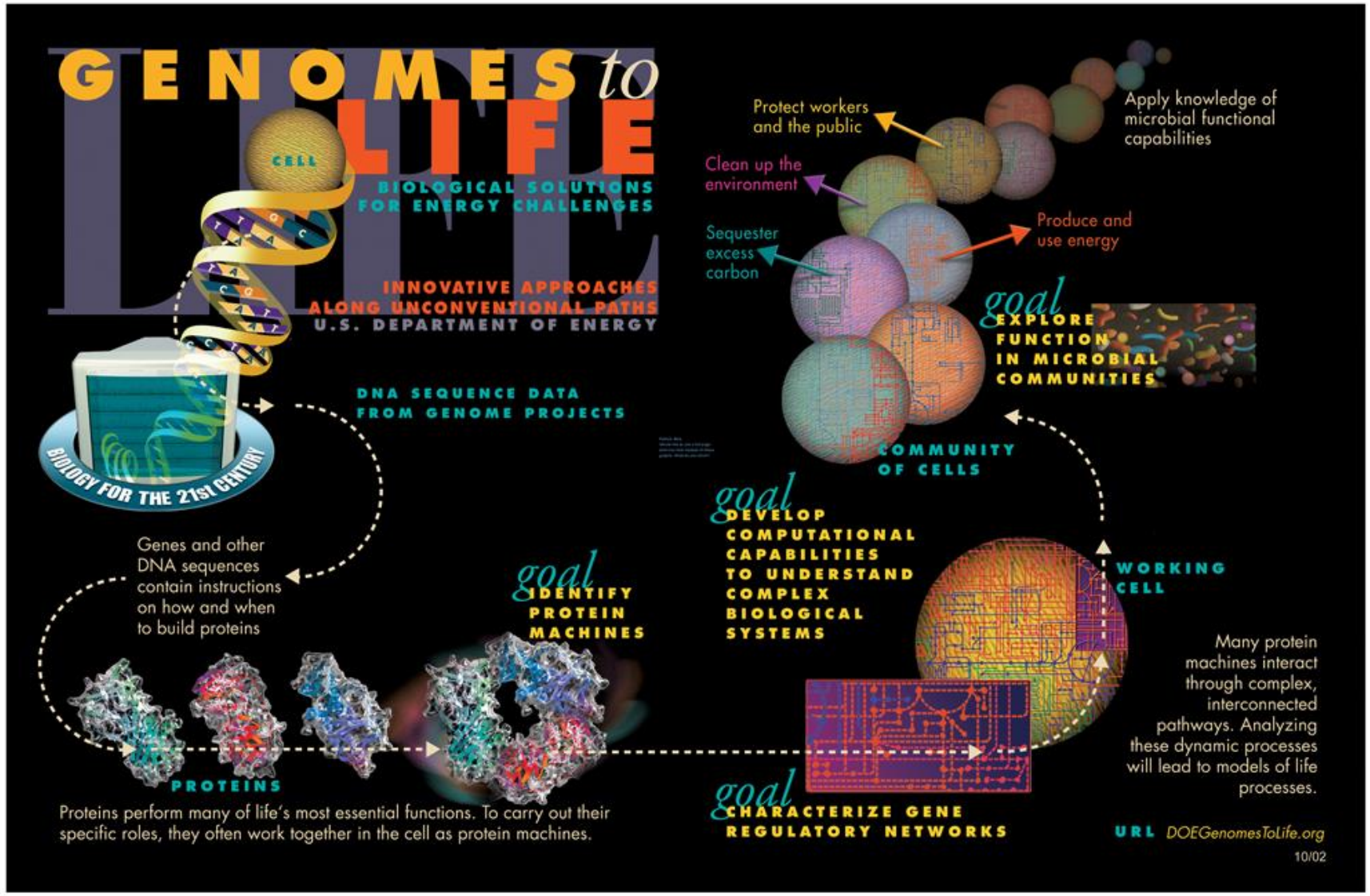
Prof. Sergey Shityakov



Infochemistry Scientific Center (ISC)
ITMO University
Saint-Petersburg, 2024



Systems biology



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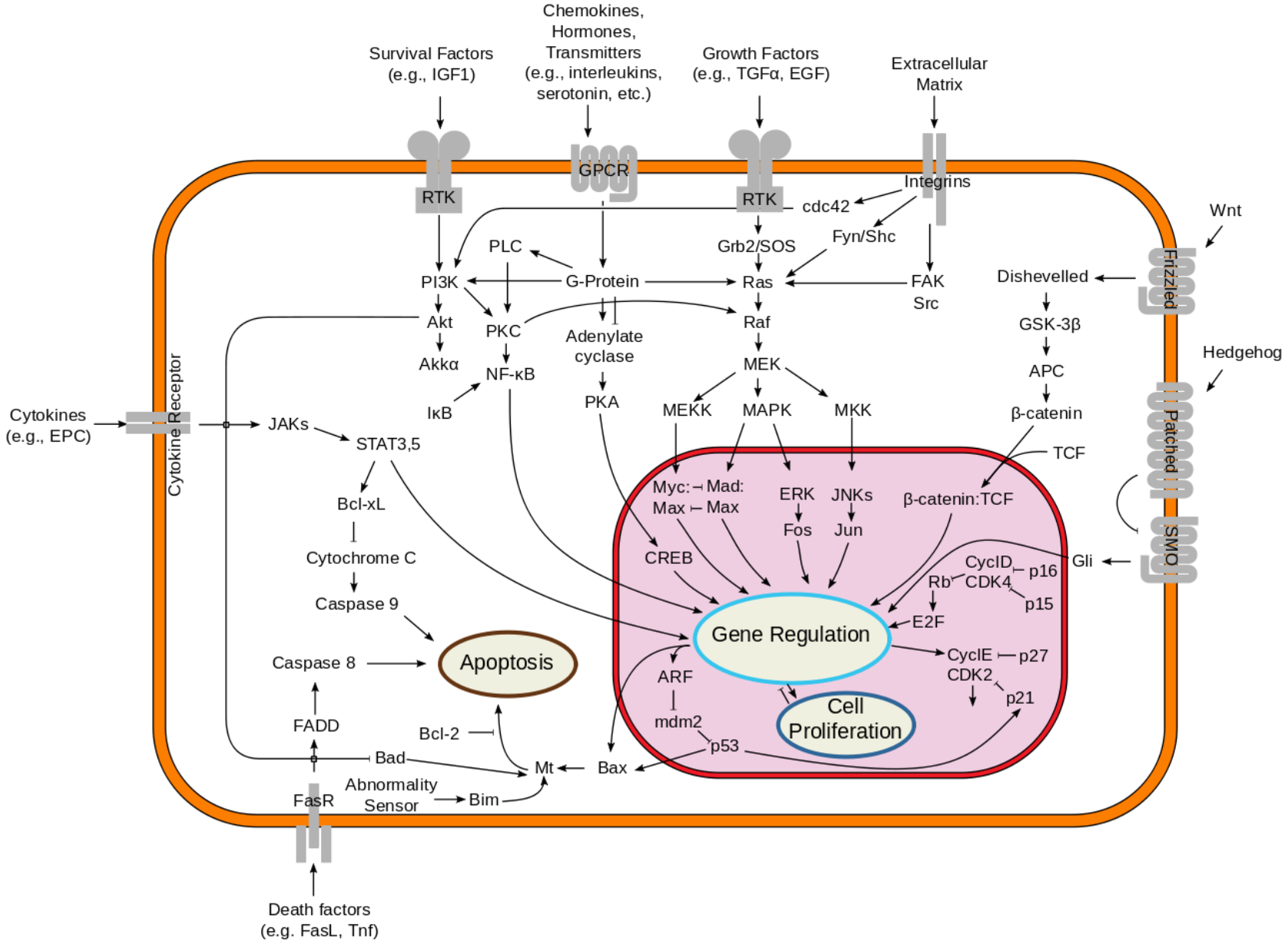
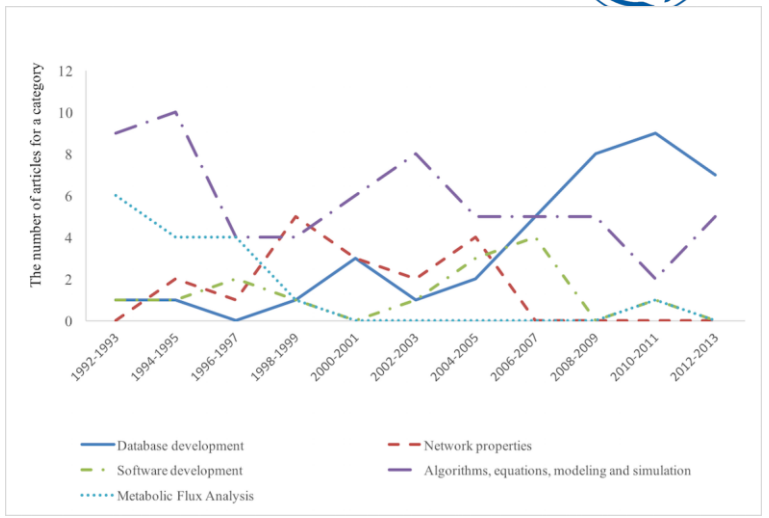
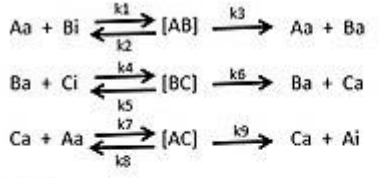
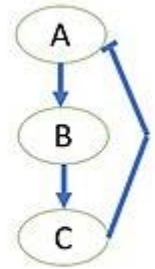


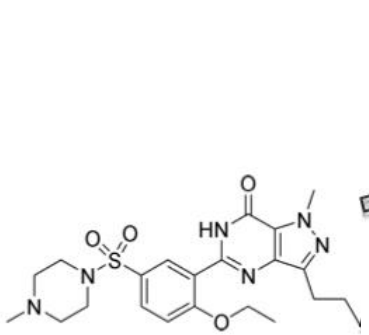




Ai: k9[AC]
Aa: -k1[Aa][Bi] + k2[AB] + k3[AB] – k7[Ca][Aa] + k8[AC]
Bi: -k1[Aa][Bi] +k2[AB]
Ba: k3[AB] – k4[Ba][Ci] + k5[BC] + k6[BC]
Ci: -k4[Ba][Ci] + k5[BC]
Ca: k6[BC] – k7[Ca][Aa] + k8[AC] + k9[AC]
[AB]: k1[Aa][Bi] – k2[AB] – k3[AB]
[BC]: k4[Ba][Ci] – k5[BC] –k6[BC]
[AC]: k7[Ca][Aa] – k8[AC] – k9[AC]

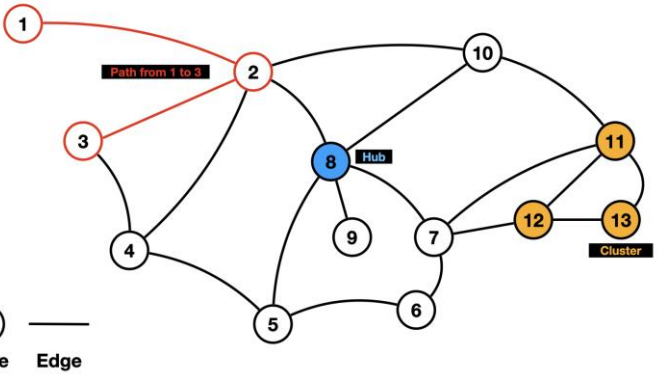


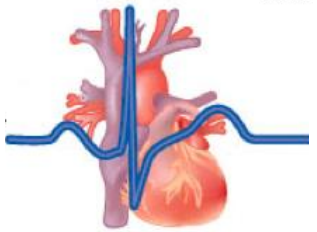
Clinical effect of drug compounds



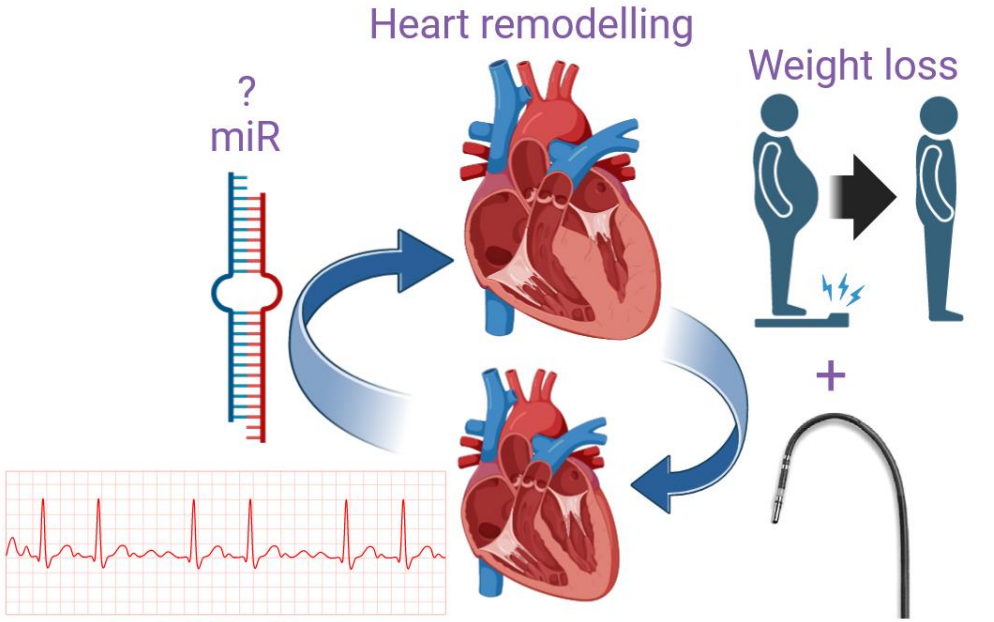
Compound 1

Target 1

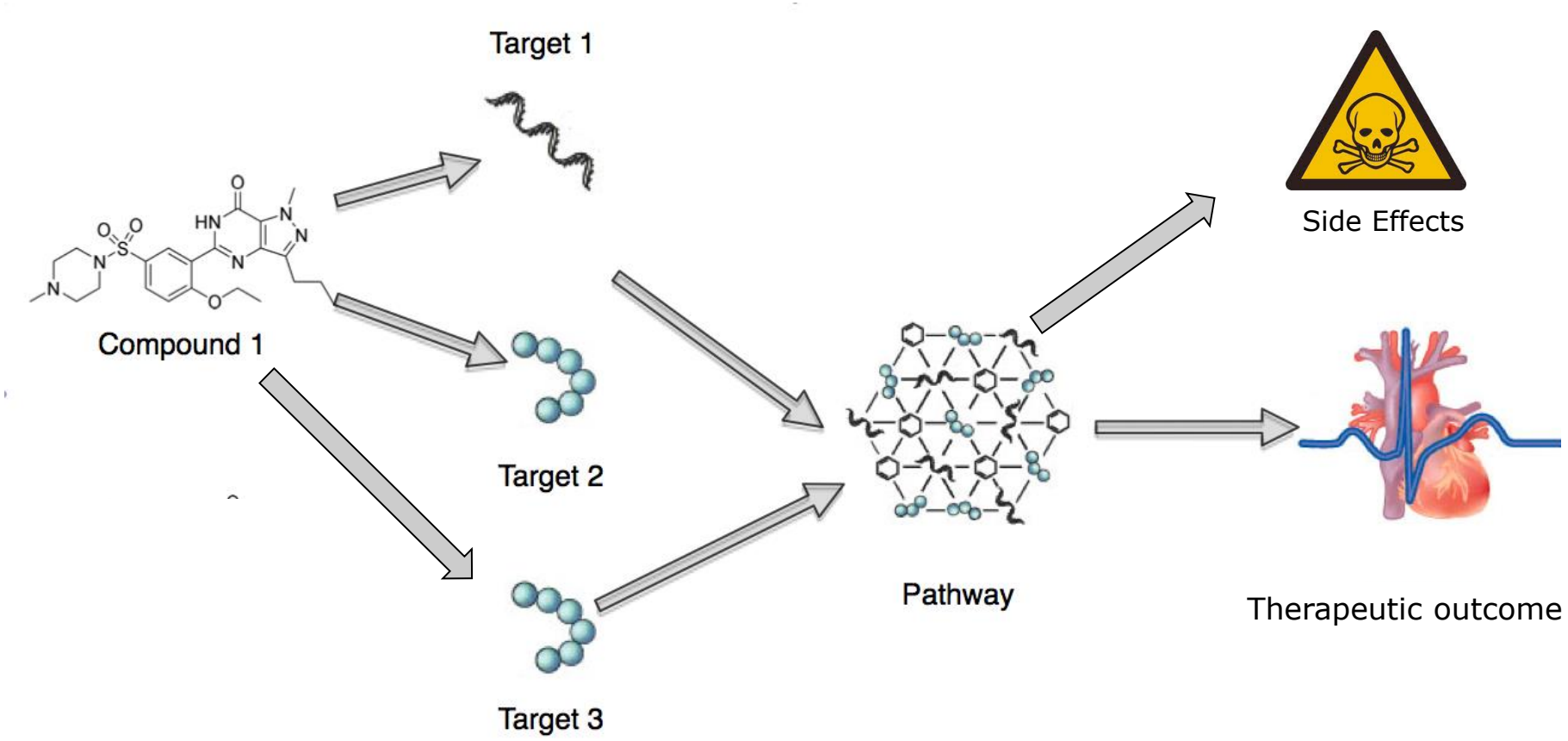




Therapeutic outcome



Clinical effect of drug compounds



Clinical effect of drug compounds

- Drug **selectivity** towards a single target is more often the exception than the rule
- Many effective drugs act via modulation of **multiple** targets
- Some drugs may have yet unknown therapeutic applications(drug **repurposing**)
- Many **adverse drug reactions** are due to activity towards multiple targets

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Drug repurposing

Sildenafil (a.k.a Viagra, Vitamin V, the Blue Pill, etc)

- Potent inhibitor of **cGMP-specific phosphodiesterase type 5** (PDE5), an enzyme that regulates blood flow
- Initially developed to treat **pulmonary hypertension** (market name: Revatio)
- Sales account for 90% of the global market for **erectile dysfunction**
- Recently discovered uses include alleviation of **altitude sickness** and **jetlag**

Adverse Drug Reactions

- Cisapride: serotonin receptor agonist
  - Relief of gastrointestinal symptoms

- Astemizole: histamin receptor antagonist
  - Antihistamine

BOTH WITHDRAWN DUE TO INHIBITION OF THE hERG CARDIAC ION CHANNEL

Adverse Drug Reactions

Many different studies demonstrate a link between **depression**, **schizophrenia** and **diabetes**.

But what is the link?

Suspicions that antipsychotic drugs interfere with **pathways** involved to **insulin resistance**

Systems Chemical Biology

Systems chemical biology

Oprea *et al. Nature Chem Biol* **(2007)** 3, 447-450

Tudor I Oprea, Alexander Tropsha, Jean-Loup Faulon & Mark D Rintoul

The increasing availability of data related to genes, proteins and their modulation by small molecules has provided a vast amount of biological information leading to the emergence of systems biology and the broad use of simulation tools for data analysis. However, there is a critical need to develop cheminformatics tools that can integrate chemical knowledge with these biological databases and simulation approaches, with the goal of creating systems chemical biology.

Small compounds

Structural information

Bioactivity information

Human body

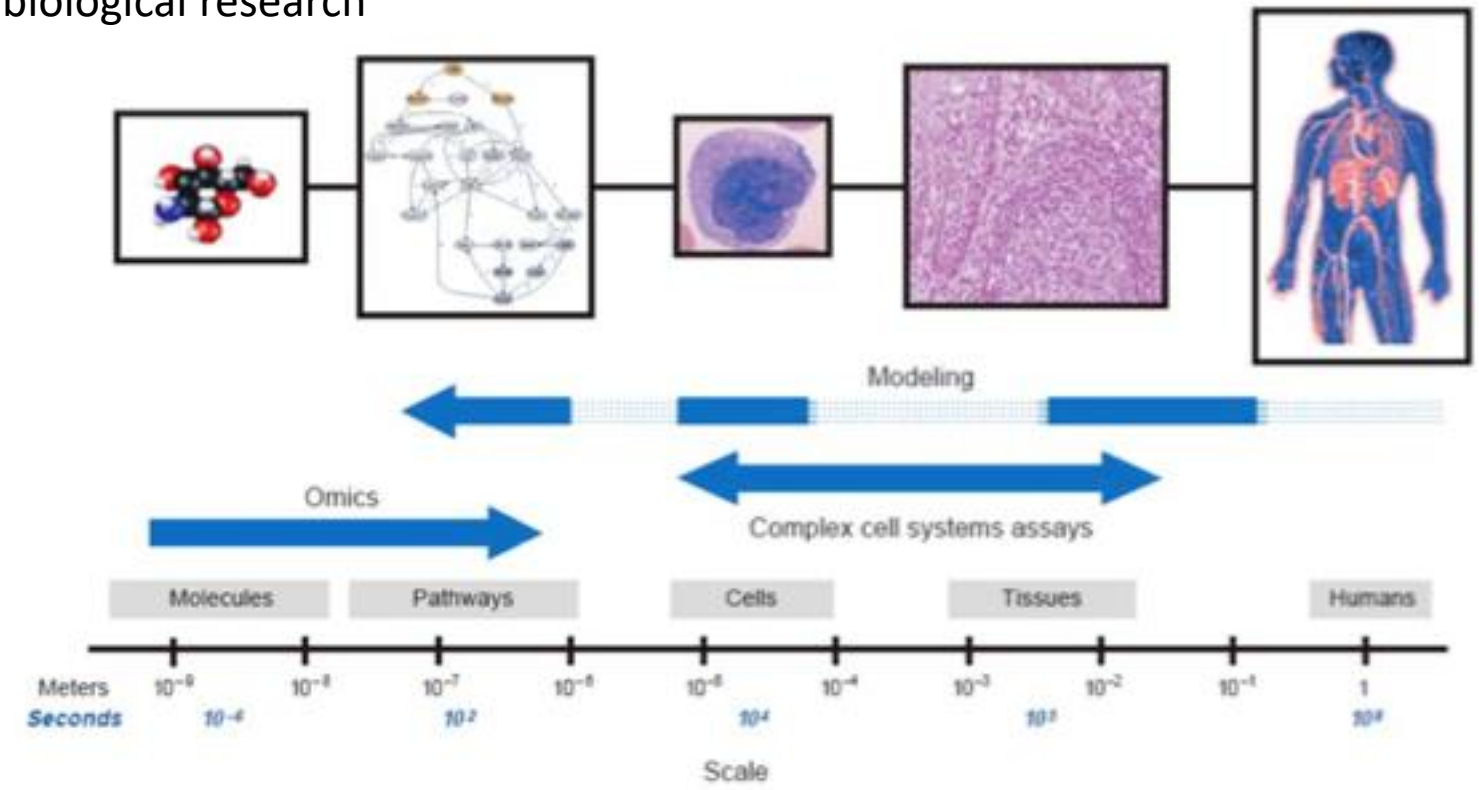
Biological pathways

Protein-protein interactions
Gene expression data
Disease phenotypes
Side effect data,
etc... etc...

POLYPHARMACOLOGY
CHEMOGENOMICS
NETWORK
PHARMACOLOGY
SYSTEMS
PHARMACOLOGY

Systems Chemical Biology

Systems biology is the computational and mathematical analysis and modeling of complex biological systems. It is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach (holism instead of the more traditional reductionism) to biological research



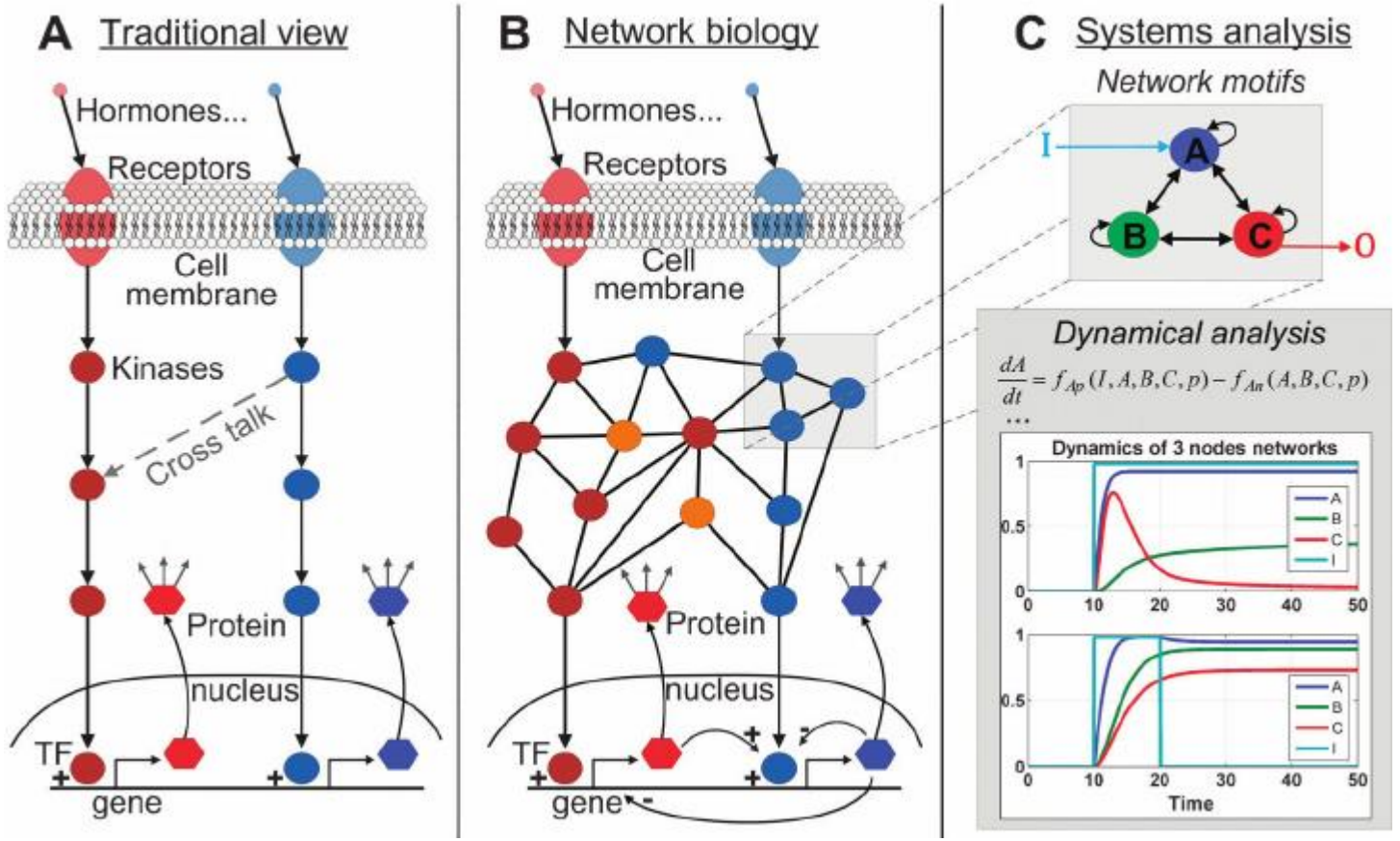
Butcher EC, Berg EL, Kunkel EJ. *Systems biology in drug discovery. Nat Biotech 2004; 22: 1253-9.*

Open-Source Databases

Table 1
Public resources for *SCB*[a]

Genes
Entrez gene: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene
Proteins
SwissProt: http://expasy.org/sprot/
Structures of biological macromolecules
PDB: http://www.rcsb.org/pdb/home/home.do
Structural genomics consortium: http://www.sgc.utoronto.ca/
Pathways
KEGG: http://www.genome.jp/kegg/
MetaCyc: http://metacyc.org/
BioCarta: http://www.biocarta.com/genes/index.asp
Reactome: http://www.reactome.org/
Receptors
GPCRdb: http://www.gpcr.org/7tm/
NHRs: http://www.nursa.org/
Ion channels: http://www.iuphar-db.org/iuphar-ic/index.html
Biochemical pathway reaction kinetics
SABIORK: http://sabio.villa-bosch.de/SABIORK/
BRENDA: http://www.brenda.uni-koeln.de/
Annotated biological models
http://www.ebi.ac.uk/biomodels/
Other MLI initiatives
NIH Roadmap: http://nihroadmap.nih.gov/

[a]Non-exhaustive list



T. Oprea et al, *Computational Systems Chemical Biology*, Chemoinformatics and Computational Chemical Biology, Ed J. Bajorath, Springer, 2011

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Network visualization

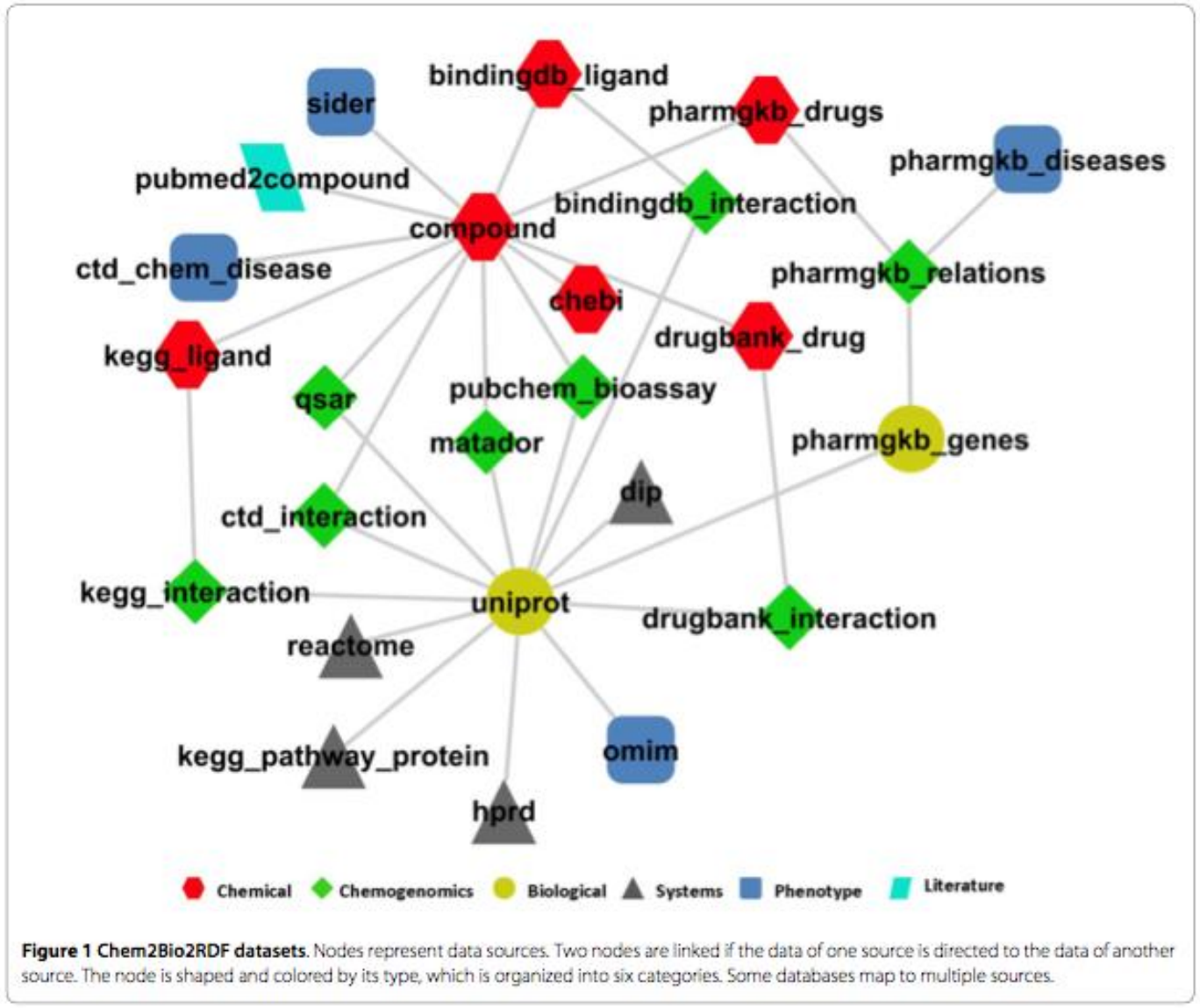
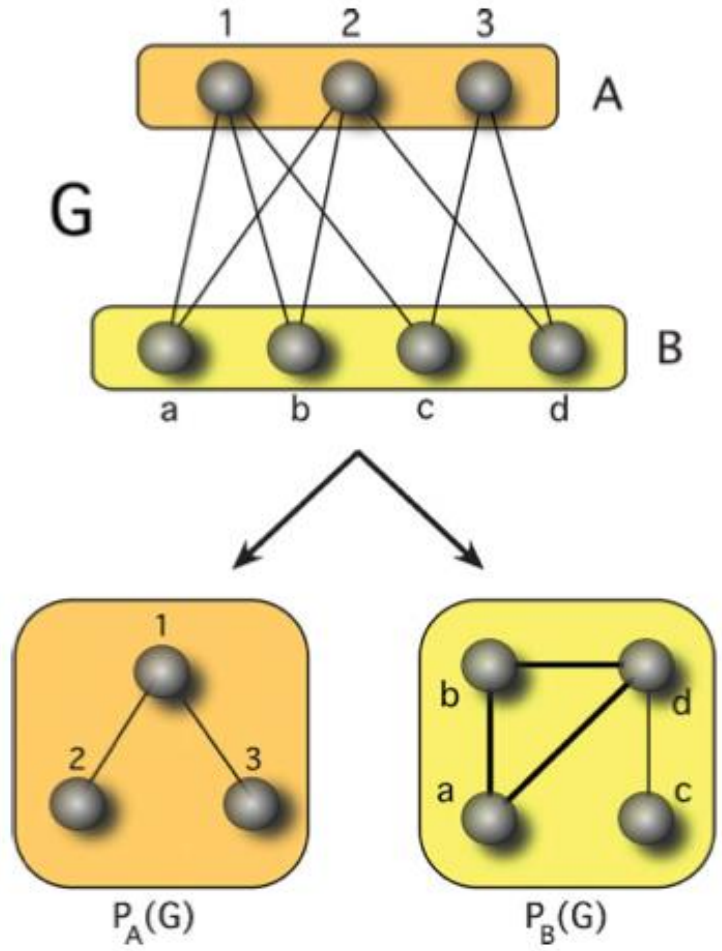


Figure 1 Chem2Bio2RDF datasets. Nodes represent data sources. Two nodes are linked if the data of one source is directed to the data of another source. The node is shaped and colored by its type, which is organized into six categories. Some databases map to multiple sources.

Chen et al., BMC Bioinformatics, 2010, 11:255

Network visualization



Bipartite network

Unipartite networks

Montanez et al., BioEssays, 2010, 32:246-256

Drug-Disease Network (bipartite)

FDA approved drugs

DrugBank

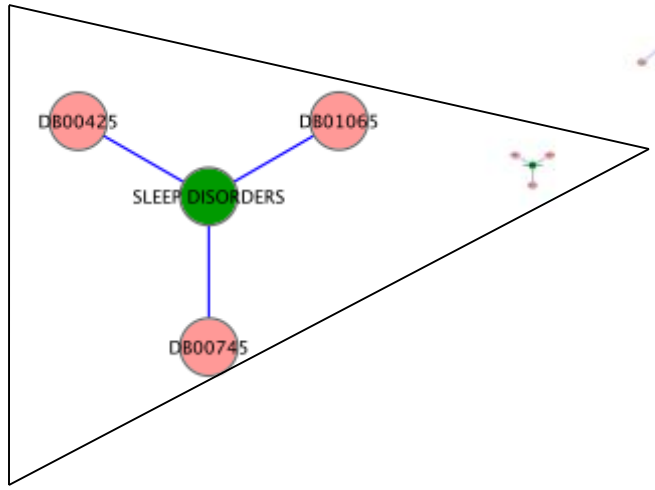
PharmGKB
Pharmacogenomics Knowledge Base

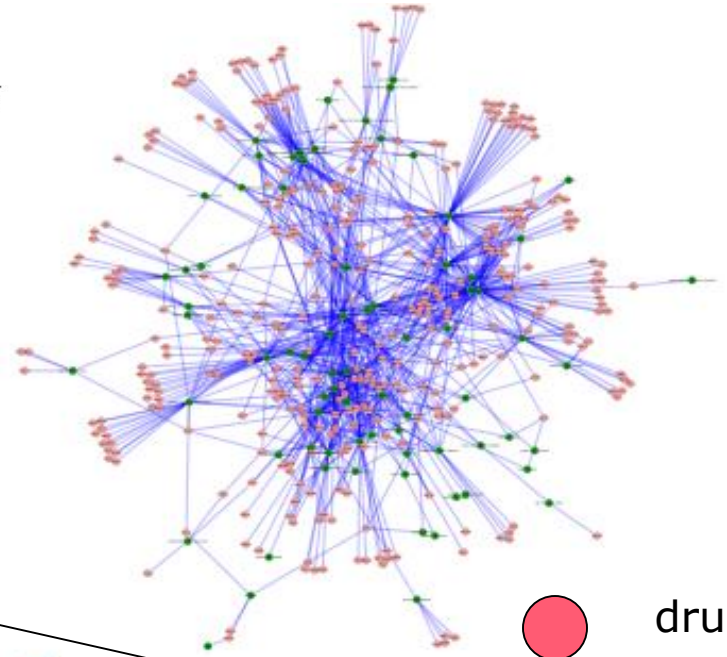
Disease names

WHO Collaborating Centre for Drug Statistics Methodology

ATC codes

Drug-Disease Network





drugs

diseases

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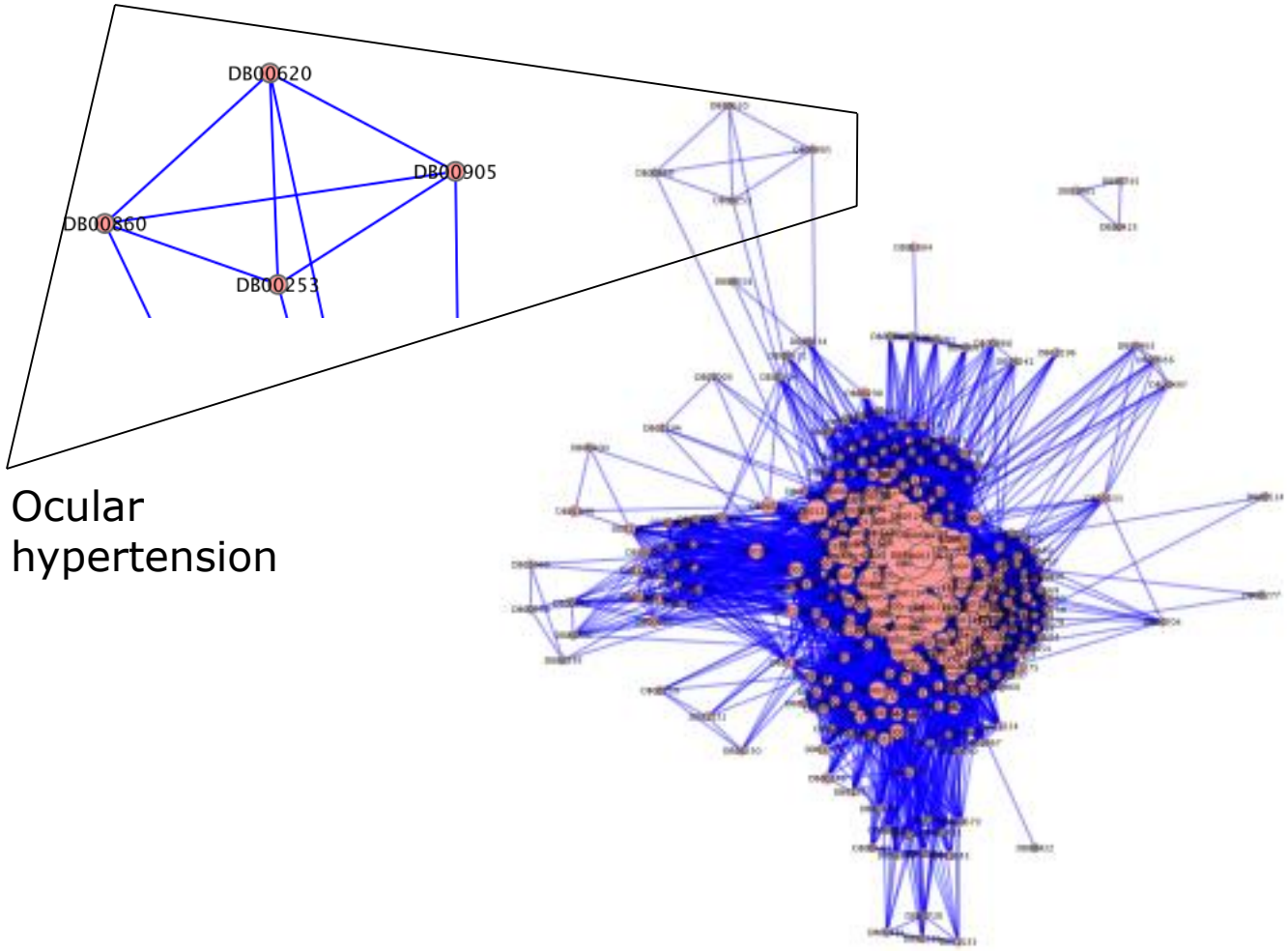
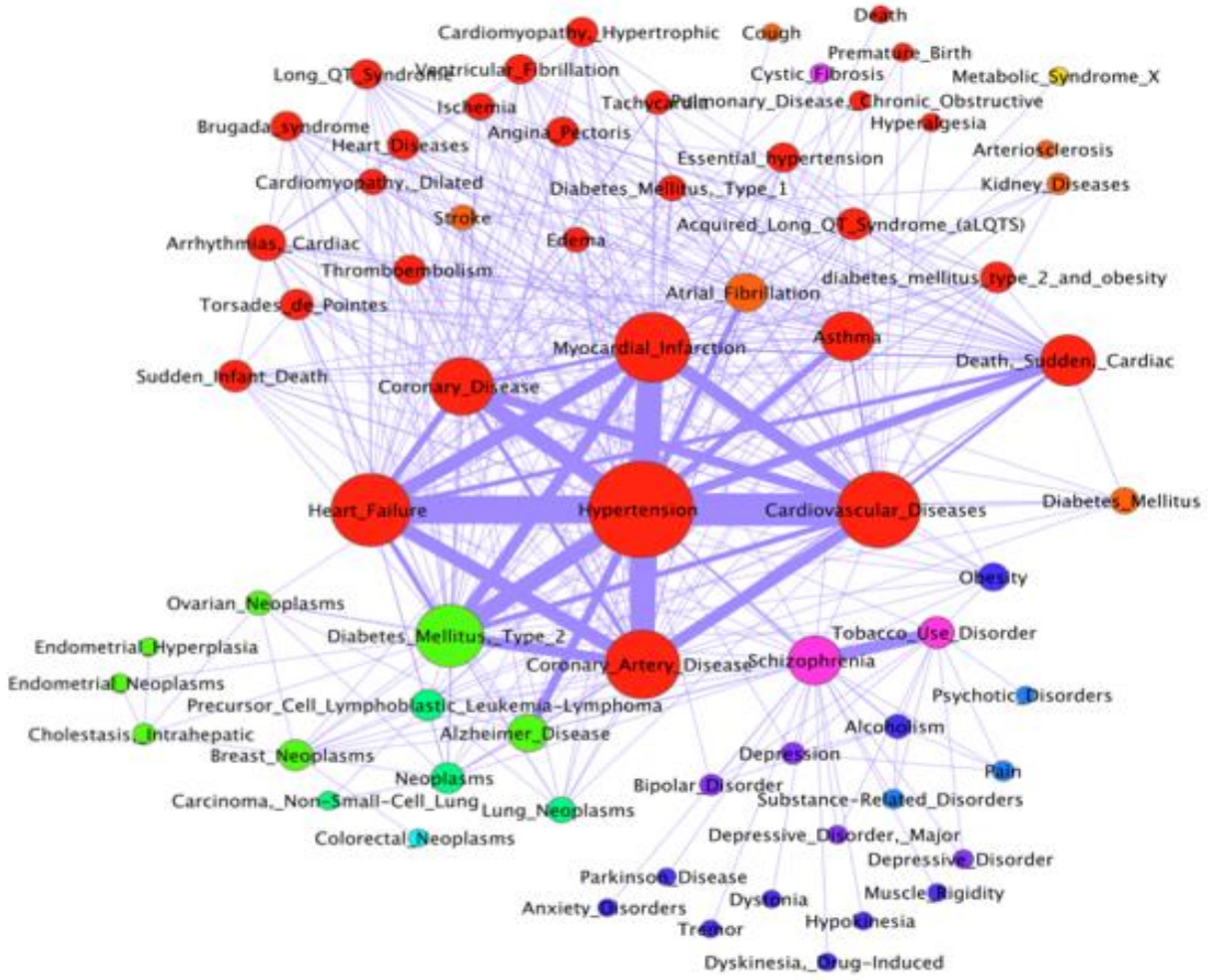
Drug-Drug Network (unipartite)

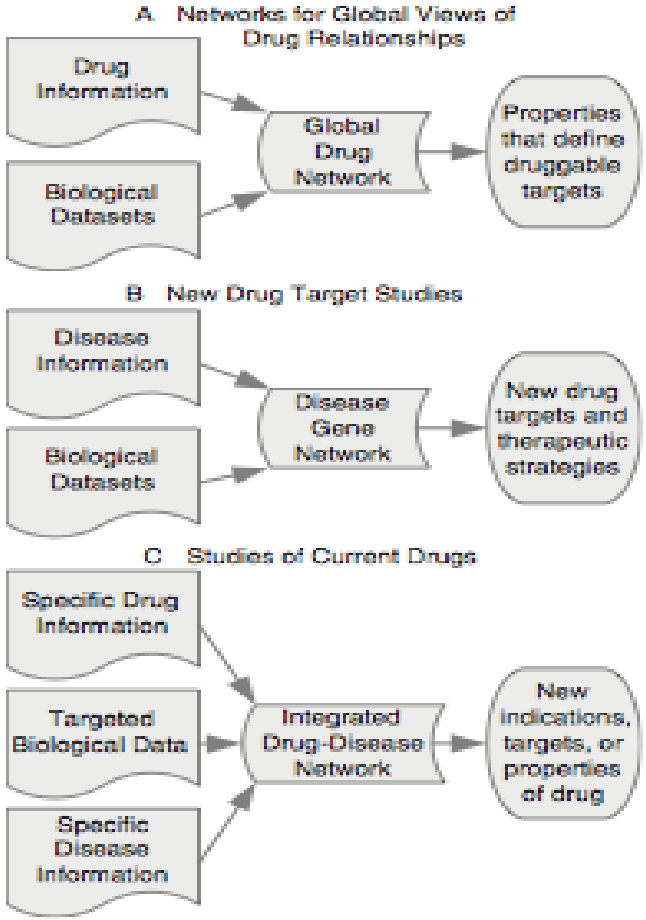


Ocular hypertension

Disease-Disease Network (unipartite)



Drug-Drug Networks



- new druggable targets
- drug repurposing
- side effects, toxicity

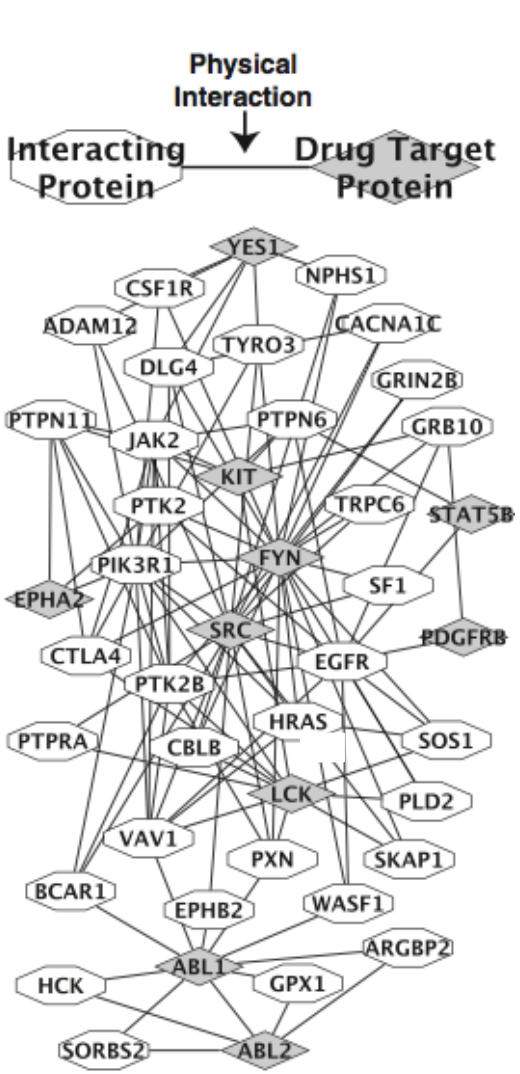
S. Berger and R. Iyengar, Bioinformatics, 2009, 25(19), 2466-72

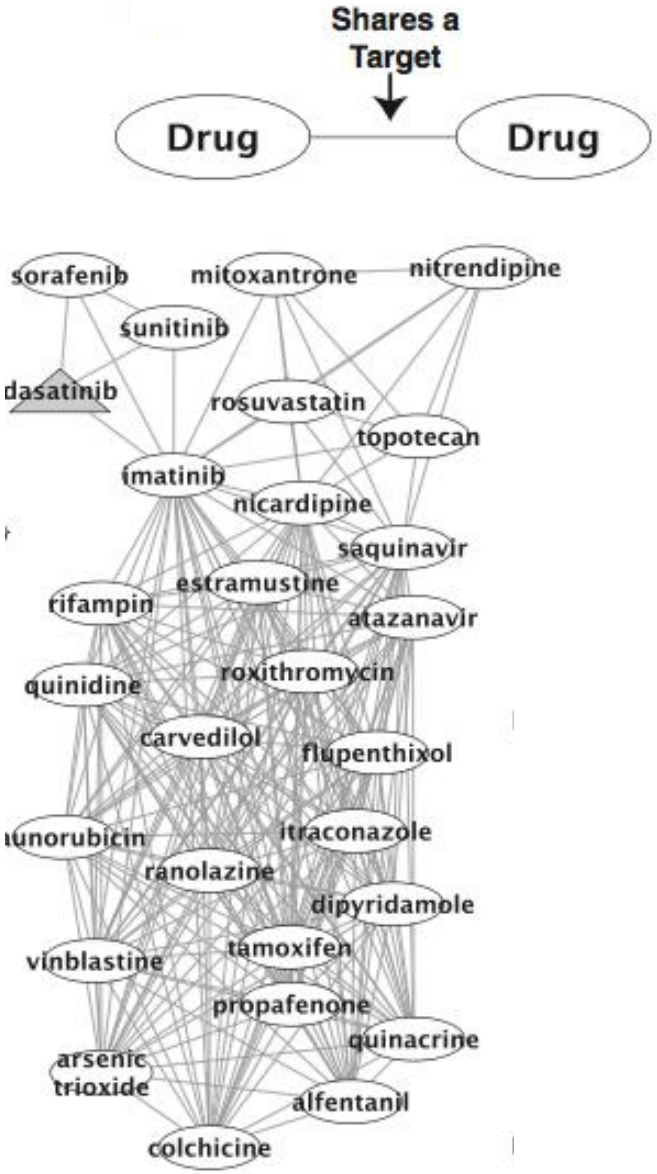
Case Study

Dasatinib:

- tyrosine kinase inhibitor
- treatment of chronic mylogenous leukemia

Case Study





S. Berger and R. Iyengar, Bioinformatics, 2009, 25(19), 2466-72

Case Study

anti-neoplastic

topical acne

anti-inflammatory

. Berger and R. Iyengar, Bioinformatics, 2009, 25(19), 2466-72

Chemical-biological triplets (drug-target-pathway)

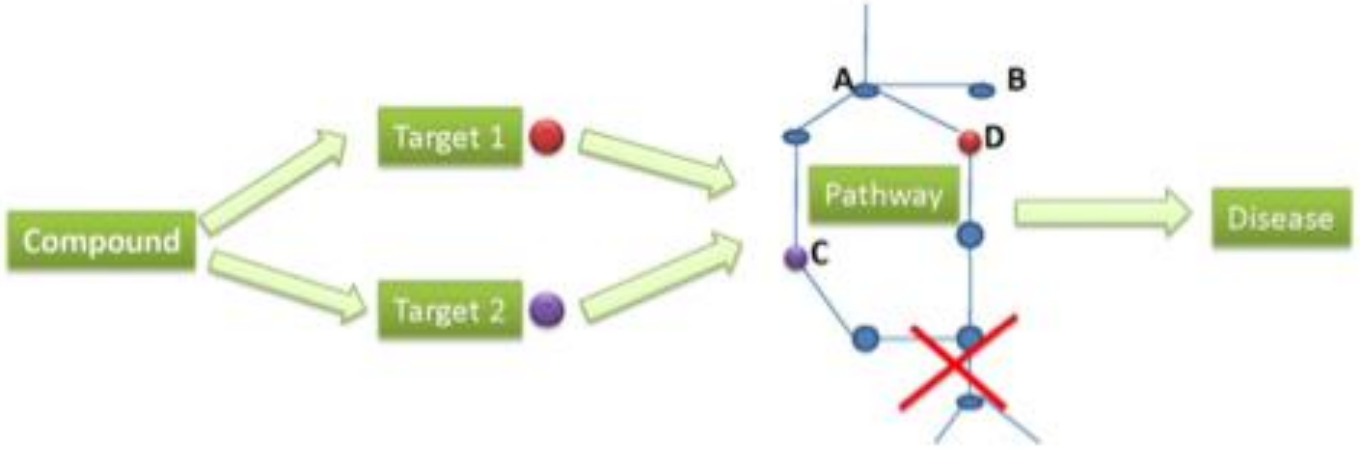
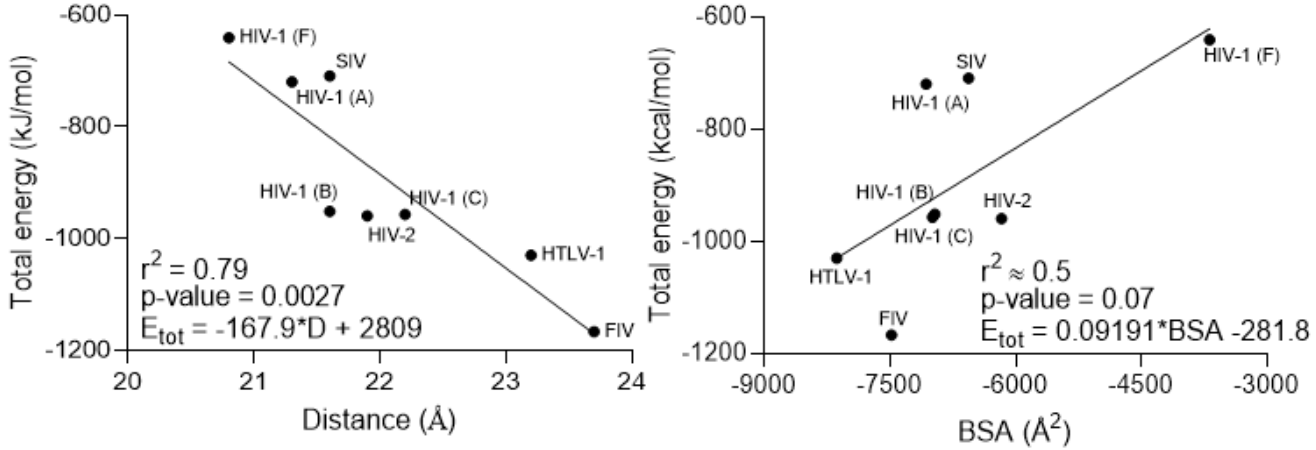
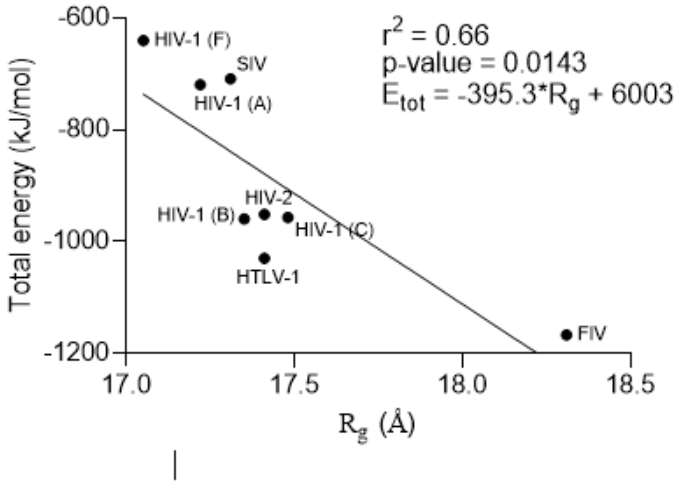


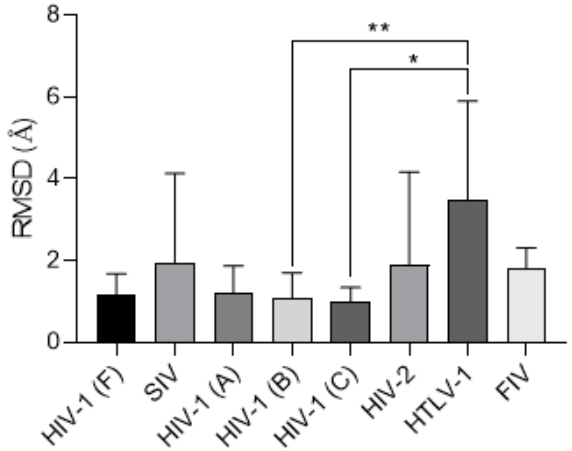
Figure 6 Illustration of polypharmacology in pathways. The compound is active against two proteins that are located in the two branches of the pathway that is associated with one disease. Targeting either node C or node D is not able to block the whole pathway.

Chen et al., BMC Bioinformatics, 2010, 11:255

Projects in chemical systems biology



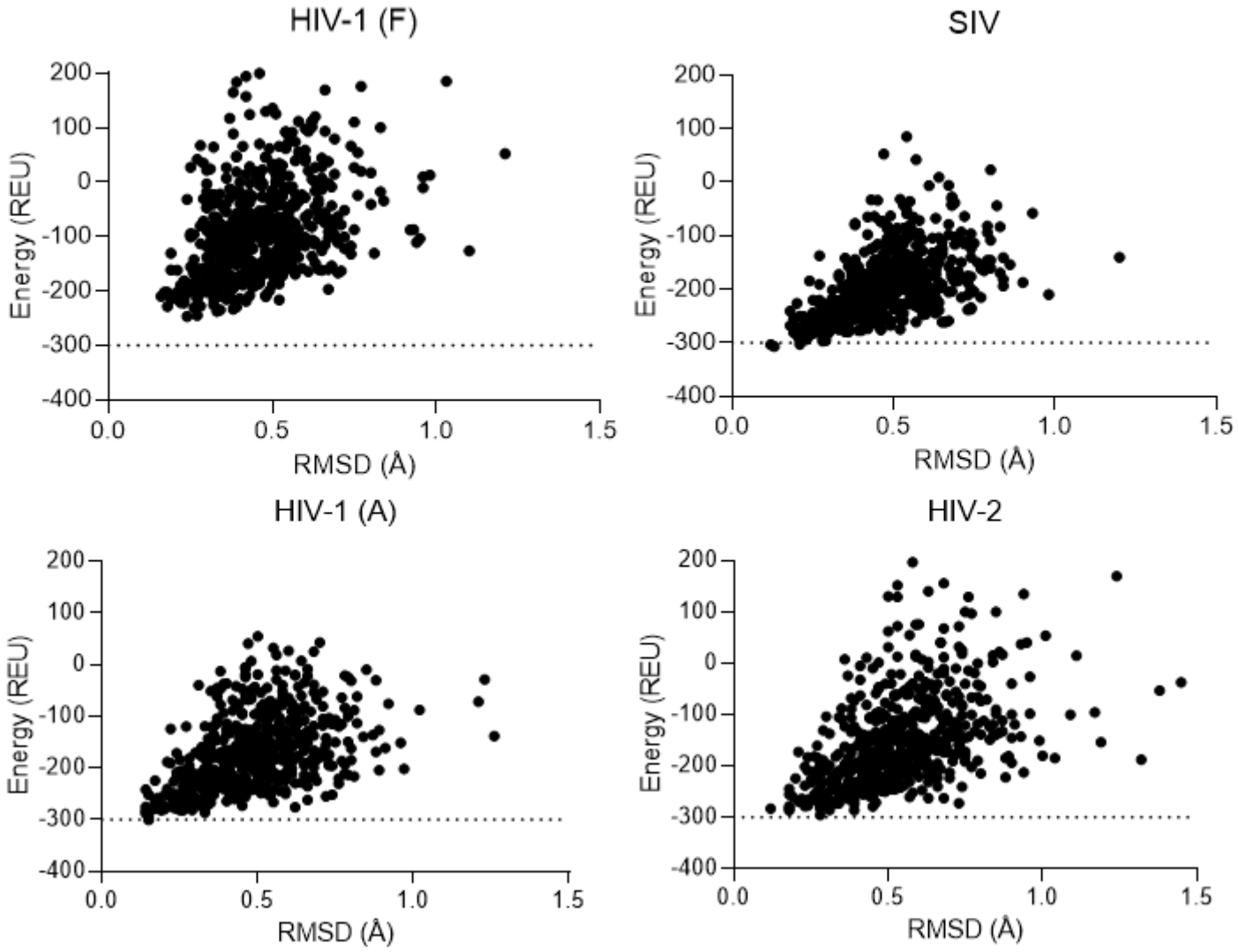




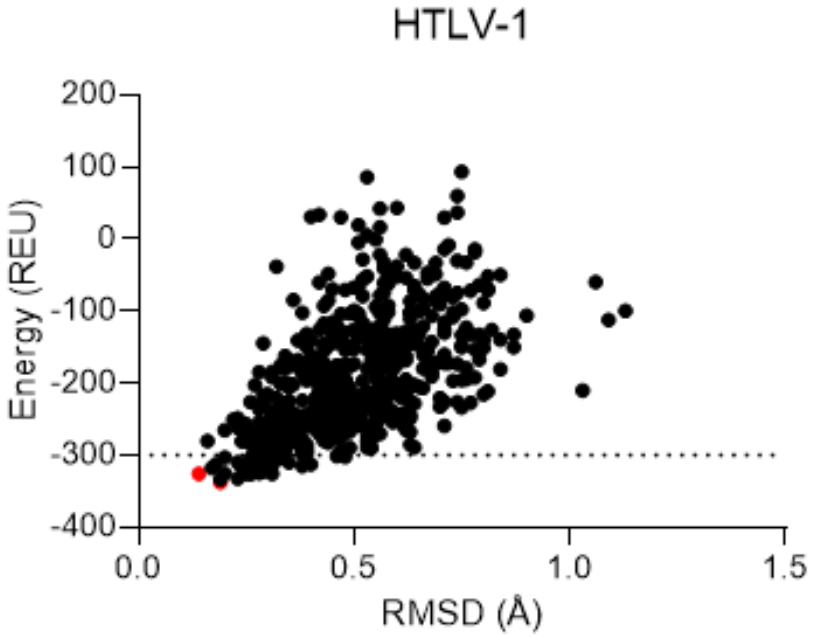
Kruskal-Wallis test (p-value = 0.0086)
*:p-value = 0.04
**:p-value = 0.03

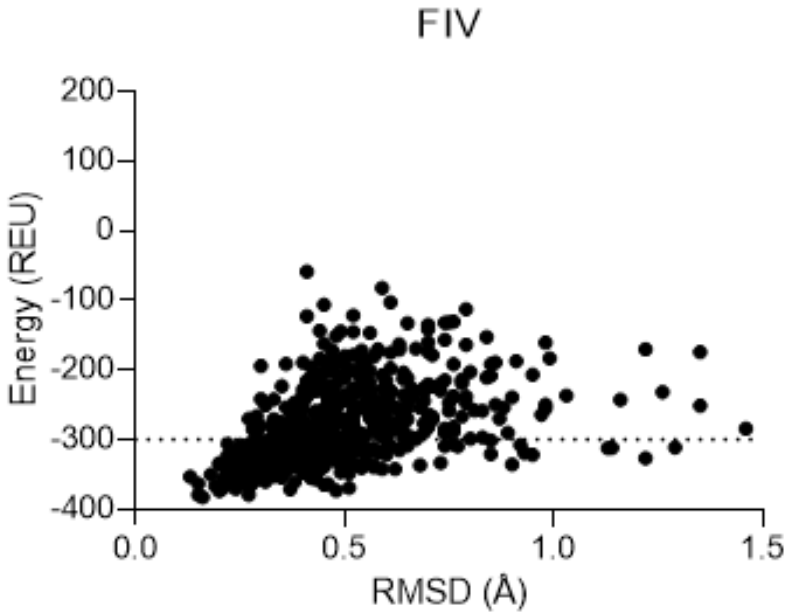
Projects in chemical systems biology

Projects in chemical systems biology

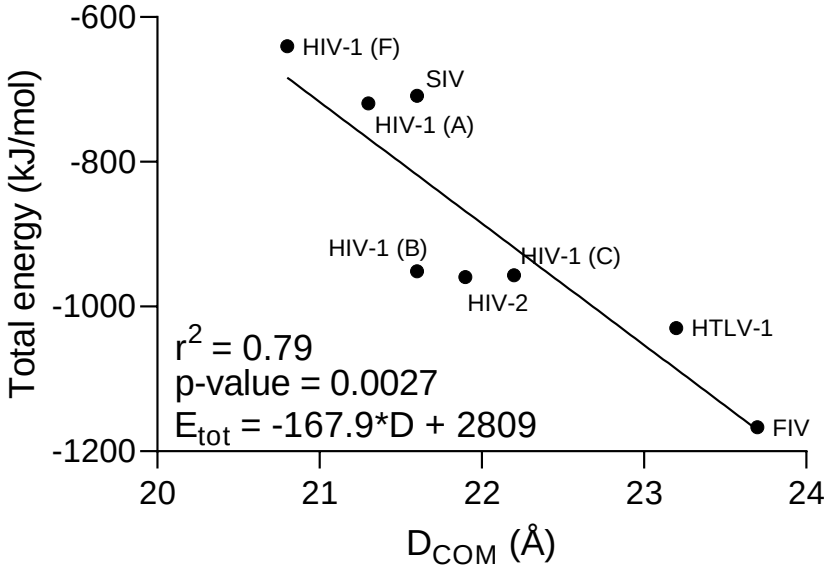


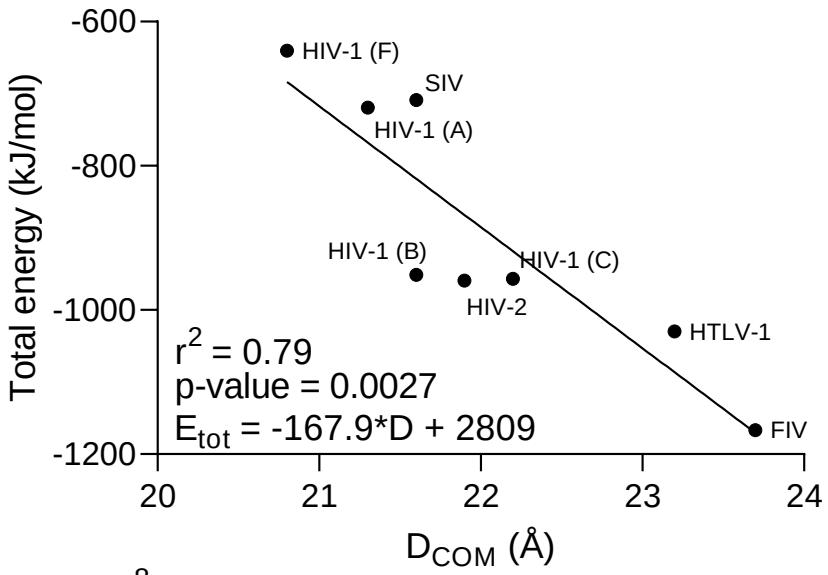
Projects in chemical systems biology

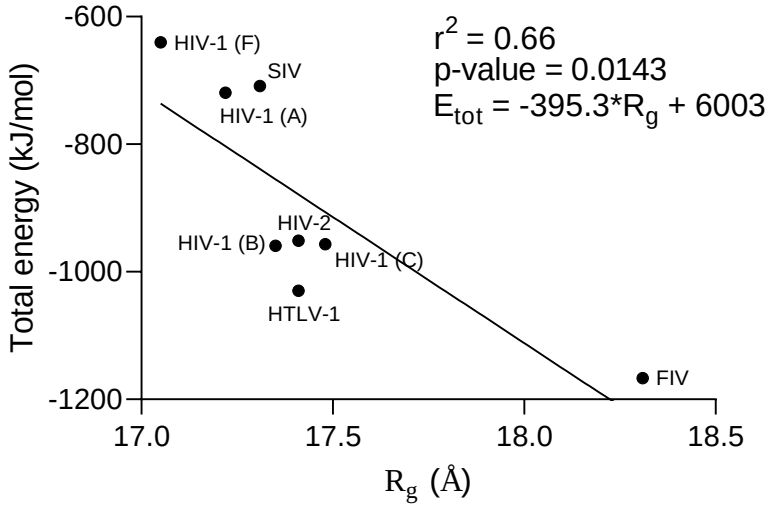


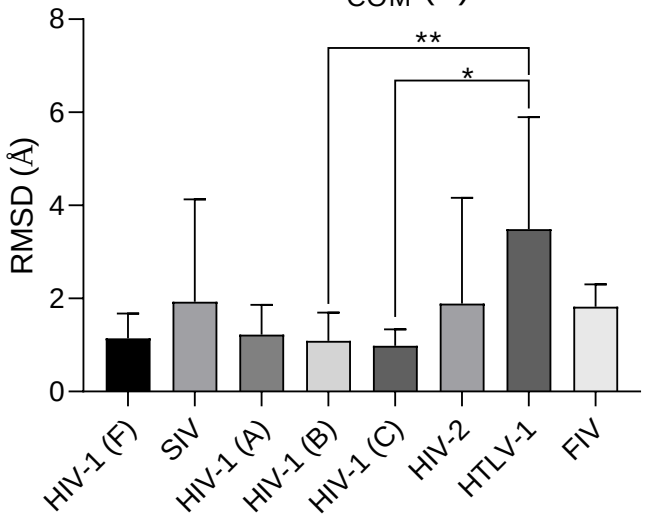


Dimerization and inhibition of retroviral proteases









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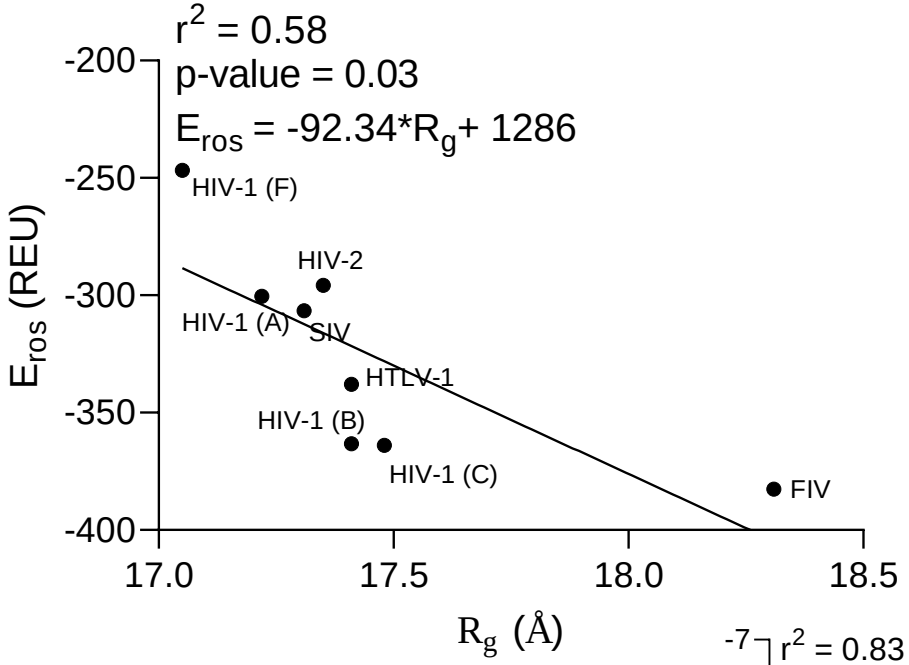
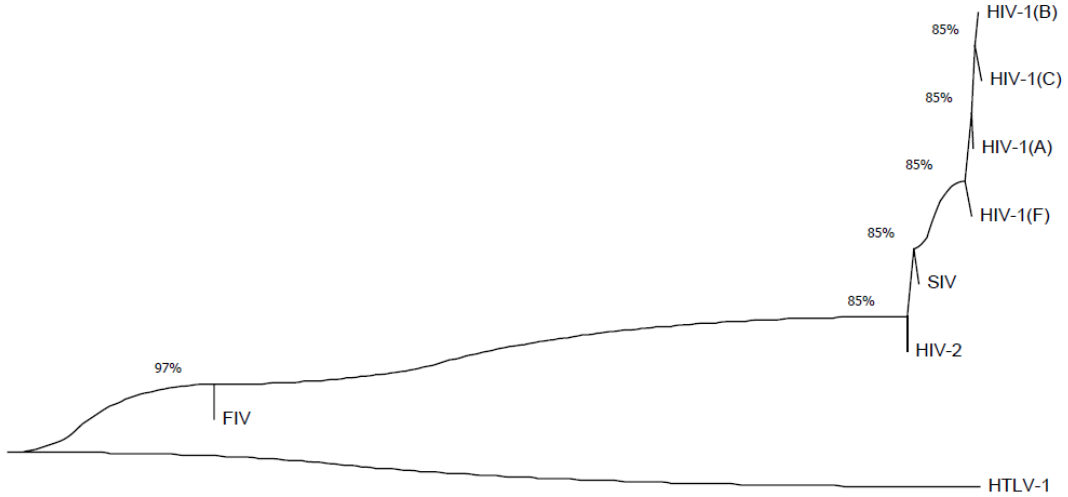
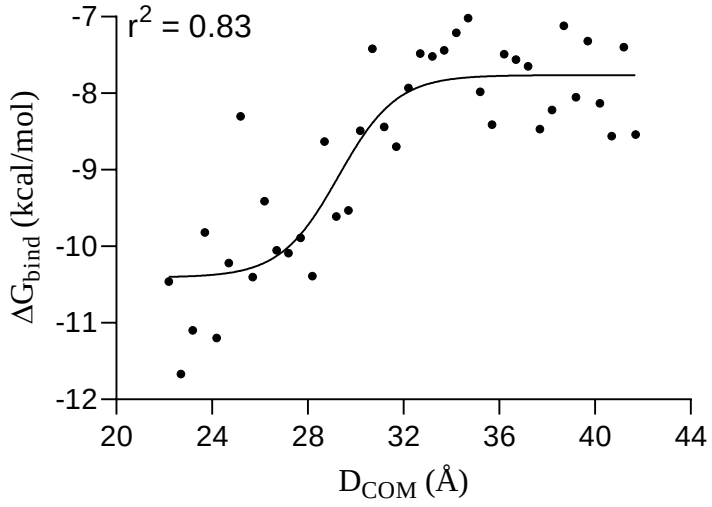
Shityakov et al., in preparation

Dimerization and inhibition of retroviral proteases

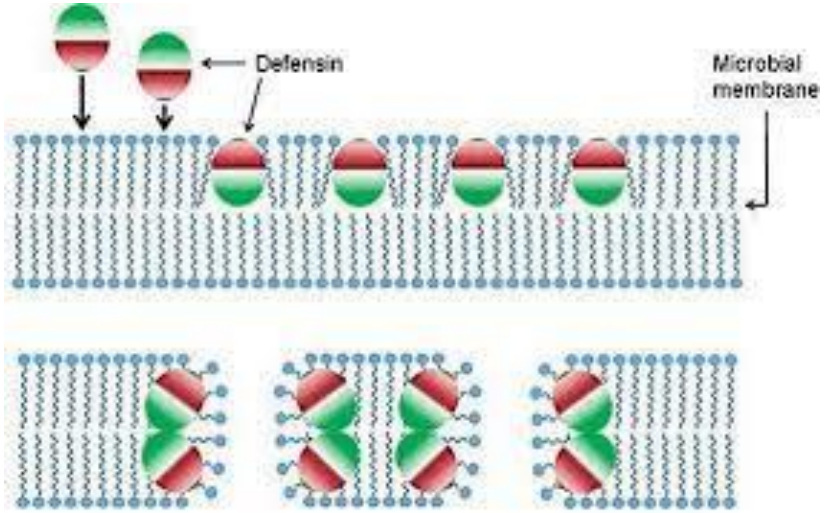


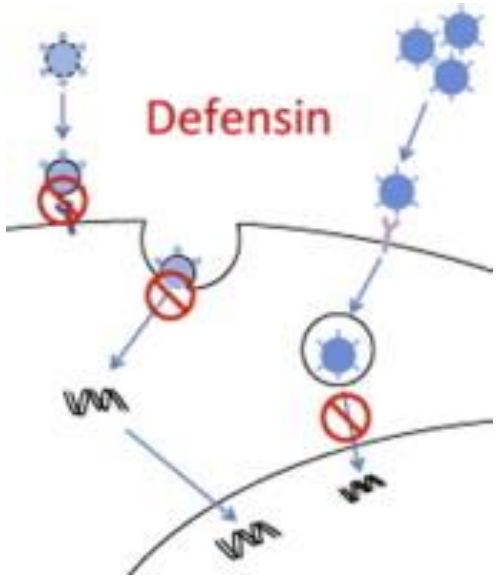


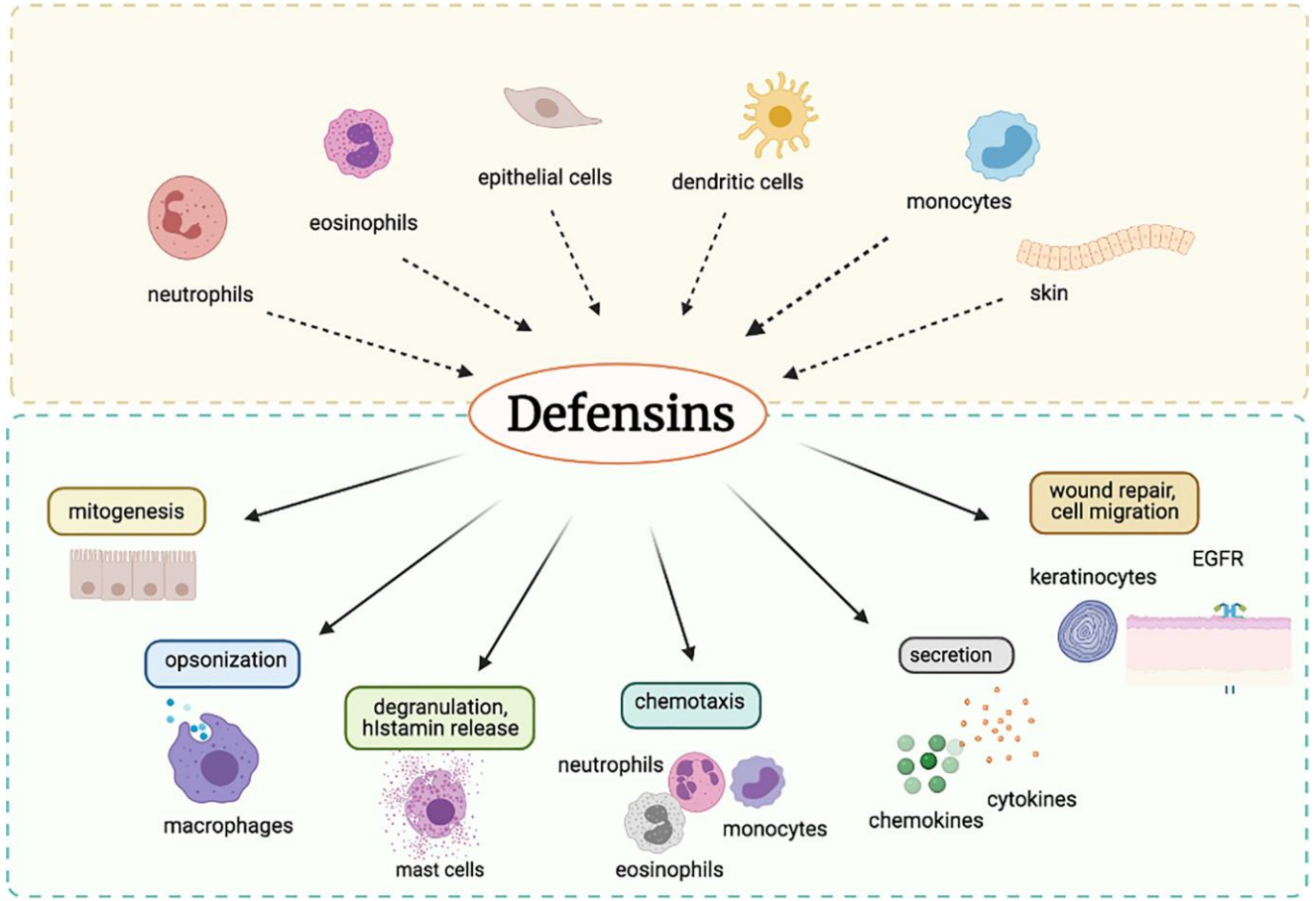


Shityakov et al., in preparation

nsSNPs in DEFB1 gene reveal impact on protein-ligand binding sites

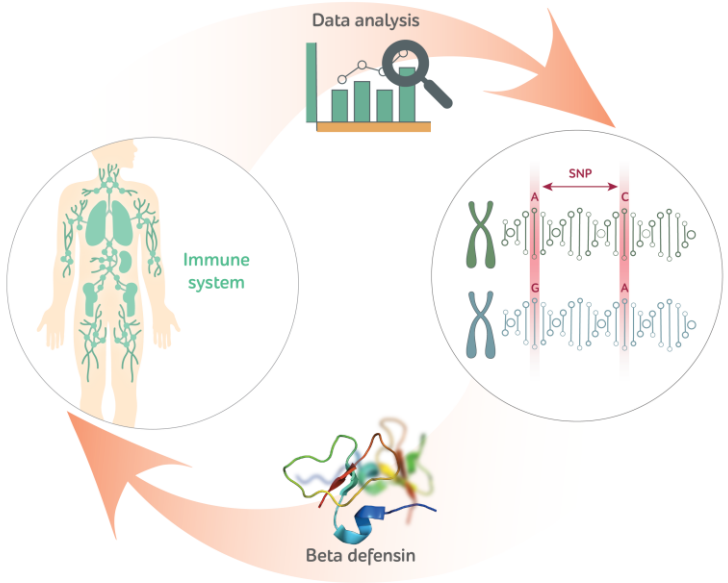


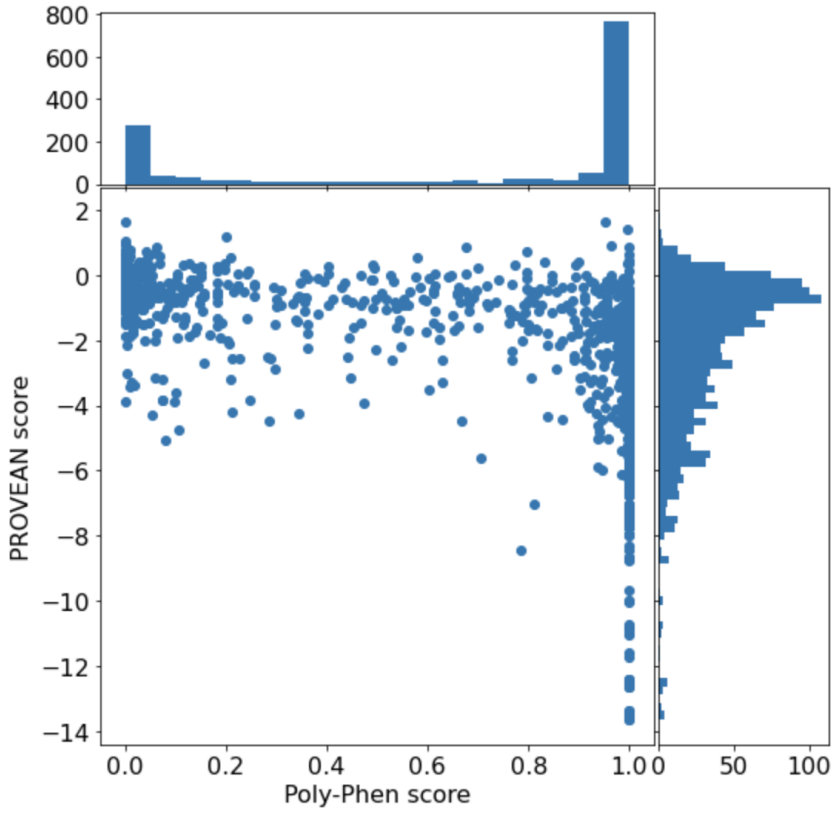


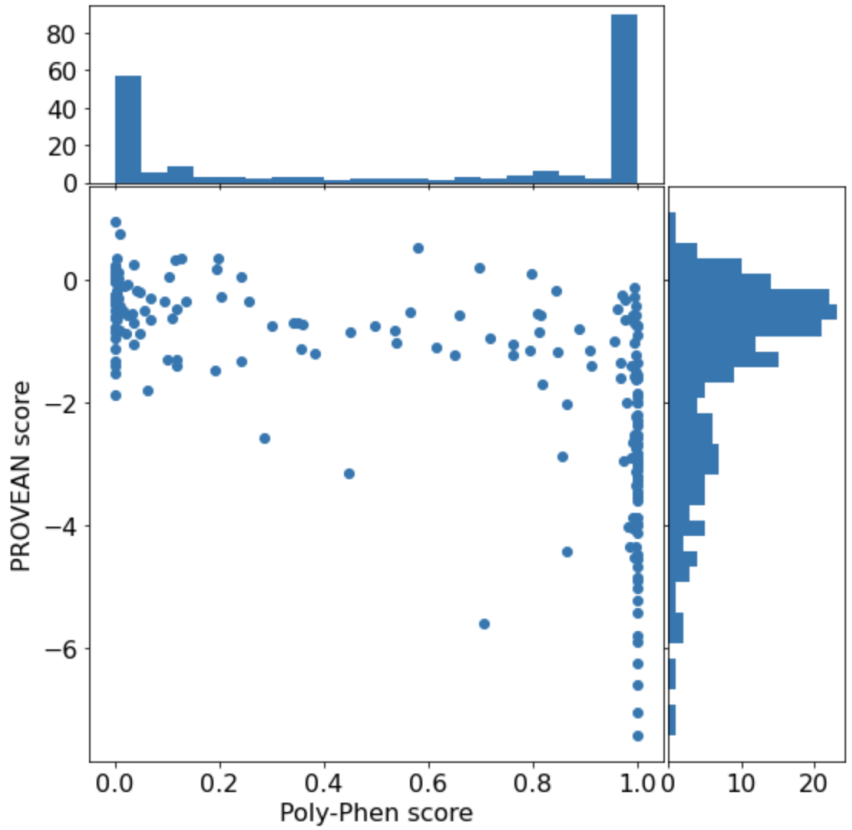


Fareed et al., Comp. Biol .Chem., 2022

nsSNPs in DEFB1 gene reveal impact on protein-ligand binding sites

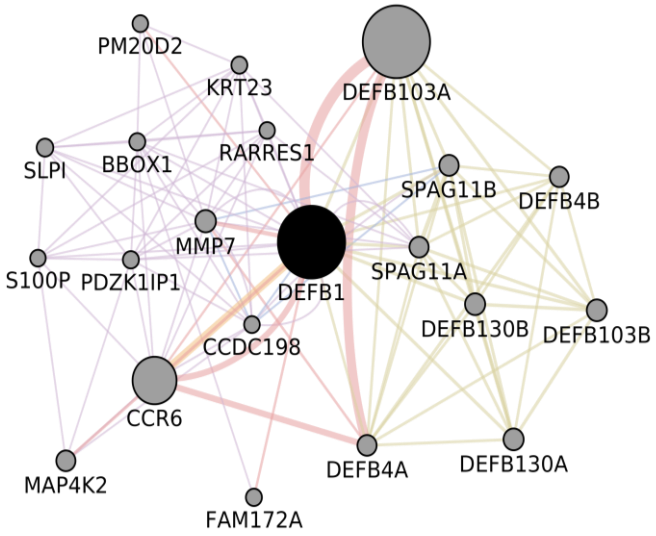


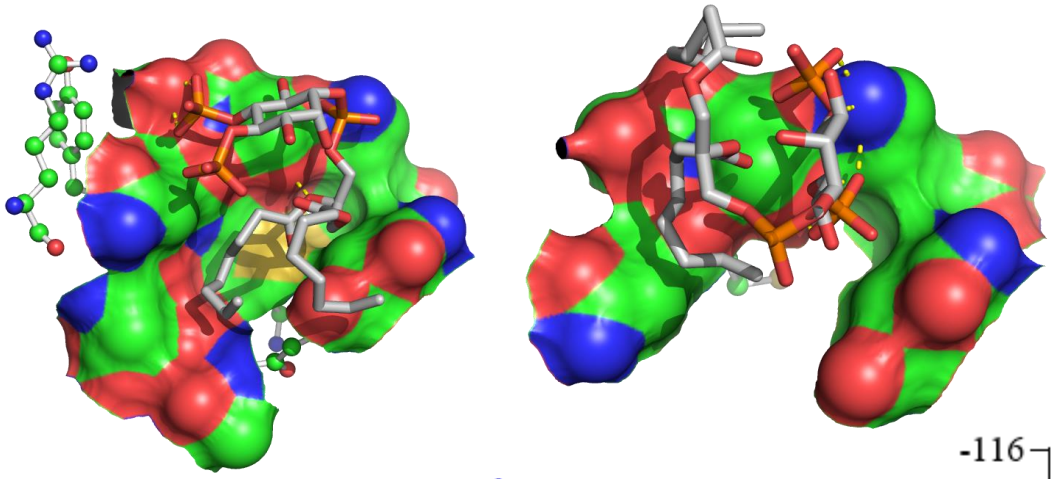


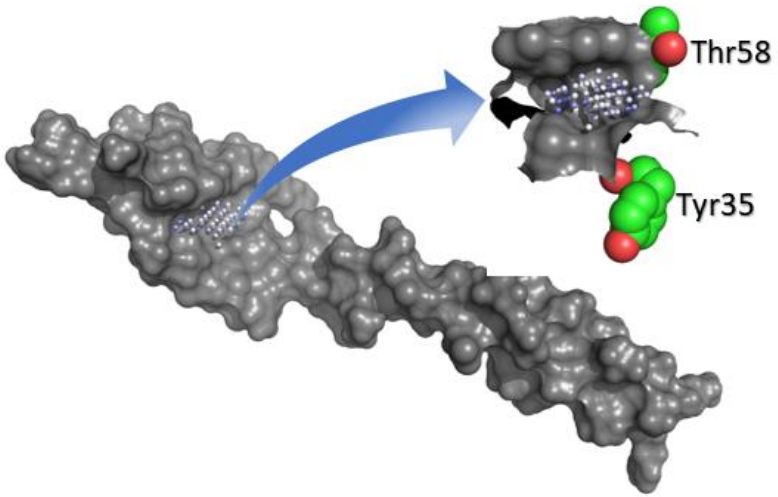


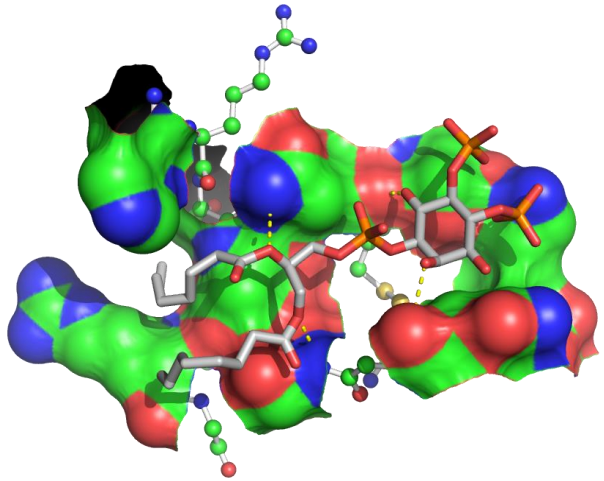
Fareed et al., Comp. Biol .Chem., 2022

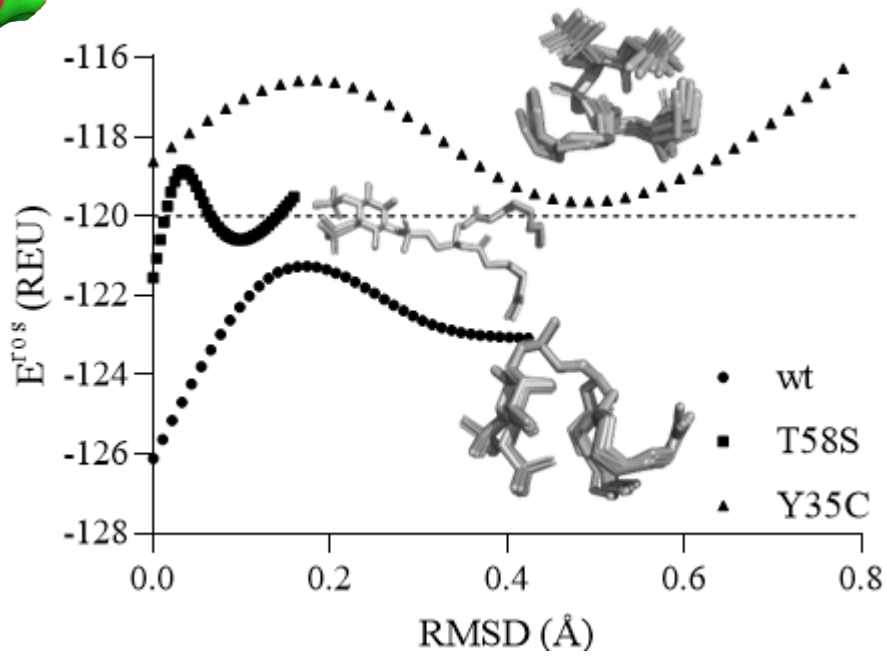
nsSNPs in DEFB1 gene reveal impact on protein-ligand binding sites











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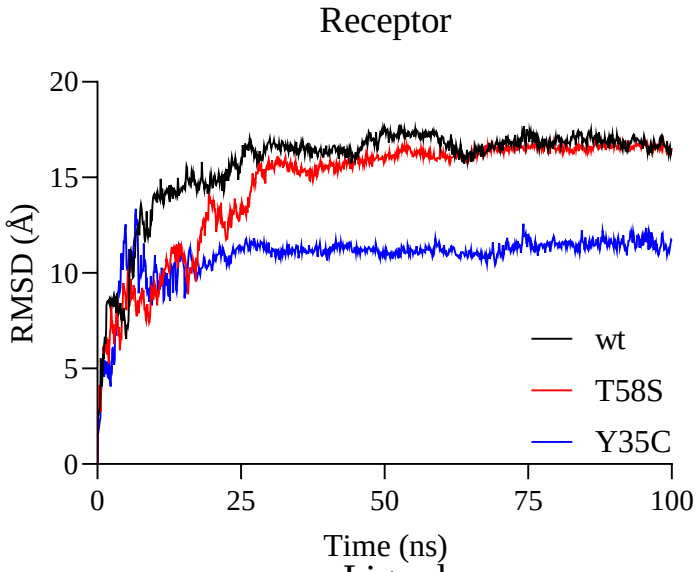

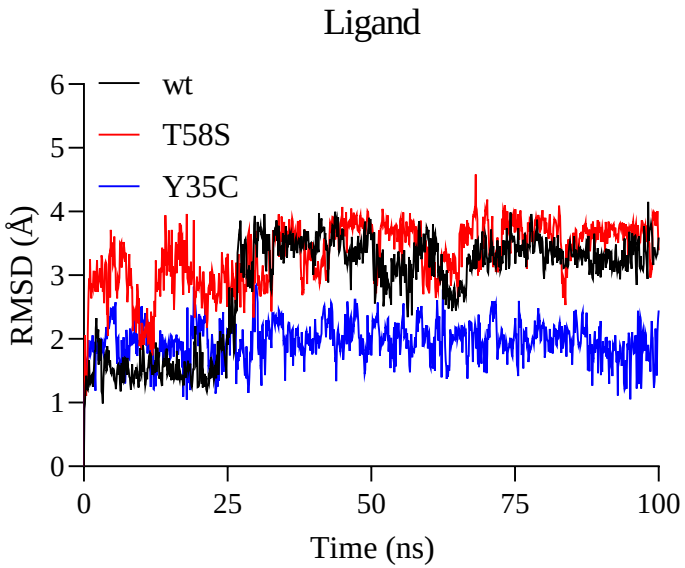

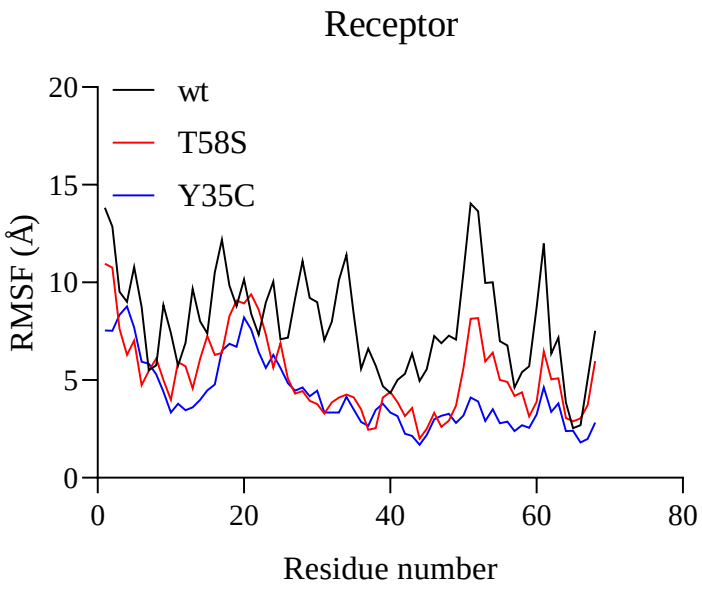

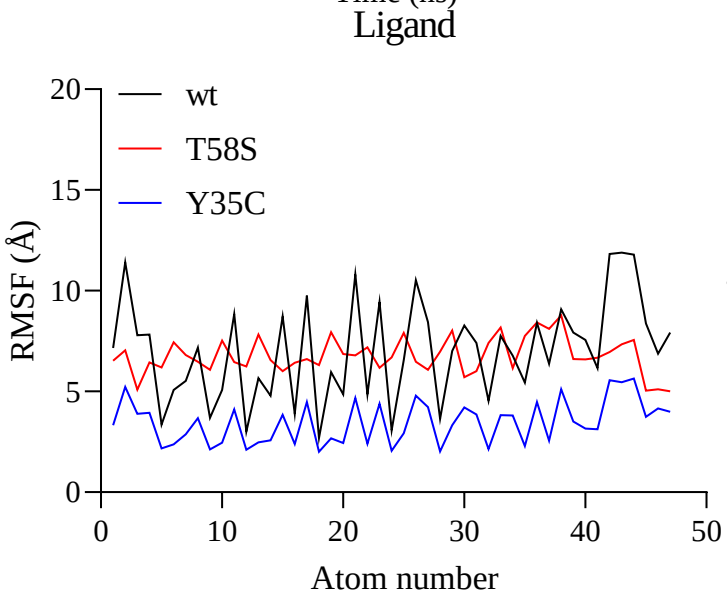

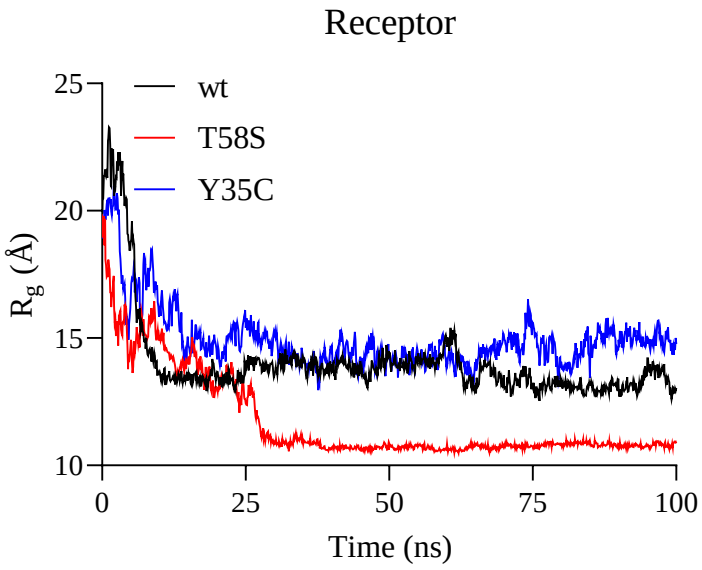

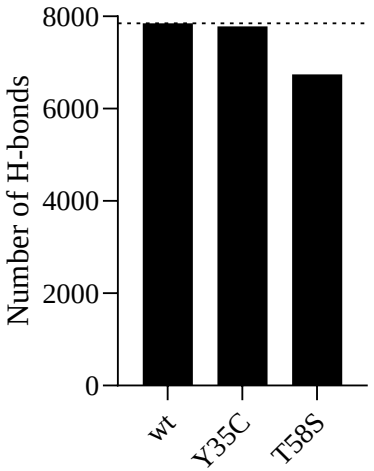

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Summarizing…

✧ Network approaches allow researchers to rapidly organize and extrapolate available knowledge by integrating different types of large datasets.

✧ Application of such methods in drug research allow:

- ✧Systems level description of drug action
- ✧Explanation of side effects
- ✧Drug repurposing
- ✧Identification of novel drug targets and therapeutic strategies
- ✧Prediction of effective drug combinations
- ✧Better understanding of complex diseases

Questions?

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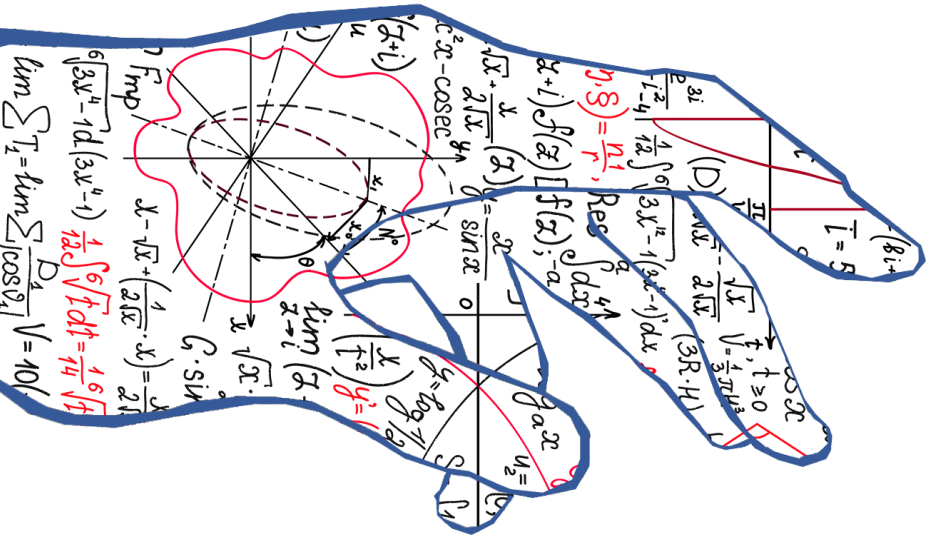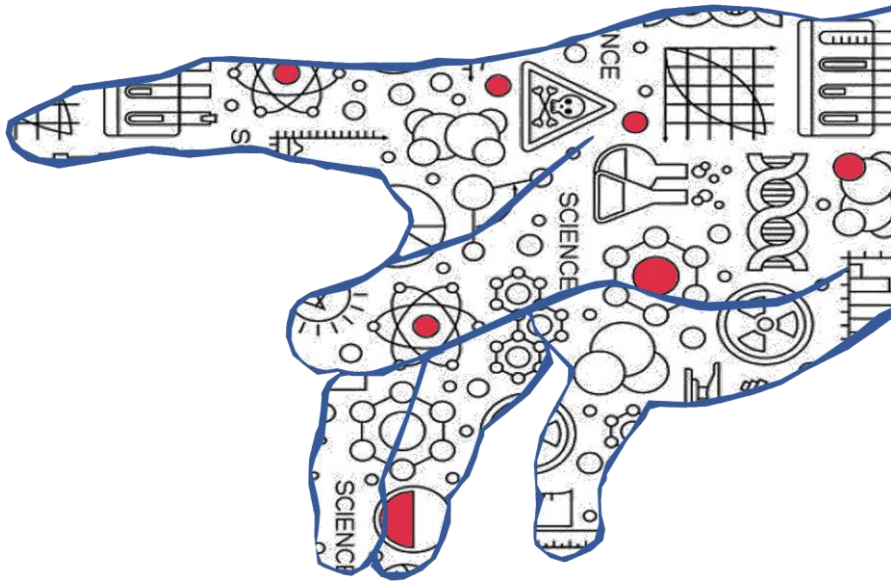
Thank you for your attention