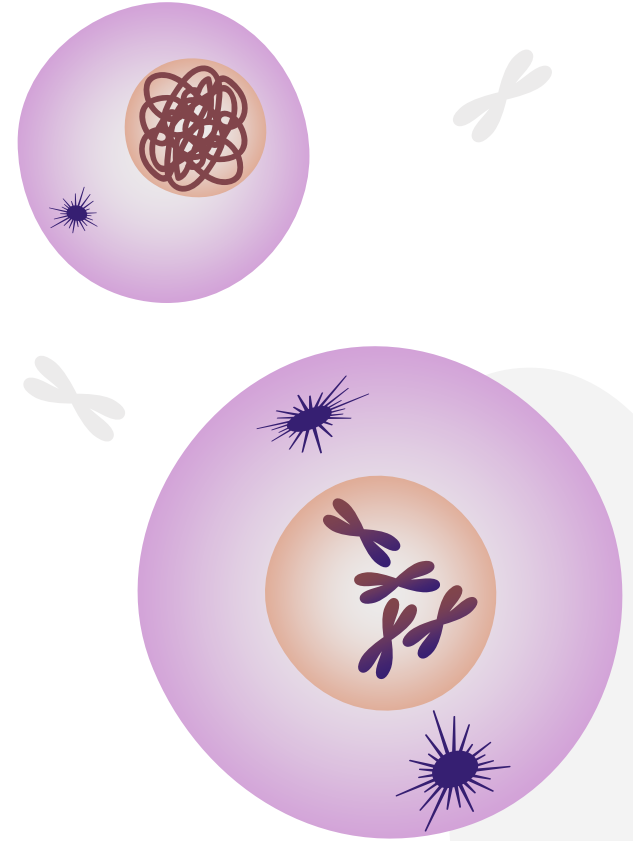


Metabolic Diseases: Pathway Analysis

Computation Health Laboratory Final Project

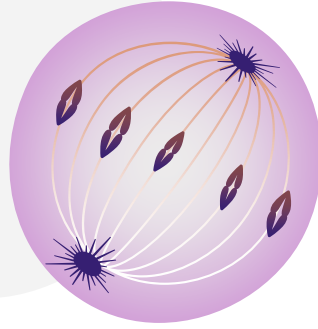
Marzeddu Simone
Raffi Jacopo



The background features a large, light gray abstract shape on the left side. Scattered around this shape are several stylized biological elements: three purple circular cells, each containing a different stage of cell division (prophase, metaphase, and anaphase), and several small, light gray chromosome icons. The text '01' is positioned in the upper right area of the slide.

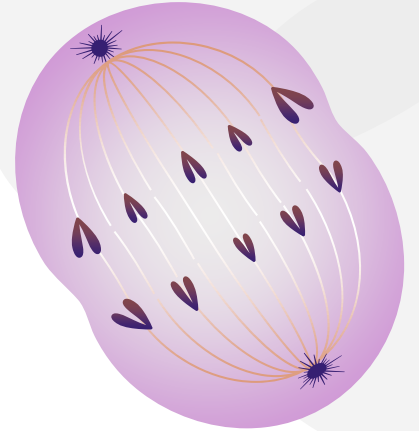
01

Project Introduction



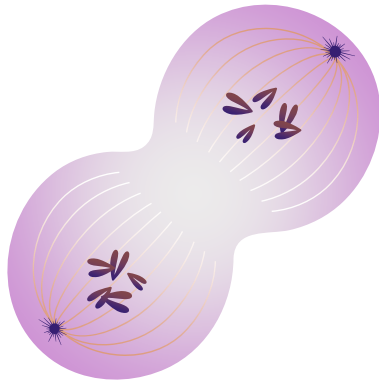
02

Metabolic Diseases: Background



Background

Metabolic Diseases



What is Metabolism?

The process of converting food to energy on a cellular level.

Metabolic Diseases Effects

These diseases affect the ability of the cell to perform biochemical reactions that involve the processing or transport of proteins, carbohydrates, or lipids.

Contraction of Diseases

Metabolic diseases are typically hereditary, yet most persons affected by them may appear healthy for days, months, or even years.

Diseases Consequences

Consequences may be severe: intellectual disability, seizures, decreased muscle tone, organ failure, blindness, or even deafness depending on which enzyme is dysfunctional.



The background features a light gray abstract shape on the left side, containing three stylized purple cells. Each cell contains a nucleus with blue and red chromosomes. The top cell shows a nucleus with four chromosomes. The middle cell shows a nucleus with four chromosomes and two blue star-like structures. The bottom cell shows a nucleus with four chromosomes and two blue star-like structures. There are also several small, light gray chromosome icons scattered around the cells.

03 Project Roadmap

Project Roadmap

Selection of the subclass of Metabolic Diseases



Disorders of
Aminoacid Metabolism

Pathways download and combination



- **Reactome**
- **Drugbank**
- **rBiopaxParser**
- **igraph**

Network Extension and Completion



- **Biogrid:** biologic interactions download and integration.
- **General human organism interactions**
- **biogridr**

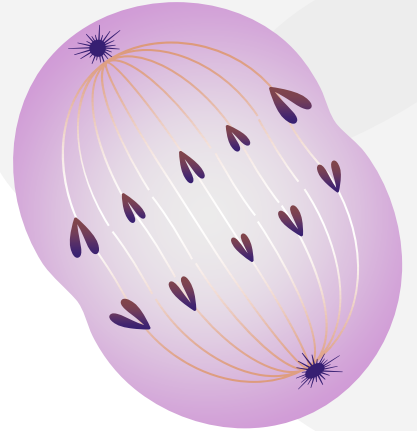
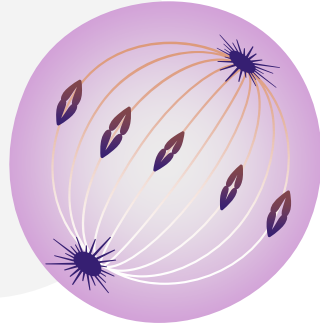
Data Analysis and Results



- **Ranking Algorithm**
- **Qualitative Validation**

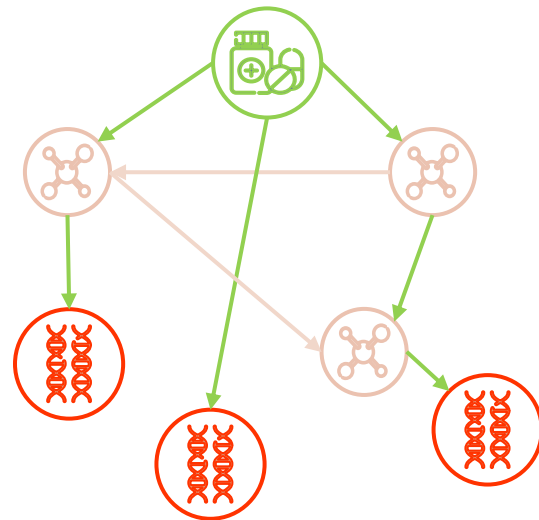
04

Drug Ranking



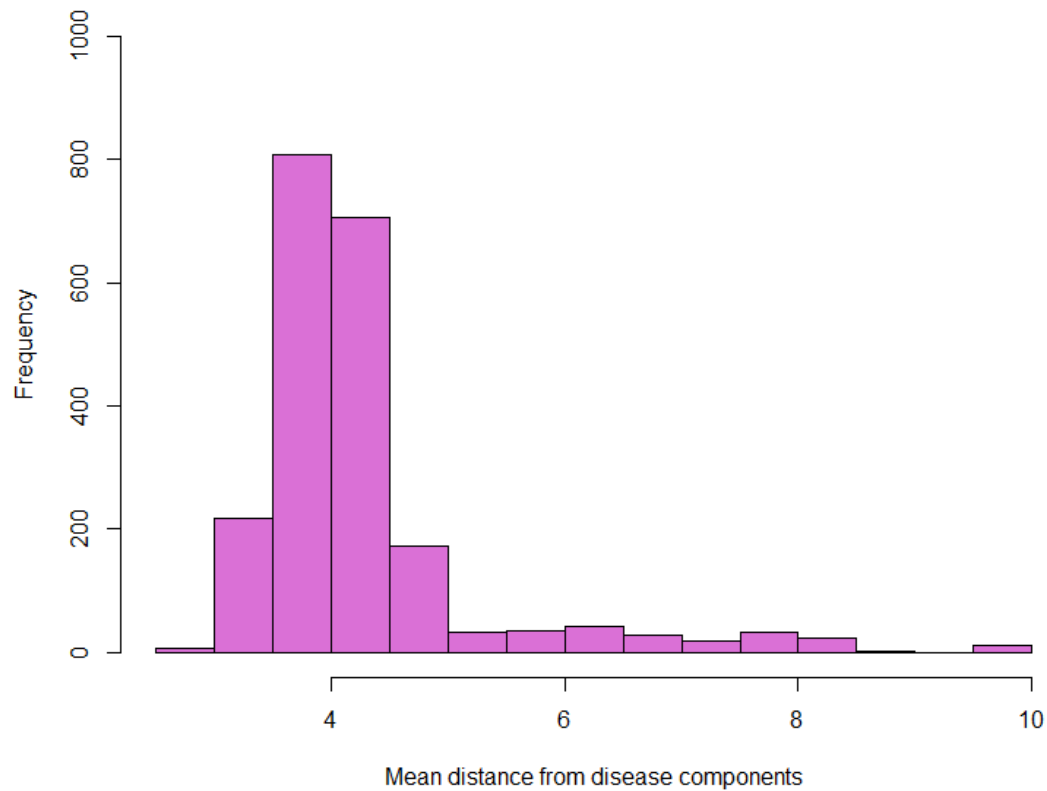
Mean Distance Algorithm

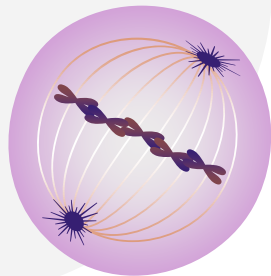
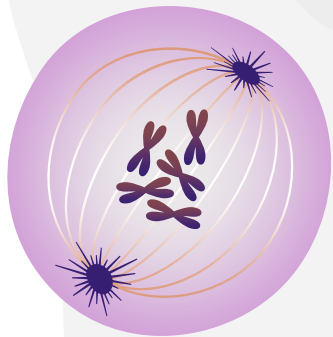
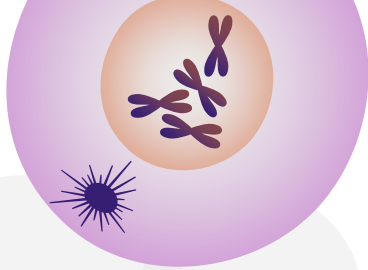
```
ranking <- function(ig, drugs, genes, directed){  
  
  # ig -> igraph representation of the global network  
  # drugs -> vector containing all drugs  
  # genes -> vector containing all the genes of the studied disease  
  # directed -> boolean: TRUE: consider edges directions, FALSE: otherwise  
  
  m = "all"  
  if(directed)  
    m = "out"  
  
  # igraph library function that calculate the shortest path lengths between two sets of nodes  
  dist = distances(ig, v = drugs, to = genes, mode = m)  
  
  # generation of a matrix containing association between drugs and mean distances from the genes of the disease  
  # columns: 1 -> drug_id ; 2 -> mean_distance; 3 -> rank; 4 -> percentage of drugs falling under this rank  
  means = matrix(nrow = length(drugs), ncol = 4)  
  for(i in 1:nrow(dist)){  
    means[i,1] = drugs[i]  
    means[i,2] = mean(dist[i,])  
  }  
  
  # sorting of the matrix based on the mean distances: -> the drugs column represent the ranking  
  means = means[order(as.numeric(means[,2]), decreasing = FALSE),]  
  
  return(means)  
}
```



Ranking Results Example

Methylmalonic Acidemia





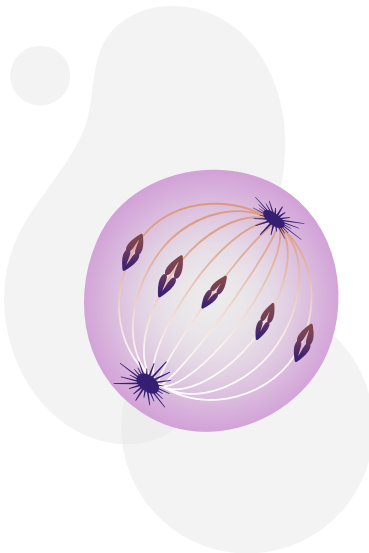
05 **Validation and Results**

Validation



First Qualitative Validation

79.17% of drugs known for the analysed diseases qualify in **high rankings** for those diseases



Mean Rank Analysis

Comparison between the mean rank achieved by **drugs** in **target diseases'** rankings and in **non target diseases'** rankings

3 out of **14** drugs **failed** this test

Interesting Insights

Among the “**new**” **drugs** that emerged from our analysis, we identified **interesting** factors

- **Drugs used for Cancer treatment**

Such as *Entinostat*, *Vorinostat*, *Belinostat* in the top ranking for **Propionic Acidemia**.

- **Drugs linked to Alzheimer treatment**

Such as *Gantenerumab*, found now linked to **Methylmalonic Acidemia**.

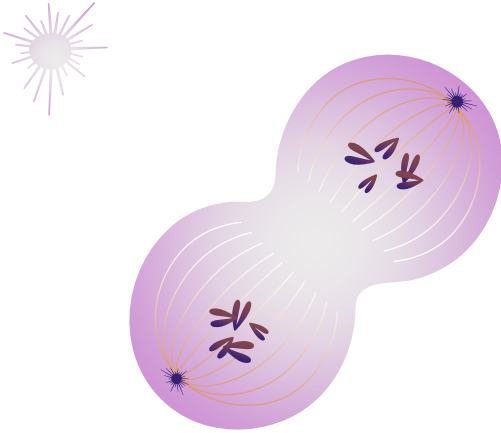
- **Drugs found in Rabies' Pathway**

Rabies Immune Globuline, in the top ranking for **Homocystinuria**.

- **Drugs/Disease links mentioned in Scientific Literature**

Vitamine **B12** and **Hydroxocobalamin**, found as the best drugs against **Methylmalonic Acidemia**.

source: [PubMed](#)



The background features a large, light gray, irregular shape on the left side. Within this shape are three purple circles representing cells. The top cell contains a smaller orange circle with four dark blue X-shaped chromosomes. The middle cell contains four dark blue X-shaped chromosomes and two dark blue star-like structures. The bottom cell contains four dark blue X-shaped chromosomes and two dark blue star-like structures. Scattered around the large gray shape are several small, light gray icons: a star-like shape in the top left, a chromosome in the top right, a chromosome in the middle right, a chromosome in the bottom left, and a star-like shape in the bottom center.

06

Future Plans

Future plans



**Test the method with
different and more
drugs**

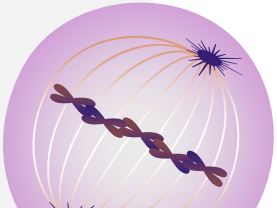


**Update the project
with less naive
approaches**



**Biological study to
confirm or reject the
implications of
rankings**

- Hyperglycinemia
- Methylmalonic Acidemia



The background features several stylized biological illustrations. In the top right, a purple circle contains a cell diagram with orange spindle fibers and dark blue chromosomes. In the bottom left, another purple circle shows a cell diagram with a central orange nucleus containing dark blue chromosomes. Scattered around are various light gray abstract shapes, including circles, irregular blobs, and small starburst or cross-like symbols.

Thank you for your attention

Marzeddu Simone – Raffi Jacopo

