Gene interaction networks inference and search for complex disease biomarkers by complex networks analysis and data integration

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Summary

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About UFABC

- Universidade Federal do ABC (Federal University of ABC - UFABC)
- 9 years old university
- Growing fast! ($\sim$ 12,000 undergrad students, $\sim$ 1,500 grad students, $\sim$ 550 professors)
- Interdisciplinarity as key to perform relevant science
- Research quality 60% superior to the world average in terms of impact factor (# 1 in Brazil)
- Strong internationalization (# 1 in Brazil)

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Systems Biology

- Systems Biology: interdisciplinary field which studies the complex networks of interactions occurring in biological systems
- Development of models and approaches to reveal emergent properties of cells, tissues and organs, which work as an integrated system
- Tipically involves studies of several types of biological networks (gene regulation, metabolic, protein interactions, cell signaling, etc...)
- Integration and analysis of massive, complex and heterogeneous datasets (Big Data)

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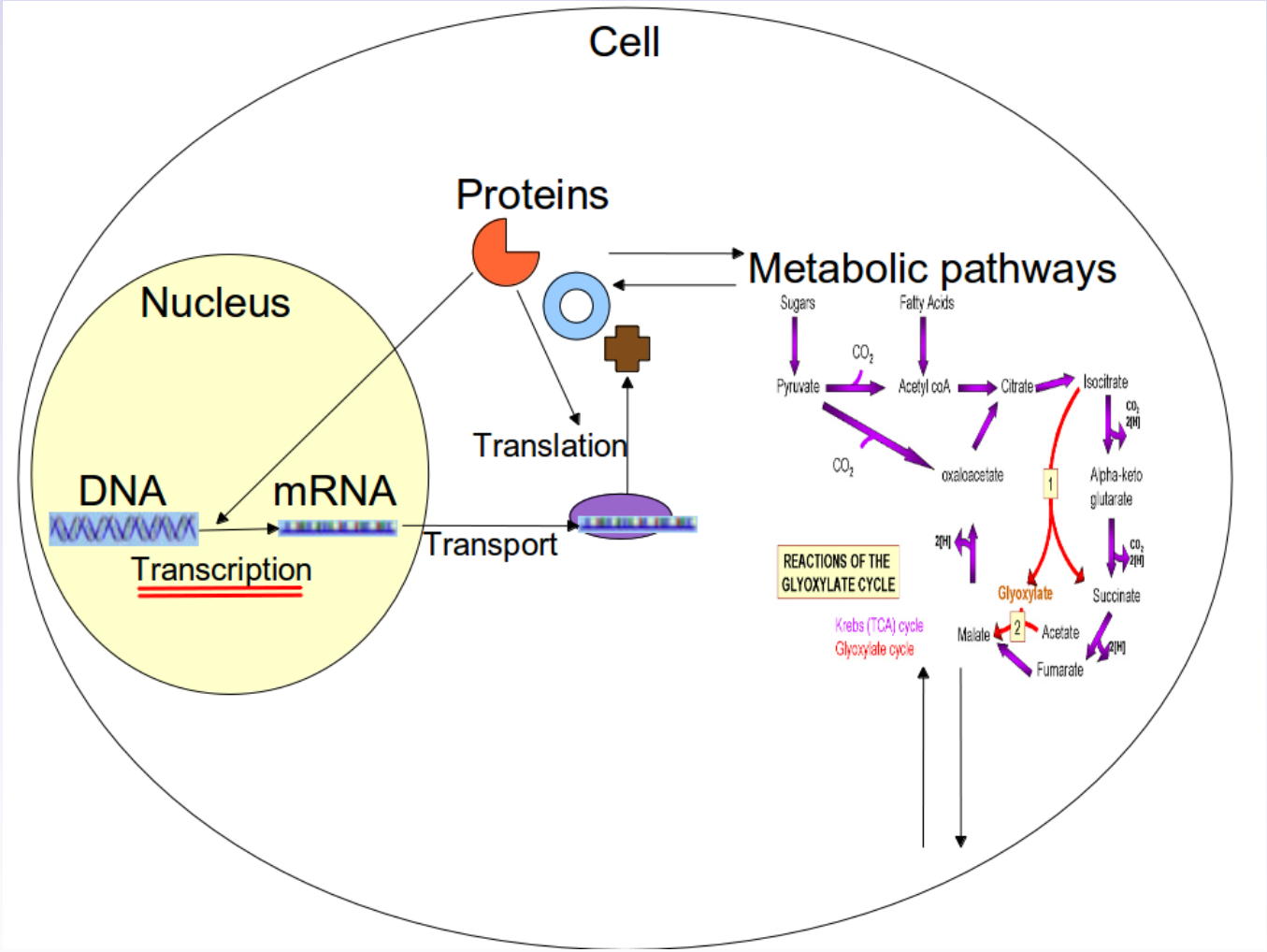

Two main research topics in Systems Biology

- Inference, modeling and simulation of gene regulatory networks (GRN)
- Prioritization of genes associated to complex diseases

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GRN inference - Motivation

- Cell control: result of a multivariate activity of genes
- Derivation of general laws on how the cell control works
- Identification of genes associated to certain biochemical features
- Investigation on how to control the dynamics of the biological system and the best way to do it (most practical, least costly, ...)
- Inference of parameters of a GRN from experimental data is one of the greatest challenges of bioinformatics
  - Small number of samples (dozens) with huge dimensionality (thousands of genes)

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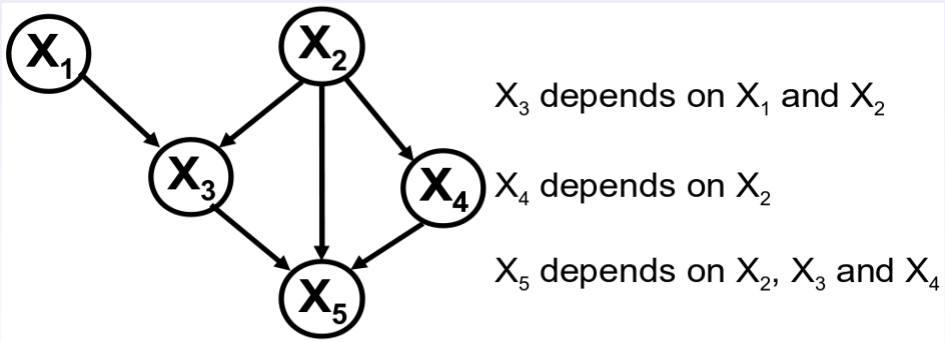
GRN inference - Definition

- GRNs are gene interaction networks where the expression level of a gene is controlled by expression levels of other genes
  - Gene expression signal: abundance of transcribed mRNA
  - They can be viewed as graphs where nodes correspond to genes and edges correspond to dependences between genes



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GRN inference - Approach: feature selection

- How to measure the degree of dependence of a gene with regard to other genes?
  - Feature selection
  - Given a target gene, apply a feature selection (search) algorithm which tries to obtain the most relevant genes subset to describe the target behavior
  - Relevance criterion: e.g., mutual information (based on entropy), coefficient of determination (Bayesian error based)

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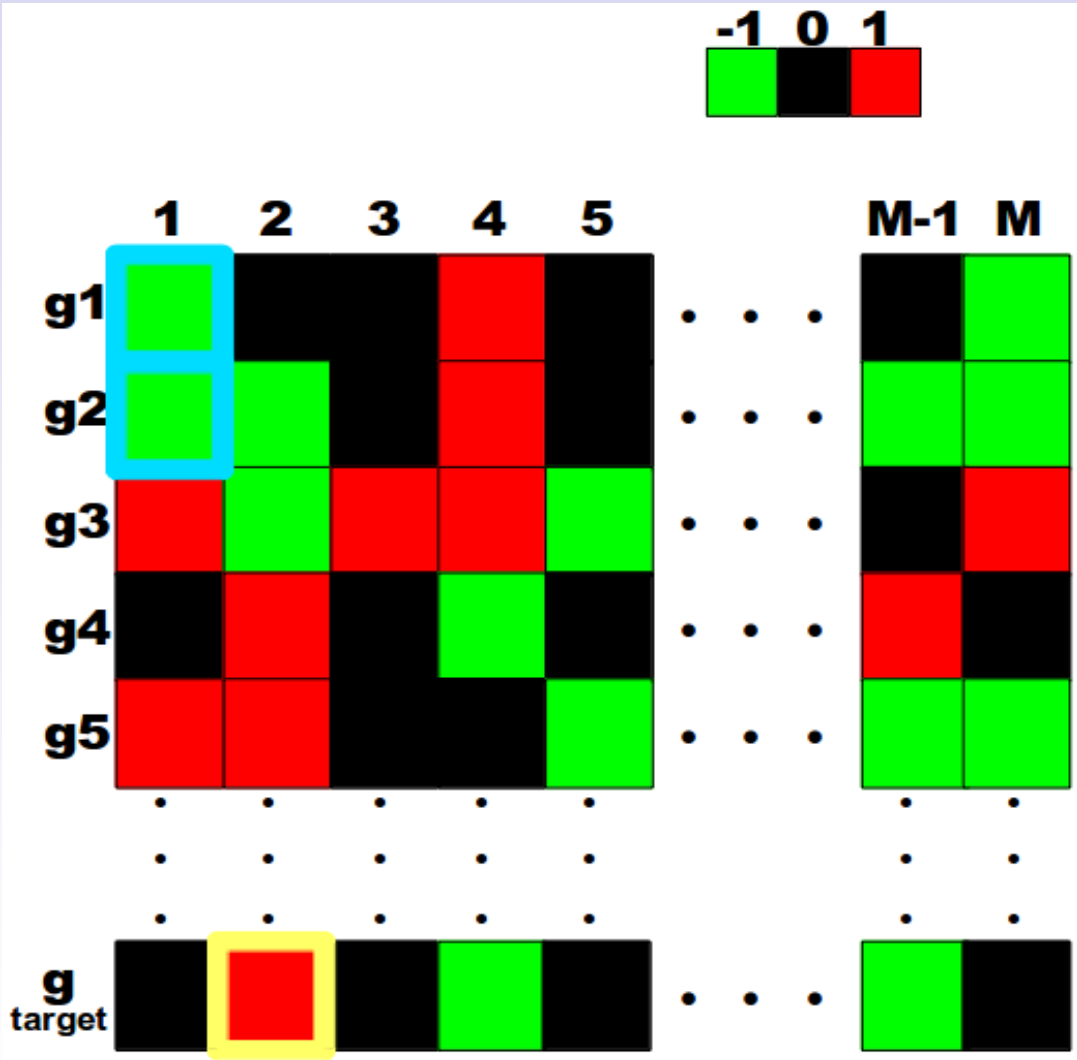

g1	g2	g target −1	0	1
−1	−1	0	0	**1**
−1	0	0	0	0
−1	1	0	0	0
0	−1	0	0	0
0	0	0	0	0
0	1	0	0	0
1	−1	0	0	0
1	0	0	0	0
1	1	0	0	0

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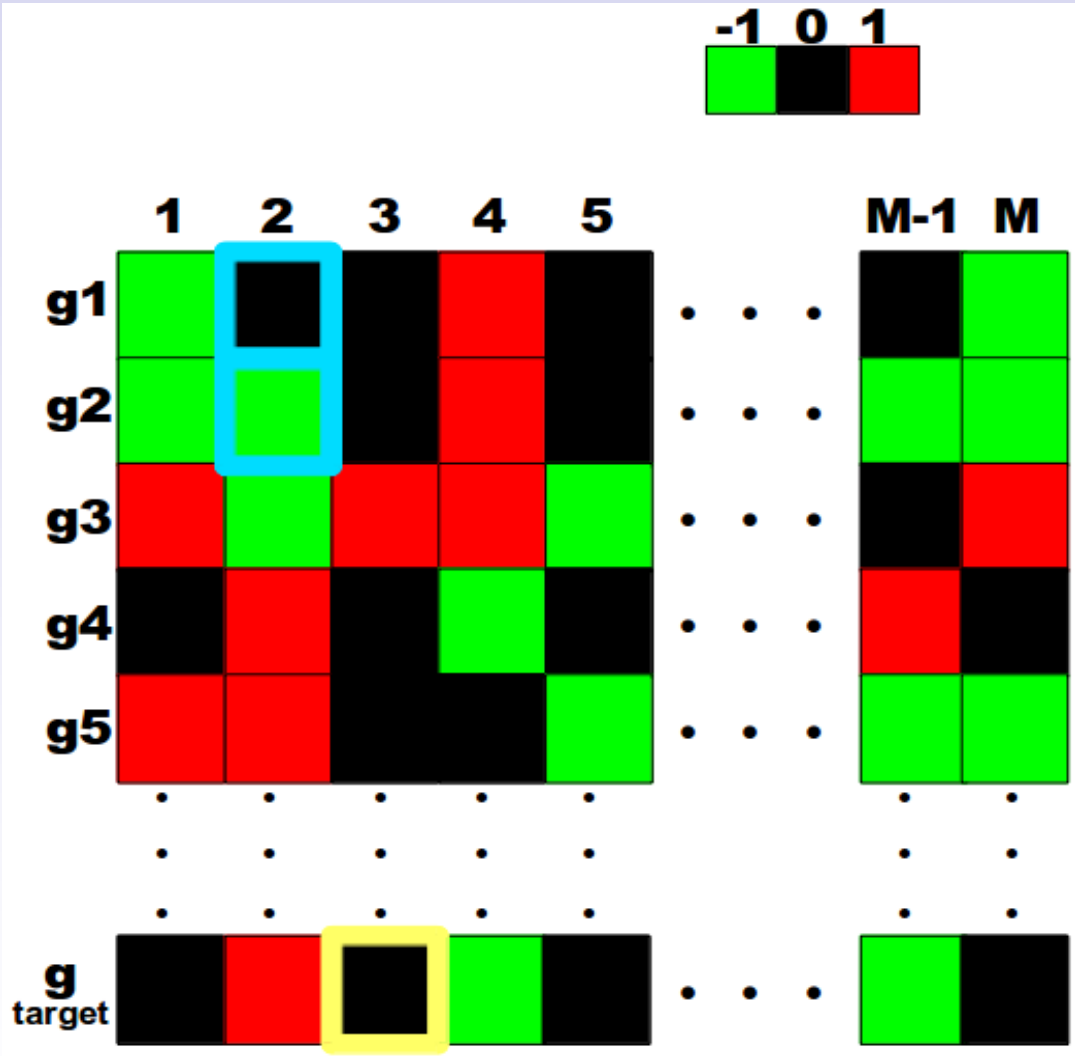
GRN inference - Approach: feature selection



g1	g2	g target −1	0	1
−1	−1	0	0	1
−1	0	0	0	0
−1	1	0	0	0
0	−1	0	**1**	0
0	0	0	0	0
0	1	0	0	0
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1	0	0	0	0
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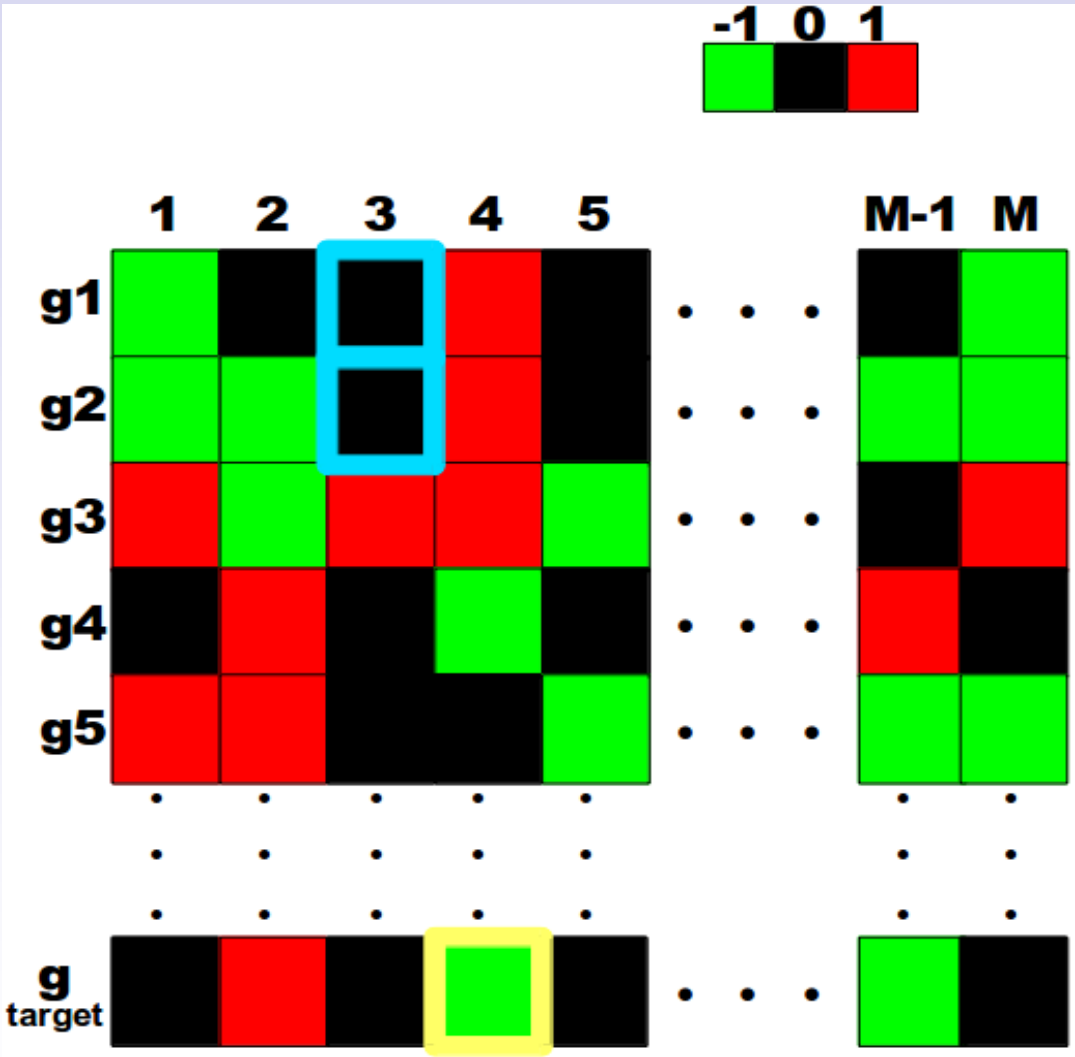

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−1	0	0	0	0
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0	−1	0	1	0
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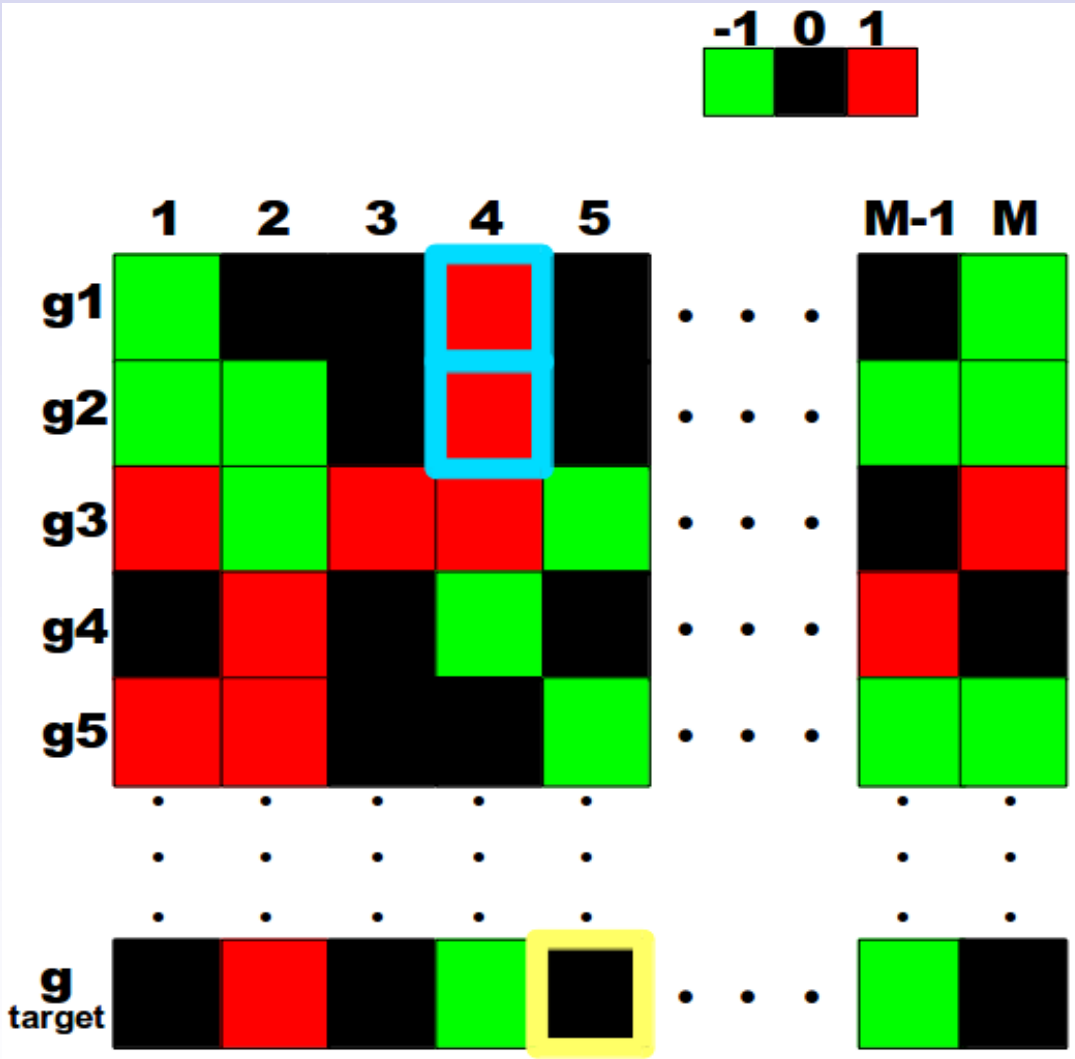

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−1	−1	0	0	1
−1	0	0	0	0
−1	1	0	0	0
0	−1	0	1	0
0	0	1	0	0
0	1	0	0	0
1	−1	0	0	0
1	0	0	0	0
1	1	0	**1**	0

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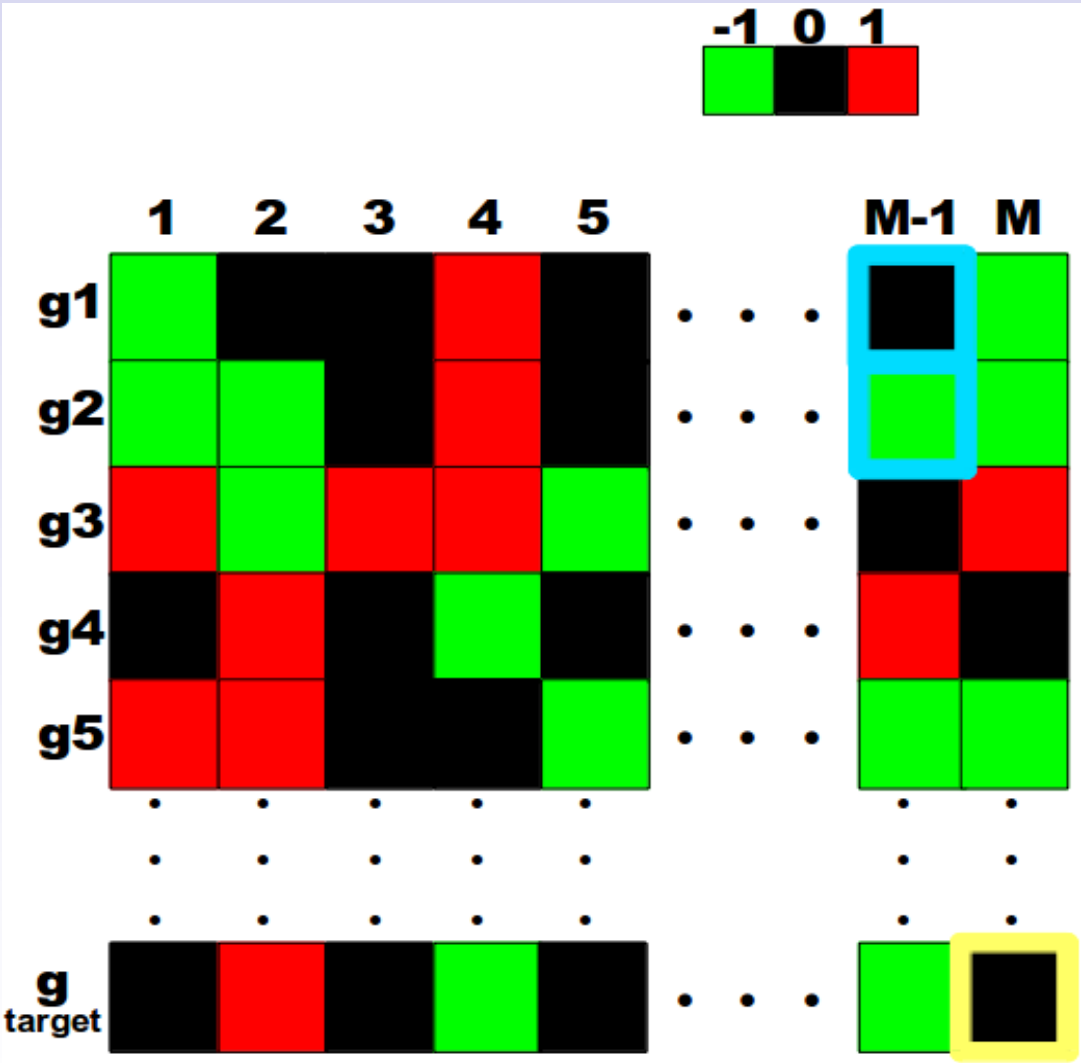
GRN inference - Approach: feature selection



g1	g2	g target −1	0	1
−1	−1	0	0	6
−1	0	7	0	0
−1	1	0	4	0
0	−1	0	9	0
0	0	5	0	0
0	1	0	0	1
1	−1	0	0	7
1	0	0	0	0
1	1	8	0	0

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GRN inference - Approach: feature selection

g1	g2	g target −1	0	1
−1	−1	0	1	6
−1	0	7	0	0
−1	1	0	4	0
0	−1	0	9	0
0	0	5	0	0
0	1	0	0	1
1	−1	0	0	7
1	0	0	0	0
1	1	8	0	0

Properties of the pair (g1,g2)

- **High** mutual information / CoD
- **Almost perfect** prediction
- **Strong candidate** to be classified between the best pairs (g1 and g2 may be connected to the target gene)

g3	g5	g target −1	0	1
−1	−1	2	2	2
−1	0	3	2	2
−1	1	0	3	1
0	−1	2	4	3
0	0	1	1	2
0	1	1	0	1
1	−1	2	3	1
1	0	1	1	0
1	1	4	2	2

Properties of the pair (g3,g5)

- **Small** mutual information / CoD
- **Very bad** prediction
- **Discarded**

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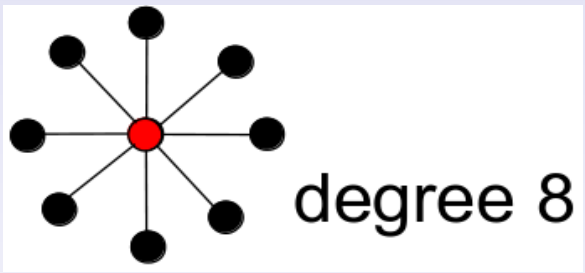
GRN inference - Ongoing research

- How to infer “hubs” from small samples? (and how to decide its input degree?)
  - Hub: gene with large input degree



  - In binary systems, a gene with degree 8 has a table with $2^8 = 256$ rows
  - If we have 30 samples, at least 226 rows are not observed (!!!)

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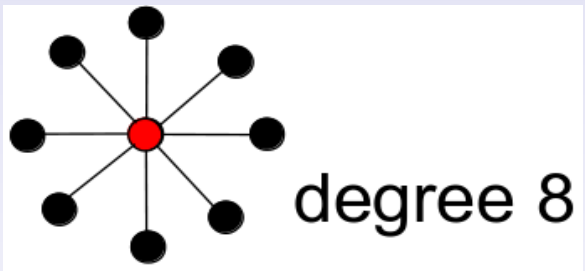

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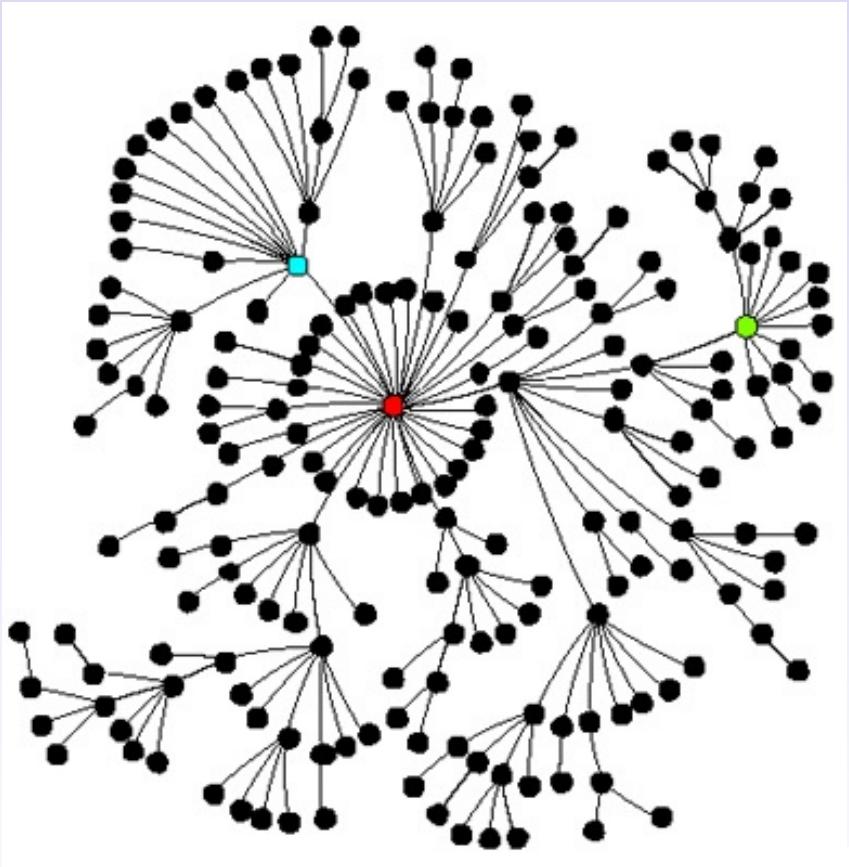
GRN inference - Ongoing research

- In particular, inference of hubs is important to infer scale-free networks
  - Small number of nodes with large input degree
  - Large number of nodes with small input degree
- Also known as Barabási-Albert (BA) network model [Barabasi:2004]



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GRN inference - SFFS-BA method

- SFFS-BA: GRN inference method guided by topological scale-free properties [Lopes:2014]

Information Sciences 272 (2014) 1–15

Contents lists available at ScienceDirect

Information Sciences

journal homepage: www.elsevier.com/locate/ins

A feature selection technique for inference of graphs from their known topological properties: Revealing scale-free gene regulatory networks

Fabrício M. Lopes [a,*], David C. Martins Jr. [b], Junior Barrera [c], Roberto M. Cesar Jr. [c,d]

[a] Federal University of Technology - Paraná, Brazil
[b] Federal University of ABC, Brazil
[c] Institute of Mathematics and Statistics, University of São Paulo, Brazil
[d] Brazilian Bioethanol Science and Technology Laboratory (CTBE), Brazil

GRN inference - SFFS-BA (summary and results)

- Adaptation of a classical feature selection method (Sequential Floating Forward Search - SFFS) to look for scale free patterns $\rightarrow$ SFFS-BA
- Comparison involving Sequential Forward Search (SFS), SFFS and SFFS-BA
- Evaluation by simulated artificial gene networks (AGN) generating scale-free topologies and probabilistic Boolean dependences
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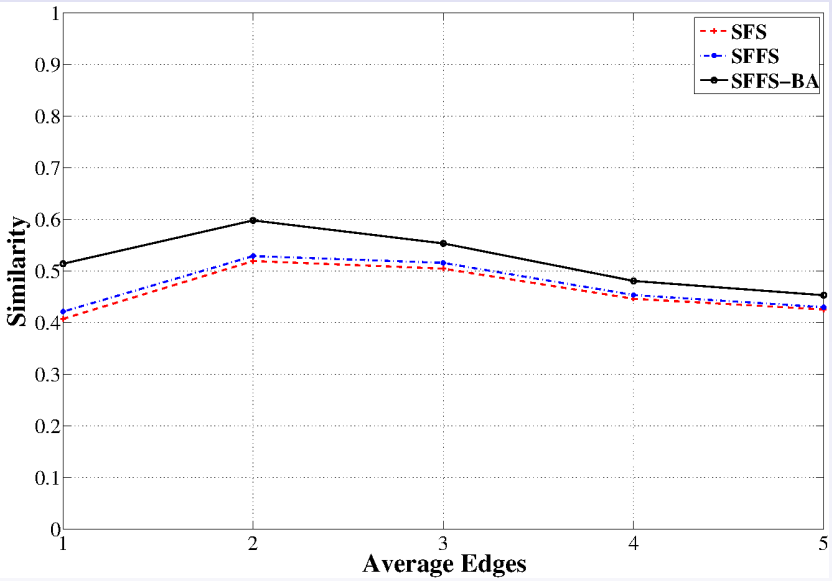
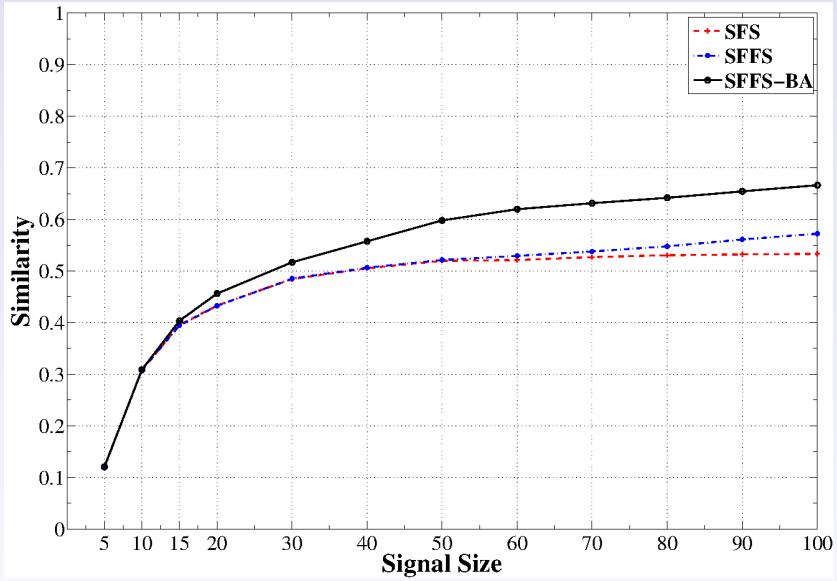
GRN inference - SFFS-BA (summary and results)

- Artificial gene networks results





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GRN inference - SFFS-BA (summary and results)

- *E. coli* results

Algorithm	*PPV*	*Sensitivity*	*Similarity*	*AUPR*(%)
SFS	0.1598	0.0169	0.0520	0.0488 (4.88%)
SFFS	0.2416	0.0315	0.0872	0.0629 (6.29%)
SFFS-BA	0.4878	0.0484	0.1537	0.0786 (7.86%)

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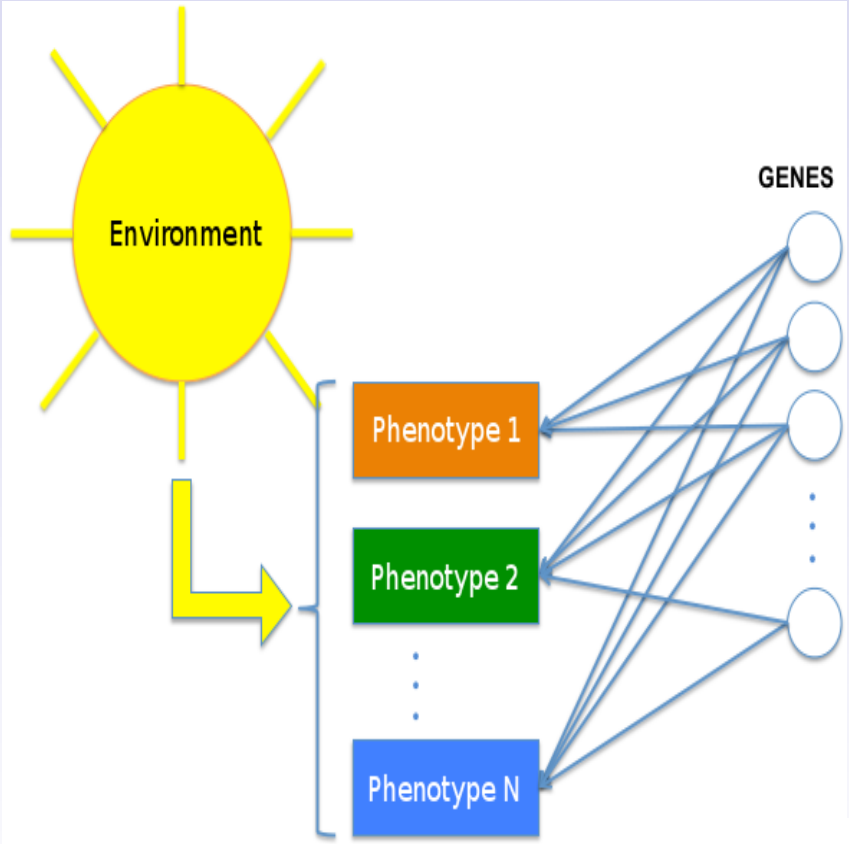
Complex diseases

- Complex diseases are polygenic and multifactorial
- Many genes can cause the same phenotype
- A single gene can cause distinct phenotypes
- → studies in complex diseases are challenging
- Distinct studies of a given complex disease usually produce gene lists with very small overlap (small replication)
- Integrative approaches from systems biology, as well as modeling and analysis of complex networks are required



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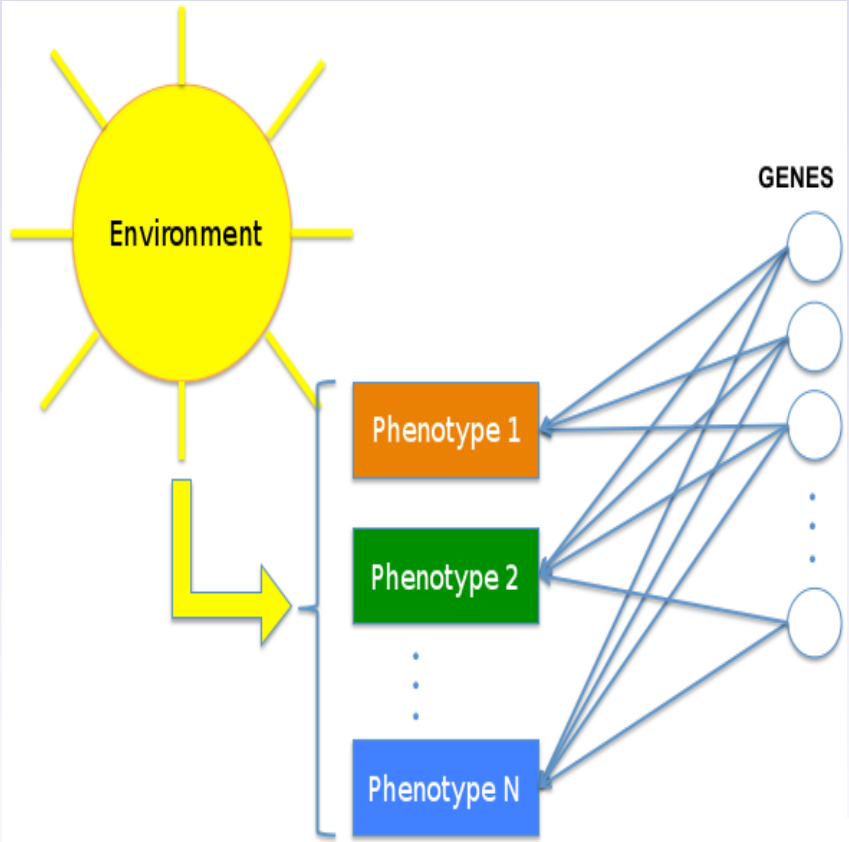

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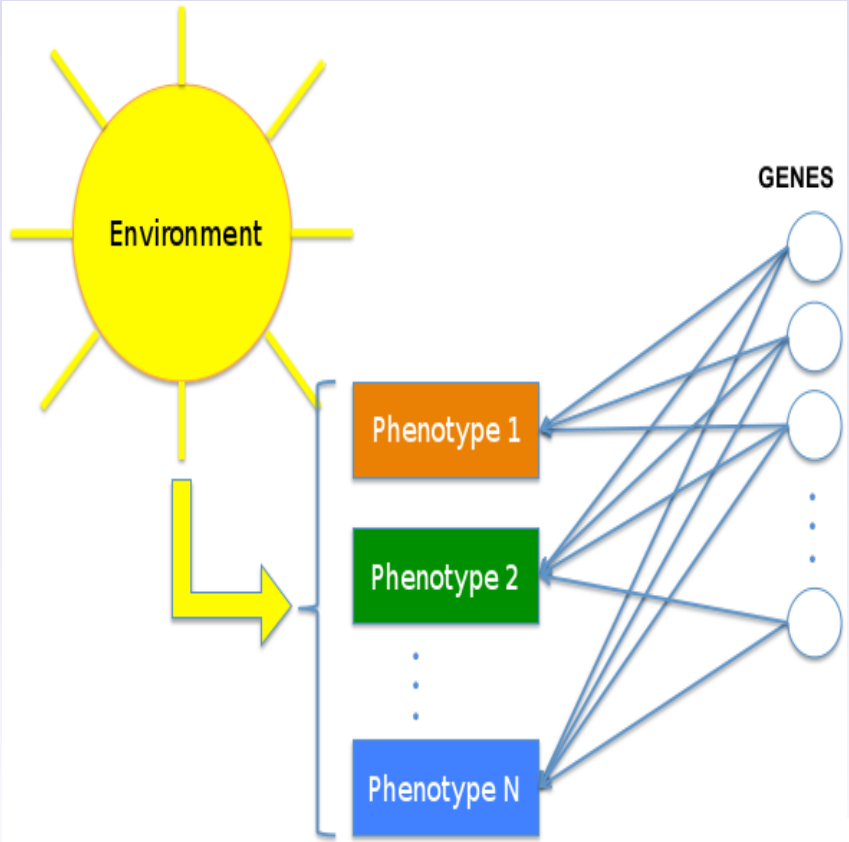

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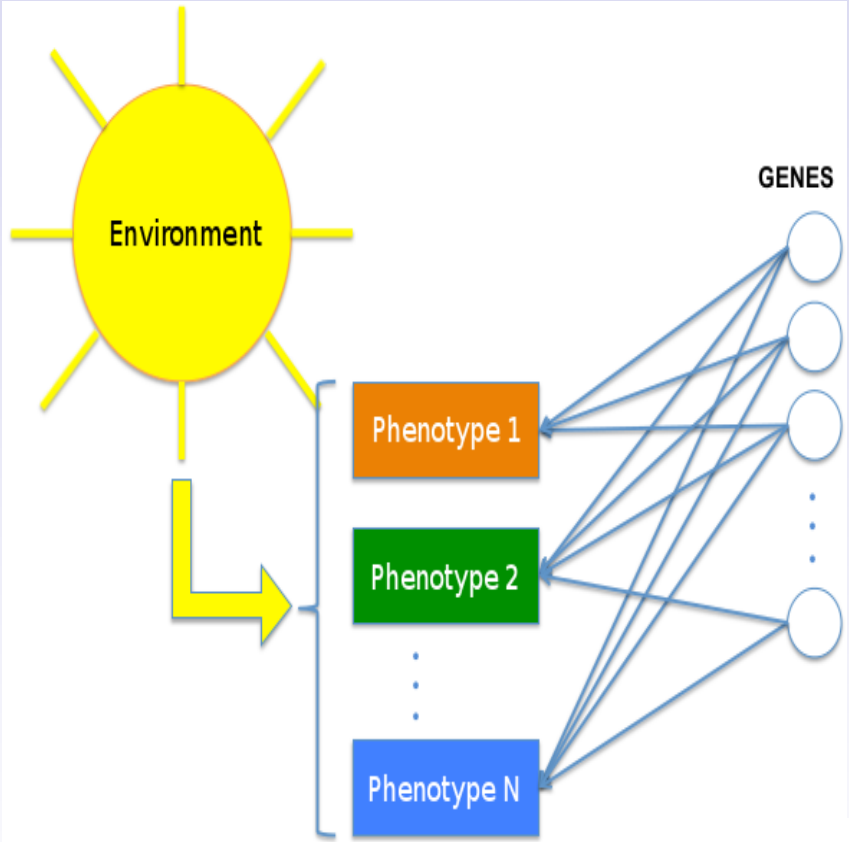

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Network Medicine hypotheses [Barabási:2011]

- Modeling of complex network theory properties and Network Medicine hypotheses to prioritize genes
- Hubs: genes/proteins of high degree are considered essential (e.g. TP53)
- Locality Hypothesis: Genes/proteins involved in the same function (or disease phenotype) possess increased tendency to interact with each other
- Modularity Hypothesis: Cellular components associated to a given function (or disease specific phenotype) tend to be in the same cluster
- Parsimony Principle: Molecular pathways usually coincide with the molecular shortest paths between components known to be associated to the disease.

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NERI method

- NERI: NEtwork Medicine Relative Importance [Simões:2015]

Simões *et al. BMC Bioinformatics* 2015, **16**(Suppl 19):S9
http://www.biomedcentral.com/1471-2105/16/S19/S9

BMC Bioinformatics

RESEARCH Open Access

NERI: network-medicine based integrative approach for disease gene prioritization by relative importance

Sérgio N Simões[1,2*], David C Martins Jr[3], Carlos AB Pereira[1], Ronaldo F Hashimoto[1], Helena Brentani[4,5,6]

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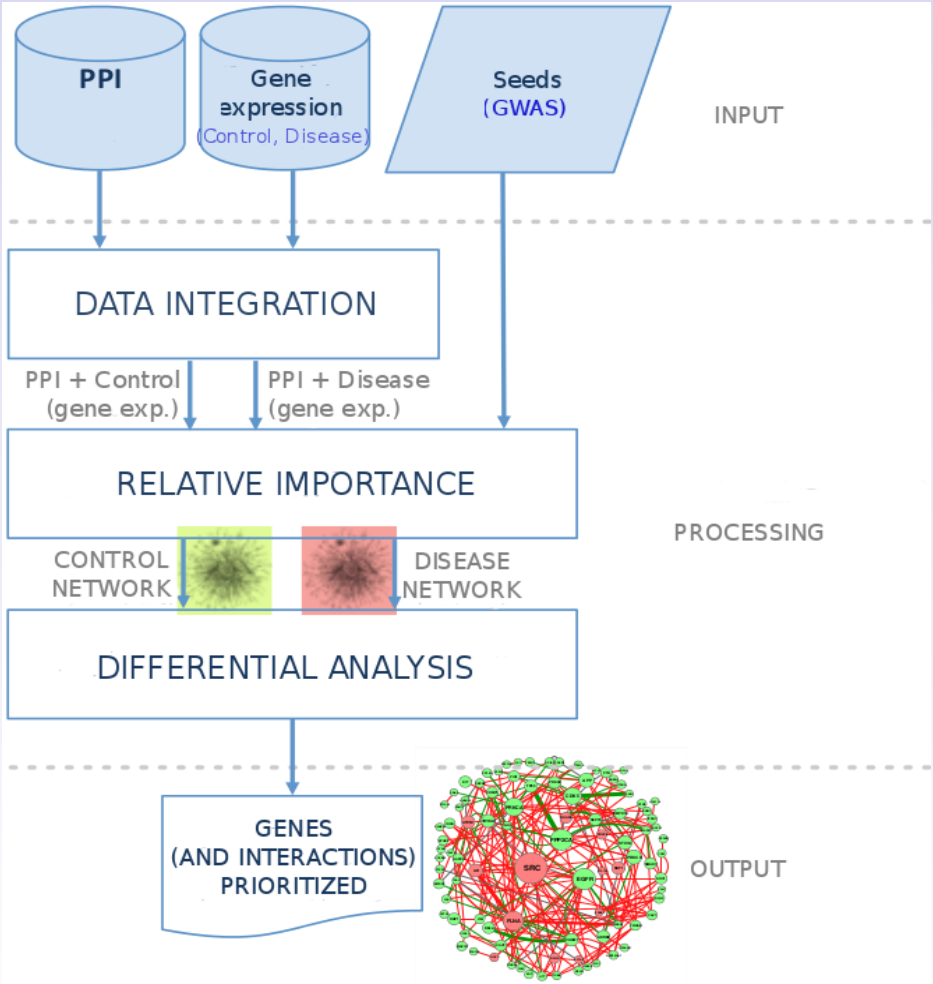
NERI method - Overview



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NERI method - Overview

- Modeling the locality, modularity and parsimony hypotheses
- Integration of seeds (genome-wide association studies - GWAS), gene expression and protein-protein interaction networks (PPI) data
- Obtainment of two PPI network cuttings around the neighborhood of the seeds: one for control and one for disease conditions
- Cutting: best shortest paths (according to gene expression concordance) connecting the seeds
- Two relative importances are assigned to each gene: one for control and another for disease condition
- Relative importance: mix of fequency along the shortest paths between seeds, concordance of expression along these paths and proximity to the seeds
- Genes with the largest difference in their two relative importances (control/disease) are prioritized

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NERI method - Overview

- Modeling the locality, modularity and parsimony hypotheses
- Integration of seeds (genome-wide association studies - GWAS), gene expression and protein-protein interaction networks (PPI) data
- Obtainment of two PPI network cuttings around the neighborhood of the seeds: one for control and one for disease conditions
- Cutting: best shortest paths (according to gene expression concordance) connecting the seeds
- Two relative importances are assigned to each gene: one for control and another for disease condition
- Relative importance: mix of fequency along the shortest paths between seeds, concordance of expression along these paths and proximity to the seeds
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NERI method - Results

- Case study: Schizophrenia
- 30 seed genes obtained from association studies (also known as “core genes”)
- KATO (33 C, 34 D), ALTAR (29 C, 21 D) and BAHN (33 C, 34 D) gene expression databases

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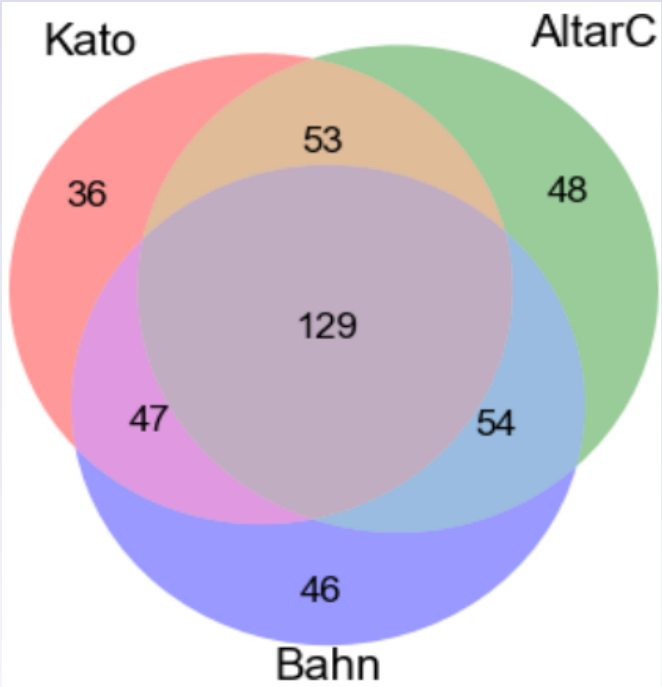
NERI method - Results

- Intersection of the top 10% genes ranked by the method in each study KATO, ALTAR and BAHN
- Intersection p-value $< 10^{-58}$ (hipergeometric test)
- Large replication among the gene expression studies



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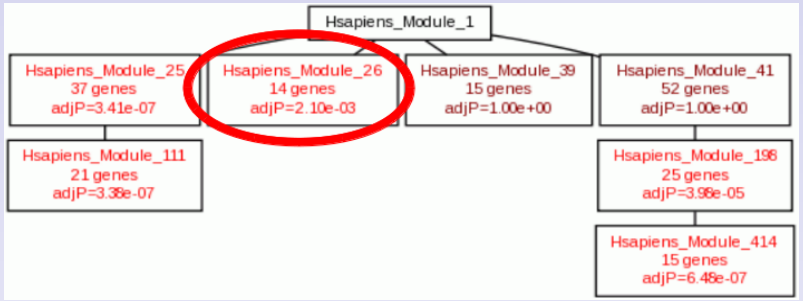
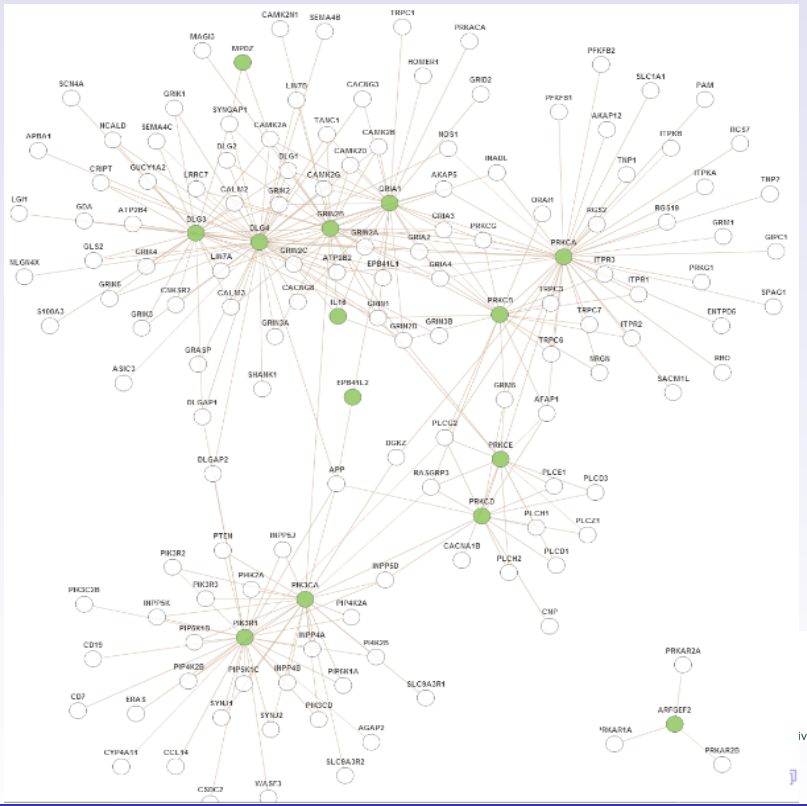
NERI method - Results

- WebGestalt protein interaction enrichment of the overlap genes list (129 genes)
- Module 26 (glutamate receptor signaling pathway) with 14 genes (green nodes)
  - Such function is known to be associated to schizophrenia





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Conclusion

Data integration and complex networks analyses are keys to improve GRN inference and gene prioritization processes

Acknowledgements

- FAPESP (procs. 11/50761-2, 13/26644-1, 14/10488-3, 15/01587-0)
- CNPq (procs. 559955/2010-3, 306991/2011-0, 304955/2014-0)
- CAPES
- Collaborators from UFABC, USP, UTFPR, IFES, Hospital A. C. Carmargo, Indian Institute of Technology and Texas A&M University

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Thank You!

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