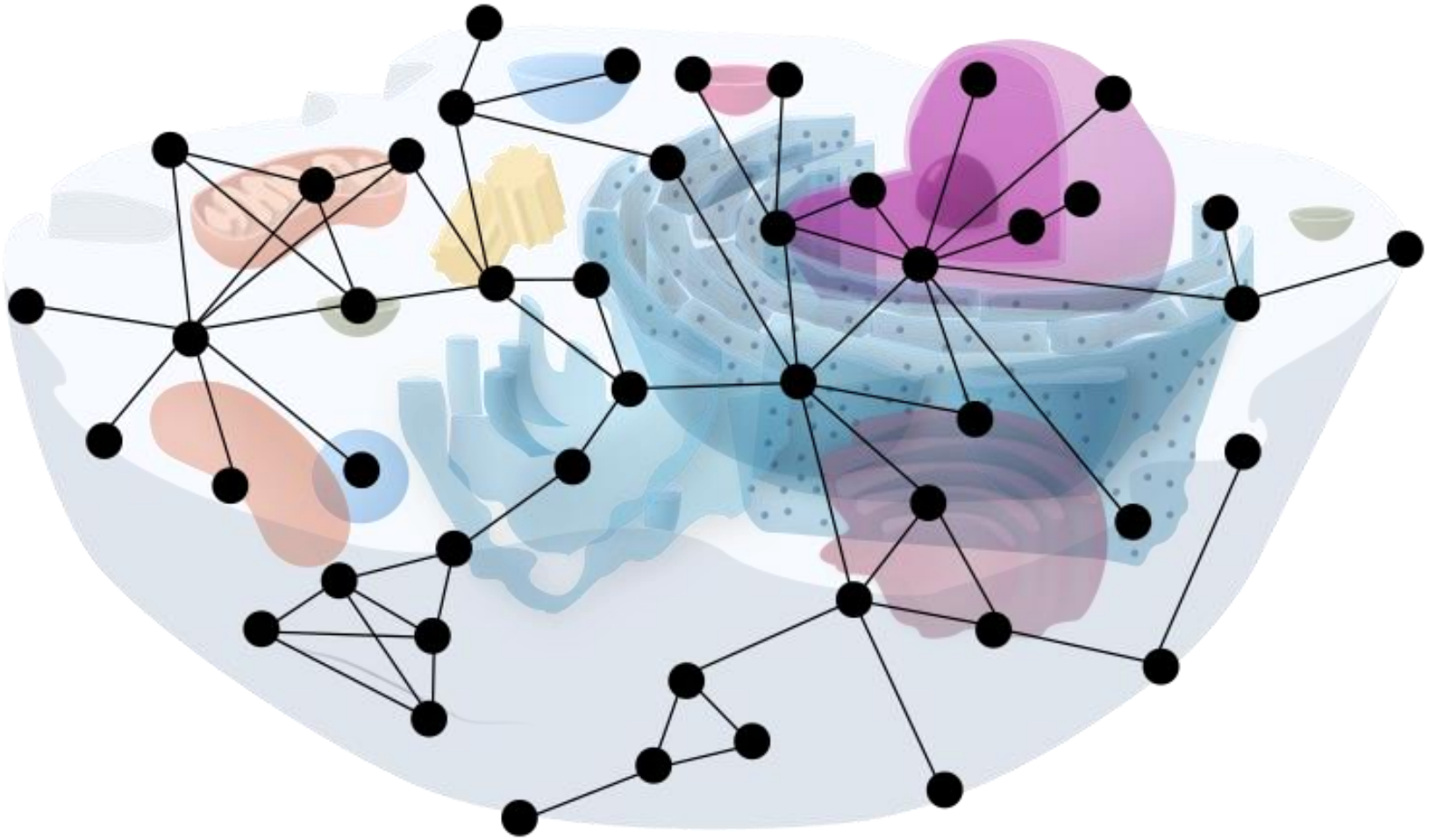
Connecting the Dots: Systems Biology at Every Scale



Ankit Agrawal
University of Würzburg
Germany

B403 Bioinformatics and Computational Biology

11. Systems Biology (4 Lecture + 1 demo)

- Introduction, need for computers in system biology
- High-throughput and *omic* approaches, difference and application
- Graph theory (Network theory)
- Gene Ontology
- Demo: KEGG and gene ontology

Outline agenda

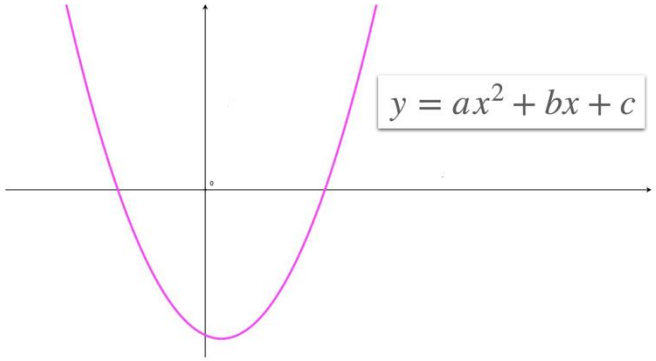
- Why do we need algorithms and computers
- What is systems biology
- Networks biology vs systems biology
- Biological networks are ubiquitous
- Basic component of a network
- Constructing and modeling networks
- Network motifs

Scan me to download the presentation and the codes

What is a function?

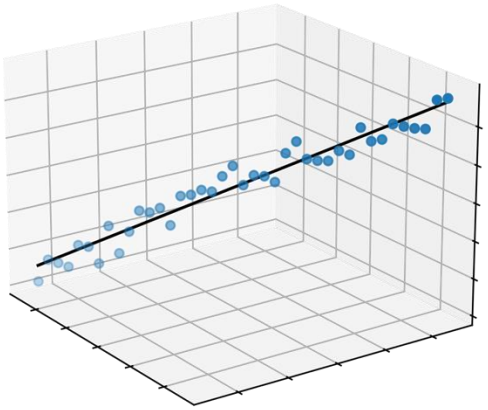
Input X → **Function f:** → Output Y = f(x)

Parabola



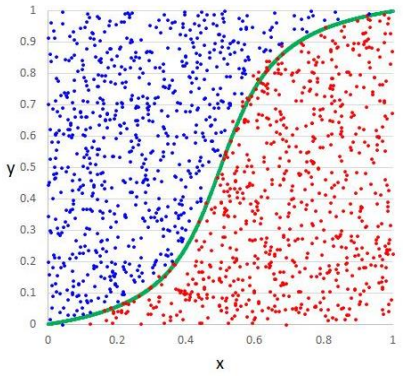
Linear Regression

y=a*x1+ b*x2+ const

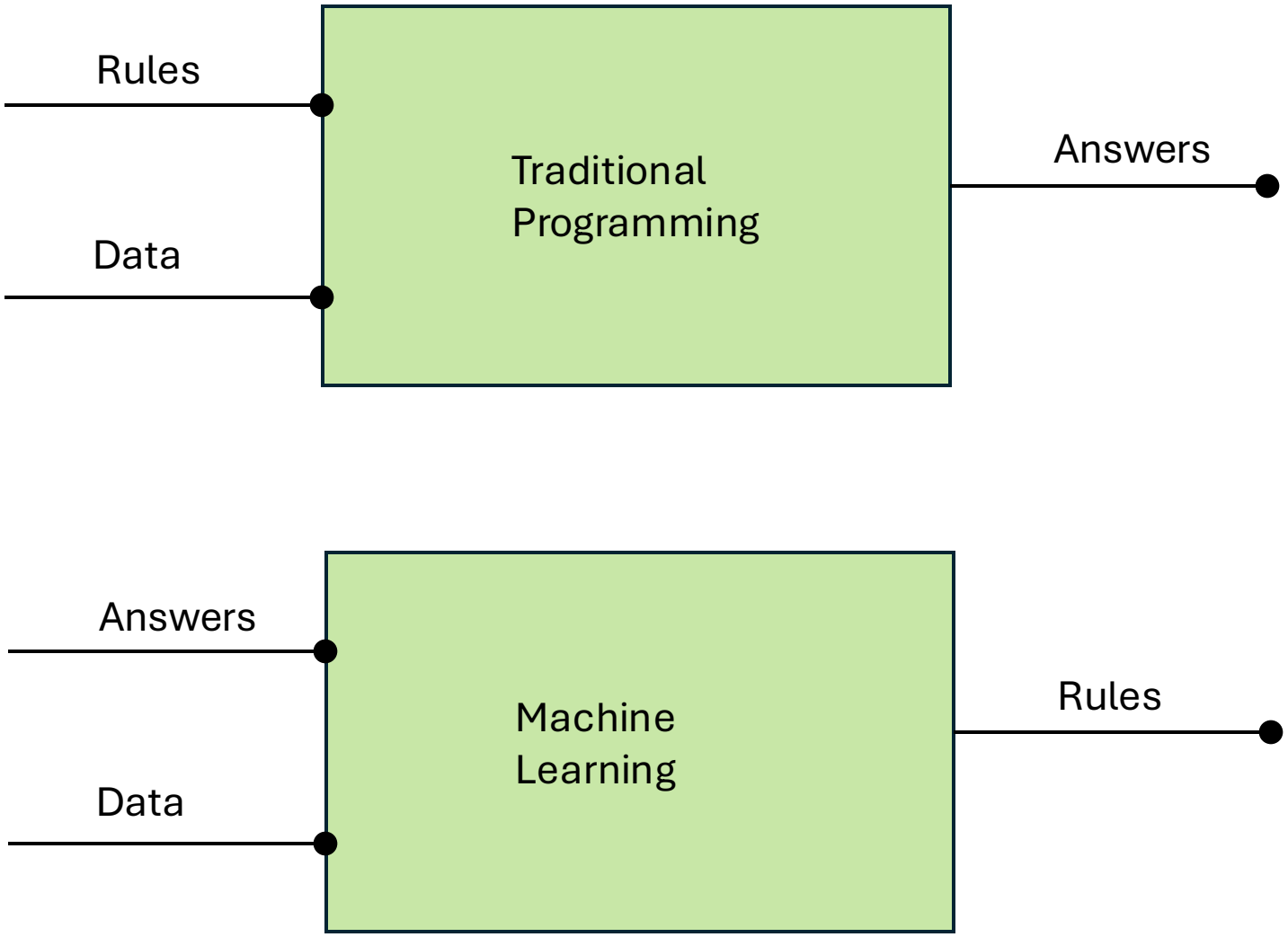


Logistic Regression

$$y = \frac{e^{(b_0 + b_1 X)}}{1 + e^{(b_0 + b_1 X)}}$$

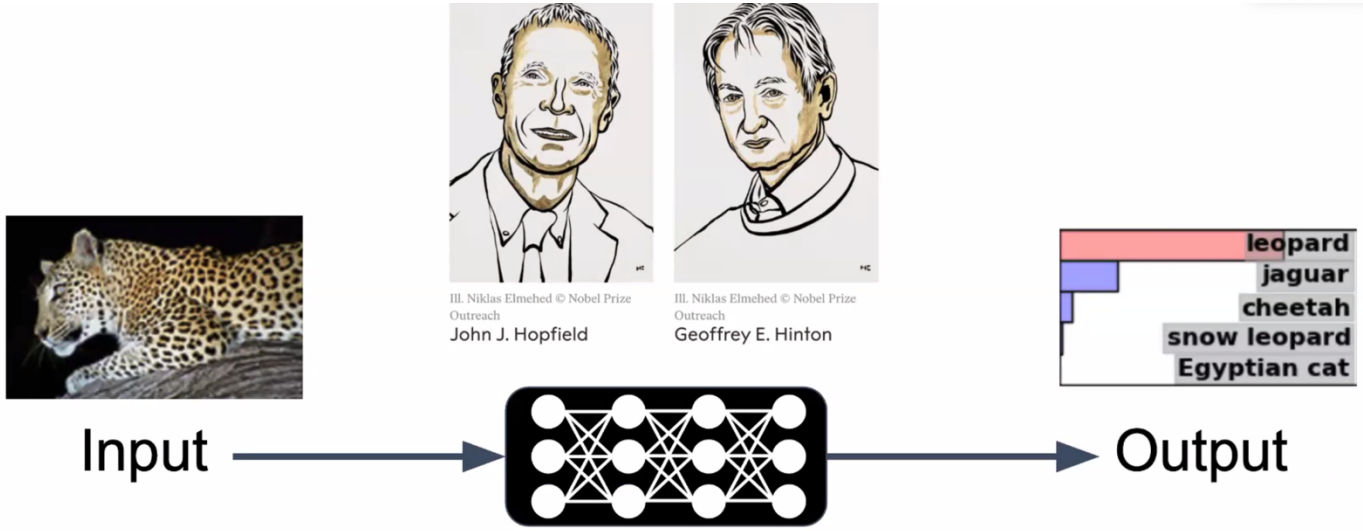


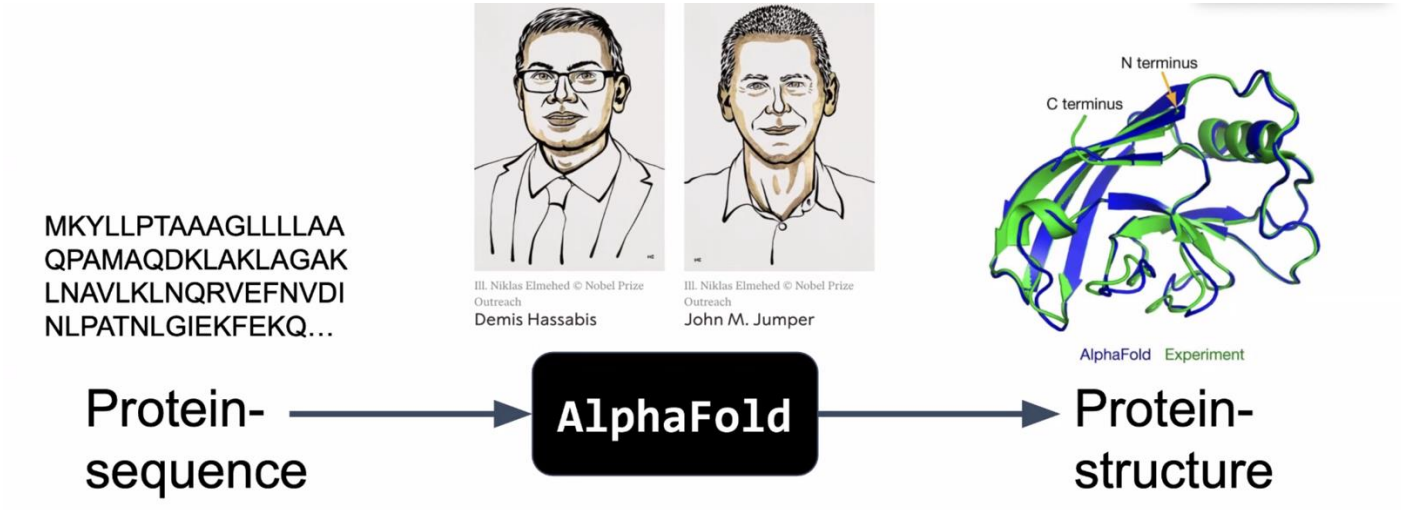
Programming vs Machine learning



In a simple terms, a machine learning task is to identify the underlying function or pattern from the input data.

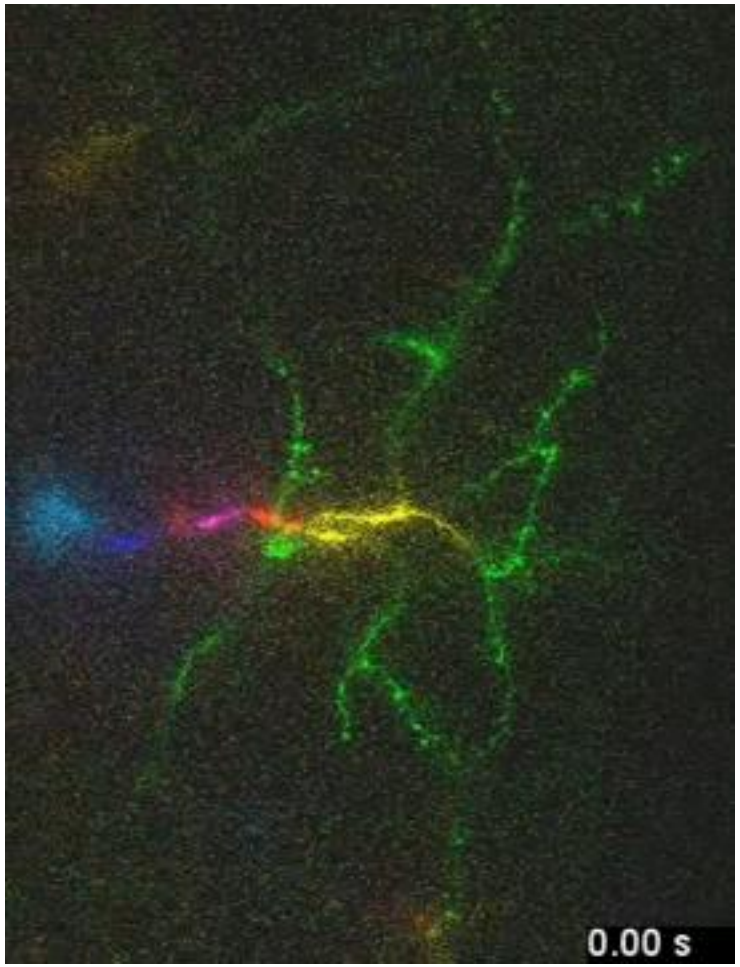
What is Artificial intelligence (AI)?





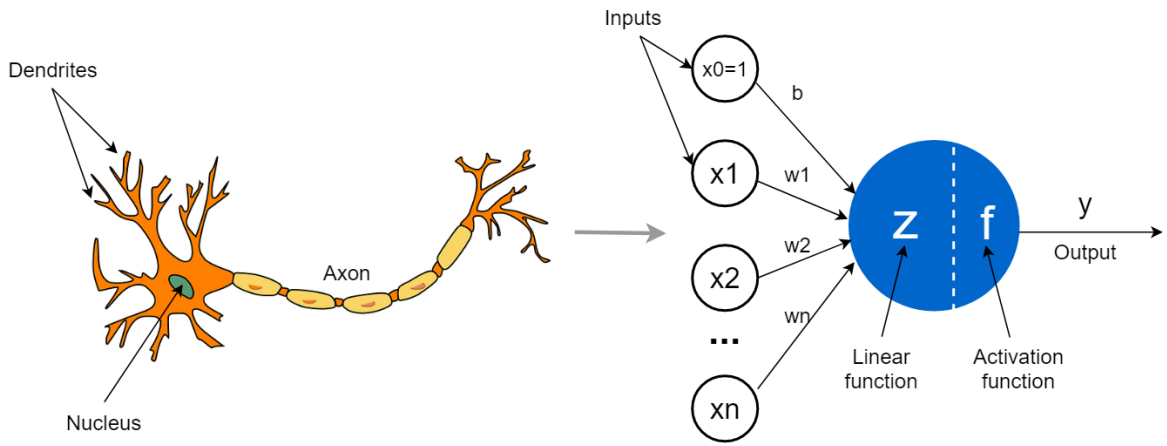
AI often uses machine learning as a method to understand data, find patterns, and make decisions or predictions that are meaningful and relevant.

Some machine learning algorithms are biologically inspired



Youtube UC Berkeley Watch a neuron fire!

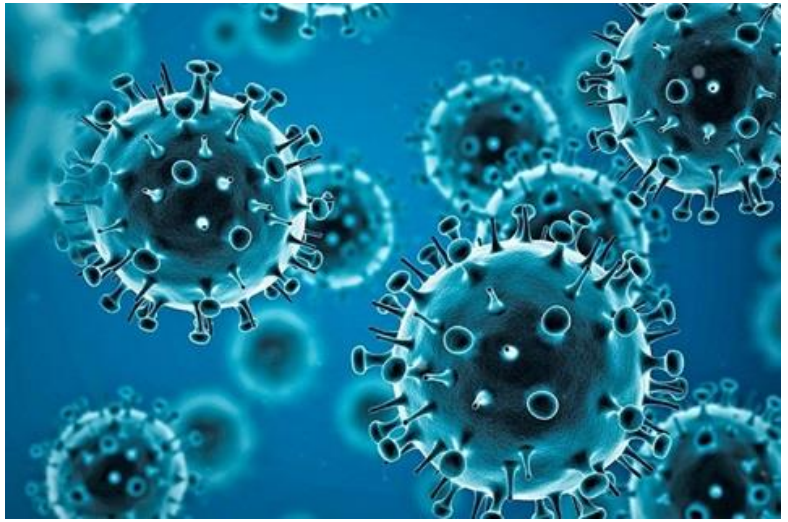
Coordination leads to collective intelligence



Emergent phenomenon

Smallest unit
Component or parts

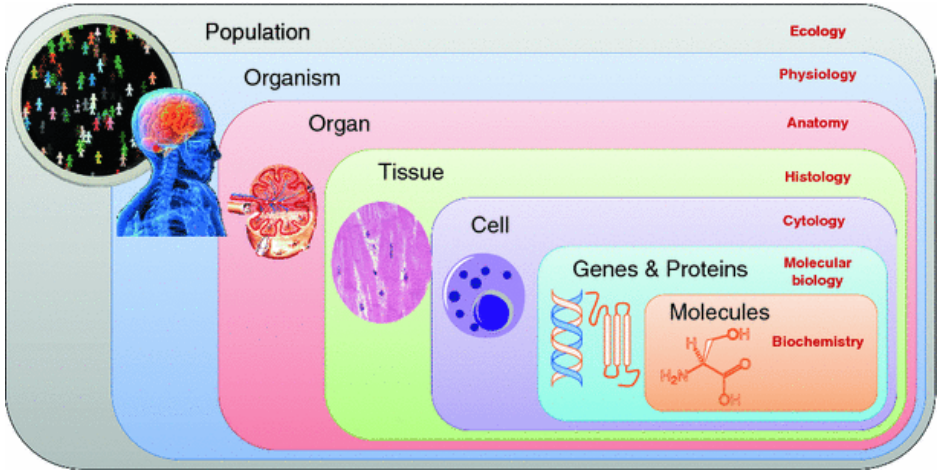
Smallest unit
Cells or molecules



Smallest unit
Single virus or protein

Systems biology (understand any biological system as a whole or system level)

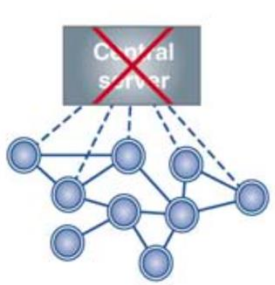
- Systems Immunology
  - Seeks to understand the complex interplay between the immune system and the body across all scales.
- Systems-thinking skills
  - Describing a system's structure and organization
  - Reasoning about relationships within the system
  - Reasoning about the system as a whole
  - Analyzing emerges from studying the interactions of parts within the biological system.



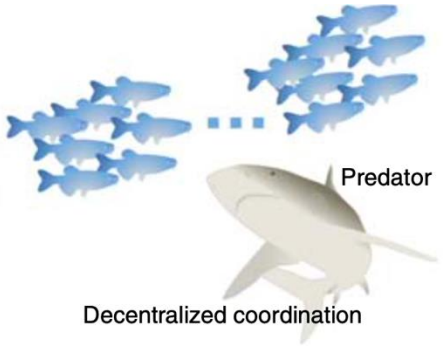
Jennifer Momsen et al CBE Life Sci Educ. 2022

Shared principles between computational and biological systems

No central control: Molecules, cells, or organisms that interact, coordinate, and make decisions without central control.

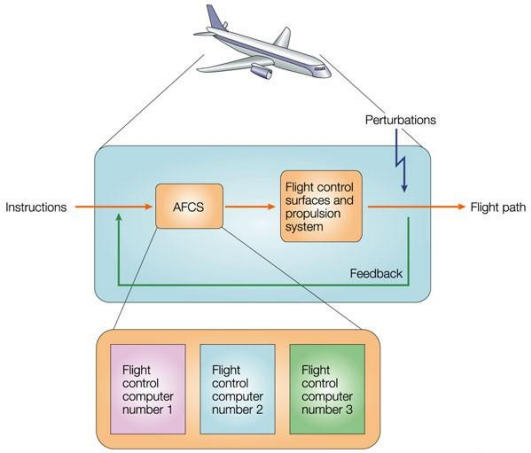


Decentralized systems

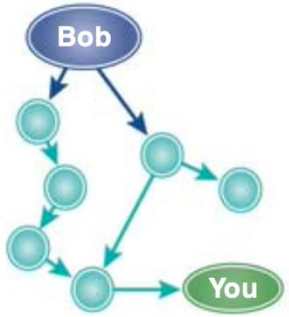


Decentralized coordination

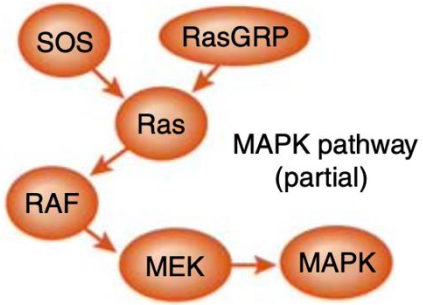
Robustness: biological processes need to be able to successfully handle failures and attacks to thrive.



Networks: serve as an important medium through which interactions occur, and information propagates.

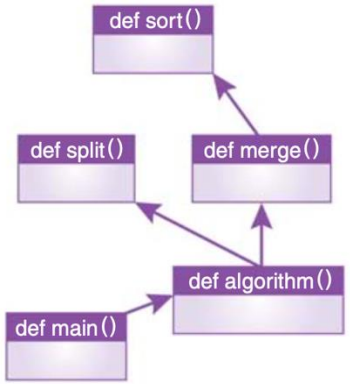


Rumor spreading

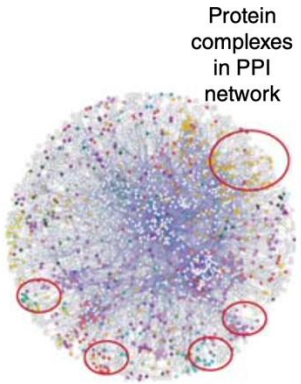


Signal propagation

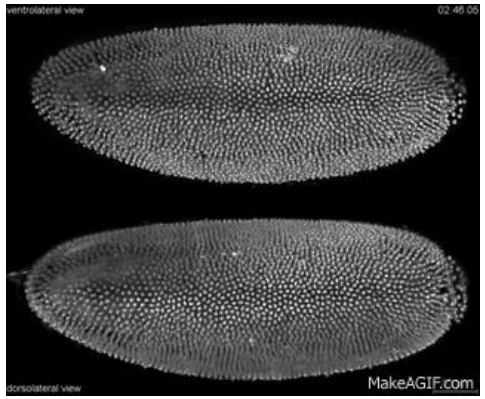
Modular: they reuse certain components in multiple, and sometimes very different, applications.



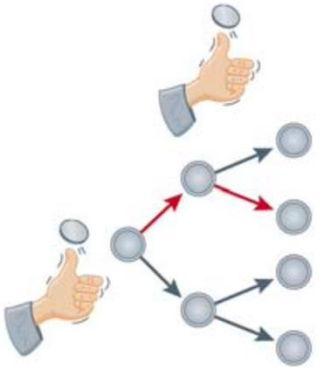
Modular programming



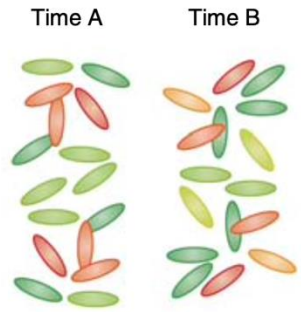
Modular structure



Random: Biological processes are often stochastic



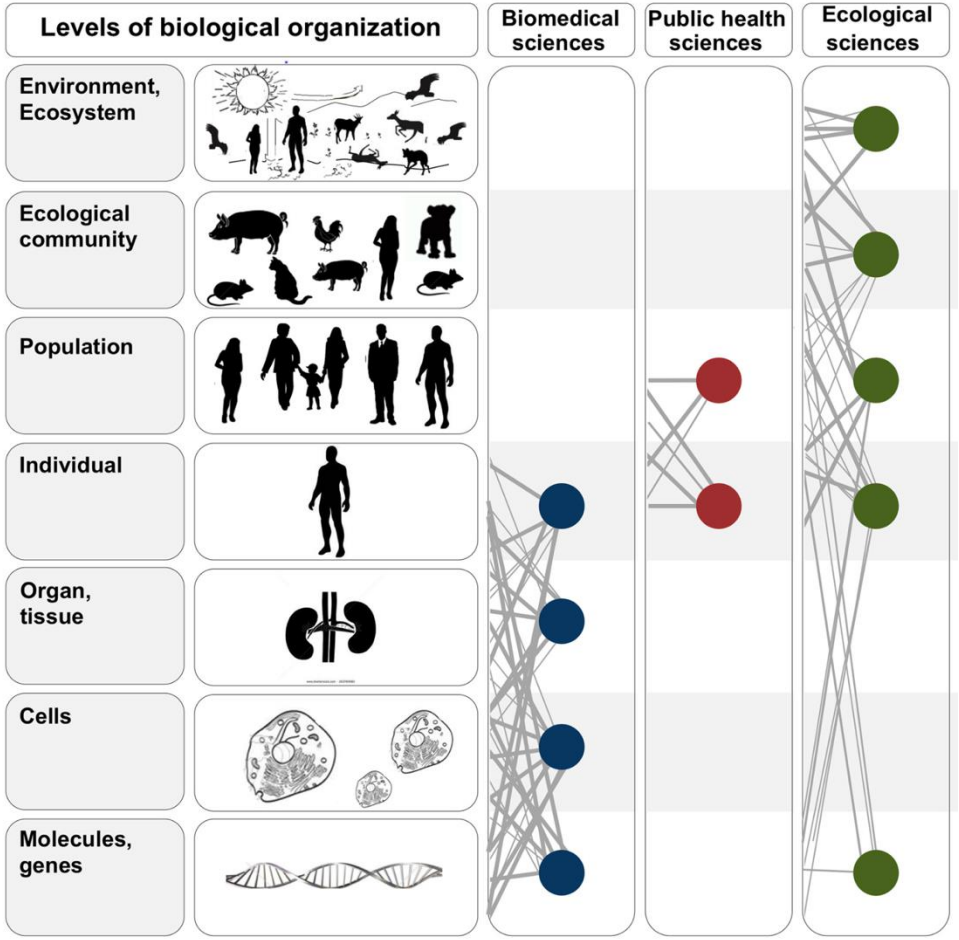
Randomized algorithms



Stochastic gene expression

Network biology vs systems biology (Hierarchy of biological organization)

Concentrates on the structural and topological organization of biological systems



Vanessa O. Ezenwa Plos Pathogens 2015

Focuses on the holistic understanding of biological systems, emphasizing how components interact to produce emergent behaviors

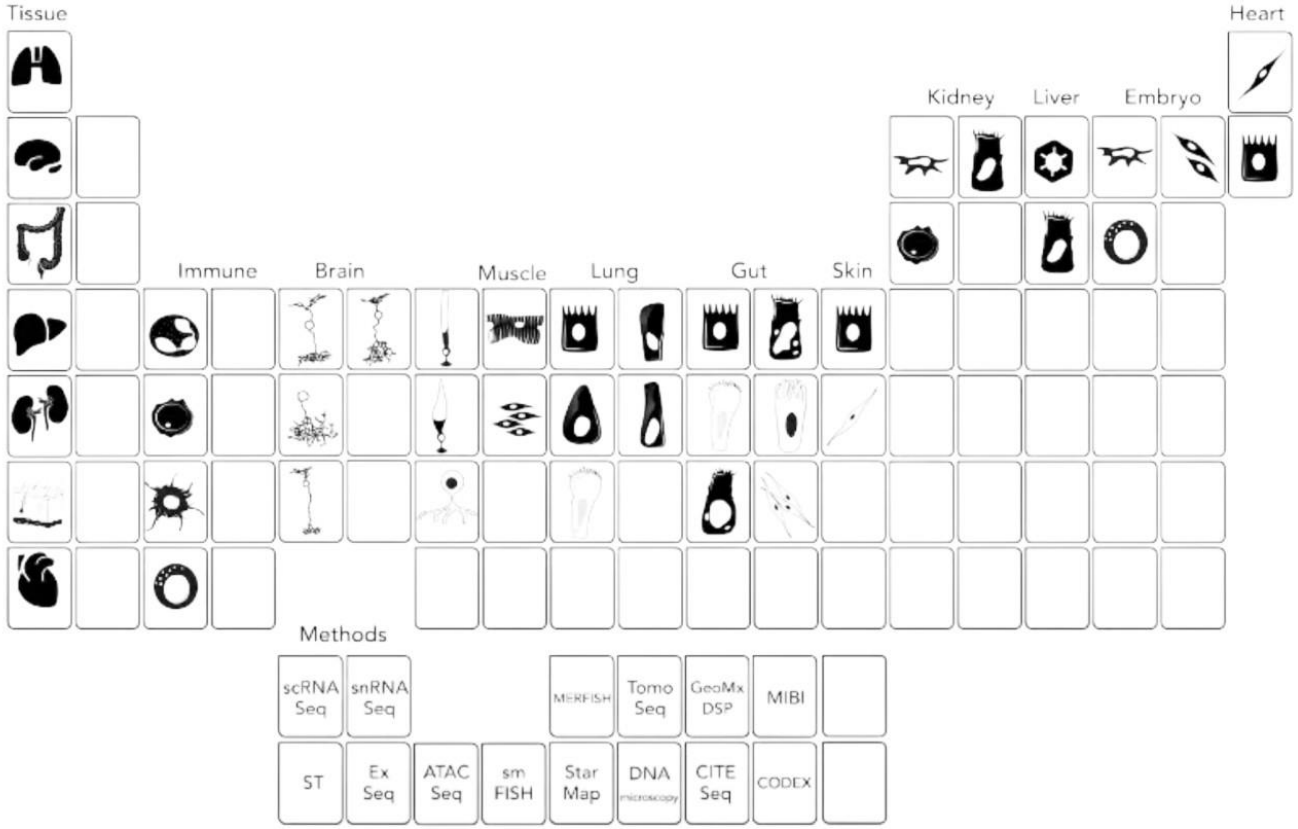
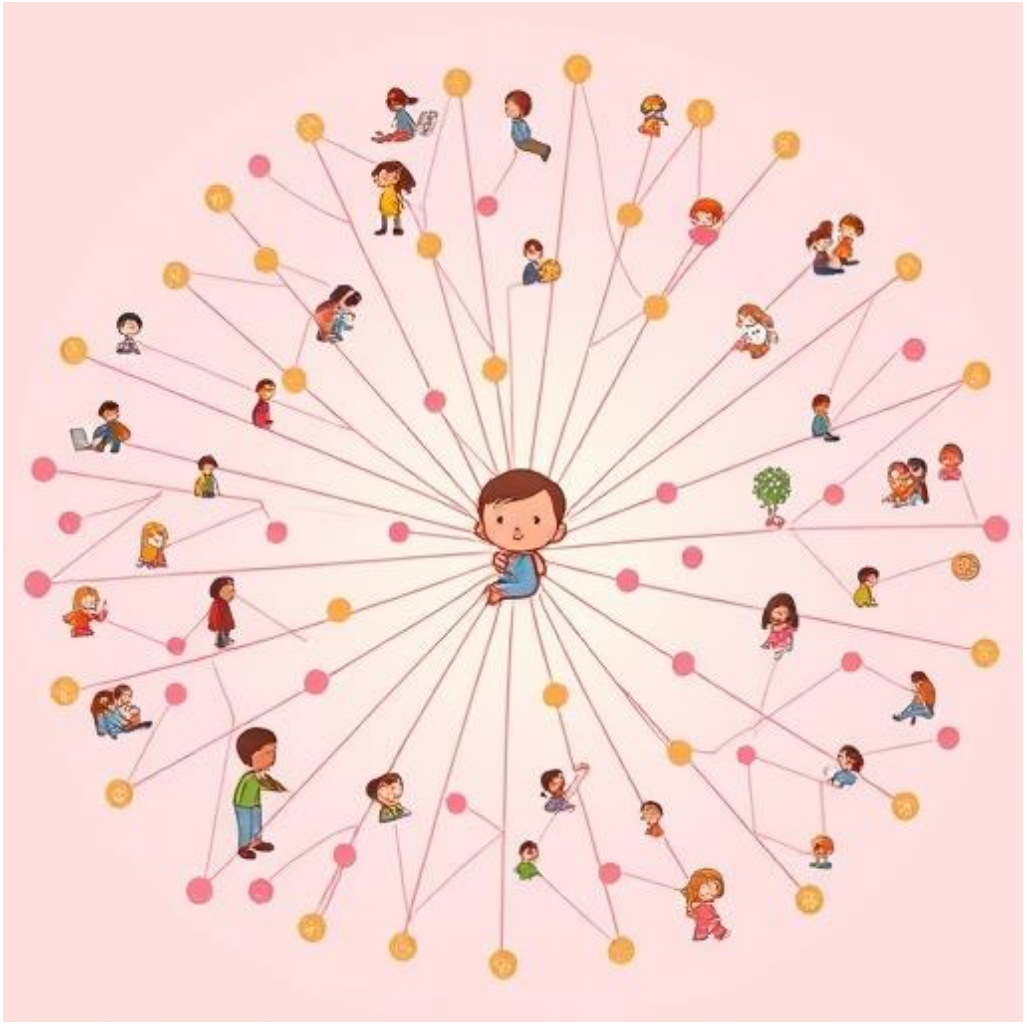


Image credit: Fabian Theis Lecture

What is networks or graphs?

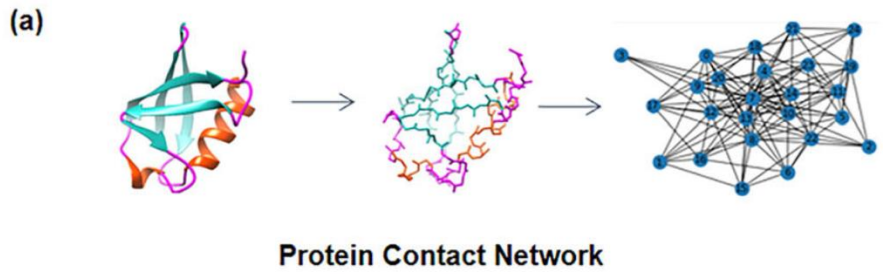
Prompt

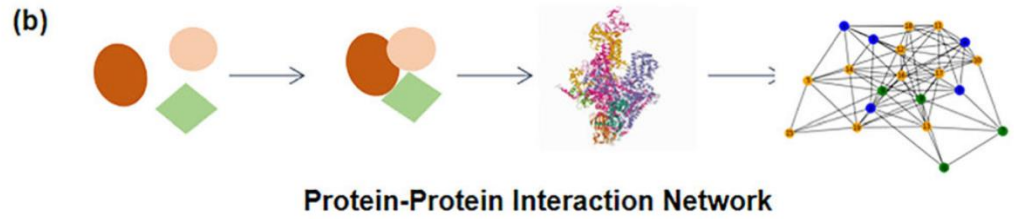
Create a cartoon-style illustration showing the evolution of a person’s social network from infancy to adulthood. Start with a baby in the center who first connects with their parents and siblings. As the child grows, add connections to extended family (grandparents, aunts, uncles), followed by friends from school, teachers, and neighbors. Then, show young adult connections branching out to university friends, mentors, and colleagues. Make the network web grow larger and more interconnected with each stage of life, symbolizing social expansion

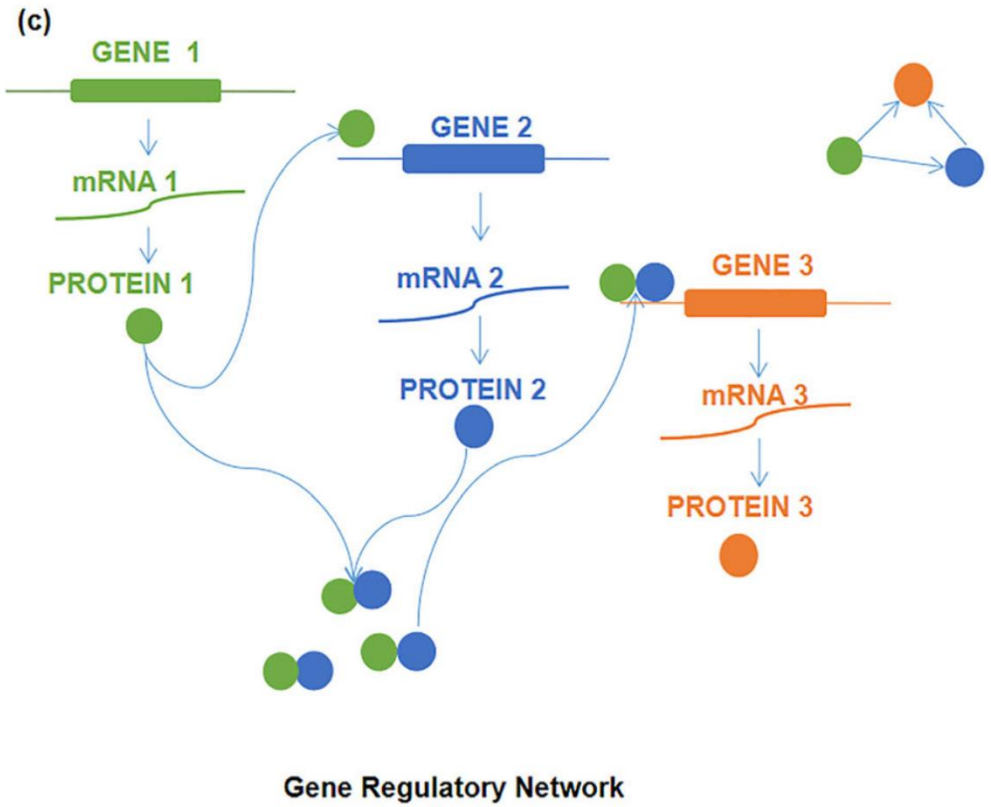


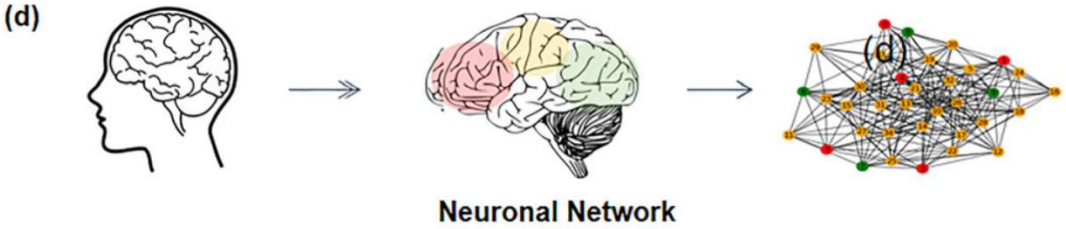
https://deepai.org/machine-learning-model/text2img

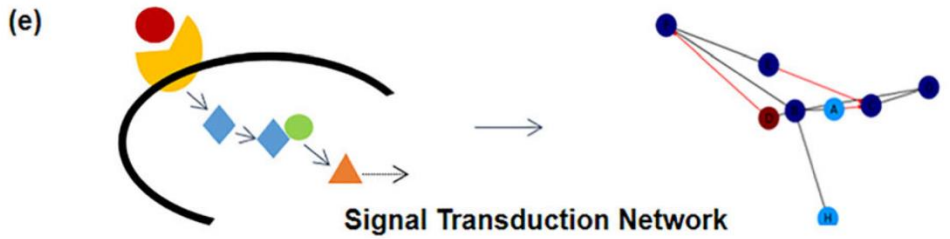
Types of Biological Network

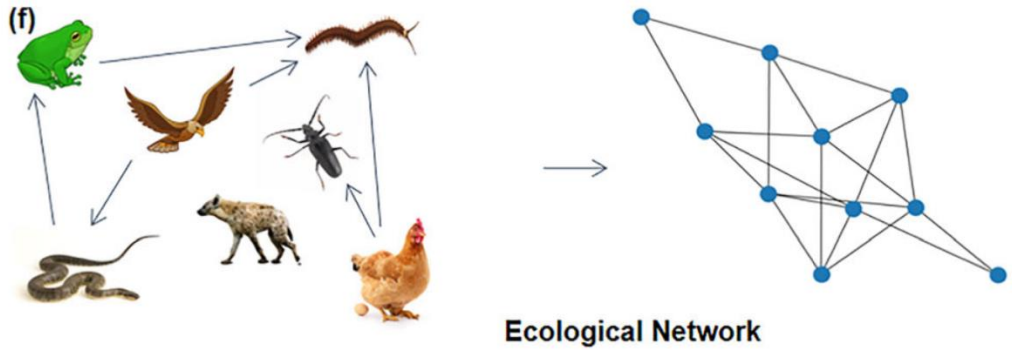






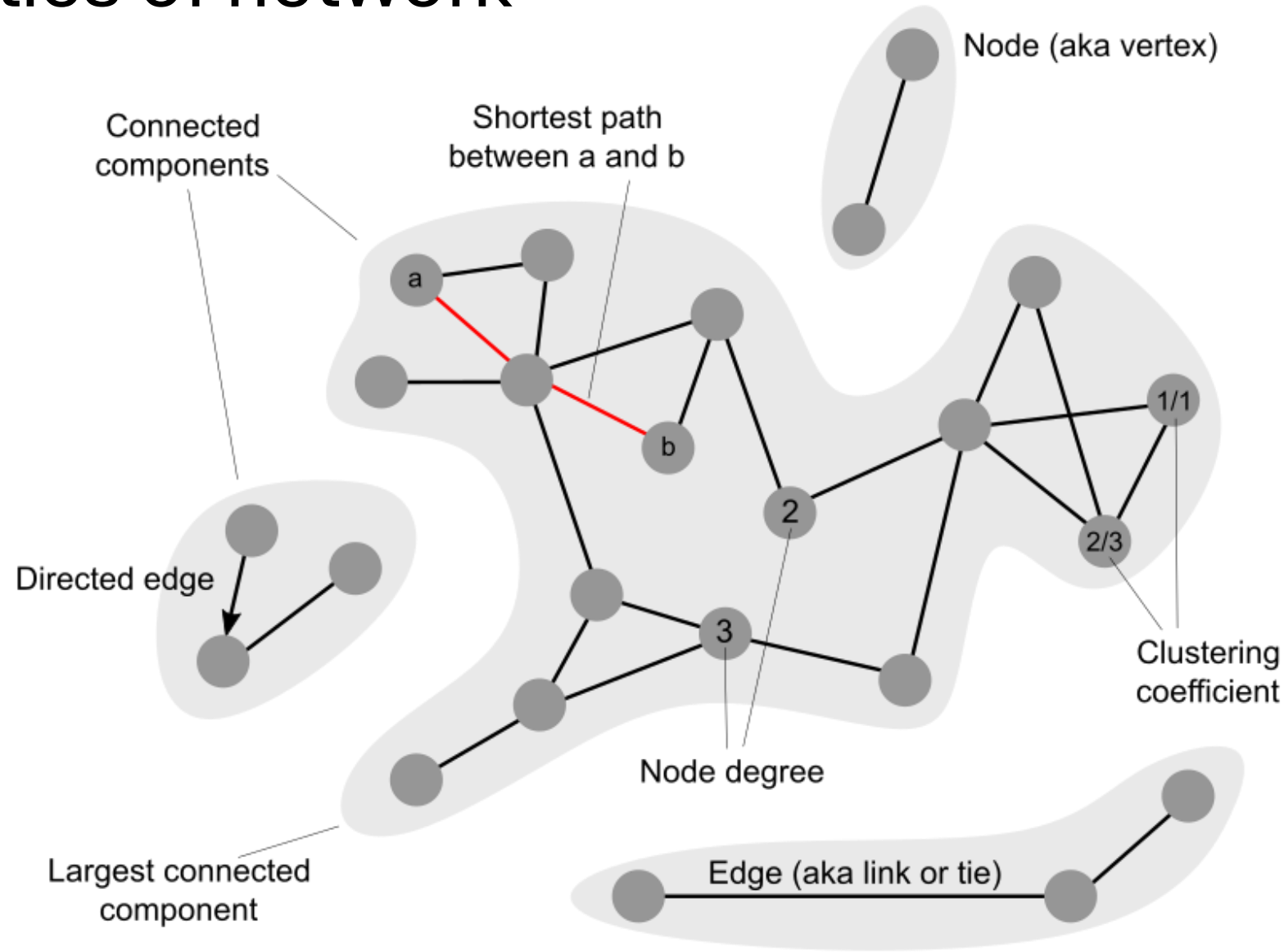






S Chaudhuri and A Srivastava J Biosci 2022

Properties of network



https://cbdm-01.zdv.uni-mainz.de/~galanisl/netbio/

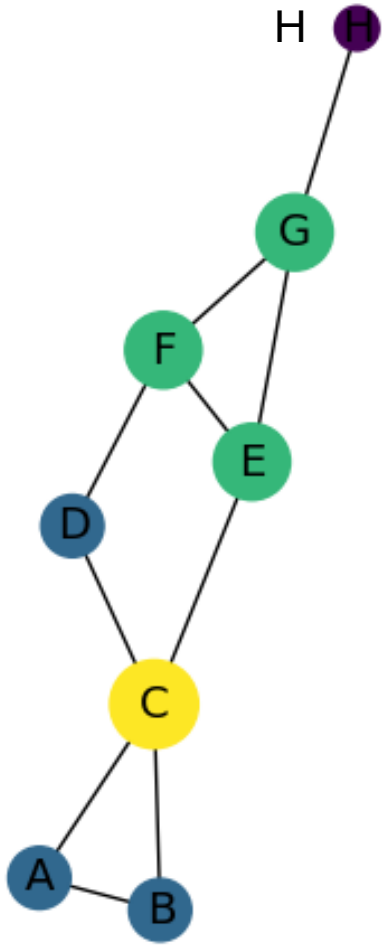
Graph representation

G = (V, E),

V is a set of vertices

E is a set of unordered pairs of vertices, whose elements are called edges or links.

G = (V, E)
V ={ A, B, C, D, E, F, G, H}
And
E = { (A,B), (A,C), (B,C), (C,D), (D,F),
(C,E), (E,F), (F,G), (E,G), (G,H)}

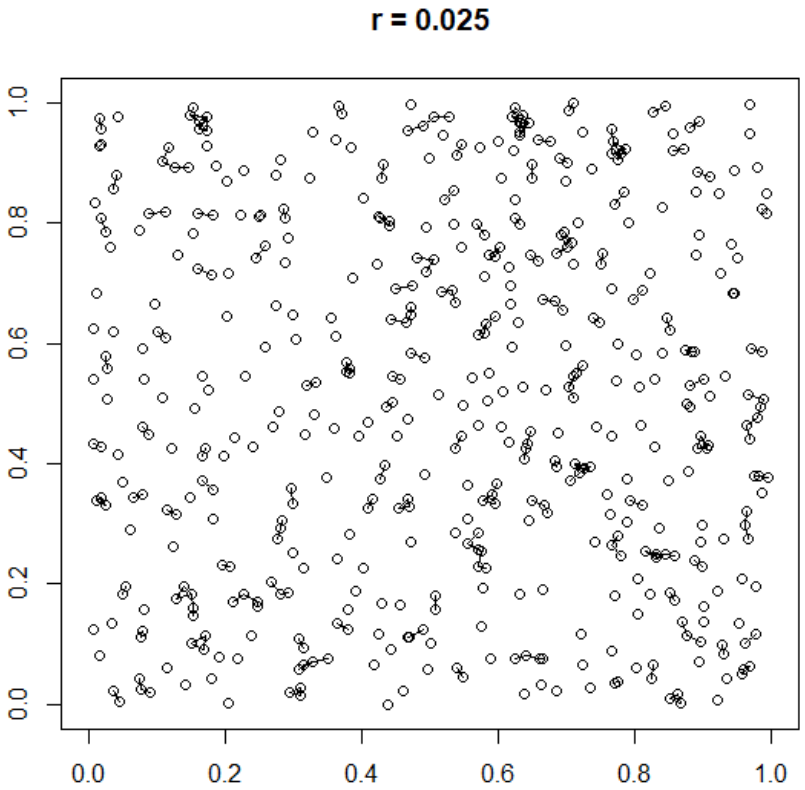


	A	B	C	D	E	F	G	H
A		1	1					
B	1		1					
C	1	1		1	1			
D			1			1		
E			1			1	1	
F				1	1		1	
G					1	1		1
H							1	

Random graph

- A graph is constructed by connecting nodes randomly.
- Each edge is included in the graph with **probability r**, independently from every other edge.

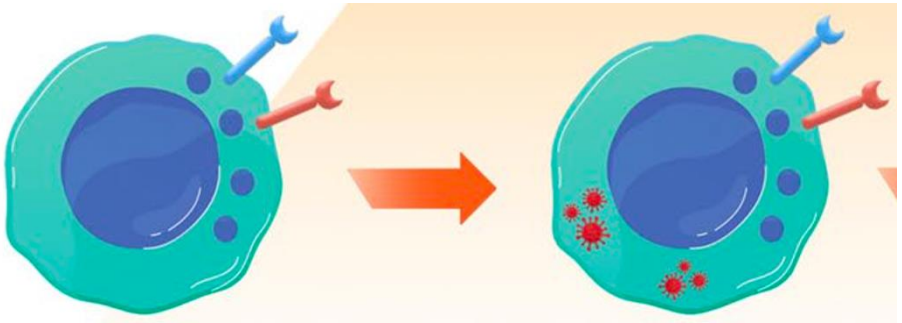
The different values are 0.025, 0,04, 0.0629, 0.075 and 0.1.



Experiment

Can we predict genes that regulate the host response to viral infection based on their topological position?

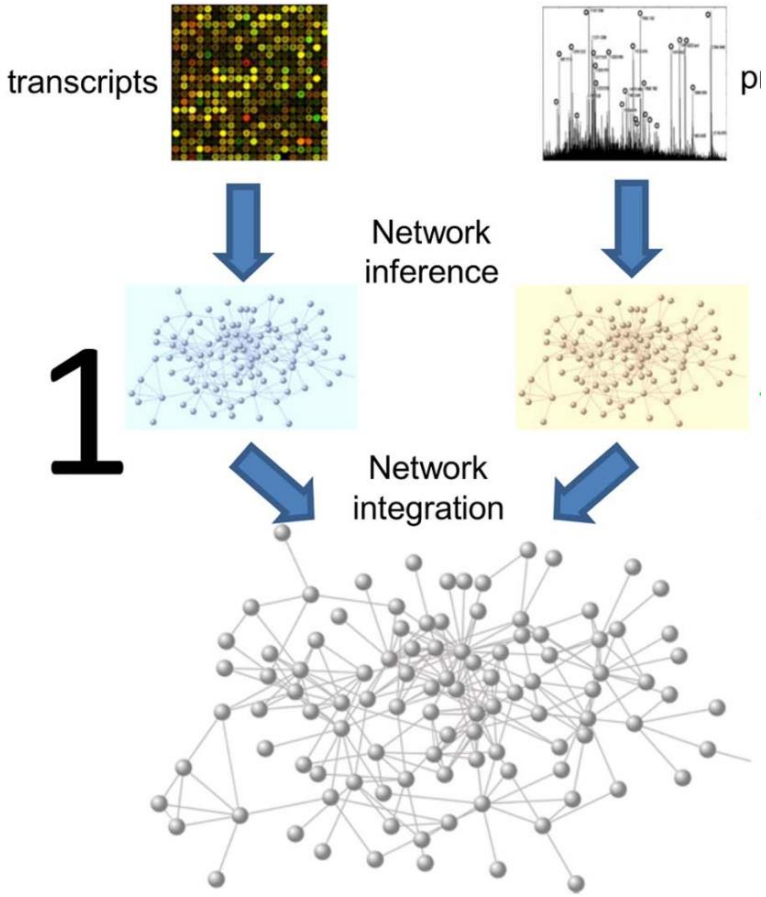
Infected with Wild type virus
HP



Infected with mutant virus
LP

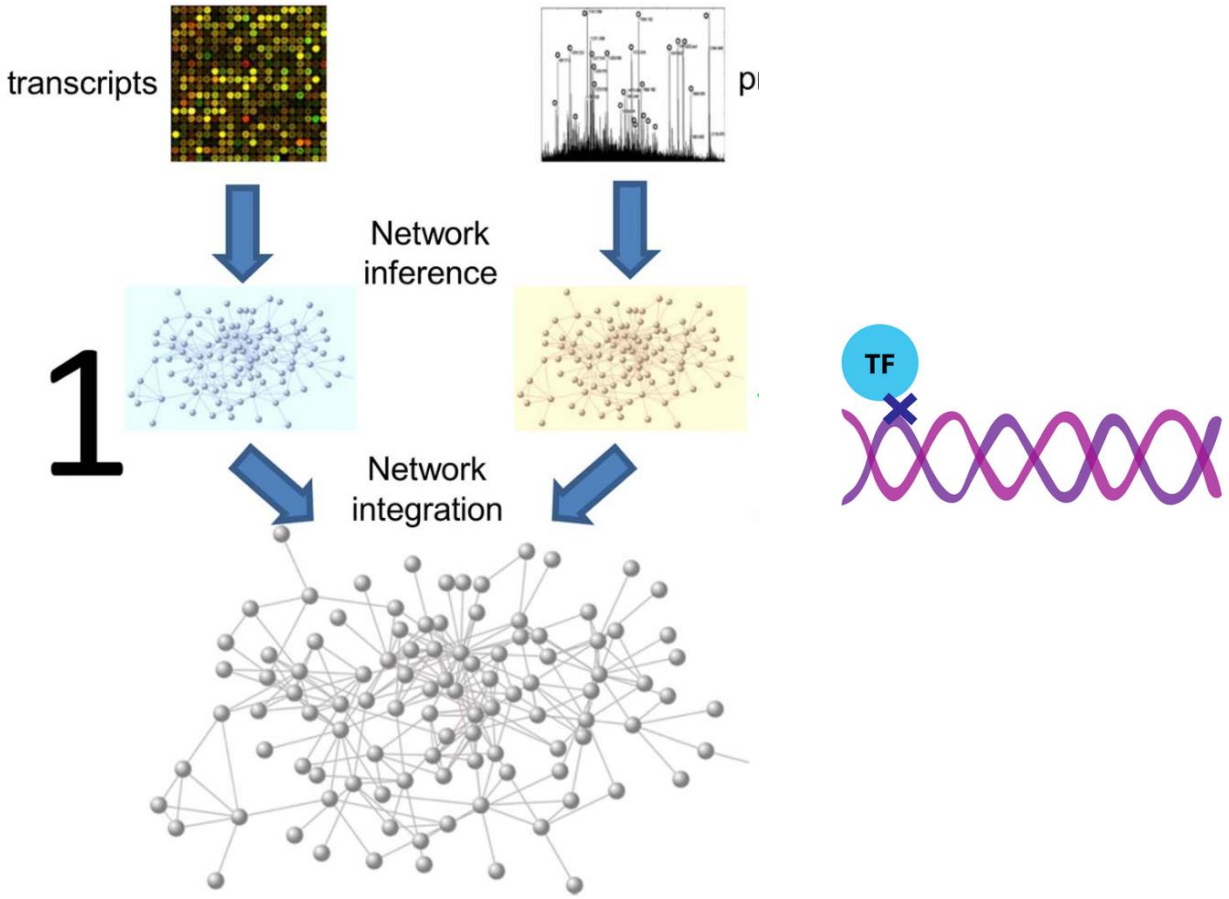
72 hours

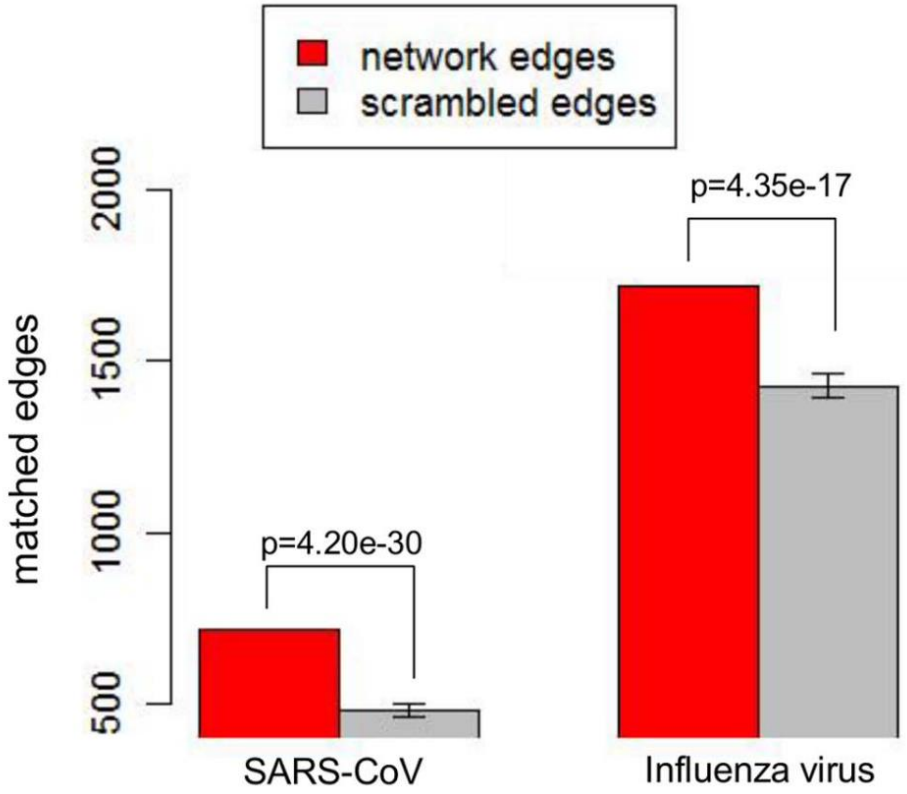
Mircoarray RNA
And
Proteomics data



Hugh D. Mitchell Plos One 2013

Inferred network edge validation



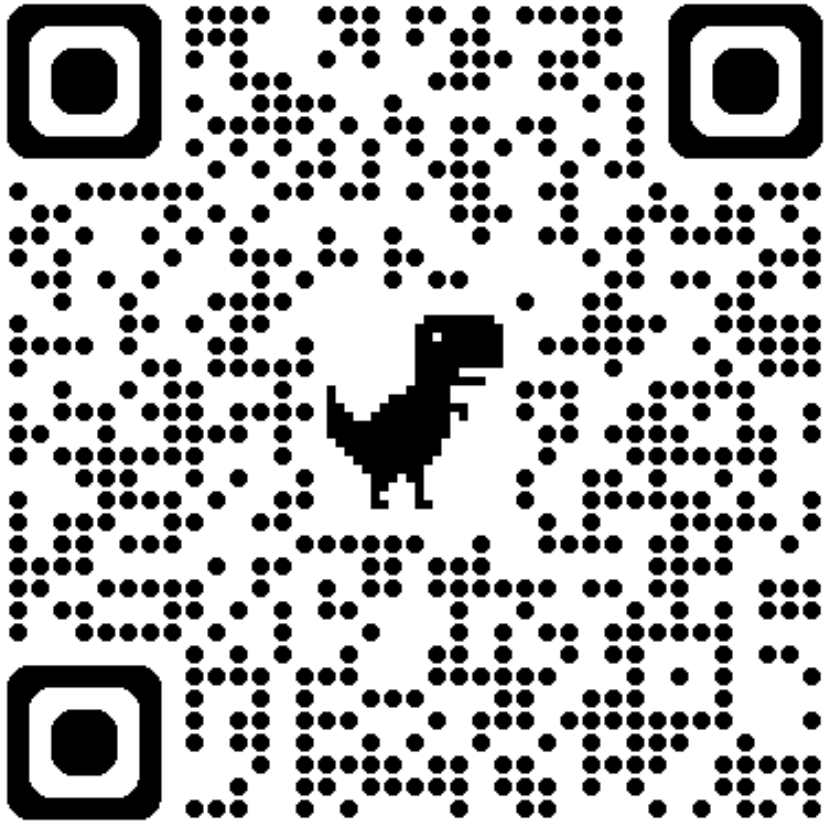


Hugh D. Mitchell Plos One 2013

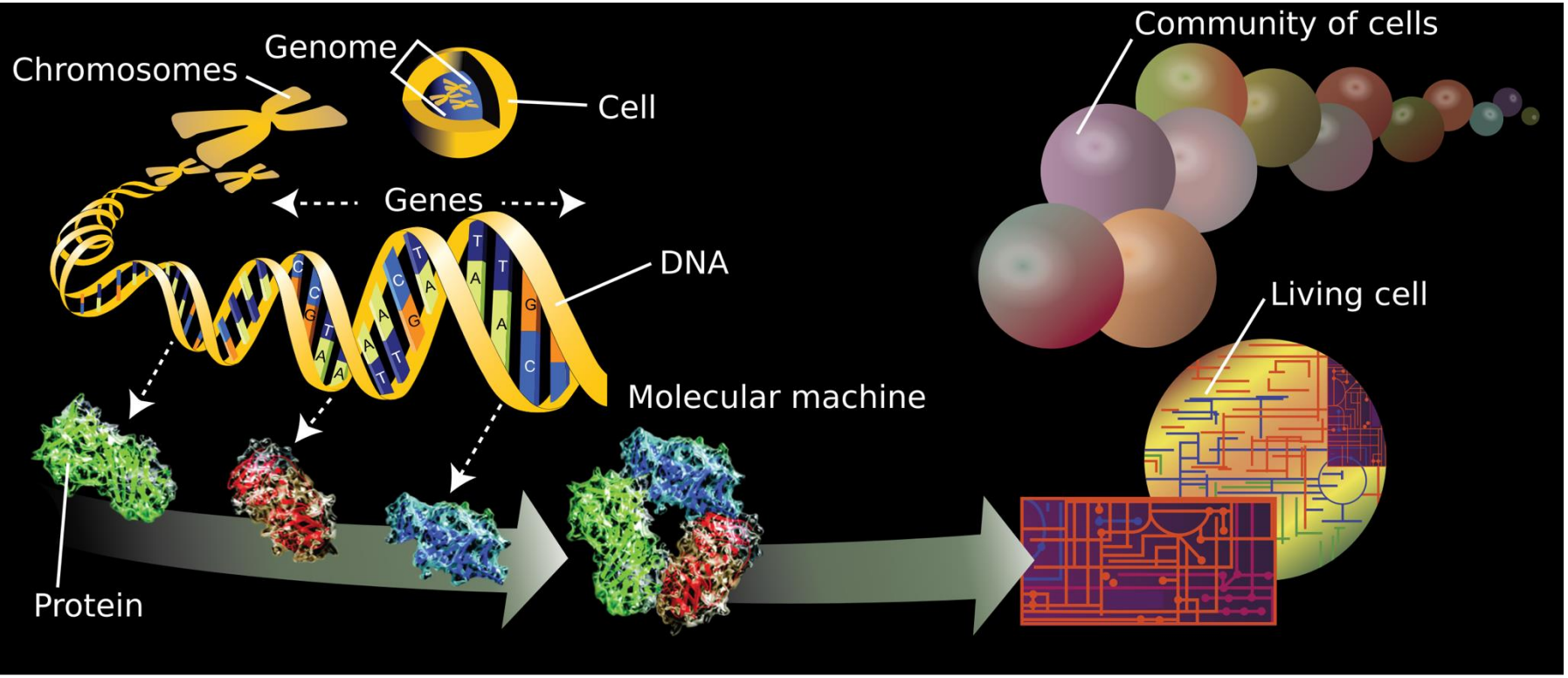
Let’s have some tutorial with python programming to make our first graph

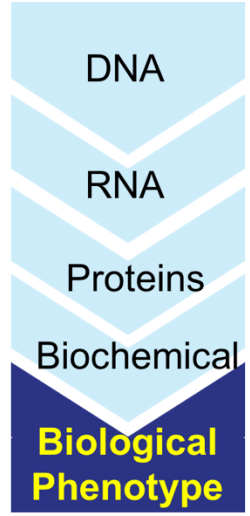
Thank you

Scan me to download the presentation and the codes



What is omics?





Genomics

Transcriptomics

Proteomics

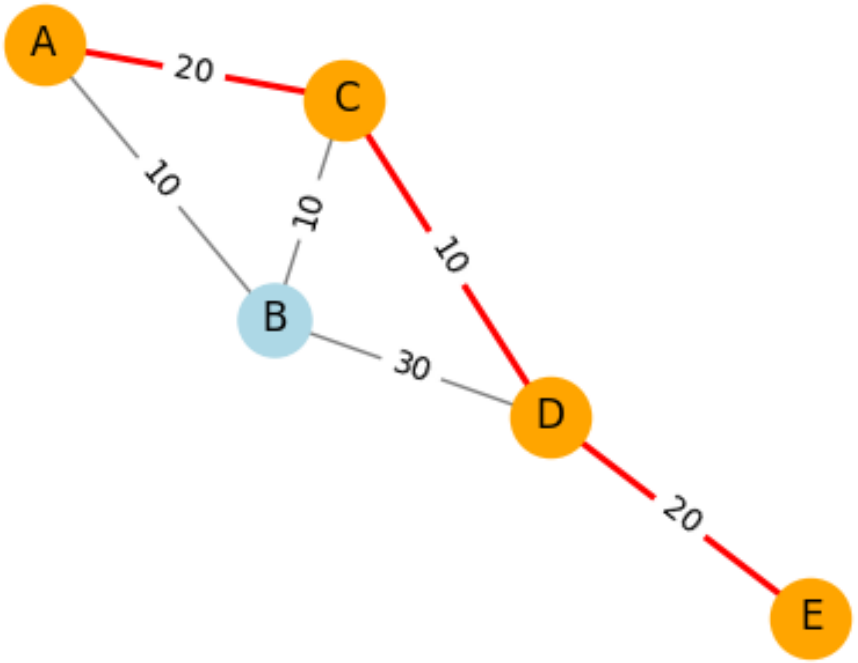
Metabolomics

Phenomics

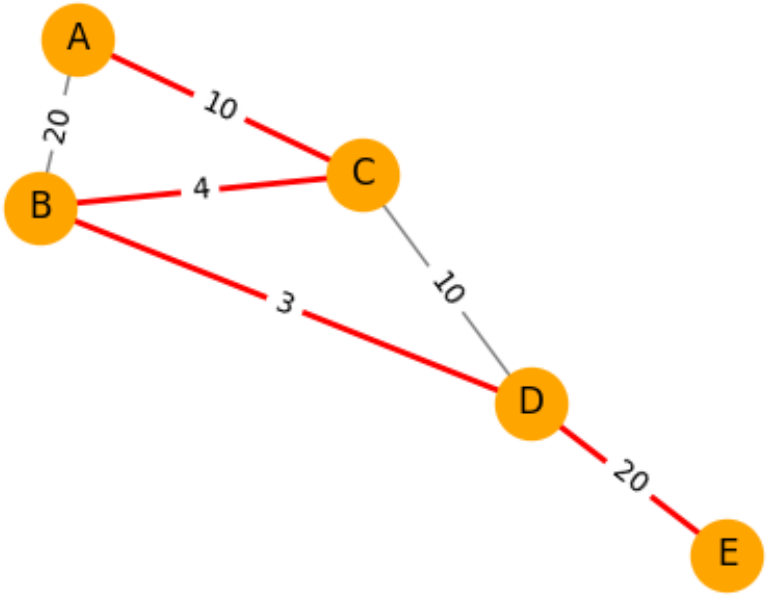
Spatial organization

Spatial-omics

Shortest path in weighted graph

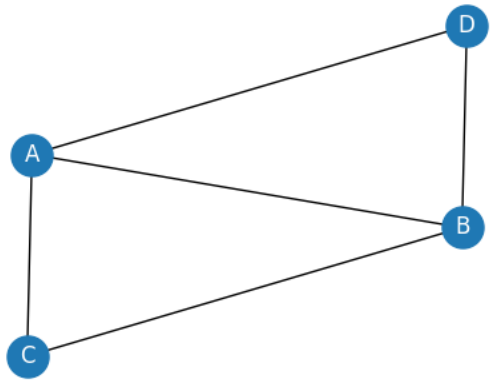


- Shortest Path (AE):
  ['A', 'C', 'D', 'E']
- Shortest Path Length: 50



- Shortest Path (AE):
  ['A', 'C', 'B', 'D', 'E']
- Shortest Path Length: 37

Centrality



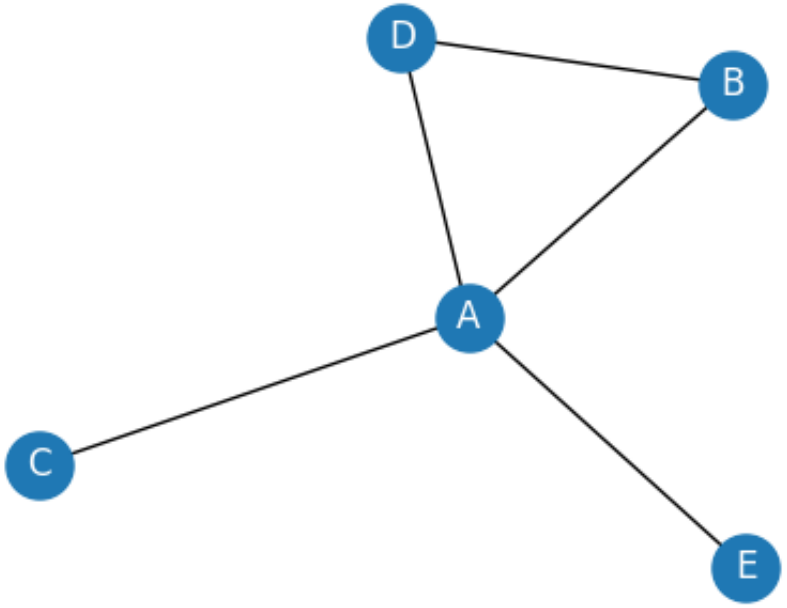
- Degree: number of nearest neighbors / (n-1)

  n is maximal possible degree
  {'A': 1.0, 'B': 1.0, 'C': 0.66, 'D': 0.66}

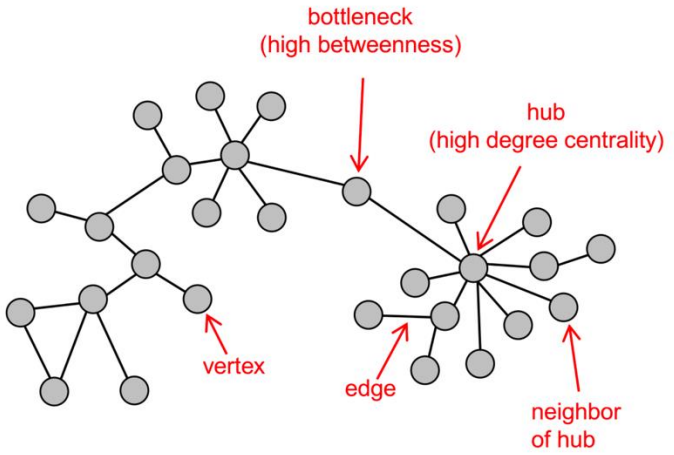
- Closeness: centrality of a node u is the reciprocal of the average shortest path distance to u over all (n-1) reachable nodes.

$$C(u) = \frac{n-1}{\sum_{v=1}^{n-1} d(v,u)}$$

A = 1.0 = 4 / (1+1+1+1) = 4/4
B = 0.66 = 4 / (1+1+2+2) = 4/6
C = 0.57 = 4 / (1+2+2+2) = 4/7
D = 0.66 same as B
E = 0.57 same as C

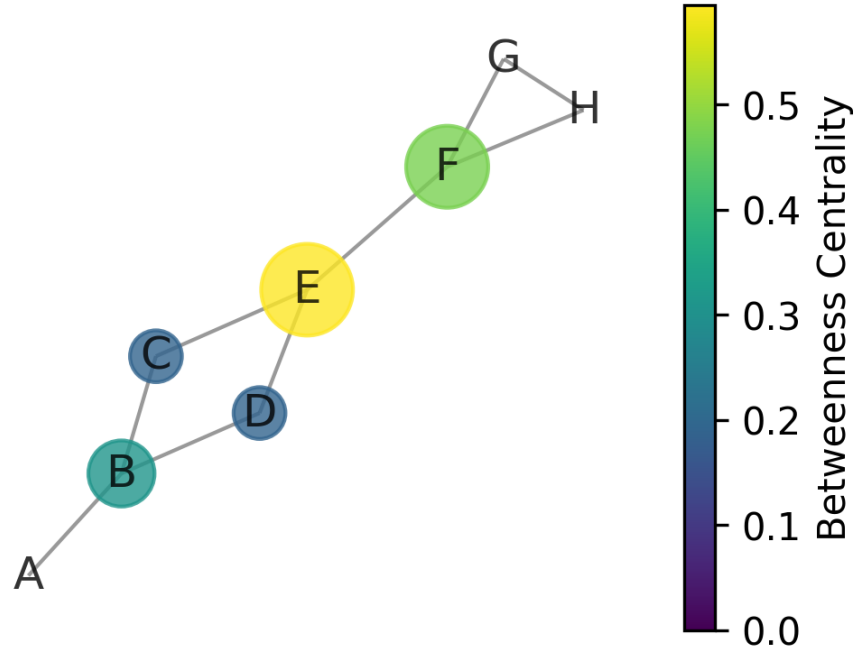


Betweeness Centrality



- Betweenness centrality of a node v is the sum of the fraction of all-pairs shortest paths that passes through v.

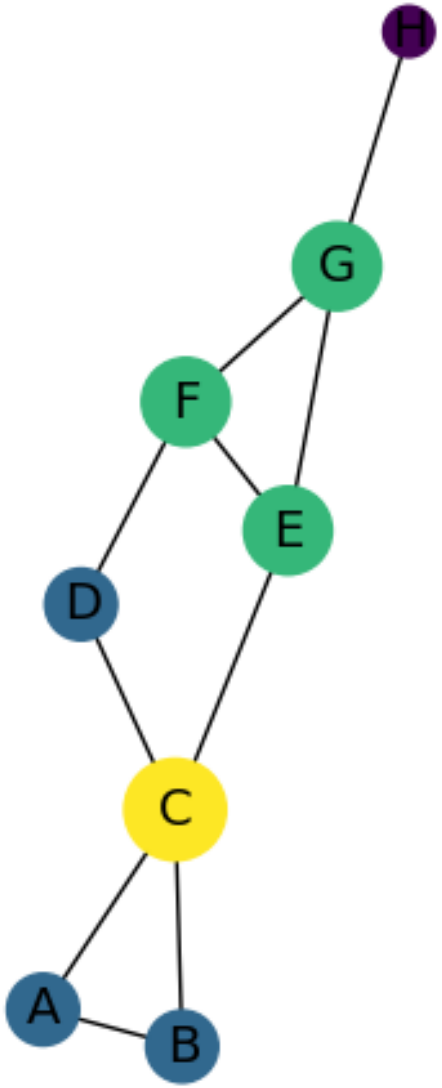
$$c_B(v) = \sum_{s,t \in V} \frac{\sigma(s,t|v)}{\sigma(s,t)}$$



A = 0.0
B = 6.5
C = 4
D = 4
E = 12.5
F = 10
G = 0.0
H = 0.0

Node E = (AF+AG+AH+BF+BG+BH+
CF+CG+CH+DF+DG+DH+CD)
=(2/2+ 2/2+ 2/2+ 2/2+ 2/2+ 2/2+
1/1+ 1/1 + 1/1+ 1/1 +1/1+1/1+1/2)

Clustering coefficient



Clustering coefficient is a measure of the degree to which nodes in a graph tend to cluster together.

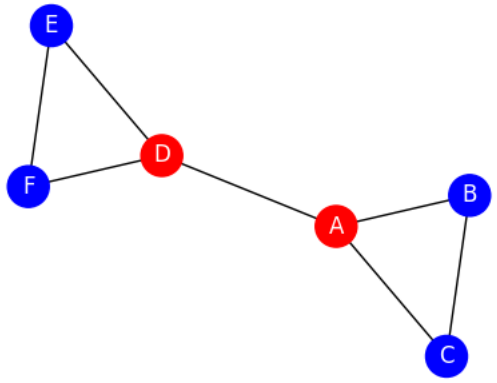
Neighbors of a given node are connected to each other.

Node	# of neigh	# possible conne	clustering coef
A	2	1	(1/1)=1
B	2	1	(1/1)=1
C	4	6	(1/6)=0.167
D	2	1	(0/1)=0
E	3	3	(1/3)=0.33
F	3	3	(1/3)=0.33
G	3	3	(1/3)=0.33

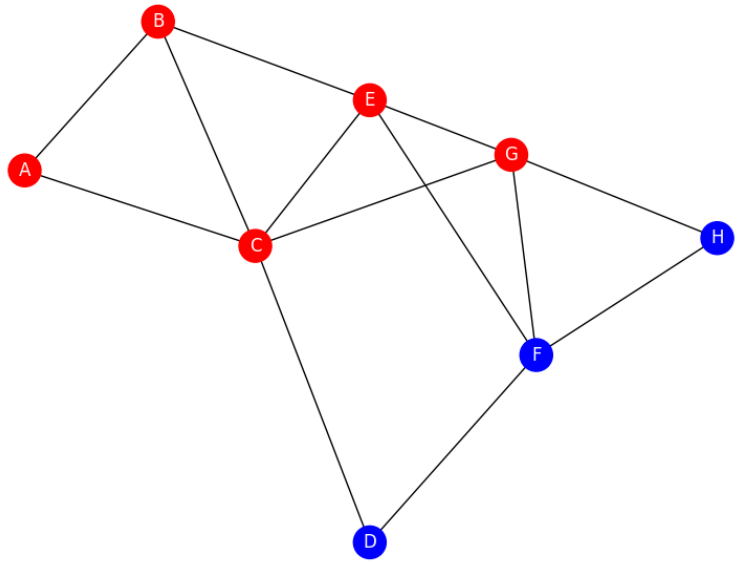
Avg coef. = 0.40

Examples

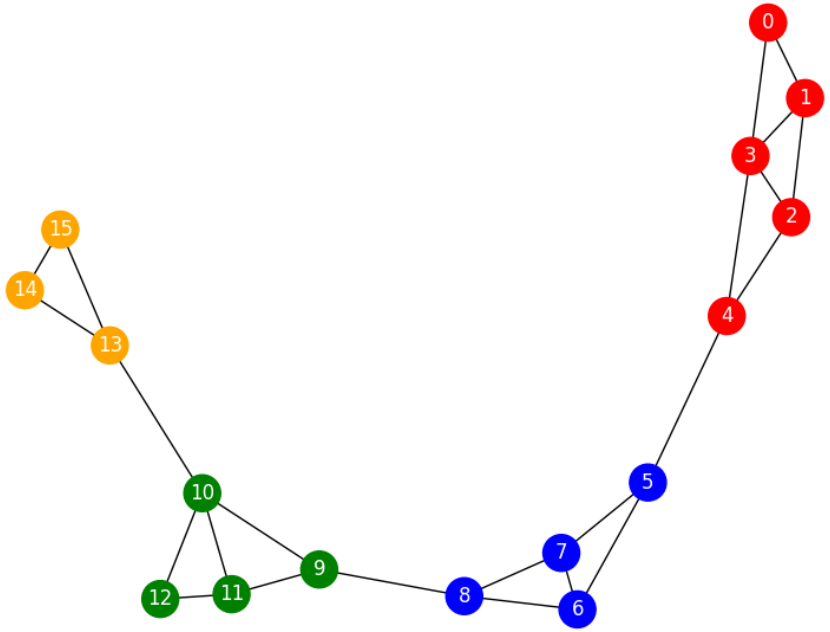
mod = nx.community.modularity(G,
nx.community.label_propagation_communities(G))



Mod=-0.08



Mod=0.12



Mod=0.60

Network modularity

- Modularity measures the strength of division of a network into modules (also called clusters or communities).
- Values
  - closer to 1 indicate strong community structures.
  - near 0 indicate no significant community structure.
  - Negative values means worse-than-random divsions.

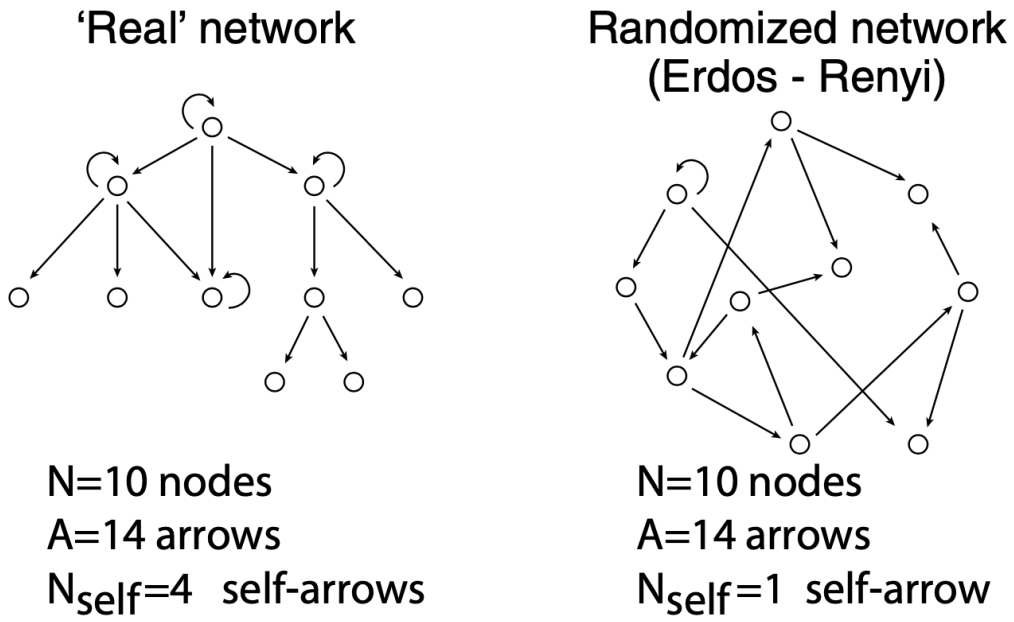
$$Q = \frac{1}{2m} \sum_{ij} \left(A_{ij} - \gamma \frac{k_i k_j}{2m} \right) \delta(c_i, c_j)$$

- m is the number of edges (or sum of all edge weights)
- A is adjacency matrix of graph G
- k_i is the (weighted) degree of noid i
- γ is the resolution parameter
- δ (c_i, c_j) is 1 if i and j are in same cluster else 0.

https://networkx.org/documentation/stable/reference/algorithms/generated/networkx.algorithms.community.quality.modularity.html

Network motifs

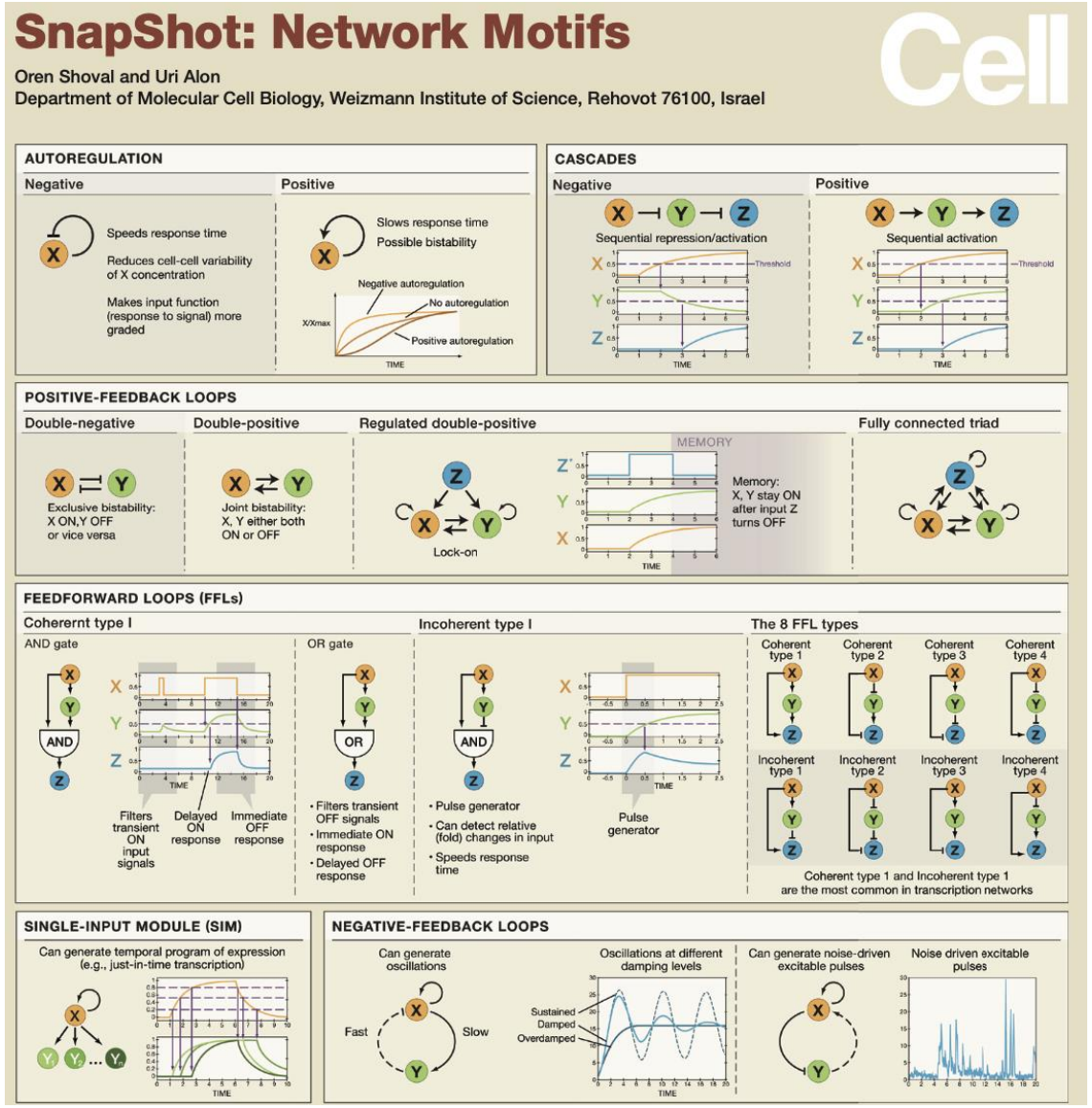
- A recurring patterns that occur in the real network significantly more often than in randomized networks with the same characteristics (number of nodes, number of edges) are called network motifs.
- Edges in the network motifs must be constantly selected in order to survive randomization forces in unexpected high amounts.



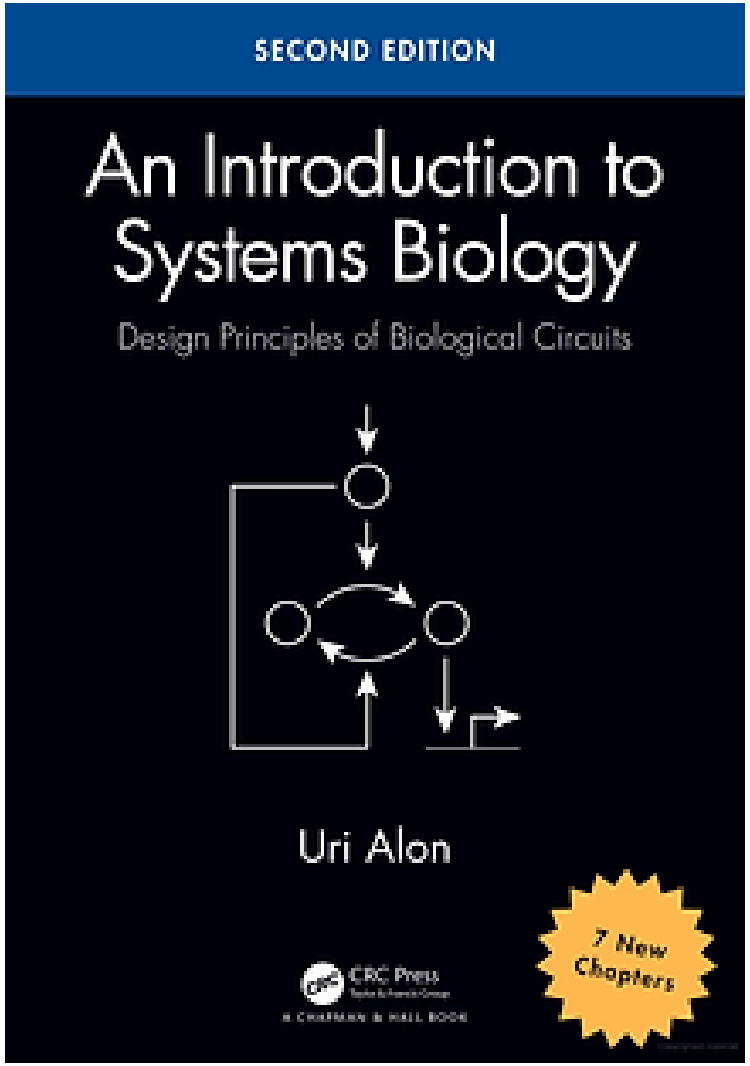
Uri Alon An Introduction to Systems Biology Design Principles of Biological Circuits -CRC Press

Let’s have some tutorial with python programming to find motifs

Resources: Motif connections to systems biology



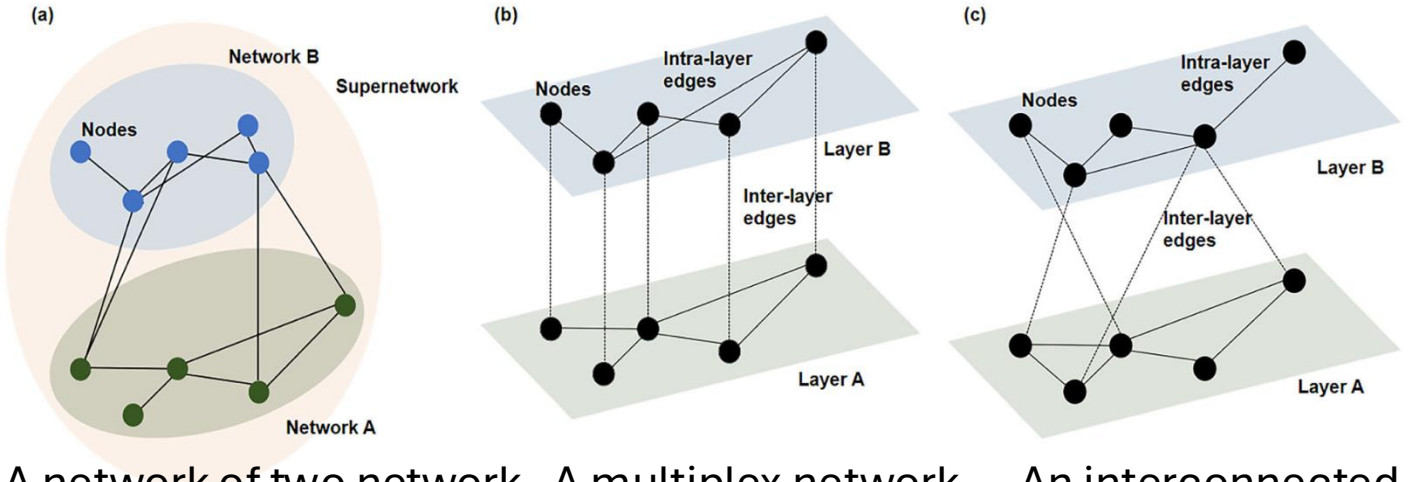
Oren Shoval and Uri Alon, Cell 2010



Multilayer networks

- Multilayer networks provide the framework to capture the complexity typical of systems of systems.
- It enable the analysis of biophysical, social and human-made networks from an integrated perspective.
- Layered structure of multilayer networks is responsible for phenomena that cannot be observed from the analysis of subsystems in isolation or from their aggregation, such as emergent mesoscale organization.

Manlio De Domenico "More is different in real-world multilayer networks" Nat Phys 2023

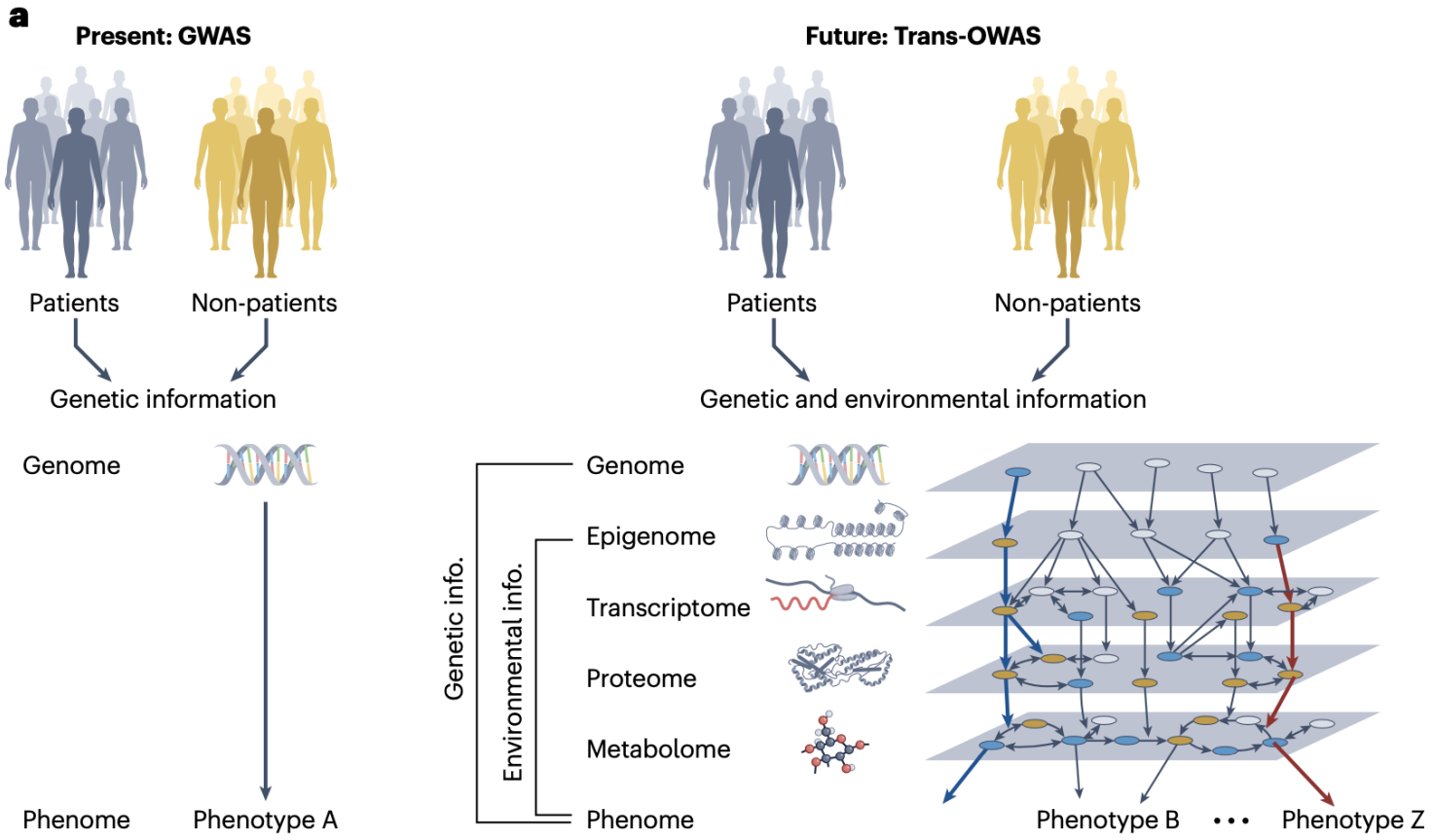


A network of two network systems A and B

A multiplex network of two layers A and B

An interconnected network of two layers A and B

Multilayer networks



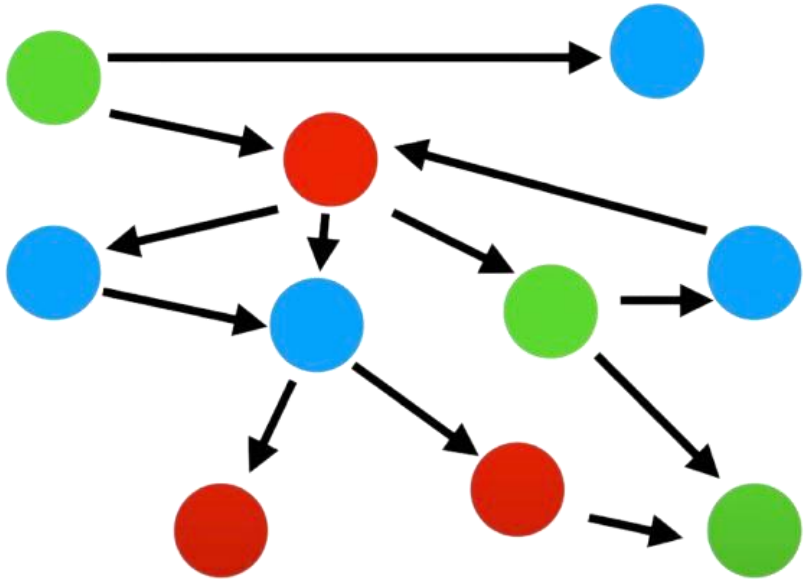
- Genetic information collected from healthy and unhealthy groups is generally used to capture information about macroscopic effects, such as a disease.
- Multi-omics makes available richer datasets that can be integrated within a multilayer network, where layers also encode interactions at the scale of the transcriptome, the proteome and the metabolome

Manlio De Domenico "More is different in real-world multilayer networks" Nat Phys 2023

Genome-wide association studies (GWAS)
Openness weighted association studies (OWAS)

Knowledge graph

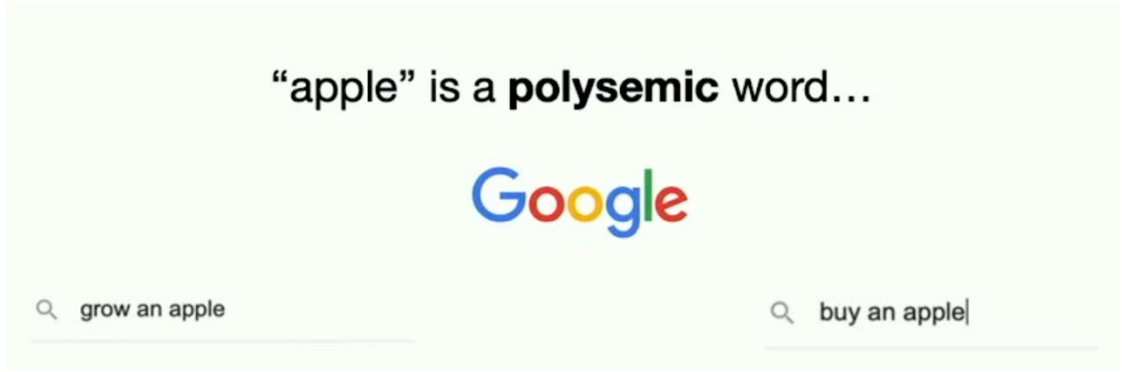
- A knowledge graph is knowledge base that is a graph and represents facts about the world.
- What is a knowledge base?
  - A knowledge base is a technology used to store complex structured and unstructured information.
  - A collection of knowledge expressed using some formal knowledge representation language.
  - A store of information or data that is available to draw on.
  - The underlying set of facts, assumptions, and rules which a computer system has available to solve a problem.
- What is a graph?



Evolution of Google search algorithm

- PageRank 1998: The order of search results returned by Google is based on this.
- Knowledge Graph 2012: Added semantic search by organizing information into entities and relationships, providing direct answers and improving contextual understanding.
- RankBrain 2015: Integrated machine learning to interpret user intent, handling queries never seen before.
- BERT 2019: Leveraged deep learning to understand the nuances of natural language, particularly context in search queries.

Biological molecule is also context dependent



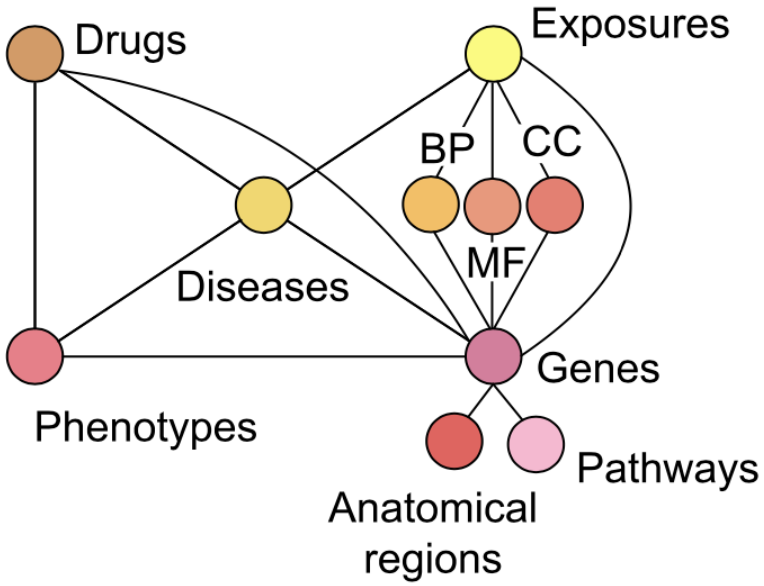
Stem	Cell	Plant	Conserved regions in the virus
Protein	Activate or repress signalling pathway	Stabilize it active confirmation	Coordinates the iron in the heme group of haemoglobin

Knowledge graph in precision medicine

- Developing personalized diagnostic strategies and targeted treatments requires a deep understanding of disease biology and the ability to dissect the relationship between molecular and genetic factors and their phenotypic consequences.
- Such knowledge is fragmented across publications, non- standardized repositories, databases and evolving ontologies describing various scales of biological organization between genotypes and clinical phenotypes.
- Knowledge graph
  - Drug repurpose
  - Clinical trial optimization
  - Patient Stratification

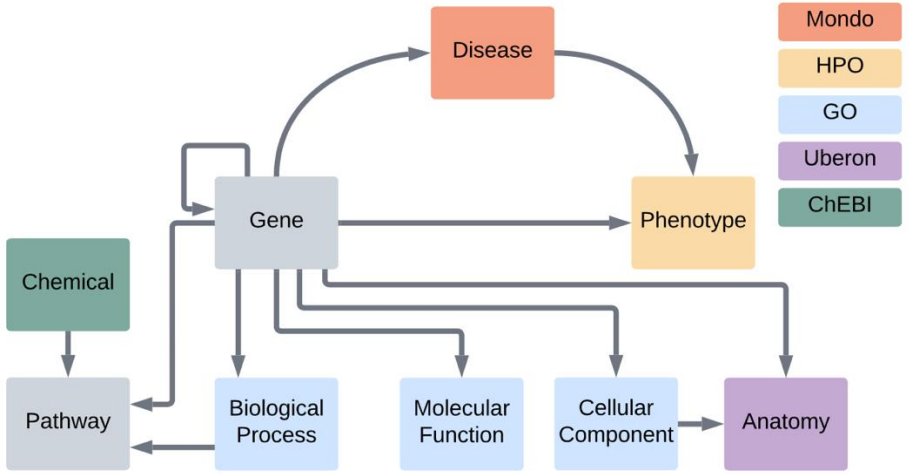
Existing knowledge graph in biomedical

It connects molecular, genetic, phenotypic, and drug-related information, enabling analyses like drug-disease interactions, disease mechanisms, and therapeutic predictions.



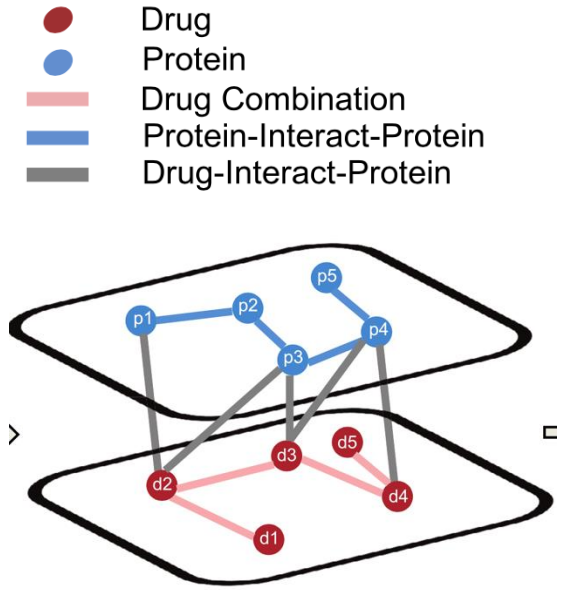
PrimeKG: Payal Chandak et al Scientific Data 2023

It is a translational research platform that integrates and analyzes genetic, phenotypic, and disease data across species using open ontologies, semantic data models, and knowledge graphs, enabling applications like variant prioritization, deep phenotyping, and patient profile matching.



Monarch: Tim E. Putman et al NAR 2024

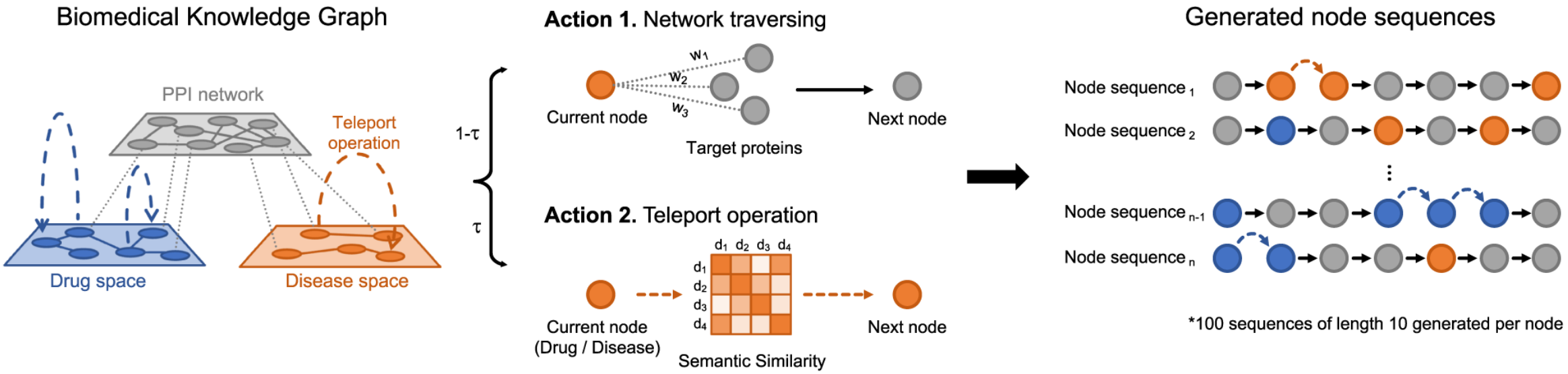
Predict Drug combination therapies (DCBs) for infectious diseases



Qing Ye et al Cell Reports 2023

Biomedical knowledge graph for drug repurposing

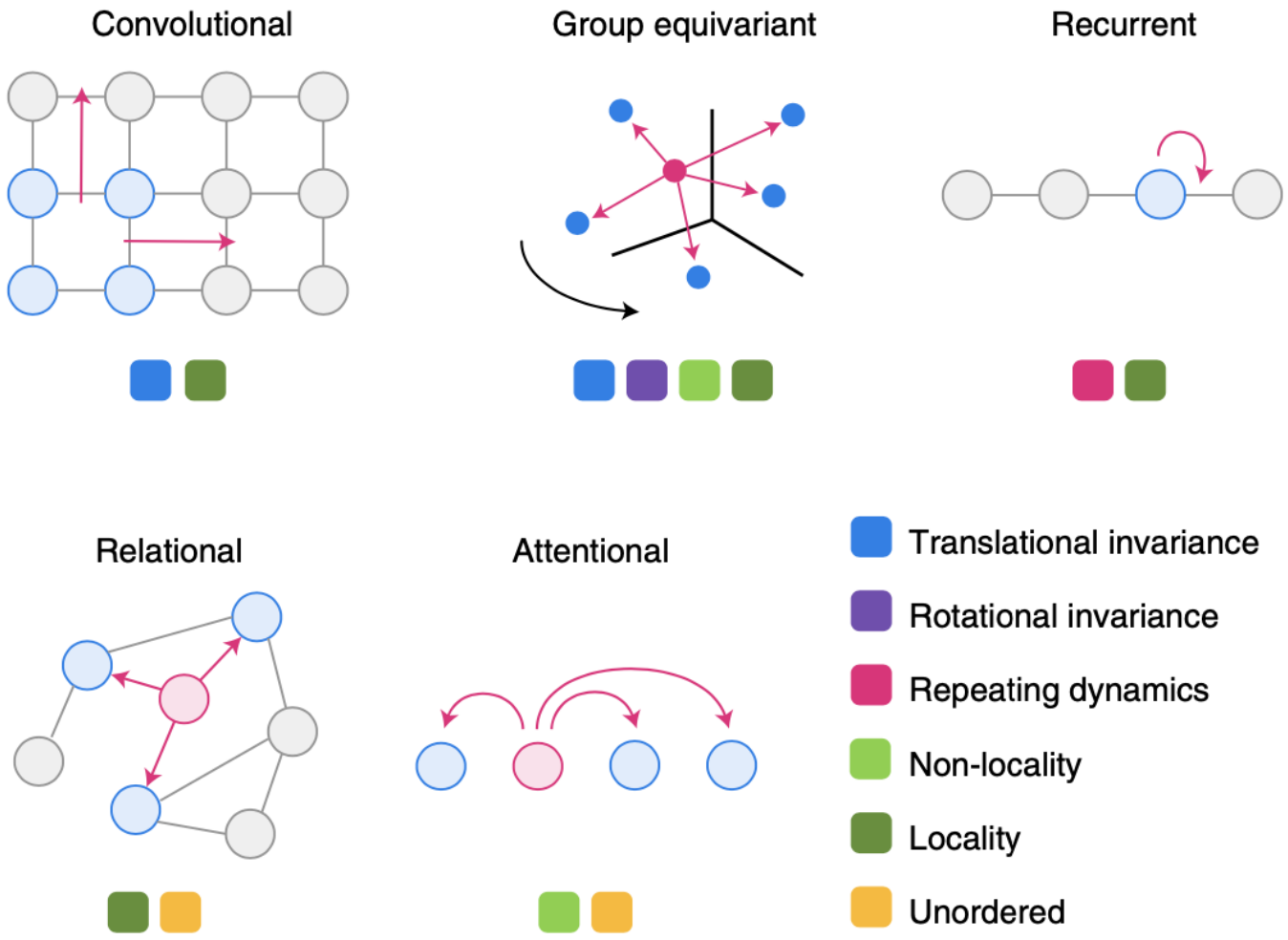
DREAMwalk map drugs and diseases into a unified embedding space, improving prediction of drug-disease associations.



Dongmin Bang et al Nat Comm 2023

Last Tutorial

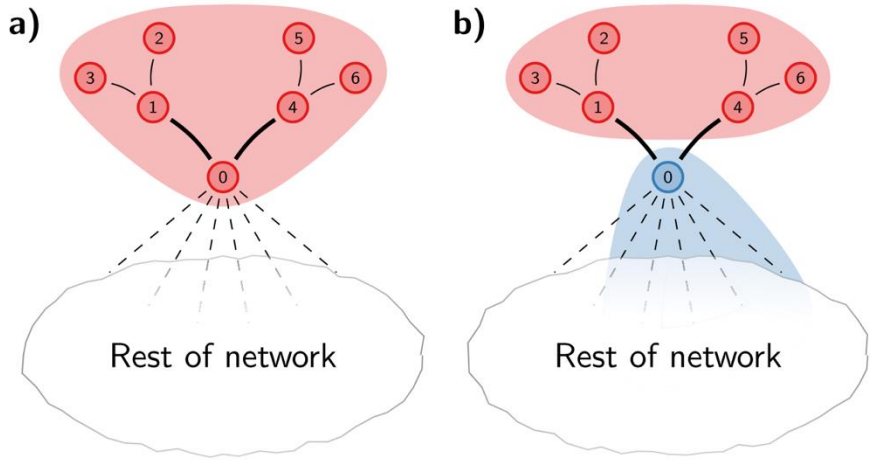
Networks in ML



Mohammed AlQuraishi and Peter K. Sorger "Differentiable biology" Nat Met 2021

Application of modularity

- Louvain clustering 2008
  - Start with a single partition where all nodes are in their own community
  - Iterat repeatedly
    - Local node movement: Move nodes to communities to maximize modularity
    - Network aggregation: Aggregate communities into new nodes within network
- Leiden clustering 2019
  - Faster and address an issue where communities may become internally disconnected but remain as one community

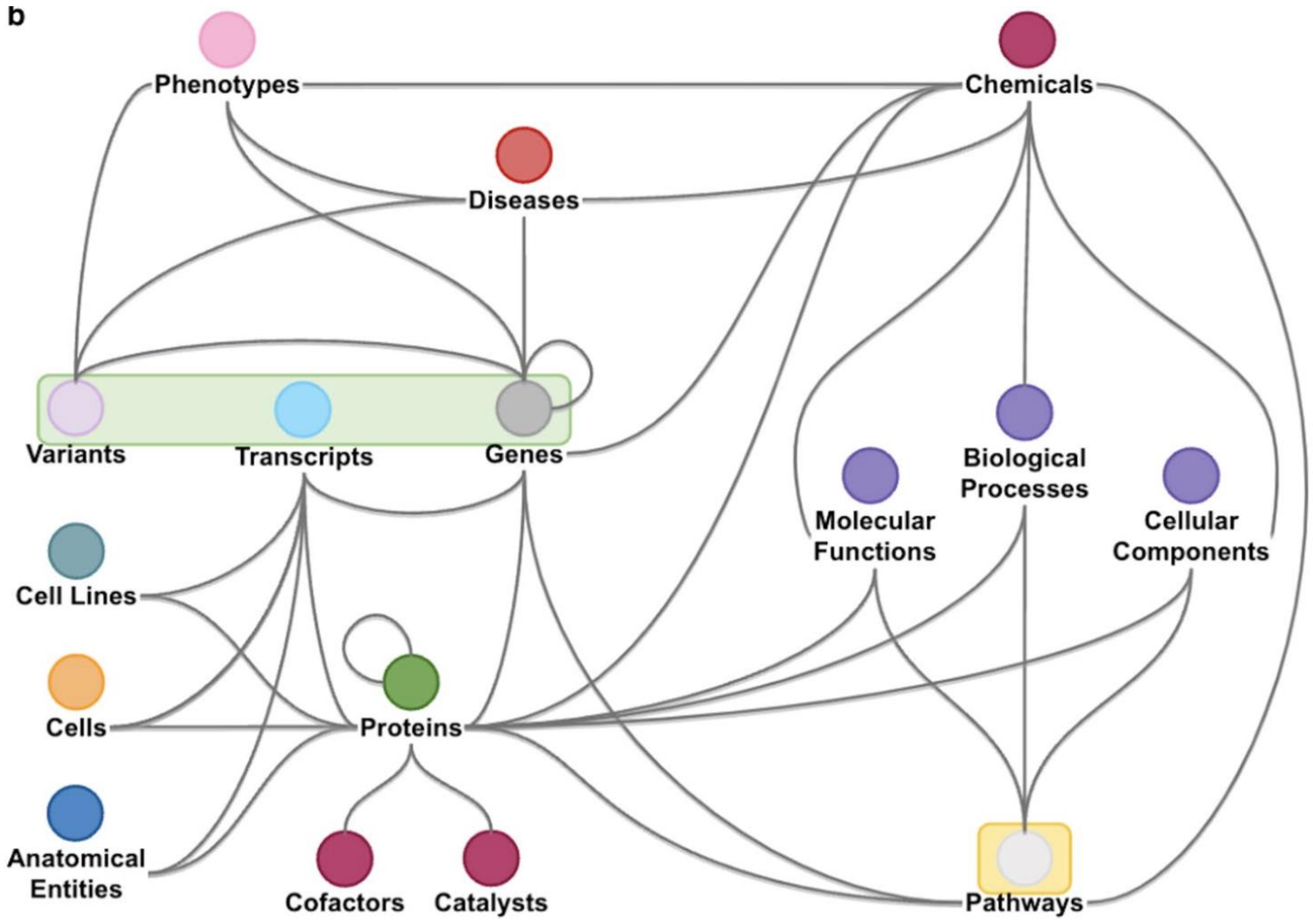


V. A. traag et al Scientific Reports 2019

Famous algorithms related to graphs

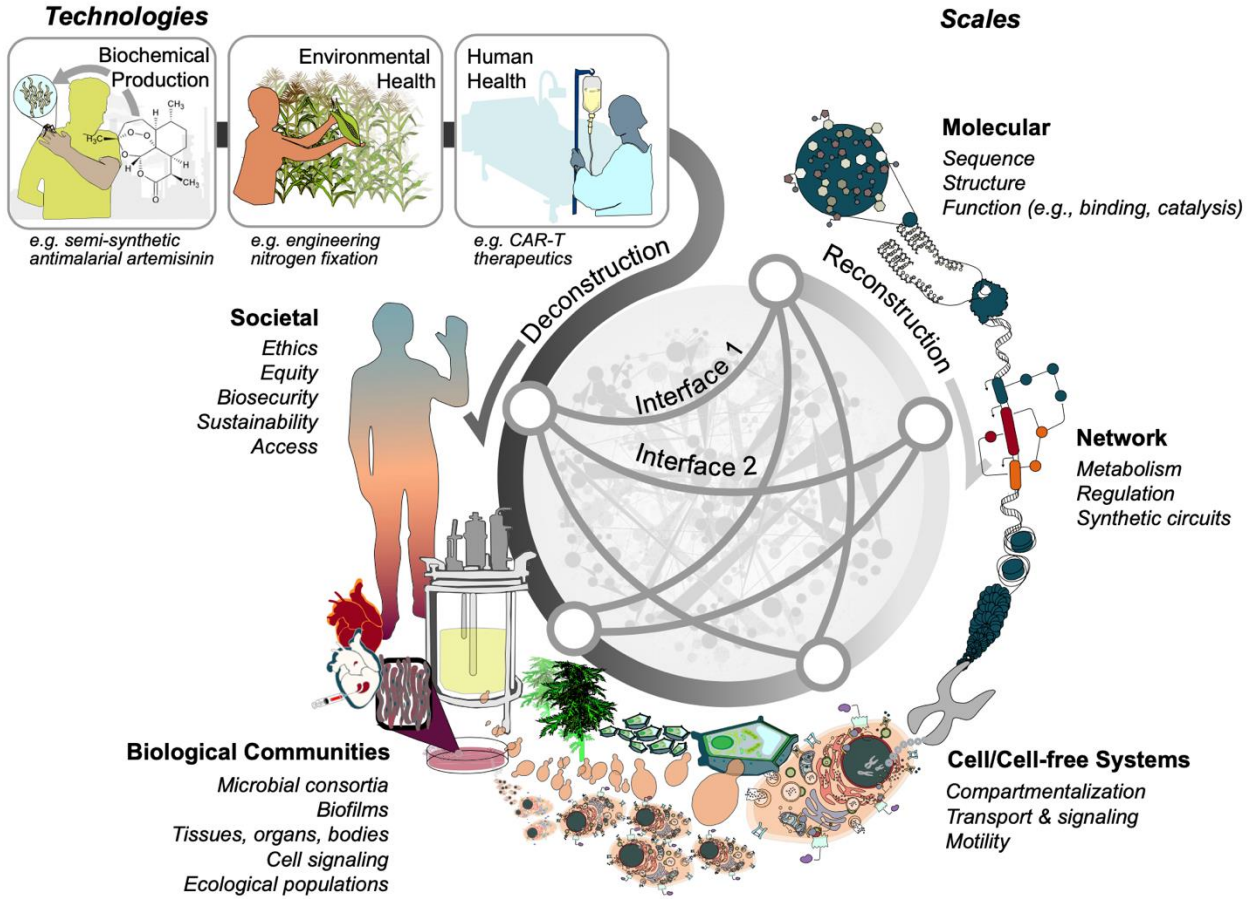
- Dijkstra’s (shortest path problem)
- PageRank
- Leiden community detection
- Kd-tree
- Random Forest
- Causal
- Markov clustering
- Search

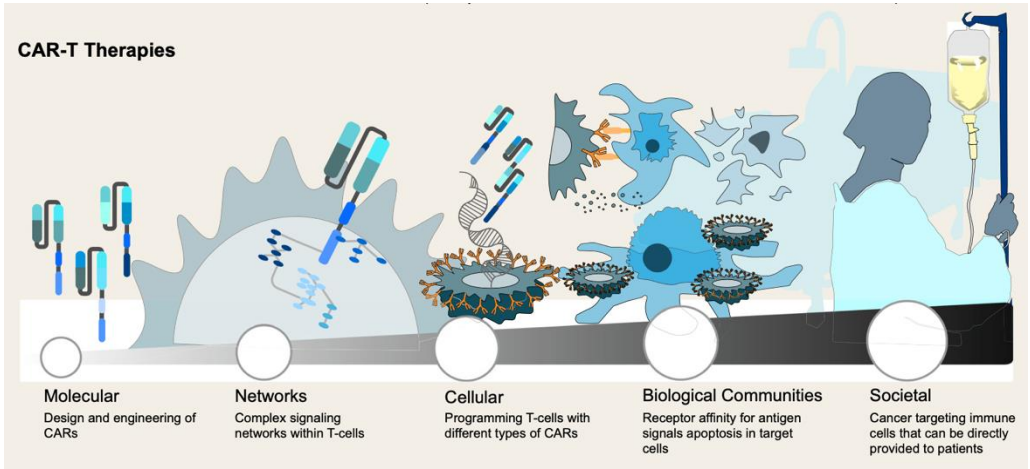
Knowledge graph of a disease



Tiffany J. Callahan et al Scientific Data 2024

Deconstructing synthetic technologies across scales

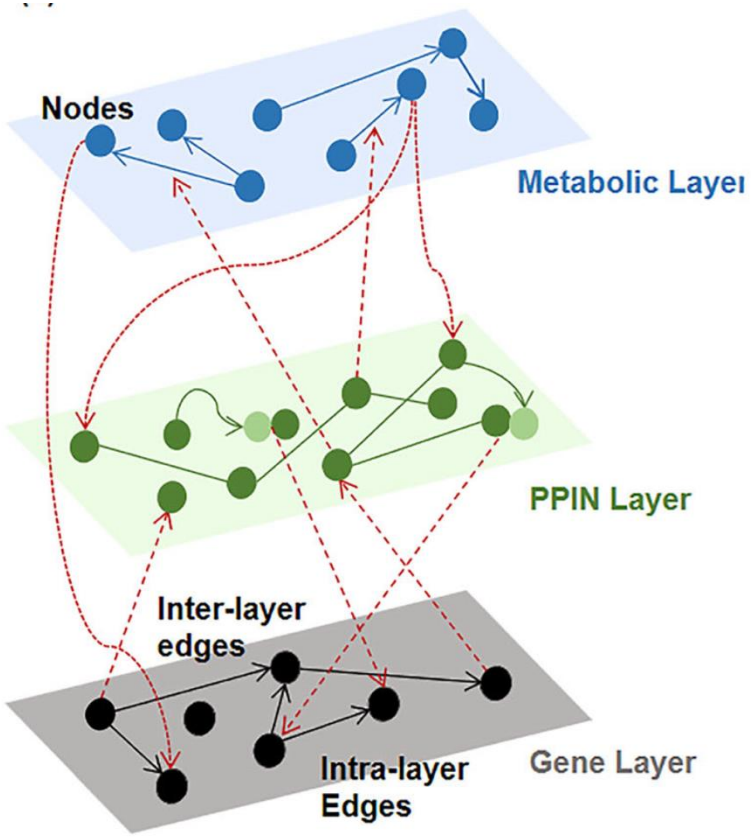




Ashty S. Karim et al Nat Comm 2024

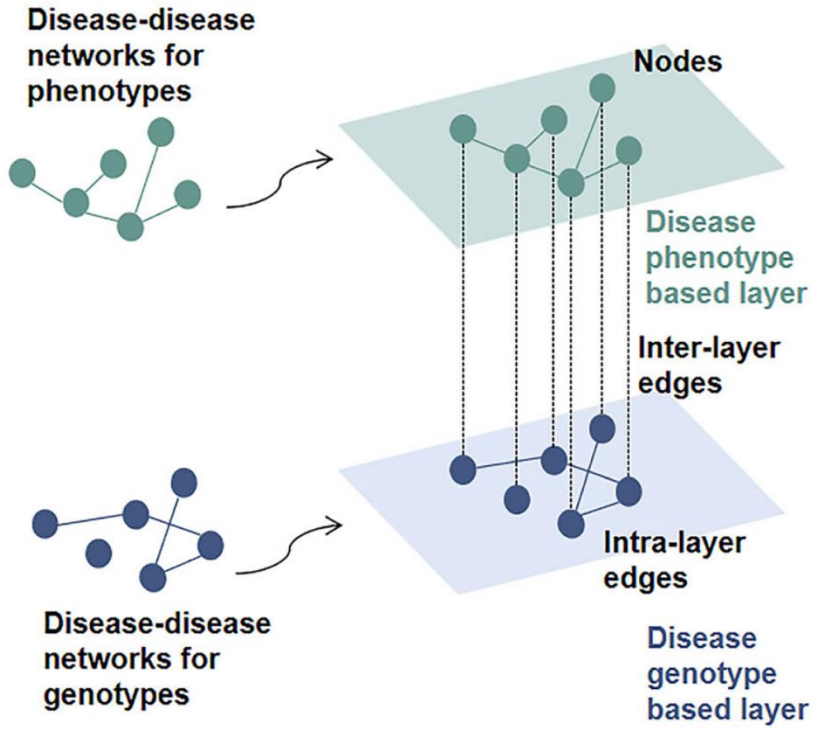
Multilayer network exa

An interdependent network of gene regulation and metabolism comprising three layers



Edges represent the inter-layer connections such as activation, repression, and catalysis.

Disease network



Disease connected by symptoms

Connections between diseases.

Diseases connected by common genes

S Chaudhuri and A Srivastava J Biosci 2022