From gene clustering to genetical genomics:

Analyzing or reconstructing biological networks

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Outline

1. **Introduction and biological issues**
   - Causal relationships: from genotype to phenotype
   - Genetical genomics
2. **Gene expression clustering with missing observations in a Markovian setting**
   - Model-based approach with Markovian dependencies
   - Leads to use Markovian modelling in a genetical genomics context
3. **Reconstruction of networks combining genetic and genomics data**
   - Existing methods
   - Artificial data set simulation
   - Learning with Bayesian Networks or with a lasso SEM regression
   - Preliminary results

Outline

Inherited phenotypes have genetic roots

- Phenotype: observed characteristic (anatomical, morphological, molecular, physiological, ethological) or *trait* in a living organism. Many of which are inherited from parents (Mendel's peas...).

- Polymorphisms (*several shapes*) control gene expression or the affinity between a protein and its target. Can be (i) complex and (ii) quantitative ($\neq$ discrete).
- Traits carried out by DNA. Information unit (for constructing and operating an organism) = gene with different forms or alleles whose inheritance is complicated by recombination of chromosomes (diploids).

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Gene Regulatory Networks

- Mutations on DNA seq.: random events that can create a new allele hence new trait(s) when viable → Basis for evolution.
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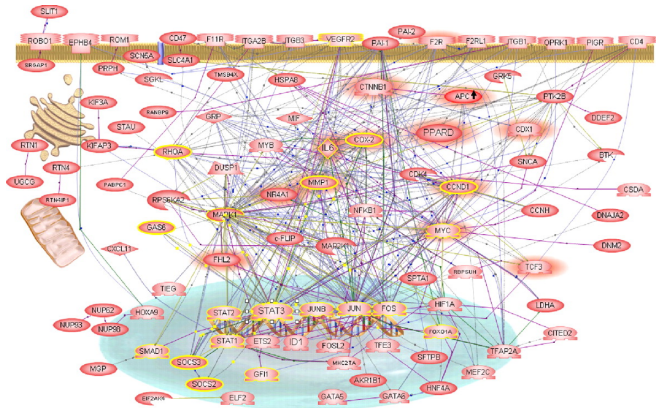

Angiogenic signaling network (Adollahi et al. 2007)

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- Links, causal dependencies between genes or genes and their products are represented into a Gene Regulatory Networks (GRN).
- Abundance of genomics data (=measurements of cell component activity). Can be directly used to infer GRN (Wehrli et al. 2006, Bansal et al. 2007).

Avowed biological target

Genetical genomics

Combine genetic information (perturbation of the network) and genomics measures (Jansen & Nap 2001) because...

- Biological goal: Understand genetic mechanisms (i) allowing observed diversity and (ii) able to accomplish many diverse functions.
- More pragmatic goal: exploiting genetic context and observed (e-)traits to reconstruct GRN or less ambitiously: identify genes with strong regulatory roles.

With...High levels of measurement replication: each allele at each QTL present in a large number of samples → the effect of the QTL on gene expression will therefore be measured many times.

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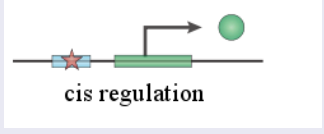
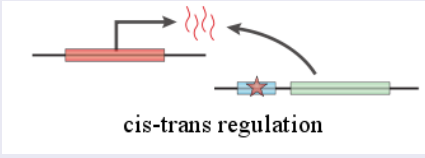
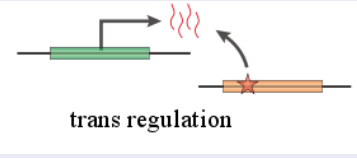
Biological ingredients

3 mechanisms to link genotype to the observed e-traits







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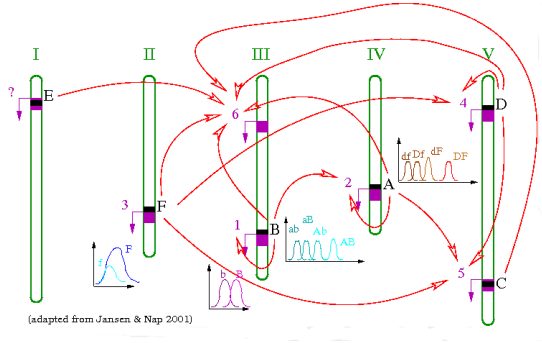
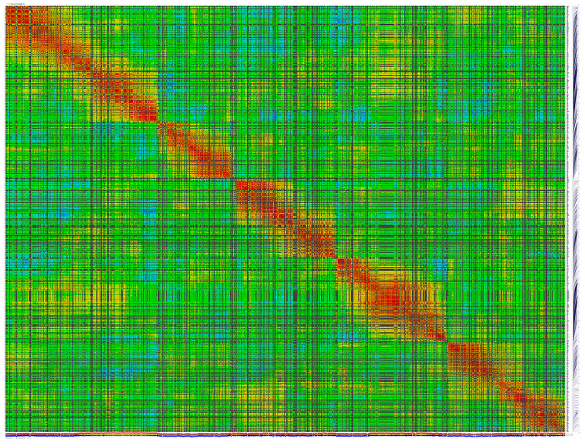


Physical map



Linkage map

Biological findings (unavowed)

- Unanswered questions so far: (i) number of loci that underlie variation in heritable phenotypes, (ii) distribution of their effect sizes, (iii) their molecular natures, (iv) mechanisms of action and interaction and (v) their dependencies on environmental variables.

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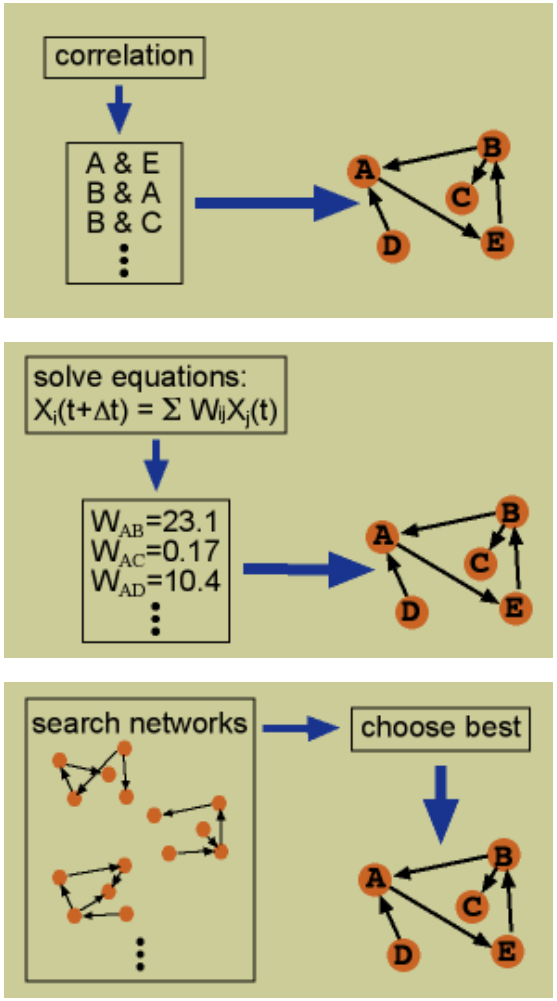
Learning GRN from expression data

- Pairwise algorithms (correlation, mutual information, hierarchical clustering...).
- Differential equation modelling.
- Network-based algorithms (boolean networks, dynamic/discrete BN...)

(Bansal et al. 2007 and V.A. Smith's website)



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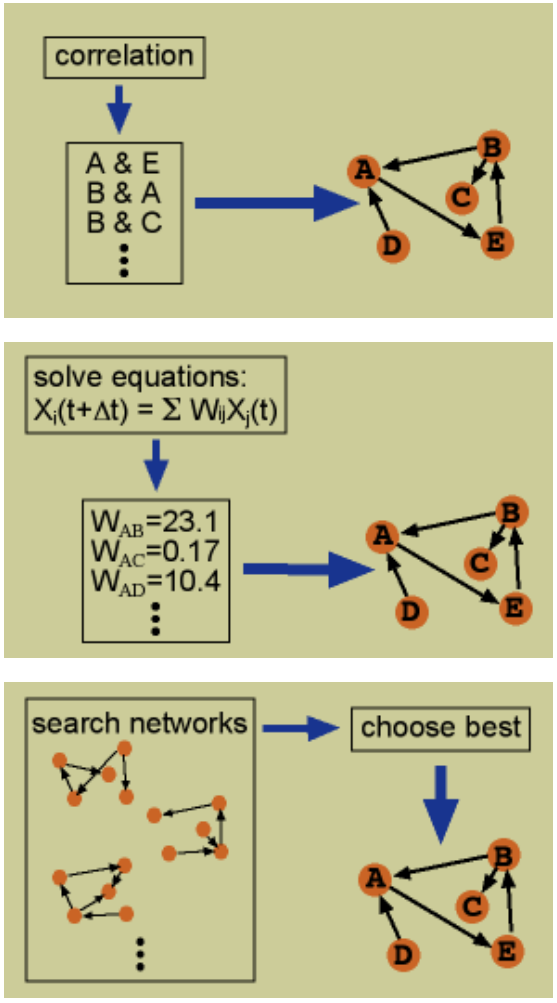

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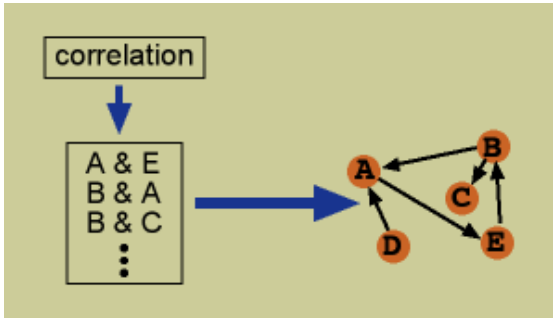

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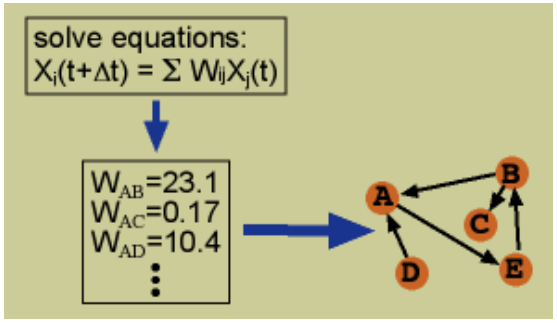

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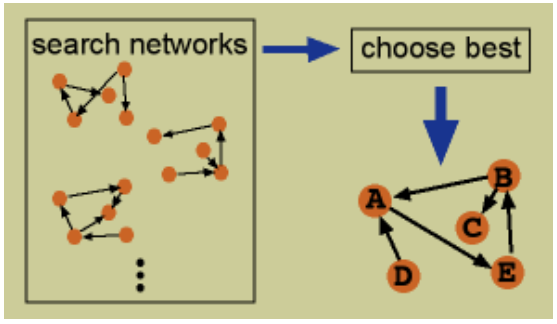

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Gene clustering with missing observations in a Markovian setting

- Data: omics measurements on individual biological entities & interactions between these entities (from experimental evidence or derived: litterature, genomic context, co-expression...).
- Network information in Markov Random Field (MRF).
- Observations modelled conditionally on node status through probabilistic distributions (e.g. Gaussian distribution specifically built for high-dimensional data, Bouveyron et al., Comput. Statist. Data Analysis 2007) so accounting for noise.

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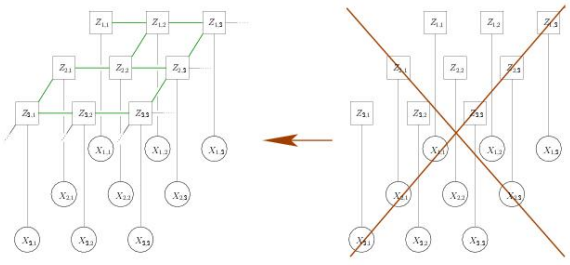

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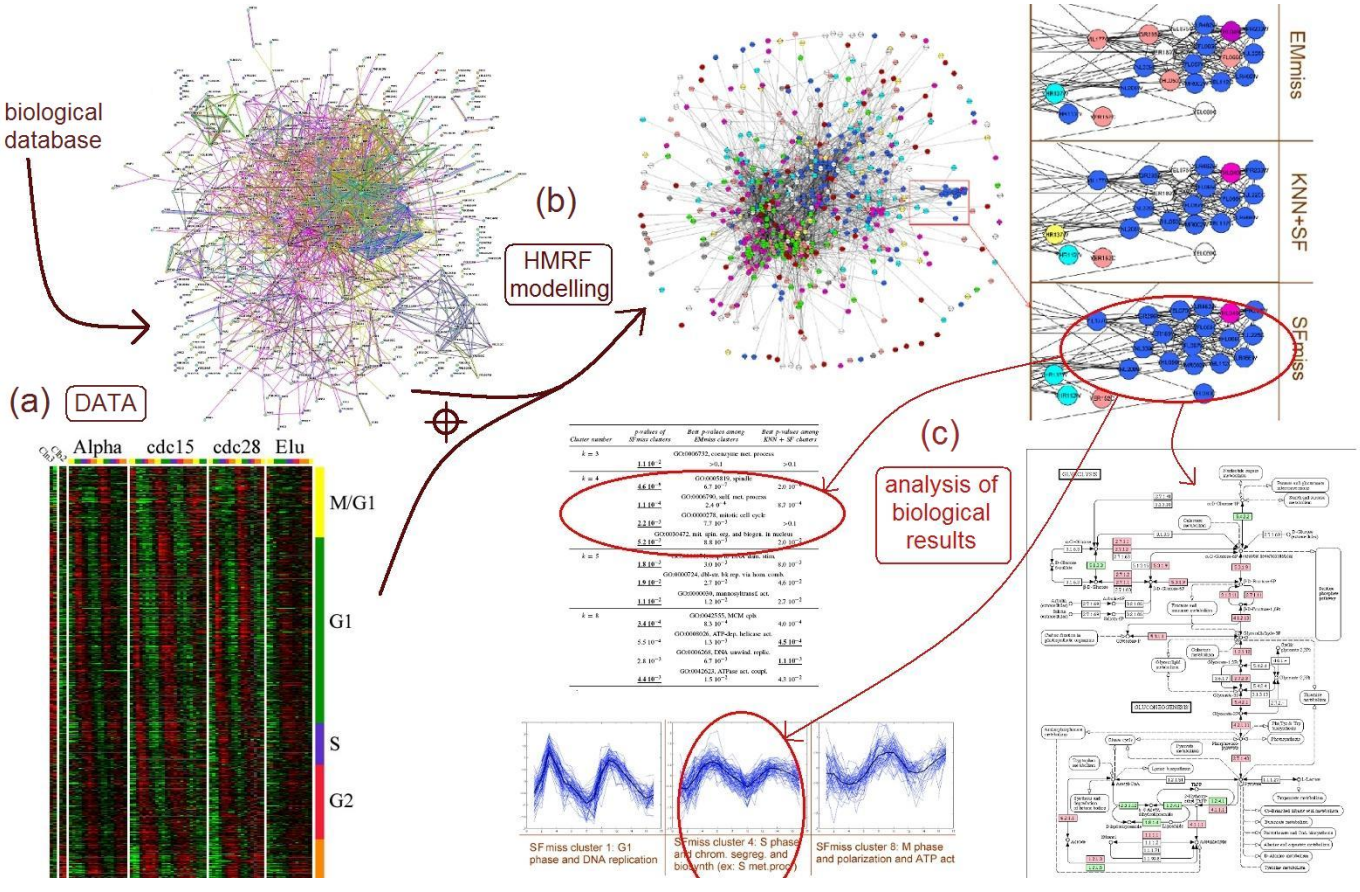
- Novel instantiation of an EM-based algorithm for model estimation: mean-field like approximations and accounting for missing observations (MAR).

Model-based approach with Markovian dependencies

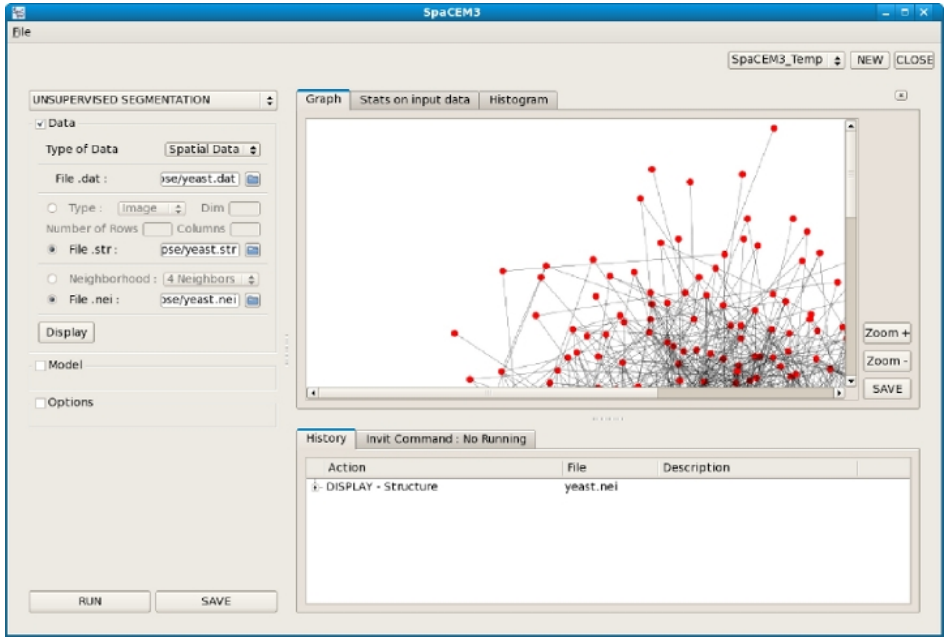
Workflow of a computational biology data analysis with our method



(from Blanchet & Vignes, J. Comput. Biol. 2009)

SpaCEM^3 software

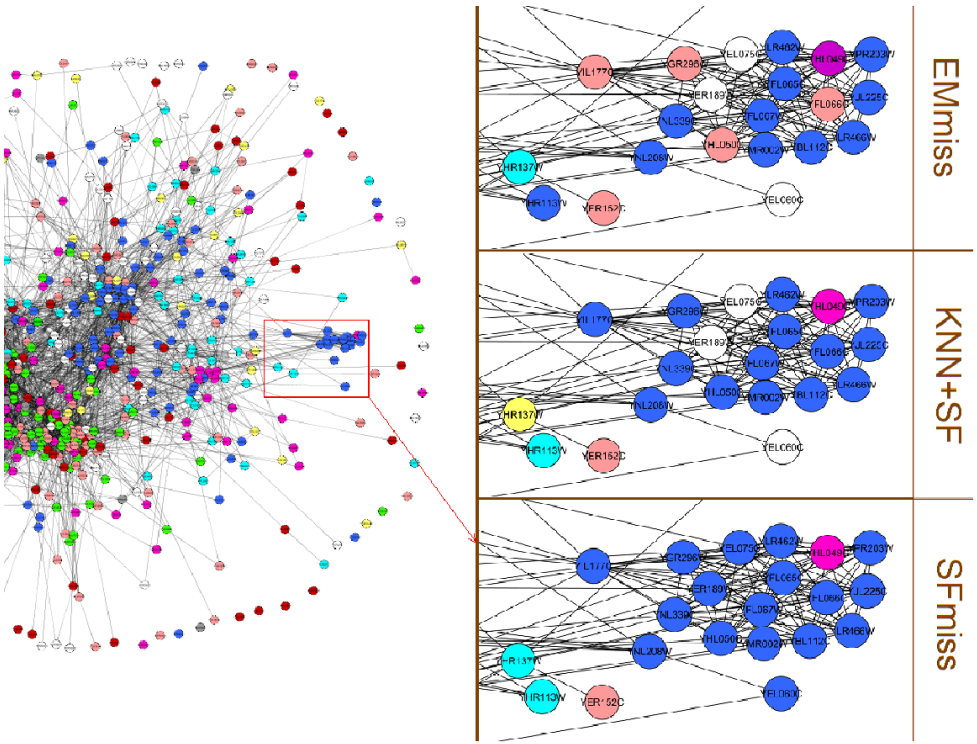
The SpaCEM^3 software allows the user to specify the structure of the model, estimate parameters, select relevant models (BIC, ICL) and visualize the results in the GUI.



(freely available at `http://spacem3.gforge.inria.fr/`)

Biological features of clusters

- Modularity
- Interpretability of cluster profiles
- GO term representativity
- Link to metabolic pathways



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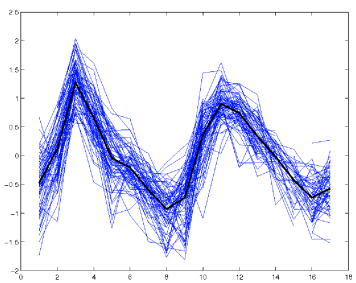
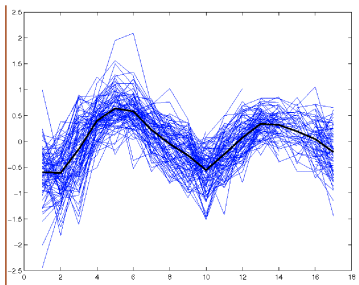
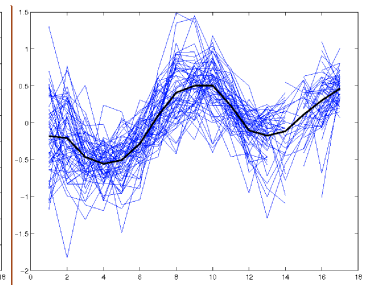


SFmiss cluster 1: G1 phase and DNA replication



SFmiss cluster 4: S phase and chrom. segreg. and biosynth (ex: S met.proc.)



SFmiss cluster 8: M phase and polarization and ATP act.

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Cluster number	*p-values of SFmiss clusters*	*Best p-values among EMmiss clusters*	*Best p-values among KNN + SF clusters*
$k = 3$		GO:0006732, coenzyme met. process	
	$\underline{1.1\ 10^{-2}}$	>0.1	>0.1
$k = 4$		GO:0005819, spindle	
	$\underline{4.6\ 10^{-9}}$	$6.7\ 10^{-7}$	$2.0\ 10^{-6}$
		GO:0006790, sulf. met. process	
	$\underline{1.1\ 10^{-4}}$	$2.4\ 0^{-4}$	$8.7\ 10^{-4}$
		GO:0000278, mitotic cell cycle	
	$\underline{2.2\ 10^{-3}}$	$7.7\ 10^{-3}$	>0.1
	GO:0030472, mit. spin. org. and biogen. in nucleus		
	$\underline{5.2\ 10^{-3}}$	$8.8\ 10^{-3}$	$2.0\ 10^{-2}$
$k = 5$		GO:0006974, resp. to DNA dam. stim.	
	$\underline{1.8\ 10^{-3}}$	$3.0\ 10^{-3}$	$8.0\ 10^{-3}$
		GO:0000724, dbl-str. bk rep. via hom. comb.	
	$\underline{1.9\ 10^{-2}}$	$2.7\ 10^{-2}$	$4.6\ 10^{-2}$
		GO:0000030, mannosyltransf. act.	
	$\underline{1.1\ 10^{-2}}$	$1.2\ 10^{-2}$	$2.7\ 10^{-2}$
$k = 8$		GO:0042555, MCM cplx	
	$\underline{3.4\ 10^{-4}}$	$8.3\ 10^{-4}$	$4.0\ 10^{-4}$
		GO:0008026, ATP-dep. helicase act.	
	$5.5\ 10^{-4}$	$1.3\ 10^{-3}$	$\underline{4.5\ 10^{-4}}$
		GO:0006268, DNA unwind. replic.	
	$2.8\ 10^{-3}$	$6.7\ 10^{-3}$	$\underline{1.1\ 10^{-3}}$
		GO:0042623, ATPase act. coupl.	
	$\underline{4.4\ 10^{-3}}$	$1.5\ 10^{-2}$	$4.3\ 10^{-2}$

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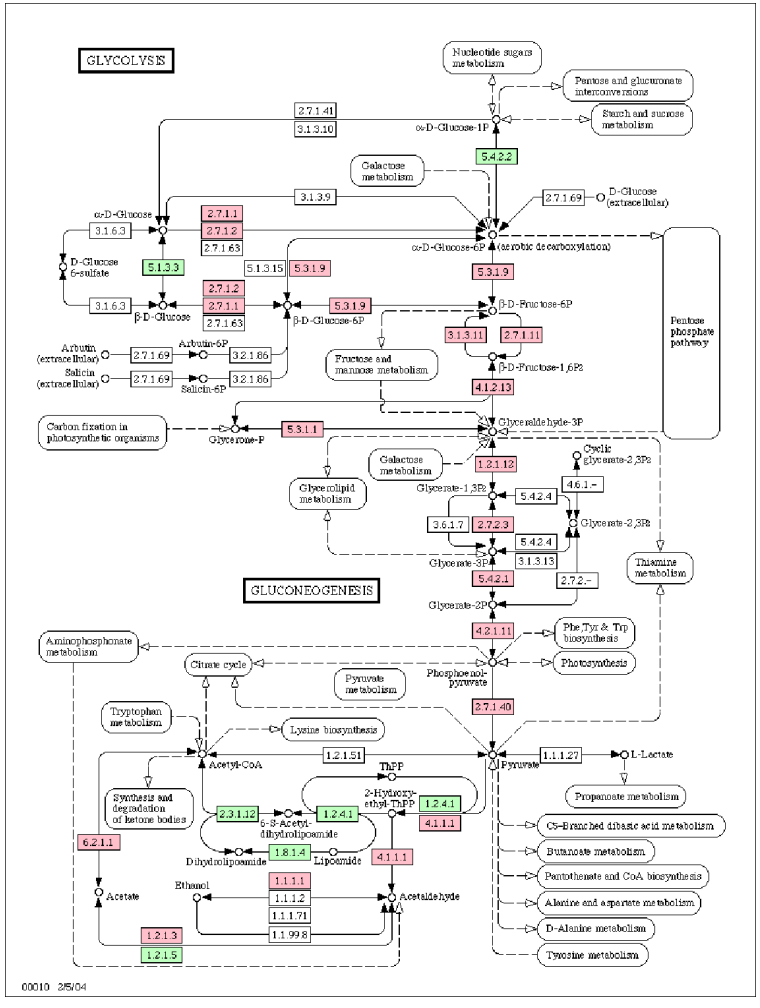

Inferring a MRF with genetical genomics data

1. Estimating weights -as a measure of uncertainty- on putative edges and fixing those on edges defined by expert knowledge.
   - ...could lead to the inference of $N(N-1)/2$ parameters.
2. *Triplet Markov fields* (Blanchet & Forbes, IEEE PAMI 2008) allowing objects to be assigned to overlapping subclasses seem an interesting lead to model genetic background of a gene by introducing an additional blanket that could encode genetic dependencies in the population.
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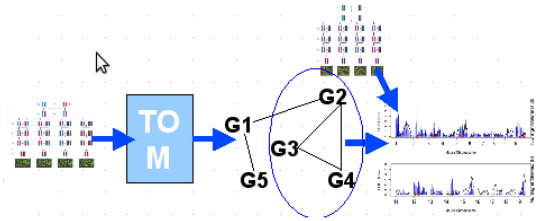
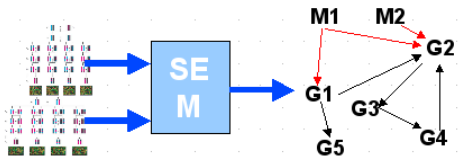
Learning networks in genetical genomics

- Pairwise algo. (Ghazalpour et al., PLOS Gen., 2006) co-expression network + module cis-eQTL



- Equation-based algo. (Liu et al., Genetics, 2008): greedy SEM with expr. levels and genotypes as covar., pre-filtered by eQTL info.
  - Nathalie Keussayan's MSc. (with Brigitte Mangin).



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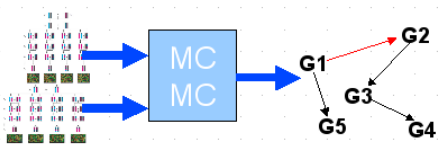

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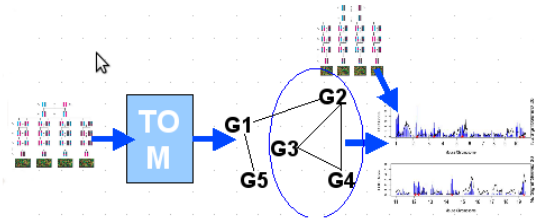

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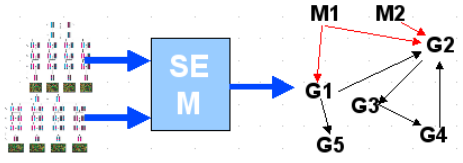

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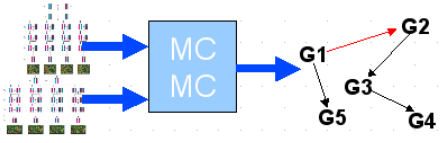

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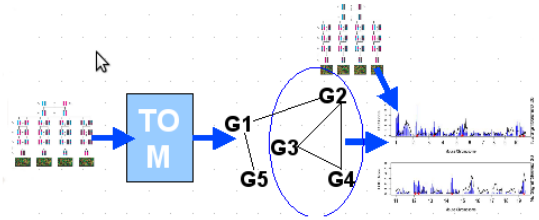

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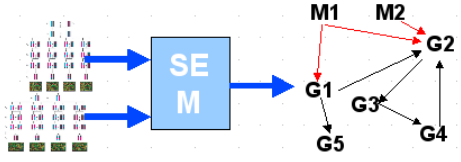

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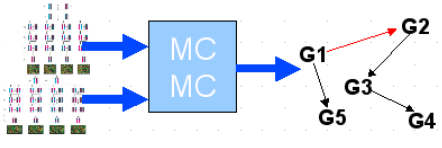

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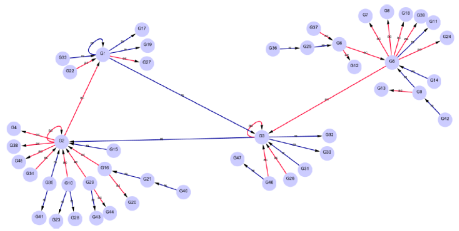
- Choose a network with features as close as possible to know features of realistic biological networks → `http://www.comp-sys-bio.org/AGN/`.



- Simulate genotype from a RIL population: pop size, chromosome size, number and distribution of markers (incl.error and missingness) → CarthaGène.
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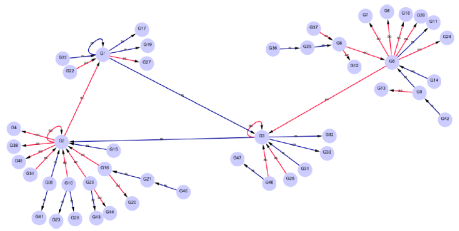

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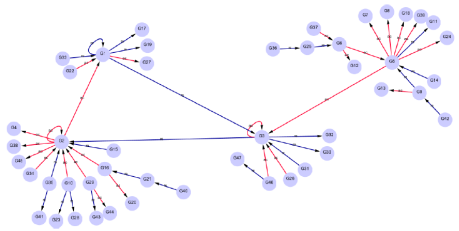

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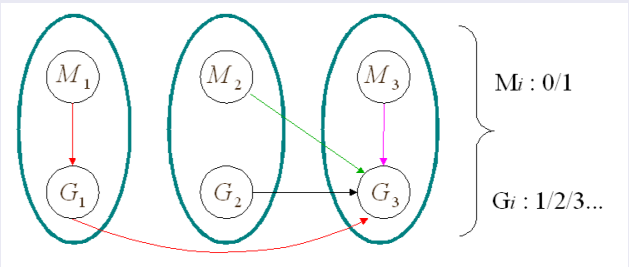
Definition of BN

Directed Acyclic Graph (DAG) & $P(V) = \prod_{i=1}^{p} P(V_i \mid V_{pa(V_i)})$, with $V_i := M_i \otimes G_i$. Clever init.: encompassing network with putative eQTL $\rightarrow$ MCQTL `http://carlit.toulouse.inra.fr/MCQTL/`.



Tested Algorithms (Matlab's BayesNet, K.Murphy and P. Leray)

1. Scoring algorithms: BIC (+ penalty for genetic linkage) with structure exploration strategies: Maximum Weight Spanning Tree (MWST), K2 (node ordering), Greedy Search (GS).
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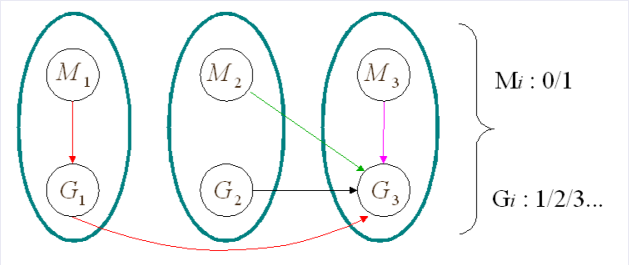

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$$\triangleright\ Y = Y.B + X.\Theta + \epsilon$$

where:
Y matrix of transcript levels ($n \times p$)
X matrix of genotypes ($n \times q$)
B_{km} direct effect of level of gene k on level of gene m ($B_{ii} = 0$).
Θ_{jm} direct effect of marker j on expression of gene m.

▷ Gene-by-gene regression

$$Y_k = Y_{\setminus k} * \beta_k + X * \Theta_k + \epsilon_k$$

β_k's and Θ_k's need to be estimated as regression coefficients.

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Lasso estimation of parameters

- Idea 1 *Least Square*: unbiased but variance on estimator becomes a problem since typically $n \ll p$.
- Idea 2 *Biased estimations*: v2.α ridge (not parcimonious), v2.β best subset (fixed number of variables can have coef.$\neq 0$), v2.final Lasso (Tibshirani J. Royal. Statist. Soc B. 1996, selects and reduces variables).

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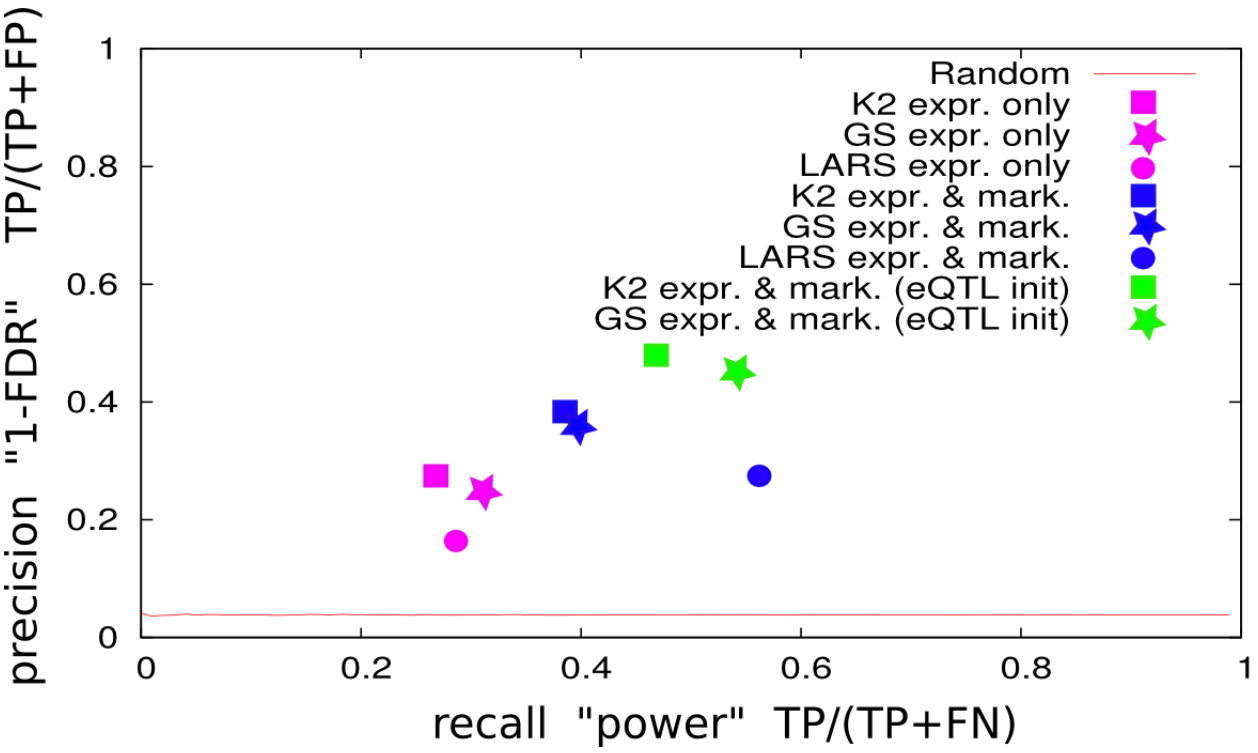
BN vs. SEM: advantages and drawbacks

	BN	SEM
Computational time	☹	☺
Continuous data	☹	☺
Modelling cycles	☹	☺
Param./likelihood estim.	☺	☹
Non-linear dependencies	☺	☹

Results: (i) BN vs. SEM and (ii) with or without genotypes



Network recovery performances on 9 artificial datasets

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- Panel of different methods to deal with genetical genomics data.
- Plausible synthetic data generation (room for improvement!).
- Obvious gain in using genetic information

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- Try these methods on a real gold standard dataset (mice, yeast, thaliana ok...What if sunflower or strawberries).

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Thanks a lot for your attention!

Questions?