Causal Model Selection Hypothesis Tests in Systems Genetics

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Correlation and Causation

"The old view of cause and effect ... could only fail; things are not in our experience either independent or causative. All classes of phenomena are linked together, and the problem in each case is how close is the degree of association."

Karl Pearson (1911)

"Causality is not mystical or metaphysical. It can be understood in terms of simple processes, and it can be expressed in a friendly mathematical language, ready for computer analysis."

Judea Pearl (2000)

Motivation

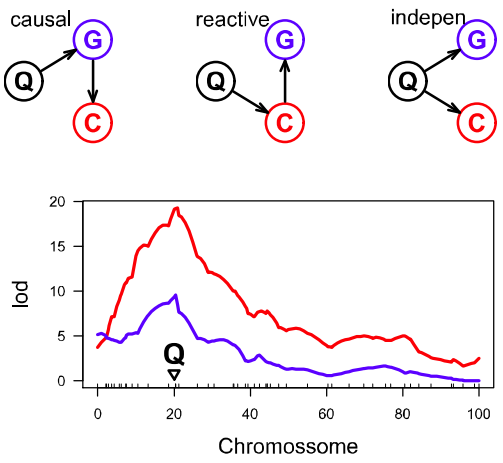
Motivation

Suppose the expression of gene G is associated with a clinical phenotype C.

We want to know whether: $G \rightarrow C$ or if $C \rightarrow G$ or if $C \leftrightarrow G$.

If G and C map to the same QTL, we can use genetics to infer the causal ordering among the phenotypes.

Motivation: Schadt et al. (2005)



Motivation

How can genetics help out in the determination of causal relationships among phenotypes?

Two cases:

1. Causal relations between QTLs and phenotypes.
2. Causal relations between phenotypes.

Causal relations between QTLs and phenotypes

Analogous to a randomized experiment.

Randomization is considered the "gold standard" for causal inference.

Causality can be inferred from a randomized experiment since:

1. Application of a treatment to an experimental unit **precedes** the observation of the outcome.
2. Because the treatment levels are **randomized** across the experimental units, the effects of confounding variables get averaged out.

Causal relations between QTLs and phenotypes

The analogy of QTL mapping and a randomized experiment was first pointed out by Li et al. 2006.

Experimental unit: individual on the segregating population.

Treatment levels: QTL genotypes (eg AA, Aa in a backcross).

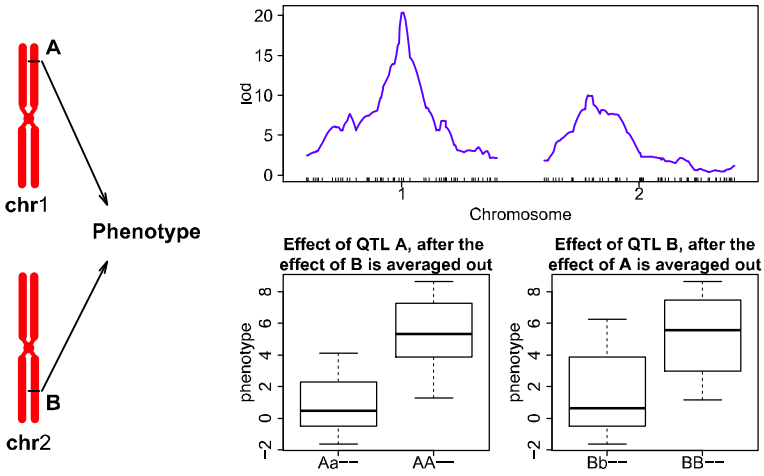
Measured outcome: quantitative phenotype.

Confounding variables: other QTLs that might affect the phenotype.

For a detected QTL:

1. Genotypes precedes the phenotype.
2. The recombination process randomly allocates the QTL genotypes to the individuals in a segregating population, averaging out the effects of other (unlinked) QTLs.

Causal relations between QTLs and phenotypes



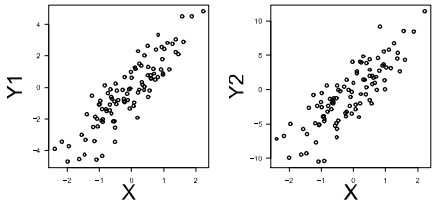
Causal relations between phenotypes

The concept of conditional independence is the key concept to understand how genetics can help out untangle causal relationships between phenotypes.

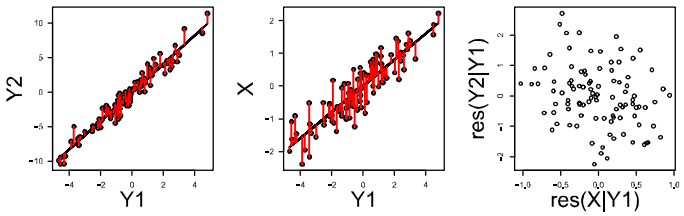
Conditional independence as the key to causal ordering

Model: $X \to Y_1 \to Y_2$

Marginal dependence:

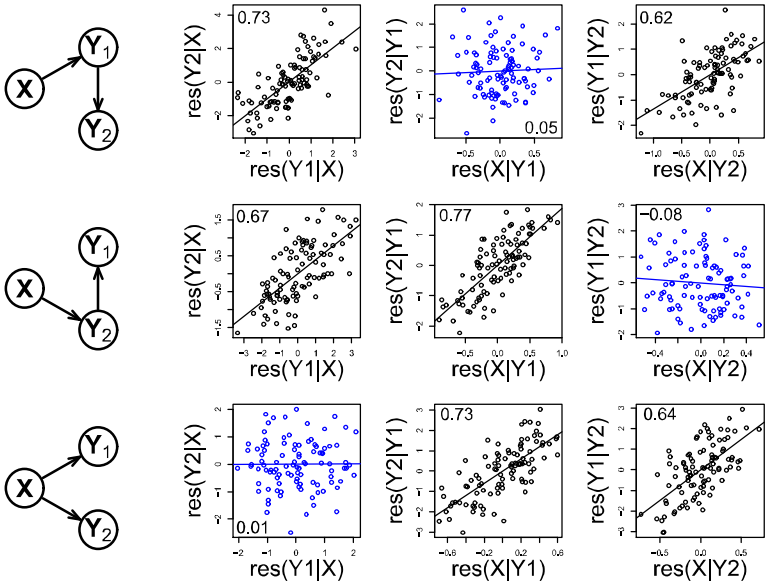


Conditional independence:



$$Cor(Y_2, X) > 0, \quad Cor(Y_2, X \mid Y_1) \approx 0$$

Conditional independence as the key to causal ordering



Statistical approaches for model selection

Two main approaches:

1. Model selection criteria.
2. Model selection via hypothesis tests.

Model selection criterions

- Based on log-likelihood scores (measure how well the data fits the model).
- When models have the same dimension, the maximized log-likelihood scores,
$$\text{loglik}_j = \log f_j(\mathbf{y} \mid \hat{\boldsymbol{\theta}}_j),$$
are usually used. The model with the highest loglik score is selected.
- For models with different dimensions, the penalized log-likelihood scores,
$$\text{ploglik}_j = \log f_j(\mathbf{y} \mid \hat{\boldsymbol{\theta}}_j) - D(k_j),$$
are usually used, where $D(k_j) = k_j$ or $0.5\, k_j \log n$ represents the AIC or BIC penalties.

The main drawback: model selection criteria do not provide an uncertainty measure for the model call.

Model selection via hypothesis tests

Two alternative approaches:

Hypothesis tests over regression coefficients: considers a series of regression models, and combines:

1. Equivalence tests to support conditional independence relations.
2. Conditional F-tests to support conditional dependence relations.

[approach adopted by CIT (Millstein et al. 2009).]

Vuong's test: attaches a p-value to a contrast of (penalized) model section scores.

[approach adopted by CMST (Chaibub Neto et al. 2012).]

CIT (Millstein et al. 2009)

Causal model: $Q \to G \to C$

Implied CI rels: $C \not\perp\!\!\!\perp Q$, $G \not\perp\!\!\!\perp Q \mid C$, $C \not\perp\!\!\!\perp G \mid Q$, $C \perp\!\!\!\perp Q \mid G$

$$
\begin{aligned}
C &= \alpha_1 + \beta_1 Q + \epsilon \\
G &= \alpha_2 + \beta_2 C + \beta_3 Q + \epsilon \\
C &= \alpha_3 + \beta_4 G + \beta_5 Q + \epsilon
\end{aligned}
$$

CI relation	hypothesis test	type	p-value
$C \not\perp\!\!\!\perp Q$	$H_{0,1} : \beta_1 = 0,\ H_{A,1} : \beta_1 \neq 0$	F-test	p_1
$G \not\perp\!\!\!\perp Q \mid C$	$H_{0,2} : \beta_3 = 0,\ H_{A,2} : \beta_3 \neq 0$	F-test	p_2
$C \not\perp\!\!\!\perp G \mid Q$	$H_{0,3} : \beta_4 = 0,\ H_{A,3} : \beta_4 \neq 0$	F-test	p_3
$C \perp\!\!\!\perp Q \mid G$	$H_{0,4} : \beta_5 \neq 0,\ H_{A,4} : \beta_5 = 0$	equiv test	p_4

Intersection-union test:

$$H_0 : H_{0,1} \cup H_{0,2} \cup H_{0,3} \cup H_{0,4}\ , \qquad H_A : H_{A,1} \cap H_{A,2} \cap H_{A,3} \cap H_{A,4}\ ,$$

$$\text{causal model p-value:} \quad p_c = \max\{p_1\ ,\ p_2\ ,\ p_3\ ,\ p_4\}$$

CIT (Millstein et al. 2009)

Reactive model: $Q \to C \to G$

Implied CI rels: $G \not\perp\!\!\!\perp Q$, $C \not\perp\!\!\!\perp Q \mid G$, $G \not\perp\!\!\!\perp C \mid Q$, $G \perp\!\!\!\perp Q \mid C$

$$
\begin{aligned}
G &= \alpha_2 + \beta_2\, C + \beta_3\, Q + \epsilon \\
C &= \alpha_3 + \beta_4\, G + \beta_5\, Q + \epsilon \\
G &= \alpha_4 + \beta_6\, Q + \epsilon
\end{aligned}
$$

CI relation	hypothesis test	type	p-value
$G \not\perp\!\!\!\perp Q$	$H_{0,5} : \beta_6 = 0,\ H_{A,5} : \beta_6 \neq 0$	F-test	p_5
$C \not\perp\!\!\!\perp Q \mid G$	$H_{0,6} : \beta_5 = 0,\ H_{A,6} : \beta_5 \neq 0$	F-test	p_6
$G \not\perp\!\!\!\perp C \mid Q$	$H_{0,7} : \beta_2 = 0,\ H_{A,7} : \beta_2 \neq 0$	F-test	p_7
$G \perp\!\!\!\perp Q \mid C$	$H_{0,8} : \beta_3 \neq 0,\ H_{A,8} : \beta_3 = 0$	equiv test	p_8

Intersection-union test:

$$H_0 : H_{0,5} \cup H_{0,6} \cup H_{0,7} \cup H_{0,8}\ , \qquad H_A : H_{A,5} \cap H_{A,6} \cap H_{A,7} \cap H_{A,8}\ ,$$

reactive model p-value: $\quad p_r = \max\{p_5\ ,\ p_6\ ,\ p_7\ ,\ p_8\}$

CIT (Millstein et al. 2009)

For a given significance level α, the decision rule for model selection is:

- Select the causal model, if $p_c \leq \alpha$ and $p_r > \alpha$.
- Select the reactive model, if $p_c > \alpha$ and $p_r \leq \alpha$.
- Select the independence model, if $p_c > \alpha$ and $p_r > \alpha$.
- Do not select any model, if $p_c \leq \alpha$ and $p_r \leq \alpha$.

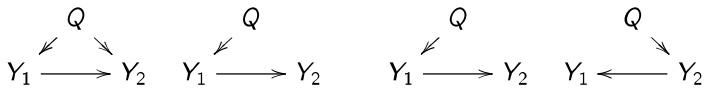
Drawbacks:

- *Computationally expensive*: the null distribution of the equivalence test is unknown and a bootstrap approach is needed.
- *Incoherent behavior*: sometimes both causal and reactive models are well supported by the CIT test.

Vuong's model selection test (Vuong 1989)

General properties:

- Attaches a p-value to a (penalized) log-likelihood ratio score, allowing the assessment of the uncertainty associated with a model selection call.
- Can handle non-nested models.

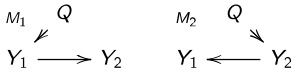


nested models non-nested models

- Fully analytical approach.
- Can handle misspecified models.

Vuong's model selection test (Vuong 1989)

Consider two competing probability models, say, M_1 and M_2,



with densities

$$f_1 = \prod_{i=1}^{n} N(y_{2,i}\,;\, \alpha_{21} + \beta_{21}\, y_{1,i}\,,\, \sigma^2_{21})\, N(y_{1,i}\,;\, \mu_q\,,\, \sigma^2_1)\, f(Q_i)\ ,$$

$$f_2 = \prod_{i=1}^{n} N(y_{1,i}\,;\, \alpha_{12} + \beta_{12}\, y_{2,i}\,,\, \sigma^2_{12})\, N(y_{2,i}\,;\, \mu_q\,,\, \sigma^2_2)\, f(Q_i)\ .$$

Let h^0 represent the true (and unknown) model.

The hypotheses assessed by Vuong's test are:

H_0: f_1 and f_2 are equally close (or distant) to h^0.
H_1: f_1 is closer to h^0 than f_2.
H_2: f_2 is closer to h^0 than f_1.

Vuong's model selection test (Vuong 1989)

Consider the Kullback-Leibler distance (Kullback 1959) of two probability models:

$$KL(h^0; f) = E^0\left[\log h^0(\mathbf{y})\right] - E^0\left[\log f(\mathbf{y} \mid \boldsymbol{\theta}_*)\right]$$

where E^0 is the expectation w.r.t. the true distribution h^0, and $\boldsymbol{\theta}_*$ is the parameter that minimizes the KLIC distance from f to the true model.

A model f_1 is a better approximation of h^0 than an alternative model f_2 iff

$$KL(h^0; f_1) < KL(h^0; f_2) \quad \Leftrightarrow \quad E^0(\log f_1) > E^0(\log f_2).$$

Vuong's model selection test (Vuong 1989)

Let $LR_{12} = \log f_1 - \log f_2$, then the direction of LR_{12} tells us which model is closer to h^0 according to the KL distance.

The null and alternative hypothesis are given by

$$H_0 : E^0(LR_{12}) = 0 , \quad H_1 : E^0(LR_{12}) > 0 , \quad H_2 : E^0(LR_{12}) < 0 .$$

The quantity $E^0(LR_{12})$ is unknown, but the sample mean and variance of

$$\hat{LR}_{12,i} = \log \hat{f}_{1,i} - \log \hat{f}_{2,i} , \qquad i = 1, \ldots, n,$$

converge, respectively, to $E^0(LR_{12})$ and $Var^0(LR_{12}) = \sigma_{12.12}$.

Then, under H_0, the scaled likelihood-ratio test statistic

$$Z_{12} = \frac{\hat{LR}_{12}}{\sqrt{n\,\hat{\sigma}_{12.12}}} \longrightarrow^d N(0,1) , \quad \text{where } \hat{LR}_{12} = \sum_{i=1}^{n} \hat{LR}_{12,i} .$$

Vuong's model selection test (Vuong 1989)

- More complex models tend to over-fit the data and always produce higher log-likelihood scores than more parsimonious models.
- Hence, when comparing models with different dimensions it is necessary to counter-balance model fit and model parsimony, by adding a penalty term proportional to the model dimension, penalizing more complex models to a greater extent.
- We replace $L\hat{R}_{12}$ by $L\hat{R}_{12} - D_{12}$, where,

$$D_{12} = k_{f_1} - k_{f_2} \quad \text{or} \quad D_{12} = (k_{f_1} - k_{f_2})(\log n)/2$$

for the AIC and BIC penalties, respectively.

Vuong's model selection test (Vuong 1989)

Interesting property:

Recall that under the null, $Z_{12} \sim N(0,1)$, and p-value for the comparison of model M_1 against M_2 is computed as

$$p_{12} = Pr(Z_{12} \geq z_{12}) = 1 - \Phi(z_{12}) \ .$$

Since $L\hat{R}_{12} = -L\hat{R}_{21}$ we have that

$$Z_{12} = \frac{L\hat{R}_{12}}{\sqrt{n\,\hat{\sigma}_{12.12}}} = -\frac{L\hat{R}_{21}}{\sqrt{n\,\hat{\sigma}_{12.12}}} = -Z_{21} \ .$$

Therefore,

$$p_{21} = 1 - \Phi(z_{21}) = \Phi(z_{12}) \ ,$$

and

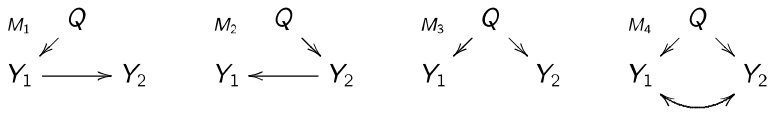
$$p_{12} + p_{21} = 1 \ .$$

This property ensures that the p-values of the intersection-union tests we develop in the next few slides, cannot be simultaneously significant.

Causal Model Selection Tests (CMST)

Vuong's test handles model selection for 2 models only.

However, we want to use data from experimental crosses to distinguish among 4 models:



Our strategy is to combine several separate Vuong's tests into a single one.

We developed 3 distinct Causal Model Selection Tests (Chaibub Neto et al. 2012):

1. Parametric CMST
2. Non-parametric CMST
3. Joint parametric CMST

Parametric CMST

Corresponds to an intersection-union test of separate Vuong's tests.

For model M_1 we consider $f_1 \times f_2$, $f_1 \times f_3$, $f_1 \times f_4$, and test:

H_0 : model M_1 **is not closer** to the true model than M_2, M_3, and M_4.

H_1 : model M_1 **is closer** to the true model than M_2, M_3, and M_4.

$$H_0 : \{E^0(LR_{12}) = 0\} \cup \{E^0(LR_{13}) = 0\} \cup \{E^0(LR_{14}) = 0\}$$

$$H_1 : \{E^0(LR_{12}) > 0\} \cap \{E^0(LR_{13}) > 0\} \cap \{E^0(LR_{14}) > 0\}$$

The p-value for M_1 is computed as: $p_1 = max\{p_{12}, p_{13}, p_{14}\}$

Similarly, for models M_2, M_3, and M_4 we have:

M_2 : $f_2 \times f_1$, $f_2 \times f_3$, $f_2 \times f_4$ $\Rightarrow$ $p_2 = max\{p_{21}, p_{23}, p_{24}\}$
M_3 : $f_3 \times f_1$, $f_3 \times f_2$, $f_3 \times f_4$ $\Rightarrow$ $p_2 = max\{p_{31}, p_{32}, p_{34}\}$
M_4 : $f_4 \times f_1$, $f_4 \times f_2$, $f_4 \times f_3$ $\Rightarrow$ $p_2 = max\{p_{41}, p_{42}, p_{43}\}$

Parametric CMST

The CMST p-values cannot be simultaneously significant.

For a fixed α:

$p_1 = max\{p_{12}, p_{13}, p_{14}\} \leq \alpha \quad \Rightarrow \quad p_{12} \leq \alpha, \ p_{13} \leq \alpha, \ p_{14} \leq \alpha$
$p_{12} \leq \alpha$ and $p_{12} + p_{21} = 1 \quad \Rightarrow \quad p_{21} \geq 1 - \alpha$
$p_{13} \leq \alpha$ and $p_{13} + p_{31} = 1 \quad \Rightarrow \quad p_{31} \geq 1 - \alpha$
$p_{14} \leq \alpha$ and $p_{14} + p_{41} = 1 \quad \Rightarrow \quad p_{41} \geq 1 - \alpha$

If $max\{p_{21}, p_{23}, p_{24}\} = p_{21} \quad \Rightarrow \quad p_2 = p_{21} \geq 1 - \alpha$
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If $max\{p_{31}, p_{32}, p_{34}\} = p_{31} \quad \Rightarrow \quad p_3 = p_{31} \geq 1 - \alpha$
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If $max\{p_{41}, p_{42}, p_{43}\} = p_{41} \quad \Rightarrow \quad p_4 = p_{41} \geq 1 - \alpha$
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If $max\{p_{41}, p_{42}, p_{43}\} = p_{43} \quad \Rightarrow \quad p_4 = p_{43} \geq p_{41} \geq 1 - \alpha$

Hence, $p_1 \leq \alpha \quad \Rightarrow \quad p_2 \geq 1 - \alpha, \ p_3 \geq 1 - \alpha, \ p_4 \geq 1 - \alpha$.

Non-parametric CMST

Vuong tests the null hypothesis that the **mean** log-likelihood ratio is equal to zero.

Alternatively, we could test the null hypothesis that the **median** log-likelihood ratio is equal to zero (Clarke 2007).

Paired sign test:

LR score	$\hat{LR}_{12,1}$	$\hat{LR}_{12,2}$	$\hat{LR}_{12,3}$	...	$\hat{LR}_{12,n}$
sign	+	+	-	...	+

Let $T_{12} = \#$of positive signs. Then under H_0, $T_{12} \sim Bin(n, 1/2)$.

The non-parametric CMST correspond to an intersection-union test of paired sign tests.

Non-parametric CMST

Observe that the p-value for comparing models 1 and 2 is the tail of a binomial distribution with success probability 0.5

$$p_{12} = P(T_{12} \geq t_{12}) = \sum_{k=t_{12}}^{n} C_k^n \, 2^{-n} \; .$$

The p-values for T_{12} and T_{21} do not add to 1 since the statistics are discrete, $p_{12} + p_{21} = 1 + C_{t_{12}}^n 2^{-n}$.

Nonetheless, the $C_{t_{12}}^n 2^{-n}$ term decreases to 0 as n increases, and, in practice, $p_{12} + p_{21} \approx 1$ even for moderate sample sizes.

Hence, in practice, the non-parametric CMST p-values cannot be simultaneously significant.

Joint parametric CMST

Z_{12}, Z_{13} and Z_{14} are not independent test statistics.

The joint CMST test corresponds to a multivariate extension of Vuong's test.

Under condition

$$\begin{pmatrix} E^0(LR_{12}) \\ E^0(LR_{13}) \\ E^0(LR_{14}) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$$

we have that

$$\mathbf{Z}_1 \; = \; \text{diag}(\hat{\mathbf{\Sigma}}_1)^{-\frac{1}{2}} \, \mathbf{L}\hat{\mathbf{R}}_1/\sqrt{n} \quad \rightarrow^d \quad N_3(\mathbf{0}, \rho_1)$$

where $\mathbf{Z}_1 = (Z_{12} \, , \, Z_{13} \, , \, Z_{14})^T$, $\mathbf{L}\hat{\mathbf{R}}_1 = (L\hat{R}_{12} \, , \, L\hat{R}_{13} \, , \, L\hat{R}_{14})^T$, and ρ_1 is a correlation matrix.

Joint parametric CMST

The joint parametric CMST test adopts

$$W_1 = \min\{\mathbf{Z}_1\}$$

as a test statistic, and tests the hypothesis:

H_0 : model M_1 is not better than at least one of M_2, M_3, M_4.
H_1 : model M_1 is better than all other models.

$$H_0 : \min\left\{E^0(LR_{12}), E^0(LR_{13}), E^0(LR_{14})\right\} \leq 0$$
$$H_1 : \min\left\{E^0(LR_{12}), E^0(LR_{13}), E^0(LR_{14})\right\} > 0$$

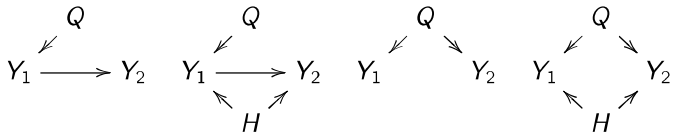
The p-value is computed as

$$\begin{aligned} P(W_1 \geq w_1) &= P(\min\{Z_{12}, Z_{13}, Z_{14}\} \geq w_1) \\ &= P(Z_{12} \geq w_1, Z_{13} \geq w_1, Z_{14} \geq w_1) \end{aligned}$$

Simulations

Simulations

Models used in the simulation study:



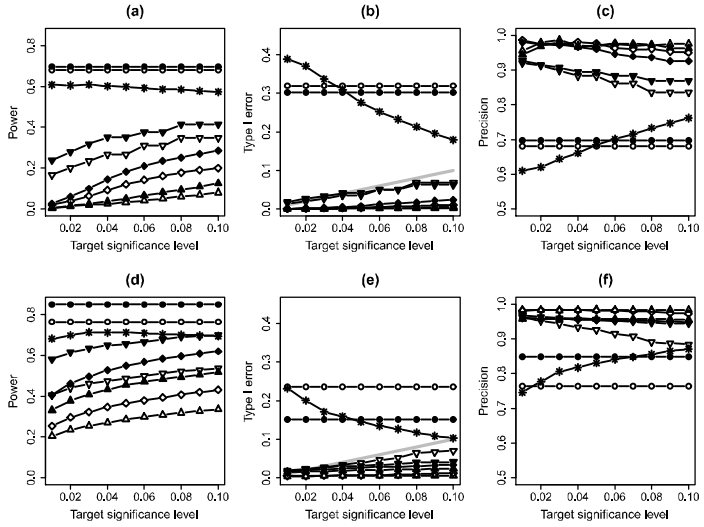
Performance measures:

$$\text{Power} = \frac{\text{true positives}}{\text{total number of tests}}$$

$$\text{Type I error} = \frac{\text{false positives}}{\text{total number of tests}}$$

$$\text{Precision} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}}$$

Overall simulation results:



○ : AIC, △ : joint CMST AIC, ◊ : par CMST AIC, ▽ : non par CMST AIC, ∗ : CIT
● : BIC, ▲ : joint CMST BIC, ♦ : par CMST BIC, ▼ : non par CMST BIC

Overall simulation results:

Overall findings:

- The AIC, BIC and CIT show high power, high type I error rates, and low precision.
- The CMST methods show lower power, lower type I error rates, and higher precision.
- The joint CMST tend to be less powerful but more precise than the other CMST approaches.
- The non-parametric CMST tend to be more powerful but less precise than the other CMST approaches.
- As sample size increase, all methods show an increase in power and precision and decrease in type I error rate.

Yeast data analysis

Data structure and QTL mapping analysis

We analyzed a budding yeast genetical genomics data set derived from a cross of a standard laboratory strain, and a wild isolate from a California vineyard (Brem and Kruglyak 2005).

Data on 112 strains with:

- Expression measurements on 5,740 transcripts.
- Dense genotype data on 2,956 markers (genotypes AA, Aa).

We performed QTL analysis using:

- Haley-Knott regression.
- Haldane's map function, with genotype error rate of 0.0001, and maximum distance between positions at which genotype probabilities were calculated set to 2cM.
- Permutation LOD threshold of 3.47, controlling GWER $< 5\%$.

Knockout signatures

- We evaluate the precision of the causal predictions using validated causal relationships extracted from a data-base of 247 knock-out experiments in yeast (Hughes et al. 2000, Zhu et al. 2008).
- In each experiment, one gene was knocked-out, and the expression levels of the remainder genes in control and knocked-out strains were interrogated for differential expression.
- The set of differentially expressed genes form the knock-out signature (ko-signature) of the knocked-out gene (ko-gene).
- The ko-signature represents a validated set of causal relations.

Validation using yeast knockout signatures

To leverage the ko information, we:

- Determined which of the 247 ko-genes also showed a significant QTL in our data-set.
- For each ko-gene showing significant linkages, we determined which other genes co-mapped to the ko-gene's QTL, generating, in this way, a list of putative targets of the ko-gene.
- For each ko-gene/putative targets list, we applied all methods using the ko-gene as the Y_1 phenotype, the putative target genes as the Y_2 phenotypes and the ko-gene's QTL as the causal anchor.

Validation using yeast knockout signatures

- In total, 135 ko-genes showed significant QTLs (both cis- and trans-).
- A gene was included in the putative targets list of a ko-gene when it showed a significant QTL, such that the 1.5-LOD support interval around the QTL's peak contained the ko-gene's QTL.
- The number of genes in the target lists varied from ko-gene to ko-gene, but, in total, there were 31,936 targets.

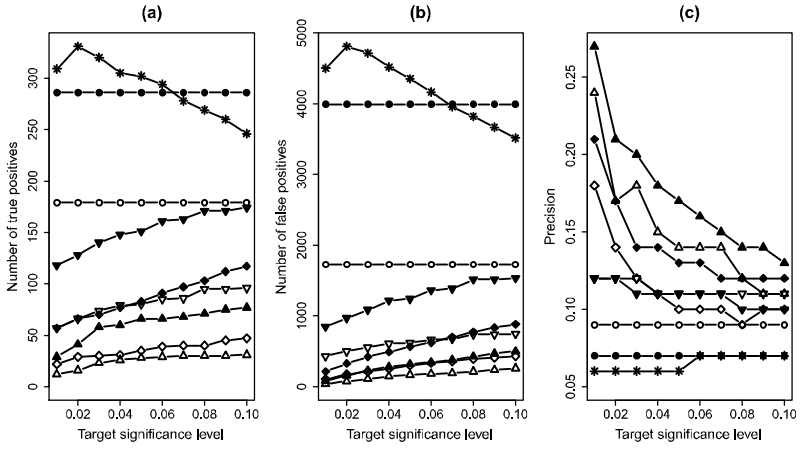
Validation using yeast knockout signatures

We summarize the method's performances in terms of "biologically validated" true positives, false positives and precision, of the inferred causal relations, where:

- A true positive is a statistically significant causal relation between a ko-gene and a putative target gene when the putative target gene belongs to the ko-signature of the ko-gene.
- A false positive is a statistically significant causal relation between a ko-gene and a putative target gene when the target gene doesn't belong to the ko-signature.
- The "validated precision", is computed as the ratio of true positives by the sum of true and false positives.

(AIC and BIC use the detected causal rels in these computations.)

Results: cis and trans ko-genes



○ : AIC, △ : joint CMST AIC, ◇ : par CMST AIC, ▽ : non par CMST AIC, ∗ : CIT
● : BIC, ▲ : joint CMST BIC, ◆ : par CMST BIC, ▼ : non par CMST BIC

Results: cis and trans ko-genes

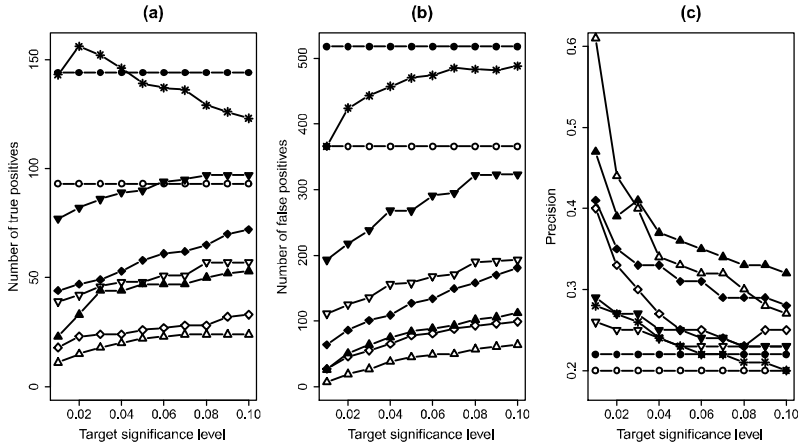
- Overall, all methods showed low precision.
- Nonetheless, the CMST methods dominated the AIC, BIC and CIT in terms of FP and precision (at the expense of reduced power to detect TP).
- The BIC-based CMST methods tended to outperform their AIC-based counterparts.

Results: cis ko-genes only

Next lets consider the results restricted to cis ko-genes.

- 27 out of the 135 candidate regulator ko-genes mapped in cis.
- We classify a gene as cis if the 1.5-LOD support interval around its LOD peak contains the gene's physical location (and if the LOD score at its physical location is higher the the LOD threshold).

Results: cis ko-genes only



○ : AIC, △ : joint CMST AIC, ◇ : par CMST AIC, ▽ : non par CMST AIC, ∗ : CIT
● : BIC, ▲ : joint CMST BIC, ◆ : par CMST BIC, ▼ : non par CMST BIC

Results: cis ko-genes only

- Overall, we see the same trends as before.
- Nonetheless, all methods perform better when the analyzes are restricted to cis ko-genes. (Note the increase in precision.)

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