Constraints on signaling networks logic reveal functional subgraphs on Multiple Myeloma OMIC data

Bertrand Miannay

Team MeForBio, LS2N
Team 11, CRCINA
Nantes, France

PhD supervisor : Olivier Roux (LS2N, Nantes)
Co-supervisors : Stéphane Minvielle (CRCINA, Nantes), Carito Guziolowski (LS2N, Nantes), Florence Magrangeas (CRCINA, Nantes)

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Summary

Historical

- Genes expression measure :
    - Decrease of cost/time during last 2 decades.
    - Used to compare expression profiles[LG06, PJvdR$^+$99].
- Biological knowledge :
    - Increase of knowledge on interactions between biological entities and their roles.
    - Formalization in databases (KEGG, GO, NCI-PID, CBN, etc.).

Accumulated regulatory knowledge and experimental observations.

Modelization

- Used for cellular phenomenas study [KDS$^+$16], disease research [LLX$^+$13, Nev01], bio-production optimization[Ate15], etc.
- Cannot work with large amounts of data due to "natural noise".
- Need pre-selection of data.

Summary

1 Context

2 Method
- Overview
- Formalism and implementation
- Components analysis
- Space solution reduction

3 Application
- Data and regulatory network
- Perfect colorations generation
- Components analysis

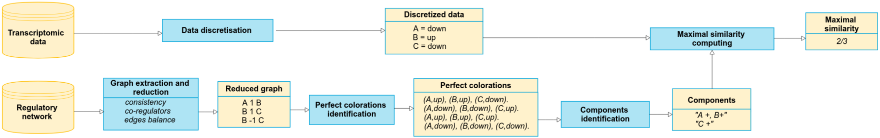
4 Conclusion & perspective

Specificity

- Identification of sub-set of data using biological interactions.
- Based on graph coloring approaches [TCSR$^+$15].
- Integrate activation and inhibition interactions in the regulatory network.
- Research of the “perfect colorations”.
- Implemented in ASP (Answer Set Programming).

Input/output

- From a regulatory network ⇒ The entities strongly associated merged in components
- From a set of observations ⇒ Measurement of the maximal similarity with the "perfect configurations" of the components.



Transcriptomic data

Data discretisation

Discretized data
A = down
B = up
C = down

Maximal similarity computing

Maximal similarity
2/3

Regulatory network

Graph extraction and reduction
consistency
co-regulators
edges balance

Reduced graph
A 1 B
B 1 C
B -1 C

Perfect colorations identification

Perfect colorations
(A,up), (B,up), (C,down).
(A,down), (B,down), (C,up).
(A,up), (B,up), (C,up).
(A,down), (B,down), (C,down).

Components identification

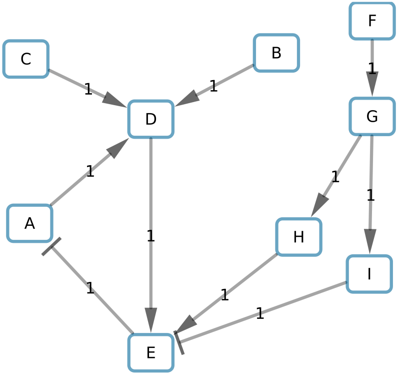
Components
"A +, B+"
"C +"

Instanciation

Graph : Set of oriented, signed (activator or inhibitor), weighted edges between nodes
Target : A node with at least, one predecessor (or regulator).

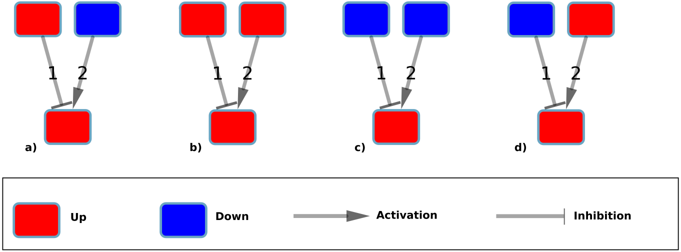
Candidate solutions generation

Colored graph : A graph in which each node is associated to a sign: up or down



Constraints

Consistent target coloring : A colored target, which is explained by at least one predecessor's coloration.
Perfect target coloring : A colored target, which is explained by all predecessor's coloration.
Imperfect weighted regulator : Weight of the edge between an imperfect target and its inconsistent regulator.



	a	b	c	d
Consistent node coloring	X	✓	✓	✓
Perfect target coloring	X	X	X	✓
Imperfect weighted regulator	3	1	2	0

Optimization

1 : Consistency maximization : Colored graphs with the maximal number of consistent targets.
2 : Perfect target coloring maximization : Colored graph with the maximal number of perfect targets.
3 : Imperfect weighted regulator minimization : Colored graphs with the minimal sum of imperfect weighted regulator

Result

Set of **perfect colorations**

node	A	B	C	D
coloration 1	up	up	up	down
coloration 2	up	down	down	up
coloration 3	down	up	up	down
coloration 4	down	down	down	up

Components identification

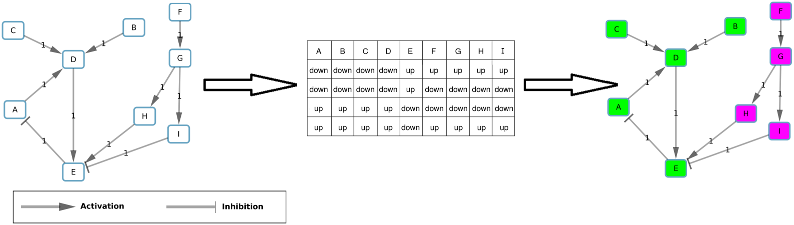
Component : set of nodes with **correlated** (positive or negative) coloration in perfect solutions.

Example

When B is up (down), C is up (down) too $\Rightarrow$ Positive correlation.
When B is up (down), D is down (up) $\Rightarrow$ Negative correlation.
Component syntax : "B +, C +, D -"

Maximal similarity computing

Component configurations : Two possibilities of colorations for a component.
Maximal similarity (MS) : For a set of observation (nodes associated to signs) and a component : the maximal percentage of observed nodes in the component with the same sign as in the configurations.



A	B	C	D	E	F	G	H	I
down	down	down	down	up	up	up	up	up
down	down	down	down	up	down	down	down	down
up	up	up	up	down	down	down	down	down
up	up	up	up	down	up	up	up	up

Toy example

Configuration : Component : "A +,B +,C +,D +,E -"

- (A,up), (B,up), (C,up), (D,up), (E,down)
- (A,down), (B,down), (C,down), (D,down), (E,up)

Observations : (B,up), (C,up), (D,up), (E, up)
MS = $\frac{3}{4}$

Coloring property

Symmetric reduction : A colored graph and its reverse coloring (up $\Longleftrightarrow$ down) have the same optimization scores.

Topological property

Consistent coloring : Identification of nodes which will have a sign correlation in consistent solutions (Figure 1-a)
Imperfect coloring : Identification of nodes which will have a sign correlation in candidate solutions with minimized imperfect colorations (Figure 1-b)
Edges balance : Deletion of balanced edges (Figure 1-c)

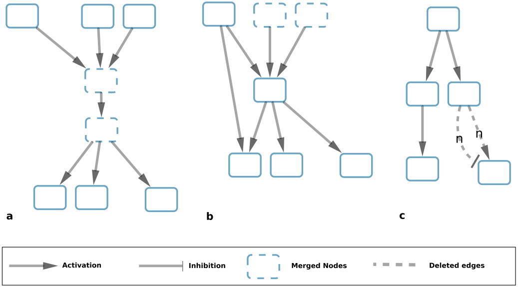


Figure : Patterns searched by the 3 reductions methods used in this study. a : nodes correlated in consistent solution. b : nodes correlated sharing the same target. c : edges with same weight, root, target and opposite signs.

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Context

- Analysis of genes expression data from Multiple myeloma patients with regulatory network.

Data

Gene expression profiles (GEP) from :

- 602 multiple myeloma patients (myeloma cells : **MC**)
- 9 healthy donors (normal plasma cells : **NPC**).

Identification for each GEP of the over-expressed (up) and under-expressed (down) genes.

Regulatory network

From Pathway Interaction database (PID)

- Extraction of the downstream events from three signaling pathways (IL6/IL6-R, IGF1/IGF1-R and CD40) [Kle10] to the variant genes

Generation of an induced subgraph from NCI-PID, containing 2269 nodes, 2683 edges and connecting 529 variant genes.

Graph reduction

- Consistent coloring, Imperfect coloring, Edges balance reductions
- New graph with 193 nodes 389 edges

Table : Computation time.

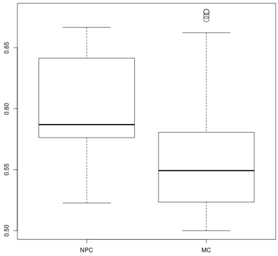
Graph	number of nodes	number of edges	time
Generated graph	2269	2683	72’,12”
Reduced graph	193	389	14”

Perfect solutions and components identification

- 16834 perfect colorations.
- 15 components identified from the regulatory network.
- Only **2 components (2 and 6)** include more than one gene.

Components validation and specification

- Computing then comparison between MS^{MC} and MS^{NPC} for each component.
- Validation by comparing with MS from random data.
- Only **component 2** is statistically different between MC and NPC.



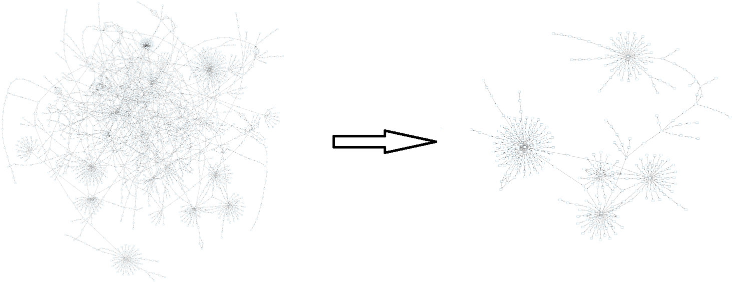
Biological analysis : gene ontology

- Genes in the component 2 (**167** genes) are strongly associated to cancer pathways (apoptotic process).
- Genes in the component 6 (**349** genes) are not associated to specific pathway.
- Genes in the graph (**529** genes) and all variant genes (**12410** genes) are not associated to specific pathway.

Summary

Conclusion

- Identification of functional subgraphs/components from a regulatory network based on perfect colorations.
- Estimation of deregulation for each components from dataset based on similarity with perfect colorations.



Perspective

- Comparison with other pathways analysis methods.
- Use other database (trrust, causal bionet, etc.)
- Improve topological reduction.
- Integration of continuous data.

Thanks for your attention

bertrandmiannay@gmail.com

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Summary

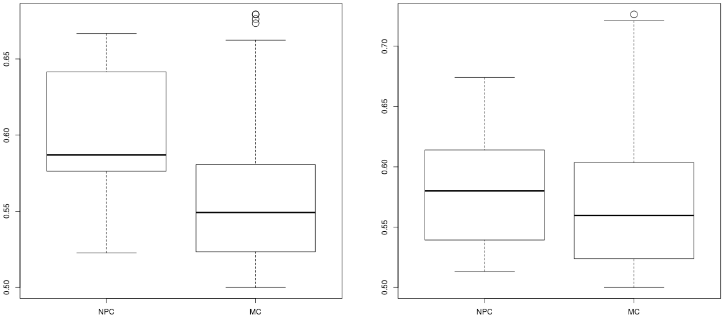


Figure : MS comparison for component 2 (left) and 6 (right).

Component	# Nodes	# Genes	Validation p-value	Specificity p-value
C^2	**422**	**167**	**8,904e-03**	**0.019**
C^6	**1832**	**349**	**7.91e-05**	**0.573**

Summary

Table : 5 first results of the Gene Ontology Enrichment Analysis for the component C^2.

GO biological process	found	expected	Fold Enrichment	P-value
regulation of cell death	75	11.98	6.26	6.46E-37
regulation of programmed cell death	73	11.21	6.51	8.33E-37
regulation of apoptotic process	72	11.11	6.48	4.90E-36
single-organism cellular process	149	77.70	1.92	9.90E-28
positive regulation of metabolic process	87	24.50	3.55	7.81E-26

Table : 5 first results of the Gene Ontology Enrichment Analysis for the component C^6.

GO biological process	found	expected	Fold Enrichment	P-value
response to organic substance	182	42.74	4.26	1.02E-68
response to chemical	203	64.12	3.17	2.13E-57
response to oxygen-containing compound	129	23.26	5.55	1.32E-56
positive regulation of biological process	233	88.29	2.64	1.39E-55
regulation of cell proliferation	132	25.67	5.14	1.98E-54

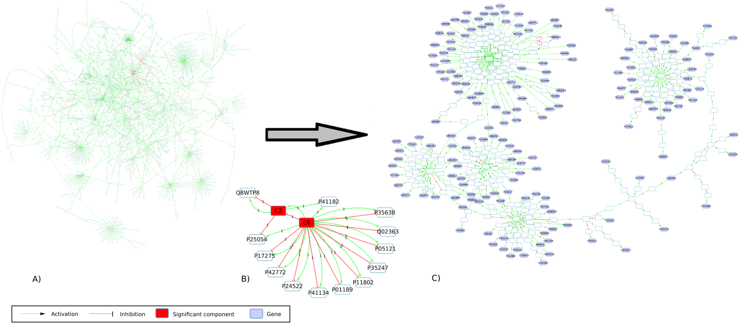
Table : 5 first results of the Gene Ontology Enrichment Analysis for the 529 genes integrated in the graph.

GO biological process	found	expected	Fold Enrichment	P-value
positive regulation of biological process	368	137.60	2.67	6.53E-94
positive regulation of cellular process	346	122.38	2.83	2.02E-91
positive regulation of metabolic process	285	80.69	3.53	3.06E-90
positive regulation of cellular metabolic process	271	75.30	3.60	6.04E-86
response to organic substance	259	68.79	3.77	4.85E-85

Table : 5 first results of the Gene Ontology Enrichment Analysis for all the variant genes (21002).

GO biological process	found	expected	Fold Enrichment	P-value
biological process	11199	10256.18	1.09	2.69E-123
cellular process	9925	8845.71	1.12	2.22E-105
cellular metabolic process	6101	5303.88	1.15	2.77E-43
biological regulation	7805	7018.07	1.11	5.08E-43
regulation of biological process	7404	6658.81	1.11	1.13E-37

Summary


A)
B)
C)
Q8WTP8
C2
C6
P41182
P35638
Q02363
P05121
P35247
P11802
P01189
P41134
P24522
P42772
P17275
P25054
1
Activation
Inhibition
Significant component
Gene