A statistical approach for carcinogenesis in transcriptomics

TICE (Transcriptomics In Cancer Epidemiology)
NOWAC (Norwegian Women And Cancer)

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Gregory Nuel, University Paris-Descartes
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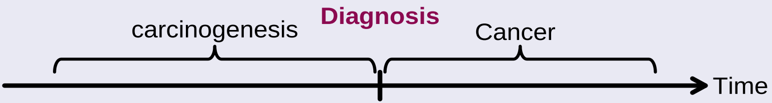
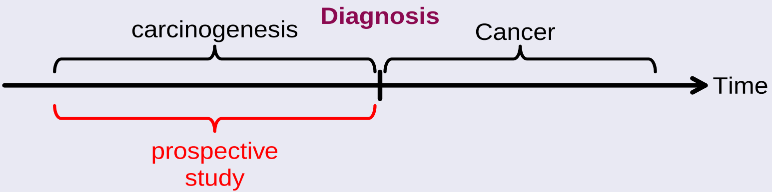
22th of May 2012

Epidemiology and Carcinogenesis



- Carcinogenesis: prior to diagnosis

Epidemiology and Carcinogenesis



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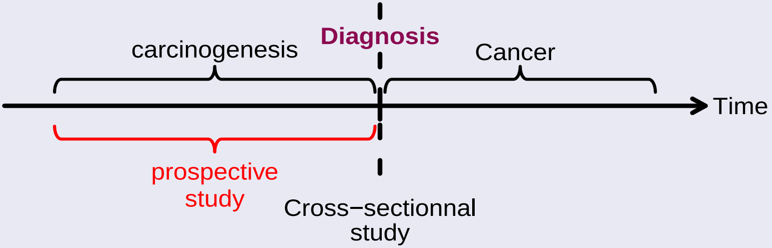

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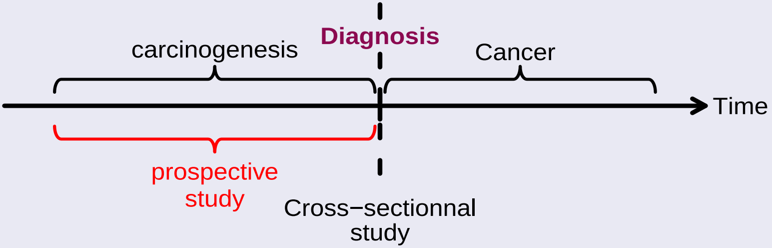

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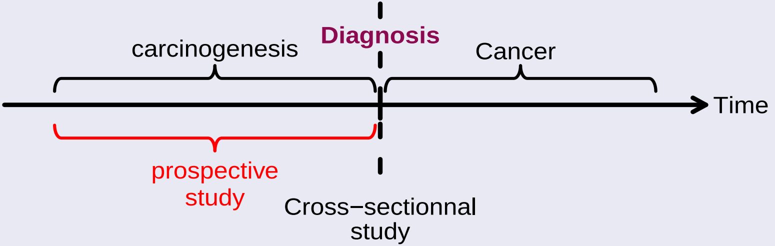

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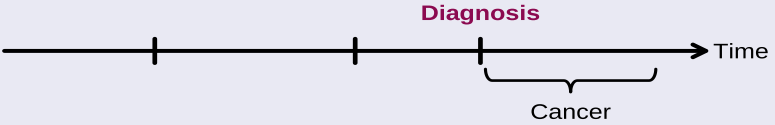

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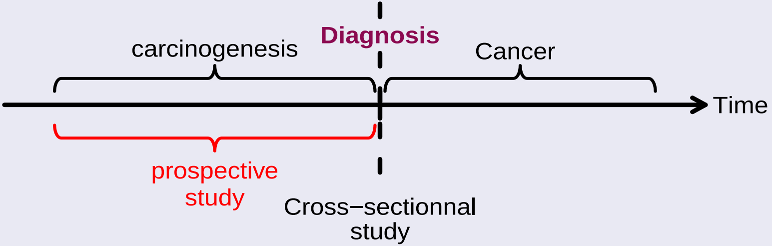

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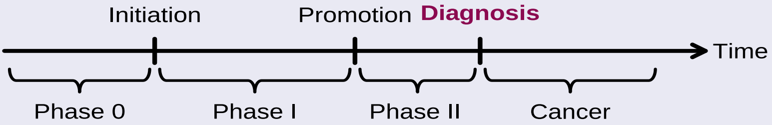

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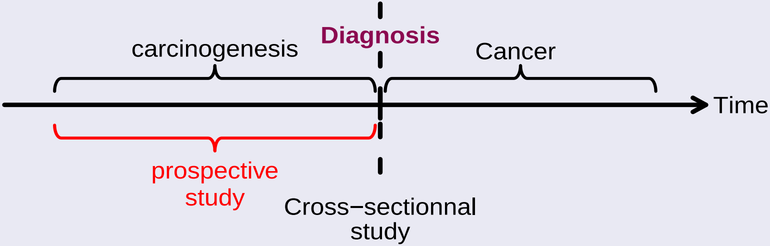

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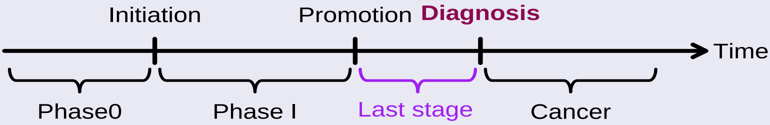

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The results from these different approaches can be compared and reinforce/validate the biological model.

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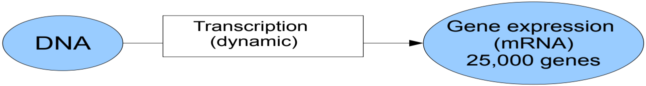

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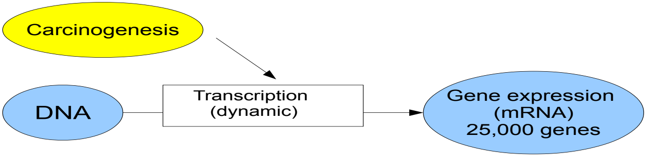

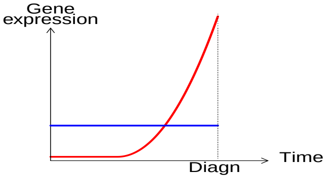

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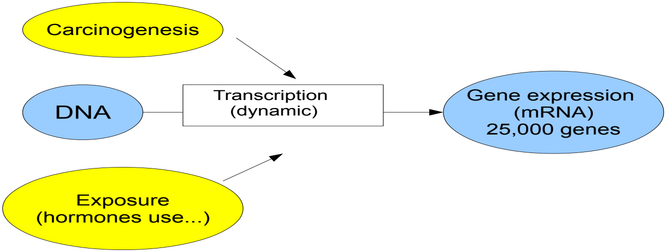
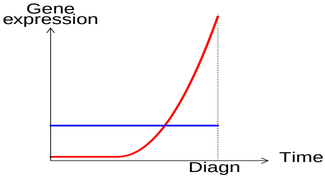
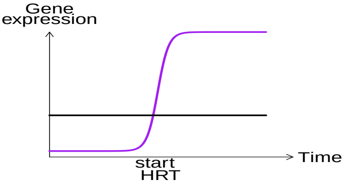


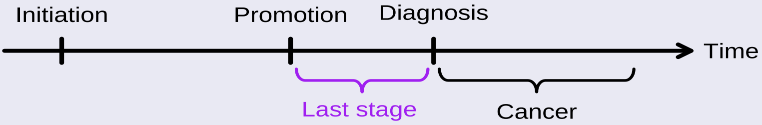




— gene involved in carcinogenesis
— gene non involved

— gene linked to HRT
— gene non-linked to HRT

Multi-stage model and gene expression



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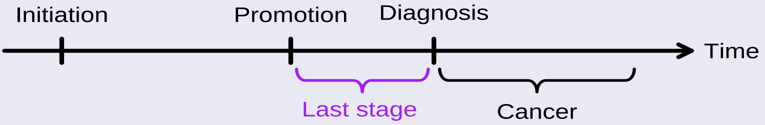
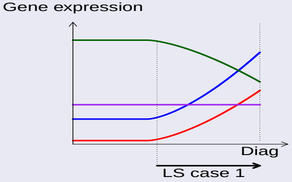
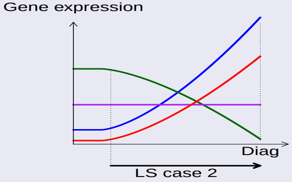


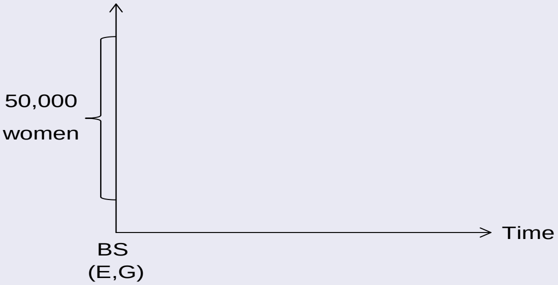
Multi-stage model and gene expression

- At beginning of last stage, the genes involved in carcinogenesis start to over/under express.
- Random last stage length (=LS)

Case 1	Case 2
	

The NOWAC cohort

Cohort of 50,000 women



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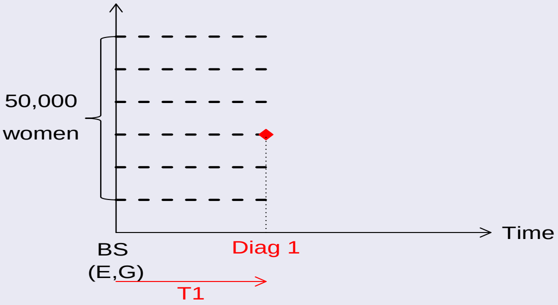

◆: case

●: control

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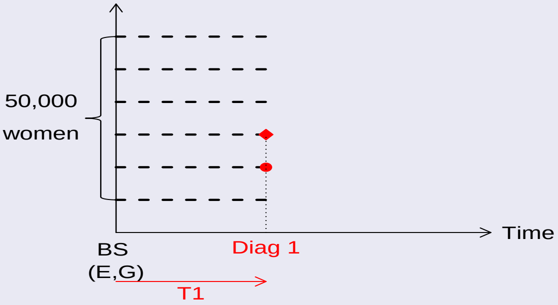

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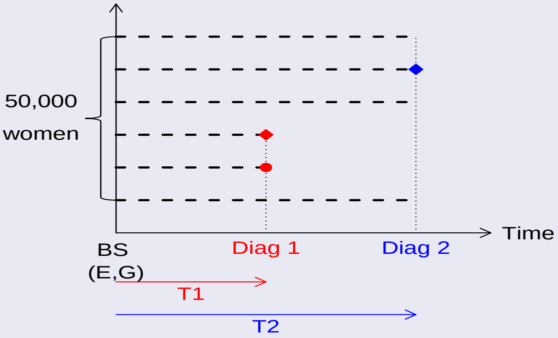

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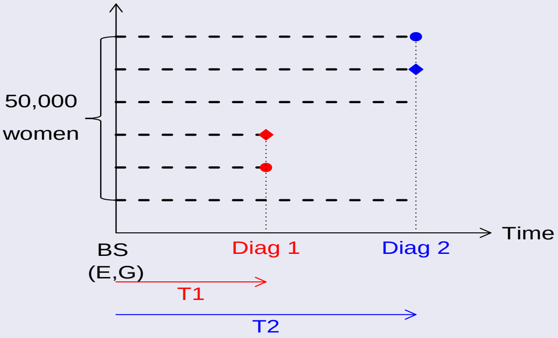

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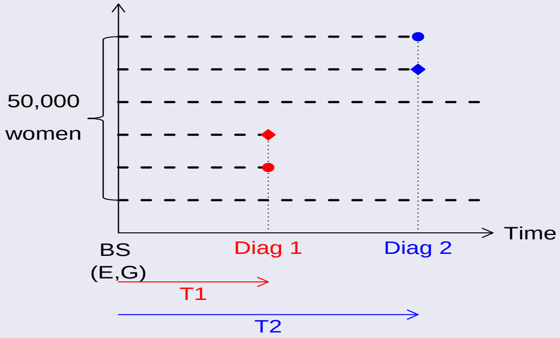

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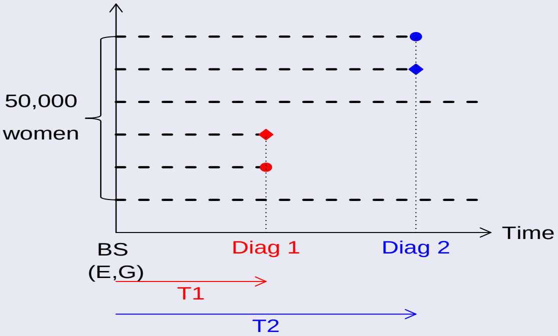

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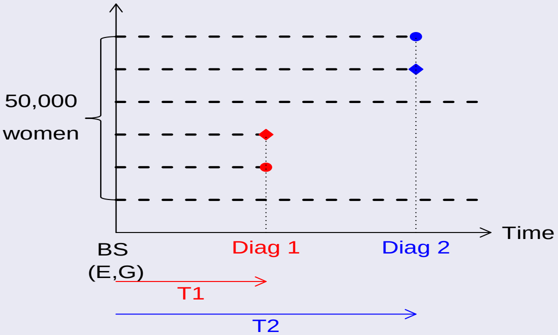

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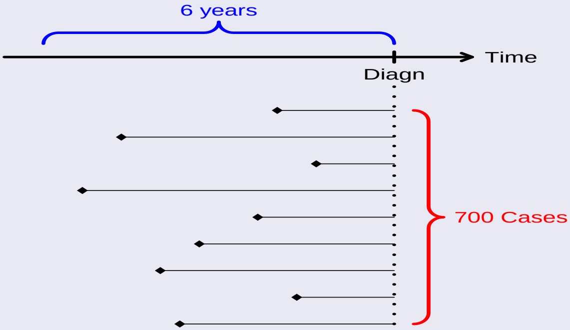
For each case-control pair:

- $(E^{\text{case}}, E^{\text{ctl}})$ = Exposure at time of BS.
- T = Follow-up time.
- DG = Difference of gene expression at time T before diagnosis (25,000 genes).

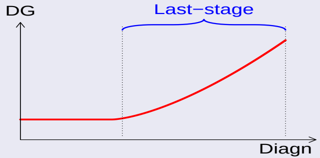
Set of data

- 6 years of follow-up.
- 700 case-control pairs.
- only one measurement by pair.



The latent last-stage model

Gene expression



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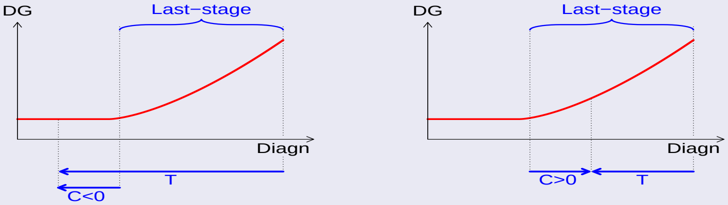

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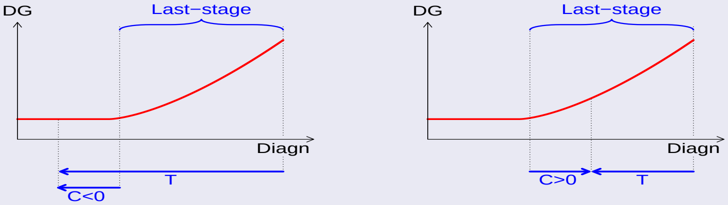

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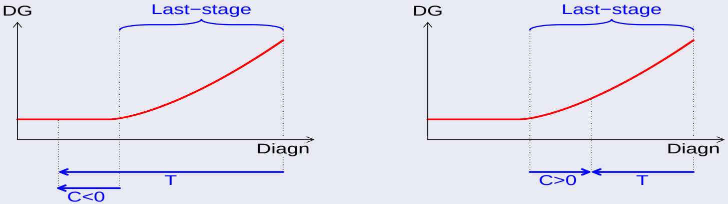

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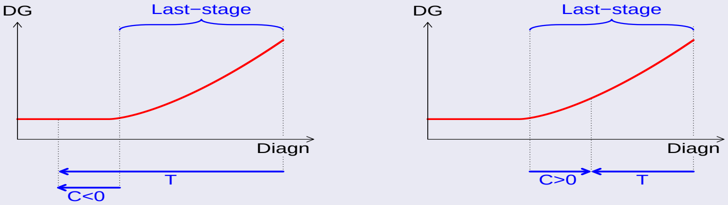

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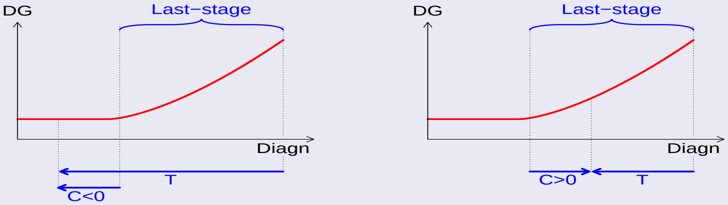

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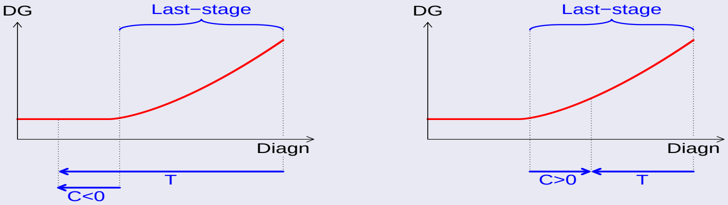

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Last-stage length

$LS \sim \Gamma(k, \theta)$, with (k, θ) dependent on the exposures of the case E^{case}

Some comments about the model

Model

For a case-control pair i, $LS_i = C_i + T_i \sim \Gamma(k, \theta)$ where

$$\begin{cases} k = 1 + \exp(\langle \kappa, E_i^{\text{case}} \rangle), \\ \theta = \exp(\langle \tau, E_i^{\text{case}} \rangle) \end{cases}$$

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  $\rightarrow$ difficult to interpret when G depends on T.
- Two main goals:
  - Estimate last-stage length distribution
  - detect genes invovled in last stage.

Parameter estimation: SEM algorithm

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2. Iteration.

$\Theta_j = (\kappa^{(j)}, \tau^{(j)}, \beta^{(j)}, \sigma^{(j)})$ $\longrightarrow$ Sample $(C_i^{(j),1}, \ldots, C_i^{(j),N})$ from $\mathbb{P}_{\Theta^{(j)}}[C_i | DG_i, T_i, E_i^{\text{case}}, DE_i]$

$\downarrow$

$(\beta^{(j+1)}, \sigma^{(j+1)})$ MLE from $\mathbb{P}_{\beta,\sigma}[DG_i | DE_i, C_i^{(j)}]$

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$\nwarrow$ (back to Θ_j)

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3. $\hat{\Theta} = \sum_{j \geqslant \text{burn-in}} \Theta^{(j)}$.

Simulations

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  - 42% of positive C.
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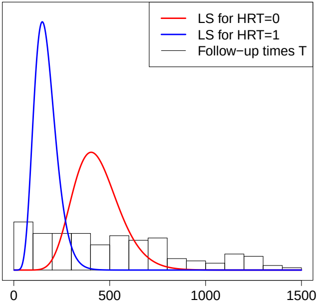
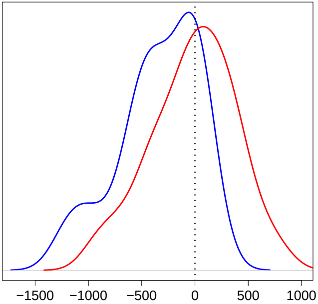
- Simulate $p = 2000$ genes. (β_0^g, β_1^g) sampled from standard gaussian distribution, (σ_g) sampled from χ^2 distribution.
- (β_2^g) sampled from $\mathcal{N}(0, 0.01)$ for $g0 = 20$ genes, and 0 for the other genes.
- Simulate DG.

Description of the simulated data (1)

Last-stage length distribution

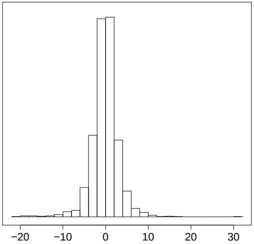


Distribution of the C_i's

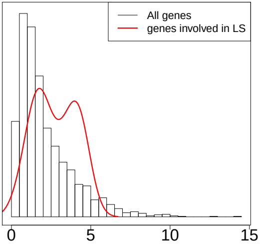


Description of the simulated data (2)

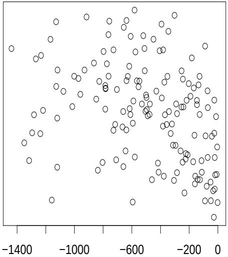
DG distribution
for one case-control pair



Gene stand. dev.
distribution

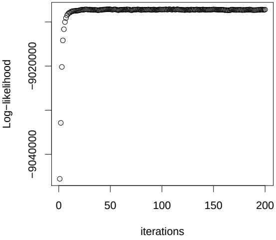


DG versus T
for one gene

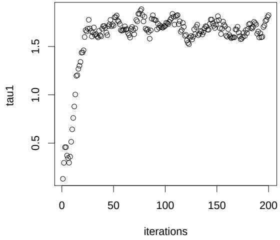


Convergence of the SEM algorithm

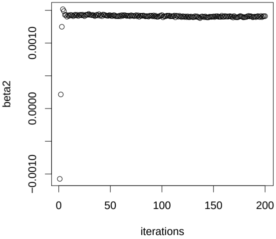
Likelihood



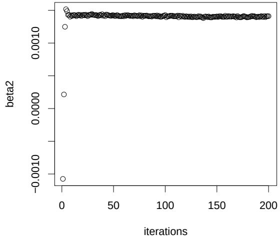
LS distribution parameter (τ_1)



β_2^g (carcinogenesis gene)



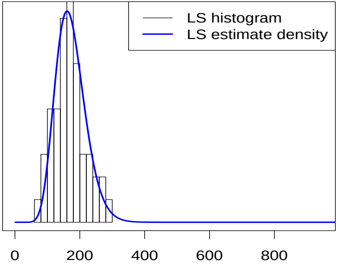
β_2^g (no carcinogenesis gene)



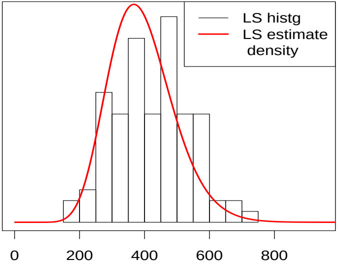
Last stage

- Histogram of the last stage LS.
- Estimated last stage density (Gamma distribution with estimated parameters): solid line.

$HRT = 1$



$HRT = 0$



Gene detection

Multiple testing

- t-test: $\beta_2^g = 0$.
- Adjust p-values (Benjamini-Hochberg).

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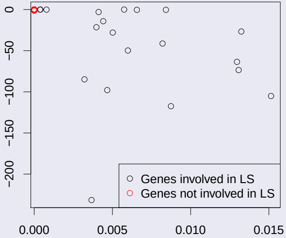
$\log 10(\text{pv})$ versus β_2^g



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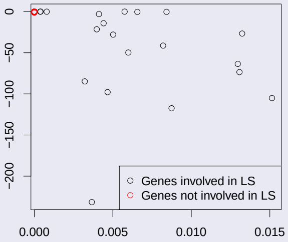
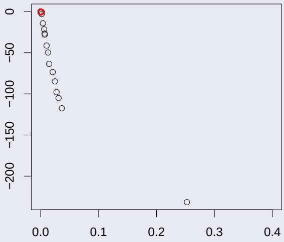


$\log 10$(pv) versus β_2^g/σ_g



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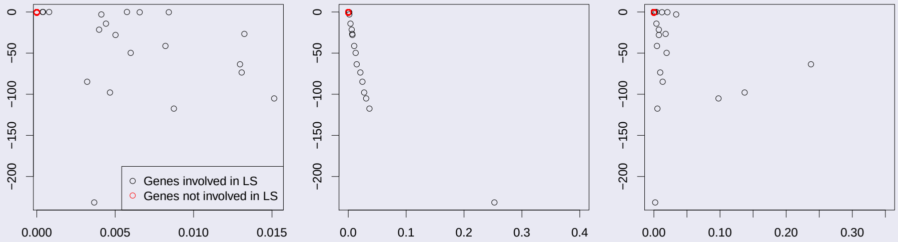
$\log 10(\text{pv})$ versus β_2^g | $\log 10(\text{pv})$ versus β_2^g/σ_g | $\log 10(\text{pv})$ versus $|\beta_2^g|/(|\beta_0^g| + |\beta_1^g|)$



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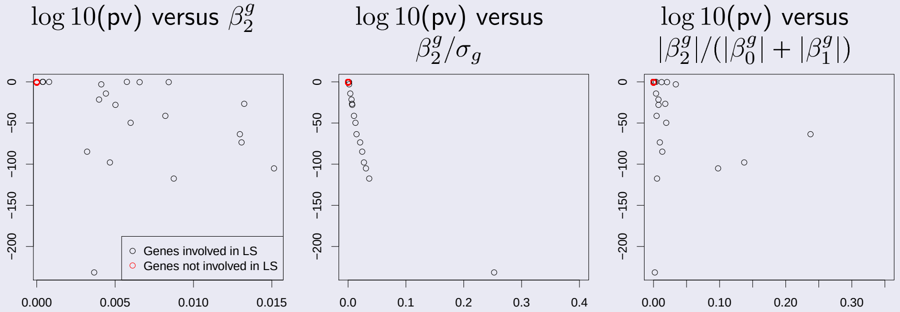

- Detection depends on signal/noise ratio
- Detection independent on constant and exposures coefficients

Sensitivity : comparison with Spearman test

Tests

- Latent last stage model
- Spearman test (DG_g , T)
- Spearman test after correction for exposures : (Res(lm($DG_g \sim DE$)) , T)

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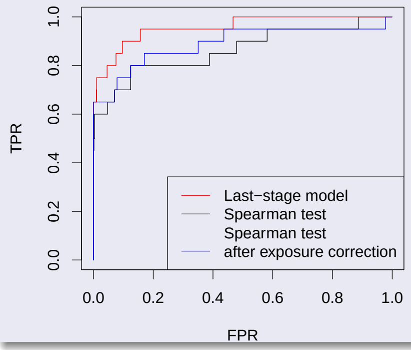
ROC curve



- Higher sensitivity with latent last-stage model
- Spearman tests: higher sensitivity after correction with exposures

Further developments

- Relevant exposures

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- Relevant exposures
- Stratification
  - Type of cancer
  - Stage of cancer

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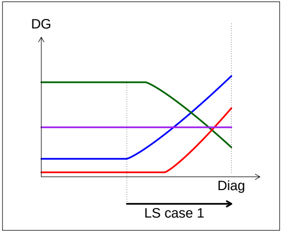
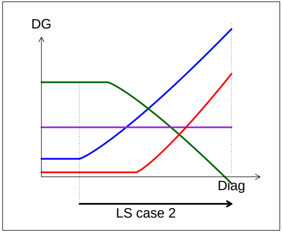
  $\rightarrow$ Shift in gene distribution.





Conclusion

- Statistical approach to study carcinogenesis on transcriptomics
- Flexible structure based on a linear model including a latent variable.
- Validation on simulations.
- Inclusion of biological assumptions