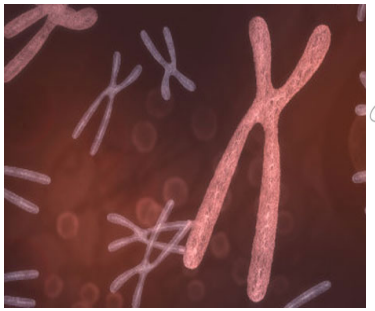
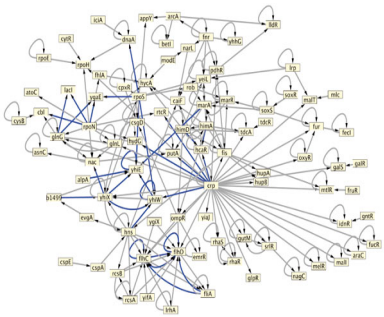
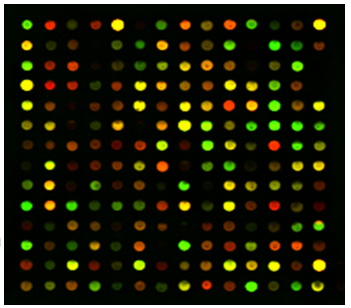
Extended Bayesian scores for reconstructing gene regulatory networks.

Jimmy Vandel

Simon de Givry & Brigitte Mangin







Université Paul Sabatier
TOULOUSE III

ECCS'10
September 16th, 2010

INRA
Institut National de la Recherche Agronomique

OUTLINES :

→ Biological background

→ State of the art

→ Score-based structure learning

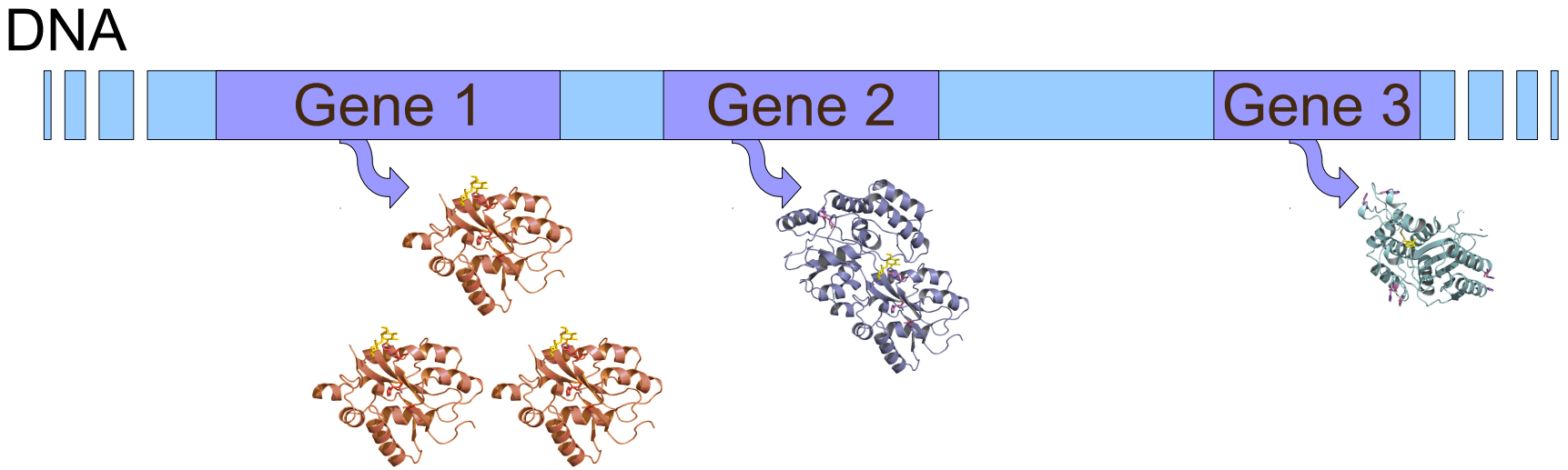
→ Model with extra biological knowledge

→ Results

→ Conclusion and perspectives

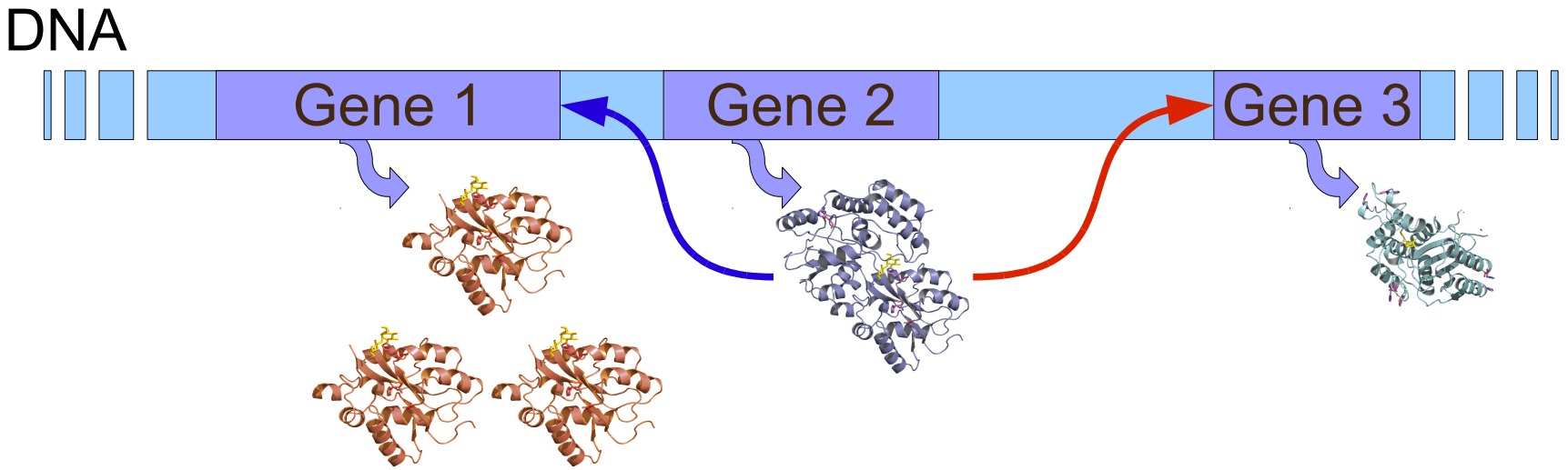
Central dogma of molecular biology

Central dogma of molecular biology



→ gene activities (mRNA concentrations)

Central dogma of molecular biology



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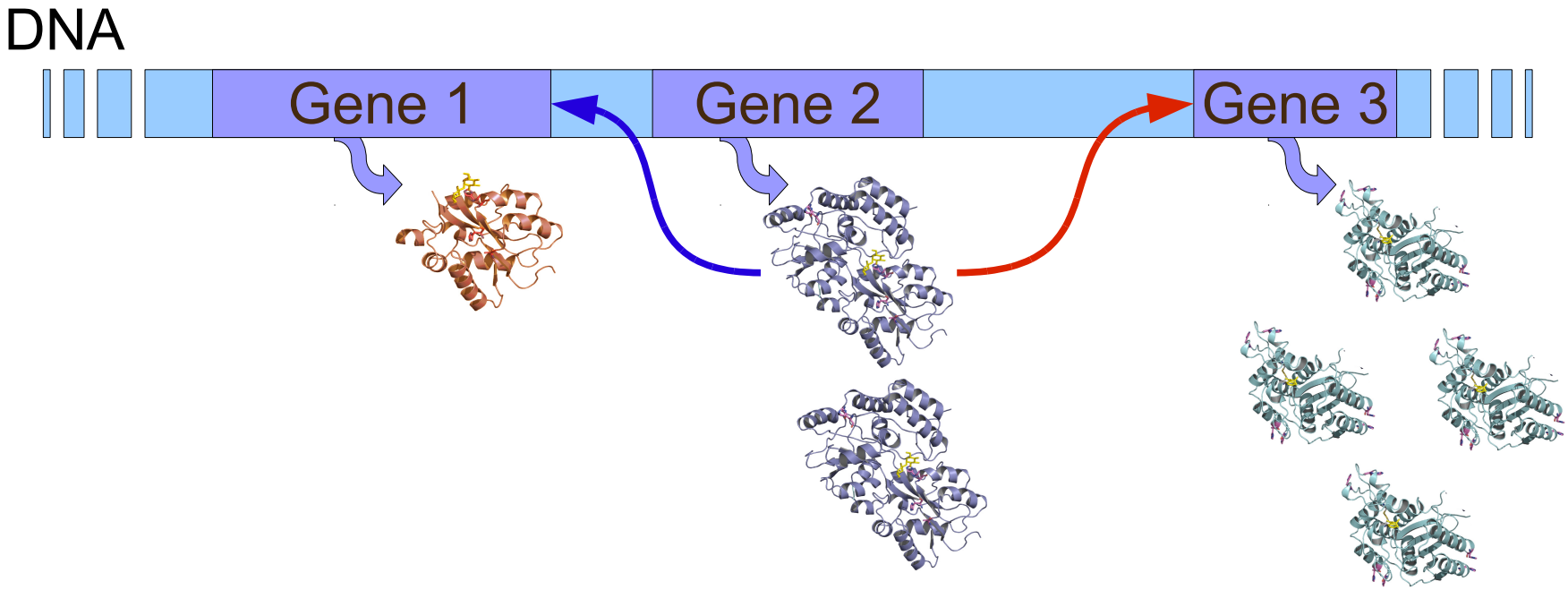
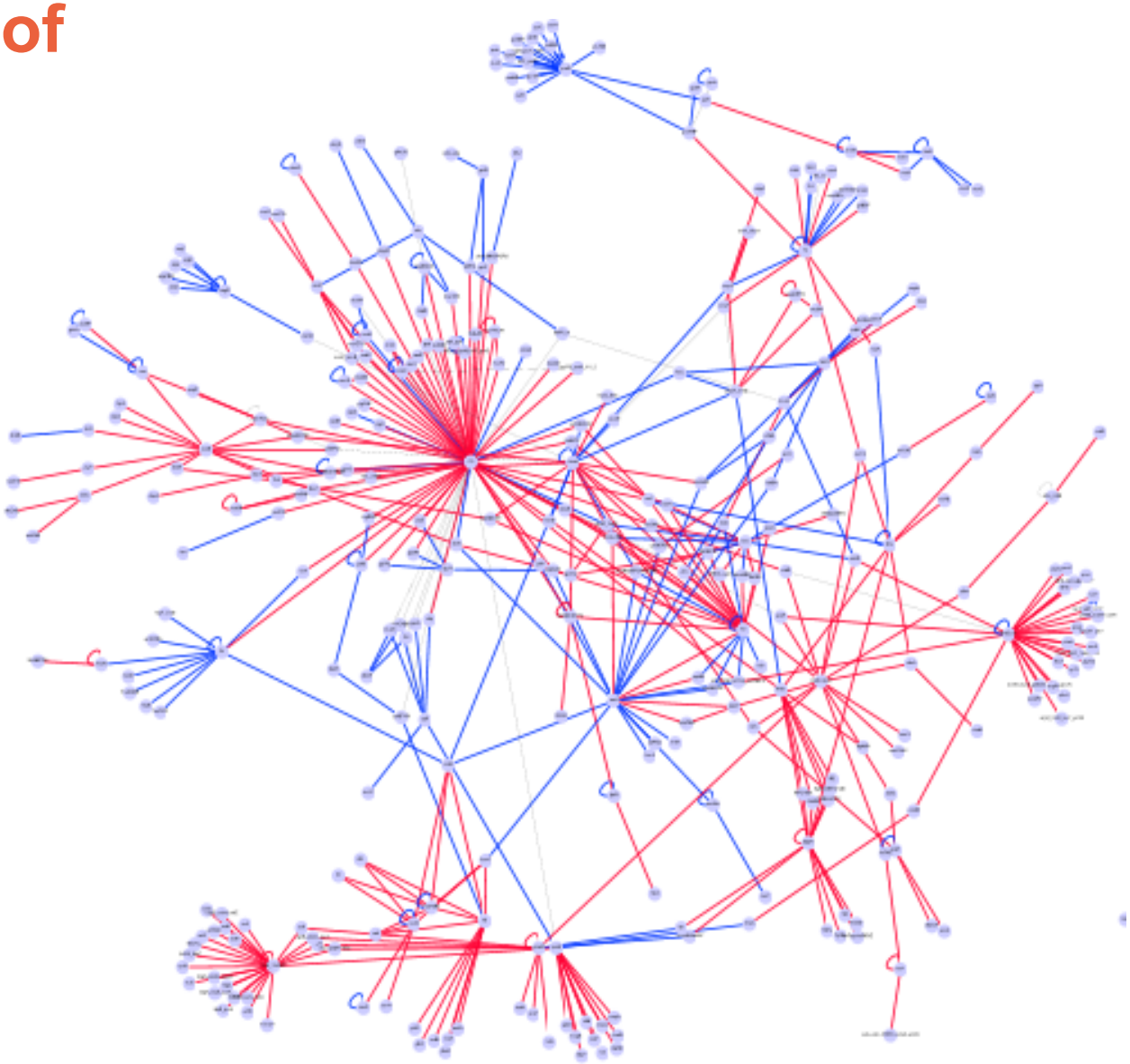


→ gene activities (mRNA concentrations)

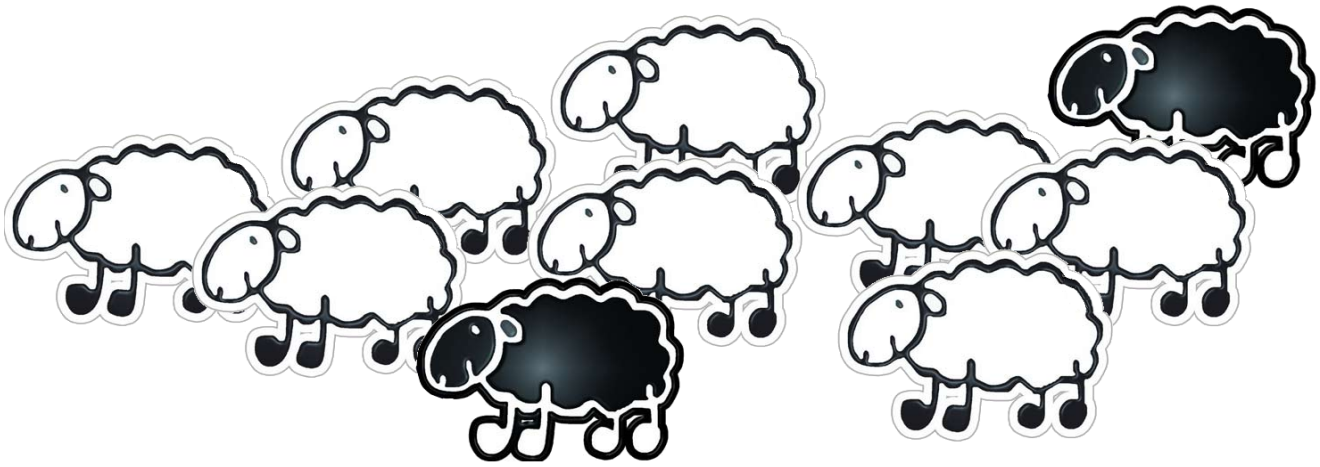
→ gene regulations

Goal : Reconstruction of gene regulatory network.

Escherichia coli
(423 genes
578 regulations)



Polymorphism



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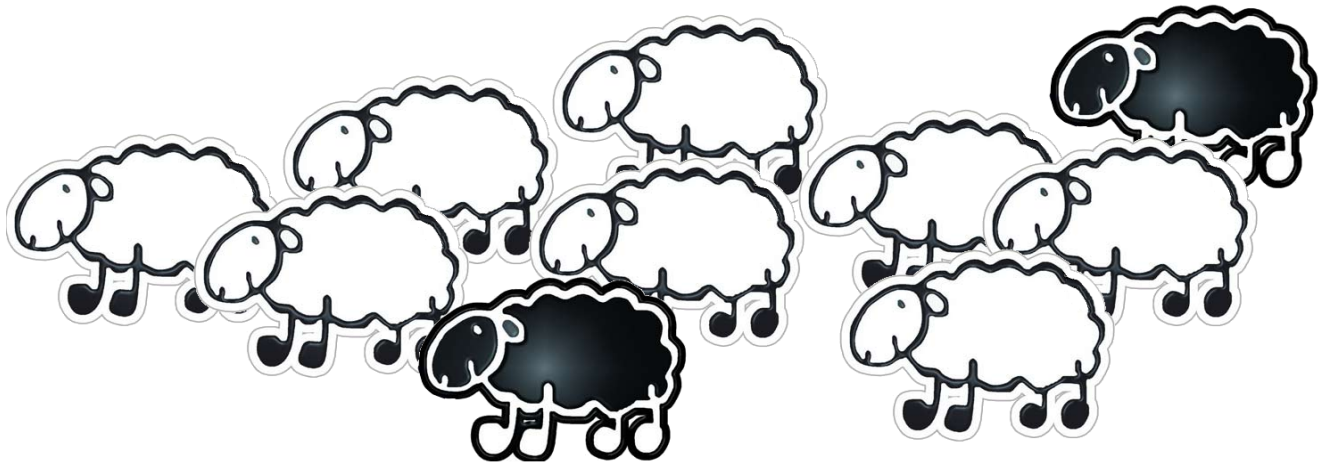

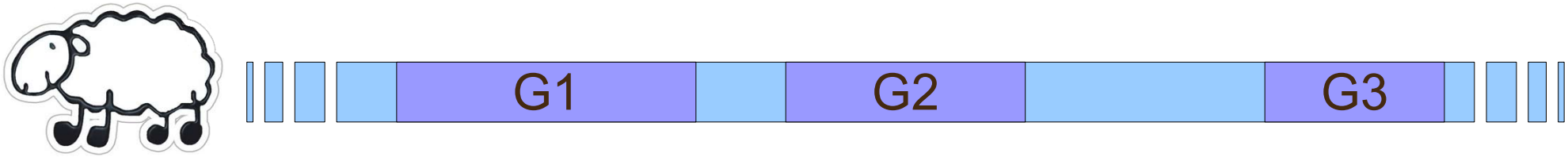

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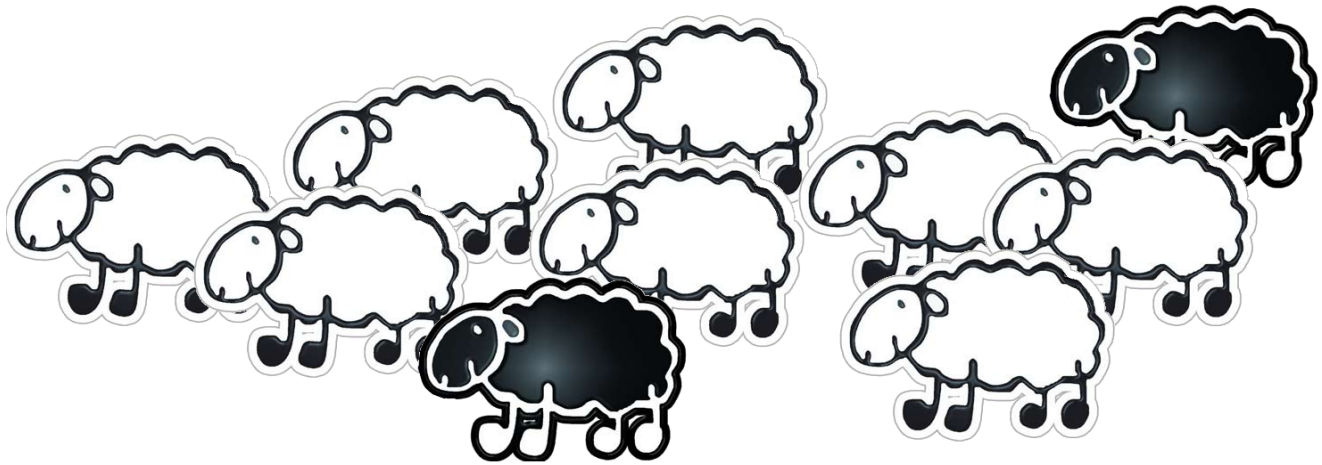

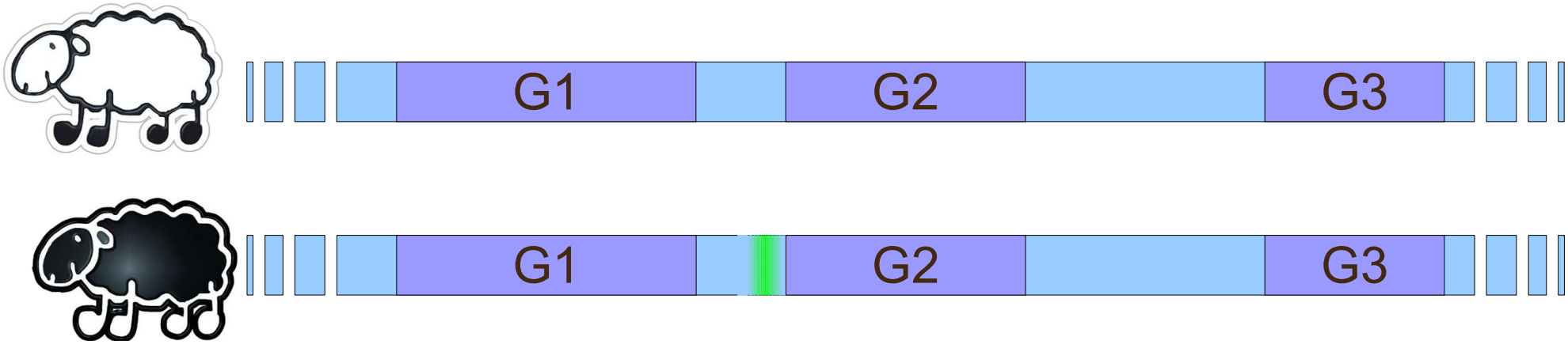

→ DNA mutations in genes - in promoter region (impact on gene activity)

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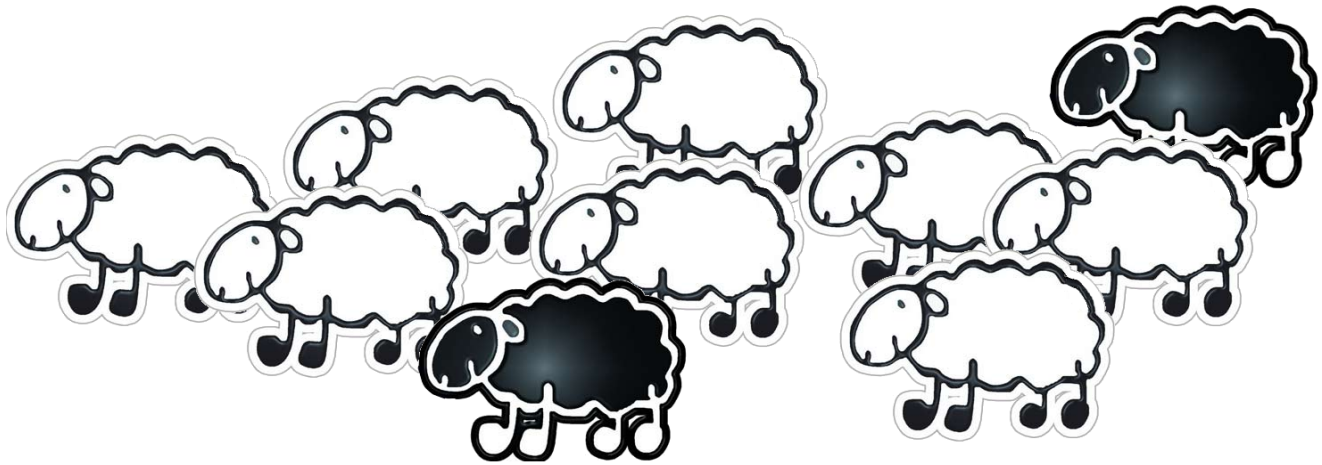

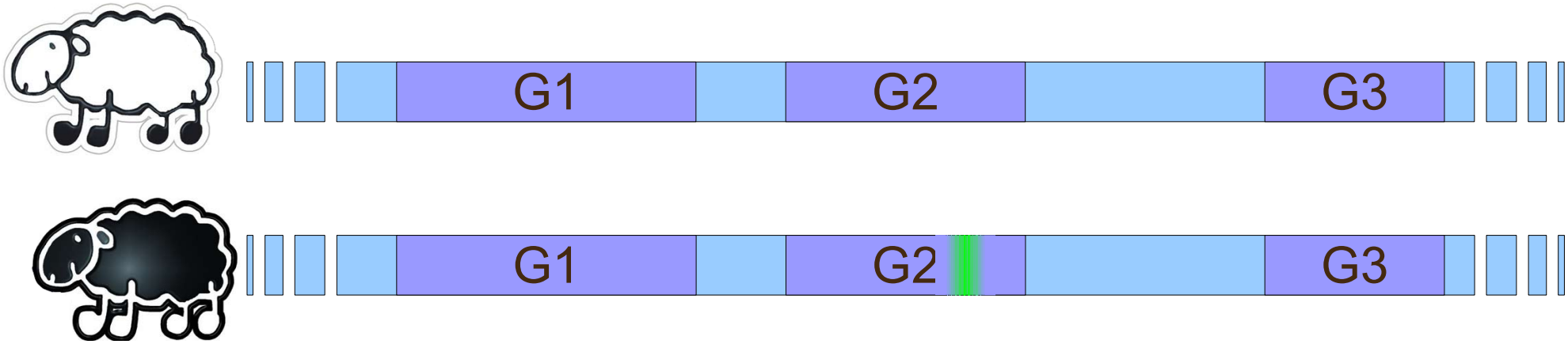

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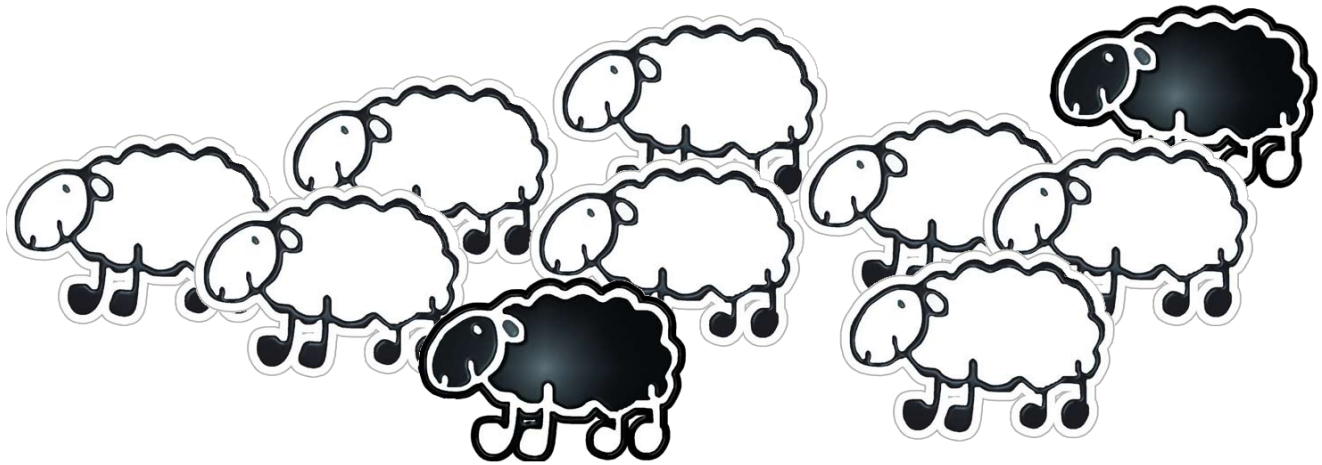

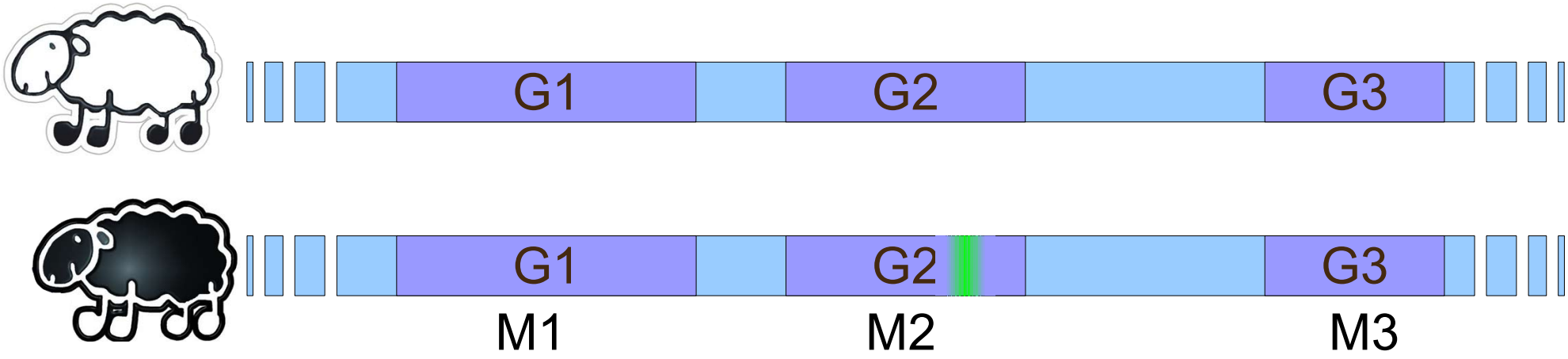

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- in coding region (modify protein structure)

→ observable through one genetic marker for each gene

State of the art of gene regulatory network inference

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Pairwise correlation model

- Correlations measurement + threshold

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Probabilistic discrete graphical model

→ Bayesian networks on discrete data (*Friedman* 2000, *Zhu* 2007)

Bayesian network

- Directed acyclic graph G composed of n variables X_i with domain size r_i

- Conditional distribution for variable X_i, given its parents Pa_i in G:

$$P_G(X_i/Pa_i^j) = \theta_{ij}$$

- Representation of a joint probability distribution :

$$P_G(X) = \prod_{i=1}^{n} P_G(X_i/Pa_i)$$

- We note $Dim(G) = \sum_{i=1}^{n} (r_i - 1) * q_i$ the dimension of the network with $q_i = \prod_{Pa_i^j} r_j$

Score based learning

We look for the graph $G_{score} = argmax_{G_i} P(G_i / D)$ with dataset D .

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  - exact under → hypothesis **B***ayesian* ***D****irichlet score*
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- $P(G_i)$:prior probability of the graph G*i*
  → assumed to be uniform

Scores

Scores

- BD Score *(**D.Heckerman** Machine learning 1995)*
  - A priori on conditional probability θ_{ij} following a Dirichlet distribution with parameter α_{ijk}

$$BD(G) = \prod_i^n \prod_j^{q_i} \frac{\Gamma(\alpha_{ij})}{\Gamma(\alpha_{ij} + N_{ij})} \prod_k^{r_i} \frac{\Gamma(\alpha_{ijk} + N_{ijk})}{\Gamma(\alpha_{ijk})}$$

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- fNML score *(**T.Silander** International journal of approximate reasoning 2010)*
  (**f**actorized **N**ormalized **M**aximum **L**ikelihood)
  - How much G explain D compare to other possible data sets D'

$$fNML(G)=\log(P(D/G,\hat{\theta}))-\sum_{i=1}^{n}\sum_{j=1}^{q_i} logC_{N_{ij}}^{r_i} \quad with \quad C_{N_{ij}}^{r_i} the\, normalizing\, sum$$

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Against principle of parsimony ?

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Against principle of parsimony ?

  - Extend BIC idea (**Chen** *Biometrika* 2008)

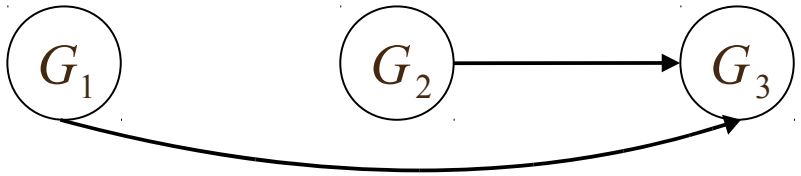
$$P(G_i^j) \propto \tau_l^{-\gamma}(G_i^j) \quad with \quad \gamma \in [0,1]$$

$$\log(P(G_i)) \simeq -\gamma \log\left(\prod_{j=1}^{n} \tau_l(G_i^j)\right)$$

→ applicable for all scores seen previously

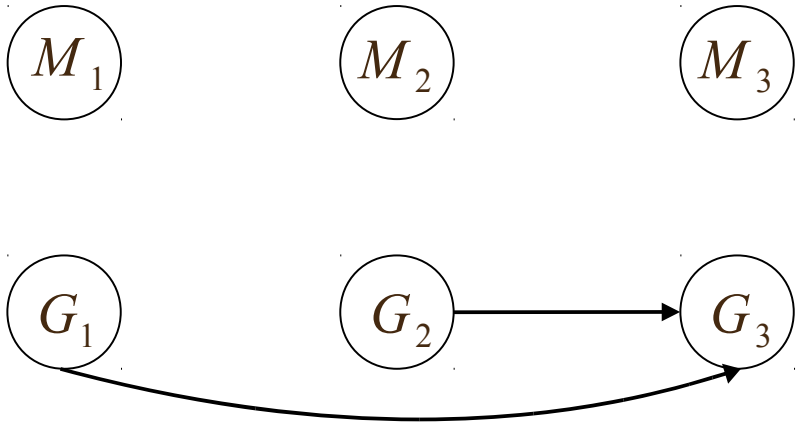
Model description and extra biological knowledge

Full observed data



Model description and extra biological knowledge

Full observed data
One marker per gene



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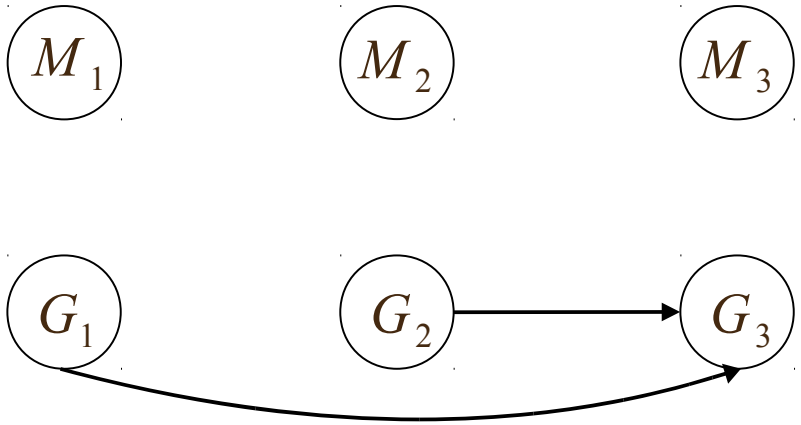
Discrete expression data



G*i* : [1,4]

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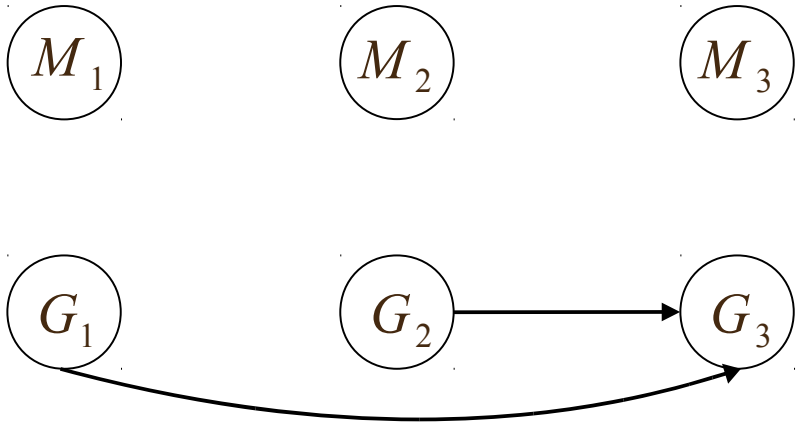
SNP markers



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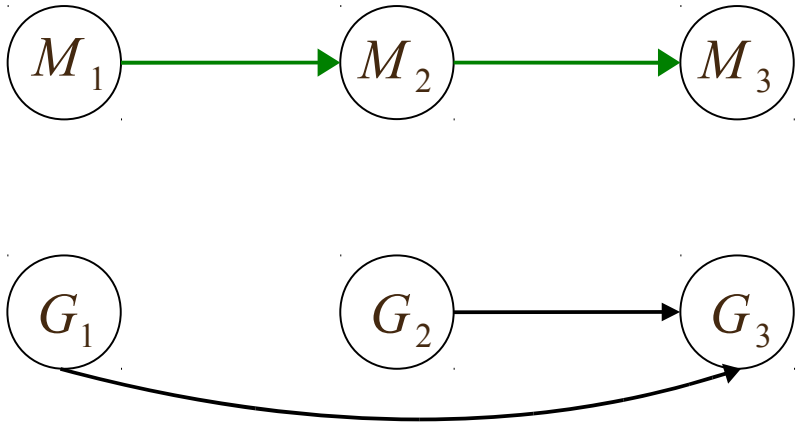

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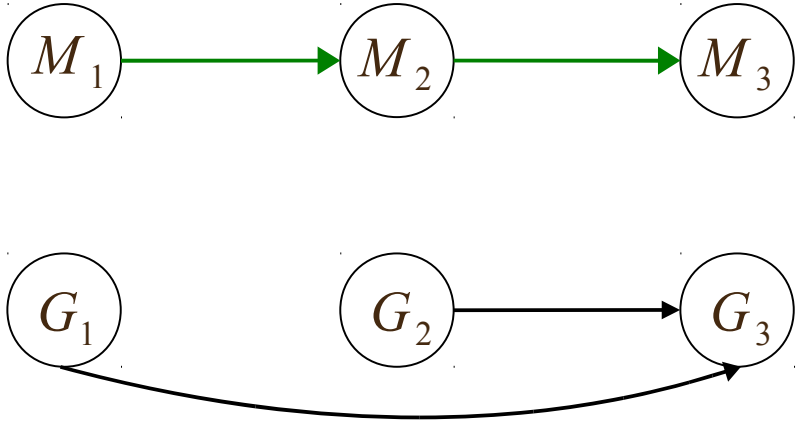

M_i : 0/1

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→ Genetic linkage between markers

→ Mutation in promoter region of G_i *(ex G_1 and G_3)*

- Force link $M_i \rightarrow G_i$
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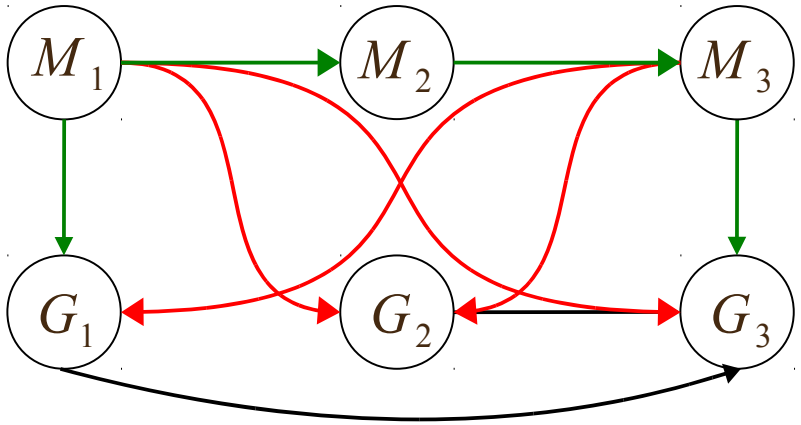

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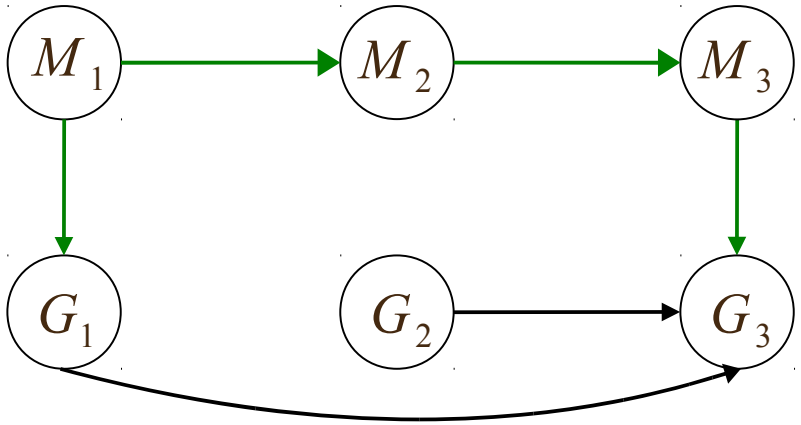

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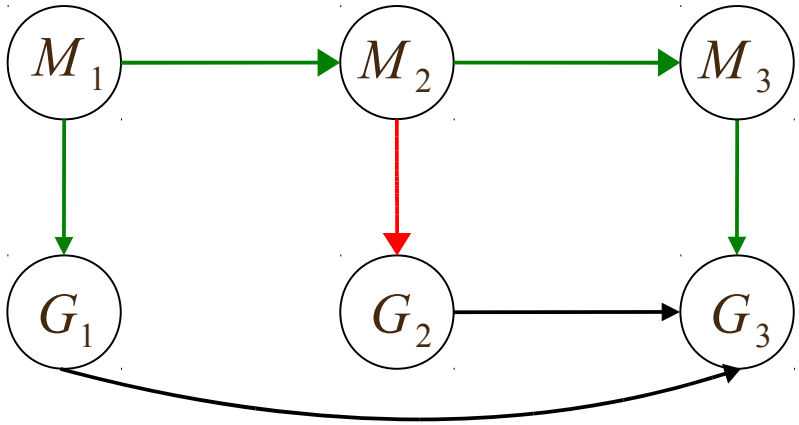

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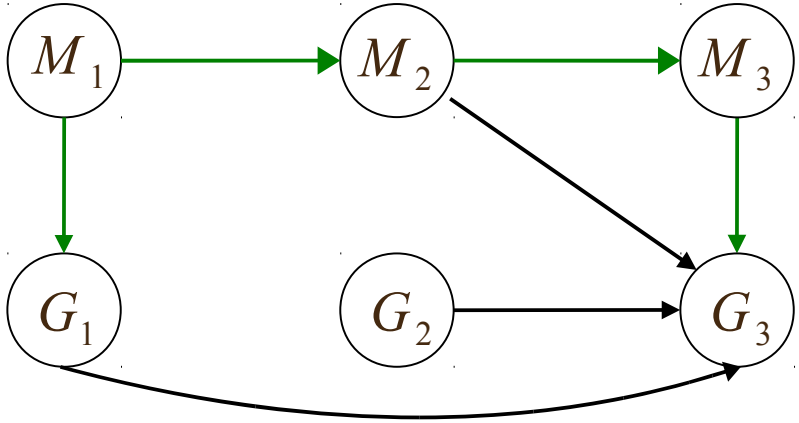

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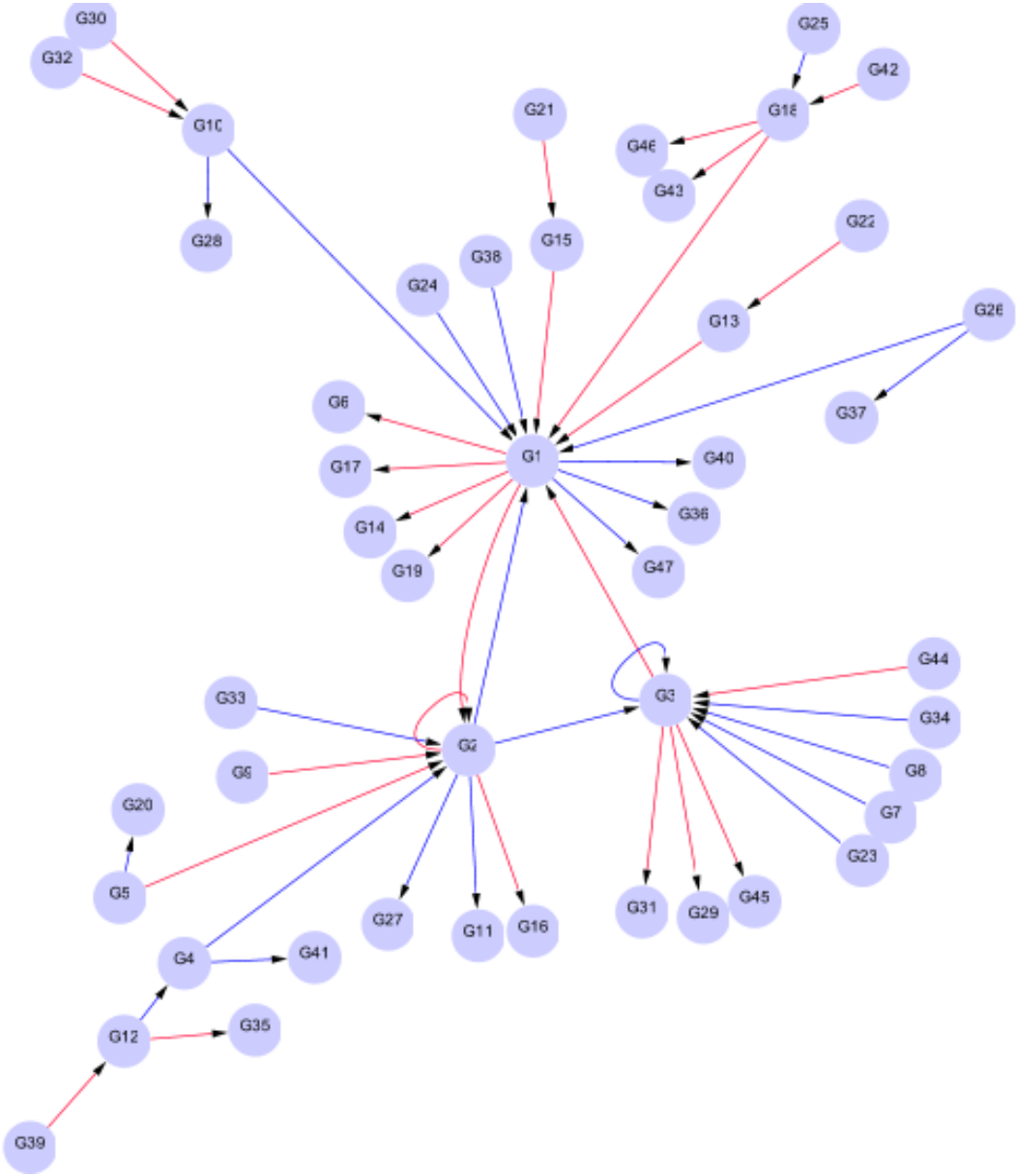
Network studied

Artificial gene networks
(Mendes et al., Bioinformatics, 2003)

- *similar structure of known networks*
- *few hubs*
- *50 nodes / 50 edges*



Network evaluation

- Mean over 50 artificial networks
- Sample size between 50 and 500 individuals
- In our model we project all $M_i \rightarrow G_j$ as a $G_i \rightarrow G_j \quad \forall\, j \neq i$
- We use Greedy search (implemented in **Banjo** *Hartemink* 2005)
- Evaluation doesn't takes into account edges orientation
- 2 common metrics Predictive value / Sensitivity

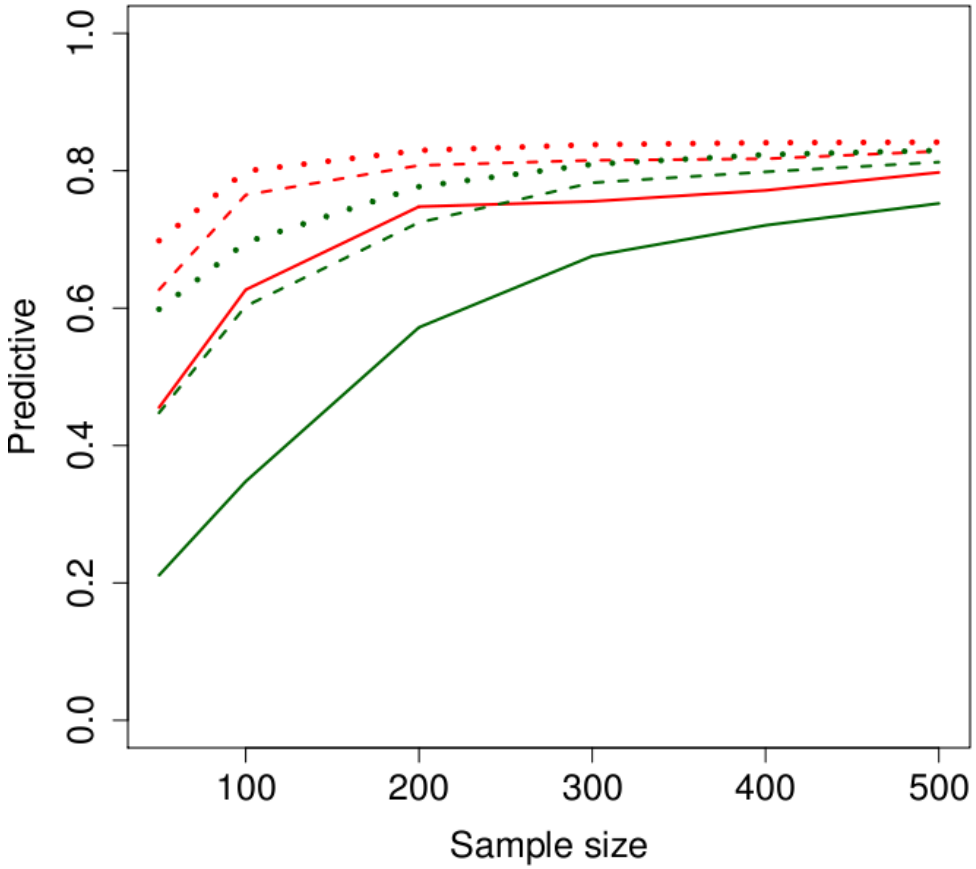
$$Predictive\,value\,(=1-FDR): \frac{TP}{TP+FP}$$

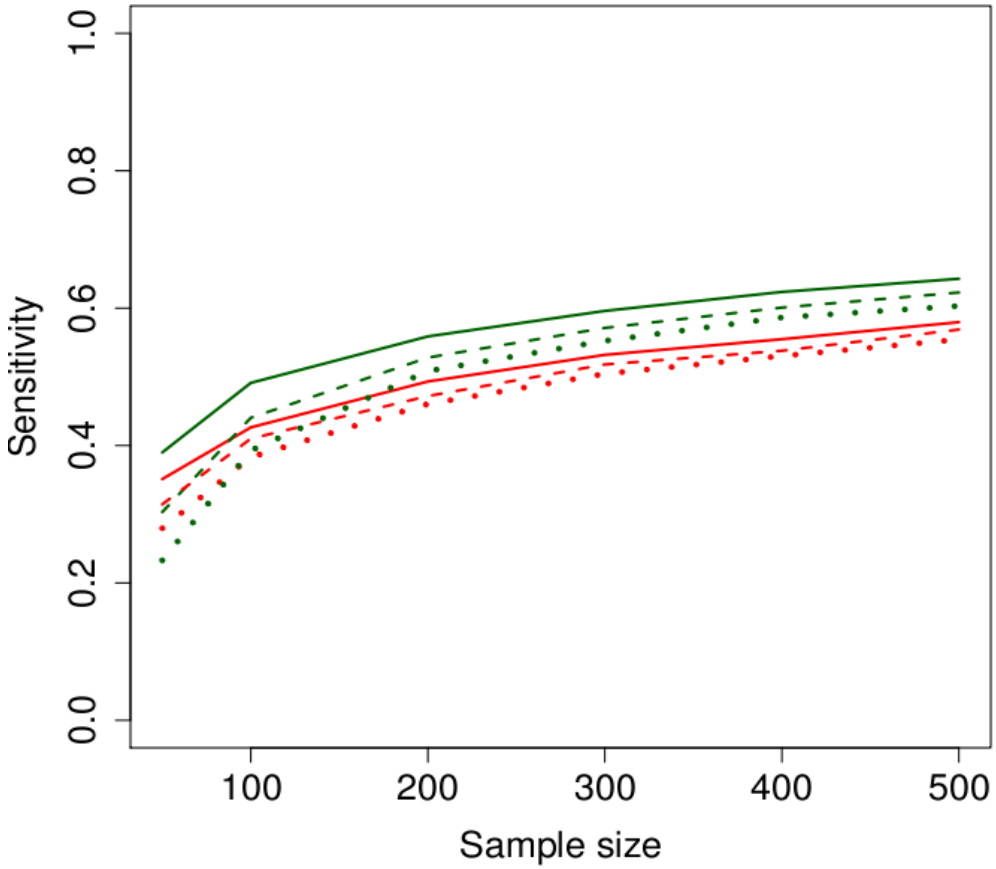
$$Sensitivity: \frac{TP}{TP+FN}$$

TP : number of correct learned edges
FP : number of wrong learned edges
FN : number of missed edges

Extended scores impact

Legend: BIC score
fNML score

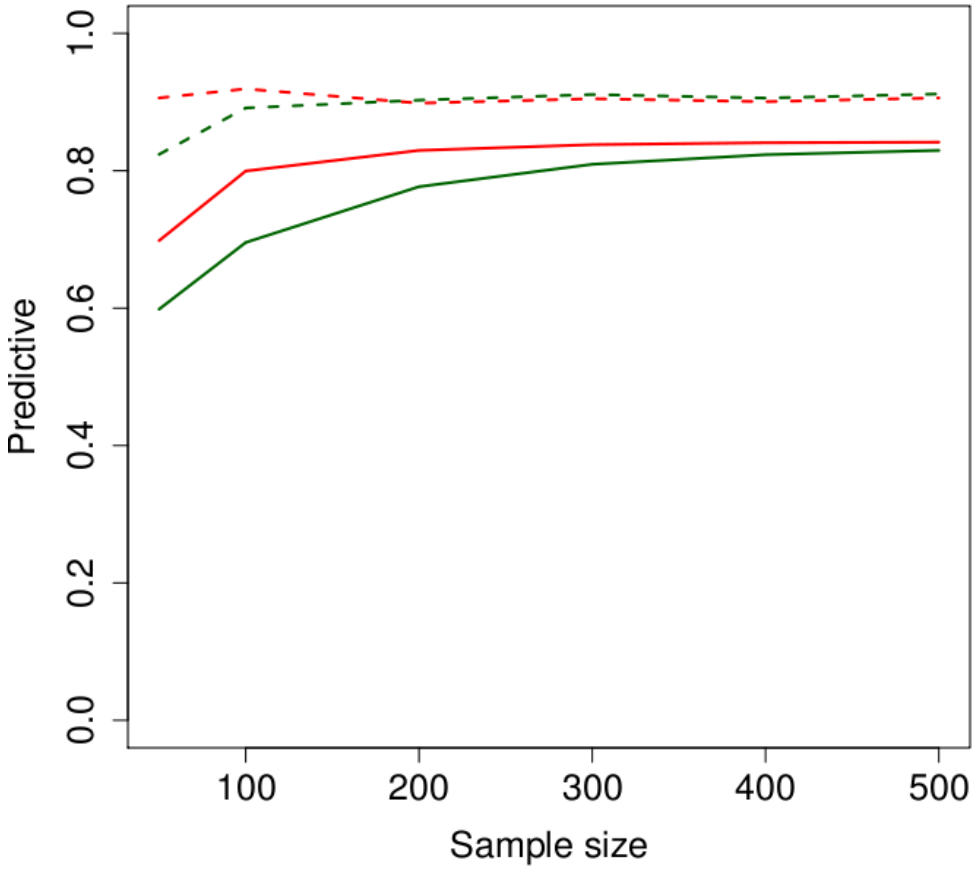


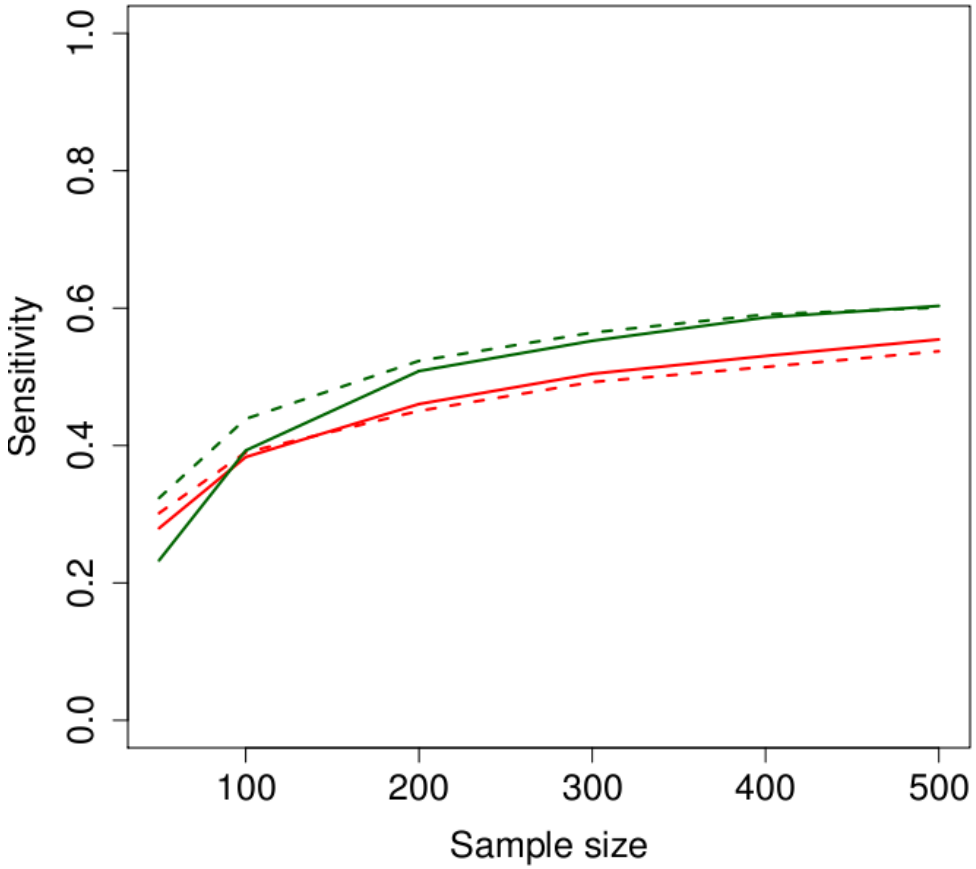


- We compare BIC and fNML scores with several γ values
  - $\gamma = 0 \rightarrow$ classic scores (solid line)
  - $\gamma = 0.5$ (dashed line)
  - $\gamma = 1 \rightarrow$ same probability over connectivity classes (dotted line)

Biological knowledge impact

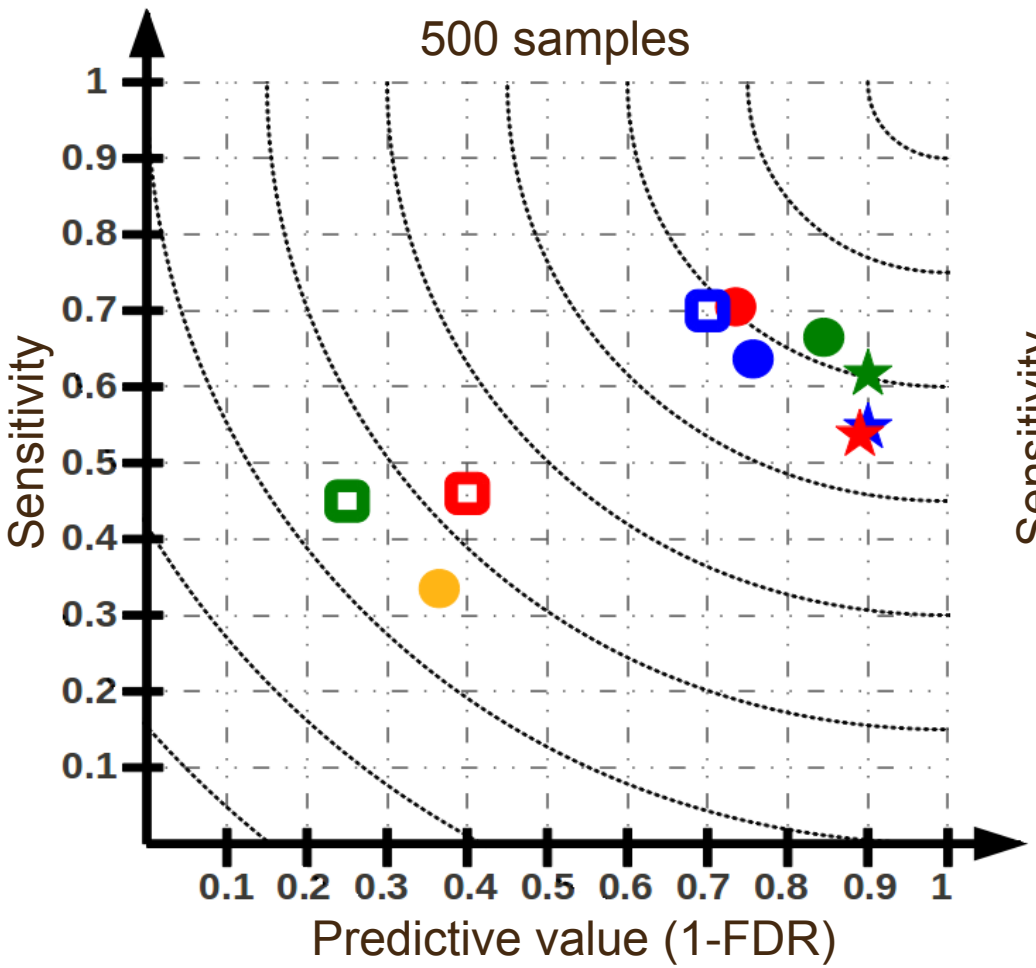
Legend: BIC score
fNML score

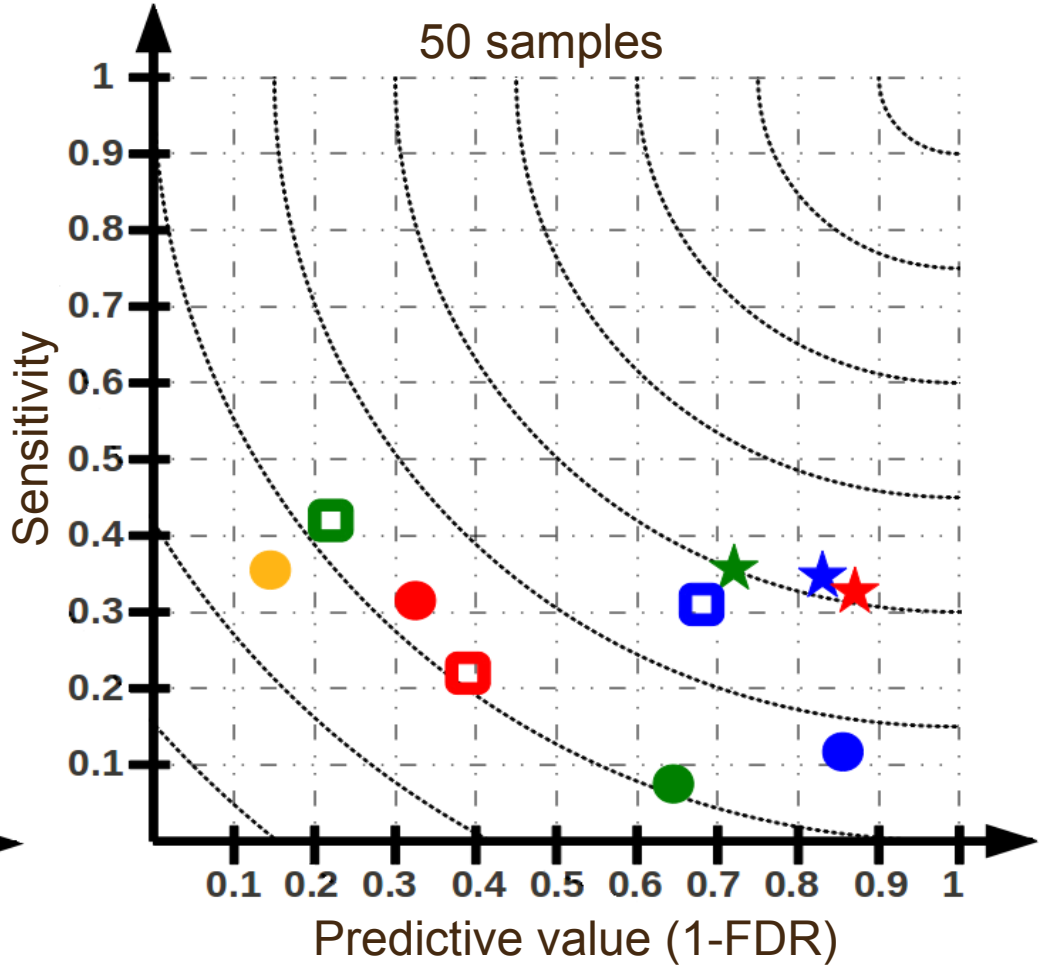




· We fix / ban relations in regulation network inference with γ=1
  · without extra biological knowledge (solid line)
  · with extra biological knowledge (dashed line)

Comparative results





Bayesian network inference : Banjo Greedy Search ($BDeu_1$ ★ / BIC_1 ★ / $FNML_1$ ★)

Linear model : SEM Lasso ●, GGMselect ●, GeneNet ●, SIMoNe ●)

Pairwise correlation : CLR □, ARACNE □, ParCorA □

Conclusion

- Scoring criteria study with uniform node in-degree prior
- Model description taking into account specific Biological knowledge
- Comparison with several regulatory network inference methods
- Robustness of Bayesian networks for sparse graphs

Perspectives

- Improve learning algorithm performance
- Study causality
- Try on real data

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