Statistical approaches to explore carcinogenic process on genome-wide transcriptomic data

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

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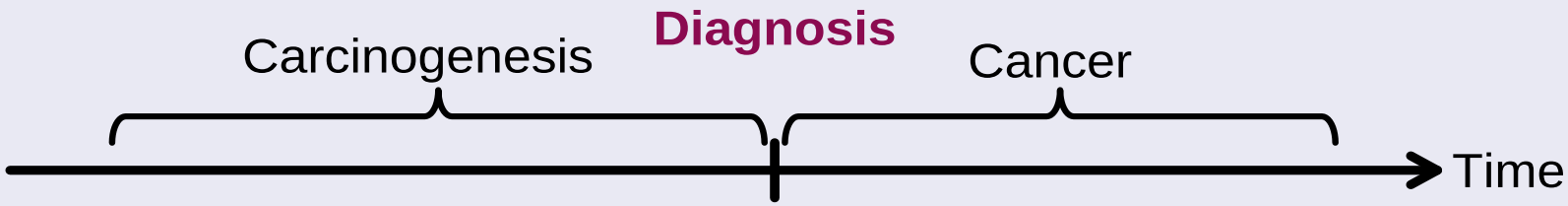
Eiliv Lund, University of Tromsø

1st of October 2012

Carcinogenesis



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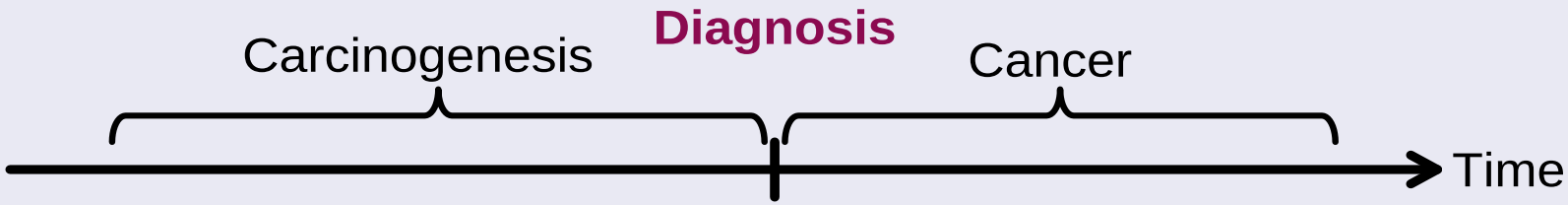
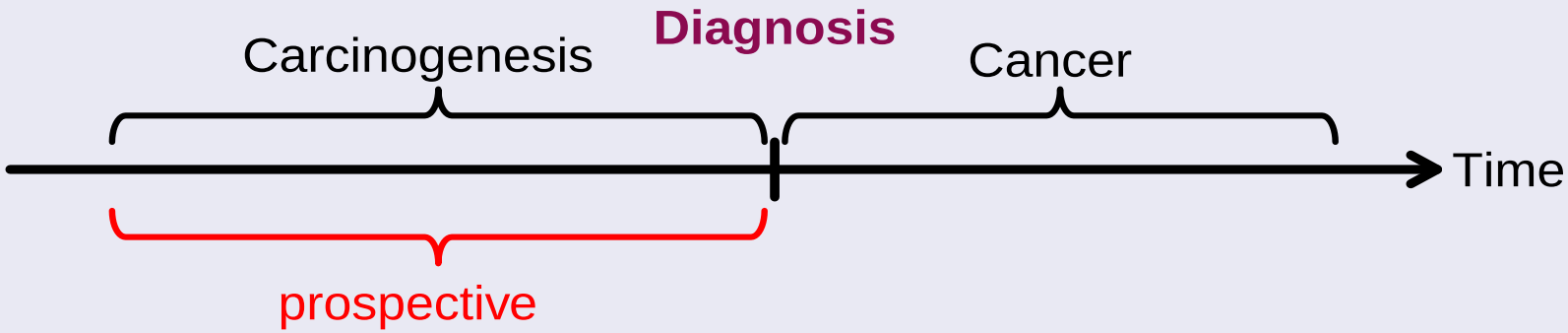


Genome Wide Association Studies (GWAS)

Carcinogenesis



Genome Wide Association Studies (GWAS)

- Prospective study: follow-up.

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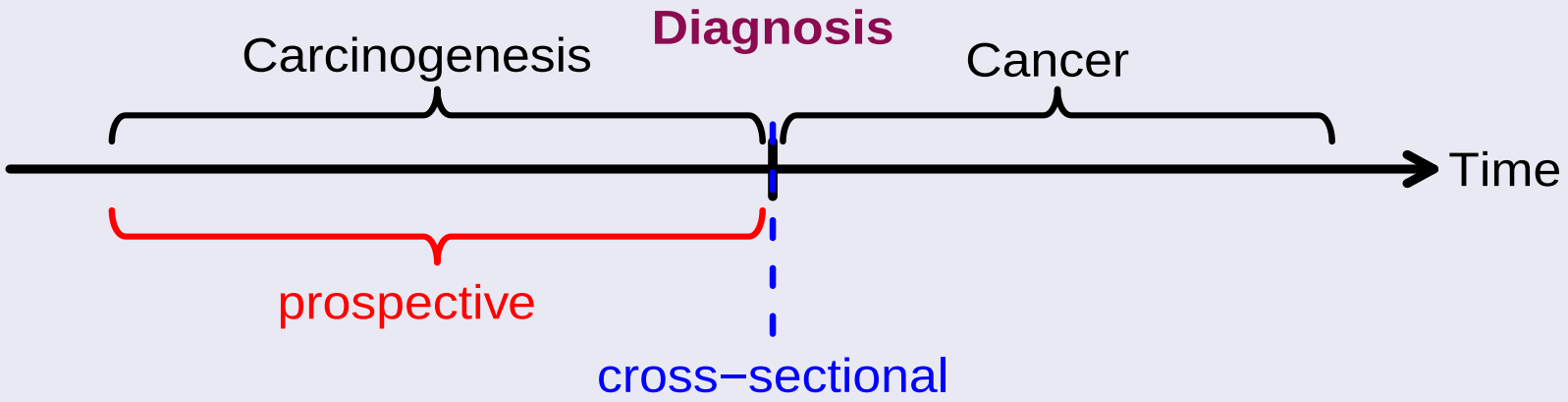

Genome Wide Association Studies (GWAS)

- Prospective study: follow-up.
- Cross-sectional study: observation at a given time.

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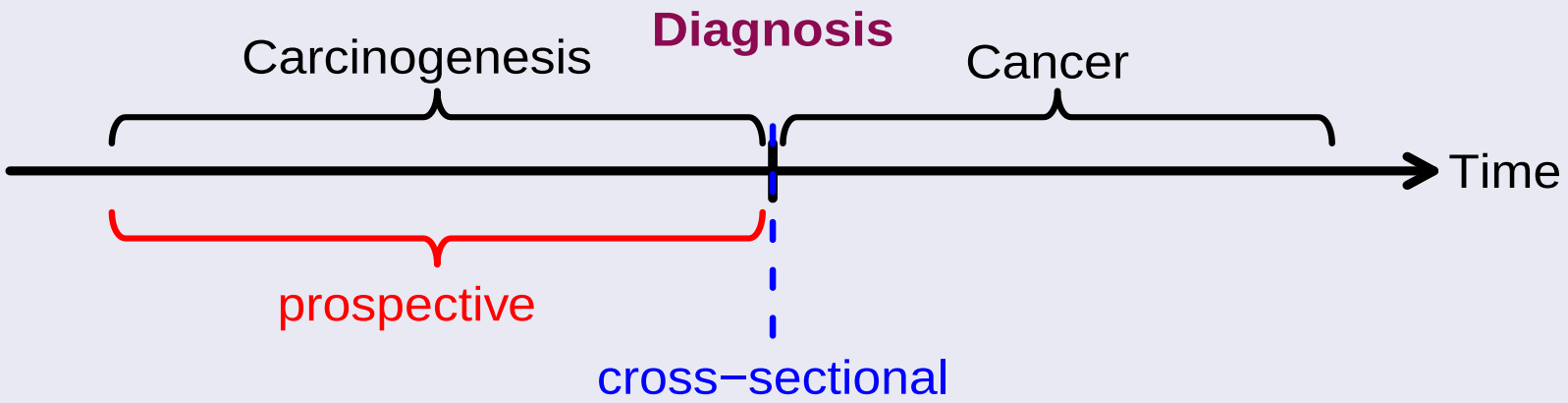

Genome Wide Association Studies (GWAS)

- Prospective study: follow-up.
- Cross-sectional study: observation at a given time.

$\hookrightarrow$ Our study: prospective design.

1. Classical prospective GWAS - Nested case-control design
2. Post-GWAS: transcriptomics in a prospective design
3. Statistical approaches for post-GWAS
   - Gene by gene model
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Cohort and nested case-control design

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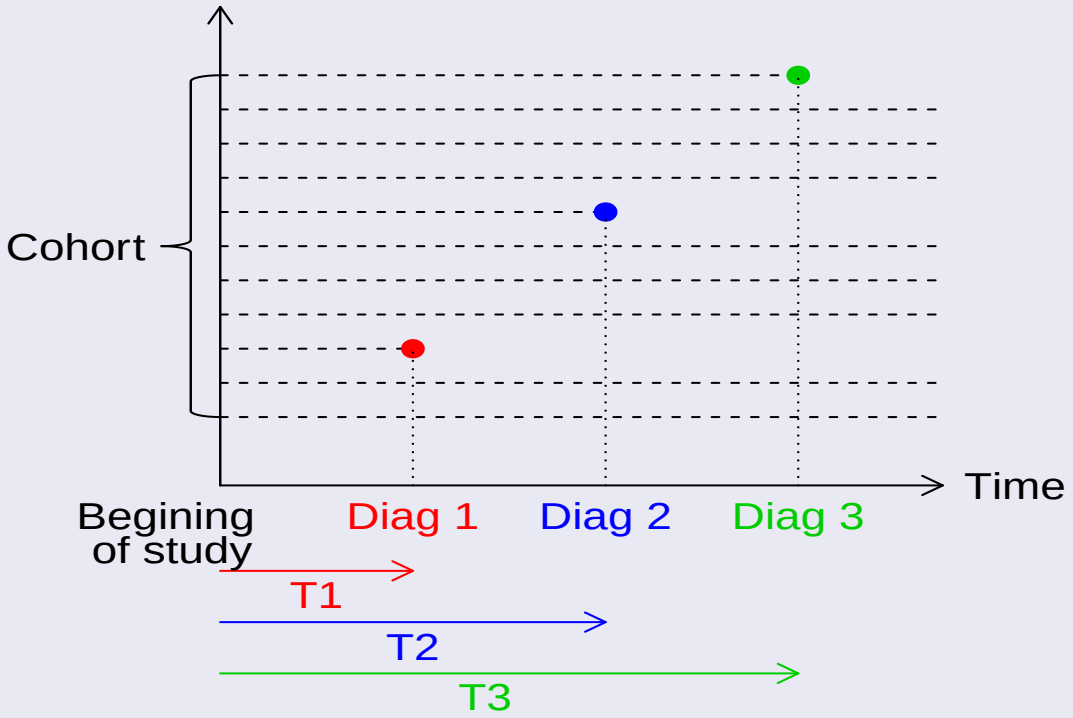

- case

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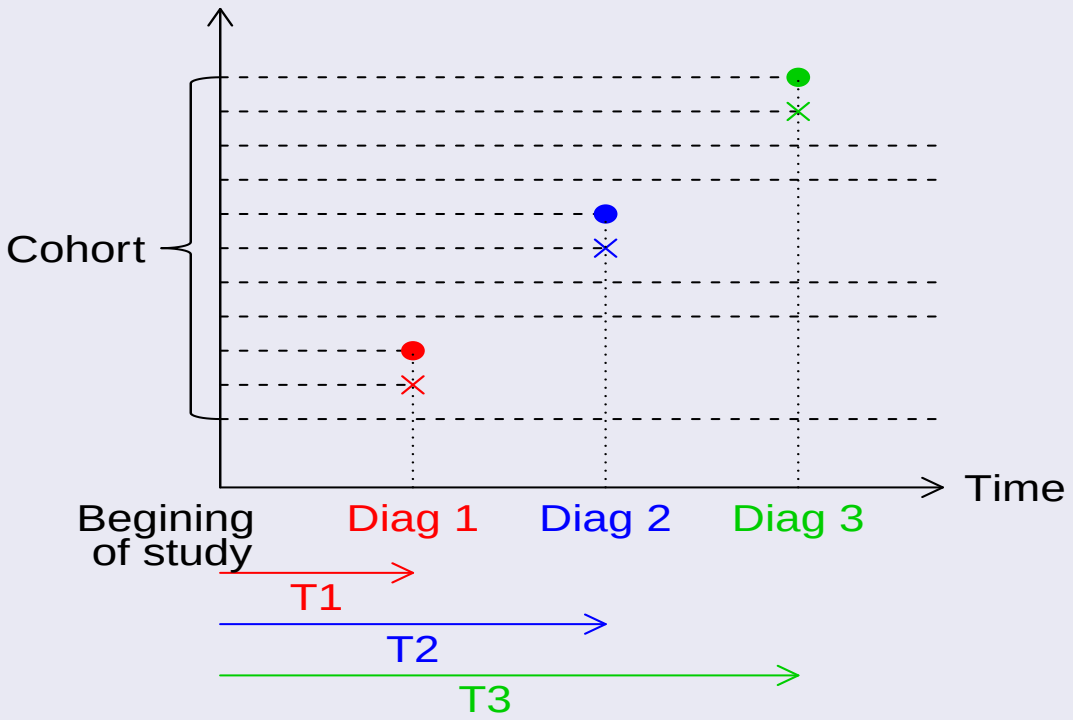

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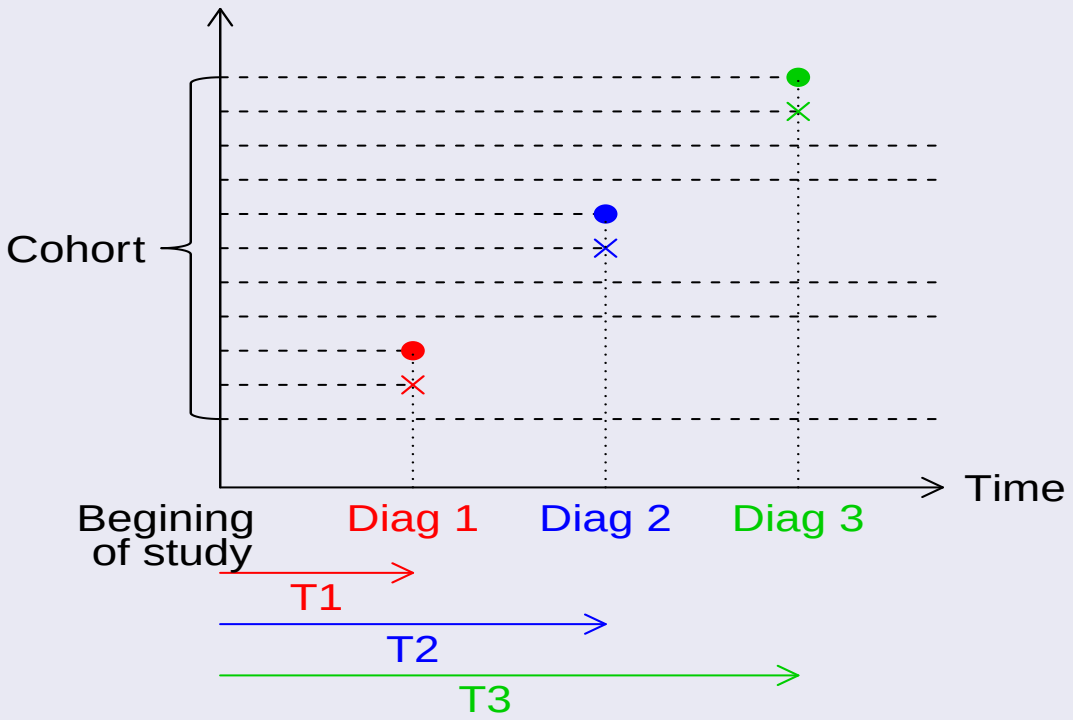

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Data

- Genomics (SNPs)
- Environmental factors

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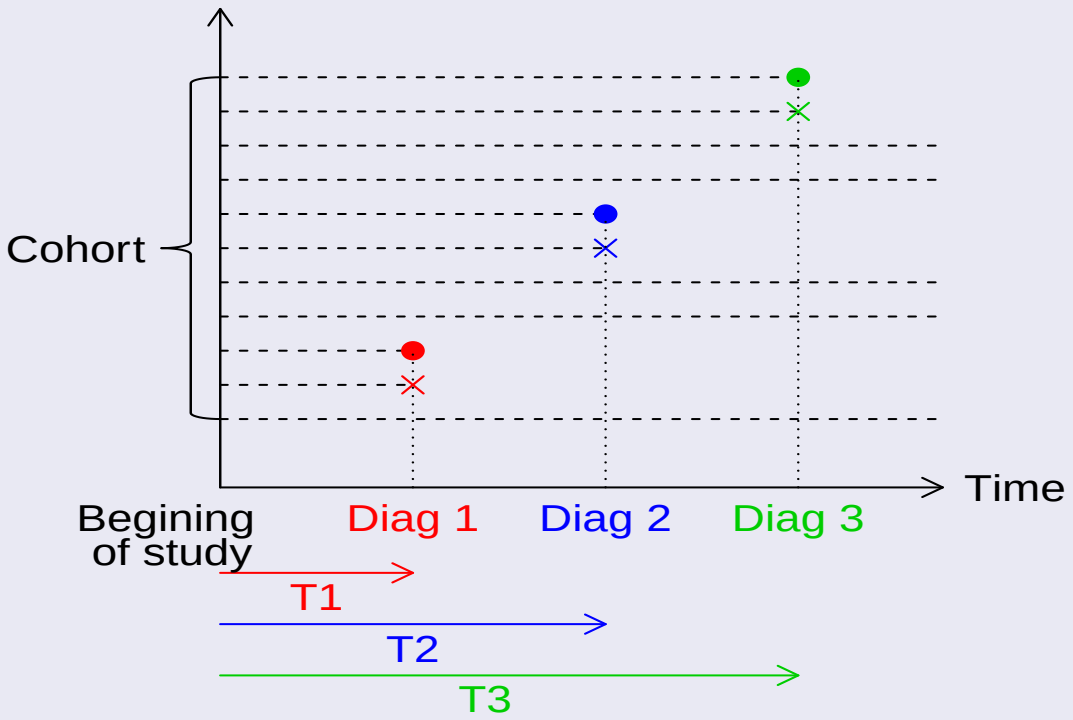

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Data

- Genomics (SNPs)
- Environmental factors

GWAS

- Interests: relative risk estimation, prediction.
- Statistical methods: survival analysis model (in particular Cox):

$$\mathbb{P}[\text{Time} \mid \text{genomics, exposures}]$$

$\hookrightarrow$ Take into account the over-representation of cases.

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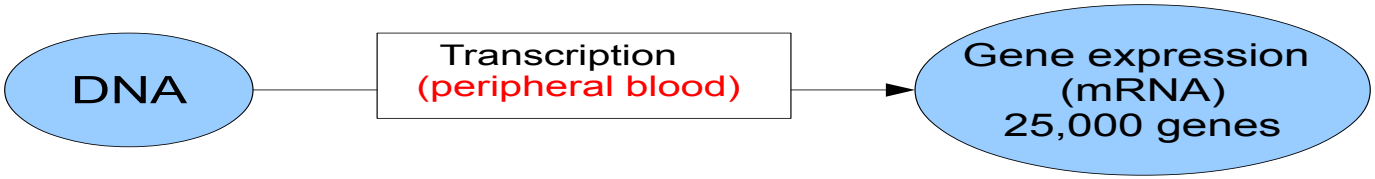
Carcinogenesis and transcription in peripheral blood



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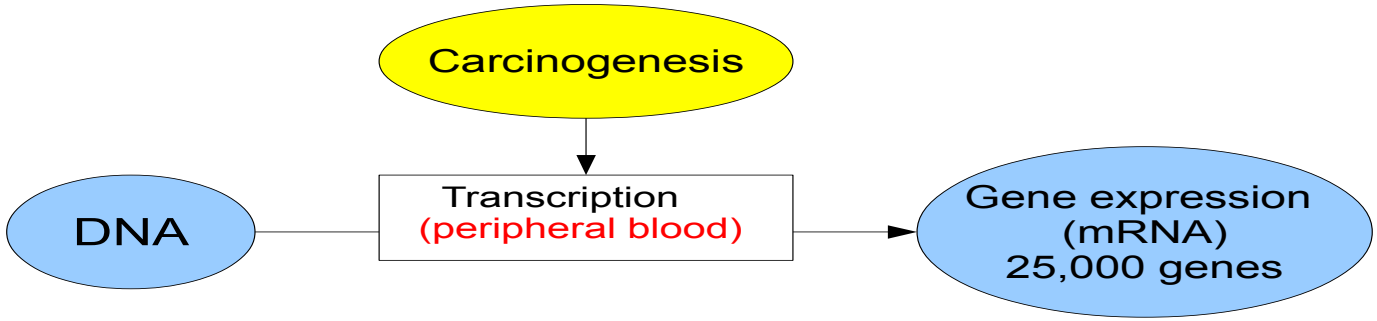
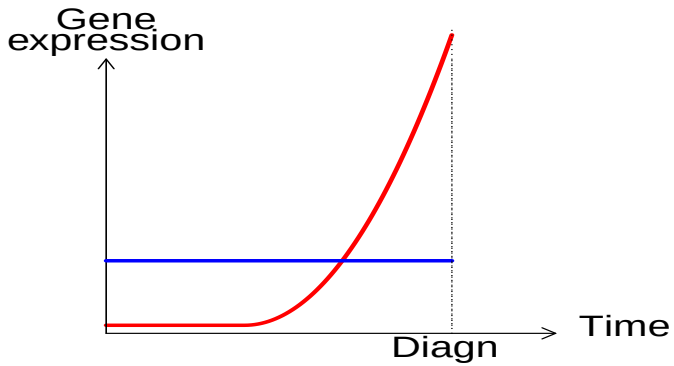
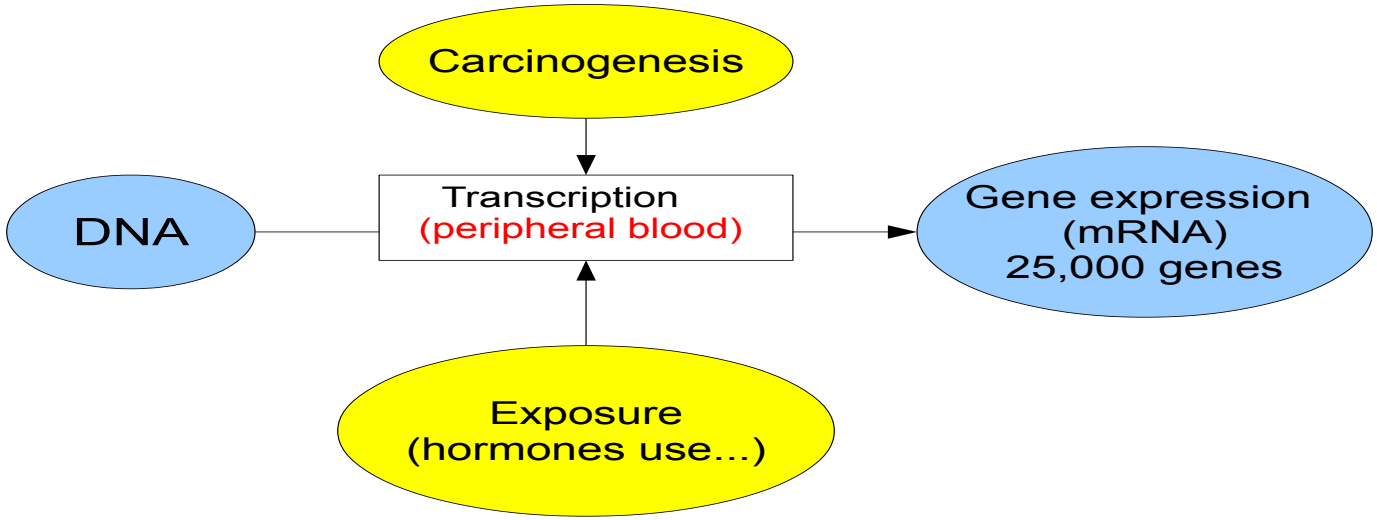


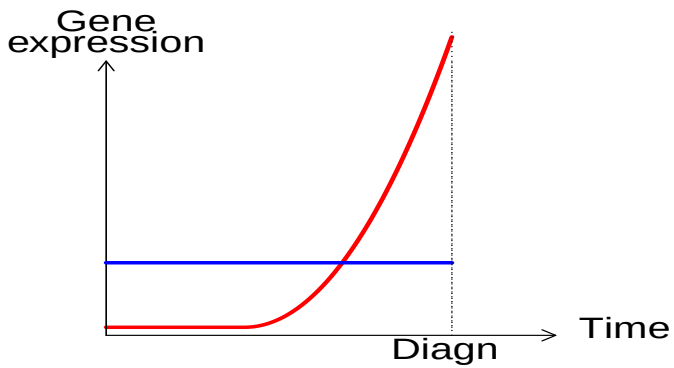


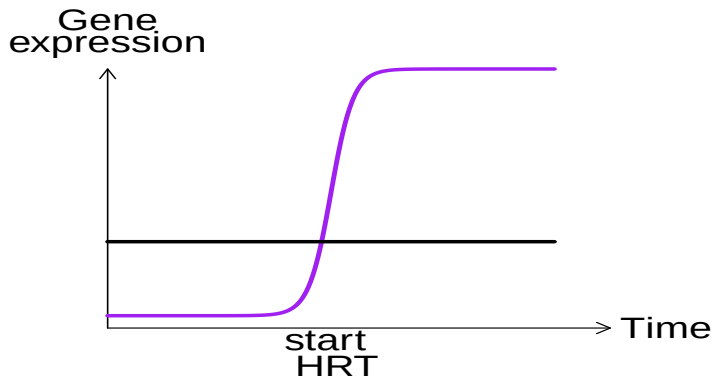
— gene involved in carcinogenesis

— gene non involved

Carcinogenesis and transcription in peripheral blood







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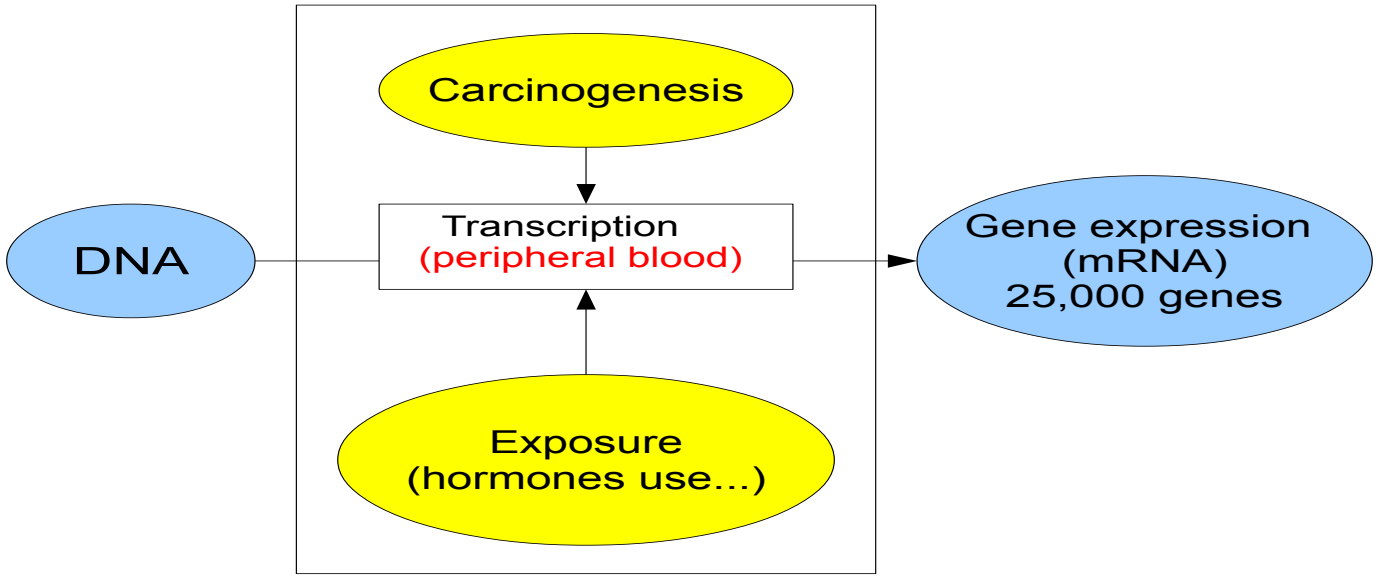

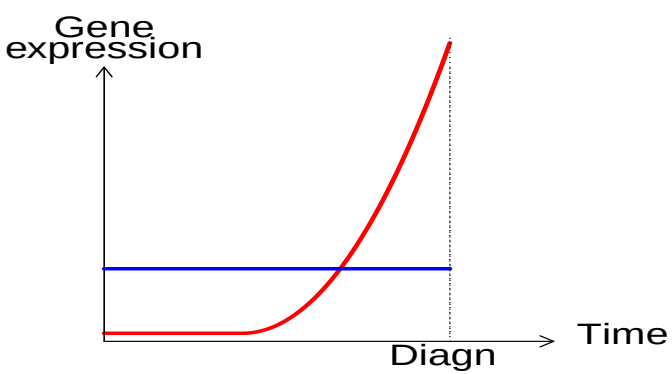

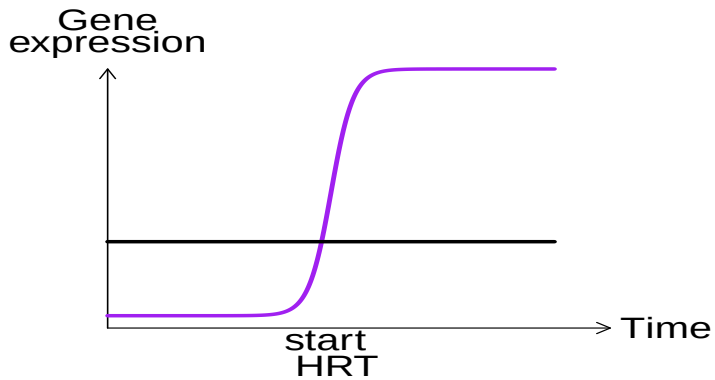

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Prospective nested case-control design

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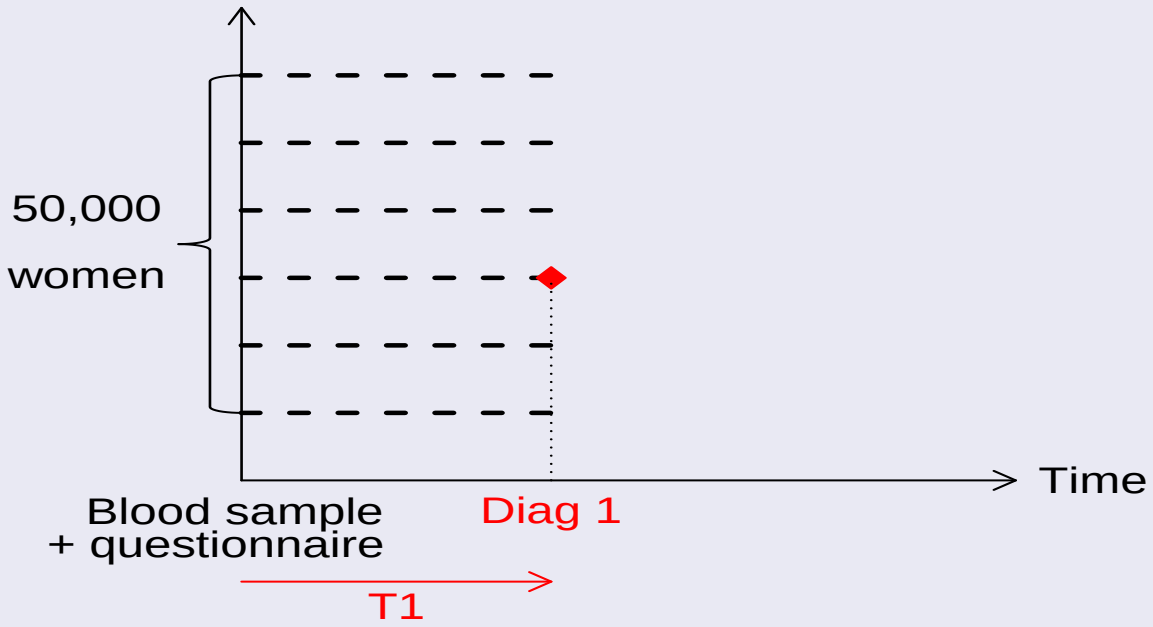

◆: case
●: control

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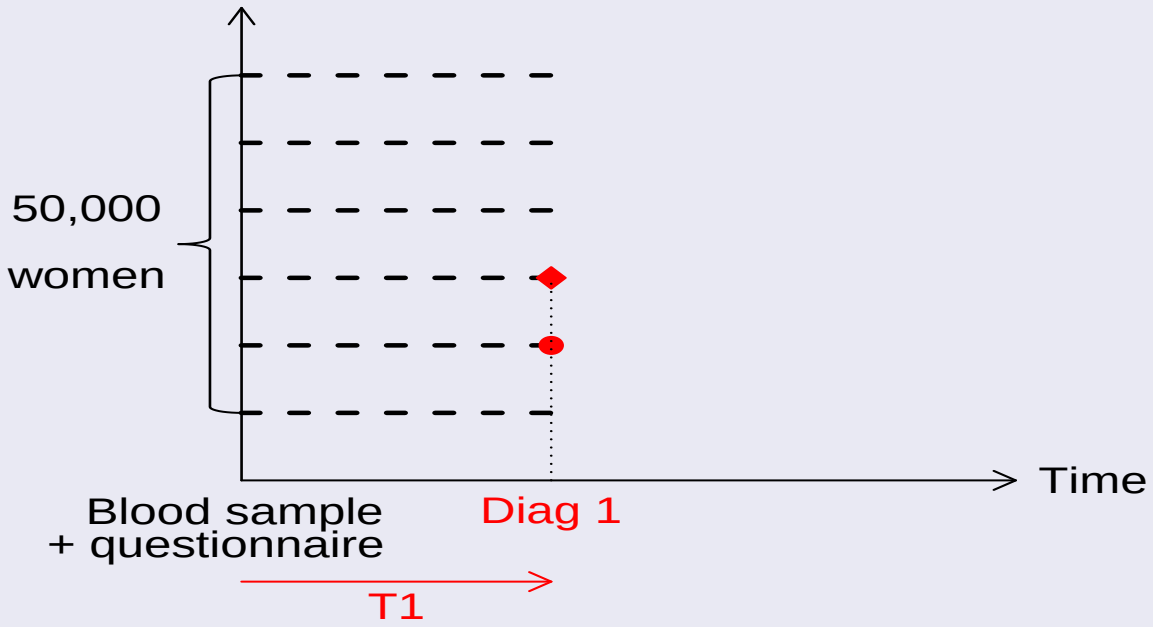

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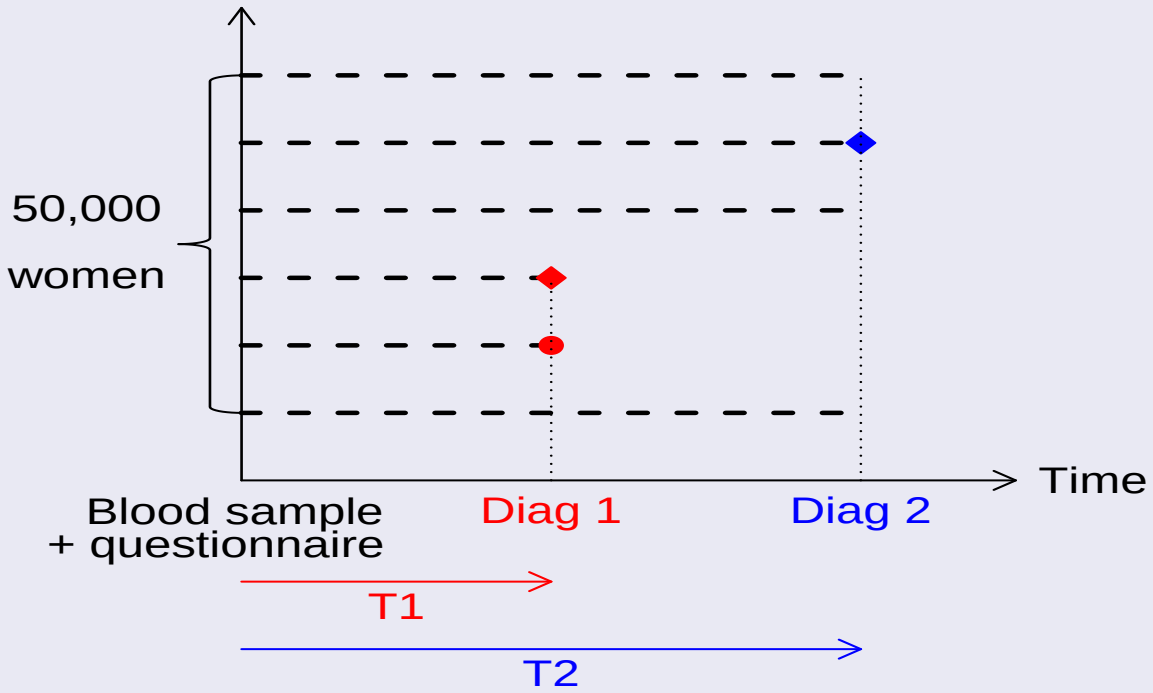

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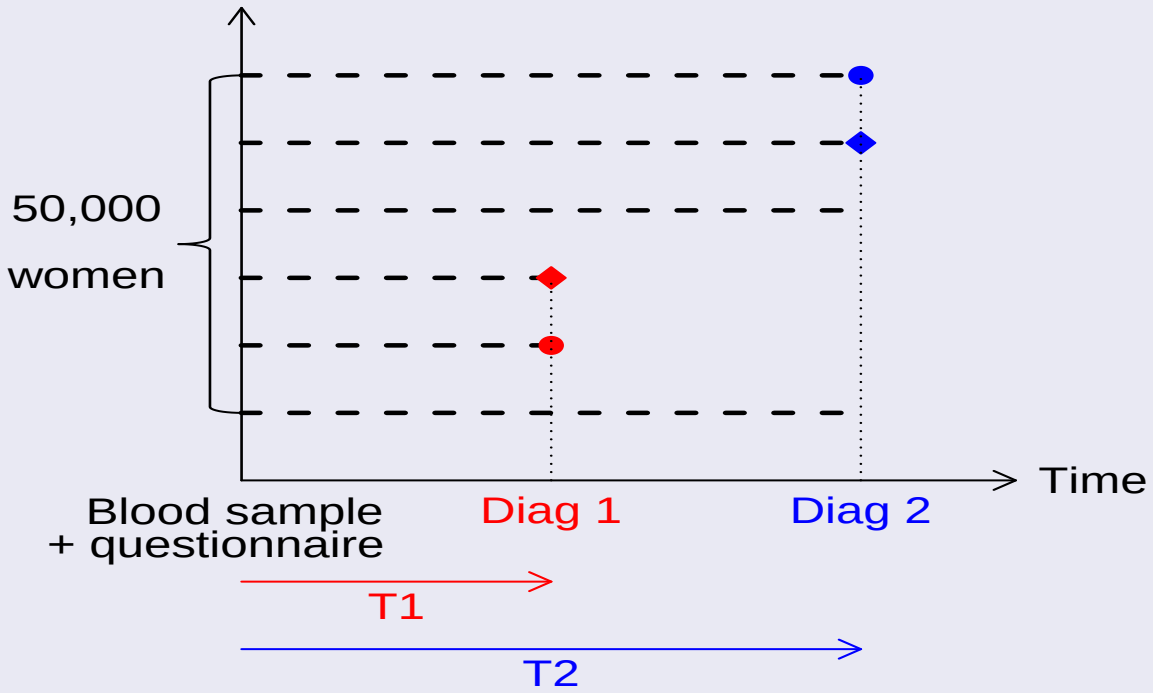

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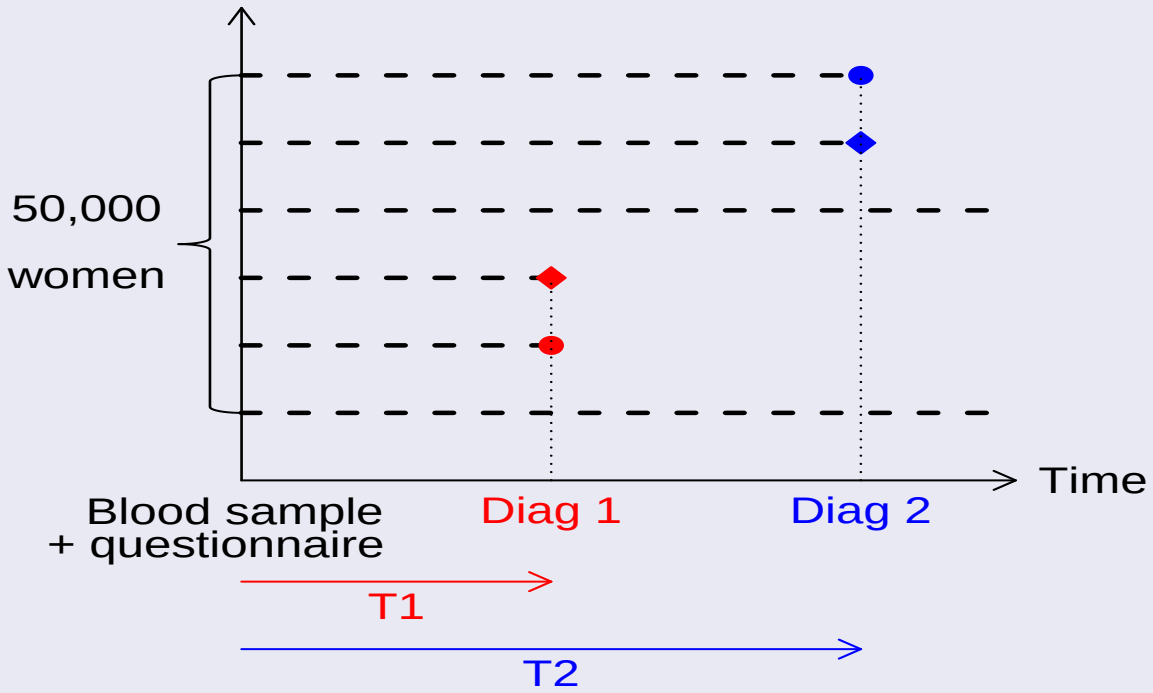

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- 6 years of follow-up
- 700 case-control pairs for breast cancer

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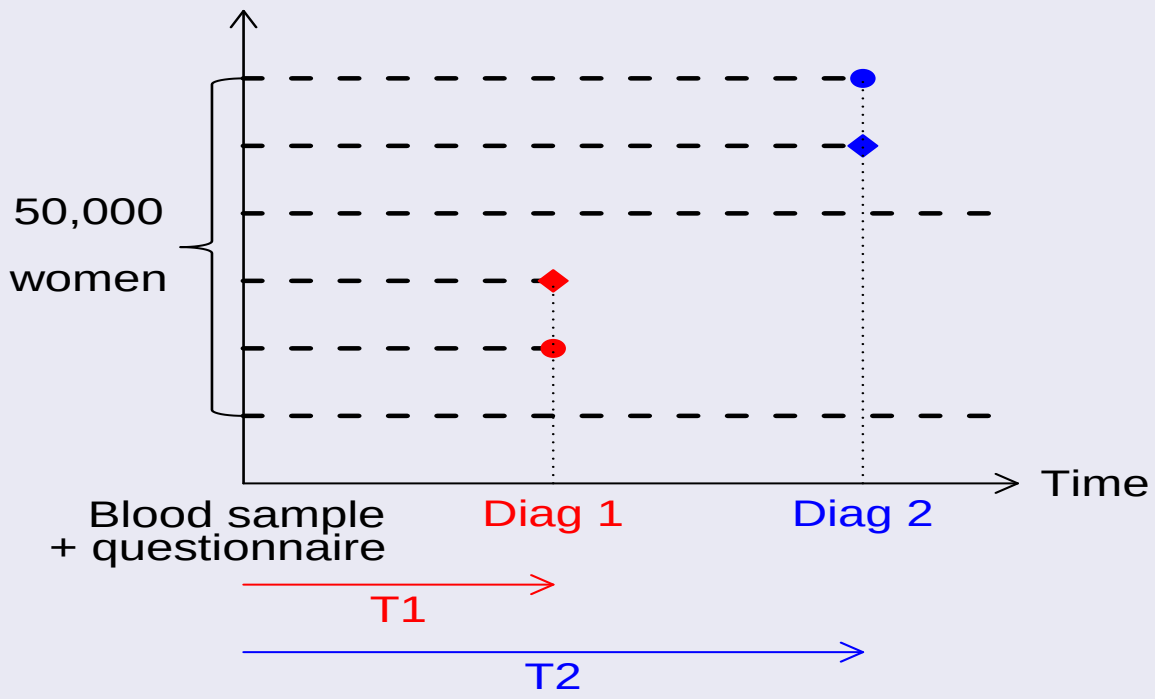

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Data: for each case-control pair i,

- T_i: Follow-up time.
- $\Delta G_i = \log G_i^{\text{case}} - \log G_i^{\text{control}}$: Difference of gene expression at time T_i before diagnosis (25,000 genes).
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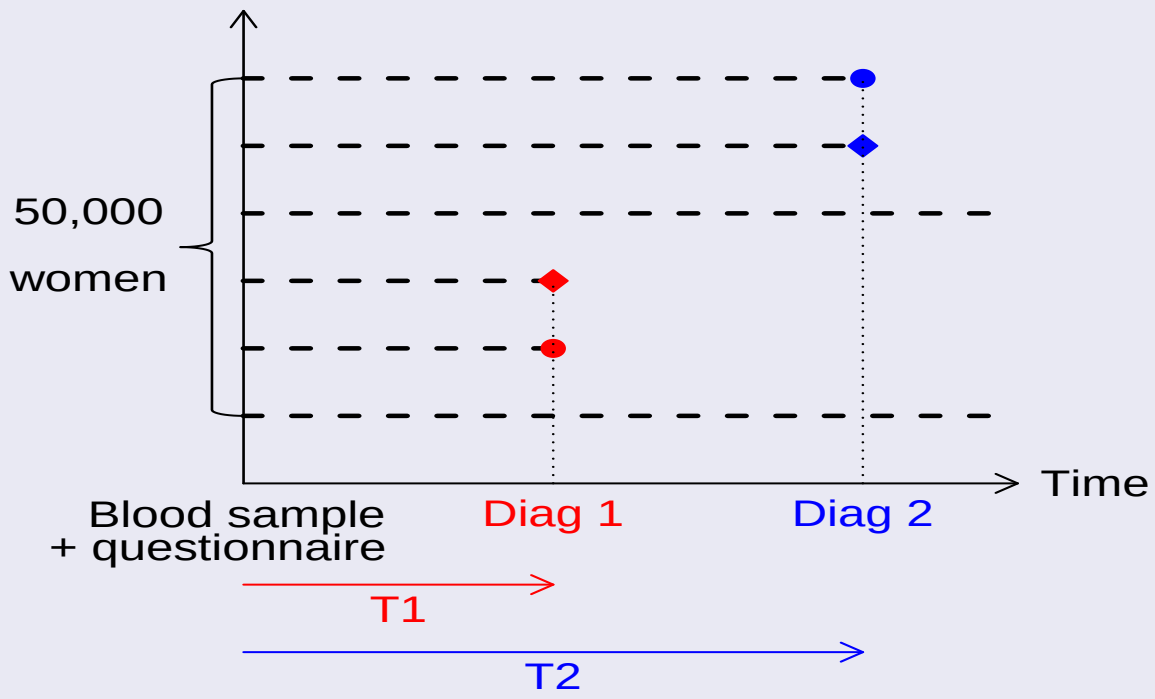

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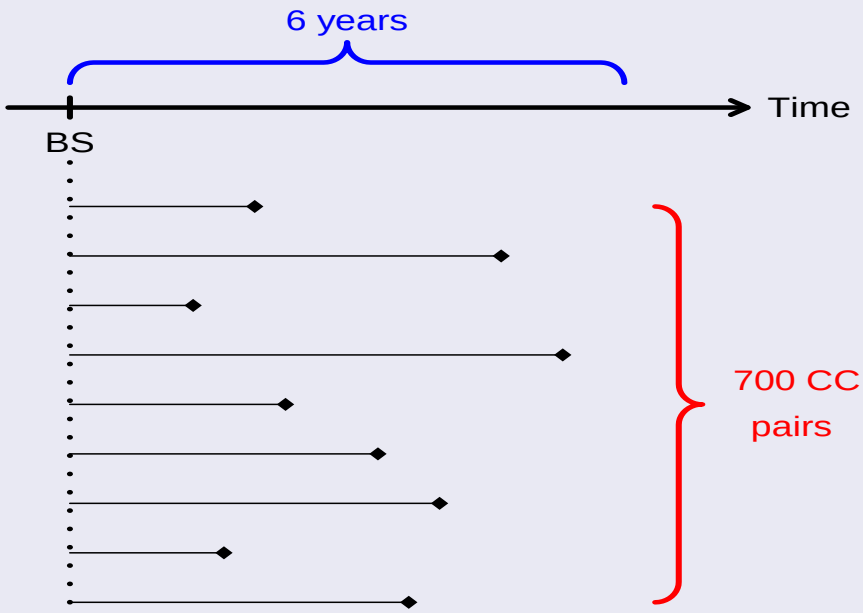

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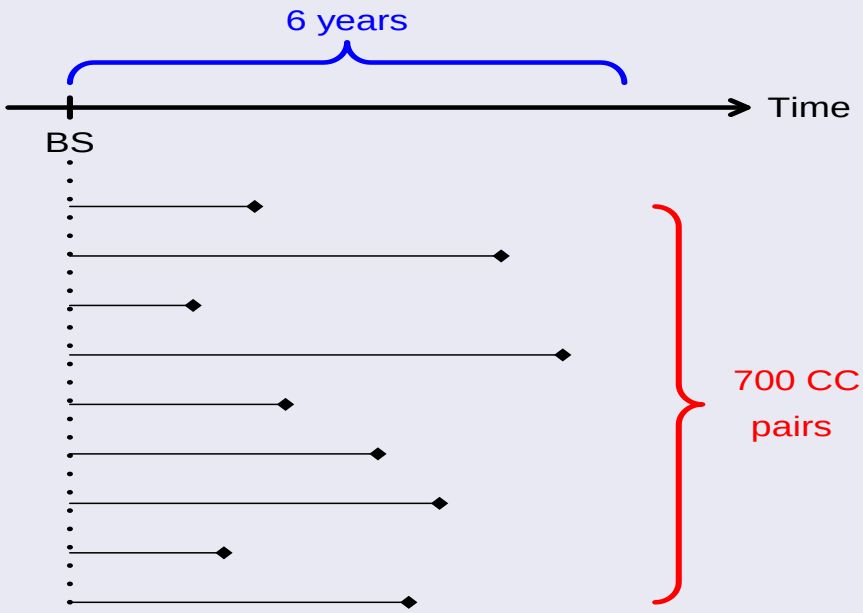
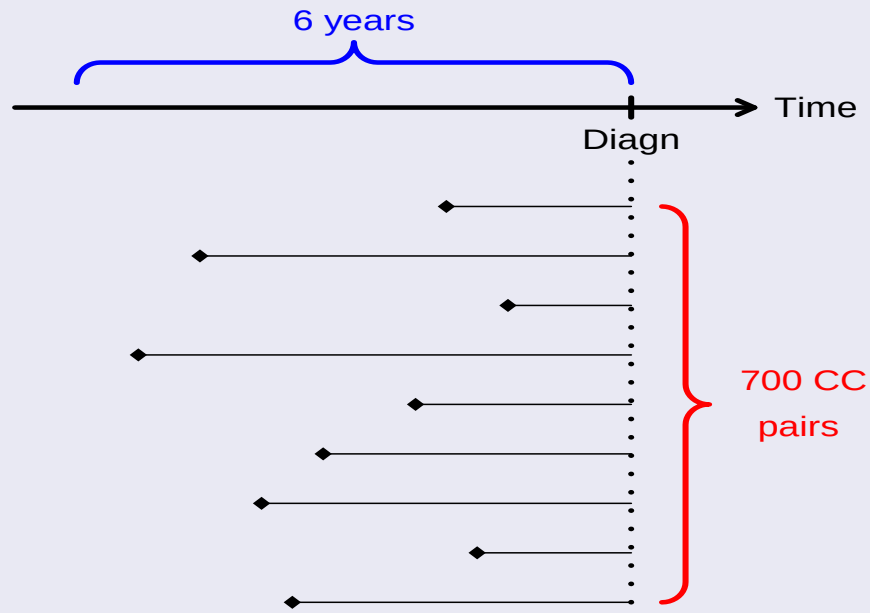


Alternative point of view



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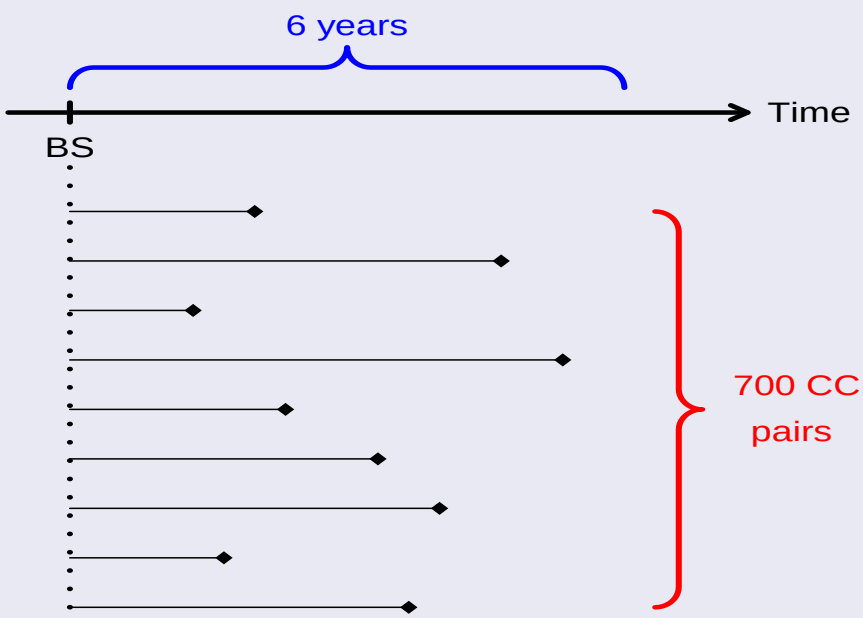

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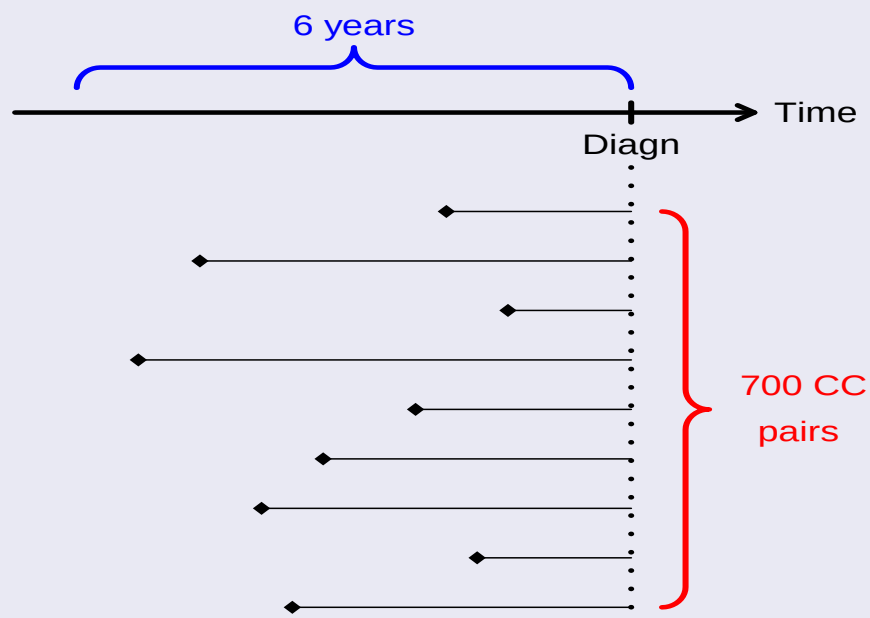

- Measurements of gene expression between 0 and 6 years before diagnosis
- Only one measurement by case-control pair.
- Explore the changes in gene expression 6 years before diagnosis.

Prospective GWAS and post-GWAS: a different statistical point of view

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Prospective GWAS

$$\mathbb{P}[T|G, E] \quad \text{with}$$

- T: time to diagnosis
- E: exposures
- G: genomic data (constant over time).

Genomics: risk factors for cancer

Goal: risk estimation and prediction.

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Post-GWAS

$\mathbb{P}[G|T, E]$ with

- T: time to diagnosis
- E: exposures
- G: transcriptomic data (depend on T)

Transcriptomics: biomarkers of carcinogenesis

Goal: study of change in gene expression during carcinogenesis.

Cox model in post-GWAS.

- Cox (proportional hazard) model: $\lambda(t|G,E) = \lambda_0(t)\exp\left(\langle\beta,(G,E)\rangle\right)$

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- Partial likelihood for nested CC:

$$L(\beta) = \prod_{i \text{ CC pair}} \Big(1 - \exp\left(\langle\beta,(\Delta G_i, \Delta E_i)\rangle\right)\Big)^{-1} + \text{pen}(\beta)$$

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Summing up

- Survival analysis for nested CC: genes that discriminate cases and controls.
- Our goal: genes that discriminate "long" and "short" follow-up times.

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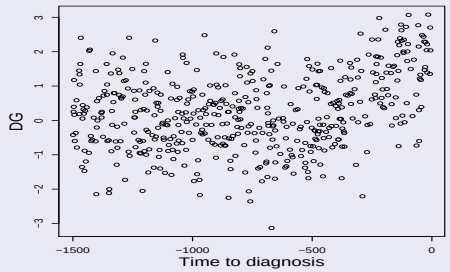
Gene-by-gene model

For each gene



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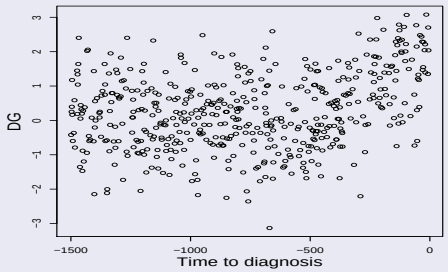

Correlation $(T, \Delta G_g)$

- Spearman test

+ multiple testing

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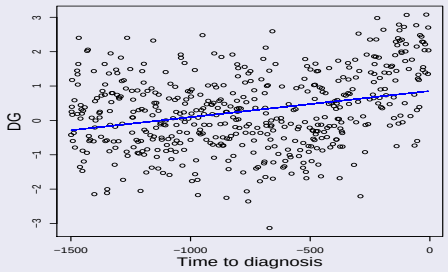

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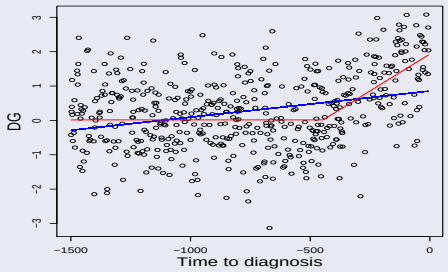

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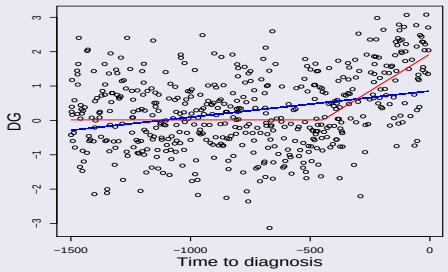

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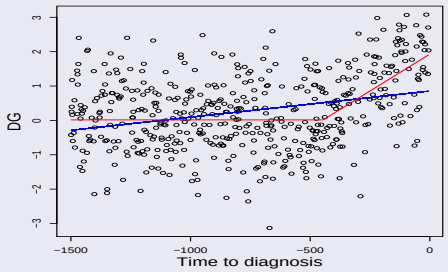
Correct for exposures

$$\Delta G_{i,g} = \alpha_0^g + \alpha_1^g \Delta E_i + \varphi(T_i | \alpha_2^g) + \varepsilon_{i,g}$$

Gene-by-gene model

For each gene



Correlation $(T, \Delta G_g)$

- Spearman test
- Linear model
- "Hockey-stick"
- ...

+ multiple testing

Correct for exposures

$$\Delta G_{i,g} = \alpha_0^g + \alpha_1^g \Delta E_i + \varphi(T_i | \alpha_2^g) + \varepsilon_{i,g}$$

General model

$$\Delta G_{i,g} = \Psi(T_i, \Delta E_i | \Theta_g) + \varepsilon_{i,g}$$

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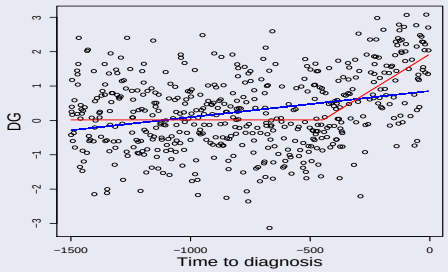

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- Hierarchical testing: pathways of genes ...

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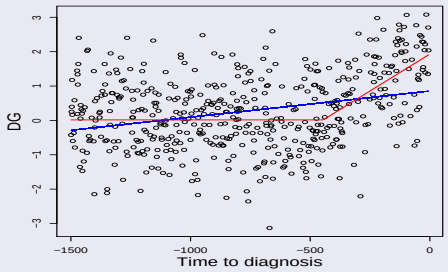

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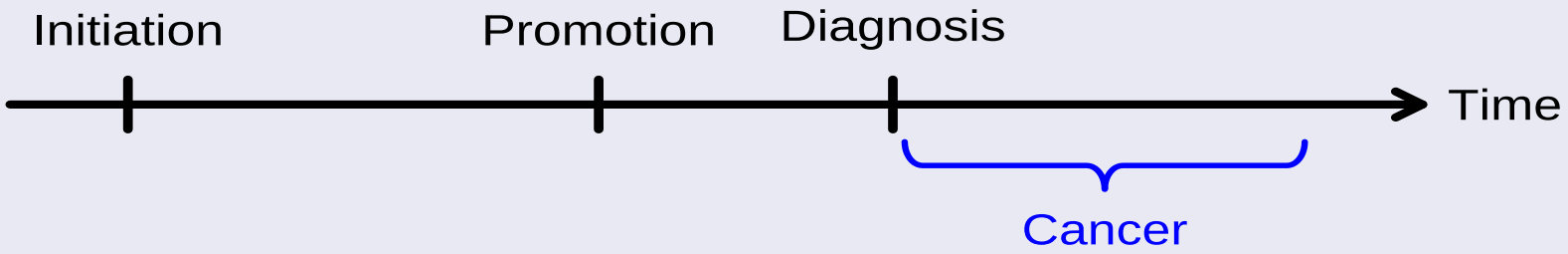
Flexible

- Cross-effect: cancer driven by exposures
- Hierarchical testing: pathways of genes ...

No account for individual dynamics

Latent last-stage model

Multi-stage model of carcinogenesis



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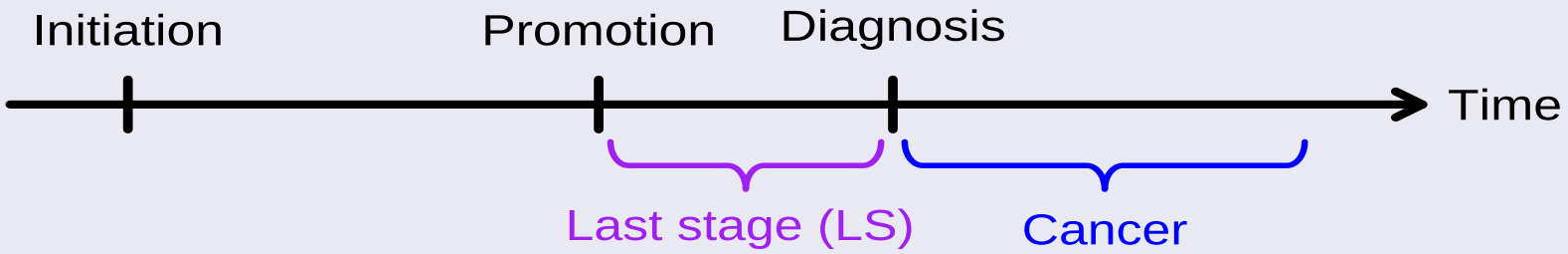

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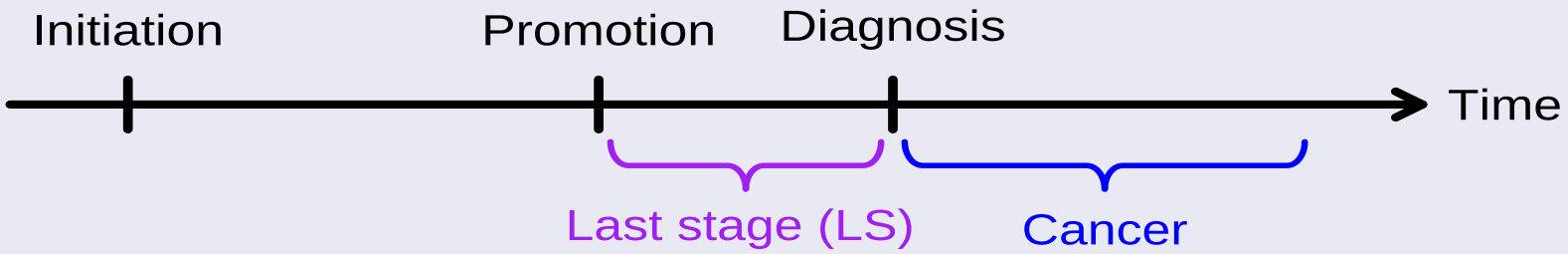
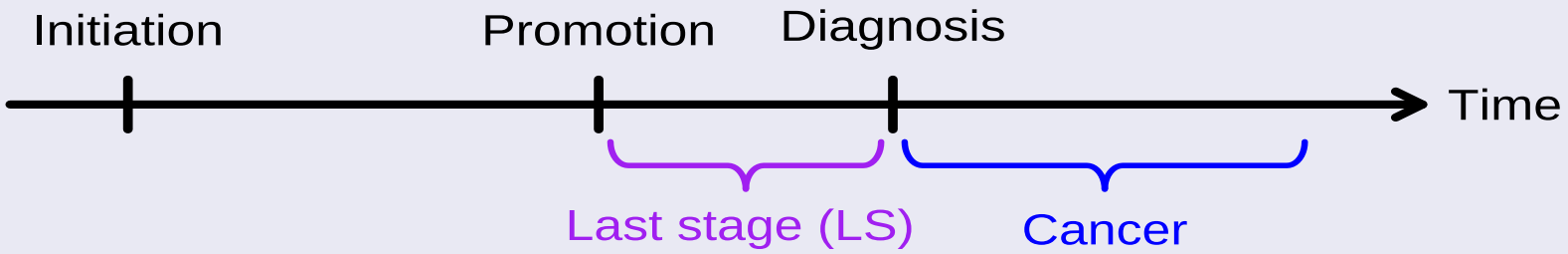


Multi-stage model and gene expression

- Last stage: genes involved in carcinogenesis over/under express.
- Random last stage length.

Latent last-stage model

Multi-stage model of carcinogenesis



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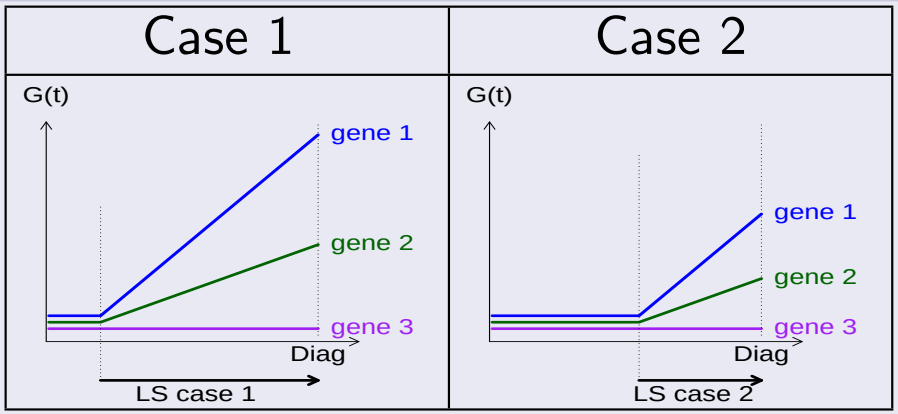

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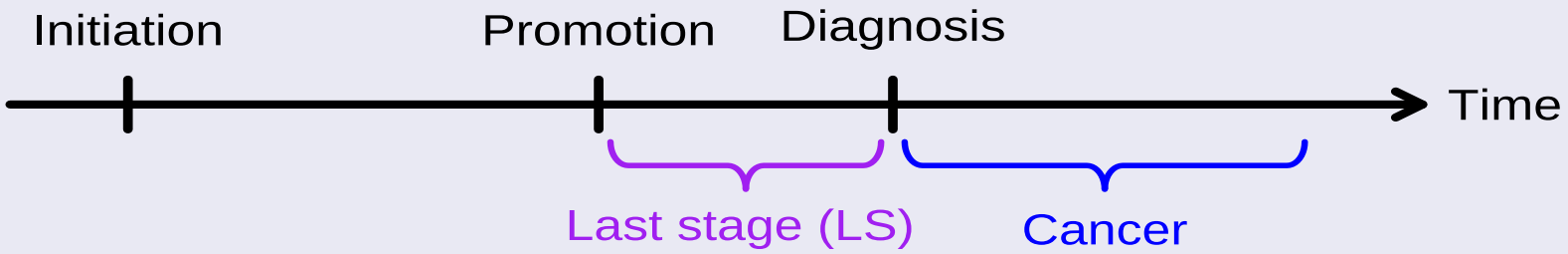

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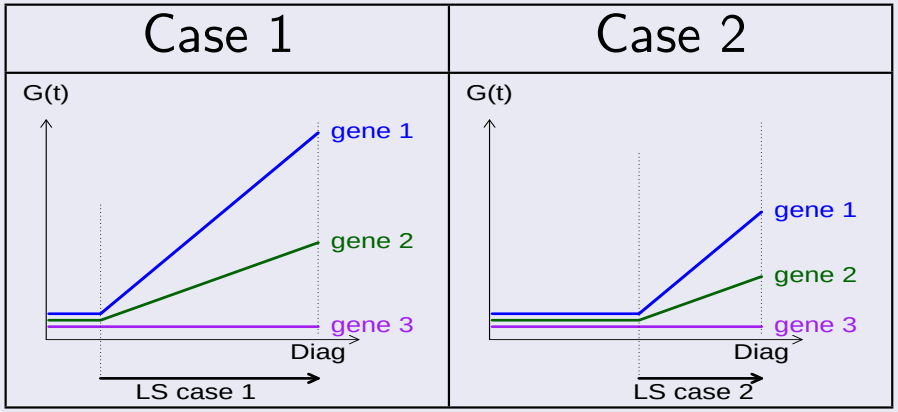
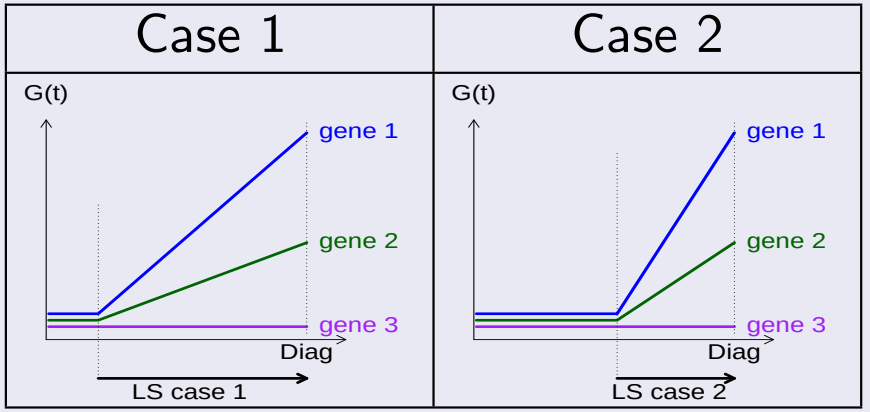


Model 2



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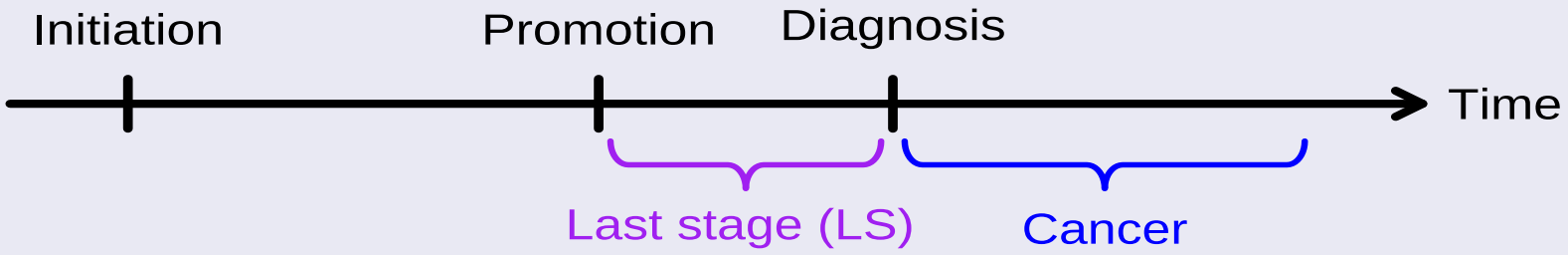

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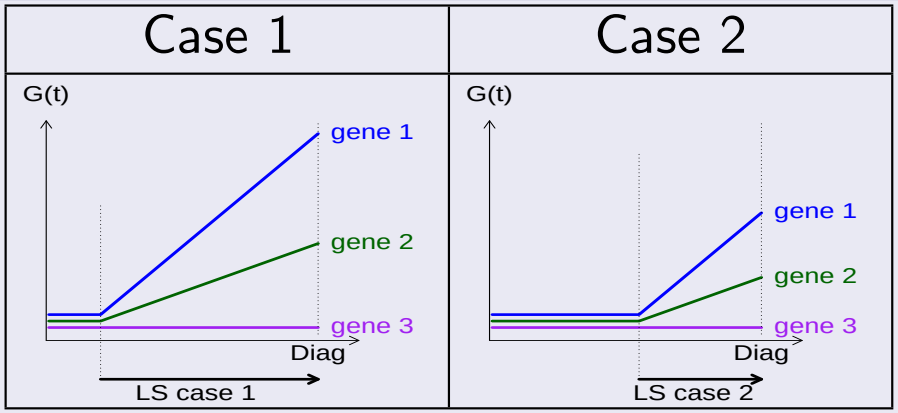
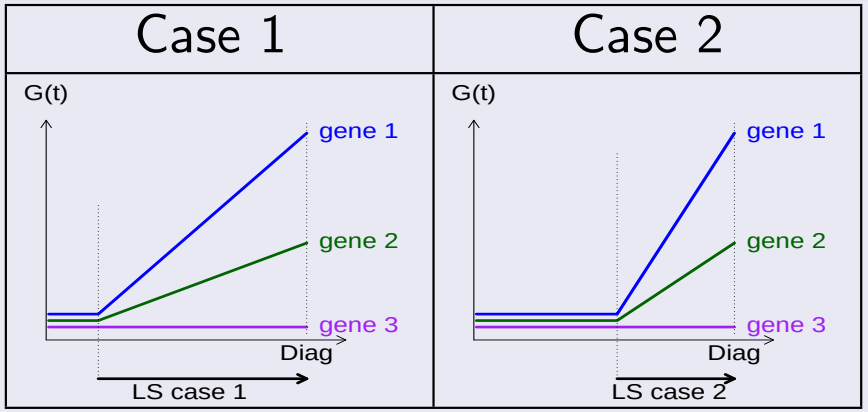


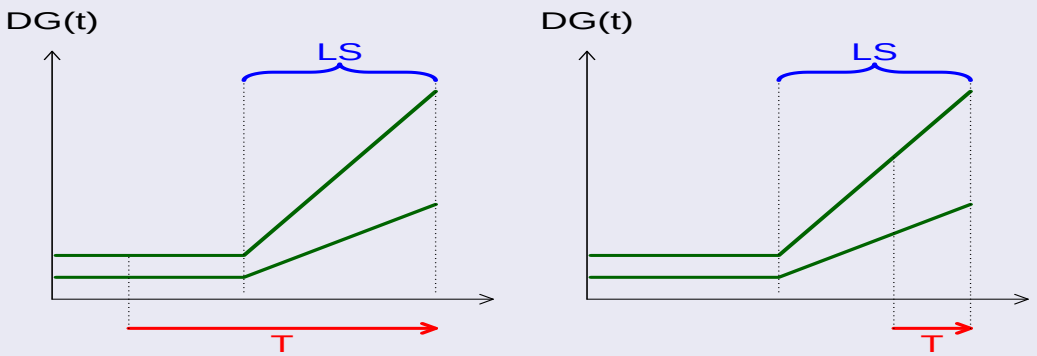
↪ Screening program

Model 2



↪ Diagnosis from symptoms

Statistical model 1



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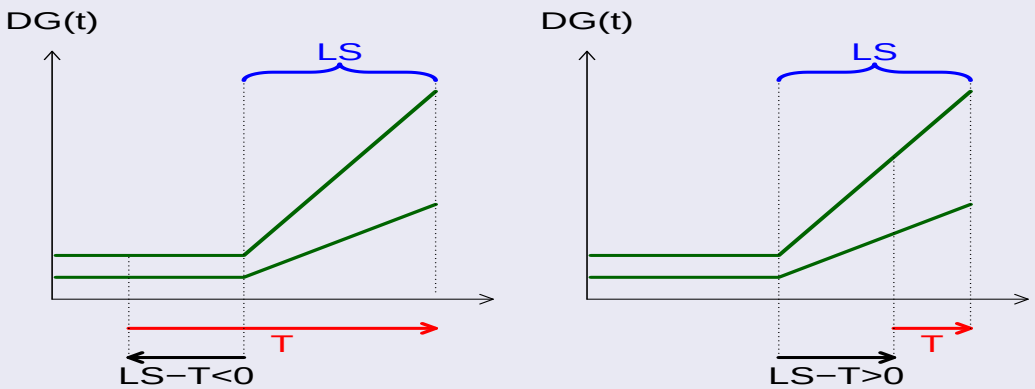

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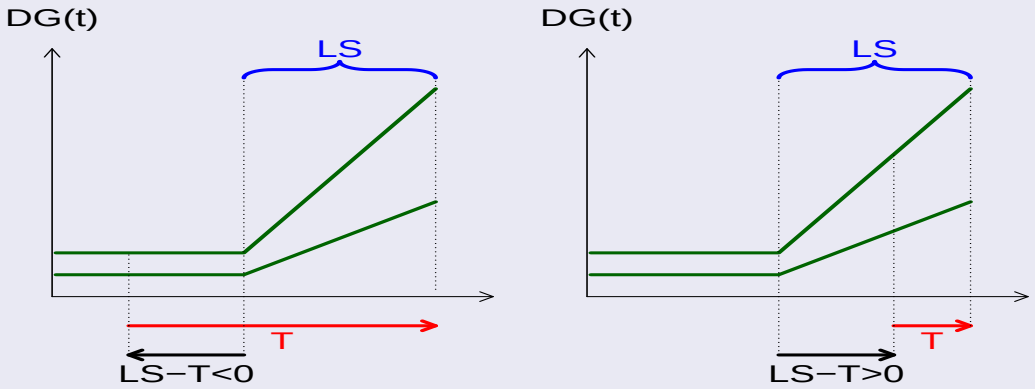

Gene expression

For each case-control pair i and gene g:

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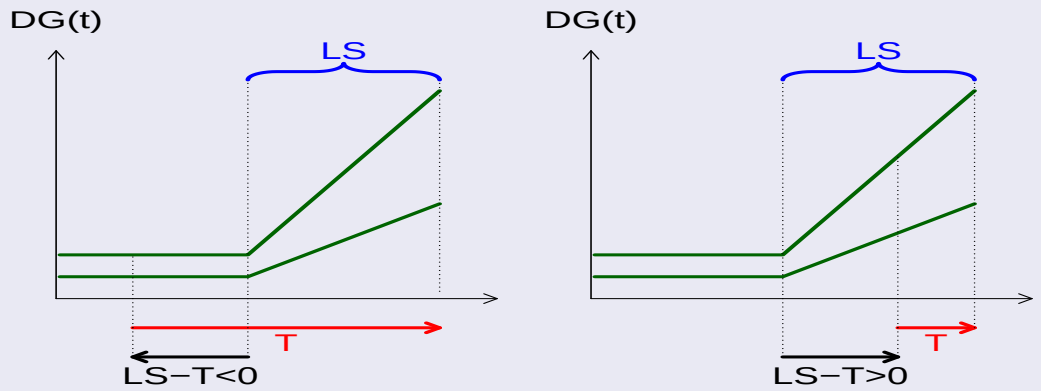

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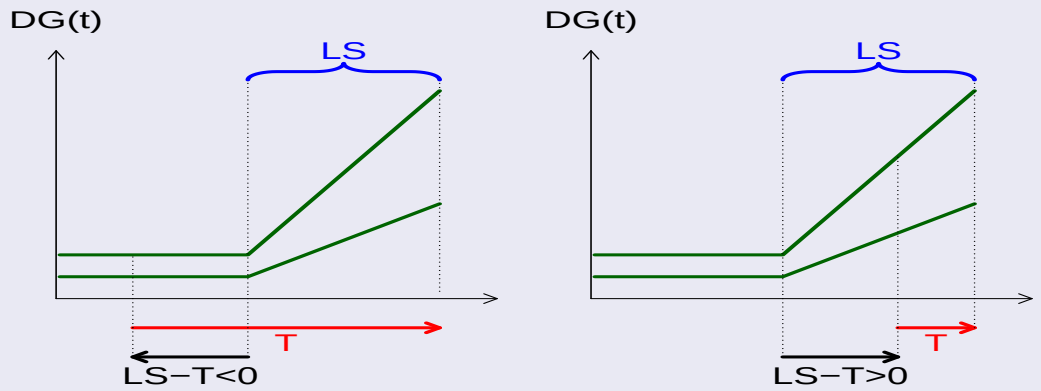

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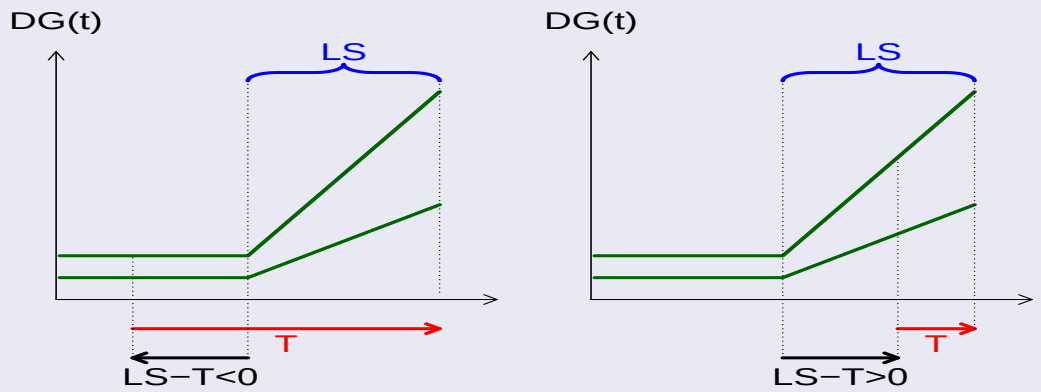

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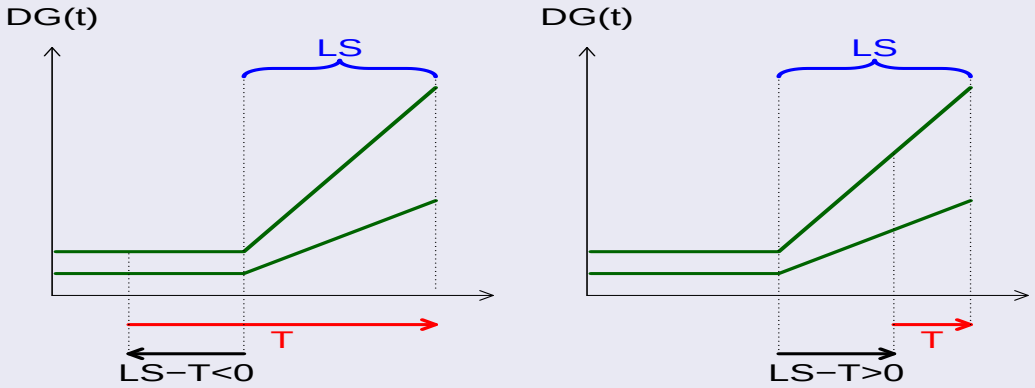

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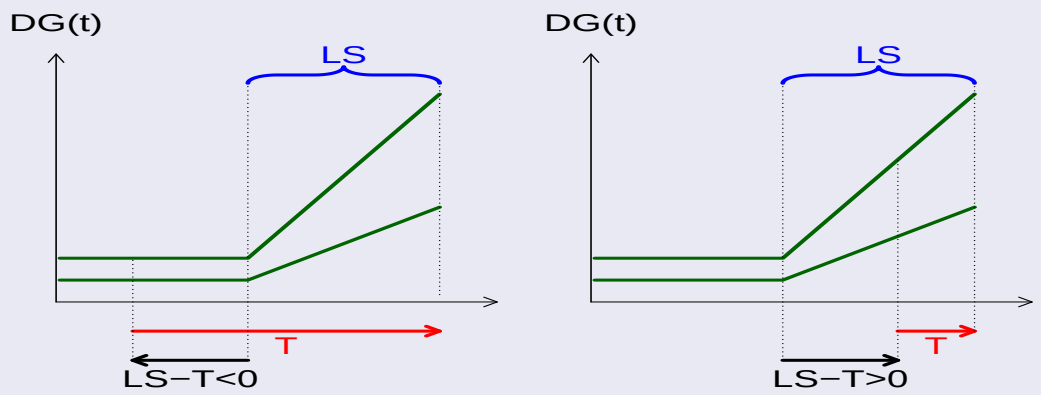

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Last-stage length

$$LS_i \sim \Gamma(k, \theta)$$

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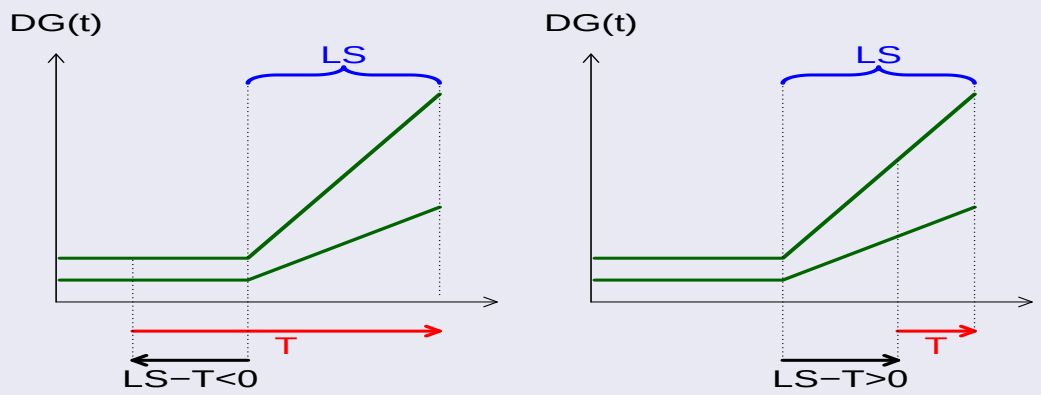

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Last-stage length

$$LS_i \sim \Gamma(k, \theta)$$

$\hookrightarrow$ (k, θ) may depends on the exposures of the case.

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

Parameter estimation

Model

$$\begin{cases} LS_i \sim \Gamma(k, \theta) \quad \text{with} \quad k = 1 + \exp(\langle \kappa, E_i^{\text{case}} \rangle), \quad \theta = \exp(\langle \tau, E_i^{\text{case}} \rangle) \\ DG_i^g = \langle \beta^g, (1, \Delta E_i, (LS_i - T_i)^*) \rangle + \varepsilon_{i,g}, \quad \varepsilon_{i,g} \sim \mathcal{N}(0, \sigma_g^2) \end{cases}$$

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1. Starting point from an heuristic.
2. j$^{\text{th}}$ iteration.

$\Theta^{(j)} = (\kappa^{(j)}, \tau^{(j)}, \beta^{(j)}, \sigma^{(j)})$ $\longrightarrow$ Sample $(LS_i^{(j),1}, \ldots, LS_i^{(j),N})$ from $\mathbb{P}_{\Theta^{(j)}}[LS|\Delta G, T, E^{\text{case}}, \Delta E]$

$\downarrow$

$(\beta^{(j+1)}, \sigma^{(j+1)})$ MLE from $\mathbb{P}_{\beta,\sigma}[\Delta G|\Delta E, LS^{(j)}]$

$(\kappa^{(j+1)}, \tau^{(j+1)})$ MLE from $\mathbb{P}_{\kappa,\tau}[LS^{(j)}|, E^{\text{case}}, T_i]$

$\nwarrow$

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

Algorithm SEM

$$\begin{cases} LS_i \sim \Gamma(k, \theta) \quad \text{with} \quad k = 1 + \exp(\langle \kappa, E_i^{\text{case}} \rangle), \quad \theta = \exp(\langle \tau, E_i^{\text{case}} \rangle) \\ \Delta G_i^g = \langle \beta^g, (1, E_i, (LS_i - T_i)^*) \rangle + \varepsilon_{i,g}, \quad \varepsilon \sim \mathcal{N}(0, \sigma_g) \end{cases}$$

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Let $\Theta^{(j)} = (\kappa^{(j)}, \tau^{(j)}, \beta^{(j)}, \sigma^{(j)})$

Simulated expectation

$$\mathbb{E}_{\Theta^{(j)}}[\log \mathbb{P}_\Theta[\Delta G_i, LS_i]] = \sum_{i=1}^{n} \int_{LS_i} \log \mathbb{P}_\Theta[\Delta G_i, LS_i] \mathbb{P}_{\Theta^{(j)}}[LS_i | \Delta G_i]$$

Sample N repetitions of $\{LS_i^{(j)}\}_{i=1:n}$ from distribution $\mathbb{P}_{\Theta^{(j)}}[LS_i|\Delta G_i]$.

$$\begin{aligned} \mathbb{P}_{\Theta^{(j)}}[LS_i|\Delta G_i] &= \frac{\mathbb{P}_{\Theta^{(j)}}[\Delta G_i|LS_i] \cdot \mathbb{P}_{\Theta^{(j)}}[LS_i]}{\mathbb{P}_{\Theta^{(j)}}[\Delta G_i]} \\ &\propto \Pi_{g=1}^{p} \underbrace{\mathbb{P}_{\Theta^{(j)}}[\Delta G_i^g|LS_i]}_{\mathcal{N}(\langle \beta_j^g, (1, E_i, (LS_i - T_i)^*) \rangle, \sigma_g)} \cdot \underbrace{\mathbb{P}_{\Theta^{(j)}}[LS_i]}_{\Gamma(k_j, \theta_j) - T_i} \end{aligned}$$

Maximization

$$\log \mathbb{P}_{\Theta}[\Delta G_i, LS_i] = \log \mathbb{P}_{\beta,\sigma}[\Delta G_i | LS_i]] + \log \mathbb{P}_{\kappa,\tau}[LS_i]$$

Thus

$$(\beta_g^{(j+1)}, \sigma_g^{(j+1)}) = \arg\max \sum_{i=1}^{n} \left(\frac{1}{N} \sum_{\ell=1}^{N} \phi(\Delta G_i^g - \langle \beta_g, (1, E_i, (LS_{i,\ell}^{(j)} - T_i)^*) \rangle) \right)$$

where ϕ is the standard normal density and

$$(\kappa^{(j+1)}, \tau^{(j+1)}) = \arg\max$$
$$\sum_{i=1}^{n} \left(\frac{1}{N} \sum_{\ell=1}^{N} \psi(LS_{i,\ell}^{(j)} | k = 1 + \exp(\langle \kappa, E_i \rangle),\ \theta = \exp(\langle \tau, E_i \rangle) \right)$$

where ψ is the gamma distribution density.

Convergence of the algorithm on simulated data

Simulations

- $n = 150$ pairs, $p = 2000$ genes and $p_0 = 100$ genes involved in the last stage.
- Draw β_1^g, β_2^g from $\mathcal{N}(0, 1)$.
- Draw $(\beta_2^1, \ldots, \beta_2^{p_0})$ from $\mathcal{N}(0, 0.01)$, and $\beta_2^{p_0+1} = \cdots = \beta_2^p = 0$.
- Draw σ from $\chi^2(3)$
- $E =$ binary variable $(0/1)$
- $T =$ uniformly samples in $(0, 800)$
- LS generated with parameters $\tau = c(3, 0.5)$, $\kappa = c(2, 0.5)$.
- ΔG generated from $P_{(\beta,\sigma,\tau,\kappa)}[\Delta G | LS, T, E]$.

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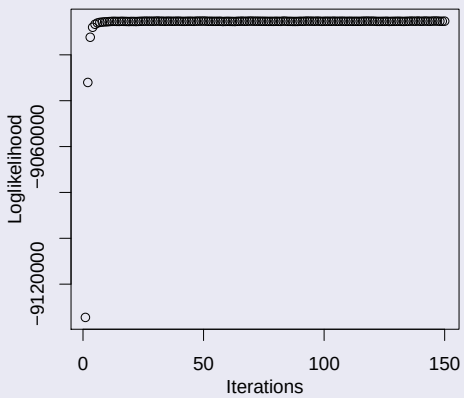
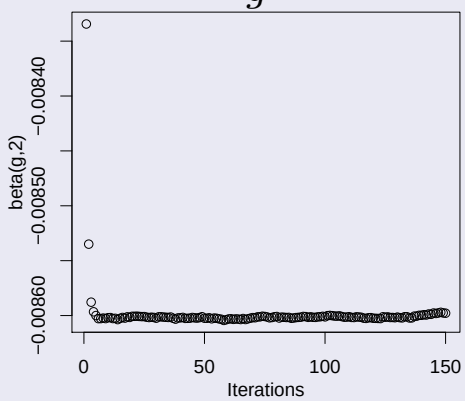
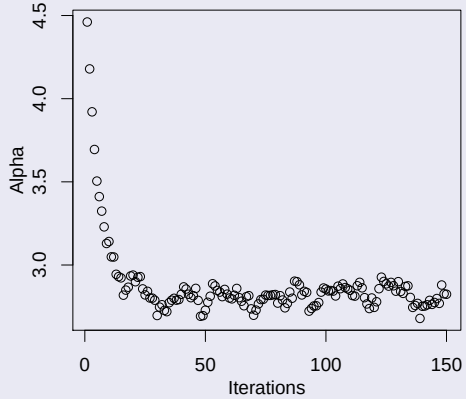
Loglikelihood



β_g^2



τ_1



Two quantities of interests

Last-stage length estimation

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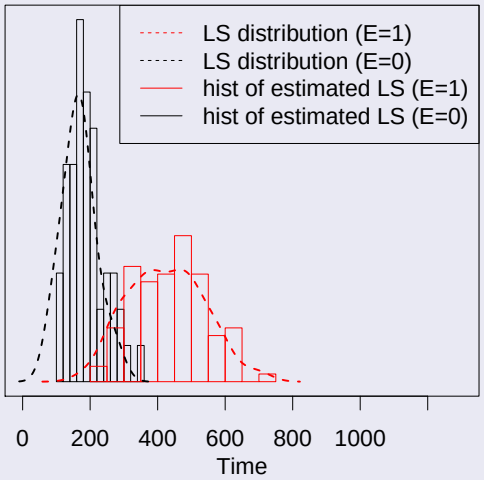
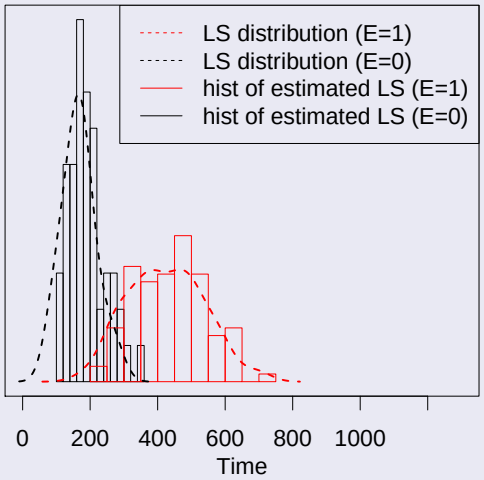
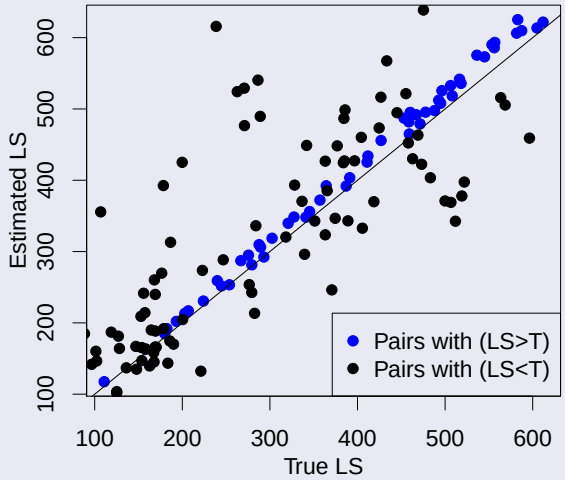
Last-stage length estimation



Two quantities of interests

Last-stage length estimation





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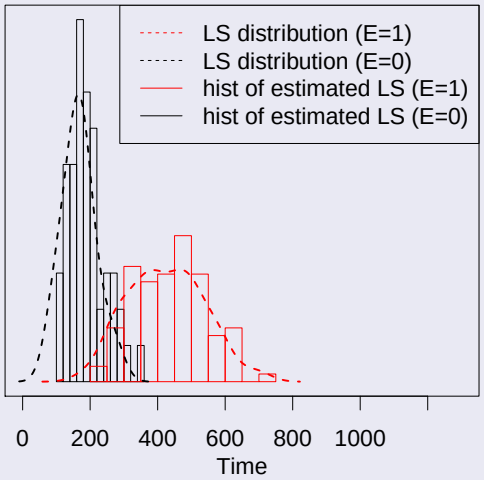

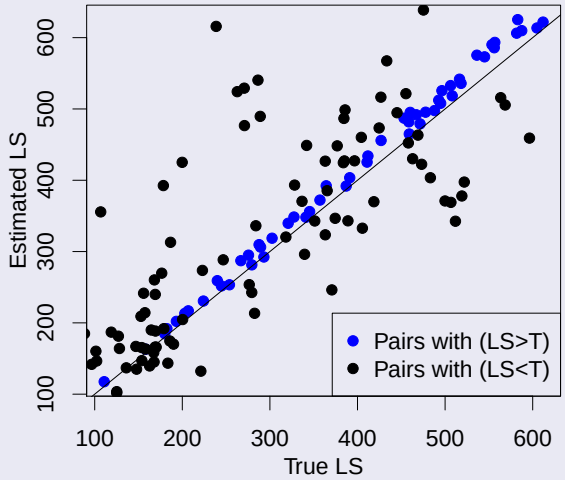

- Discrimination between $E^{\text{case}} = 0$ and $E^{\text{case}} = 1$
- More precise estimation when $LS_i > T_i$.

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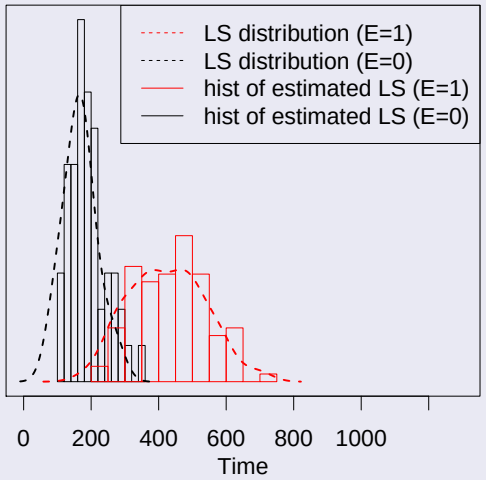

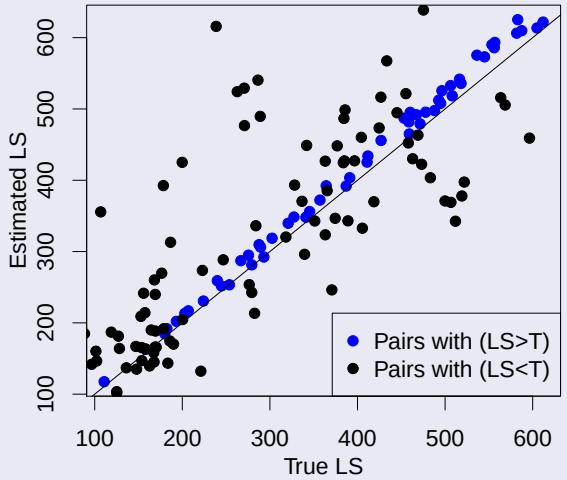

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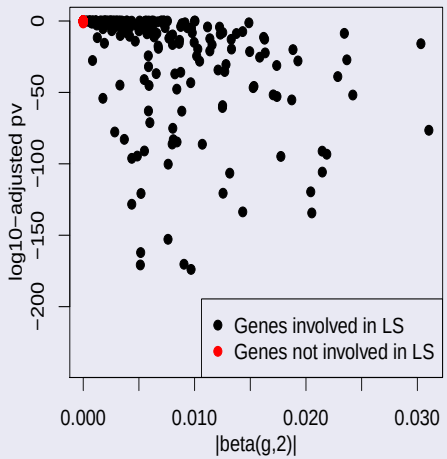
Detection of genes involved in the last-stage

F-test + FDR

$(\beta_2^g, \log\ \text{pv})$



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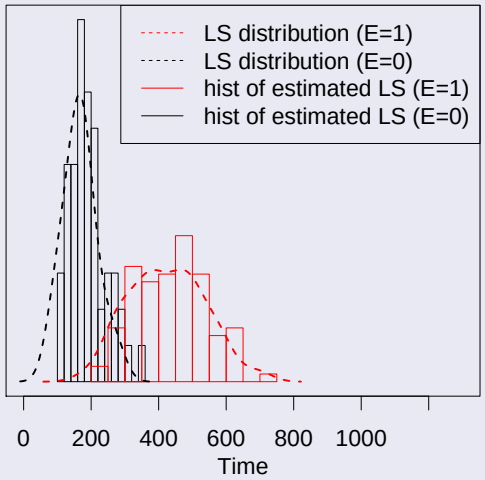

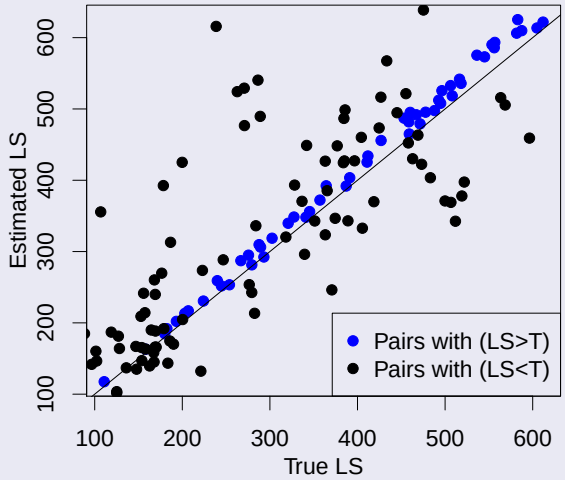

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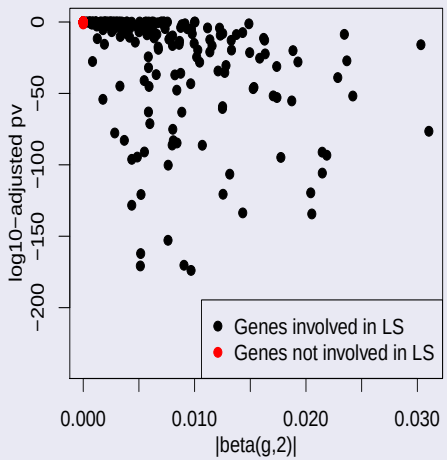
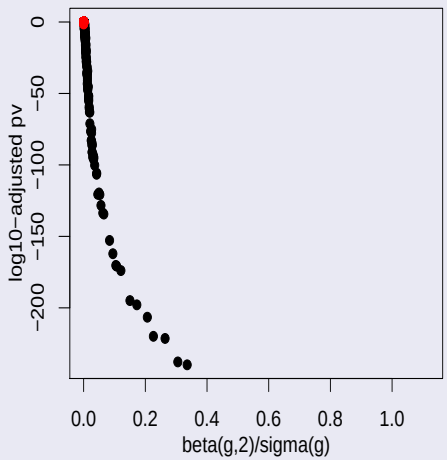


$(\beta_2^g/\sigma^g, \log\ \text{pv})$



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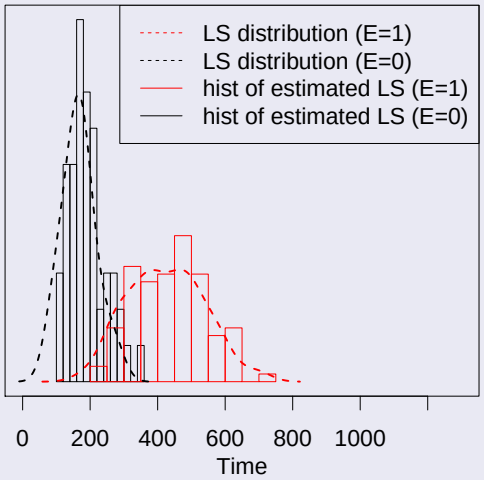

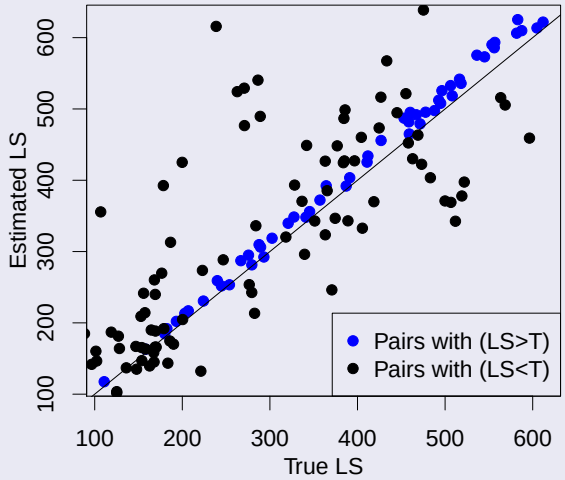

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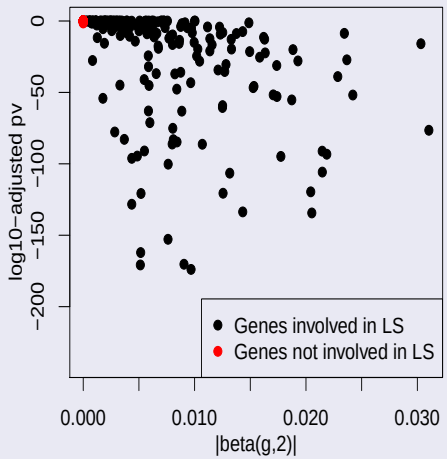
Detection of genes involved in the last-stage

F-test + FDR

- pv depends on signal/noise ratio
- weak impact of exposure + constant effect.

$(\beta_2^g, \log\ \text{pv})$



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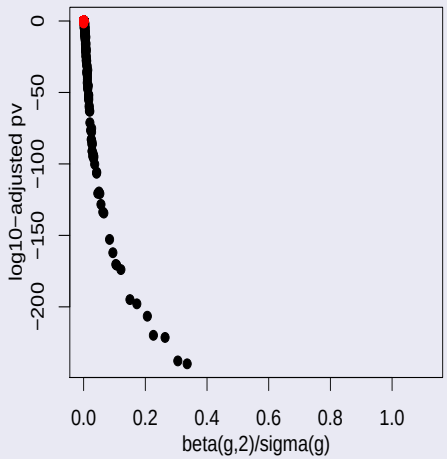
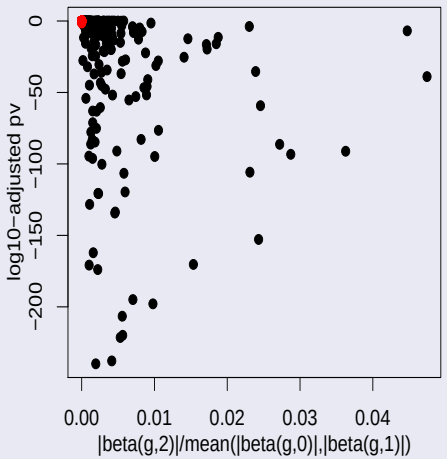


$(\beta_2^g/(\beta_0^g + \beta_1^g), \log \text{pv})$



Comparison with gene-by-gene models

Three tests are compared:

- F-test from LLS model with estimated LS:

$$DG_i^g = \beta_g^0 + \beta_g^1 \Delta E_i + \beta_g^2 (LS_i - T_i)^* + \varepsilon_{i,g}$$

- F-test in linear model:

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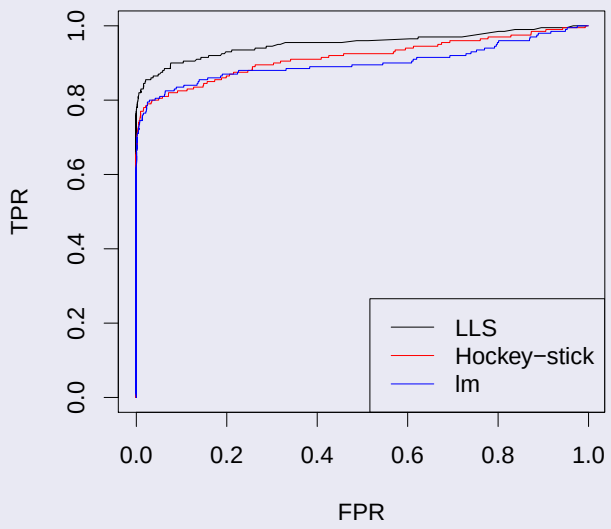
ROC curve



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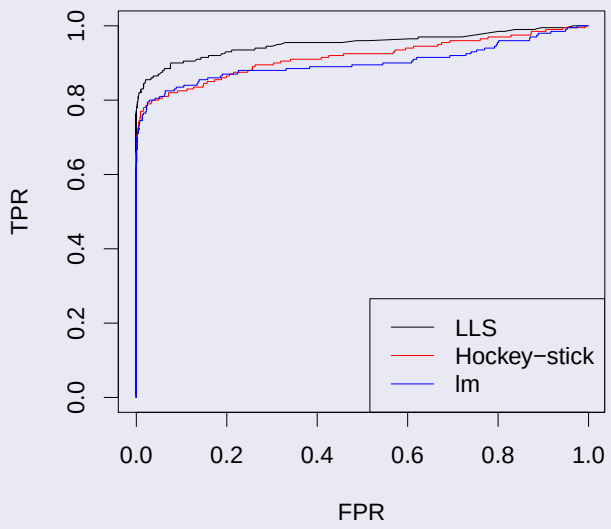

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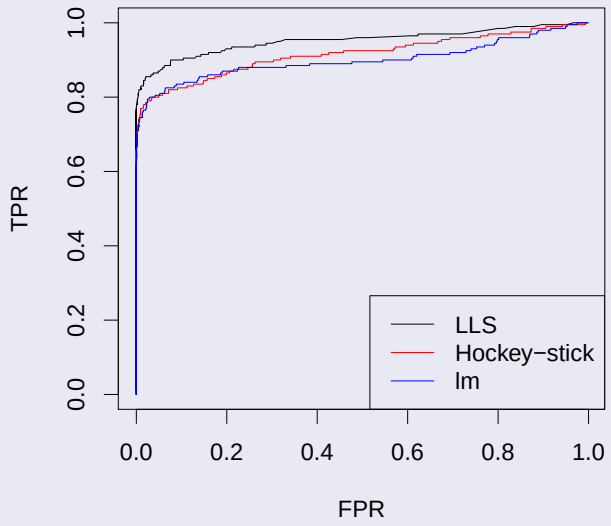

- Slightly better sensitivity for LLS.
  - ◇ data simulated according to LLS model → favorable situation.
- LLS model provides additional information about individual dynamics.

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Account for dependence between genes.

Conclusion

From GWAS to post-GWAS design:

- New goals: exploration of functional changes on transcriptomic data.
- Novel statistical approaches:

Prospective GWAS: $\mathbb{P}[T|G,E]$ ◆ Post-GWAS: $\mathbb{P}[G|T,E]$

Gene-by-gene model

- Flexible
- Inclusion of biological assumptions.

Latent last stage model

- Validated on simulated data

Require further developments to be applied on data:

- Choice of parametrization and relevant exposures.
- Account for dependence between genes.