From gene clustering to genetical genomics: analysing or reconstructing biological networks

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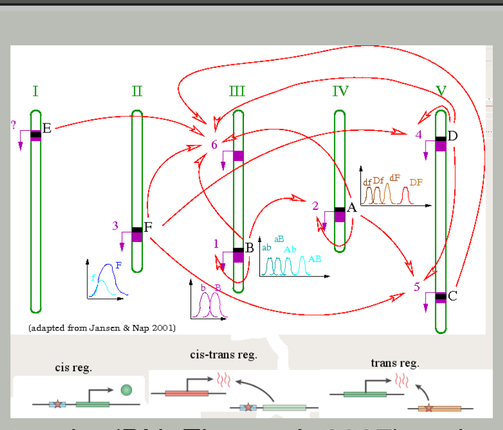
Introduction & Biological issues

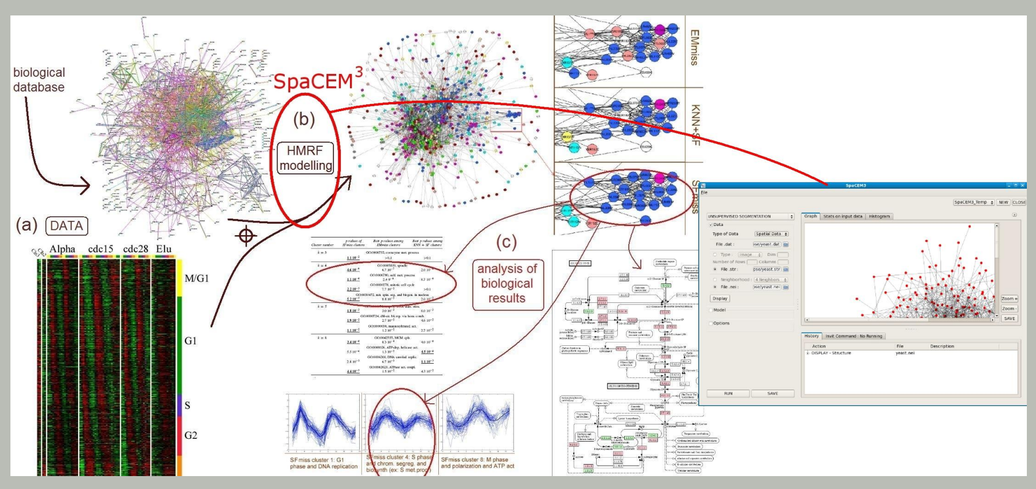
- Goal: Gene Regulatory Network (GRN) inference.
- Means: 2 kinds of information available. (i) Polymorphisms on genes (eQTL), observed in crosses between 2 known strains, as causes for (ii) variation on RNAm levels (snapshot of cell activity).



- Considered approaches: Discrete Bayesian Networks (BN, Zhu et al. 2007) and Structural Equation Modelling (SEM, Liu et al. 2008).
- Results on synthetic data in the context of genetical genomics data.

1 - Gene expression clustering accounting for missing observations in a Markovian setting

- Noisy observations **Y**, some possibly missing (at random), network structure on labels **Z** between the p biological entities.
- Tool: Hidden Markov Random Fields with genuine EM algorithm with mean-field like approximations for model learning. Implemented in SpaCEM[3] available at `http://spacem3.gforge.inria.fr/`.
- Model: $P(Y, Z) = P(Y \mid Z).P_G(Z) = \prod_1^p f(Y_i, \theta_{Z_i}).\exp(-H(Z;\Delta))/W(\Delta)$; model selection: BIC.



- Biological analysis for validation (Blanchet & Vignes 2009).

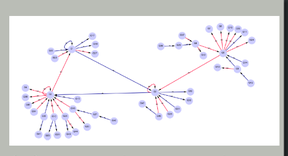
Gene network reconstruction with genetical genomics data

- Estimating weights on edges to infer (partially) the graph.
- Include genetic information in an additional blanket **X** on the graph: Triplet Markov Fields (Blanchet & Forbes 2008)
  $P(Y, X, Z) \propto \exp\left(-\sum_{c\in\mathcal{C}} V_c(X_c, Z_c) - \sum_i \log(f(Y_i \mid \theta_{X_i,Z_i}))\right)$ at present only limited to supervised classification.

2 - Reconstruction of networks combining genetic and genomics data

2.1 Genetical genomics data simulation

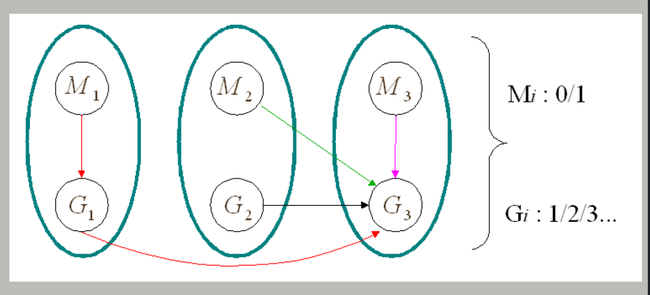
- Choose network with features close to known features of biological networks → `http://www.comp-sys-bio.org/AGN/`.



- Simulate genotype given a RIL population, chromosome(s) size(s), number and distribution of markers → CarthaGène `http://www.inra.fr/mia/T/CarthaGene/`.
- Compute steady state gene expression levels from coupled ODE (mimicking biochemistry) → COmplex PAthway SImulator `http://www.copasi.org`.

2.2 Structure learning of a discrete Bayesian Network

- BN = DAG $\oplus$ $P(V) = \prod_{i=1}^p P(V_i \mid V_{pa(V_i)})$; tested score-based (BIC) algorithms: Greedy Search, K2...
- Fig.: M_i: genotype, G_i: transcript level of gene i.



- eQTL analysis with MCQTL `http://carlit.toulouse.inra.fr/MCQTL/`.

2.3 SEM of genetical genomics data

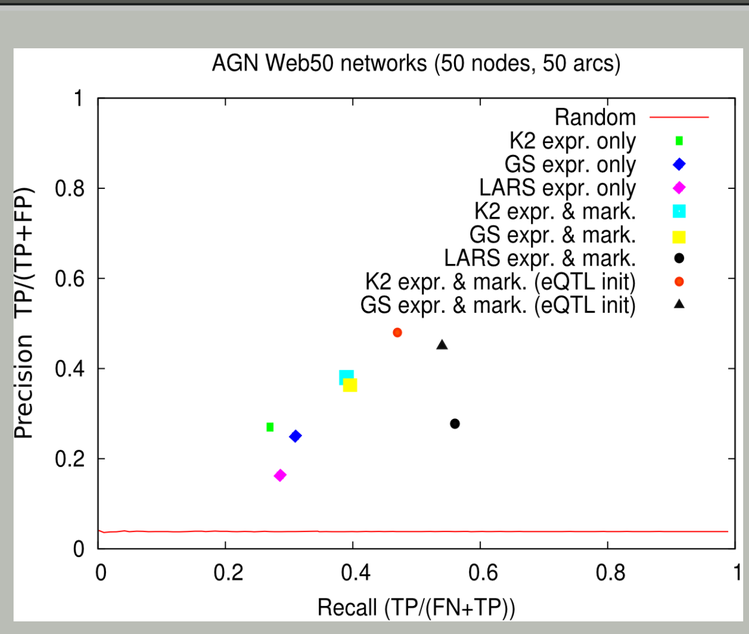
- $Y = Y.B + X.\Theta + \epsilon$, where: Y transcript levels, X genotypes, B_{km} direct effect of expr. k on expr. m and Θ_{jm} direct effect of marker j on expr. m.
- Lasso gene-by-gene regression to estimate paramater $\neq 0$: $\widehat{\begin{bmatrix} B_k \\ \Theta_k \end{bmatrix}} = \arg\min |Y_k - [Y_{\setminus k} X].\begin{bmatrix} B_k \\ \Theta_k \end{bmatrix}|_{L_2} + \lambda|\begin{bmatrix} B_k \\ \Theta_k \end{bmatrix}|_{L_1}$ ($|\widehat{\begin{bmatrix} B_k \\ \Theta_k \end{bmatrix}}|_{L_1} \leq \tau$); LAR algorithm (refs on `http://www-stat.stanford.edu/~tibs/lasso.html`); BIC and Meinshausen criteria to determine the best λ.

2.4 BN vs. SEM – pros and cons

	Continuous data	Comput. time	Model. cycles	Param./likelihood estimation	Non-lin. depend.
BN					
SEM					

(thanks to lars)

2.5 Comparative results



Conclusion and prospects

- Wide range of available methods to integrate genetic and genomics data to infer GRN.
- Gain in using genetic information to infer the network.
- Plausible synthetic genetical genomics dataset simulation, but Gold standard dataset on model organism needed.
- Prospects: (i) fairly assess merits of different approaches and develop algorithms to optimize score devoted to data at hand (ii) analyze data from collaborations (SUNYFUEL, FRAGENOMICS...).

References

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