Gene regulatory networks reconstruction from simulated System Genetics data

what we tried, what we learnt

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- Issues here: (i) formal adequate modelling framework and (ii) identification of a network that best represents the system.
- Focus in this presentation on (simulated) 'Systems Genetics' or 'Genetical Genomics' data, only looking at the level of genes.

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Dataset generation recipe

Choose simulation parameters, choose a network, generate individual genotypes and then simulate steady-state gene g expression data from:

$$\frac{\mathrm{d}\,G_g}{\mathrm{d}\,t} = Z_g^c \cdot V_g \cdot \theta_g^{syn} \cdot \prod_k \left(1 + A_{k,g} \frac{G_k^{h_{k,g}}}{G_k^{h_{k,g}} + (K_{k,g}/Z_k^t)^{h_{k,g}}}\right) - \lambda_g \cdot \theta_g^{deg} \cdot G_g$$

from SysGenSIM, [Pinna et al. 2011]

Listing possible interactions

Cis regulation

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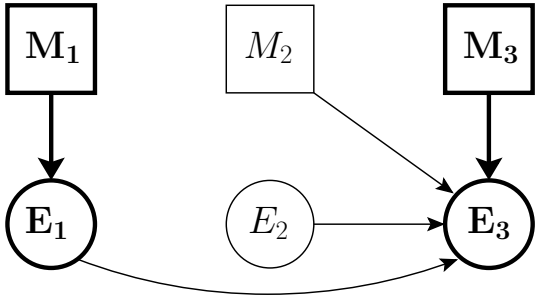
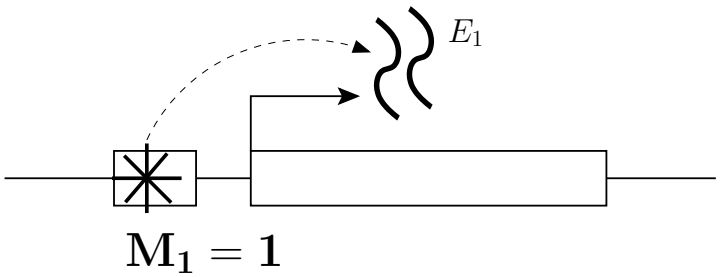


$M_i = 0$ or 1

$E_i \in \mathbb{R}$



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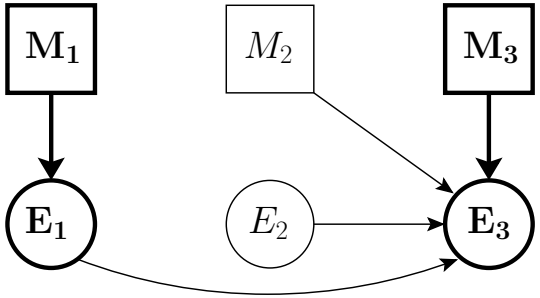

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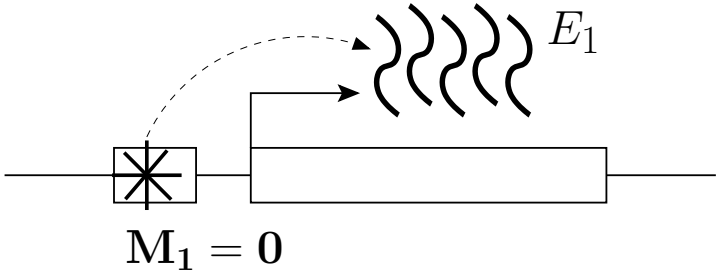

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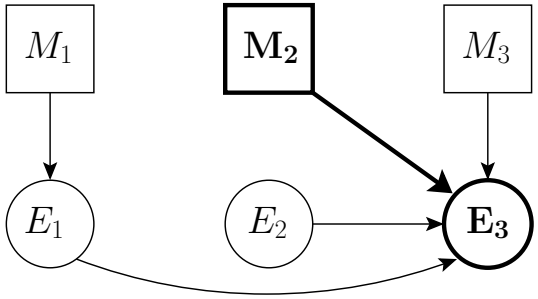

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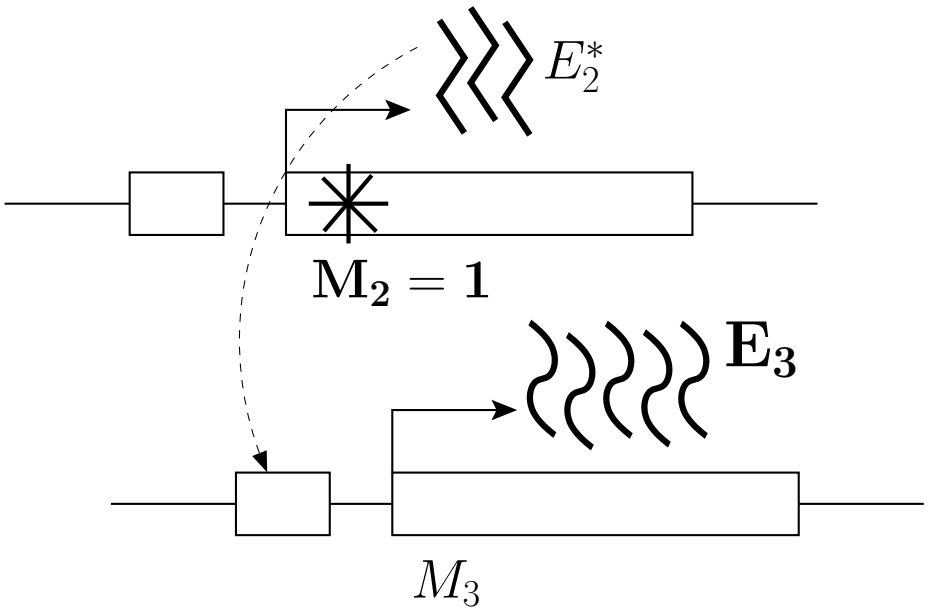

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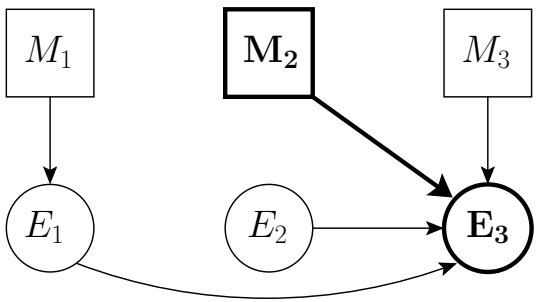

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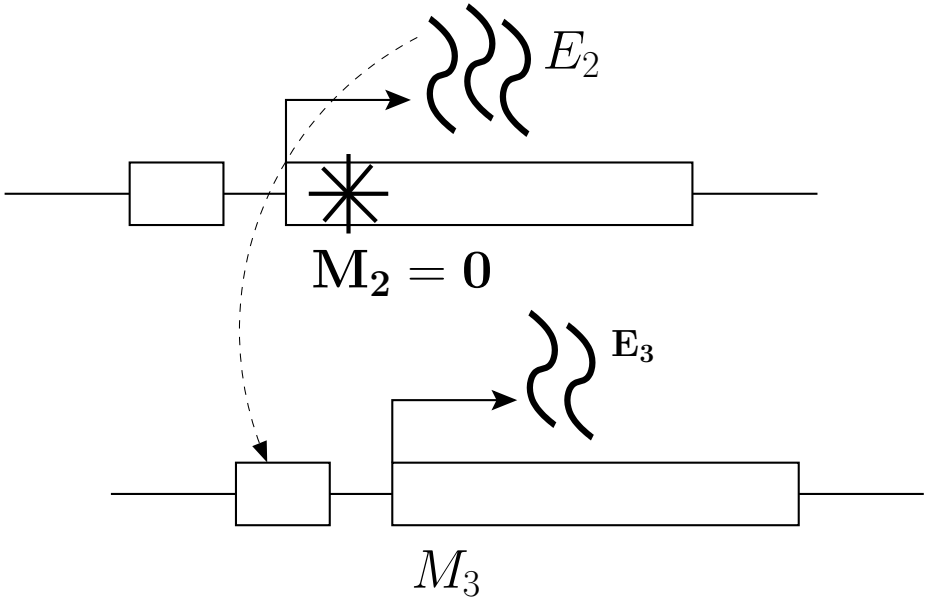
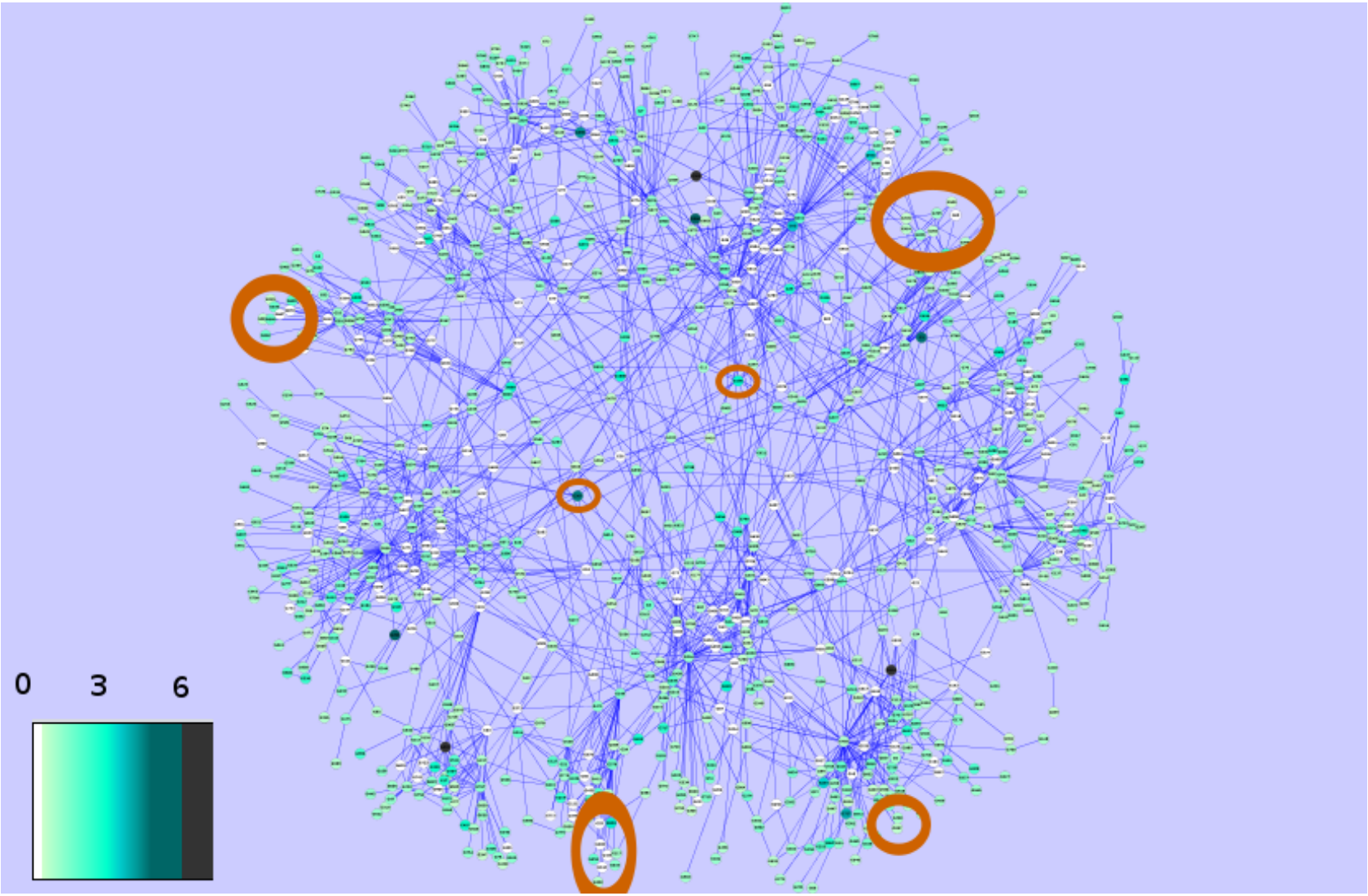


Marker multifactorial effect visualisation



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Data bootstrap [Efron 1981]

- strategy used to get confidence on predictions and overcome noise effect.
- implementation: randomly draw (with replacement) N_{boot} replicate data-sets of identical sample size as the original data, replicate the computation (drawback 1) and store the N_{boot} models to estimate distribution of the desired statistics (e.g. edge weight).
- did not make use of the offered possibility to study the behaviour of any (lack of) fitness function (e.g. likelihood, MSE) from out-of-bootstrap samples (but for RF) since each replicate doesn't use $\sim 37\%$ of the original samples (drawback 2 when n is small).

Penalised linear regressions

Solve individual linear regression for each gene:

$$E_g = \sum_{j=1}^{p} \alpha_{gj} M_j + \sum_{\substack{j=1 \\ j \neq g}}^{p} \beta_{gj} E_j + \varepsilon_g$$

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lasso penalisation [Tibshirani 1996]

Both shrinks (bias) and selects variables according to:

$$\begin{aligned}(\hat{\alpha}, \hat{\beta})^{lasso} &= \arg\min_{\alpha,\beta} \mid\mid E - M\alpha - E\beta \mid\mid_{\ell_2}^2 + \lambda \mid\mid (\alpha, \beta) \mid\mid_{\ell_1} \\ &= \arg\min_{\alpha,\beta} \mid\mid E - M\alpha - E\beta \mid\mid_{\ell_2}, \text{ subject to } \mid\mid (\alpha, \beta) \mid\mid_{\ell_1} \leq t\end{aligned}$$

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Dantzig selector [Candès & Tao 2007]

Slightly different constaint (related to gradient of RSS):

$$\begin{aligned}
(\hat{\alpha}, \hat{\beta})^{dantzig} &= \arg\min_{\alpha,\beta} \| (\alpha, \beta) \|_{\ell_1} \text{ s.t. } \| (E, M)^\top (E - M\alpha - E\beta) \|_{\ell_\infty} \leq \delta \\
&= \arg\min_{\alpha,\beta} \| (E, M)^\top (E - M\alpha - E\beta) \|_{\ell_\infty}, \text{ s.t. } \| (\alpha, \beta) \|_{\ell_1} \leq t
\end{aligned}$$

Building weights for edges predictions

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- Estimate weights $w_{M_j \to E_g}$ by the ratio of $\alpha_{gj}^{boot,pen} \neq 0$ and $w_{E_j \to E_g}$ by $\frac{\#\{\beta_{\mathbf{gj}}^{boot,pen} \neq 0\} + \#\{\beta_{\mathbf{jg}}^{boot,pen} \neq 0\}}{4qN_{boot}}$: post-symetrisation of $E_g \to E_{g\prime}$ edges and higher confidence in $M_g \to E_{g\prime}$ relationships.

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- [Bach 2008] established that under "some conditions" (sparsity, size effect and unique λ_n), the bootstrap lasso identifies correct edges with probability 1 and selects false positives with probability < 1 when $n \to \infty$. Our ranking should be related to edge existence !

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- Algorithm for BN inference are of two kinds: based either on independence tests or on **scores**: Bayesian (BD, BDeu. . .) or information theoretic (AIC, BIC . . .).
- NP hard problem (even if indegree ≤ 2 [Chickering 1996]): a simple greedy search is already very computation demanding: number of parents limited to 5.

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6. Scores are then simply the ratio of edge detection among the bootstraps.

Network post-processings

Ultimate goal (in our simulated context): list of directed interactions between genes, not list of causal eQTLs and gene expression influences

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Other cleverer post-processings can be built but time was lacking to thoroughly assess them in the different configurations !

Results 1: AUPR for $1,000$ gene networks

	AUPR with edge orientations				AUPR without edge orientations			
	Methods				Methods			
Network/configuration/data-set	Lasso	Dantzig	RF	BN	Lasso	Dantzig	RF	BN
Net4-Conf1-DS25-300SH	11.65	12.02	9.63	**14.20**	15.76	**16.41**	11.06	15.90
Net4-Conf2-DS26-900SH	15.88	15.66	17.95	**18.30**	**21.97**	21.68	20.05	20.08
Net4-Conf3-DS27-300SL	11.20	11.35	3.88	**11.83**	16.64	**17.18**	5.29	15.01
Net4-Conf4-DS28-900SL	21.49	21.78	9.64	**27.28**	32.46	**33.30**	11.31	32.95
Net4-Conf5-DS29-300DH	4.89	5.02	**7.31**	7.13	6.97	7.29	8.41	**8.60**
Net4-Conf6-DS30-900DH	9.68	10.05	13.82	**20.15**	13.81	14.53	15.60	**22.23**
Net4-Conf7-DS31-300DL	8.60	9.57	3.09	**13.18**	13.07	14.95	4.38	**16.59**
Net4-Conf8-DS32-900DL	16.20	17.43	7.39	**23.24**	24.20	26.71	9.12	**28.76**
Net5-Conf1-DS33-300SH	16.05	15.71	16.16	**16.96**	**21.52**	21.27	17.81	18.89
Net5-Conf2-DS34-900SH	22.17	21.71	23.96	**30.46**	31.08	30.64	26.28	**32.25**
Net5-Conf3-DS35-300SL	14.55	**14.61**	5.56	13.28	21.69	**22.10**	7.42	16.89
Net5-Conf4-DS36-900SL	24.57	24.70	13.53	**25.56**	37.38	**37.85**	15.86	31.37
Net5-Conf5-DS37-300DH	6.66	6.74	**9.04**	8.71	9.34	9.63	**10.58**	10.27
Net5-Conf6-DS38-900DH	12.80	12.67	21.76	**23.74**	17.55	17.76	23.73	**25.66**
Net5-Conf7-DS39-300DL	10.71	11.16	3.60	**15.36**	17.10	18.19	5.20	**18.71**
Net5-Conf8-DS40-900DL	17.42	17.92	11.04	**25.57**	26.33	27.75	12.86	**30.71**
Net6-Conf1-DS41-300SH	13.07	12.83	13.34	**15.75**	**17.90**	17.64	15.05	17.72
Net6-Conf2-DS42-900SH	17.54	17.59	23.63	**24.13**	24.81	24.80	25.56	**26.14**
Net6-Conf3-DS43-300SL	12.62	12.72	4.32	**13.40**	19.00	**19.38**	5.64	17.02
Net6-Conf4-DS44-900SL	20.72	**21.07**	10.67	20.14	32.06	**32.72**	12.69	26.12
Net6-Conf5-DS45-300DH	5.43	5.51	**7.41**	5.70	7.79	7.98	**8.83**	6.98
Net6-Conf6-DS46-900DH	8.55	8.43	**15.90**	12.34	11.91	11.95	**17.67**	14.13
Net6-Conf7-DS47-300DL	8.70	9.23	2.57	**10.07**	13.69	**14.84**	3.98	13.42
Net6-Conf8-DS48-900DL	14.68	15.33	7.82	**16.11**	22.86	**24.41**	10.06	21.36

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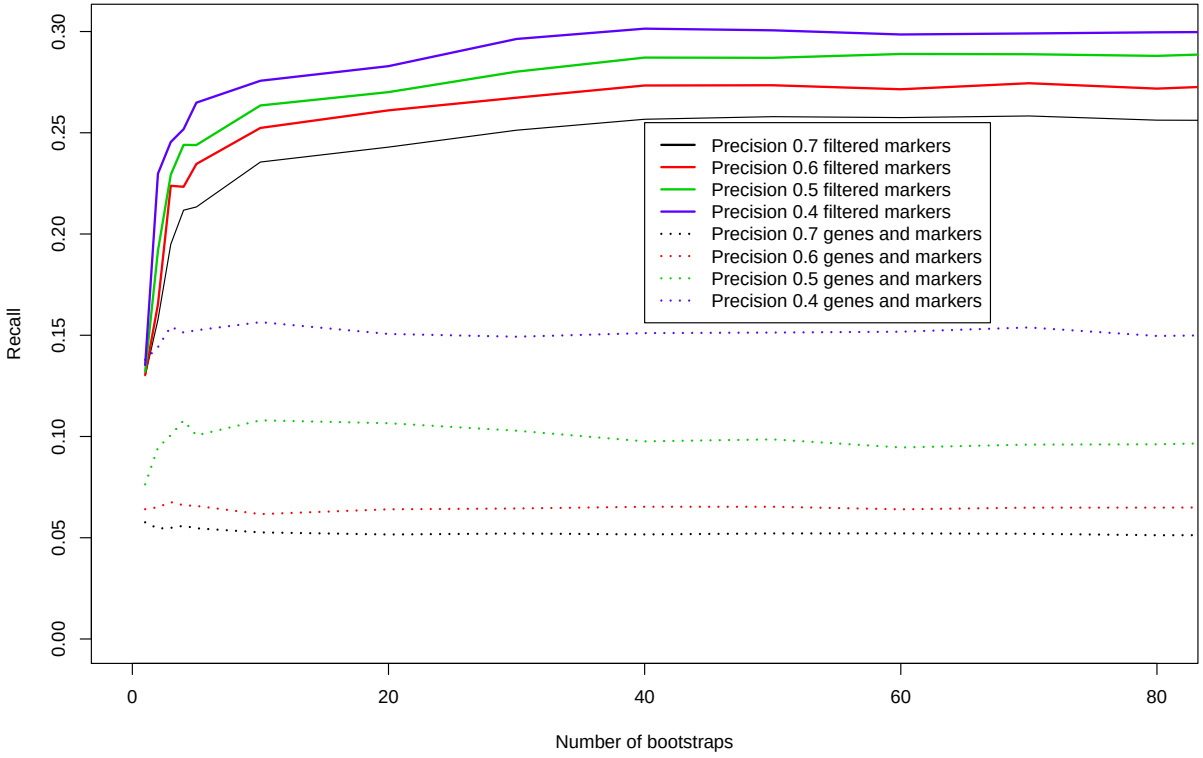
- BUT this is "in principle": gene expression heritability and marker density are interlocked:

	Gene expression heritability	
Chromosome density	High	Low
Dense		
Sparse		

Results 3: Effect of bootstraps



Mitigated good news.

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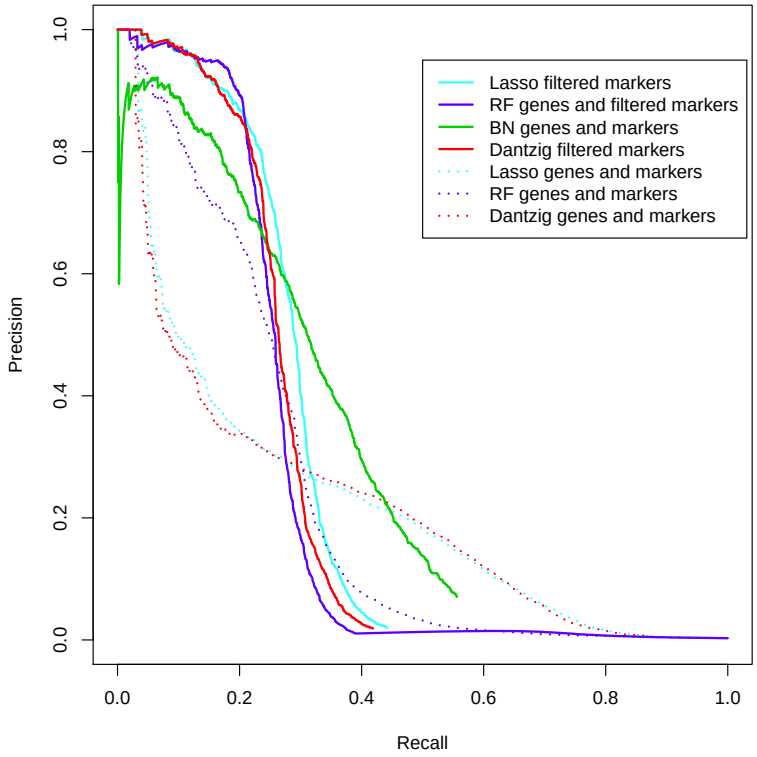
Don't want to feel to depressed ? [Marbach et al 2012]'s wisdom of crowds: an infinite number of independent (better than random) inference methods is consistent !

Results 4 encore: comparison of some inference methods

Post-processing also matters !



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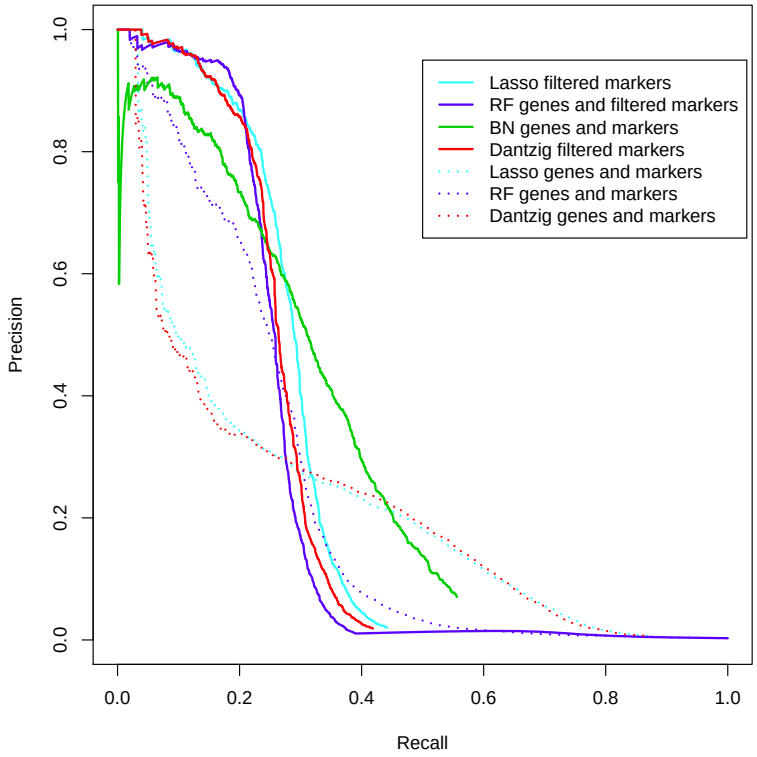

But this may be the other way round on another configuration !

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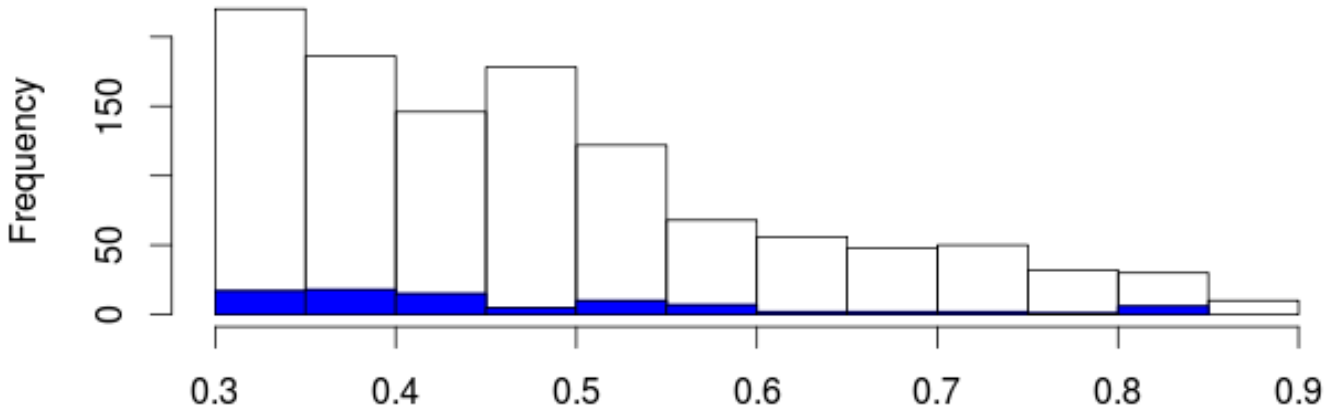
But what are we trying to infer: (absolute correlations between gene expressions)



Same situations for correlations between markers and gene expressions

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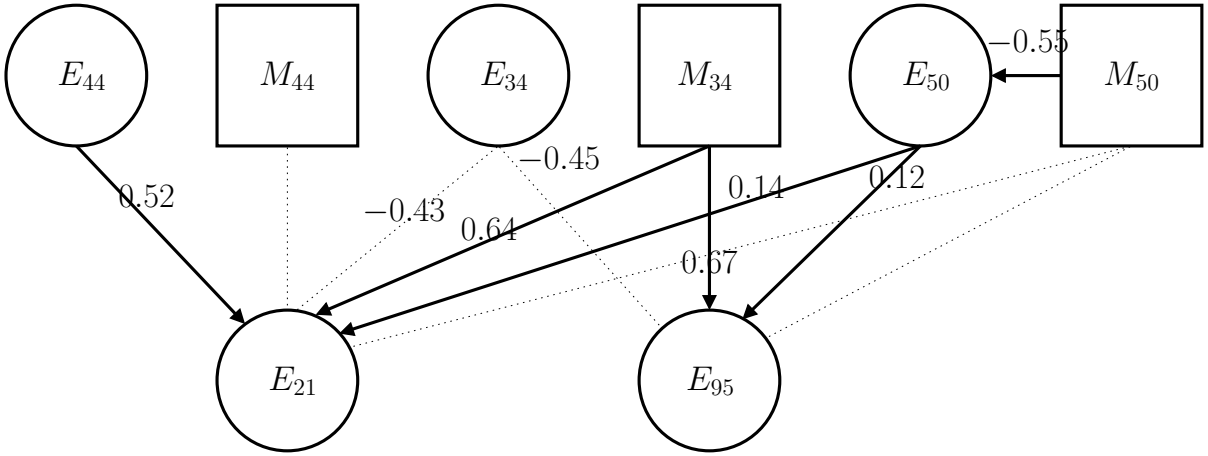
Into details:



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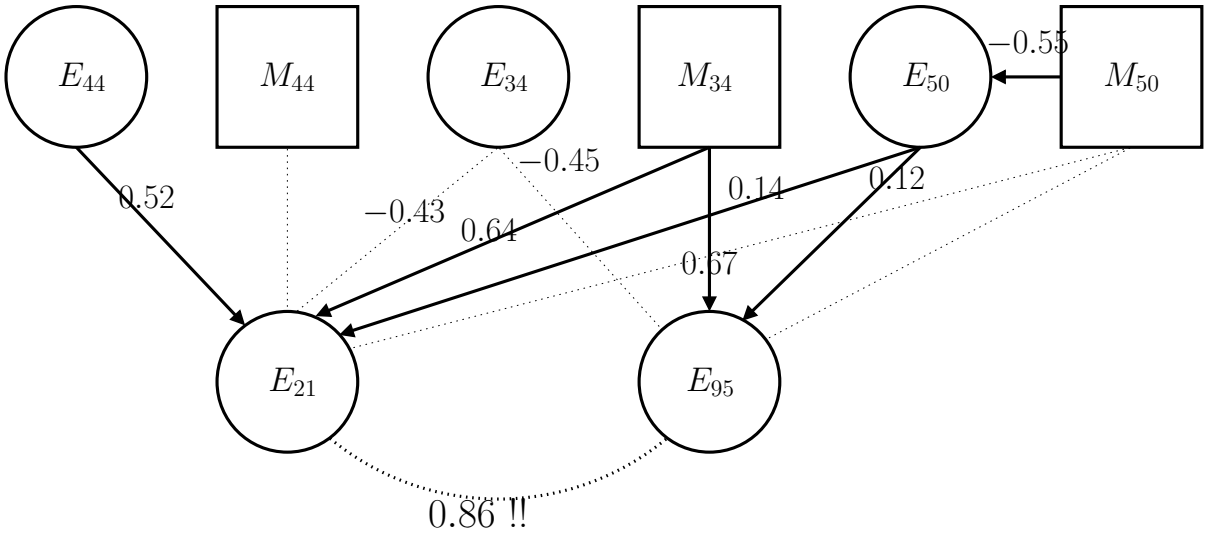

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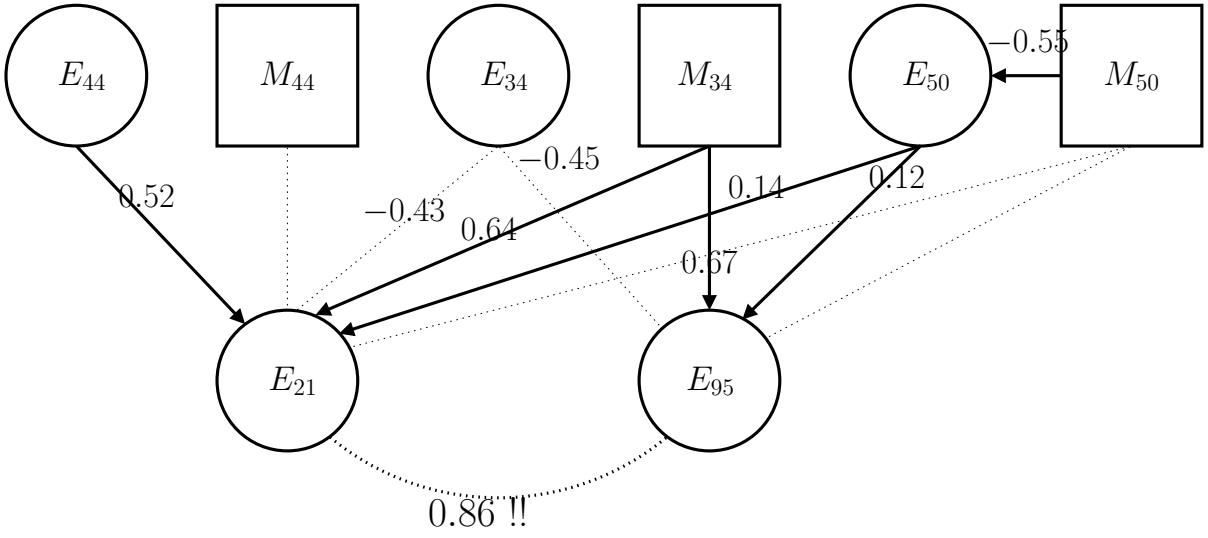
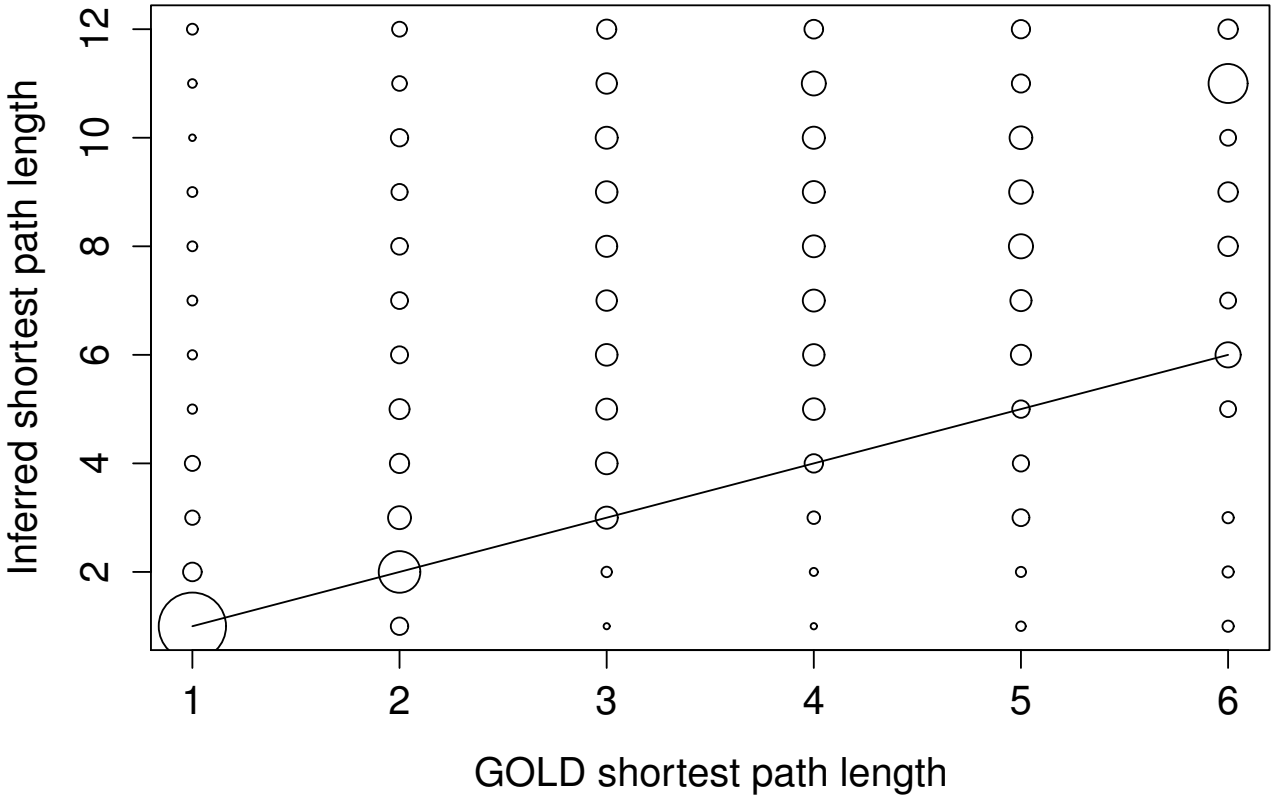


Logically, we get $G_{21} \leftrightarrow G_{95}$ as prediction No. 12, $G_{34} \rightarrow G_{95}$ as No. 19, $G_{44} \rightarrow G_{21}$ as No. 192 (reverse is No. 214), $G_{34} \rightarrow G_{21}$ as No. 252...$G_{50} \rightarrow G_{21}$ is prediction No. 2449, $G_{50} \rightarrow G_{95}$ is No. 6559 . . . and many more FP inbetween !!

Building longer/shorter paths ?

Shorter path length comparison



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- Lessons from this data set analysis: not there yet ! Was it too difficult ? Too exotic ? At least it kept us occupied full-time during summer 2012 !
- Penalised linear regressions, BN, RF . . . are nice models, which actually capture some important interactions with an acceptable degree of precision but: room for improvement ??

Conclusions 2

Future work

- Still some **work to be done**: try data transform (no magic remedy) ? Other naive/sophisticated Machine Learning tools (neural networks, SI algorithms . . .) ?
  Assess the impact of missing information (function, gene) in the system ? Evaluate the potential to find direct **causal** relationships on other data sets ?

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- Many thanks for your attention !