Functional profiling

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Unidad de
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Bioestadística

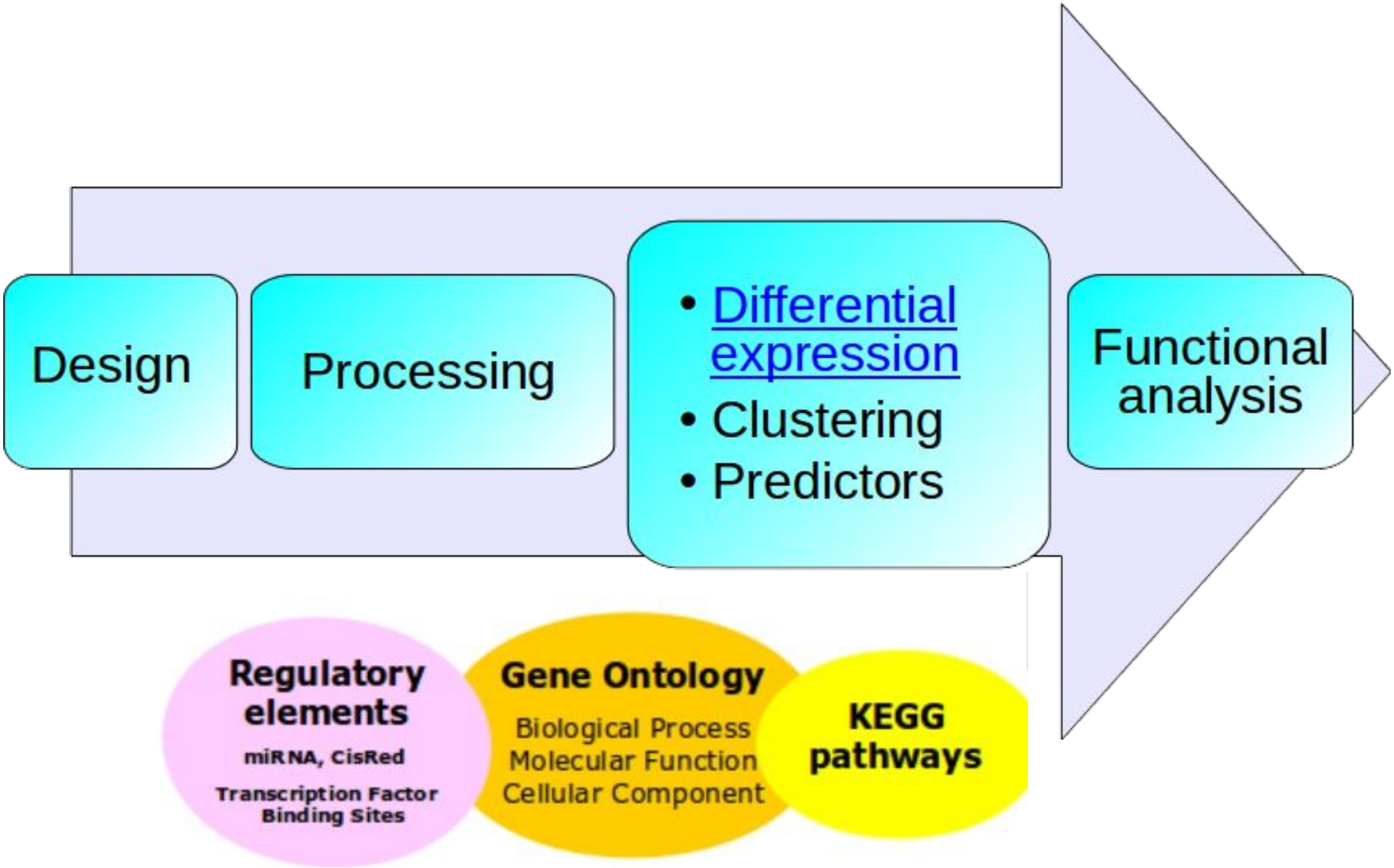
PRINCIPE FELIPE
CENTRO DE INVESTIGACION

WODA
WEB-BASED OMICS DATA ANALYSIS

Outline

- Introduction
- Over-Representation Analysis (ORA)
- Gene Set Analysis (GSA)
- Network Analysis (NA)

Omics data analysis pipeline



Design

Processing

- Differential expression
- Clustering
- Predictors

Functional analysis

Regulatory elements

miRNA, CisRed

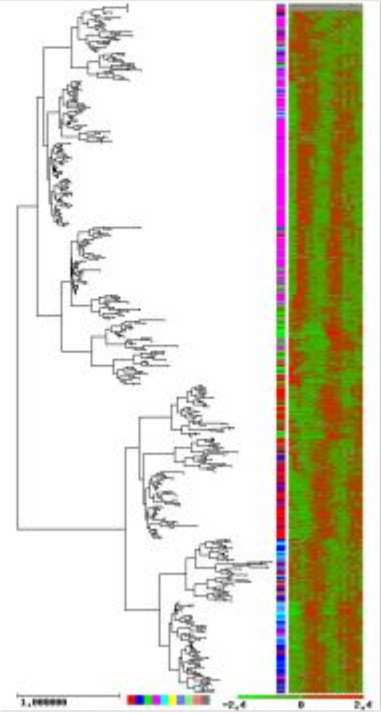
Transcription Factor Binding Sites

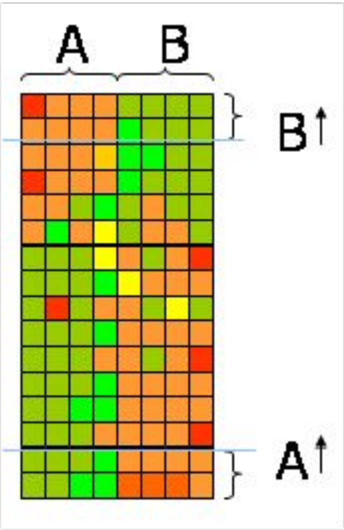
Gene Ontology

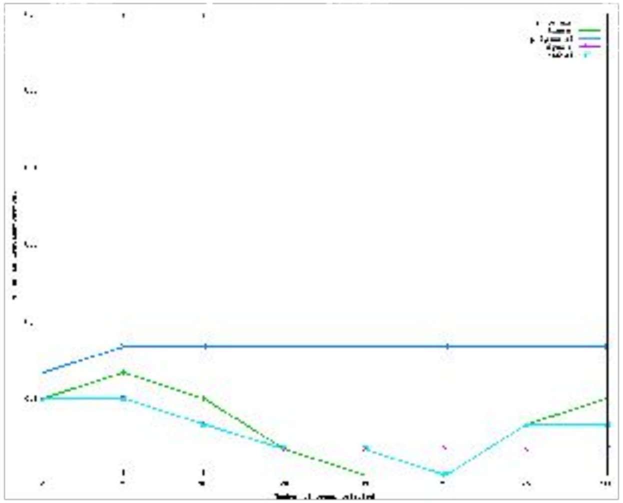
Biological Process
Molecular Function
Cellular Component

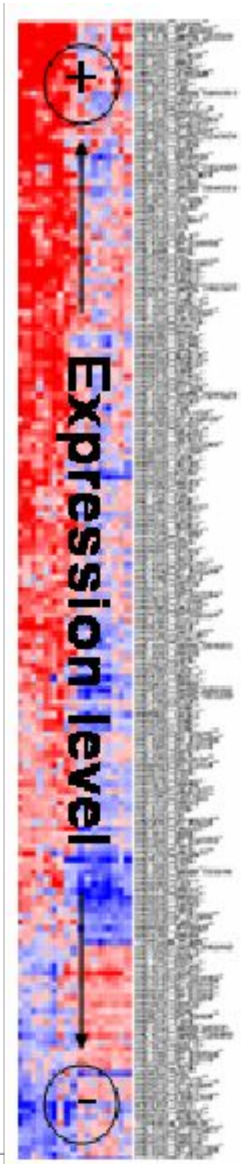
KEGG pathways

Genome-scale experiment output

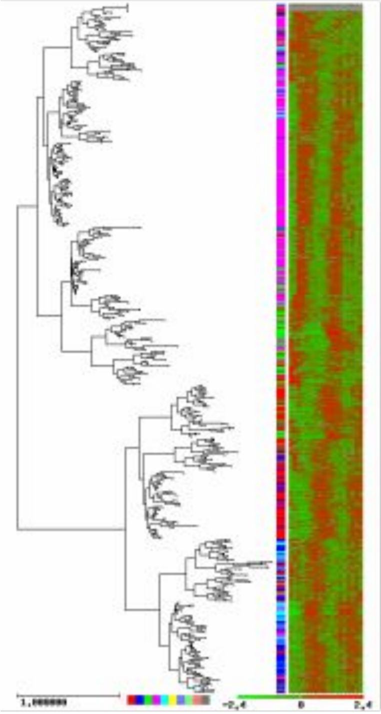




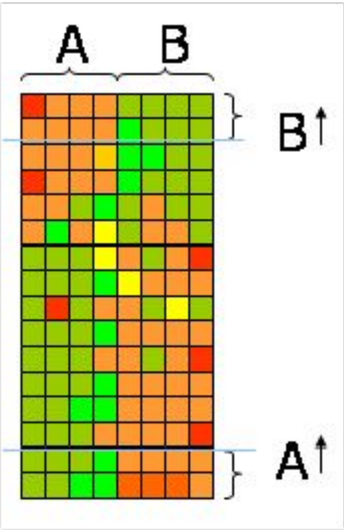




Genome-scale experiment output



BEST1
BRCA2
FIT
BRCA1



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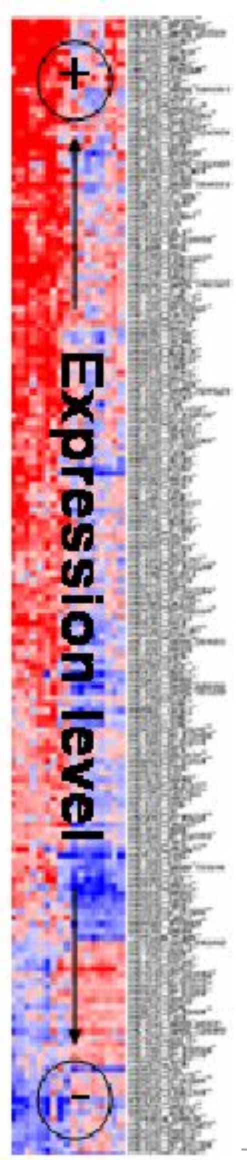
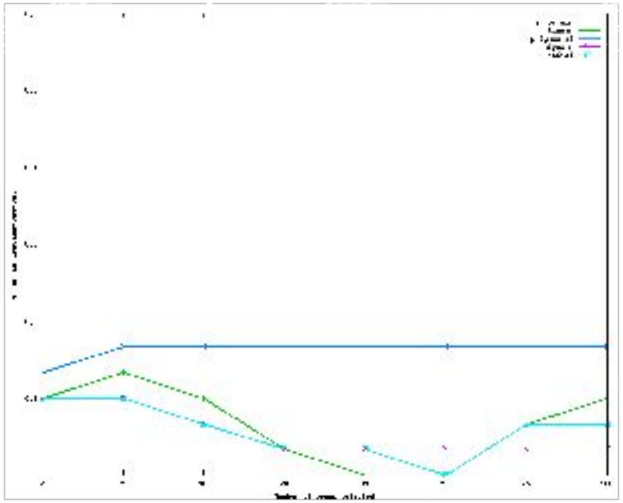
1053_at	11.5
117_at	10.3
121_at	10.2
1255_g_at	9.9
1294_at	9.3
1316_at	8.2
1320_at	8.1
1405_i_at	7.7
1431_at	7.4

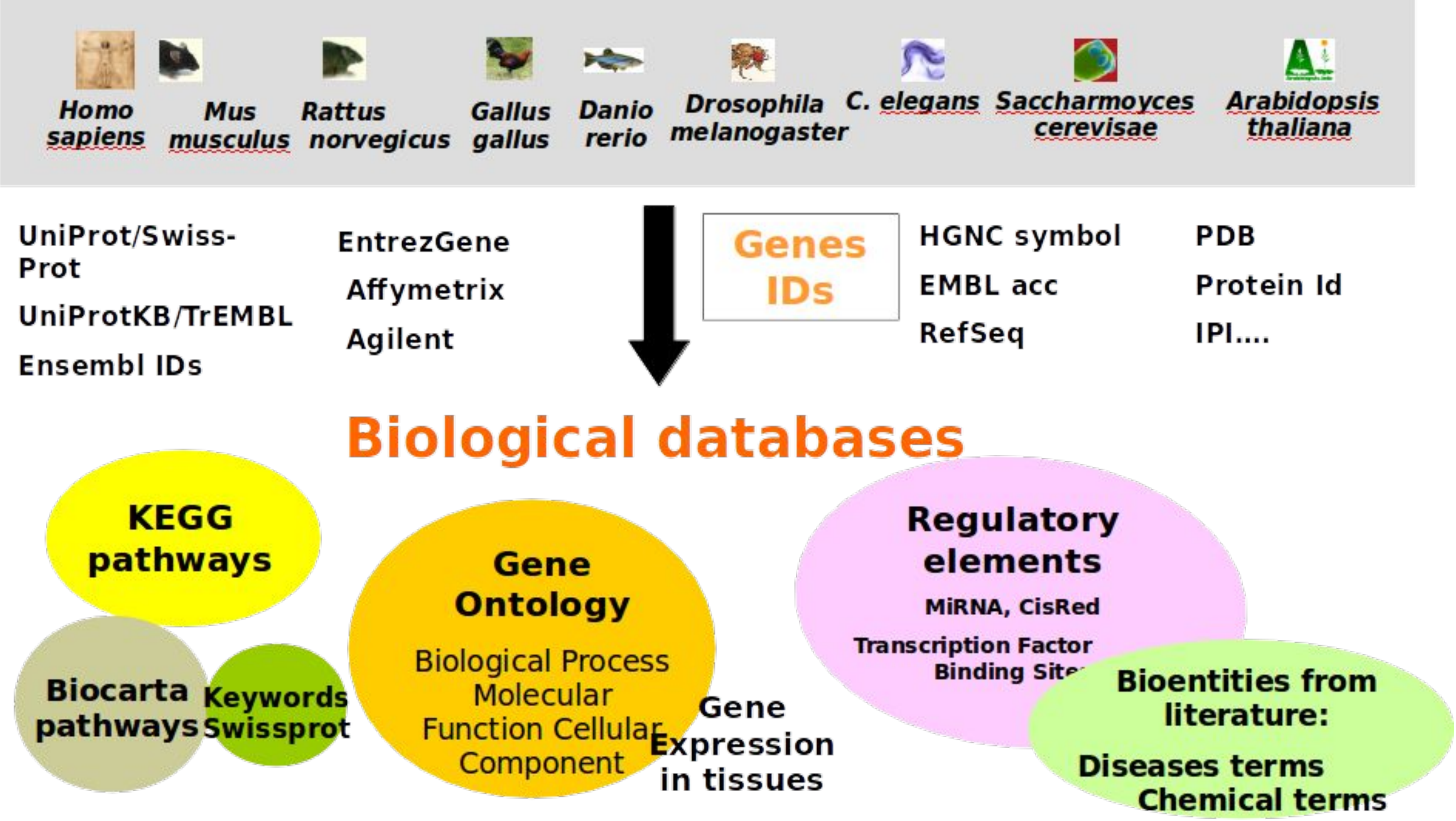




Questions we try to answer

- Is there any significant functional enrichment in my gene list / gene sets?
- Are these genes involved in common pathways?
- Do they share specific regulation?
- Are they involved in the same disease?

Functional databases



Homo sapiens *Mus musculus* *Rattus norvegicus* *Gallus gallus* *Danio rerio* *Drosophila melanogaster* *C. elegans* *Saccharmoyces cerevisae* *Arabidopsis thaliana*

UniProt/Swiss-Prot

UniProtKB/TrEMBL

Ensembl IDs

EntrezGene

Affymetrix

Agilent

Genes IDs

HGNC symbol

EMBL acc

RefSeq

PDB

Protein Id

IPI….

Biological databases

KEGG pathways

Biocarta pathways

Keywords Swissprot

Gene Ontology

Biological Process Molecular Function Cellular Component

Gene Expression in tissues

Regulatory elements

MiRNA, CisRed

Transcription Factor Binding Site

Bioentities from literature:

Diseases terms

Chemical terms

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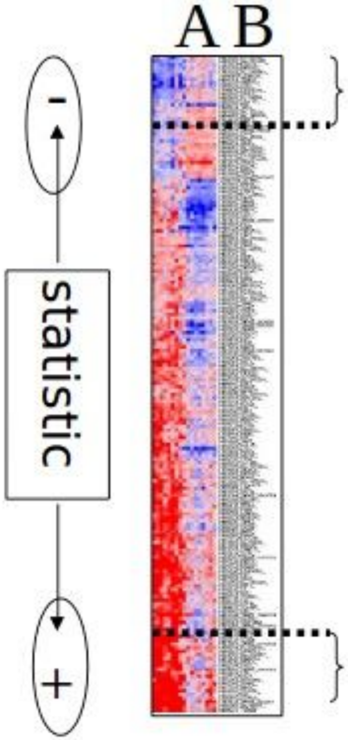
Over-Representation Analysis



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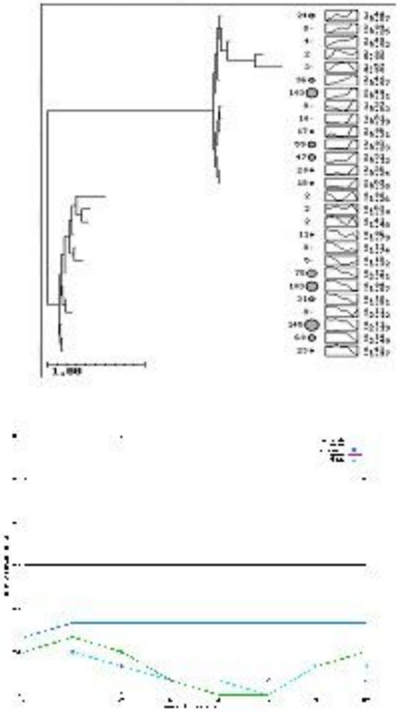

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1438_at
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160020_at
1729_at
1773_at
177_at
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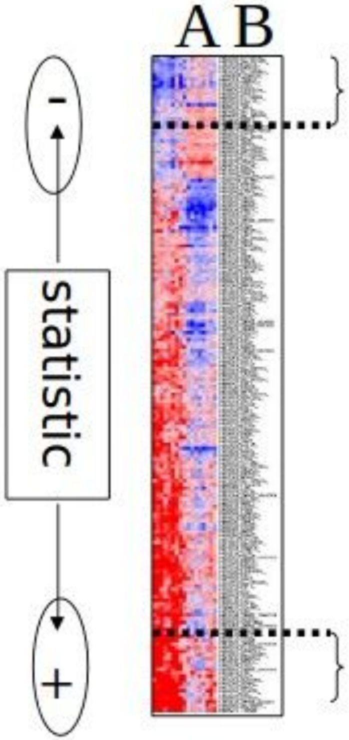
Over-Representation Analysis



1007_s_at
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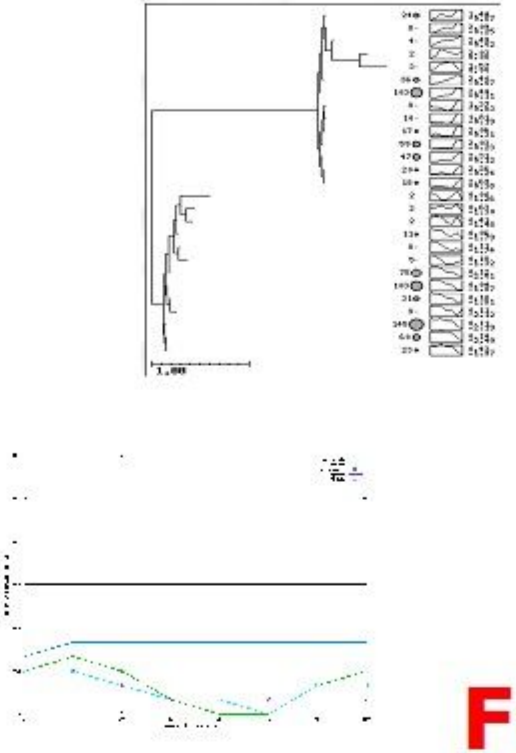
Function

4/7



1320_at
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1494_f_at
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177_at
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Function

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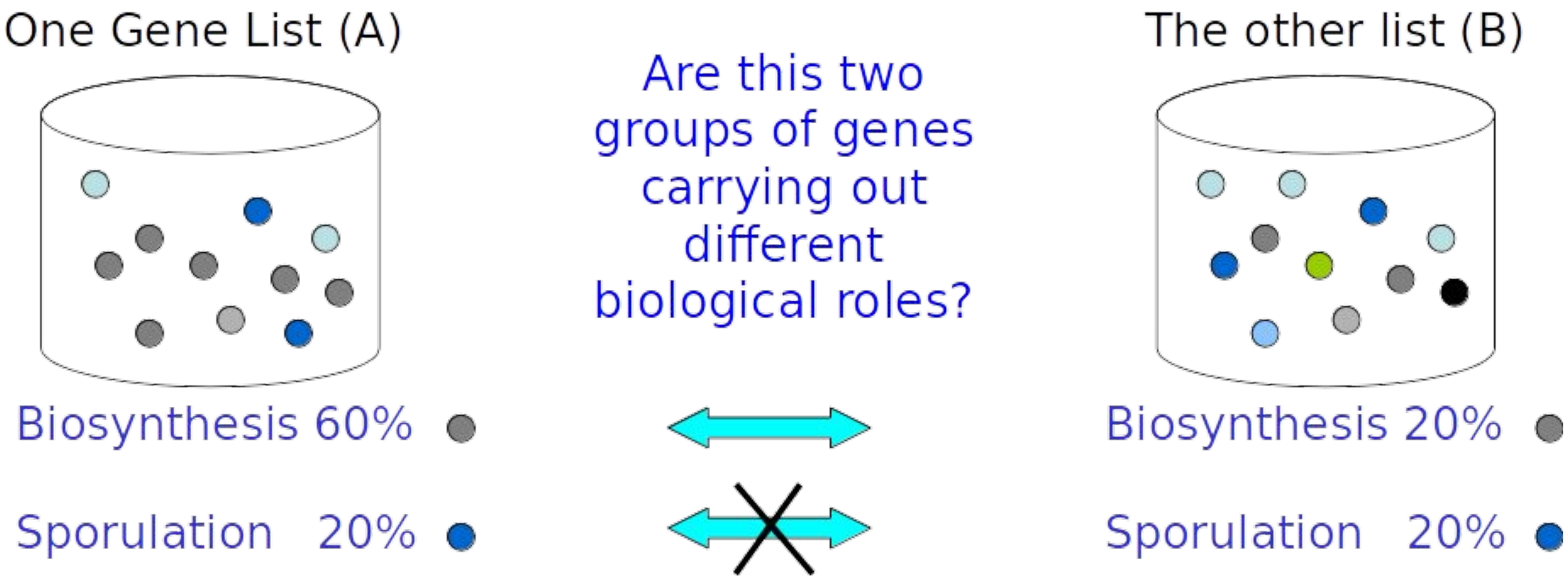
Over-Representation Analysis

FatiGO test



One Gene List (A)

The other list (B)

Are this two groups of genes carrying out different biological roles?

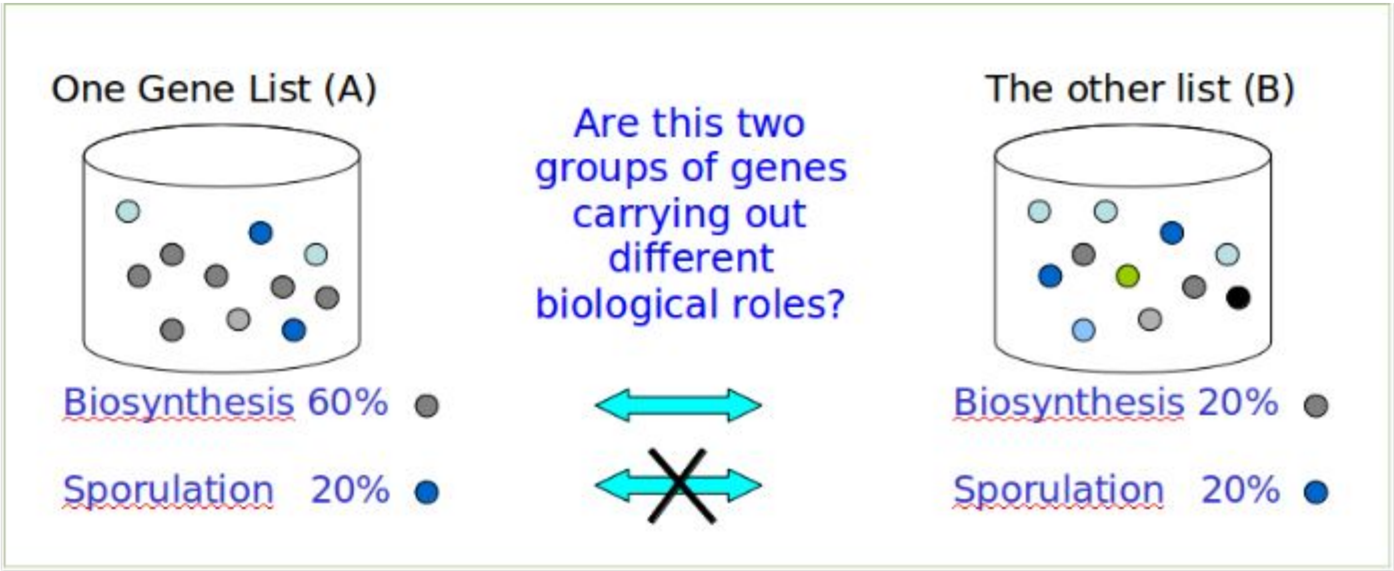
Biosynthesis 60% ●

Biosynthesis 20% ●

Sporulation 20% ●

Sporulation 20% ●

Over-Representation Analysis



Genes in group A have significantly to do with biosynthesis, but not with sporulation.

	A	B
Biosynthesis	**6**	**2**
No biosynthesis	**4**	**8**

We do this for each term (GO, miRNA, Interpro , ...)
Thousand of terms, so Multiple Test Correction is needed!!!

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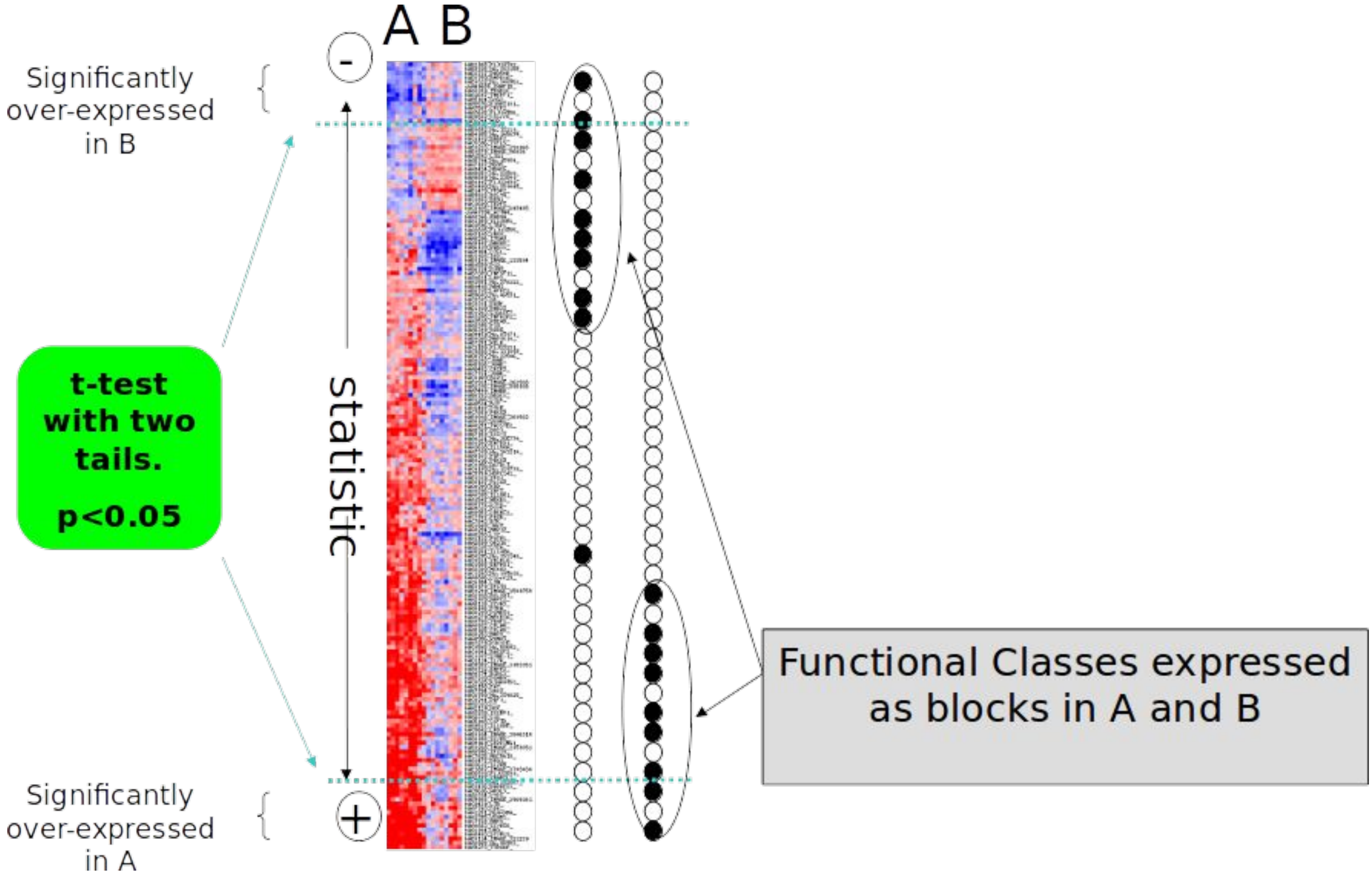
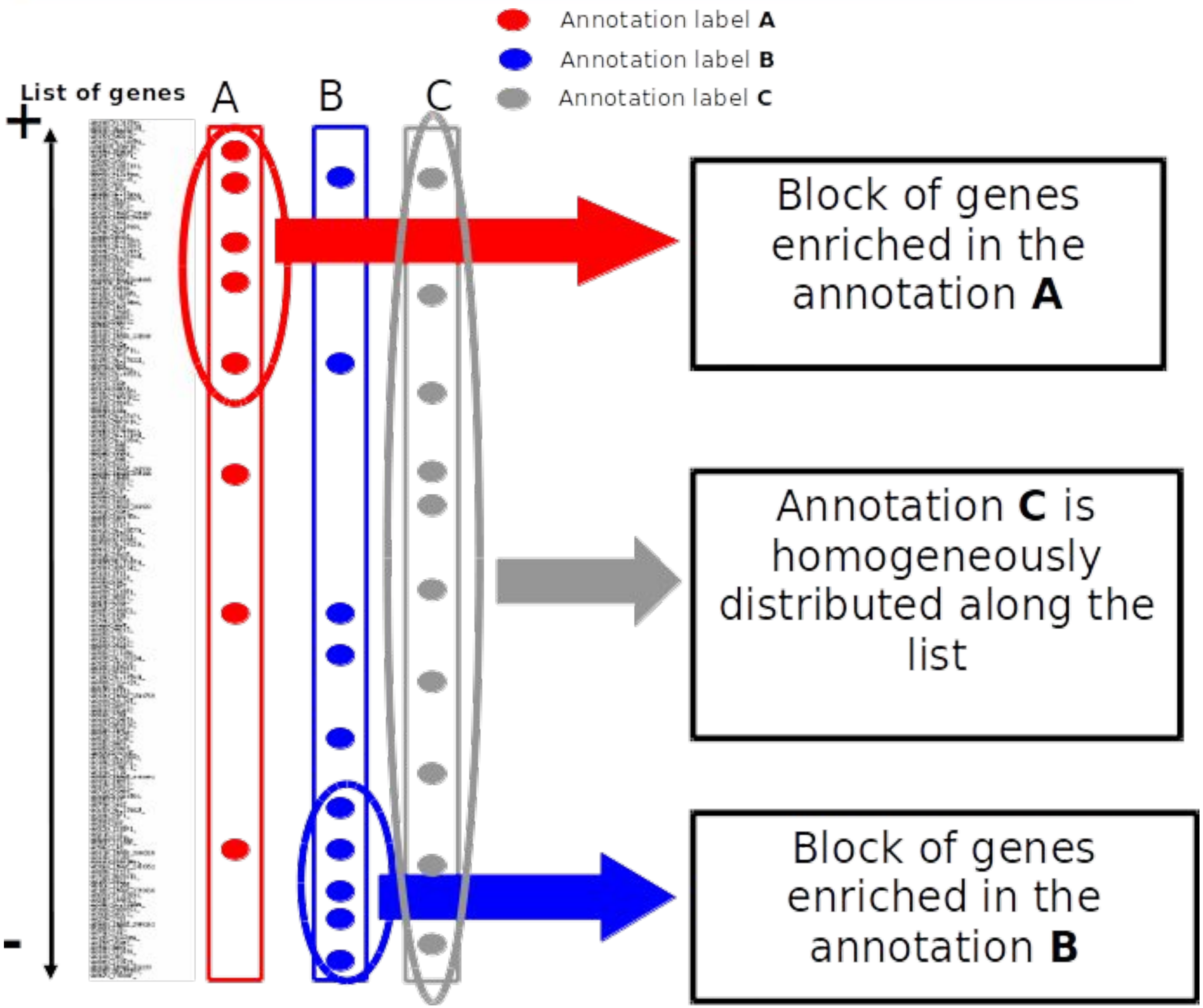
Gene Set Analysis



Gene Set Analysis



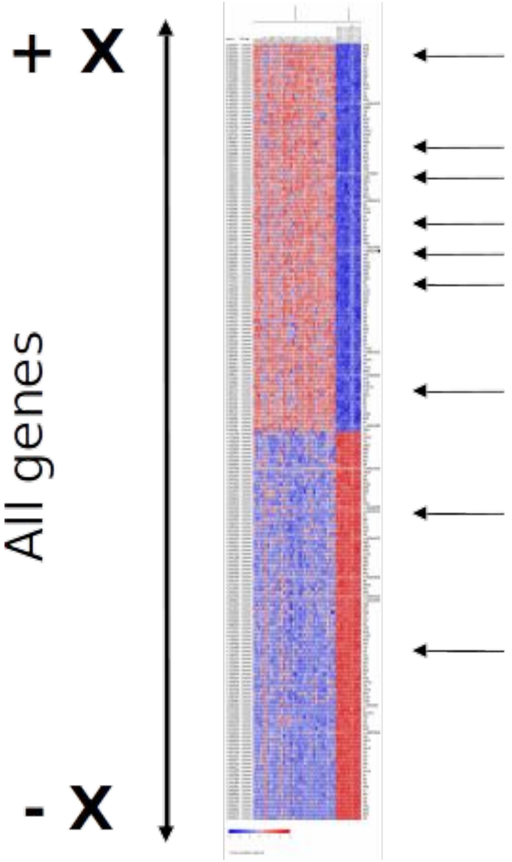
● Annotation label **A**
● Annotation label **B**
● Annotation label **C**

Block of genes enriched in the annotation **A**

Annotation **C** is homogeneously distributed along the list

Block of genes enriched in the annotation **B**

Gene Set Analysis



$$\ln\left(\frac{P(g\in F)}{P(g\notin F)}\right) = K + \alpha X$$

alpha > 0 : **increasing** X increases the probability of the gene to be annotated

alpha < 0 : **decreasing** X increases the probability of the gene to be annotated

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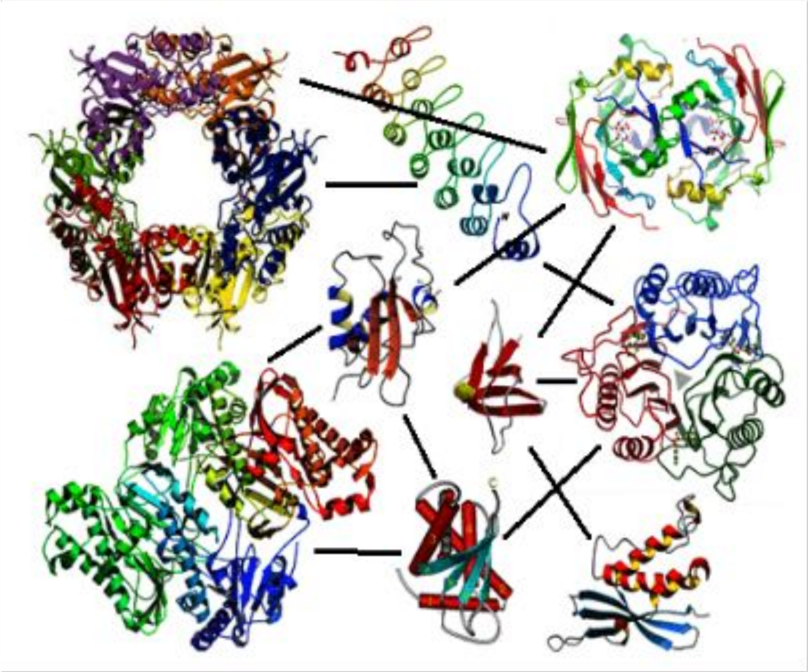
Protein-Protein Interactions (PPI)

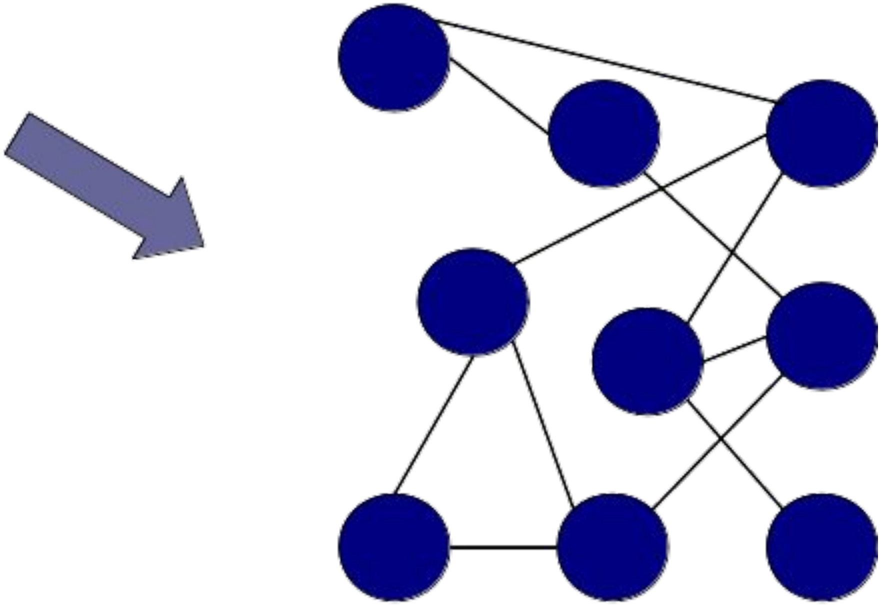
- How to extract information about **sets** of genes?
- How to perform **functional enrichment analysis** using protein-protein interactions as annotation source?
- How to **prioritize candidate genes**?
- How to get **new functional candidate genes**?

Graph Theory

Set of proteins interacting



Undirected graph



structured data

Nodes = proteins
Edges = interaction events

Graph Theory

Graph theory may help us to study protein networks.
Some interesting parameters:

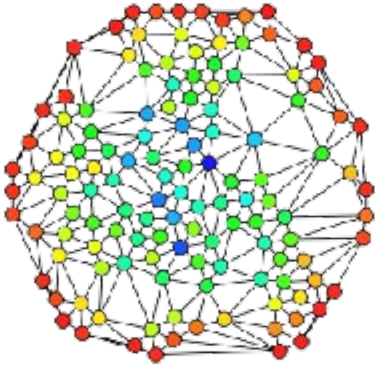
- **Degree (connectivity or connections)**: number of edges connected to a node. Nodes with high degree are called hubs.

- **Betweenness**: A measure of centrality of a node, it is defined by:

$$C_B(v) = \sum_{s\neq v\neq t\in V} \frac{\sigma_{st}(v)}{\sigma_{st}}$$

σ_{st} is total number of shortest paths in the graph.

$\sigma_{st}(V)$ is the number of shortest paths that pass through node V

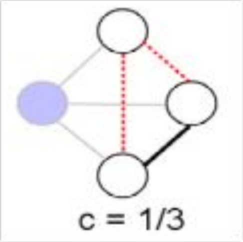


Graph Theory

- **Clustering coefficient** (of a node): A measure of how interconnected the neighbours of that node are. Proportion of links between the nodes within its neighbourhood divided by the number of links that could possibly exist between them.

$$C_i = \frac{2e_i}{n_i(n_i - 1)}$$

e_i is the number of edges among the nodes connected to node 1
n_i is the number of neighbours of node i



To differentiate between **star-shaped** nets and more **interconnected** nets.

Graph Theory

Some Graph Theory concepts:

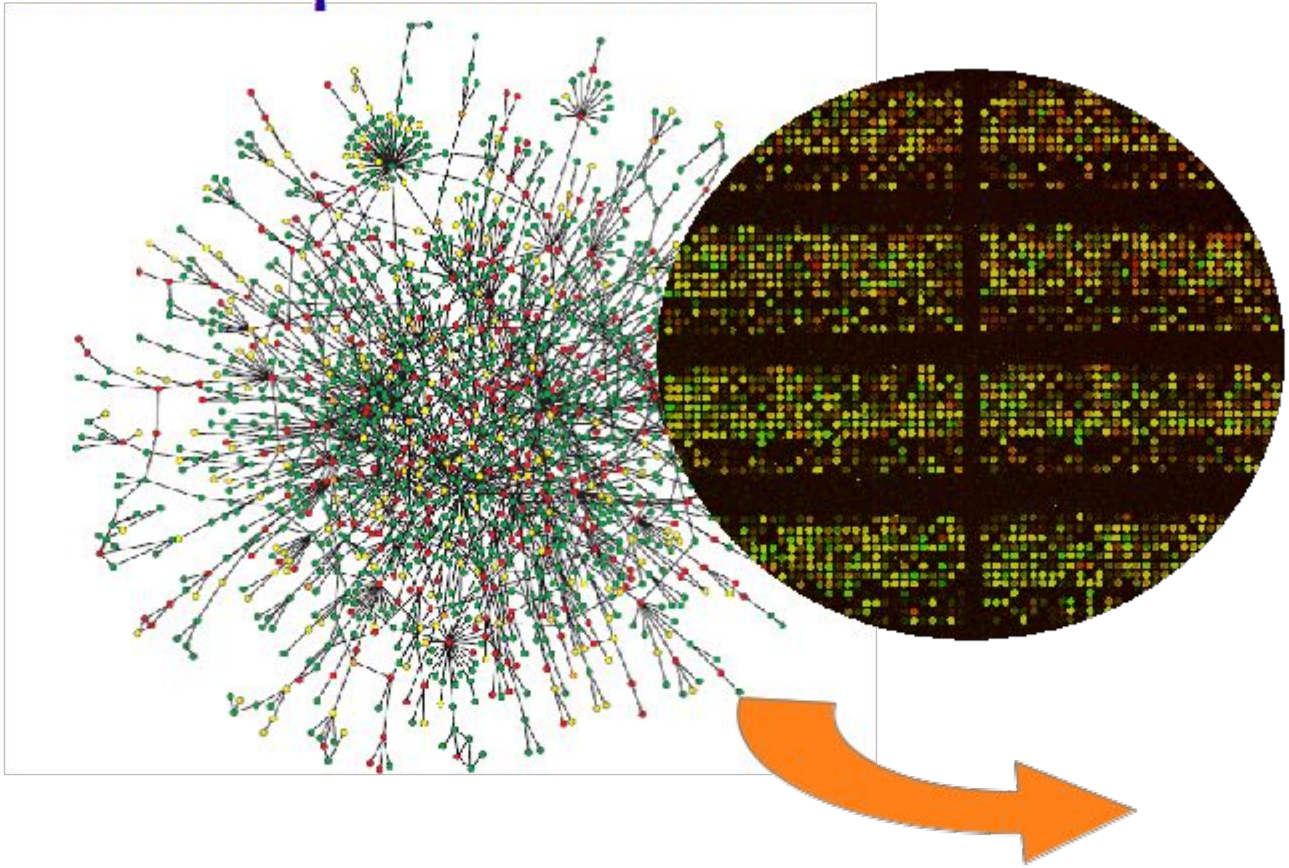
Shortest path. The path with less edges that connects two nodes.

Component. A group of nodes connected among them.

Bicomponent. A group of nodes connected to other group of nodes by only an edge. The edge that joins two bicomponents is called articulation point.

Interactome & Transcriptome

- **Interactome.** Complete collection of protein-protein interactions in the cell.
- **Transcriptome** determines the real interactome.



Set of
active
ppis

Interactome & Transcriptome

Goal

To develop a methodology that may extract from lists of proteins/genes the ppi networks acting and evaluates whether they have importance in the cooperative behaviour of the list.

How we evaluate the cooperative behaviour of a list of proteins/genes in terms of its ppi network parameters?

Two different approximations:

- Importance in **complete interactome**
- Cooperative behaviour - **Minimal Connected Network**

Any question?