GraMoFoNe: a Cytoscape plugin for querying motifs without topology in Protein-Protein Interactions networks

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Outline

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Motivations

25000 30000 45000

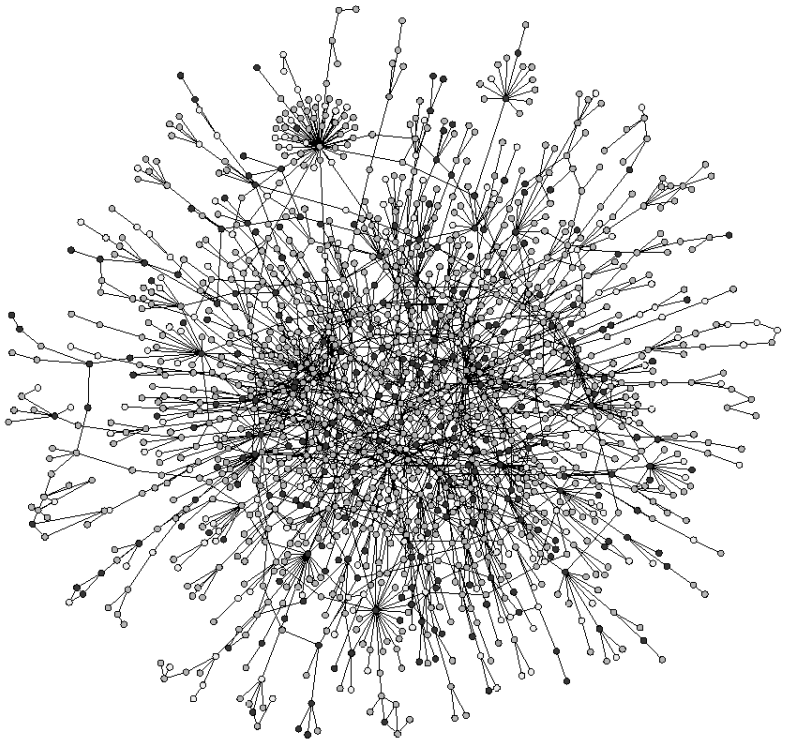
- Human complexity $\Leftrightarrow$ # of genes ?
- Human complexity $\Leftrightarrow$ proteins ?

Proteins..

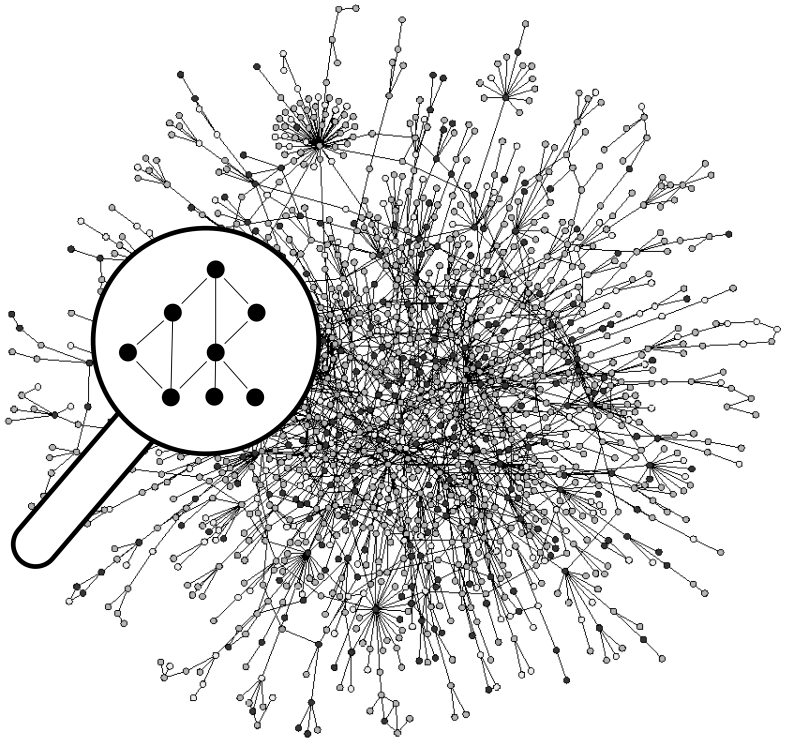
- New interest on proteins...
- ... and on their physical interactions: Protein-Protein Interactions (PPI)
- Biologically obtained... with noise !

Proteins network

- Proteins can interact with other proteins



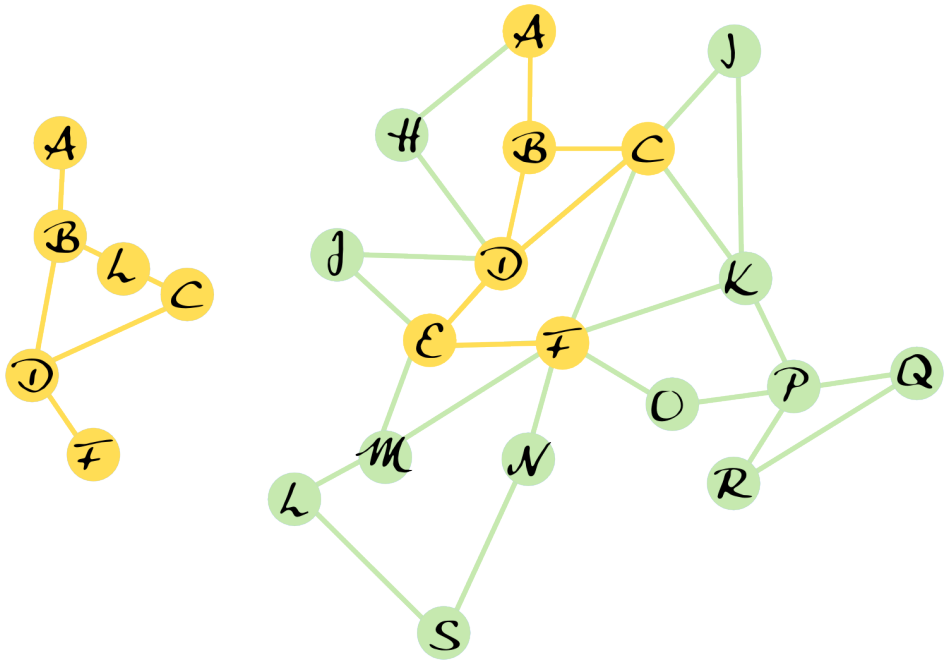
Proteins network



- Use a (weighted) graph representation
  - Proteins are nodes
  - Interactions are edges
  - Edges can be weighted by interaction probability

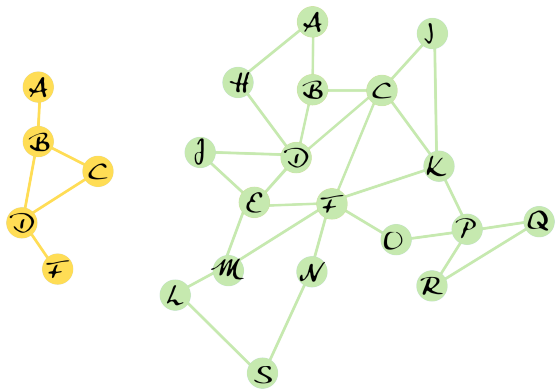
Searching patterns

- Searching patterns (set of proteins) in a PPI Network can be important to deduce information
- A protein is said to be **homologous** to another protein according to a BLAST sequence analysis



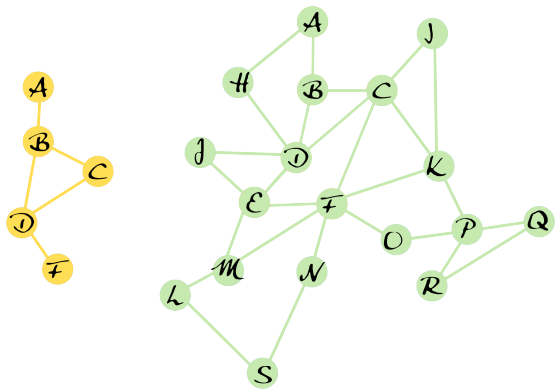
Search patterns

- Large part of the litterature deals with motif provided with a topology
  - A path
  - A tree
  - A graph under conditions
  - ...



Search patterns

- Large part of the litterature deals with motif provided with a topology
  - A path
  - A tree
  - A graph under conditions
  - ...
- New point of view : a functionnal one
- No topology given for the motif



Outline

Graph Motif

- Fact : biological data are noisy
  - Missing informations, false negatives. About 50% [Gavin et al. 2002]
  - Erroneous informations, false positives. About 65% [Reguly et al. 2006]
- Topology of the motif can be unknown *a priori*

Graph Motif [Lacroix et al. 2006]

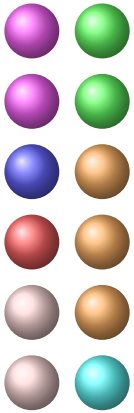
- Each network node is colored by its "function" $\longrightarrow$ network is a vertex-colored graph
- Motif is a (multi) set of colors
- Does the motif appears as a subgraph of the network ?

GRAPH MOTIF [LACROIX ET AL. 2006]

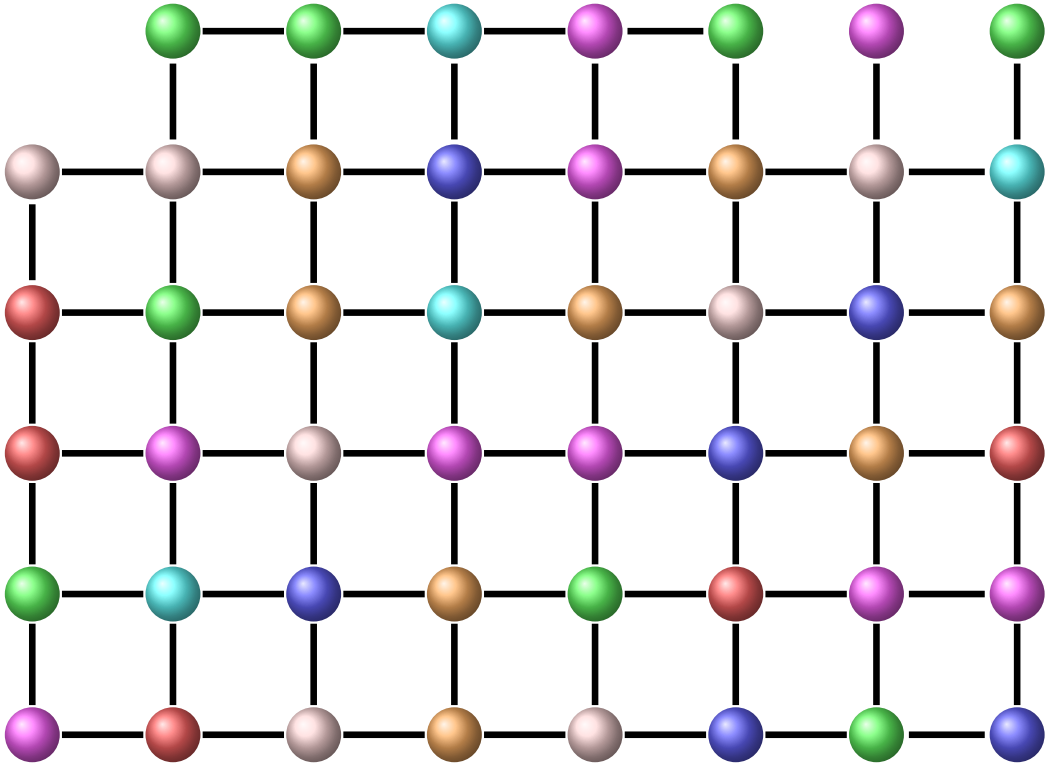
- Each network node is colored by its "function" $\longrightarrow$ network is a vertex-colored graph
- Motif is a (multi) set of colors
- Does the motif appears as a subgraph of the network ?

- Applied to different biological networks [LACROIX ET AL. 2006]
  - In the case of PPI networks, each motif protein gets a color
  - A network node has the color *c* if it is homologous to the protein colored by *c* in the motif
- Can be used for other networks (social networks,...) [BETZLER ET AL. 2008]

Graph Motif – An example

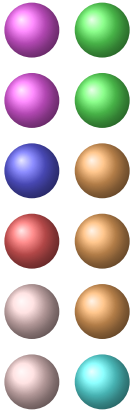


M



$G = (V, E)$

GRAPH MOTIF – An example



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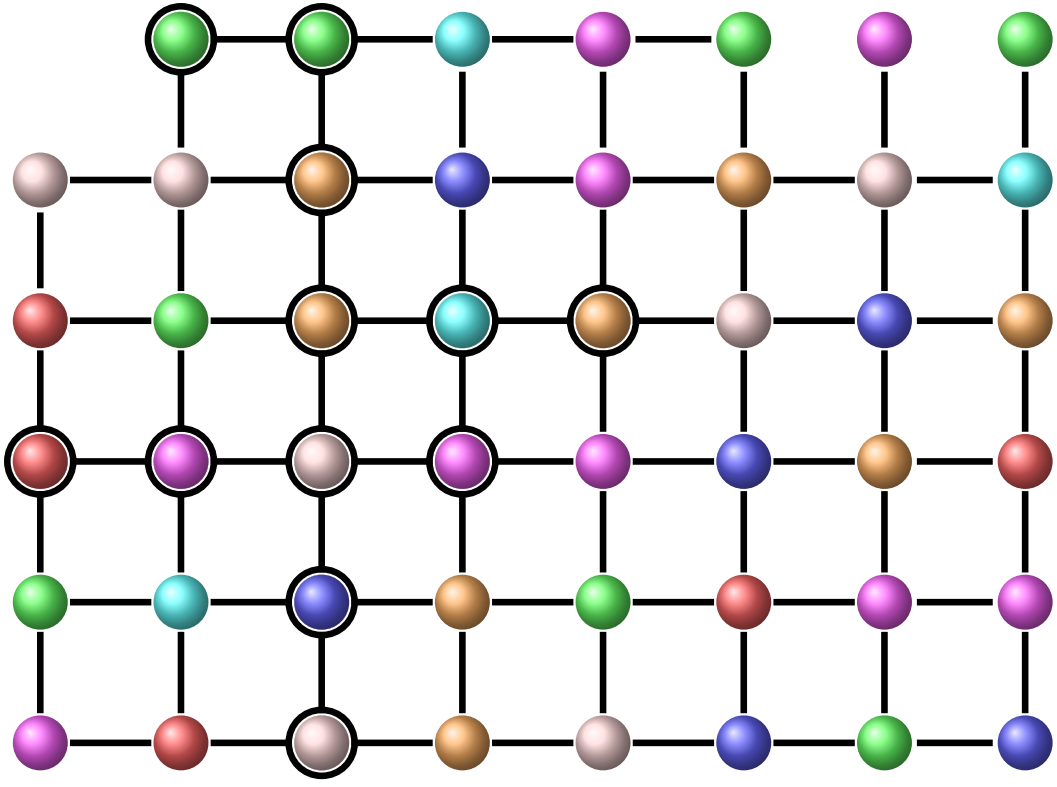
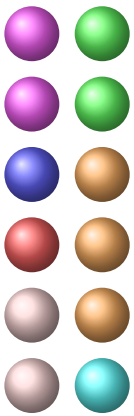


$G = (V, E)$
a possible $V' \subseteq V$

Graph Motif – An example



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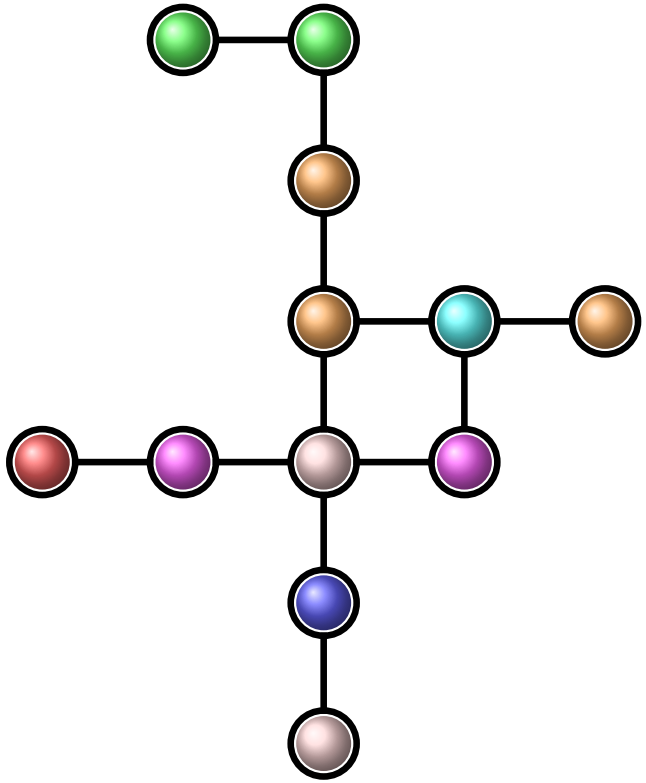


$G[V']$

Softwares for GRAPH MOTIF

- A lot of theoretical results exists... (NP-Complete even for strong restrictions, FPT, W[1]-hard,...)
- Only two softwares

- Torque [BRUCKNER ET AL. 2009] : web service (only) considering colorful motifs
- GraMoFoNe : a Cytoscape plugin

Outline

GraMoFoNe – Cytoscape (2002)

- A free platform, open-source, in Java for
  - importation / exportation from/to a lot of format, DB,...
  - visualizating, analyzing interaction networks
  - integrating annotations, gene expression profiles and other state data to the networks
- Widely used (”hundreds” of articles cited cytoscape for analyzing...)
- Up to date...
- Plugins !

GraMoFoNe – PB

- We modelize GRAPH MOTIF with Linear Pseudo-Boolean programming
- *i.e.* linear programming with boolean variables

GraMoFoNe – PB

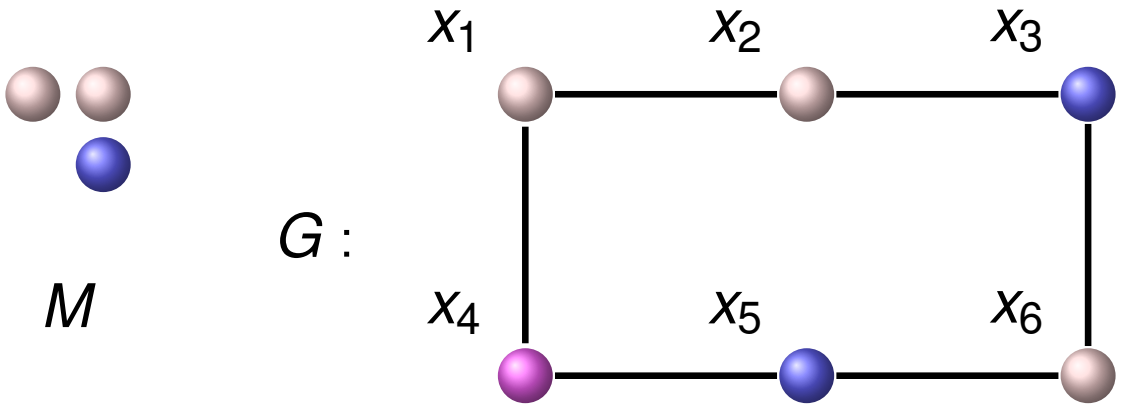
- Find a variable assignment which satisfies constraints and maximizes an objective function
- A simple example :
  - **Variables** : $x_i \in \{0, 1\}, \forall i = 1, 2, 3$
  - **Objective** : $\max x_1 + 2x_2 - x_3$
  - **Contraints** :
    1. $2x_1 - 2x_2 + 3x_3 \geq 2$
    2. $x_1 + x_2 + x_3 = 1$
- Solution : $x_1 = 1, x_2 = 0, x_3 = 0$

GraMoFoNe – PB

- We use 23 constraints and 9 domains of variables
- Recall : we look for an occurence of a motif M in a graph G
- To respect :
  1. Solution size
  2. Solution coloration equals to the motif
  3. Connectedness of the solution (hardest part)

GraMoFoNe – Variables

- A variable x for each node



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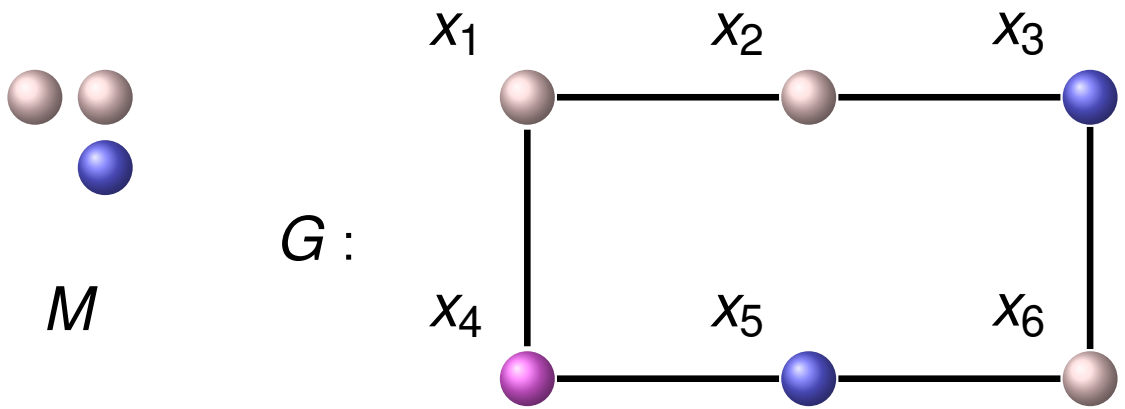

- Constraint "solution size" : $\sum_{v \in V} x_v = |M|$:
  - $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 = 3$

GraMoFoNe – Variables

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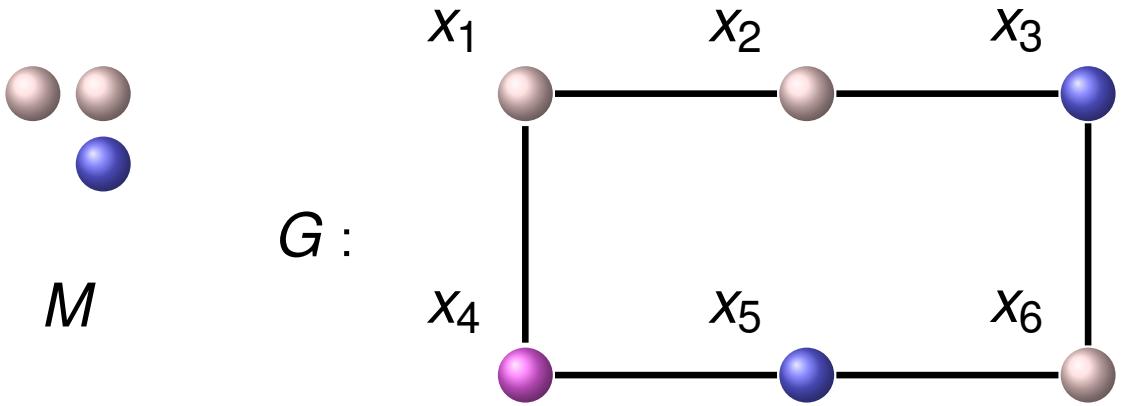
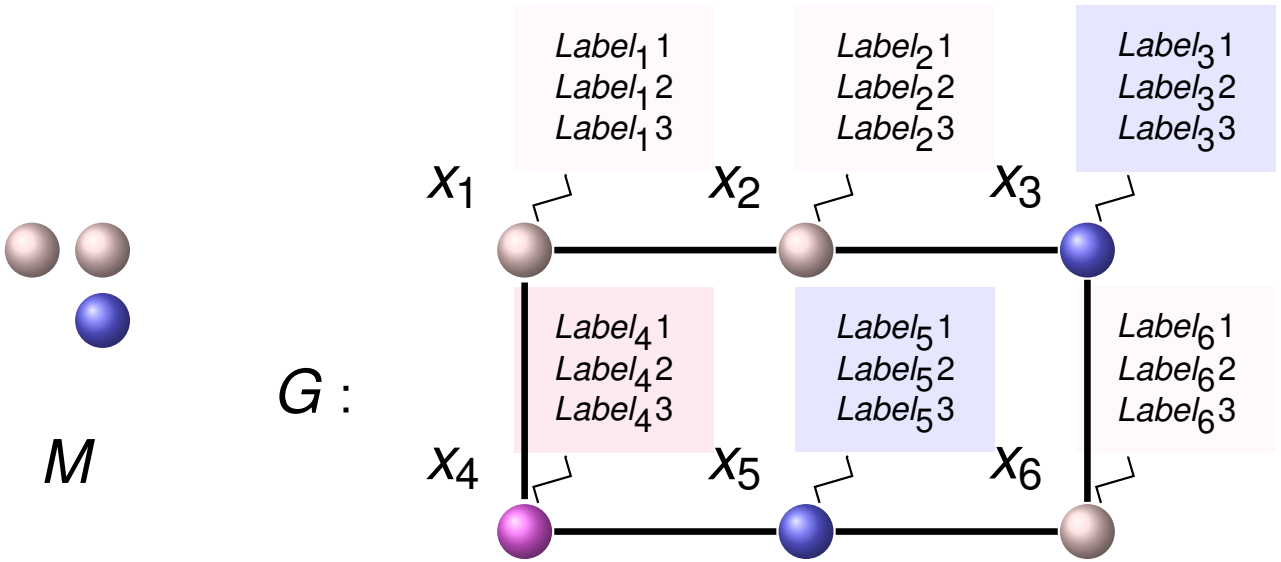


- Constraint "solution size" : $\sum_{v \in V} x_v = |M|$:
  - $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 = 3$
- Contraints "coloration" $\sum_{\substack{v \in V \\ c \in col(v)}} x_v = occ_M(c)$:
  - $x_1 + x_2 + x_6 = 2$ (white)
  - $x_3 + x_5 = 1$ (blue)
  - $x_4 = 0$ (pink)

GraMoFoNe – Variables

- Connected solution : $|M|$ variables $Label_v$ for each node v



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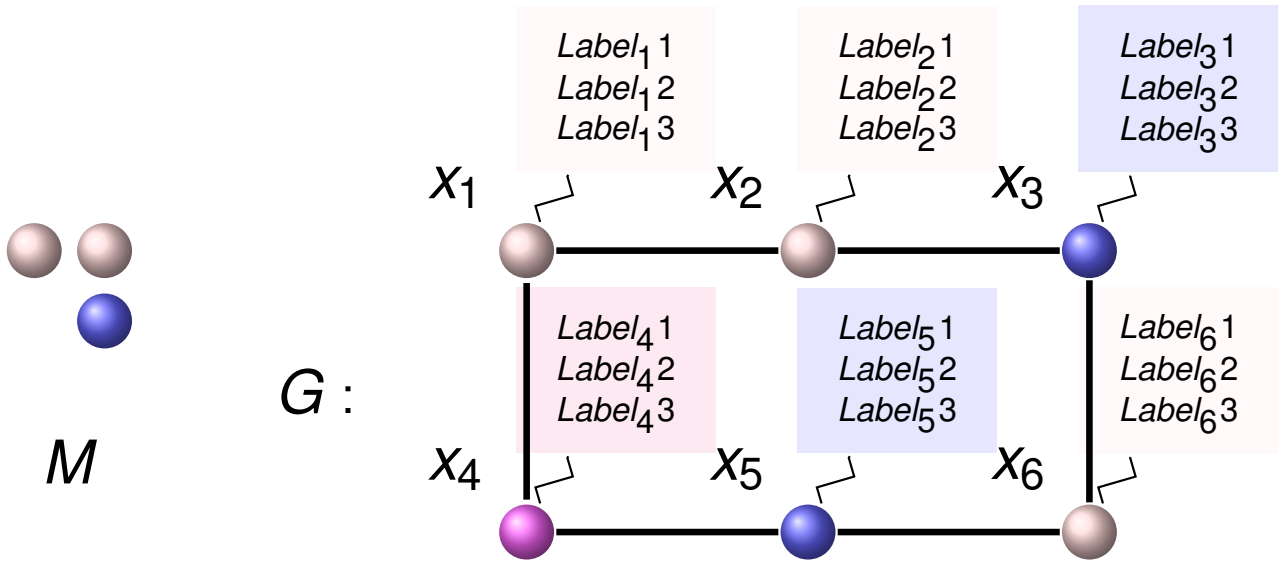

- $|V|$ constraints "one label by node in the solution" :
  - For each v, $x_v \Rightarrow (\sum_{i=1}^{|M|} Label_v i = 1)$

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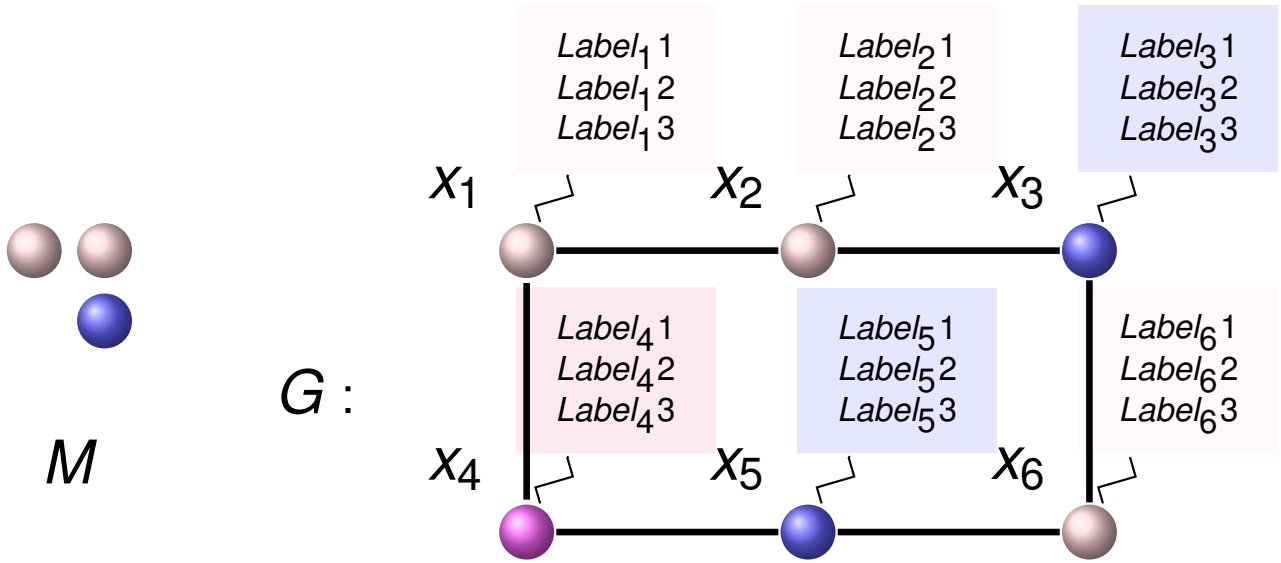
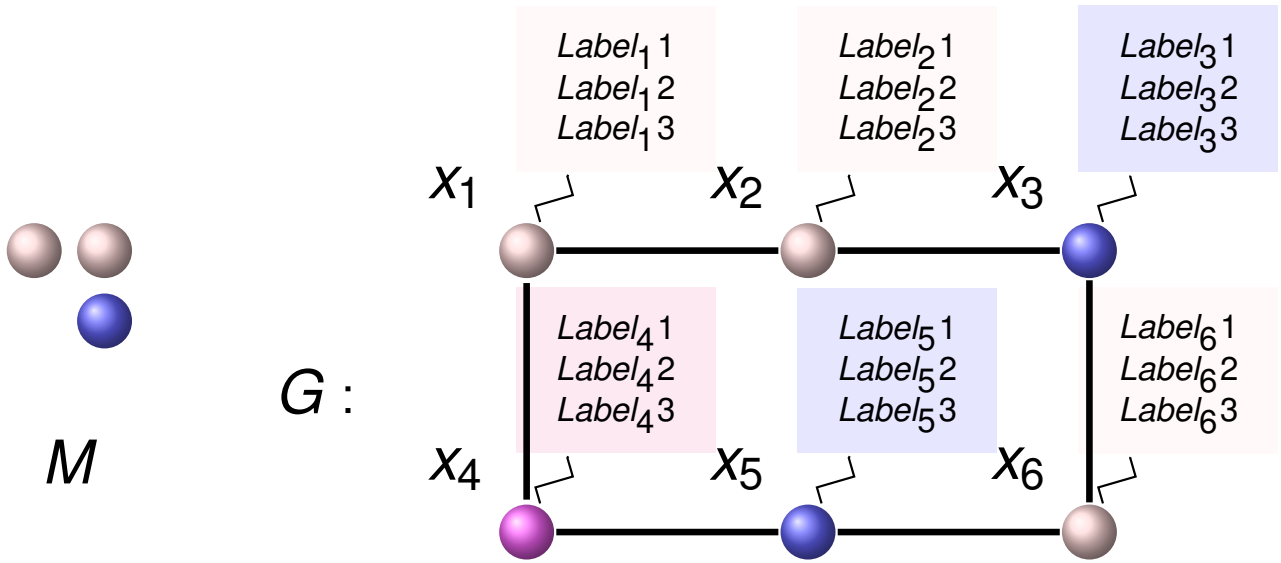


- $|V|$ constraints ”one label by node in the solution” :
  - For each v, $x_v \Rightarrow (\sum_{i=1}^{|M|} Label_v i = 1)$
- $|M|$ constraints “a node for a given label”
  - For a given label i, $\sum_{v \in V} Label_v i = 1$

GraMoFoNe – Variables

- Connected solution : $|M|$ variables $Label_v$ for each node v



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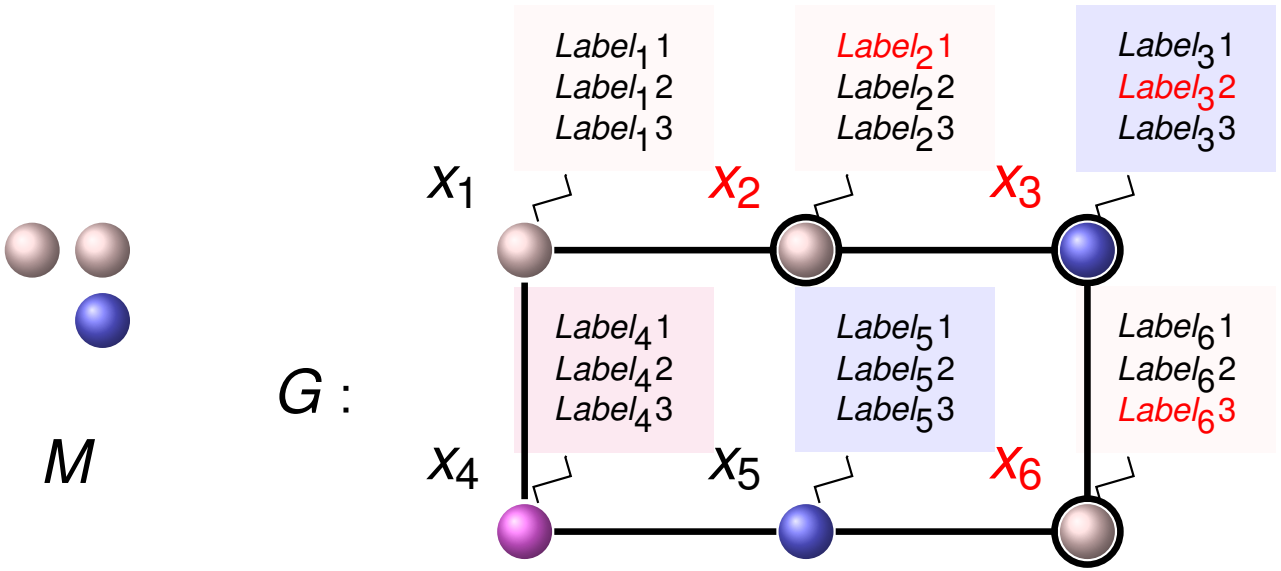
  - For each v, $x_v \Rightarrow (\sum_{i=1}^{|M|} Label_v i = 1)$
- $|M|$ constraints "a node for a given label"
  - For a given label i, $\sum_{v \in V} Label_v i = 1$
- $|V|.|M|$ constraints "one node with a label has a neighbor with a greater label" (except the last one)
  - $Label_v i \Rightarrow (\sum_{u \in N(v)} \sum_{j>i} Label_u j \geq 1)$

GraMoFoNe – A solution



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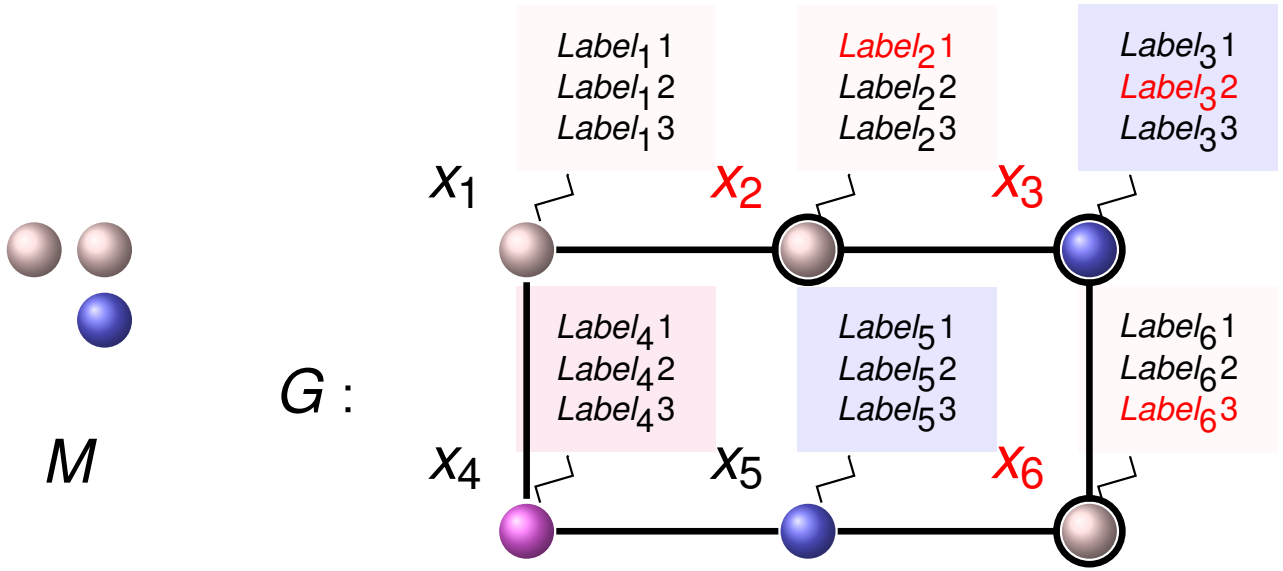

- size" : $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 = 3$
- "coloration":
  - $x_1 + x_2 + x_6 = 2$ (white)
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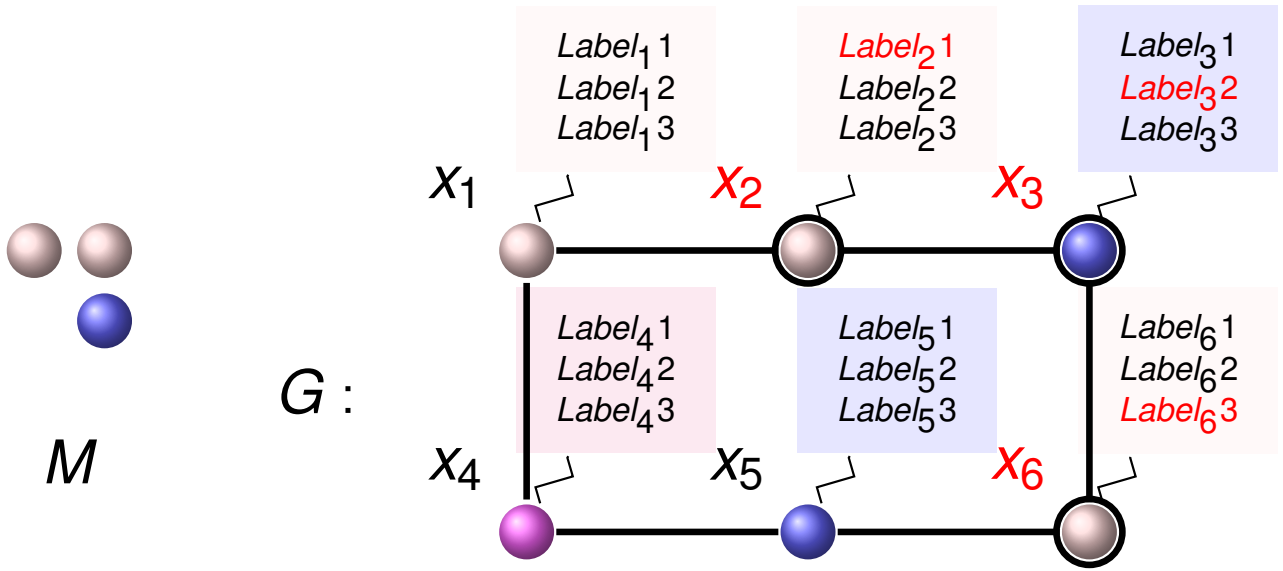
GraMoFoNe – A solution



- "one label by node" : $\forall v,\ x_v \Rightarrow (\sum_{i=1}^{|M|} Label_v i = 1)$
- "one node by label" : $\sum_{v \in V} Label_v i = 1$
- "neighbor with a greater label" : $Label_v i \Rightarrow (\sum_{u \in N(v)} \sum_{j>i} Label_u j \geq 1)$

GraMoFoNe – Extensions

- With a solver over these variables and constraints
  - "Classic" GRAPH MOTIF (set or multiset motifs)
- With Pseudo-Boolean Programming, we get a set of possible solutions

GraMoFoNe – Extensions

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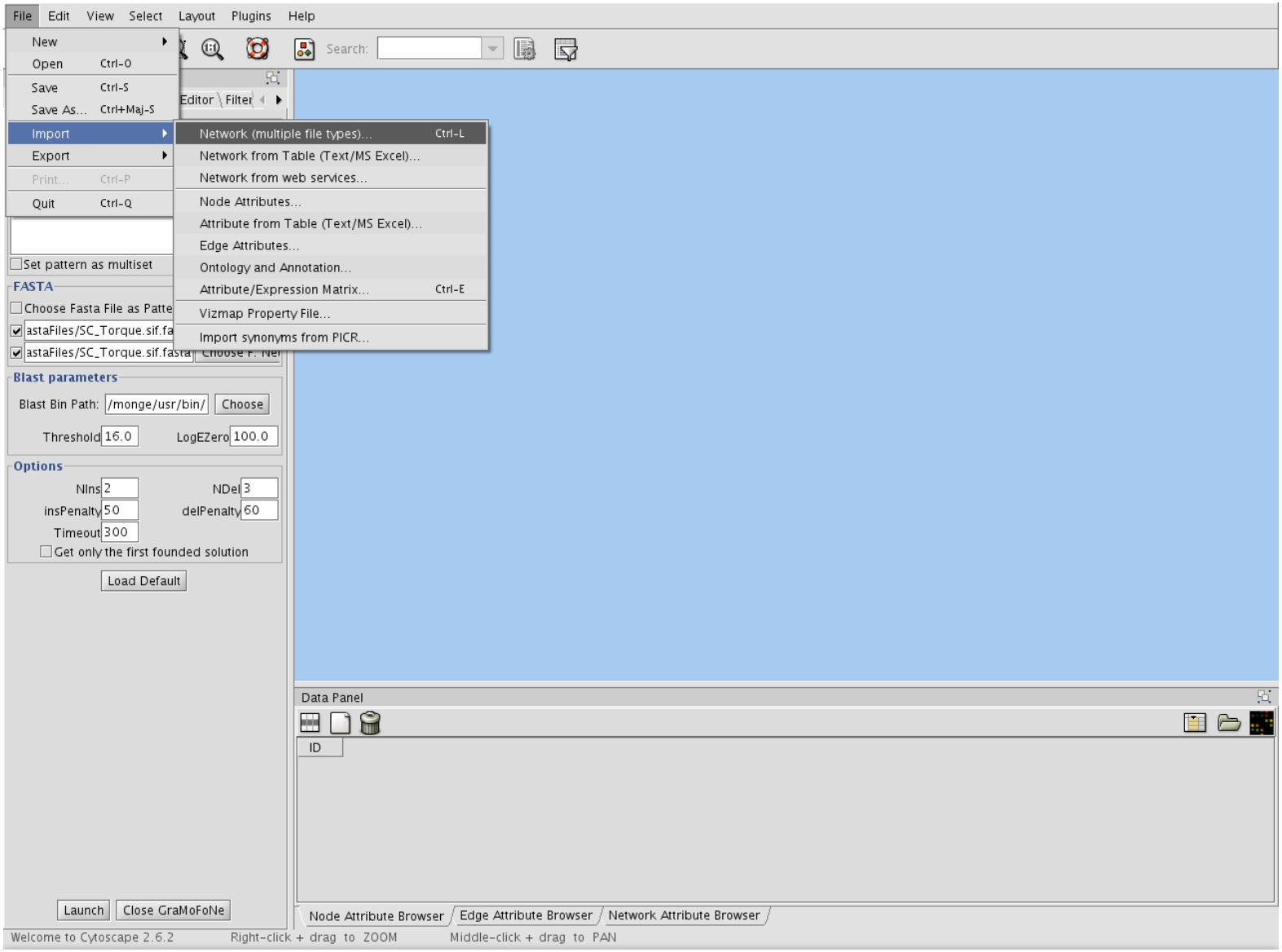
  - "Classic" GRAPH MOTIF (set or multiset motifs)
- With Pseudo-Boolean Programming, we get a set of possible solutions
- With more variables and constraints, we can manage
  - Insertions
  - Deletions
  - A set of colors associated to any graph node (a protein can have more than one function)

GraMoFoNe – GUI



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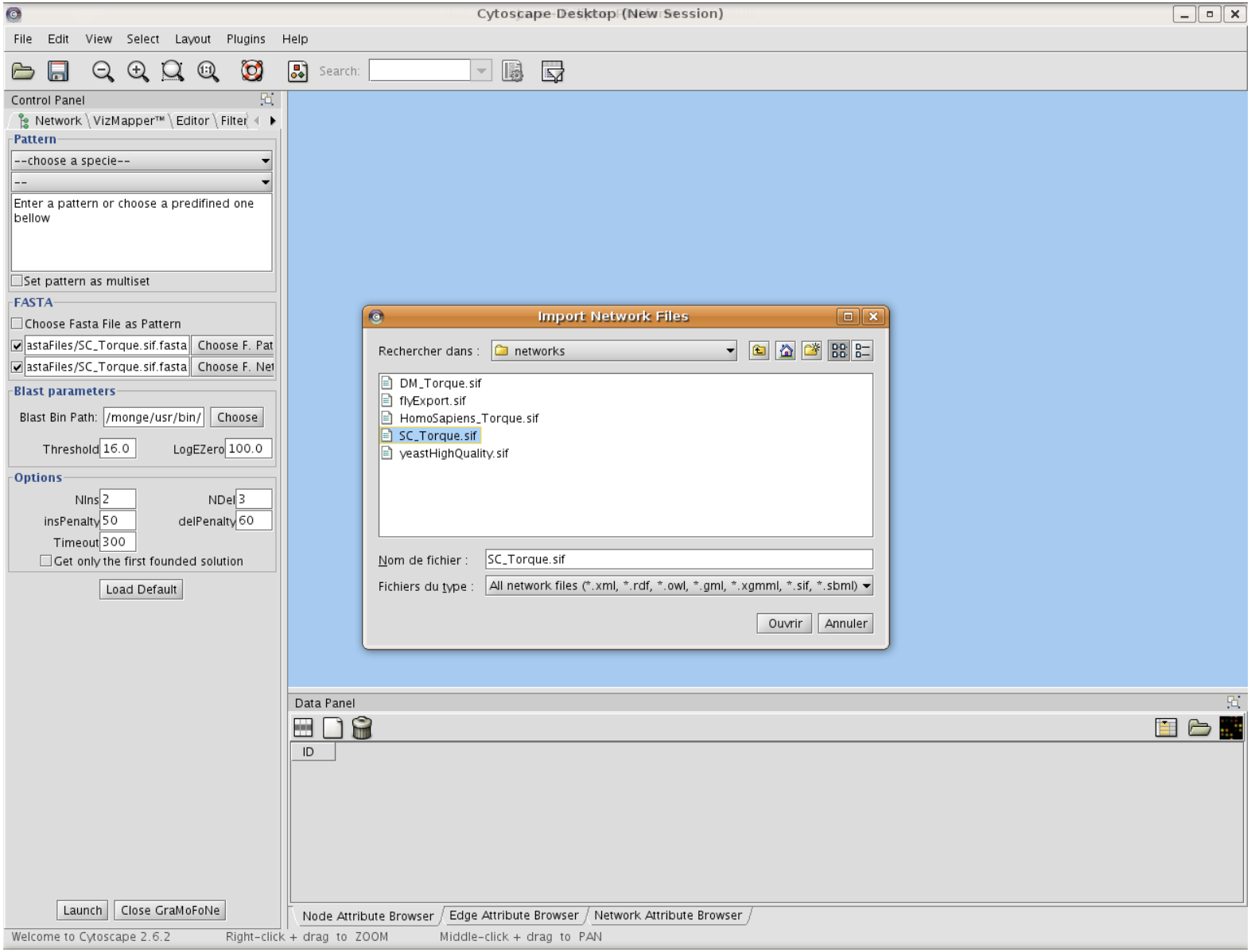

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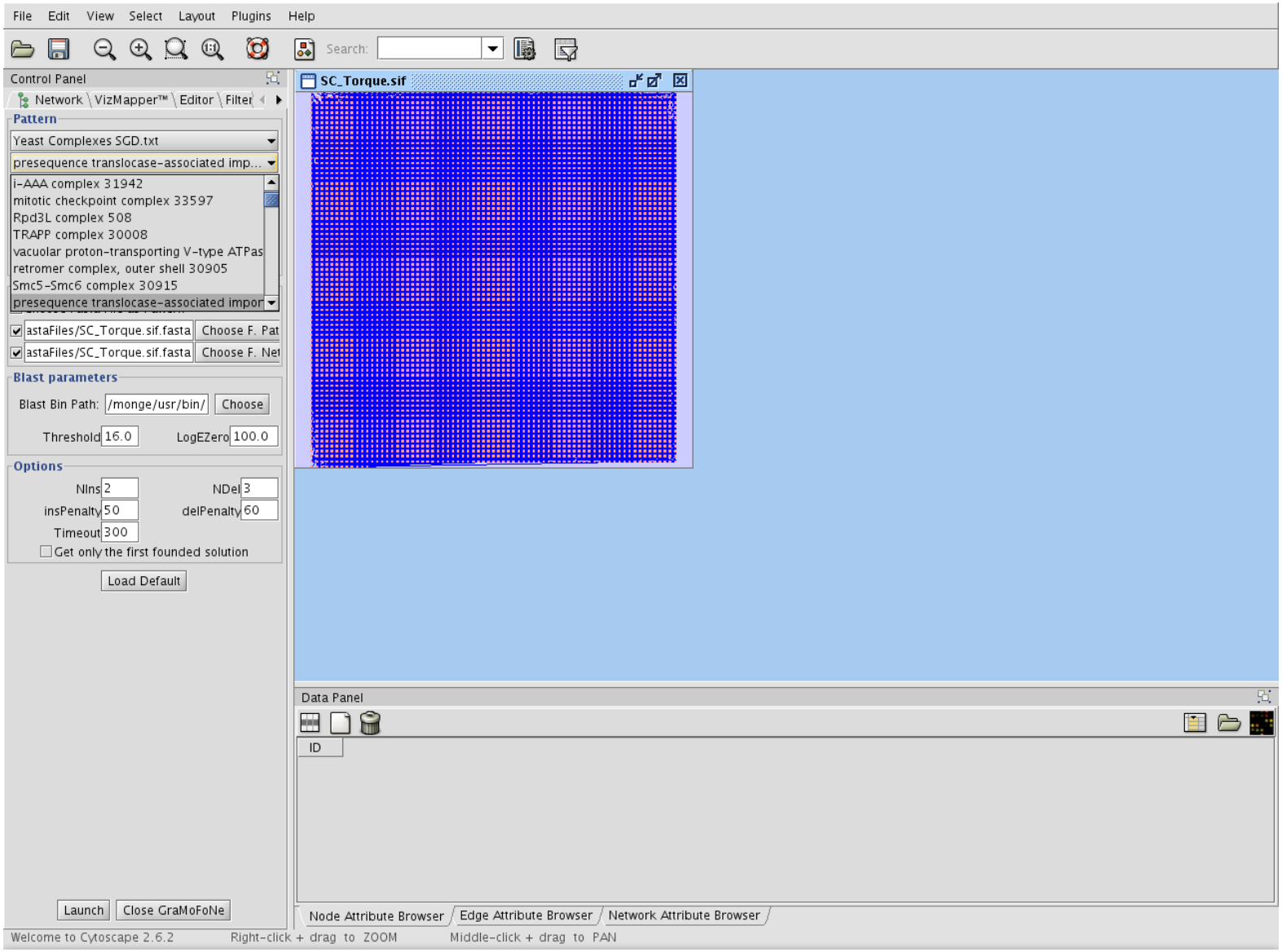

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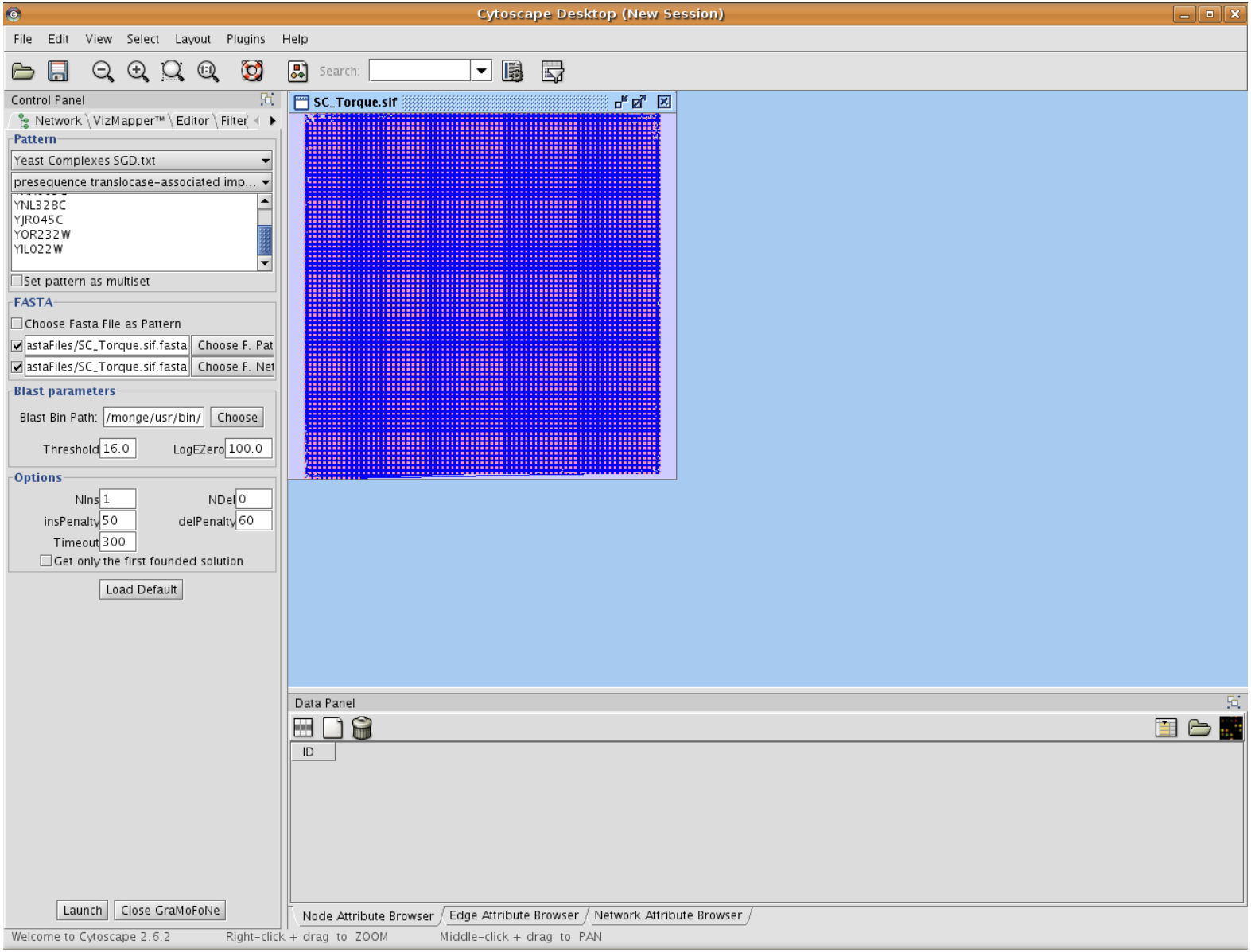

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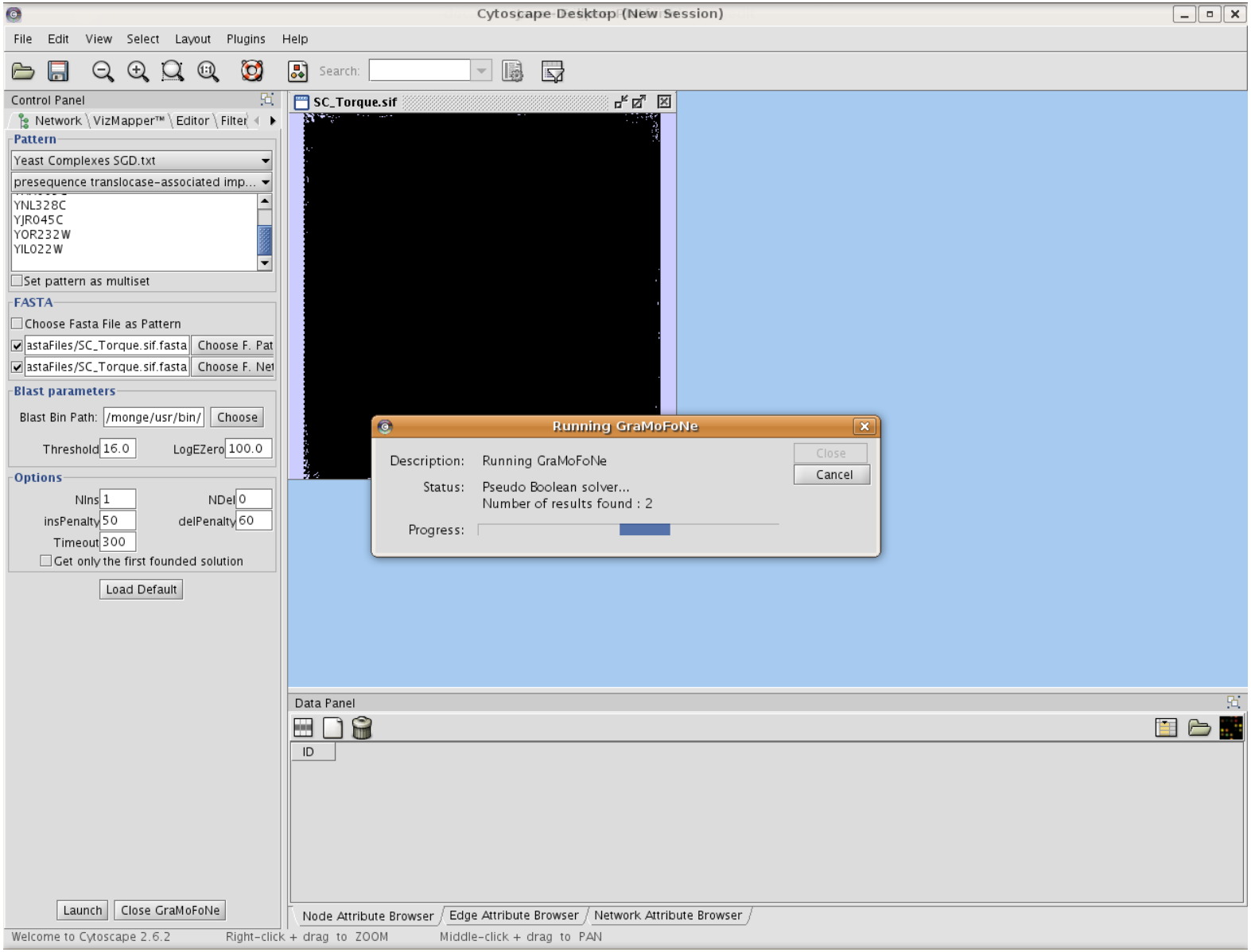

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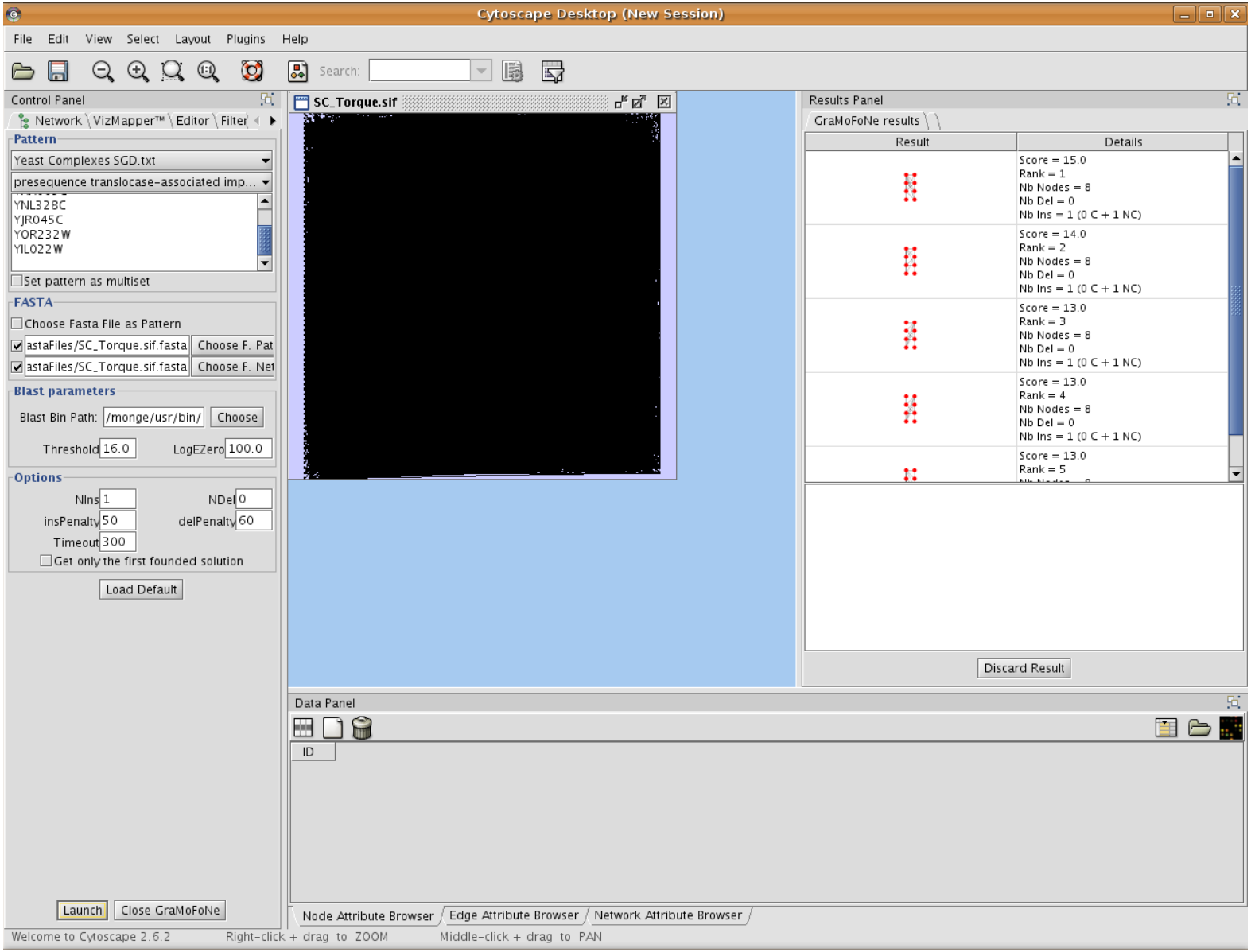

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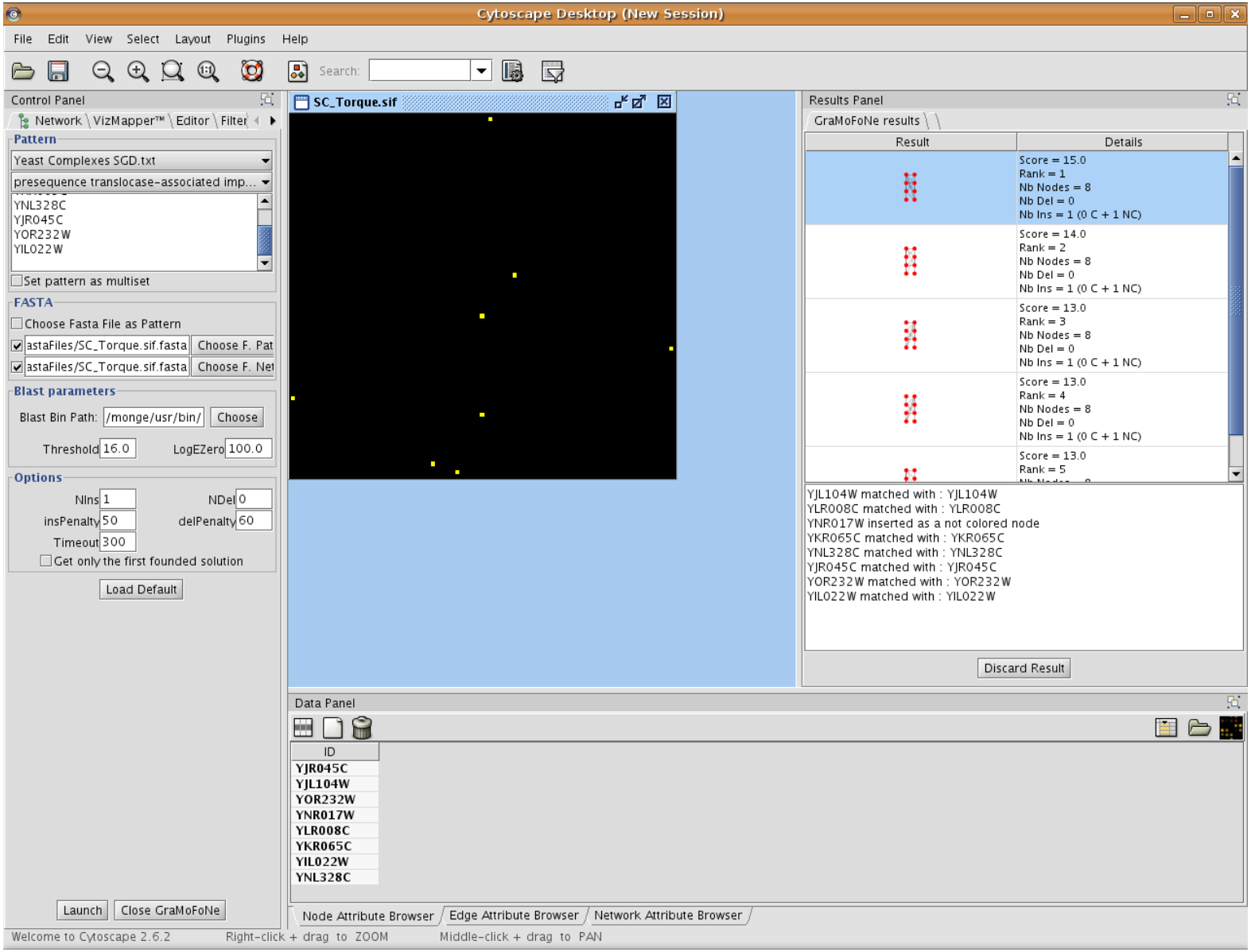

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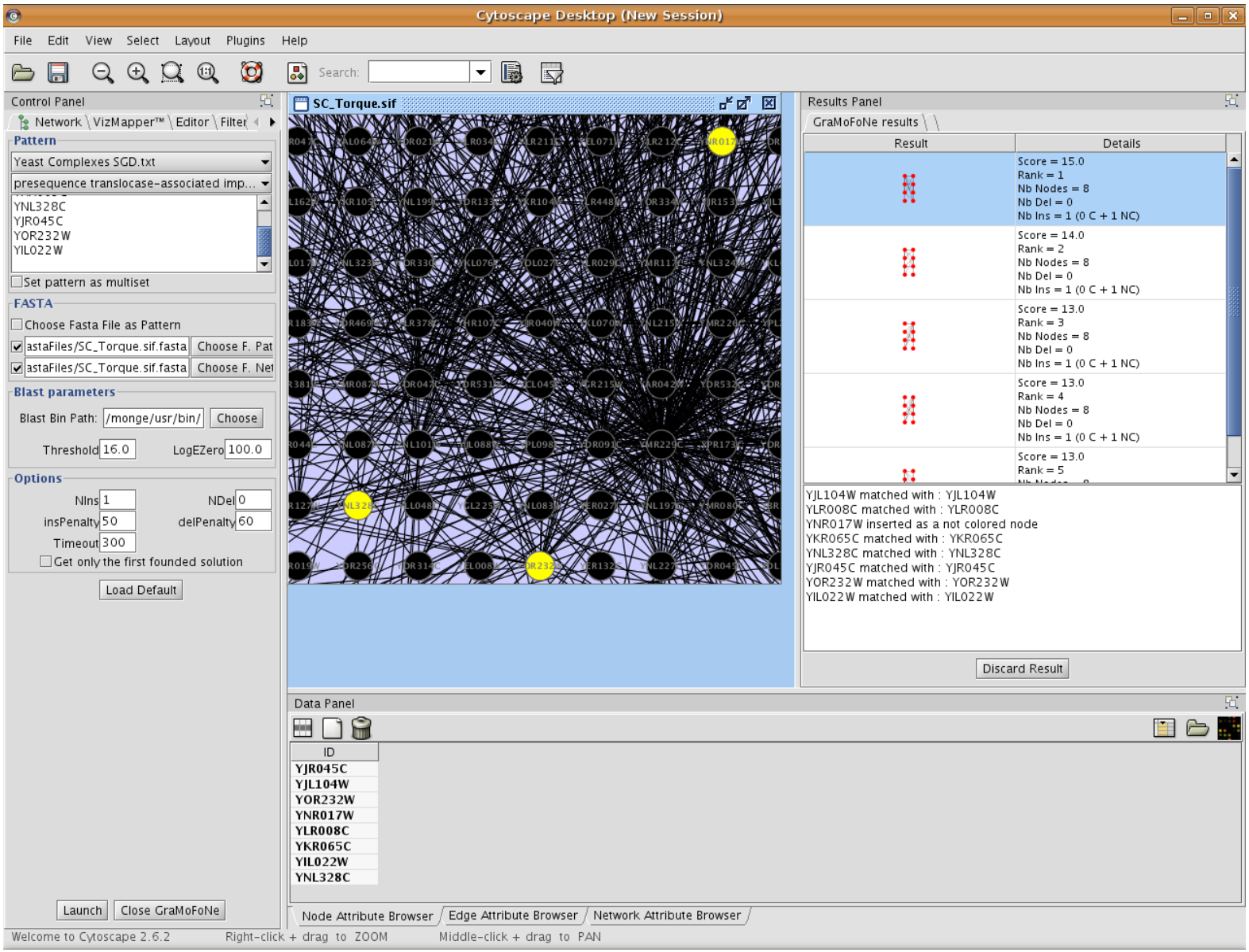

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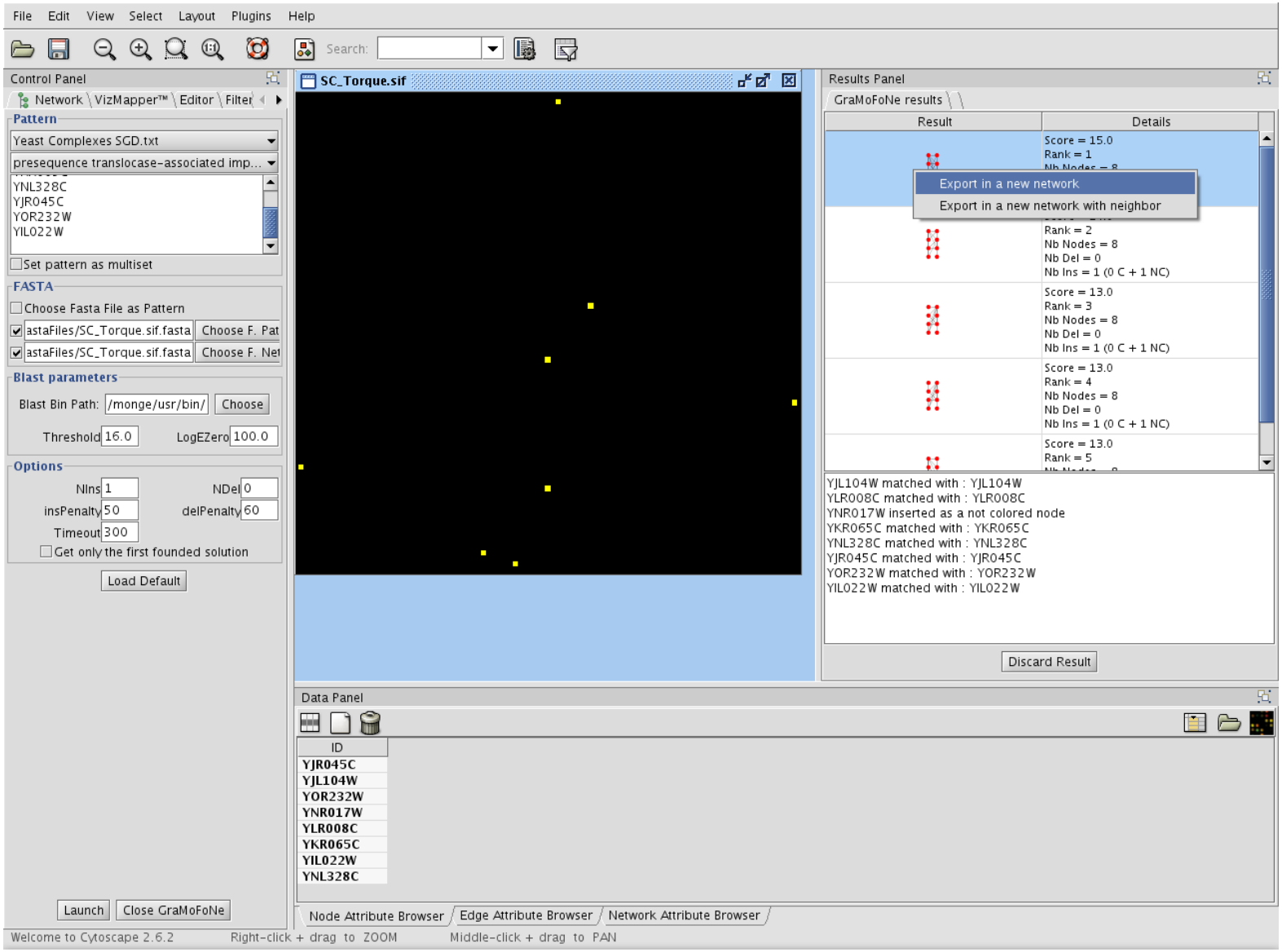

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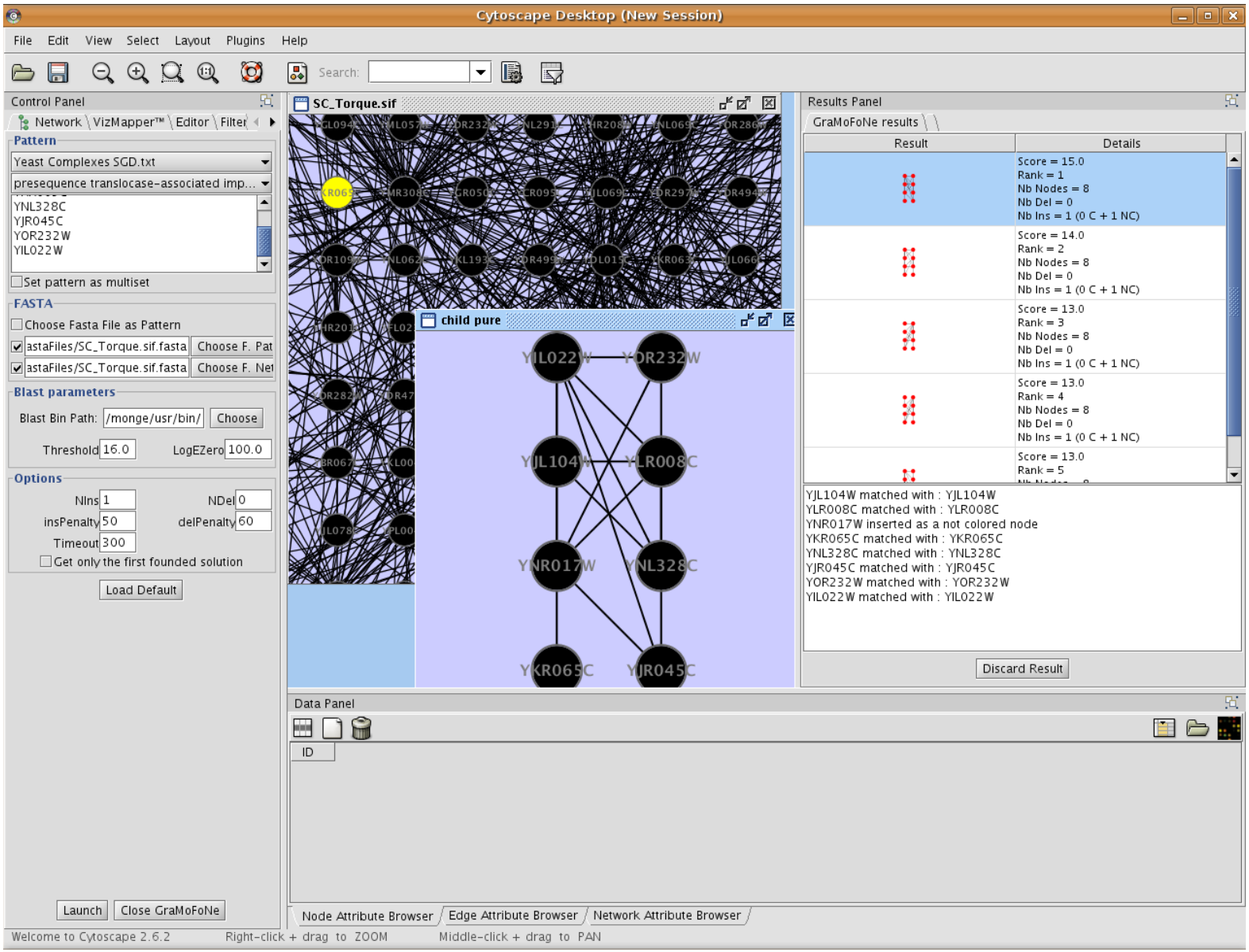


Outline

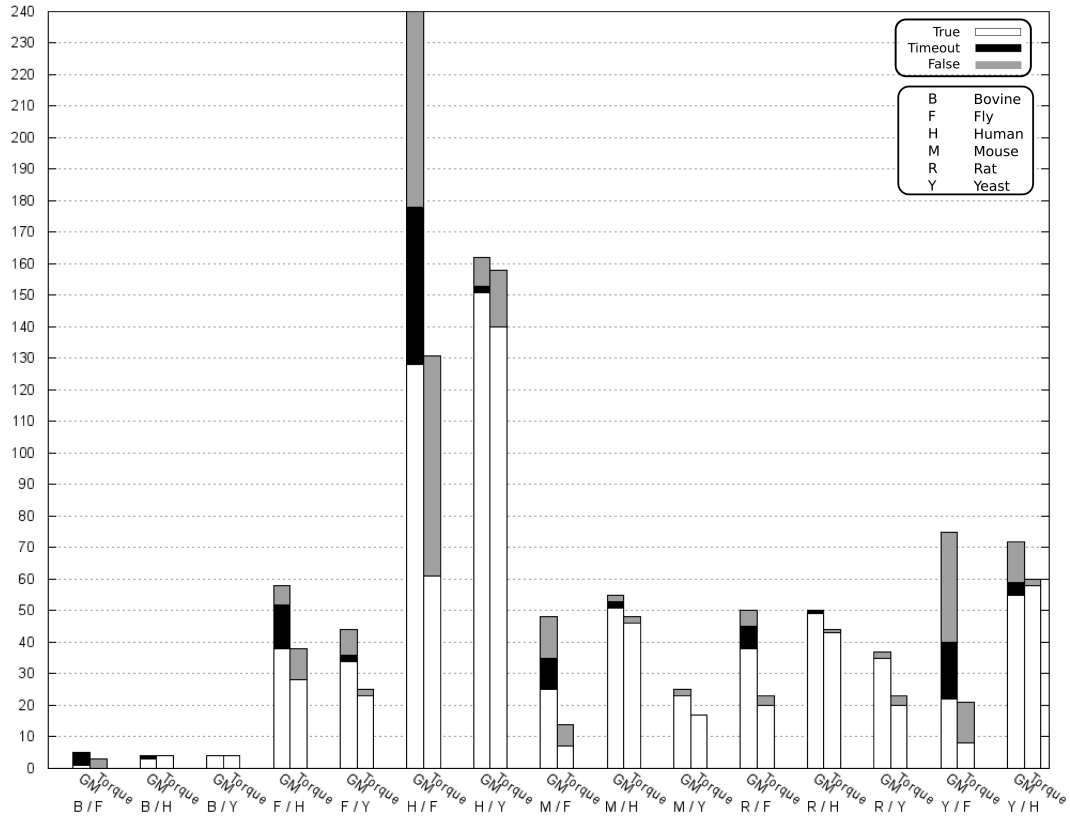
GraMoFoNe – “batch mode”

- Used for large scale tests
- Search for dozen of proteins complexes in other species networks
- Data :
  - Motifs of 6 species (yeast, fly, homo sapiens, mouse, bovine, rat)
  - Network of 3 species (yeast, fly, homo sapiens)
  - Same data as Torque (from up to date DB (SGD, AmiGo, Corum,...) and recent papers)
  - From 2 to 4 indels allowed according to the motif size

GraMoFoNe – “batch mode”

- For each motif
  - Motif found (Before the timeout)
  - Motif does not exist in the network (Before the timeout)
  - Timeout reached

GraMoFoNe – “batch mode”



- False negatives disconnect, false positives give “bad solutions”
- 5-20s (small M), 40-60s (large). Hard to predict time of PB

Conclusion

- We provide a software as a Cytoscape plugin
- Which manage the GRAPH MOTIF problem and some of its variants with Linear Pseudo Boolean Programming
- Freely available at :
  - `http://igm.univ-mlv.fr/AlgoB/gramofone/`
  - Cytoscape plugin page
- Coloration method given in terms of sequence similarity. Other measures ?
- Other relaxations ?

Thank you !

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GRAPH MOTIF [LACROIX ET AL. 2006]

- Given a (multi)-set of colors M and a vertex-colored graph $G = (V, E)$
- Find a subset $V' \subseteq V$ s.t.
  - $G[V']$ is connected
  - Colors of V' equals M (there is a bijection between the motif and solution colors)

GRAPH MOTIF – NP-Complete

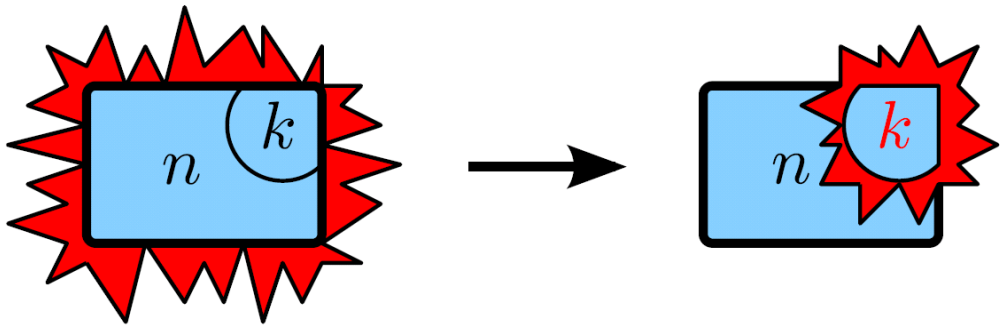
- A lot of theoretical results...
- GRAPH MOTIF is NP-Complete, even on strong conditions:
  - Network is a tree [LACROIX ET AL. 2006]
  - Network is a tree with maximum degree 3 and the motif is a colorful set [FELLOWS ET AL 2008]
  - Motif is over 2 colors and the network is a bipartite graph of maximum degree 4 [FELLOWS ET AL 2008]
- Exact solution $\longrightarrow$ exponential runtime

GRAPH MOTIF – Coping with hardness

- Fact : **patterns are smaller** ($\sim 5 - 15$) than the network (e.g. $\sim$ 5.000 for the yeast)
- Restrict the exponential part to k instead of n: **parameterized complexity**

FPT Algorithms

- An FPT algorithm [Downey & Fellows 1999]:
  exact algorithm **exponential** only in its **parameter k** (not in the input size n)
- $f(k).n^c$, with c a constant and f any function



FPT Algorithms

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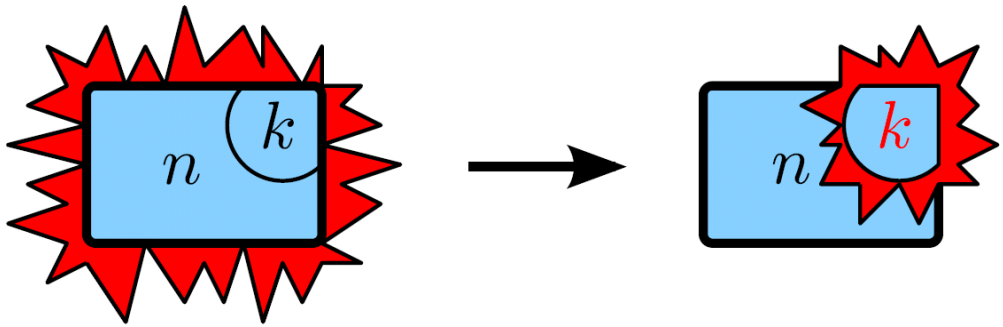
  exact algorithm **exponential** only in its **parameter k** (not in the input size n)
- $f(k).n^c$, with c a constant and f any function
- Warning, $2^{2^{2^{2^{2^{2^k}}}}}.n$ is FPT...



Graph Motif – Coping with hardness

- Sharp borderline between tractable and intractable instances of the problem :
  - FPT if the parameter is the size k of the motif [Lacroix et al. 2006]
    - $\mathcal{O}^*(2^k)$ if the motif is colorful [Bruckner et al. 2009]
    - $\mathcal{O}^*(4.32^k)$ if the motif is a multiset [Betzler et al. 2008]

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  - But: GRAPH MOTIF is W[1]-hard if the parameter is the number of colors [FELLOWS ET AL. 2008] (no FPT algorithm possible with this parameter)

GraMoFoNe – Extensions

- We have to be careful
- If there is 1 insertion and 1 deletion, the size of the solution is equals to the size of the motif
- But we can not bound the number of in/del
- We have to look for each different color...

- A node with a set of colors can not match more than one color of the motif (need a bijection)

GraMoFoNe – “batch mode”

- Preprocessing
  1. Proteins without homologous protein in the network are apriori “deleted”
  2. If a colored network node is “too far” from another colored network node, we delete it

GraMoFoNe – “batch mode”

- A motif is “feasible” if
  1. Size 4-25
  2. Less than a fixed number of motif proteins without homologous in the network
  3. A connected component with “enough” colored nodes
- For each motif
  - Before the timeout
    - Motif found
    - Motif do not exists in the network
  - Timeout reached