

Leveraging Existing Biological Data and Making Sense of it

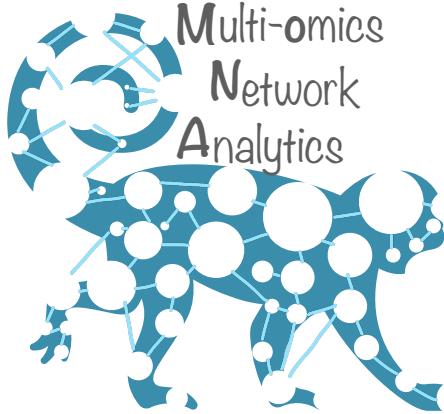
Finding, Accessing, Integrating and Reusing

Alberto Santos - Multi-omics Network Analytics

24 June 2024



Introduction



Multi-omics

Using **multimodal data** to have a comprehensive view on **(micro) biology problems**

Network

Exploiting **graphs** to **structure, represent, integrate** and **analyse** data

Analytics

Applying **Machine Learning** to answer **complex biological questions**

Mision

Getting a holistic view of **biological systems and their context** to understand their complexity and provide new insights and applications that can benefit **human and environmental health**

Located at:

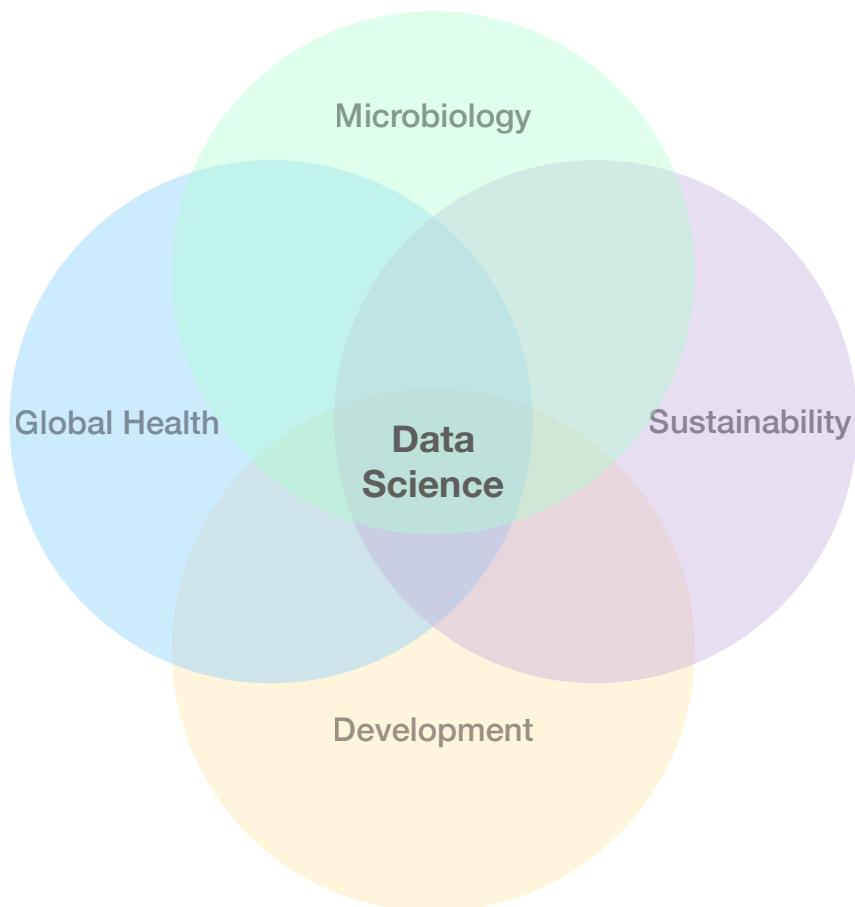


Danmarks
Tekniske
Universitet



Research Areas

Data science at the intersection of microbiology, global health, sustainability, and development to tackle some of the world's most pressing challenges through data-driven approaches



Interconnected fields

Microbiology

Understanding the underlying molecular factors that impact planetary and human health

Global health

Contributing to improving health outcomes in connection with climate change and biodiversity decline and with special interest in infectious diseases

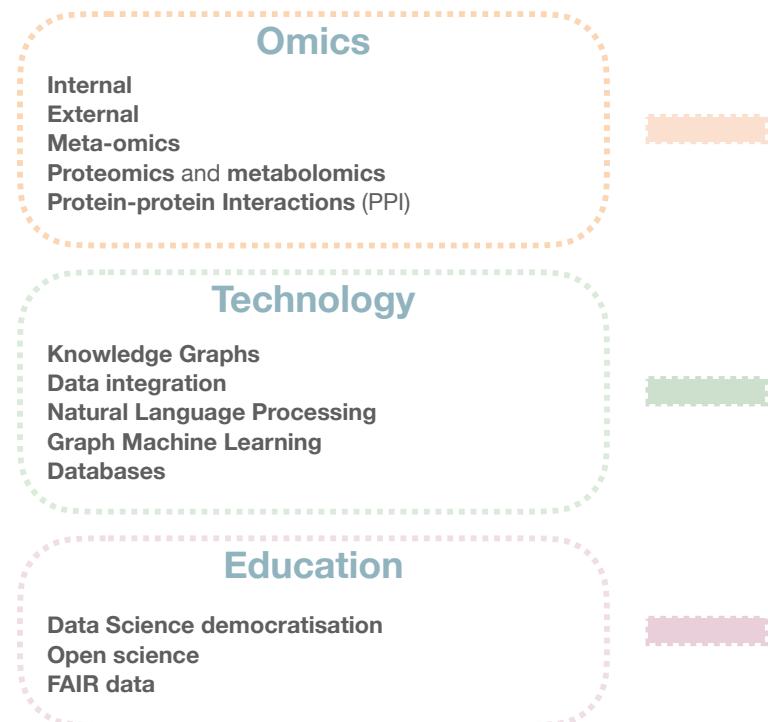
Sustainability

Gathering and analysing data on environmental impacts, resource use, and the social and economic implications

Development

Efforts to improve the economic, social, and political well-being of communities and countries through education, analysis of inequality to climate change and resource depletion, etc.

Computational Lab



Me
WANTS
DATA



Data

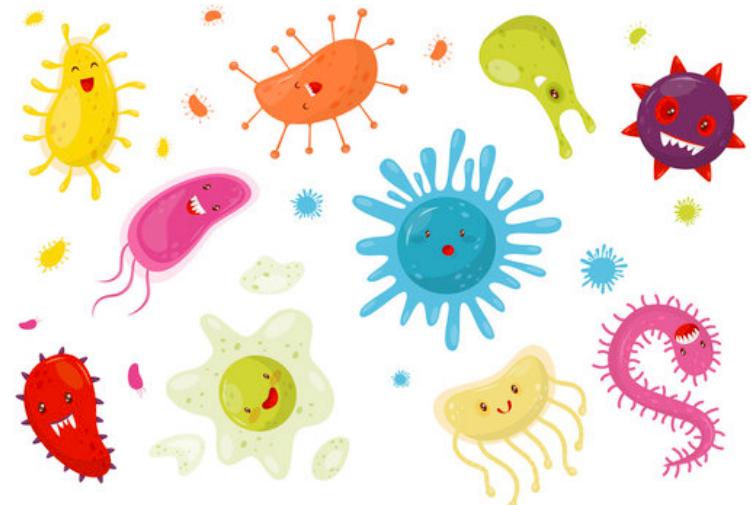
Objectives

- Show
 - The **value** of **Open** and **standardised data**
 - How to **generate** and **find** these data
 - How to **access** and **use** them
 - Some **examples**

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How to become a data parasite



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6258825/>

Course website

[https://github.com/Multiomics-Analytics-Group/course synthetic biology data](https://github.com/Multiomics-Analytics-Group/course_synthetic_biology_data)

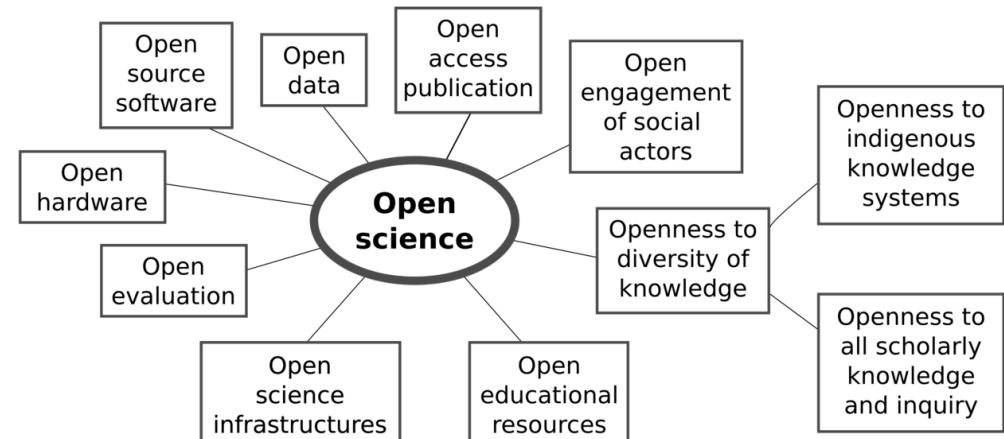


Open Science

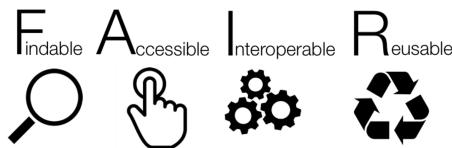
What is Open Science

Impact, Contribution, Trust

- Make scientific research **accessible** to all levels of society:
 - Publications
 - Samples
 - **Methods**
 - **Software**
 - **Data**
- Advantages:
 - **Reproducibility** and **replicability**
 - Societal **responsibility** — publicly funded, publicly available
 - **Multi-purpose** of research outputs
- Disadvantages: concerns of data **misuse**



FAIR Data and Software



- **Findable and Accessible**

- Add enough **metadata** — data about your data
- Deposit your data in **public repositories** or make them available in **databases**

[Minimum Information for Biological and Biomedical Investigations](#)

[Zenodo](#)
[Figshare](#)
[Pride](#)
[Metabolights](#)
[GEO](#)
[GitHub](#)

- **Interoperable:**

- Use **standard** and **open formats**
- Provide **all data needed** to reproduce your analysis

- **Reusable:**

- **Describe** your data well, e.g., good metadata but also
- Attach a **license**

Provide README files describing the data
Use descriptive column headers for the data tables

Challenges Sharing and Reusing

The marshmallow test – delayed gratification

- Open does not mean FAIR
- Requires an effort
- Metadata becomes the most important data
- In many cases there are no standards or multiple ones
- Most of the data out there not FAIR



<https://imgflip.com/memegenerator>

https://en.wikipedia.org/wiki/Stanford_marshmallow_experiment

Standardisation and Ontologies

- Data **standardisation** requires defining **terminologies** and **vocabularies** that:
 - Assign **unique identifiers** to entities/concepts such as proteins, genes, diseases
 - **Describe** those entities/concepts and **provide meaning**
 - **Relate** those concepts to other terms
 - Classify those entities/concepts into **categories**
- **Solution** → **Ontologies**
- **Ontology**:

formal way of representing knowledge in which concepts are described both by their meaning and their relationship to each other

A collection of terms and their definitions for a specific domain

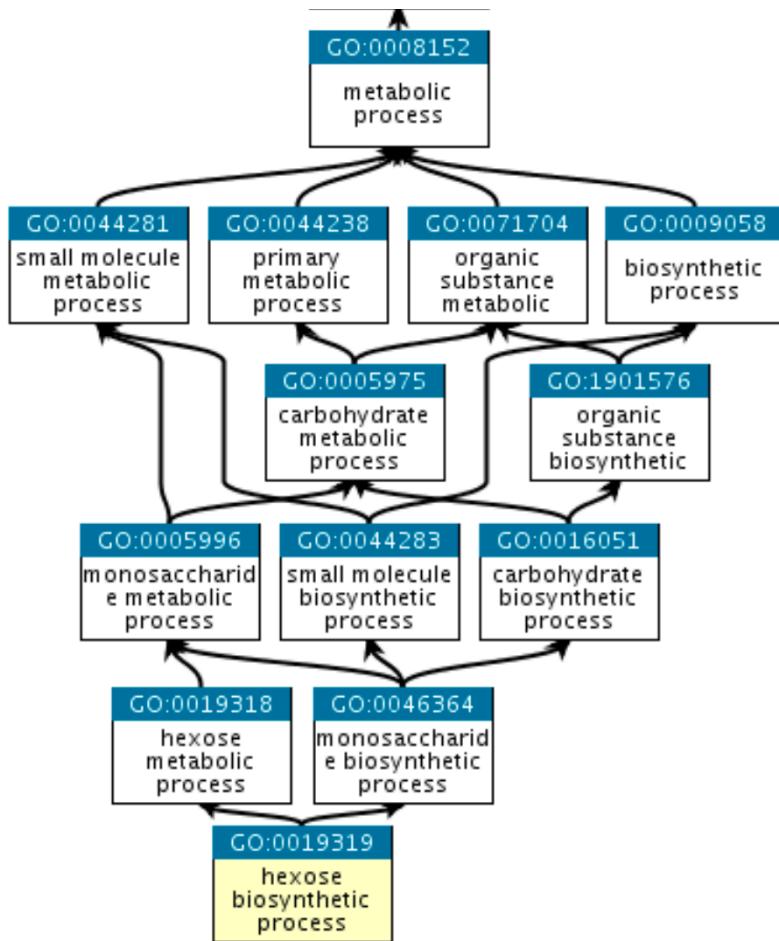


<https://www.ebi.ac.uk/ols/index>

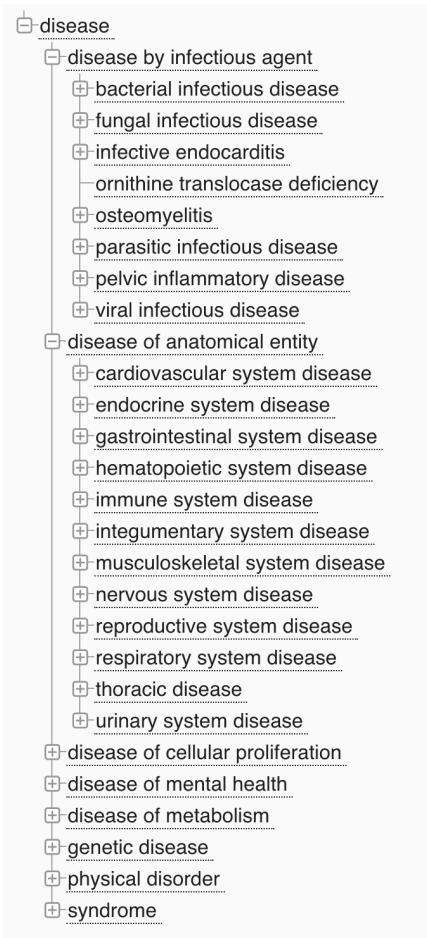
<https://www.nature.com/articles/nrg1295>

Ontologies

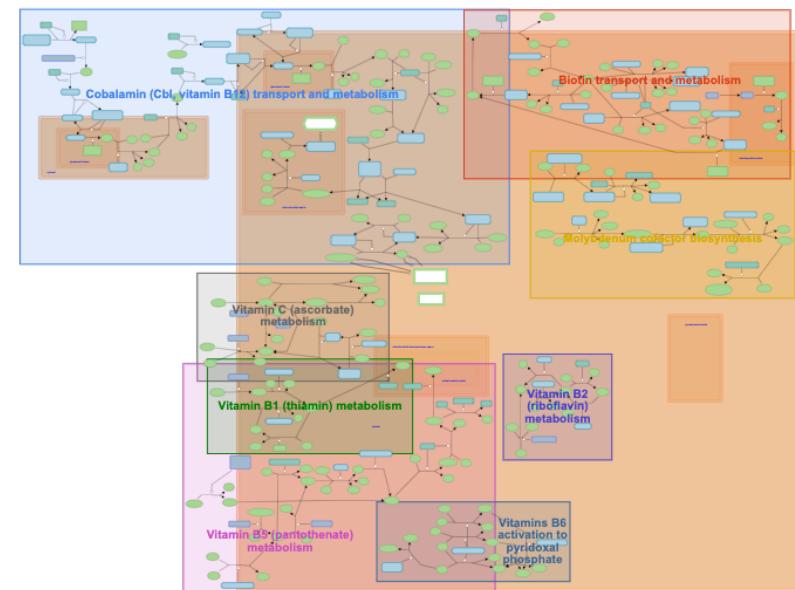
Gene Ontology



Disease Ontology



REACTOME Pathways



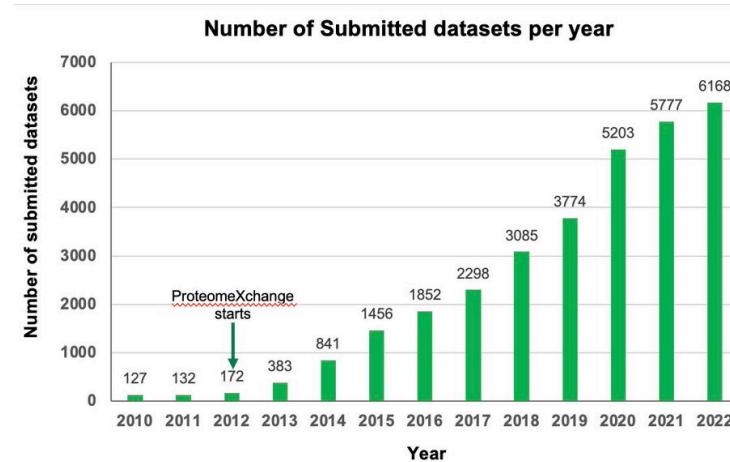
<https://www.ebi.ac.uk/ols/ontologies>

<https://reactome.org/>

<http://geneontology.org/>

Publicly Available Resources

- **Do not reinvent the wheel**
- **Extend the life and purpose** of publicly available **data**
- Build **in-silico hypotheses** before jumping into experiments (cheaper, higher success rate)
- **Download – Use – Test – Transform – Upload**
- **Growing number of resources** and **datasets** available



<https://www.ebi.ac.uk/pride/>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6258825/>

Data Sources

NCBI

Organisms Database

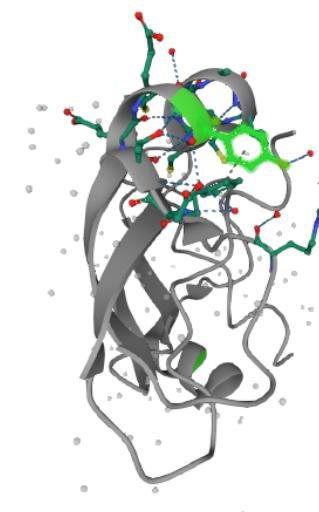
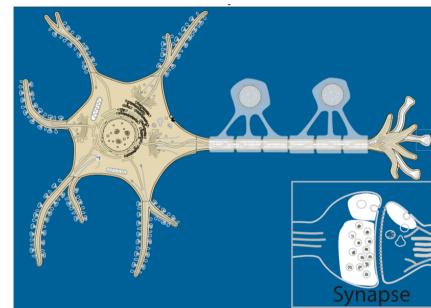
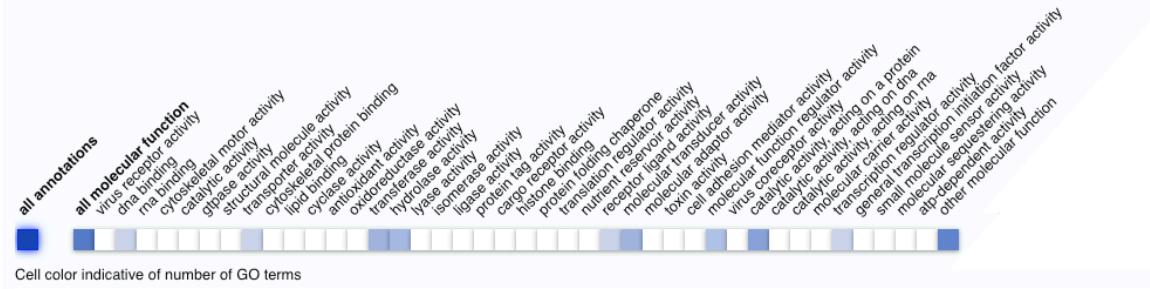
- The **NCBI Taxonomy** database allows **browsing** of the **taxonomy tree**, which contains a classification of organisms
- Provides information about:
 - Taxonomic identifier** for organisms
 - Genomic overview**
 - Link-outs to **domain-specific databases**

Entrez records			
Database name	Subtree links	Direct links	Links from type
Nucleotide	2,721,504	2,578,488	7,410
Protein	22,445,169	20,989,652	-
Structure	2,632	1,230	-
Genome	1	1	-
Popset	1,043	1,043	-
Conserved Domains	10	8	-
GEO Datasets	6,794	4,153	-
PubMed Central	111,167	111,167	-
Gene	128,094	3,304	-
SRA Experiments	41,306	33,055	-
GEO Profiles	141,600	141,600	-
Protein Clusters	7,547	7,547	-
Identical Protein Groups	3,556,802	3,524,631	-
BioProject	2,896	2,004	-
BioSample	56,942	49,071	15
Assembly	21,782	21,326	9
PubChem BioAssay	12,338	10,607	-
Taxonomy	383	1	-

UniProt

Protein Database

- Comprehensive view on **proteins**
- Aggregates information about:
 - **Function**
 - **Sequence features**
 - **Subcellular localisation**
 - **Tissue expression**
 - **Disease association**
 - **Variants and PTMs**
 - **Interactions**
 - **Structure**



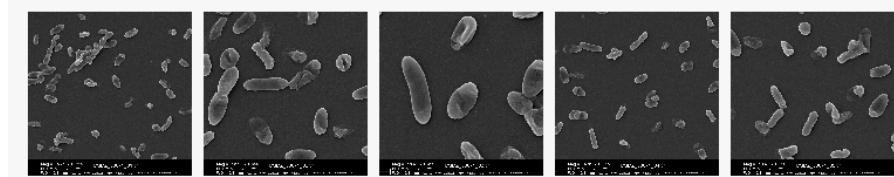
BacDive

Bacterial Database

- Largest database for **standardised bacterial phenotypic information**
- Collects information about:
 - **Bacterial classification**
 - **Morphology**
 - **Culture and growth conditions**
 - **Physiology and metabolism**
 - **Environment**
 - **Genome-based predictions**

Pseudomonas aeruginosa DSM 50071 is a thermophilic, Gram-negative, rod-shaped human pathogen of the family Pseudomonadaceae.

Gram-negative rod-shaped human pathogen thermophilic 16S sequence Bacteria genome sequence



The Microbial Metabolites Database

MiMeDB

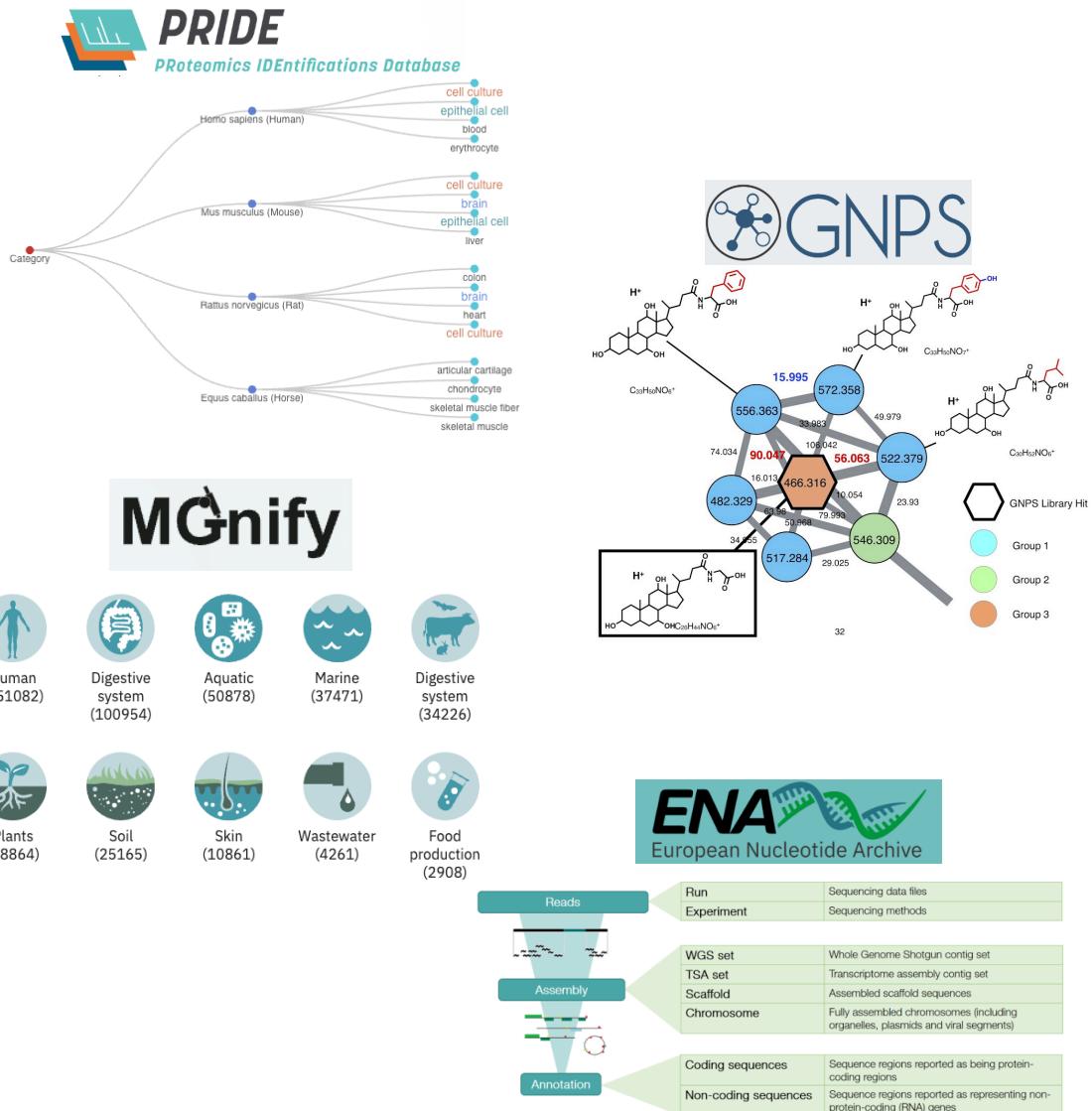
- The **human microbiome** is believed to produce or process **>55,000 different compounds** – many of which **affect** human **health, behavior and disease**
- **Microbes synthesise primary metabolites** required for their own survival, but they also **produce** other **compounds arising from substrates or host-derived food sources**

E.g., microbes transform xenobiotics from food constituents, food additives, phytochemicals, drugs, cosmetics and other exogenous or man-made chemicals

- MiMeDB is a **database of small molecule metabolites found in the human microbiome**
- Provides links between **metabolites, microbes, hosts, health and exposure** data

Metadatabases Data Repositories

- **PRIDE:** Mass Spectrometry-based (MS-based) Proteomics
- **GNPS:** MS-based Metabolomics
- **MGnify:** Microbiome data
- **ENA:** sequencing information, covering raw sequencing data, sequence assembly information and functional annotation



Protein-Protein Interactions

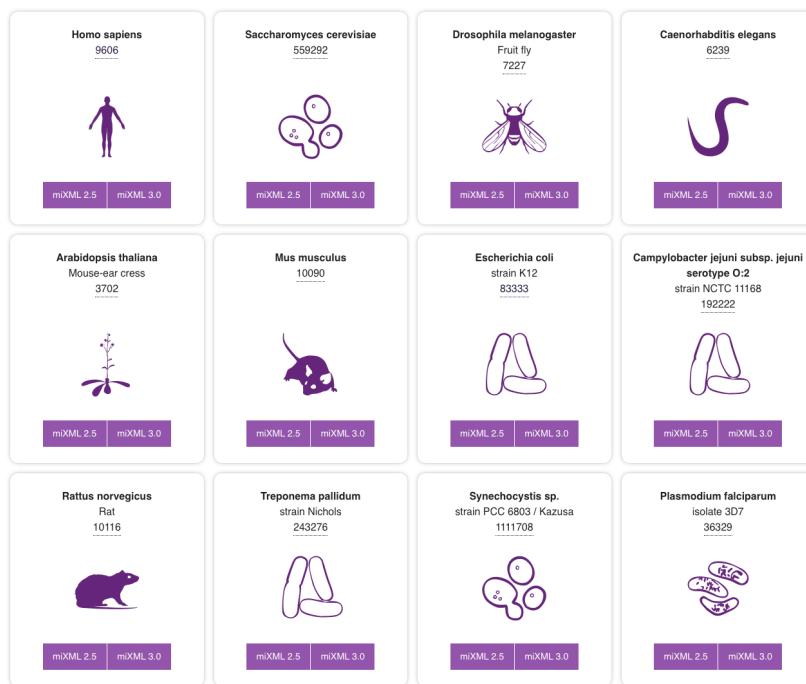
Interactions

- **STRING:** PPIs and functional enrichment



<https://string-db.org/>

- **Intact:** intra- and inter-species PPIs



<https://www.ebi.ac.uk/intact>

Other Resources

ALEdb 1.0: a database of mutations from adaptive laboratory evolution experimentation <https://aledb.org/>

Web of microbes (WoM): a curated microbial exometabolomics database for linking chemistry and microbes <https://metatlas.nerc.gov/wom/project-begin.view>

MicroPhenoDB Associates Metagenomic Data with Pathogenic Microbes, Microbial Core Genes, and Human Disease Phenotypes <http://www.liwzlab.cn/microphenodb>

MASI: microbiota—active substance interactions database <http://www.aiddlab.com/MASI/>

iModulonDB: a knowledgebase of microbial transcriptional regulation derived from machine learning <https://imodulondb.org/index.html>

MIBiG 3.0: a community-driven effort to annotate experimentally validated biosynthetic gene clusters <https://mibig.secondarymetabolites.org/>

FooDB: most comprehensive resource on food constituents, chemistry and biology <https://foodb.ca/>

Accessing Data

GUI vs API



Graphical User Interface

- **View** the data
- **Facilitates** initial work
- Limited to the **interface**



Application Programming Interface

- **Access** the data
- **Free** to do whatever you want
- Limited to **provided data**

Jupyter Notebooks

<https://jupyter.org/>



- **Web-based development environment** for **creating, running and sharing Python** (and other languages) code
- A **notebook** is an interactive document that combines **live code, equations, text or markdown, and visualisations** (output of your code)
- Notebooks are divided into **cells** that **run sequentially!** (Need to pay attention)
- It **requires** having **Python installed** on your local machine



Colab Notebooks

<https://research.google.com/colaboratory/faq.html>

- Google Colab is based on **Jupyter Notebook** open source project **hosted on Google's servers**
- Advantages:
 - Requires **no setup** to use (no python installation)
 - Provides **free** access to **computing resources** on Google's servers including GPUs
 - **Notebooks** can be **shared** just as you would with Google Docs or Sheets.
 - You can **import** existing **Jupyter notebooks**
- **Own data and notebooks** need to be accessed through **Google Drive** – Need Google account

Example: https://colab.research.google.com/github/biosustain/data_club/blob/main/notebooks/data_annotation/uniprot_api-solved.ipynb

Sharing Data

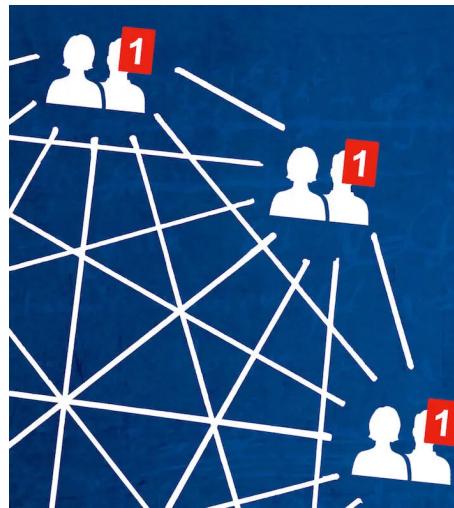
Community Repositories



scientific **data**

Graphs

Graphs



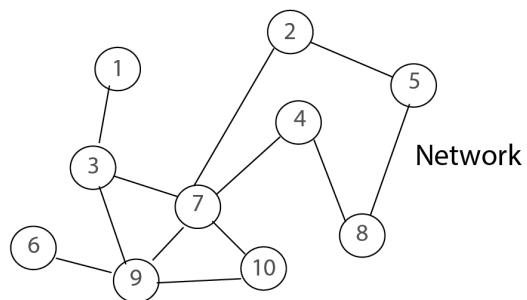
Graphs



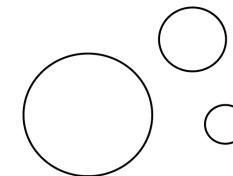
Node



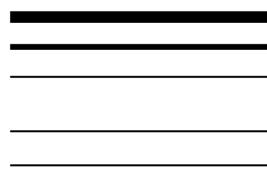
Edge


$$\begin{bmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \end{bmatrix}$$

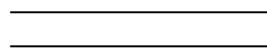
Adjacency matrix



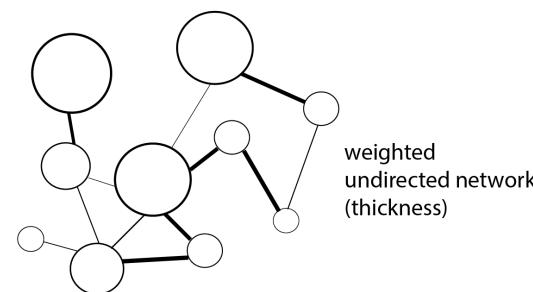
weighted nodes (size)



weighted edges (thickness)

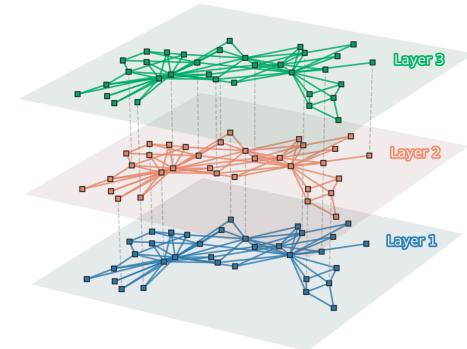
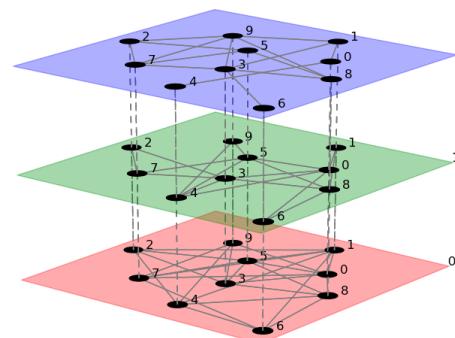


undirected edge
directed edge



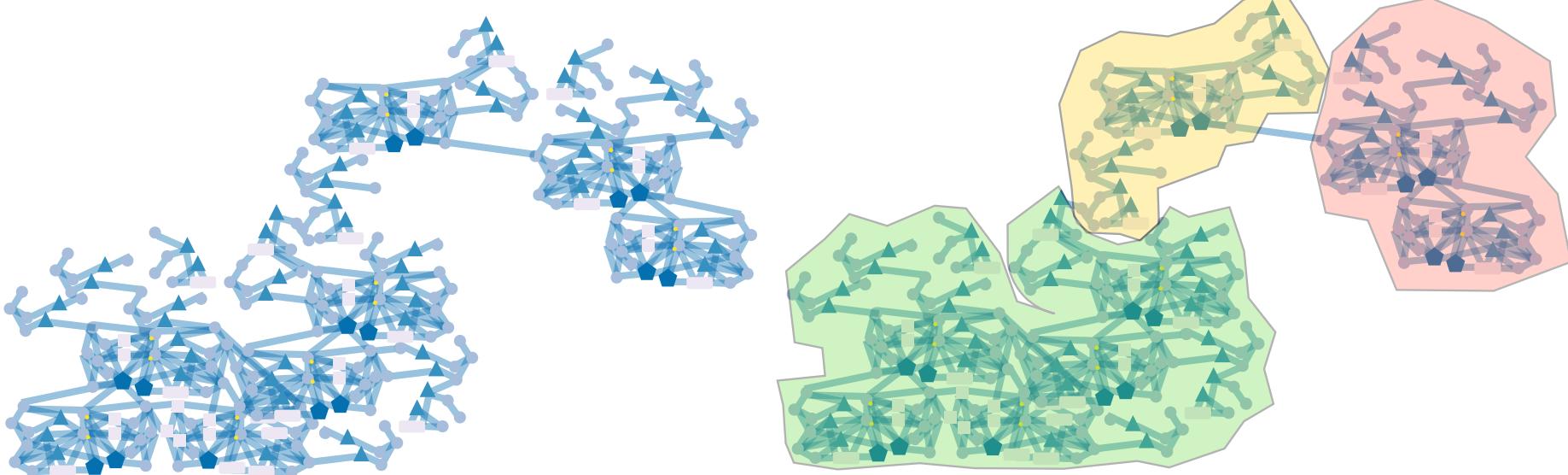
$$\begin{bmatrix} 0 & w_{1,2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & w_{2,3} & 0 & w_{2,4} & 0 & 0 & 0 \\ w_{1,2} & 0 & 0 & 0 & 0 & w_{3,4} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & w_{3,4} & 0 & 0 & 0 & 0 \\ 0 & w_{2,3} & 0 & 0 & 0 & 0 & w_{4,5} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & w_{4,5} & 0 & 0 & 0 \\ 0 & w_{3,4} & w_{4,5} & 0 & 0 & 0 & w_{5,6} & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{4,5} & 0 & w_{5,6} & 0 & w_{6,7} & 0 & 0 \\ 0 & 0 & w_{3,4} & w_{5,6} & 0 & 0 & w_{6,7} & 0 & w_{7,8} & 0 \\ 0 & 0 & 0 & 0 & w_{5,6} & w_{6,7} & 0 & w_{7,8} & 0 & 0 \end{bmatrix}$$

Weighted adjacency matrix



What is a Graph/Network?

- Data structures of **components (nodes)** connected by **relationships (edges)**
- Allows us to **model** and **analyse** data
- Provides a **mathematical framework** to analyse complex relationships:
Graph theory

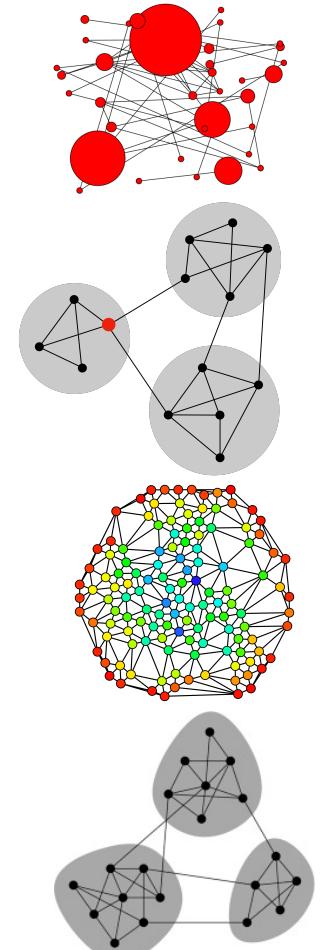


Why Graphs?

- These structures allow:
 - Quick **integration of heterogeneous data** based on relationships
 - **Graph theory** methods can be used to **analyse** and **interpret** data, e.g., topological properties can be used to explain:
 - The possible **role** of specific components
 - The **flow** of information
 - The **robustness** of the system
- **Visualize** data

Graph Metrics

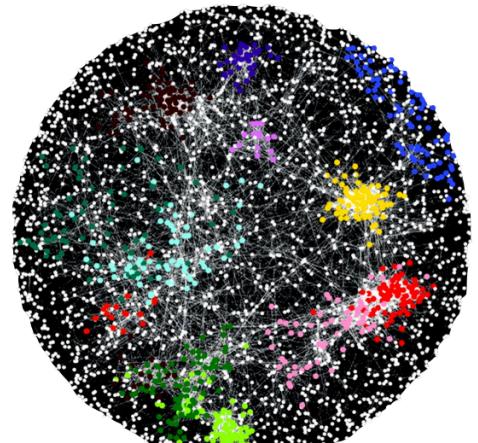
- **Degree:** number of edges in (in-degree) and out (out-degree) of a node
node importance
- **Connectivity:** minimum number of elements (nodes or edges) that need to be removed to get two or more isolated subgraphs
graph resilience
- **Distance:** length of shortest path between two nodes
- **Centrality:** ranking of nodes according to their position
node importance
 - **Degree centrality**
 - **Closeness centrality:** the average length of the shortest path between the node and all other nodes in the graph
 - **Betweenness centrality:** number of times a node acts as a bridge along the shortest path between two other nodes
 - **Eigenvector centrality:** It assigns relative scores to all nodes in the network based on the concept that connections to high-scoring nodes contribute more
 - **Katz centrality:** number of all nodes that can be connected through a path (distant nodes are penalised)
- **Clustering:** partitioning a graphs into different groups that share some form of similarity



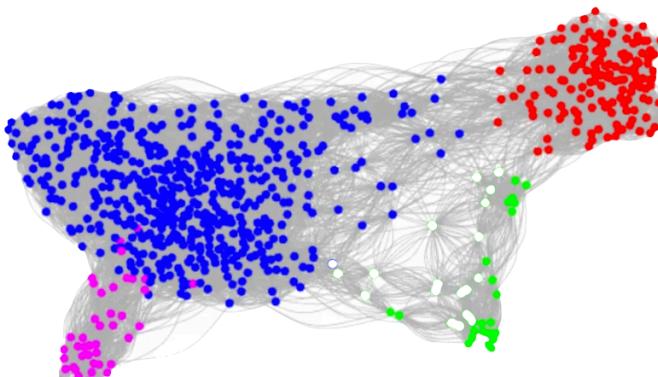
[https://en.wikipedia.org/wiki/Degree_\(graph_theory\)](https://en.wikipedia.org/wiki/Degree_(graph_theory))
[https://en.wikipedia.org/wiki/Distance_\(graph_theory\)](https://en.wikipedia.org/wiki/Distance_(graph_theory))
<https://en.wikipedia.org/wiki/Centrality>
[https://en.wikipedia.org/wiki/Connectivity_\(graph_theory\)](https://en.wikipedia.org/wiki/Connectivity_(graph_theory))
<https://www.sciencedirect.com/topics/computer-science/clustering-graph>

Graphs in Biology

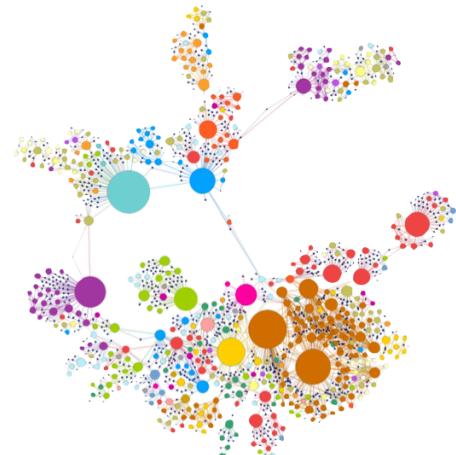
Protein-protein Interaction Networks



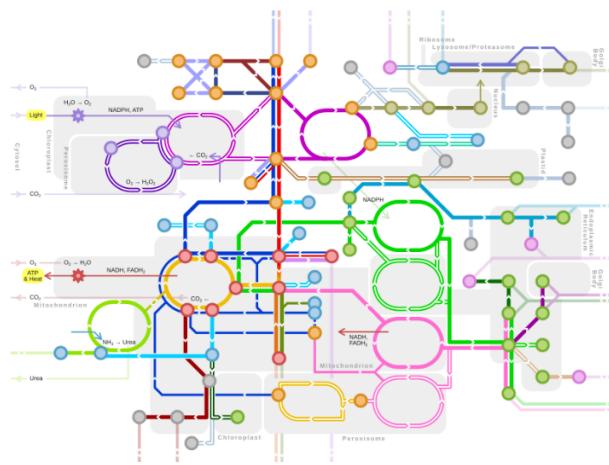
Single cell Networks



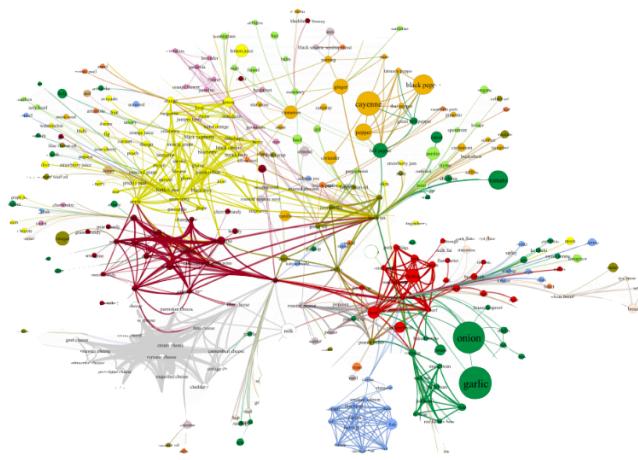
Disease Networks



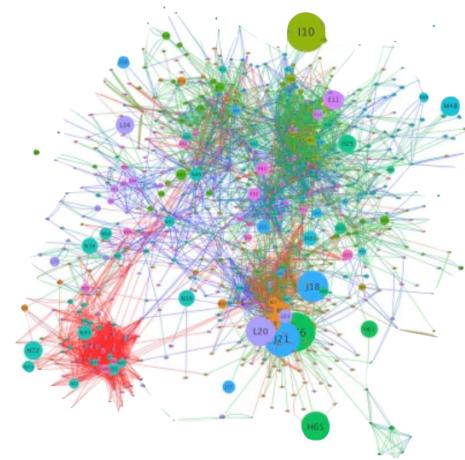
Metabolic Networks



Food Networks



Diagnosis Progression Networks



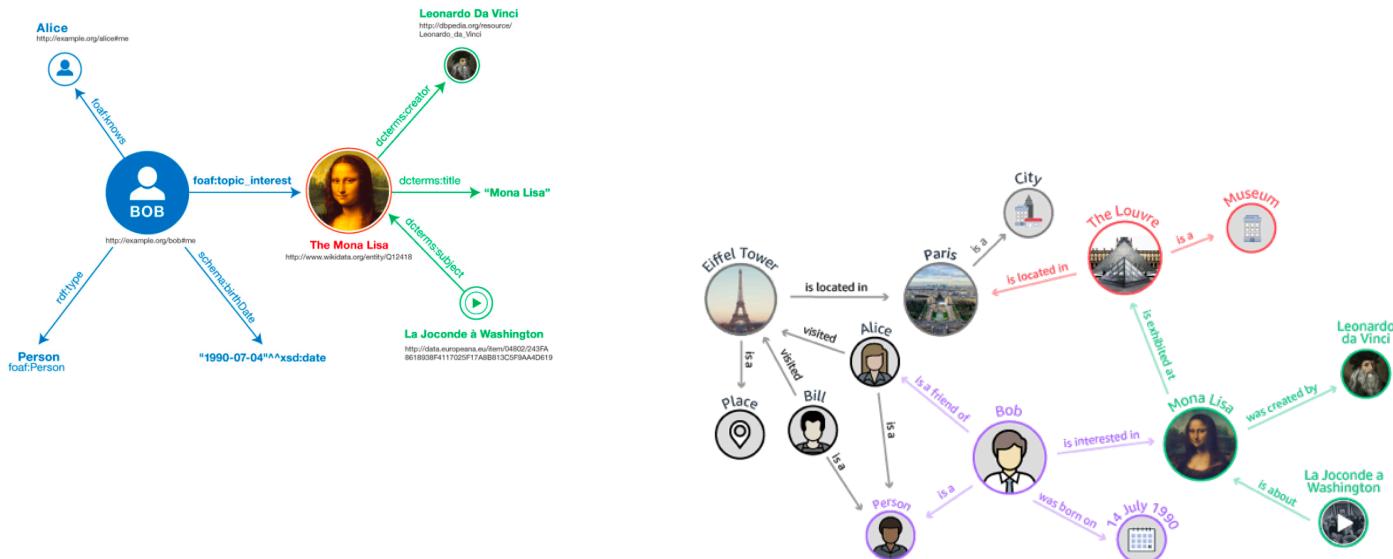
<https://towardsdatascience.com/umap-for-data-integration-50b5cfa4cdcd>
<http://snap.stanford.edu/deepnetbio-ismb/ipynb/Human+Disease+Network.html>
<https://cytoscape.org/cytoscape-tutorials/presentations/ppi-tools1-2017-mpi.html#/>
https://en.wikipedia.org/wiki/Metabolic_network
<https://www.scienceandfood.org/the-flavor-network/>

Knowledge Graphs

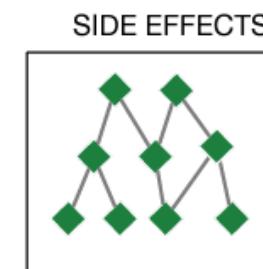
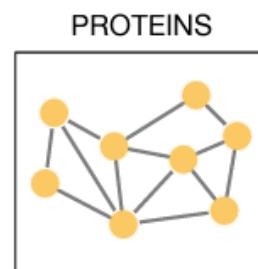
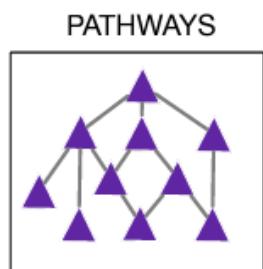
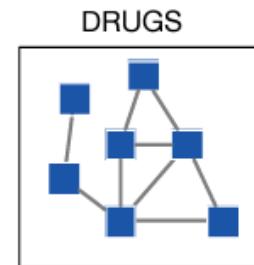
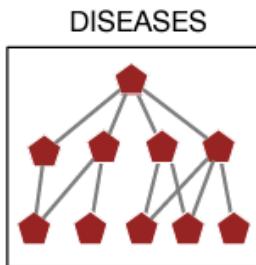
What is a Knowledge Graph (KG)

Relationships firsts everything else second

- A way to organise **knowledge/information** by defining **associations or relationships**
- These relationships facilitate the **integration, management and enrichment** of data
- The **objectives** when setting up a KG:
 - Standardisation
 - Quality
 - Reusability
 - Interpretability
 - Automation
 - Representation/Visualisation

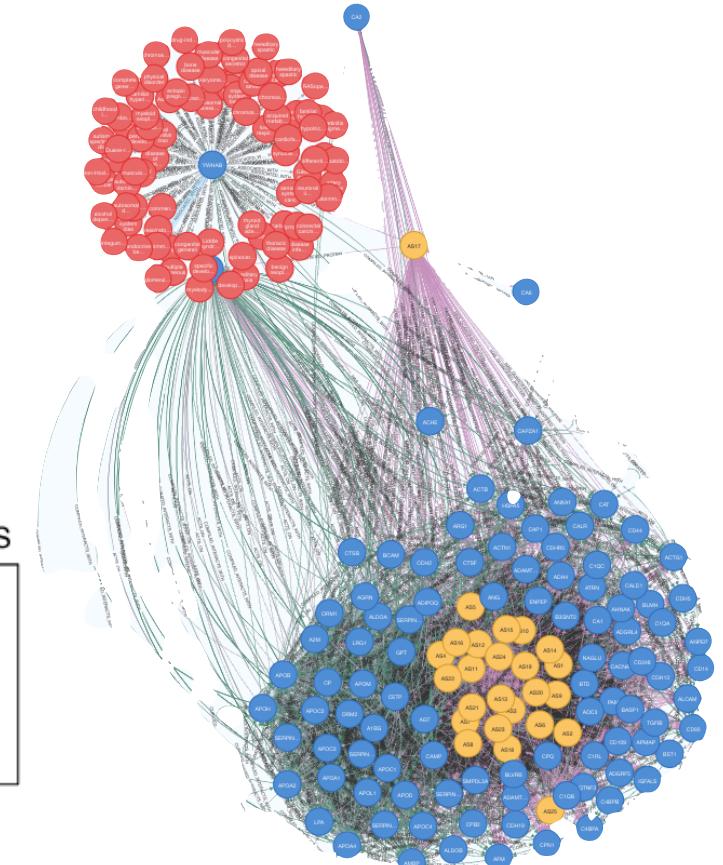
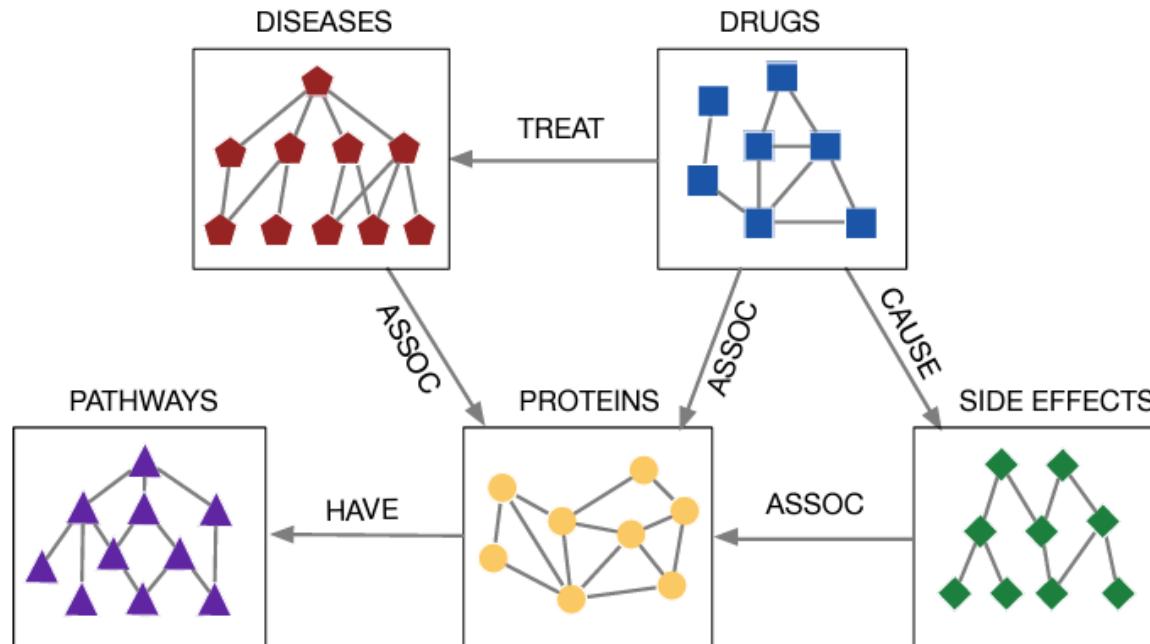


Knowledge Graph vs Graph Database



Knowledge Graph vs Graph Database

Focus on data integration to represent complex biological systems and be able to reason over them

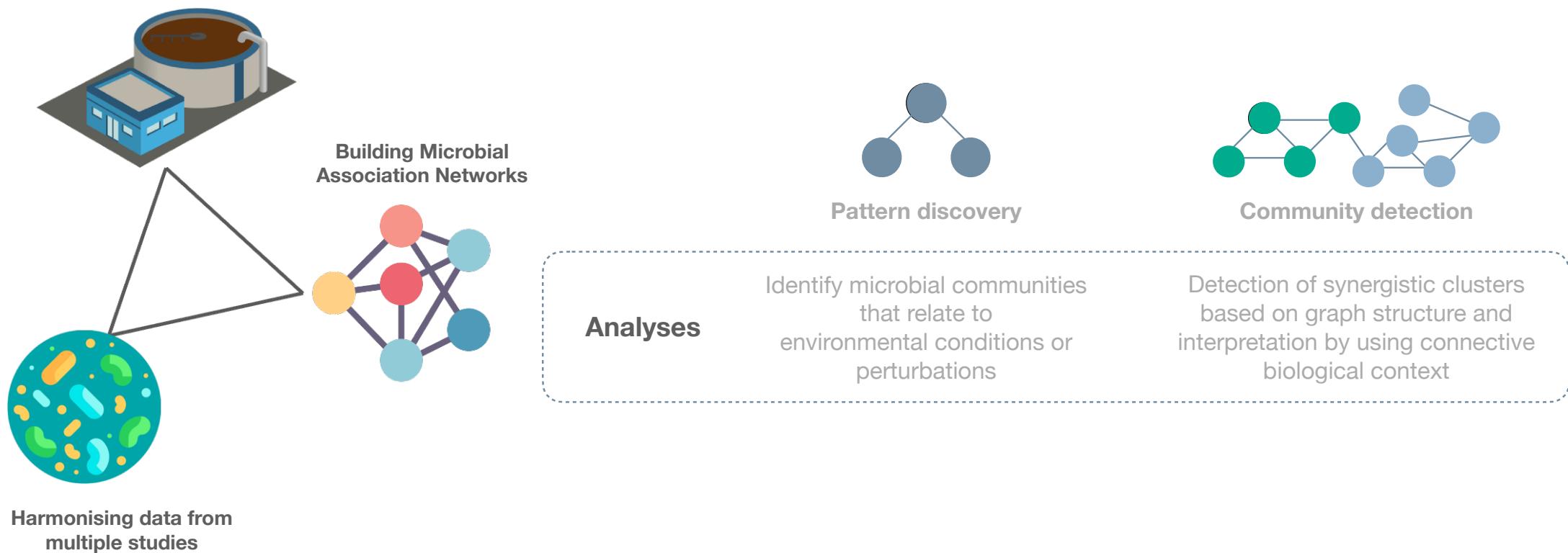


Knowledge Graph Use Case

Wastewater Microbial Communities

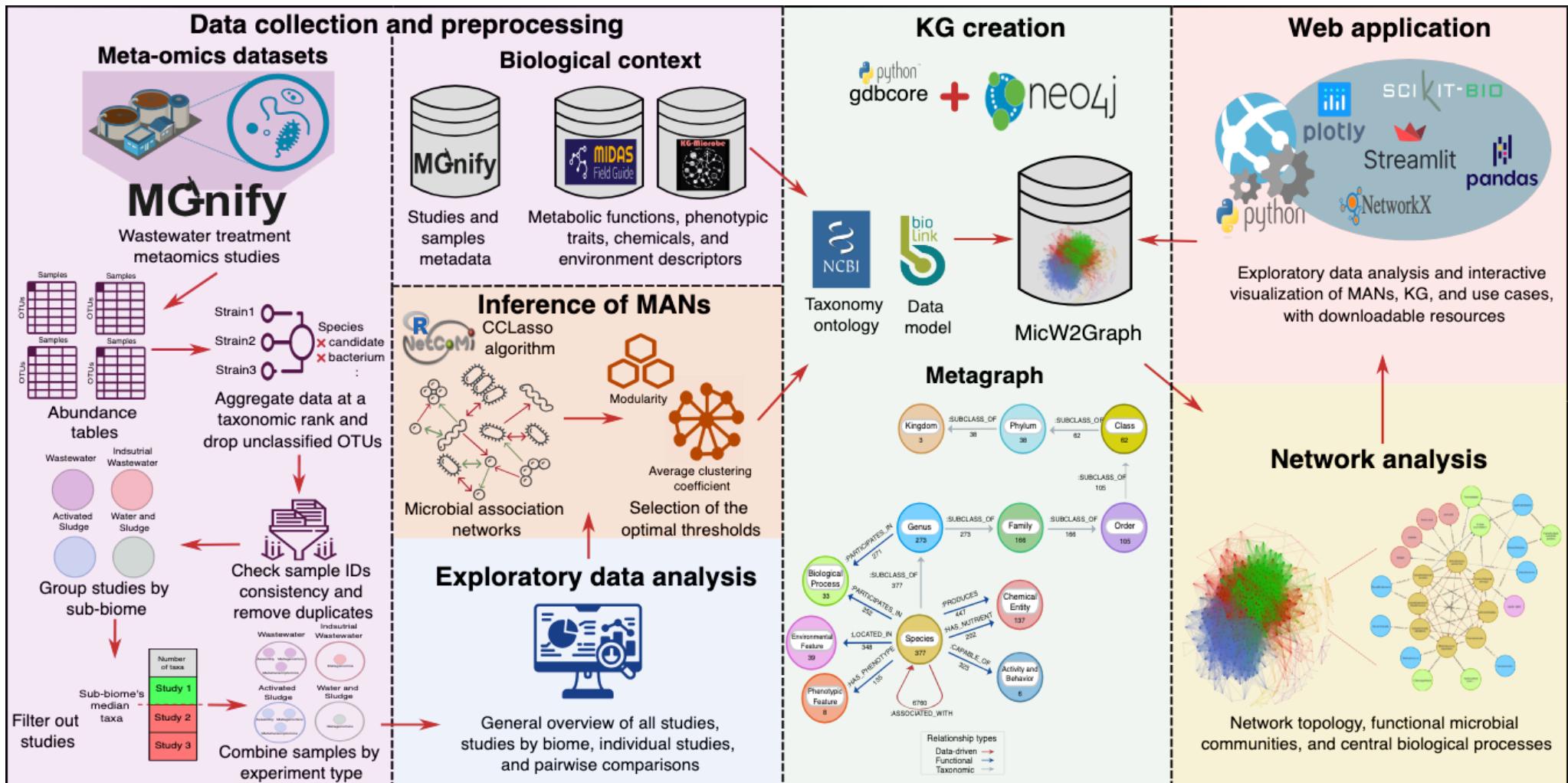


Sebastian Ayala Ruano



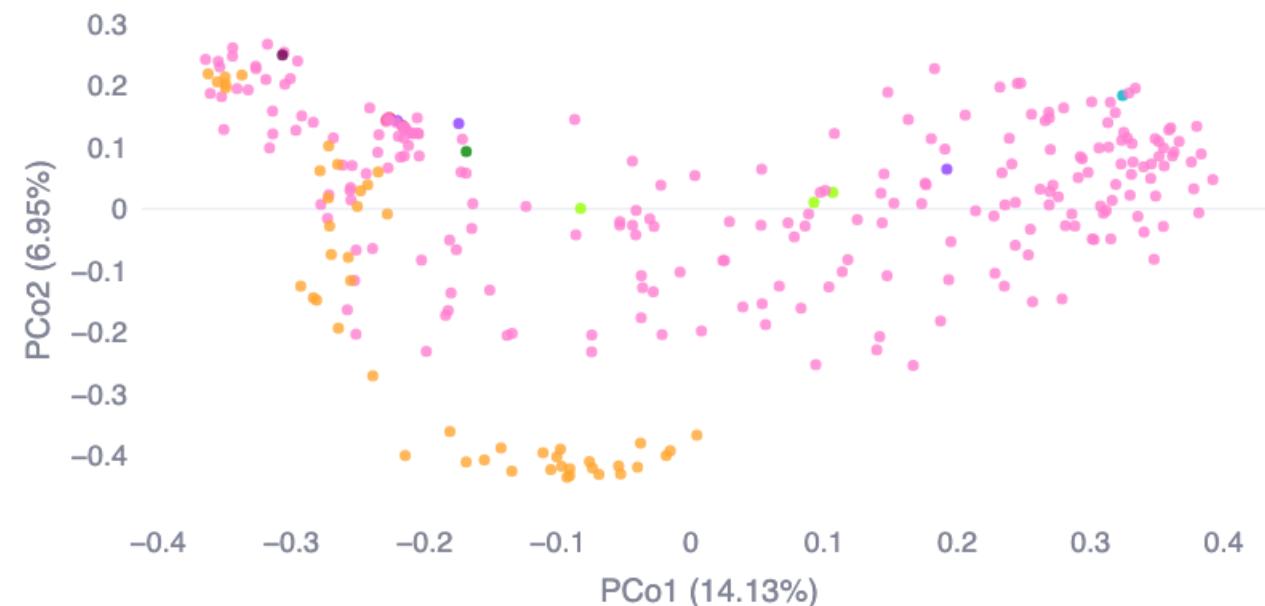
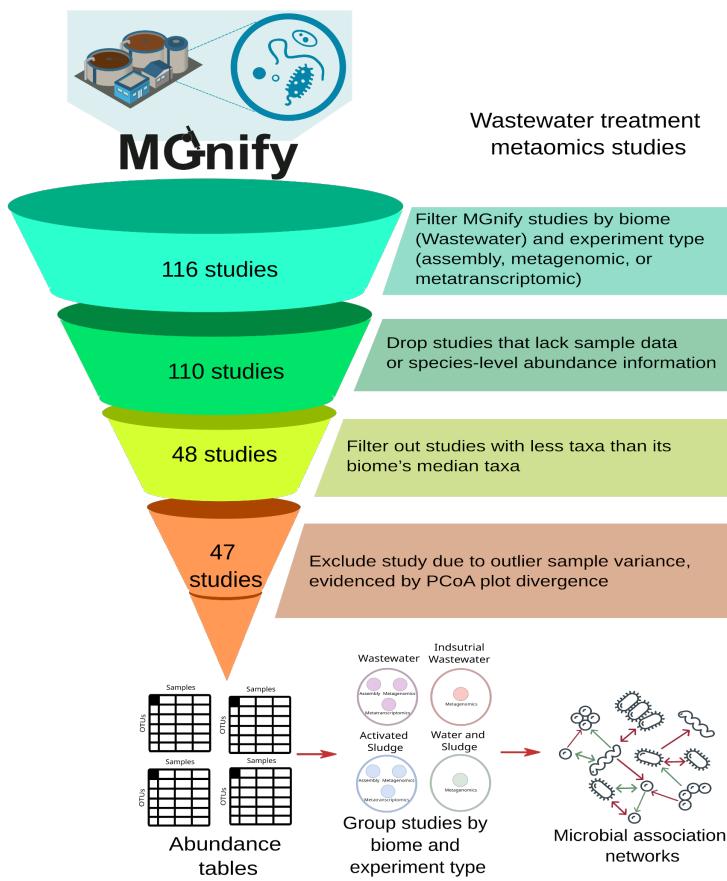
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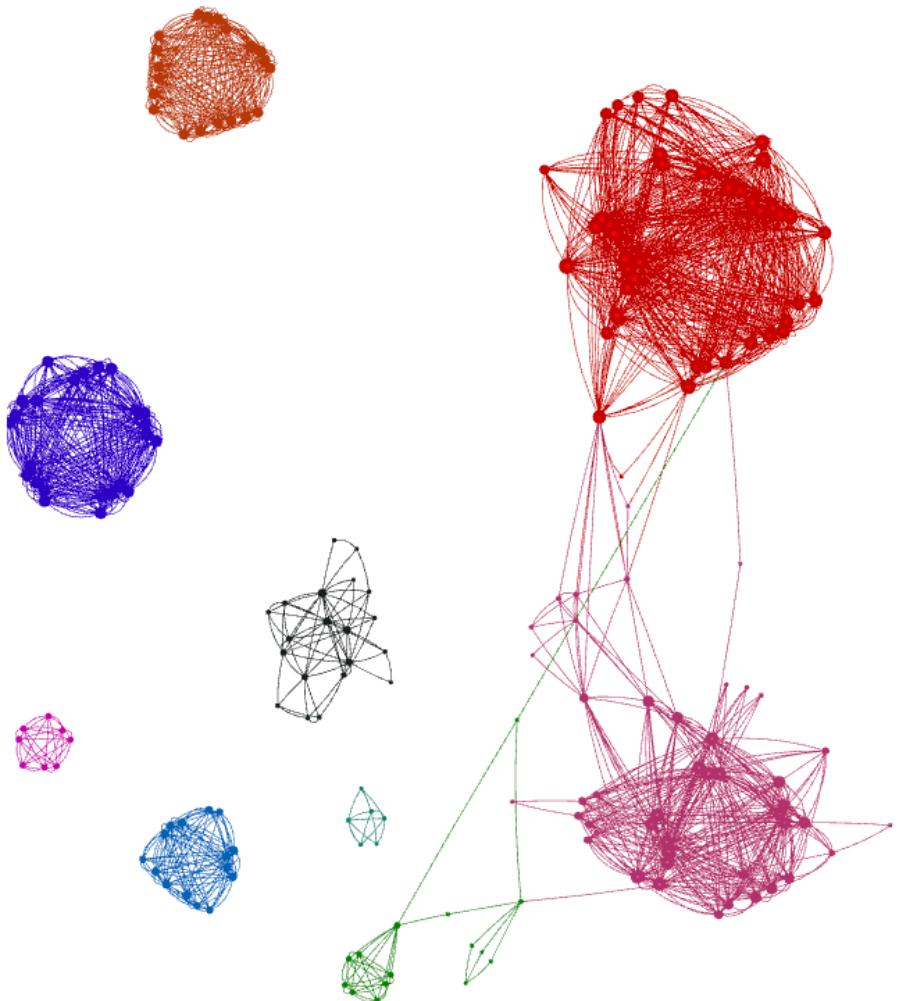
Knowledge Graph Use Case

Wastewater Microbial Communities



- thermophilic anaerobic methanogenic reactor - water
- thermophilic anaerobic methanogenic reactor - biofilm
- Wastewater treatment plant - Sewage
- Activated Sludge - Reactor
- mesophilic anaerobic reactor - wastewater
- Wastewater
- closed biogester - sludge
- wastewater treatment plant - water

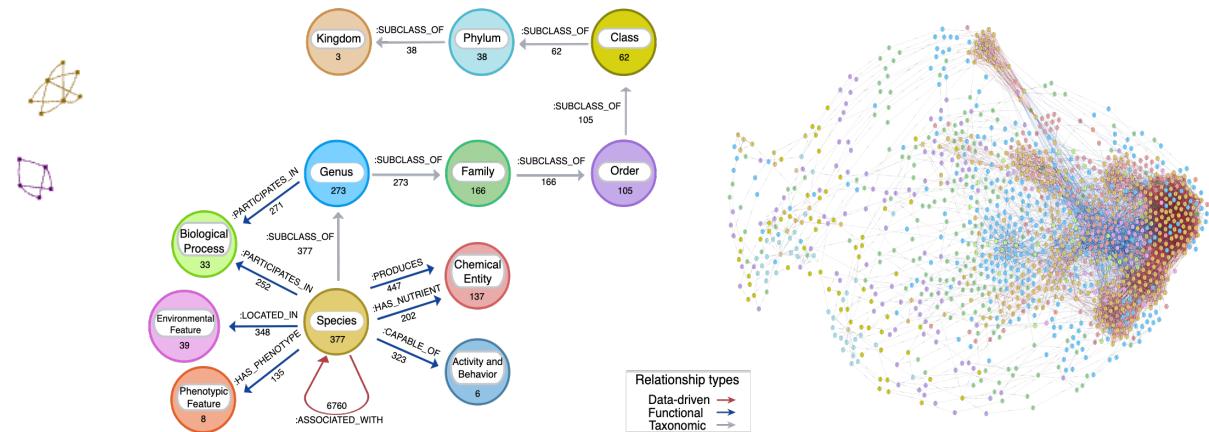
Microbial Association Networks



Microbial Association Network built using CCLASSO method — co-abundance.

Colors indicate microbial communities identified using Louvain clustering.

Functional Annotation:
Using MIDAS and KG Microbe



NetCoMi: network construction and comparison for microbiome data in R ⚡

Stefanie Peschel ✎, Christian L Müller, Erika von Mutius, Anne-Laure Boulesteix,
Martin Depner



Home

Exploratory data analysis

* Microbial association networks

Knowledge graph

Case studies

MicW2Graph

Building a knowledge graph of the wastewater treatment microbiome and its biological context

Microbial association networks by wastewater treatment sub-biome and experiment types

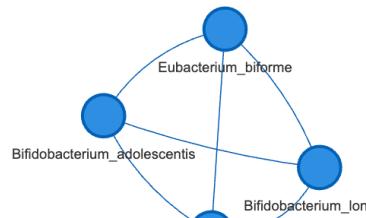
Water and sludge

Metagenomics

Number of nodes: 9

Number of relationships: 14

Add panel to control layout

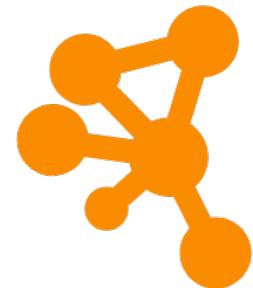


<https://micw2graph.streamlit.app/>

Tools

Cytoscape

<https://cytoscape.org/>



- An open source **software platform** for **visualising and analysing complex networks**
- Used for any kind of networks but **specialised on biological domains**:
e.g, Molecular interaction networks and biological pathways and integrating these networks with annotations, gene expression profiles and other state data.
- **Additional features** are available as freely available **Apps** (<https://apps.cytoscape.org/>)



[Getting Started](#)

Gephi

<https://gephi.org/>

- Open source **platform** for **graph visualisation** and **analysis**
- Used across **many domains** and by **many industries**
- **Performs well** for large graphs
- **Connects to Graph databases** such as Neo4j
- Some of the **visualisations and analysis** require **plugins**



Code



<https://networkx.org/>

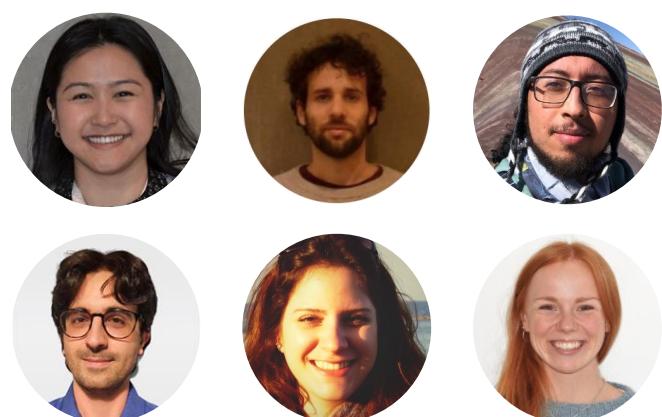


<https://r.igraph.org/>

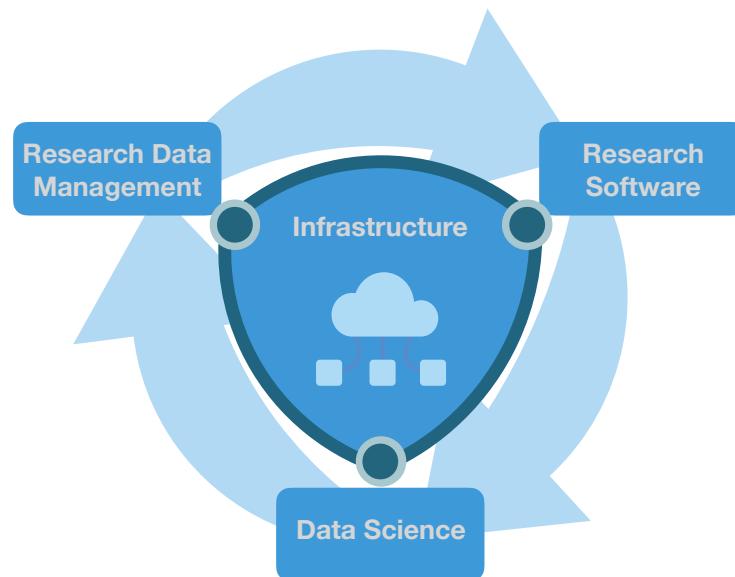
QA

Acknowledgements

Multi-omics Network Analytics



Informatics Platform



Thank you



✉ albsad@dtu.dk

🐦 @albsantosdel

💻 <https://github.com/Multiomics-Analytics-Group>

🌐 <https://multiomics-analytics-group.github.io/>

