Contributions to transcriptomic data analysis and gene regulation network inference

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Overview

Inferring regulation networks from transcriptomic static data

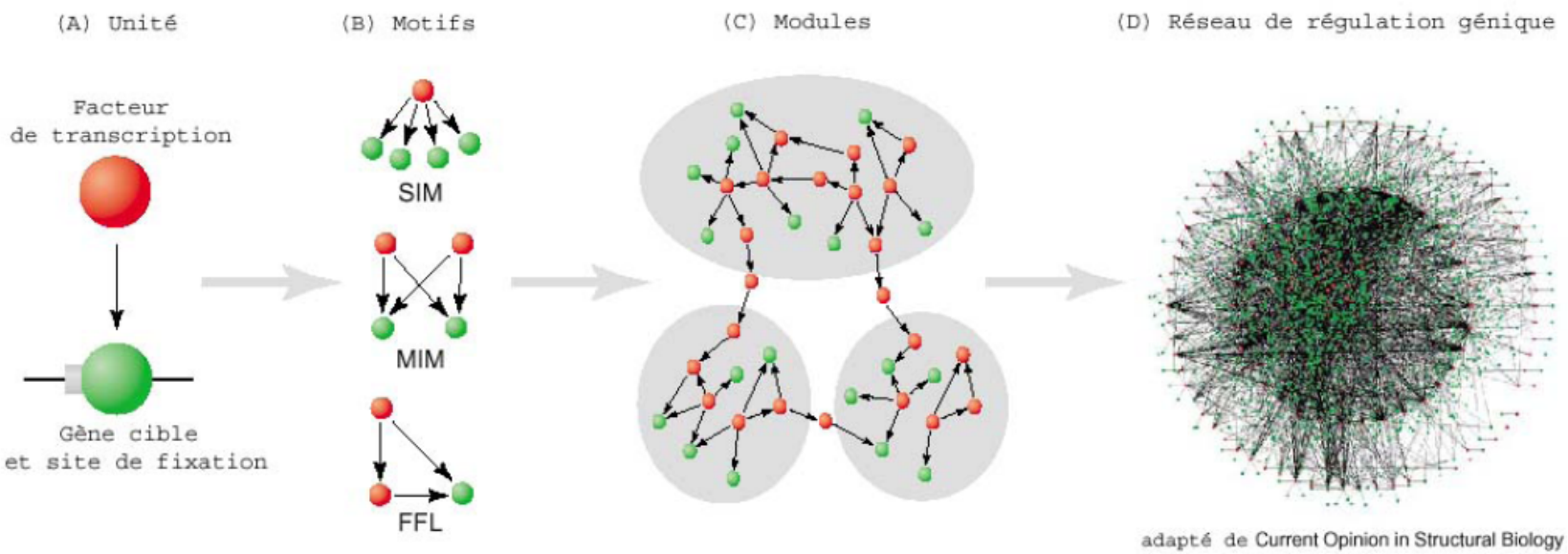
- Motivations and goals
- Methods
- Evaluation

Finding dense regions in binary contexts

- Motivation and goals
- Methods
- Experiments and results

Regulation network inference

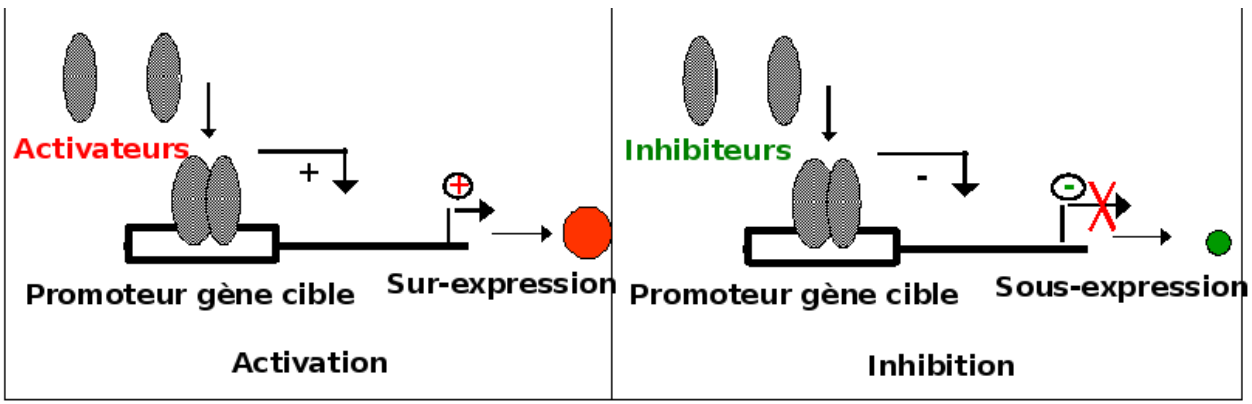
Buiding a regulation graph for a biological process



Transcriptional regulation

A **transcription factor is** :

- a proteine, **that binds to specific sequences of DNA** adjacent to the genes that they regulate
- controls the flow (**activates and/or respress**) this gene's transcription



Cahier des charges

- learning cooperative regulation relations from gene expression only
- no time series data available
- without any a priori assumption concerning the gene expression distribution
- local approach (one network / gene)

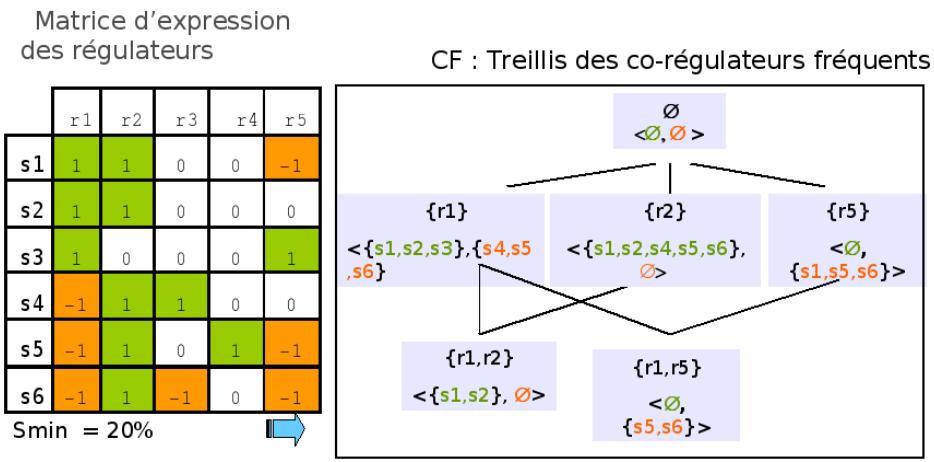
LICORN

LICORN (Elati et al., Bioinformatics 2007) follows these 3 steps:

1. Build a set of candidate co-regulators (predicate invention) for all genes ;
2. Build a set of candidate regulation networks for each target gene g ;
3. Select the best candidate network(s) for each gene g, and assign a significance score to this (these) network(s)

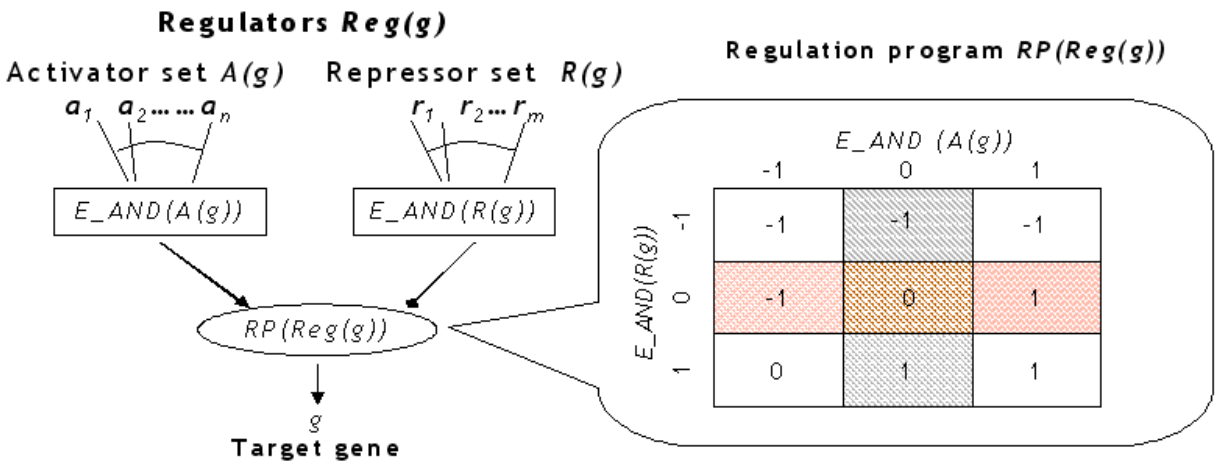
Co-regulators computation

- Goal: find all formulas of a language L that satisfy a constraint q on a dataset r, $Th(r, L, q)$.
- r : discrete matrix r of m observations described with n attributes $A = g_1, g_2, \ldots, g_n$ ($n >> m$)
  L : language describing itemsets on A (2^A).
  q : constraint of interest, *e.g.* frequency of a pattern p in r : p is frequent if $freq(p) \geq min_{supp}$
- Extension of Apriori (Agrawal et al., 1994) for computing frequent/closed itemsets from discrete data



Cooperative regulation model

- potentially, several cooperative activators/repressors
- AND-agregation for activators/repressors + deterministic function for computing target gene state given the aggregated states of its activators/repressors.



Generating candidate co-regulators for a target gene

Let C be a co-regulator and g be a target gene. $\mathcal{S}_x(C)$ and $\mathcal{S}_y(g)$ denote their support for the values $x, y \in \{-1, 1\}$.

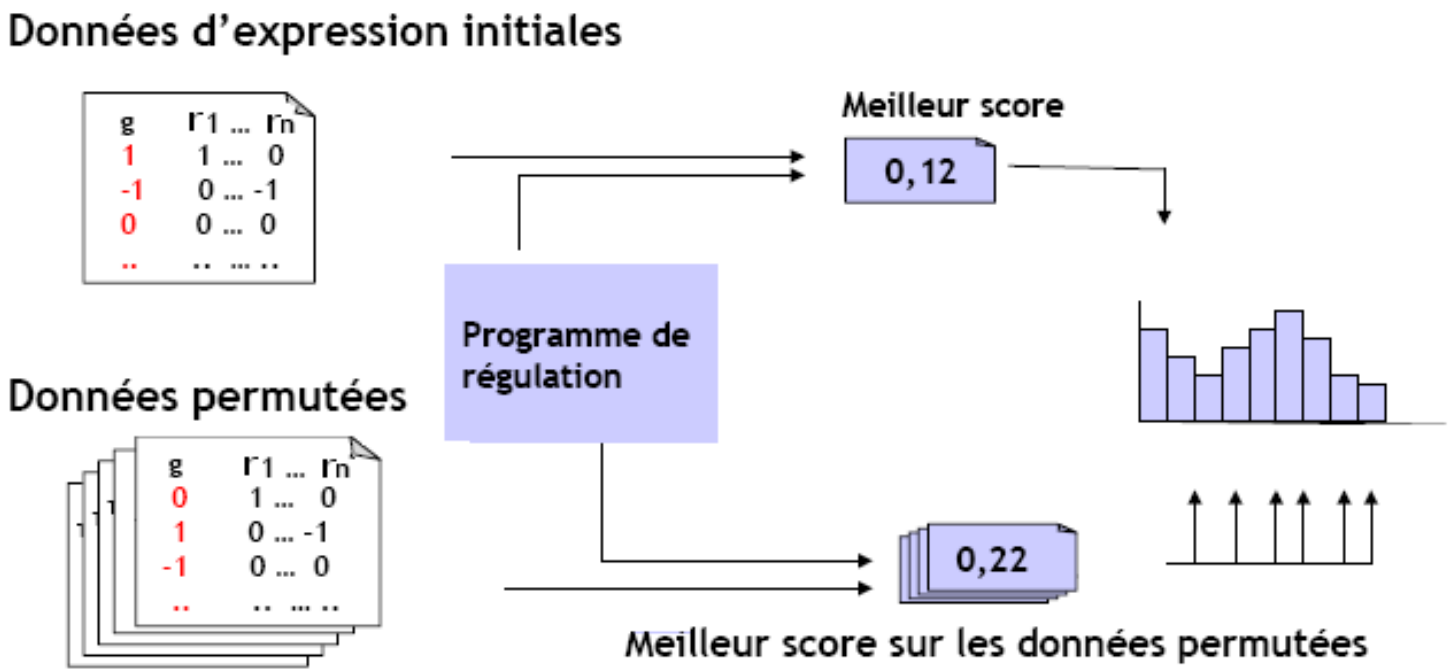
Definition (Overlap constraint)

C in state x *co-varies* with g in state y, denoted $\mathbf{cov}(\mathcal{S}_x(C), \mathcal{S}_y(g))$ if and only if $\frac{|\mathcal{S}_y(g) \cap \mathcal{S}_x(C)|}{|\mathcal{S}_y(g)|} \geq min_{overlap}$, a user-defined minimum overlap threshold.

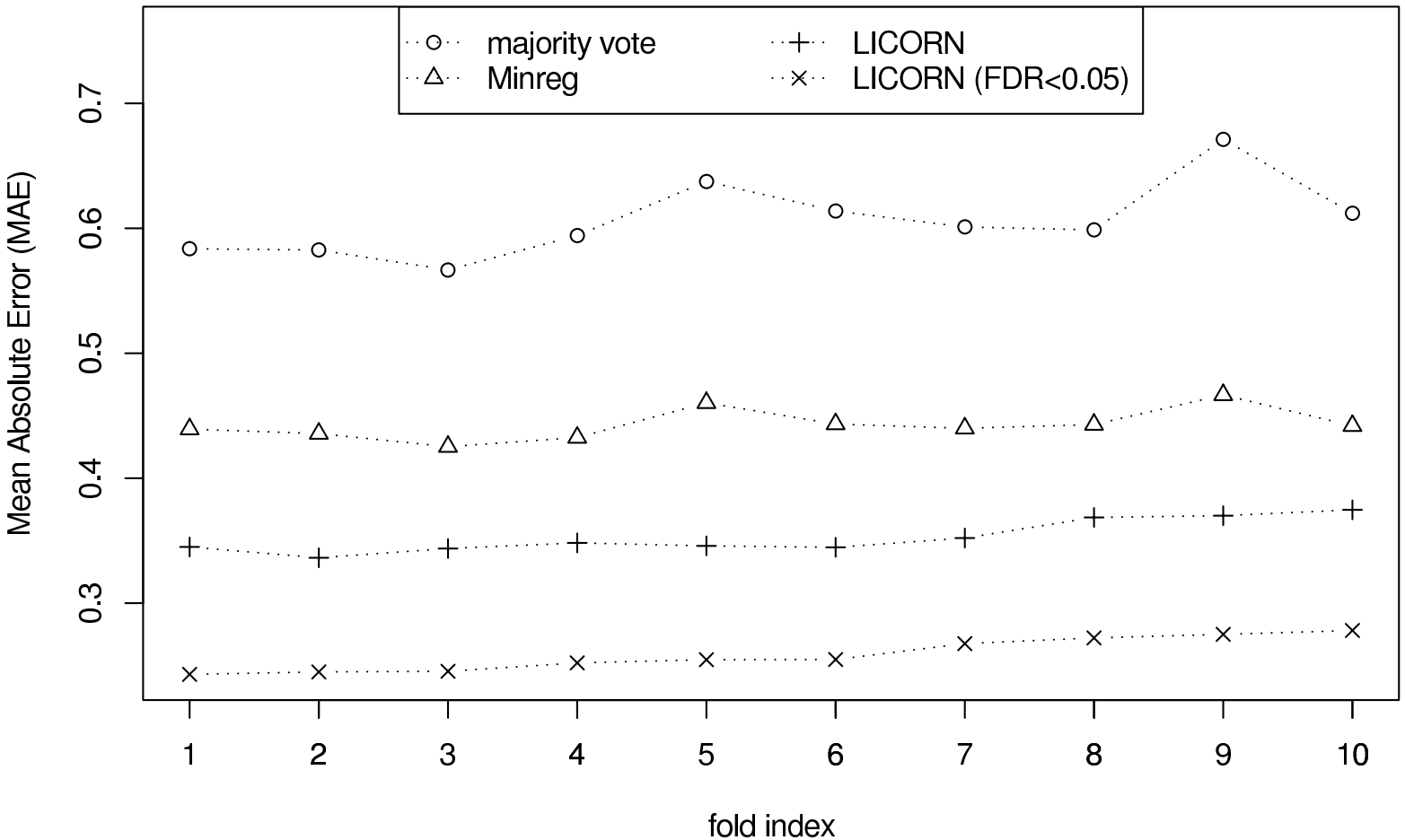
Best-first search for the k-best co-activators and repressors of g.

Assessment of candidate networks

- Rank candidate networks ((A, I) pairs) wrt a local score (MAE)
- Select (n-)best network(s)
- Associate a statistical sigificance to those networks : non-paramteric approach, permutation-based (Benjamini et al., 2001).

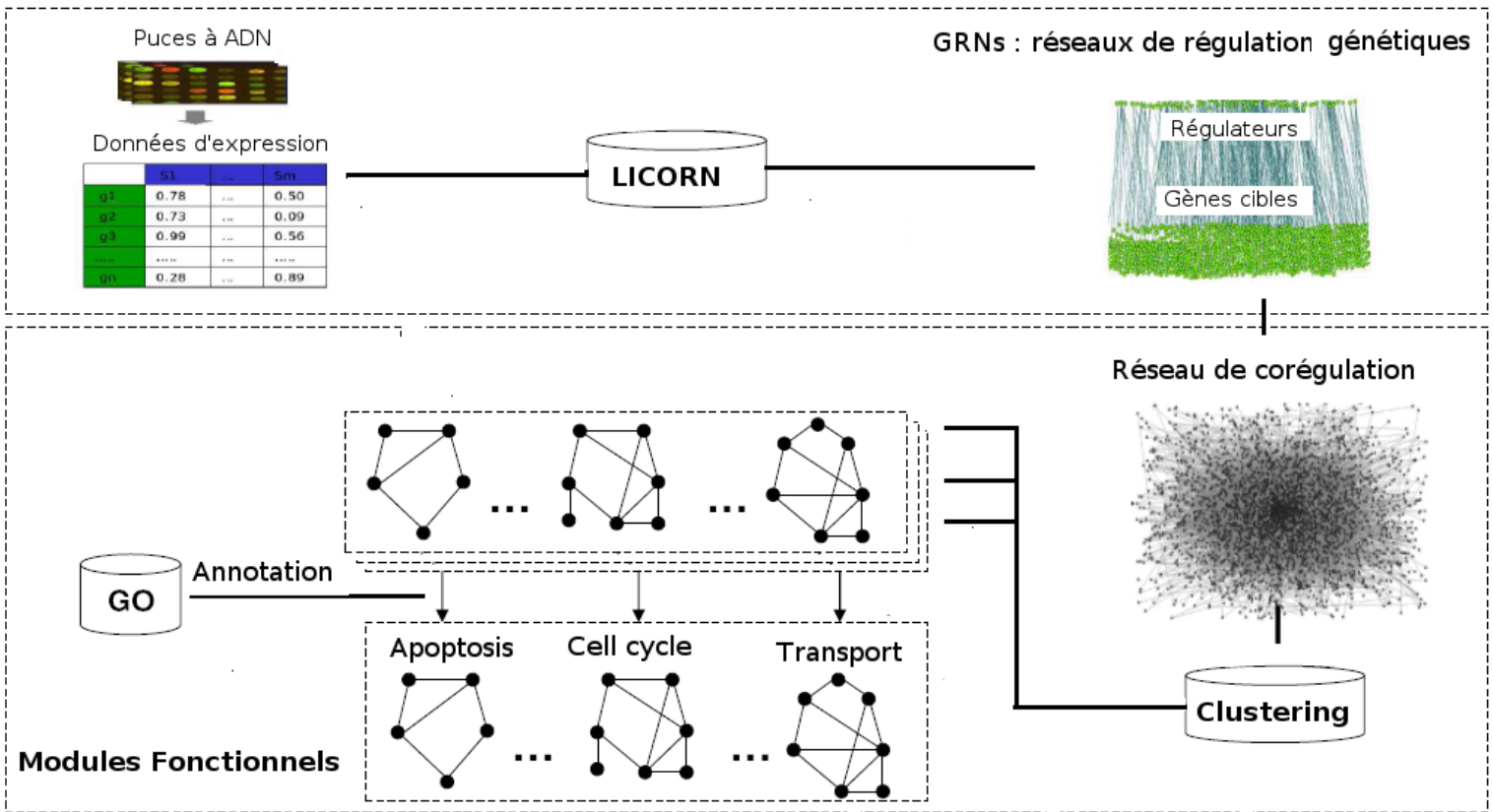


10-CV evaluation



From local to global patterns

(Birmelé et al. BMC 2008)

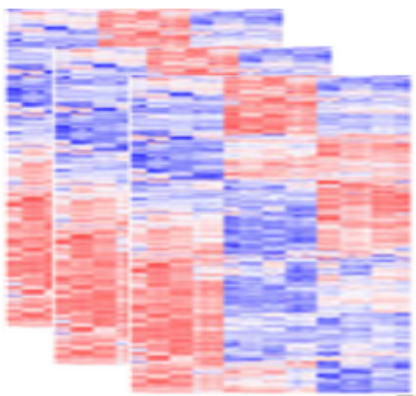


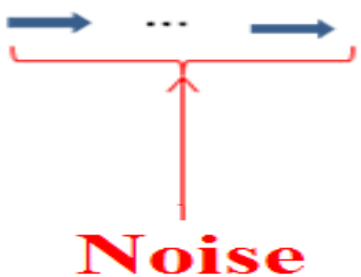
On-going work - Perspectives

- Combine local networks to build a gloabl regulation graph (ILP, frequent graph mining, ...)
- Integrate other information sources (promoter sequence, genomic alterations, miRNA, proteins, epigenetic, ...)
- More powerful evaluation for networks : select networks that are supported by some domain model

Context

- A bioinformatics task from gene expression dataset:
  - Mining co-expressed genes (Sets of genes that are jointly expressed) $\rightarrow$ discretisation + extraction of frequent/closed/maximal itemsets (e.g. Apriori [Bor02]).

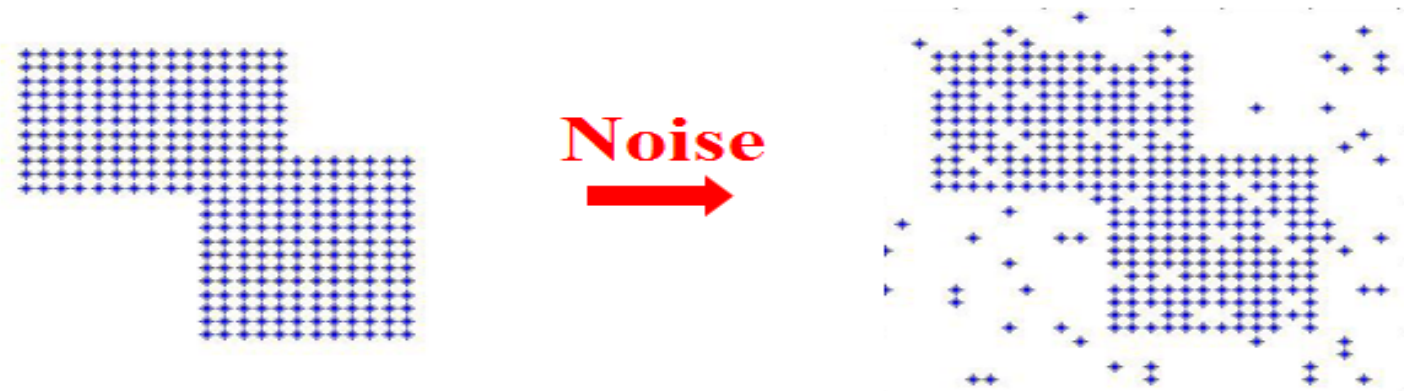




	p_1	p_2	...	p_m
f_1	1	0	...	0
f_2	0	1	...	1
f_3	1	0	...	0
...	...	...	...	...
f_{n-1}	1	0	...	0
f_n	0	1	...	1

The problem

- **Effect of noise**
  - Shattering relevant itemsets into a small irrelevant itemsets $\rightarrow$ explosion in the number of resulting itemsets.



- **Aim and intuition**
  - Mine efficiently a small number of maximal regions of 1, *p*otentially overlapping, and verifying density and minimal support constraints.
  - by combining data mining methods with graph algorithms.

Related work

- **Complete approaches**
  - Methods based on the level-wise principle [Man04, Bes05, Bes06, Liu06, Che06]
  - Handle anti-monotone constraints to prune the space search
  - Quasi-biclique methods [Uno08].

  X Large number of itemsets extracted.
  X Very expensive in execution time for dense data
- **Non-complete approaches**
  - Bi-clustering methods [Pre06]

  X Difficulty in the choice of parameters.
  - Heuristic methods [Mou11]

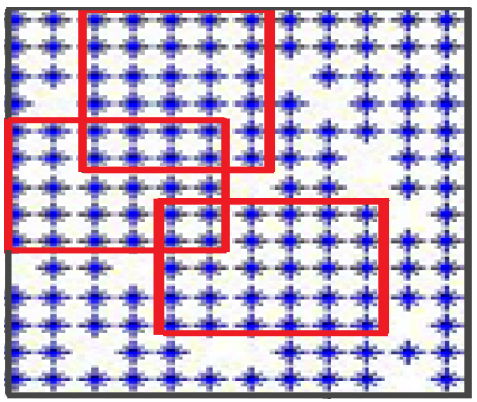
  X Still too many results and redundancy.

HANCIM : Hybrid Approach for Noisy Contexts Itemset Mining

- Consists of two main steps:
  - Identification of a seed pattern s_i
  - Construction of a dense region (O, A) such that $s_i \subseteq A$
- Extracts the maximal regions $M = (A, O)$ such that:
  - Density : $density(M) \geqslant \delta$
  - Minimal support : $\frac{|O|}{|O_{context}|} \geqslant \sigma$.

Seed patterns and the adaptative support

- Use all maximal frequent patterns of D as seeds [Mou11]
  X A high redundancy in the obtained results.
  X Quite expensive especially for dense contexts.



- Seed patterns should :
  - be small enough to be easy to compute
  - favour the extraction of diverse seeds (small overlap) to avoid redundancy in the resulting regions

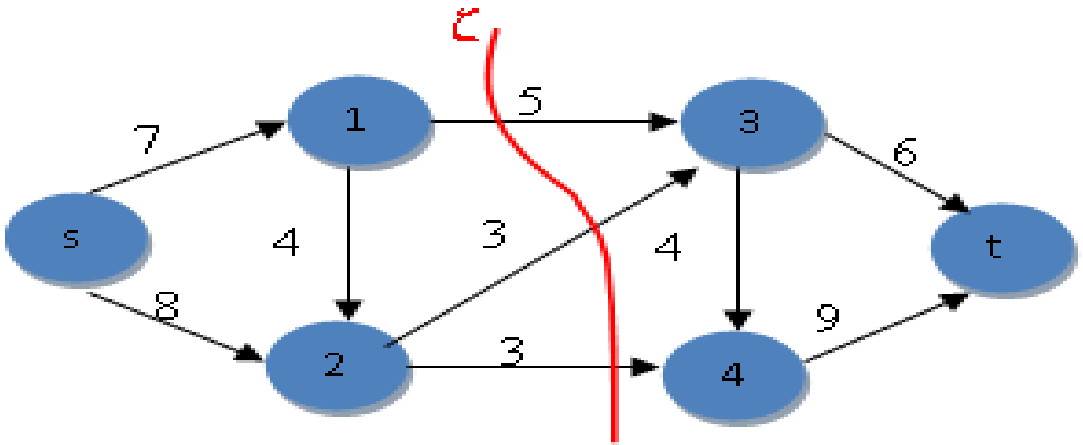
Seed patterns and the adaptative support (ctd.)

- O set of observations, A set of attributes, two contexts on A and O : D and D_{cs} (updated after each new seed is extracted)

while $\exists$ *seed pattern* $s_i \subseteq D_{cs}$ **do**
Compute the region $(O', A') \subseteq D$ such as $(s_i \subseteq A')$ and $(\frac{|O'|}{|O|} \geqslant \sigma)$ and (density$((O', A'))\geq \delta$)
$Updated\_D_{cs}$: D_{cs} where all elements of (A', O') are set to zero
Support = $\frac{Support \times density(UpdatedD_{cs})}{density(D_{cs})}$; $D_{cs} = updated\_D_{cs}$;
end

Searching for dense regions

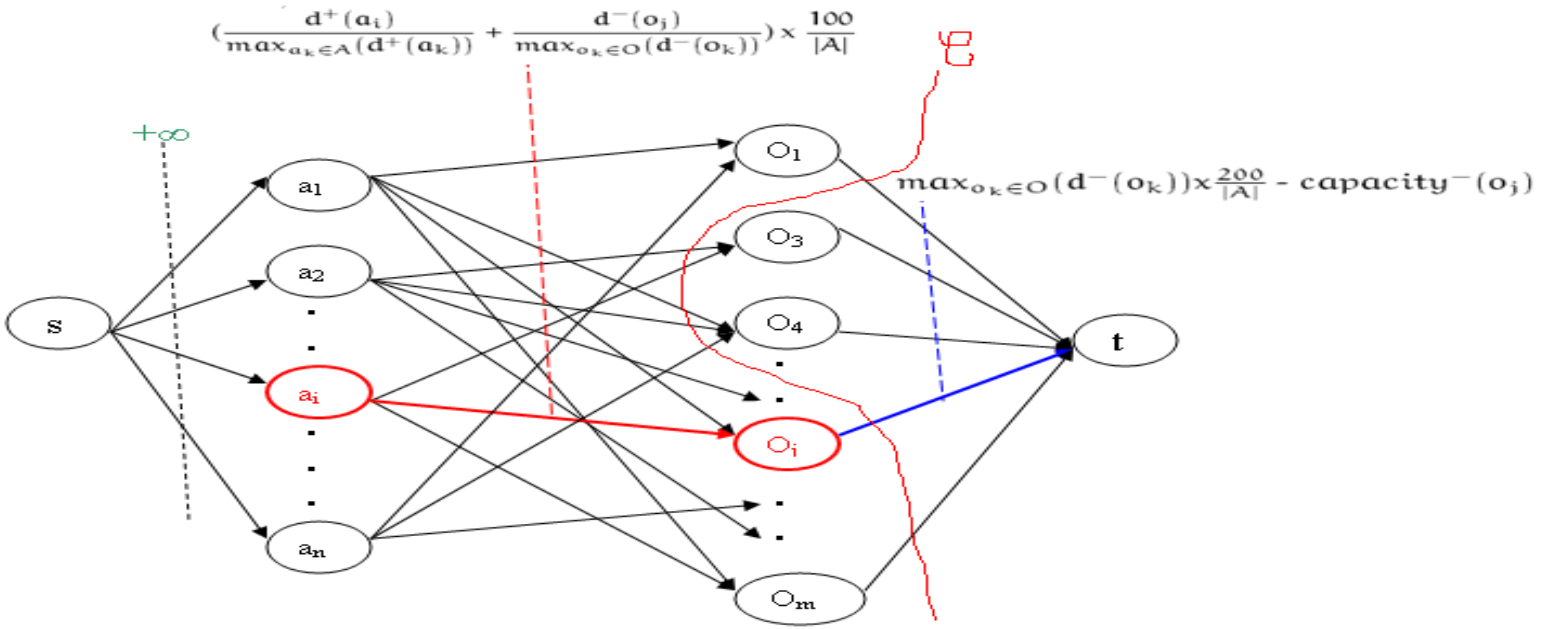
- Searching for a maximal dense region including a seed pattern s_i
- Based on graph algorithms: maximal flow/minimal cut.



Searching for dense regions

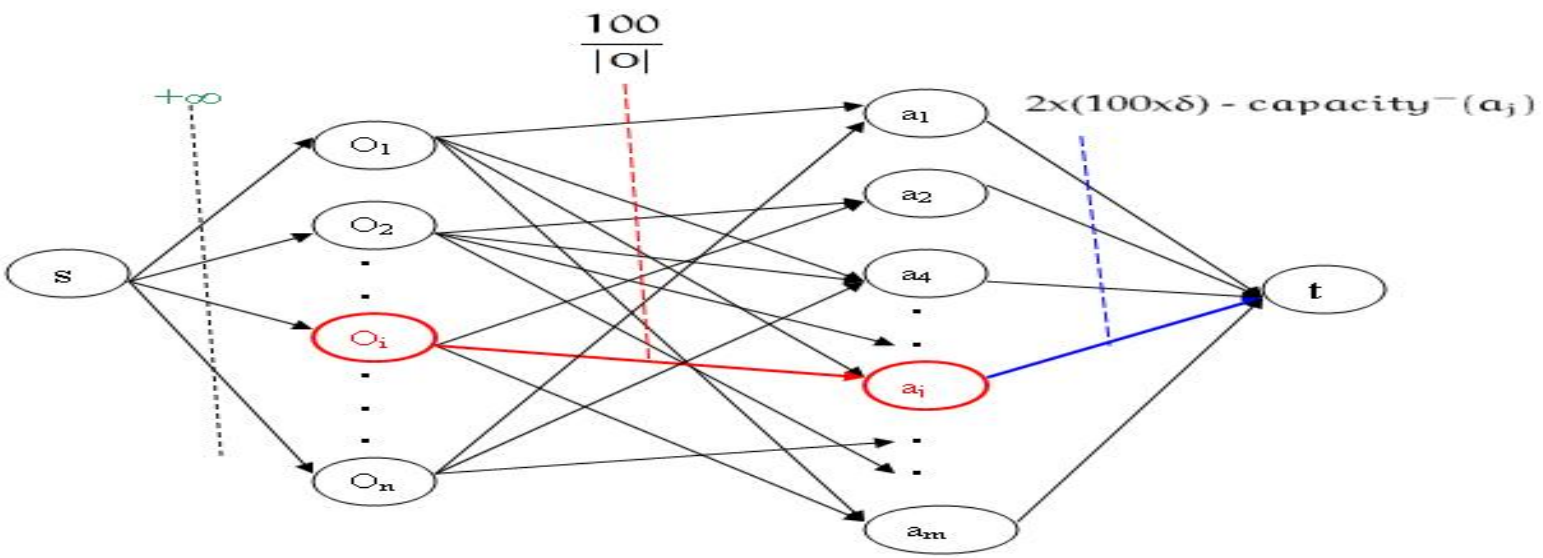
Searching for the maximal dense region including a seed pattern s_i

- Construct the augmented and weighted bipartite graph corresponding to s_i
- Compute a minimal st-cut : push-relabel [Che97]
  $\Rightarrow$ a dense subgraph $G_0=(O_0, s_i)$ where the observations O_0 are strongly linked to the attributes s_i



Searching for dense regions

- Construct the augmented and weighted bipartite graph corresponding to O_0
- Compute a minimal st-cut
  $\Rightarrow$ a dense subgraph $G_1=(O_0, A_1)$ where $s_i \in A_1$ and each attribute of A_1 has a density greater than δ



Experiments on gene expression datasets

- Detection of co-expression relationships between genes from the **Gasch dataset** [Gas00]
  - Expression measures of 2993 genes over 173 observations.
  - Discretization model described by [Pre06].
  - Parameters: σ=20% and δ=80%
- Running time :
  - *Bimax* : calculation stoped after 1 week
  - *HANCIM* : results obtained after 12 minutes.
- Comparison with 100 biclusters published by Bimax [Pre06].

Experiments on real data

- Calculate the enrichment of extracted biclusters in Gene Ontology terms (GO)[Che98].
- The 100-top biclusters extracted :
  - *Bimax* : have p-values ranging between $3e^{-2}$ and $3e^{-4}$.
  - *HANCIM* : have p-values less than e^{-5}.
- The best annotated bicluster:
  - *Bimax* : has a p-value equal to $3e^{-4}$.
  - *HANCIM* : has a p-value equal to e^{-38}.

	$< e^{-2}$	$< e^{-3}$	$< e^{-4}$	$< e^{-5}$	$< e^{-10}$	$< e^{-20}$
HANCIM	94%	48%	28%	18%	7%	4%
BiMax	34%	5%	0%	0%	0%	0%

Conclusion & Pespectives

- A new approach based on max. flow/min. cut algorithms for mining patterns in noisy contexts.
- The results are very promising regarding:
  - quality and size of the extracted patterns
  - reasonable running time
  - annotation quality of results
- Perspectives:
  - Adapt weigth one of the bipartite graph to bias search towards regions that take domaie knowledge into account
  - Links with 'noisy closure'

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