A statistical approach for the multi-stage model of carcinogenesis

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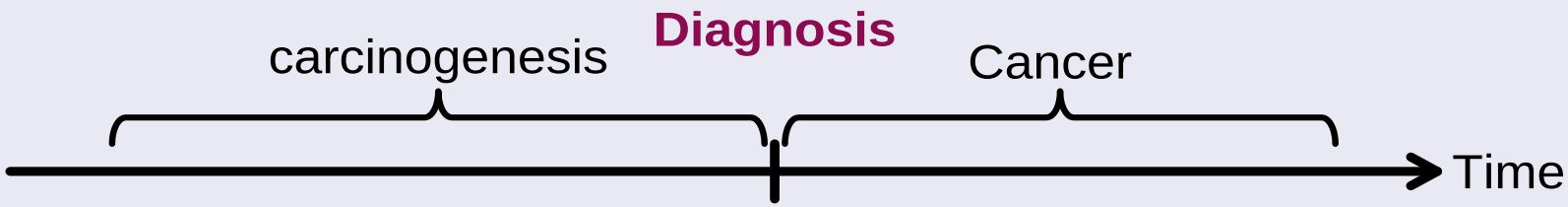
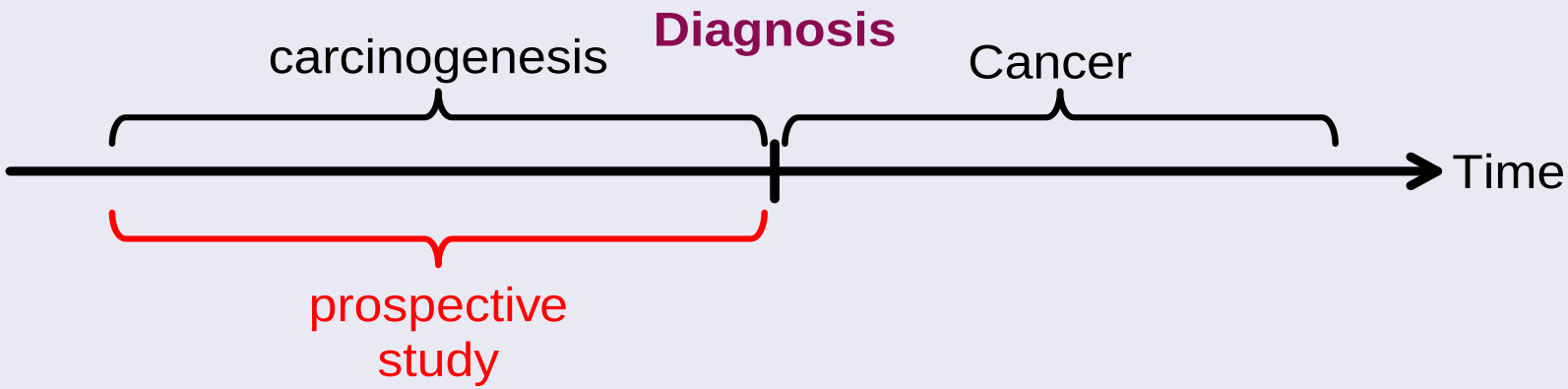
28 February 2012

Epidemiology and Carcinogenesis



- Carcinogenesis: prior to diagnosis

Epidemiology and Carcinogenesis



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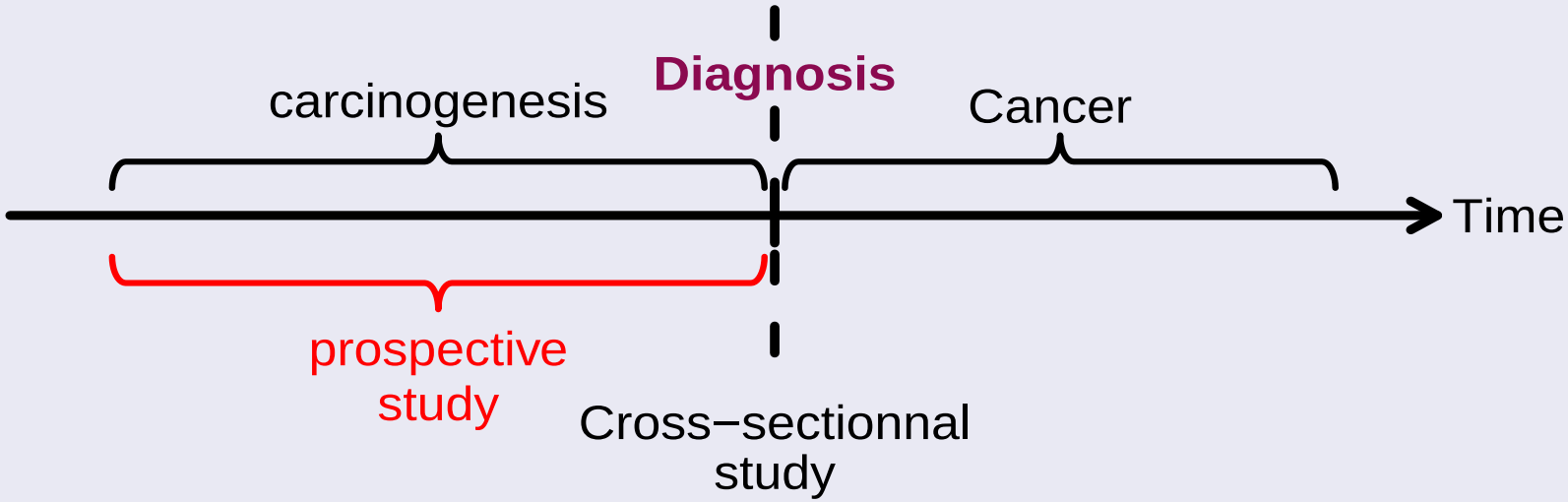

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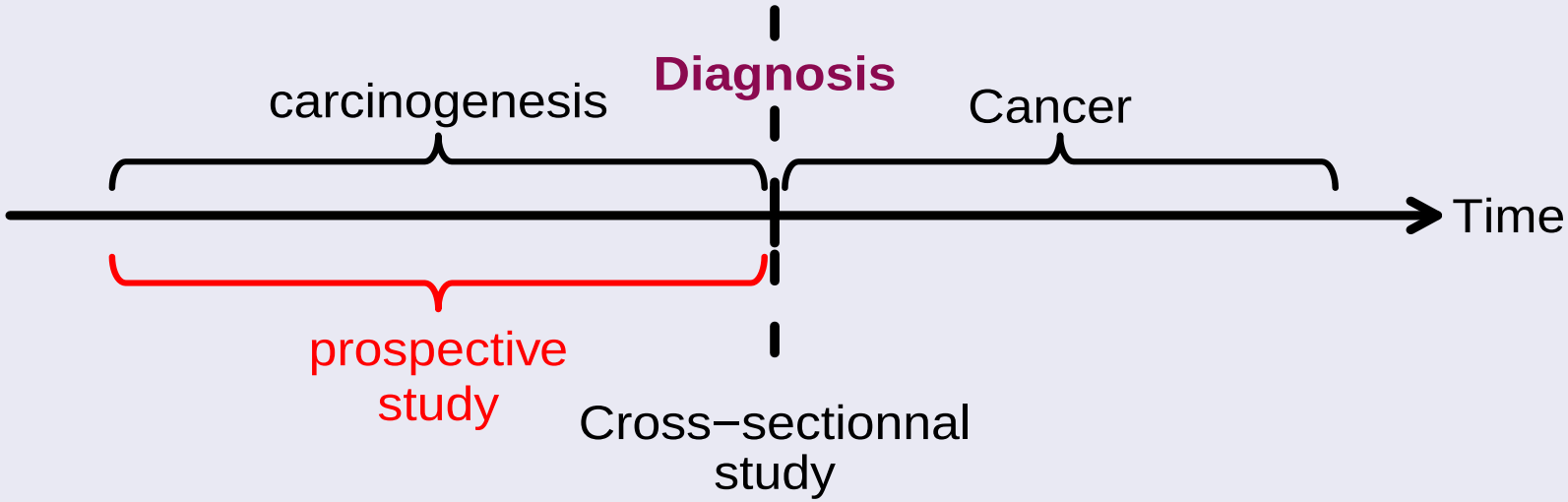

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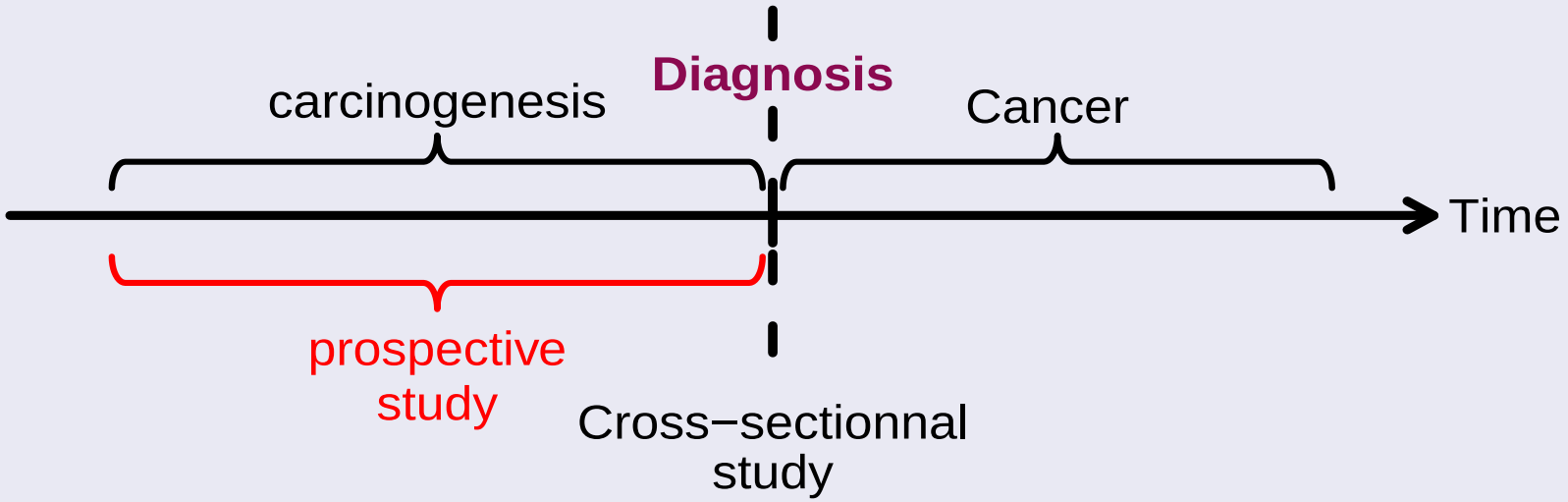

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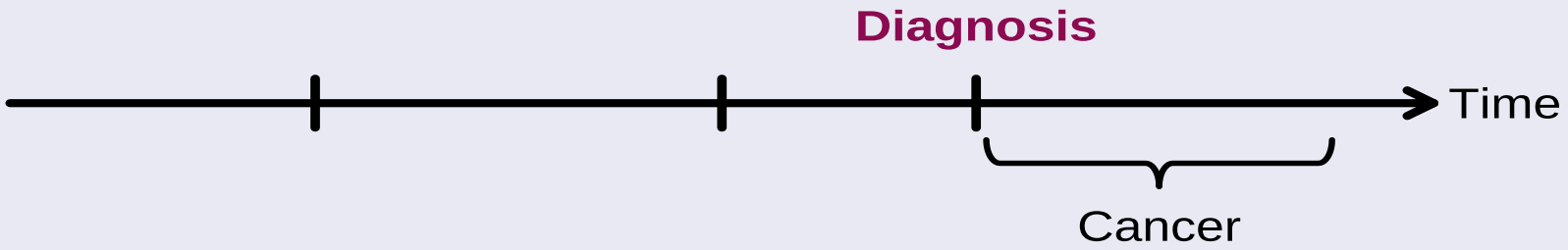

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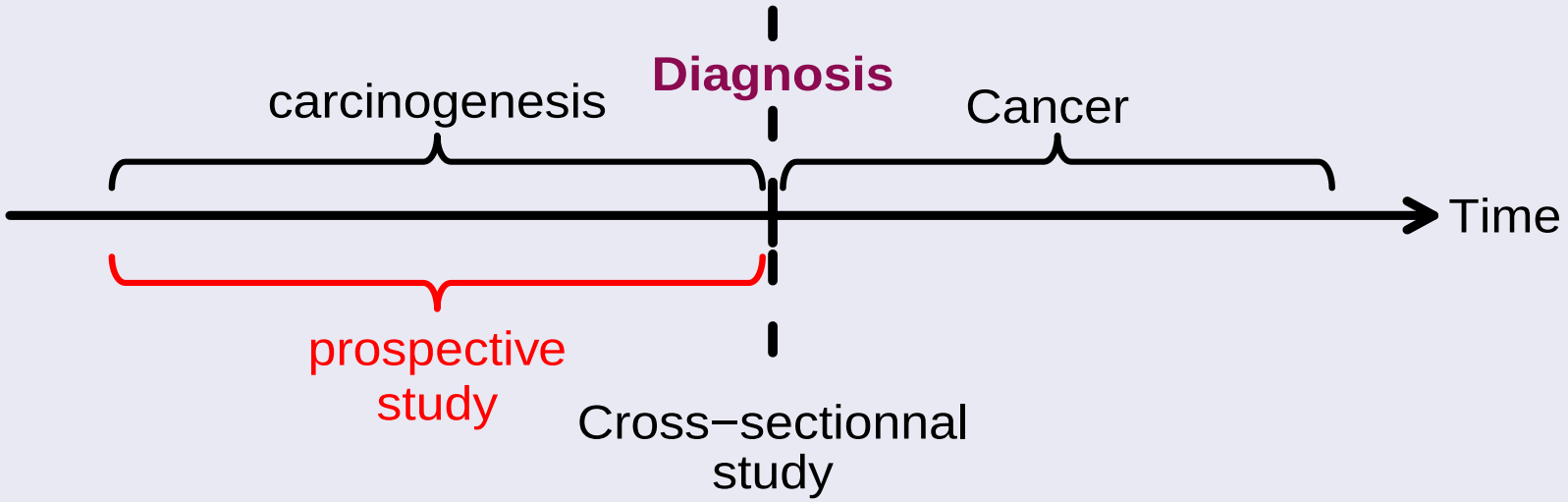

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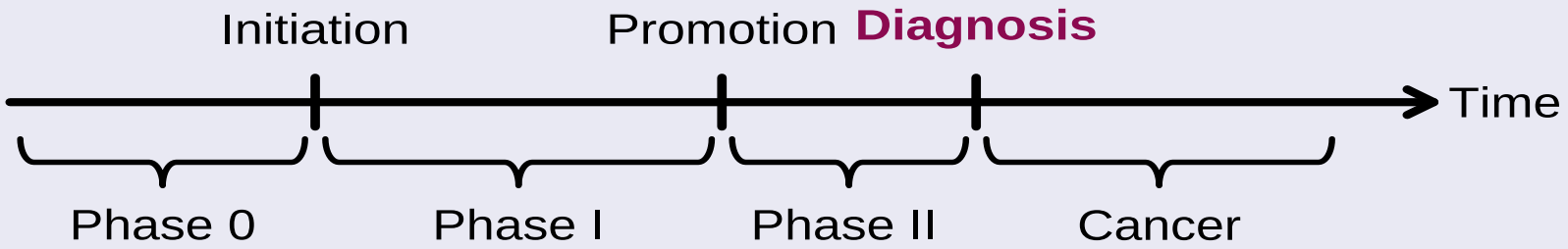

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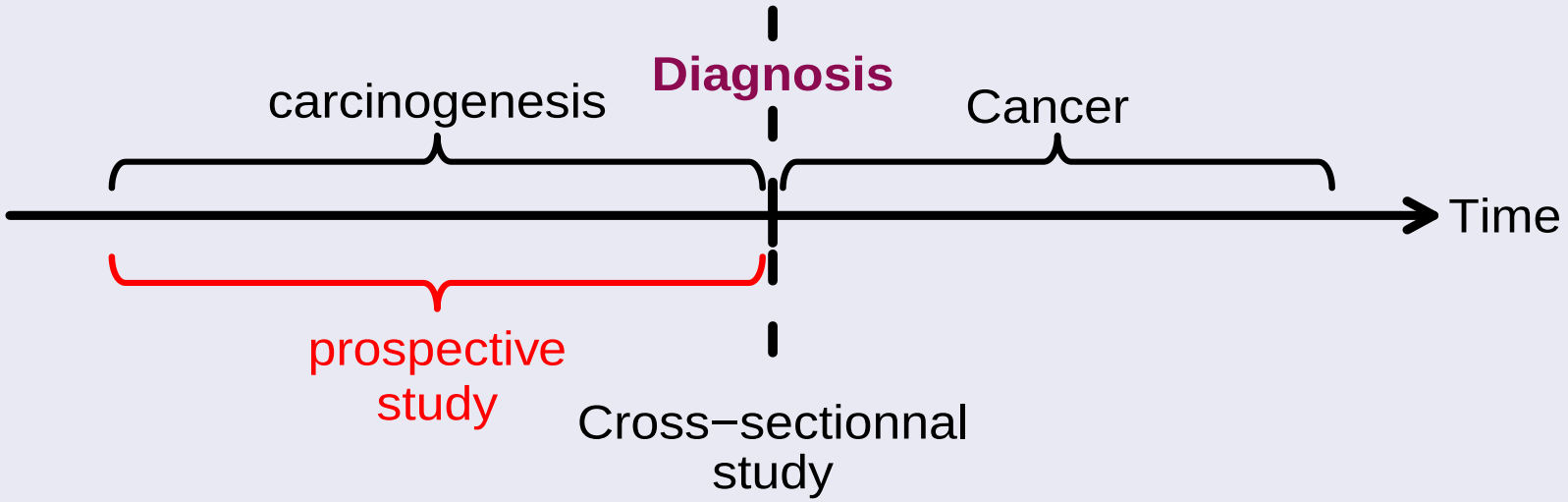

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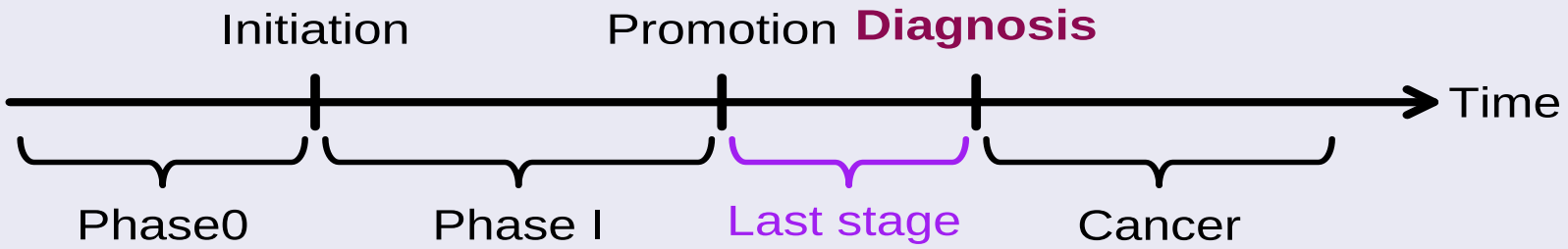

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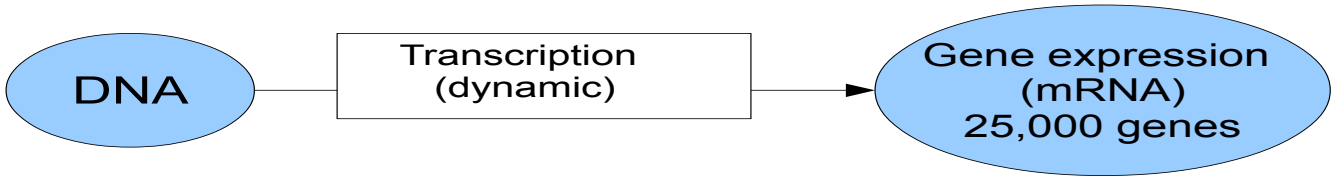
The results from these different approaches can be compared and reinforce/validate the biological model.

1. Multi-stage model and gene expression
2. The NOWAC data
3. The latent variable statistical model

Transcription



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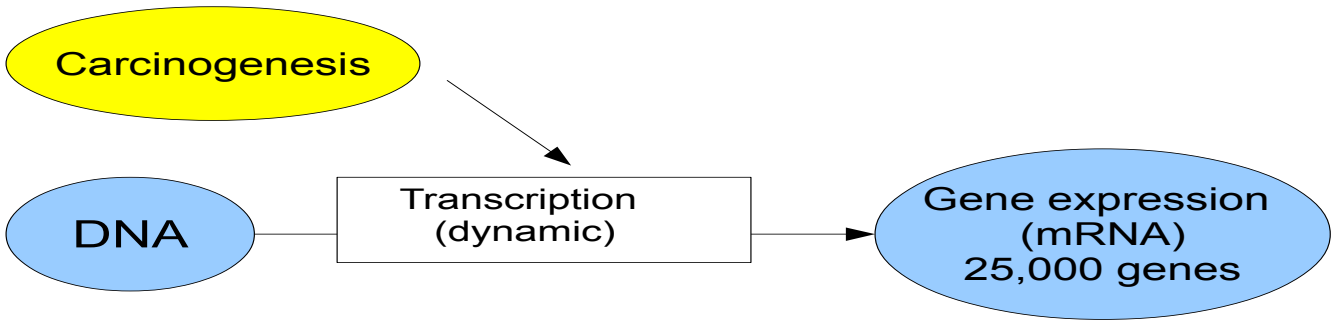

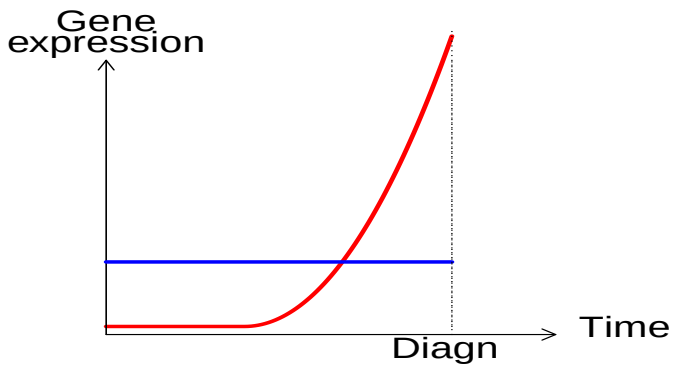

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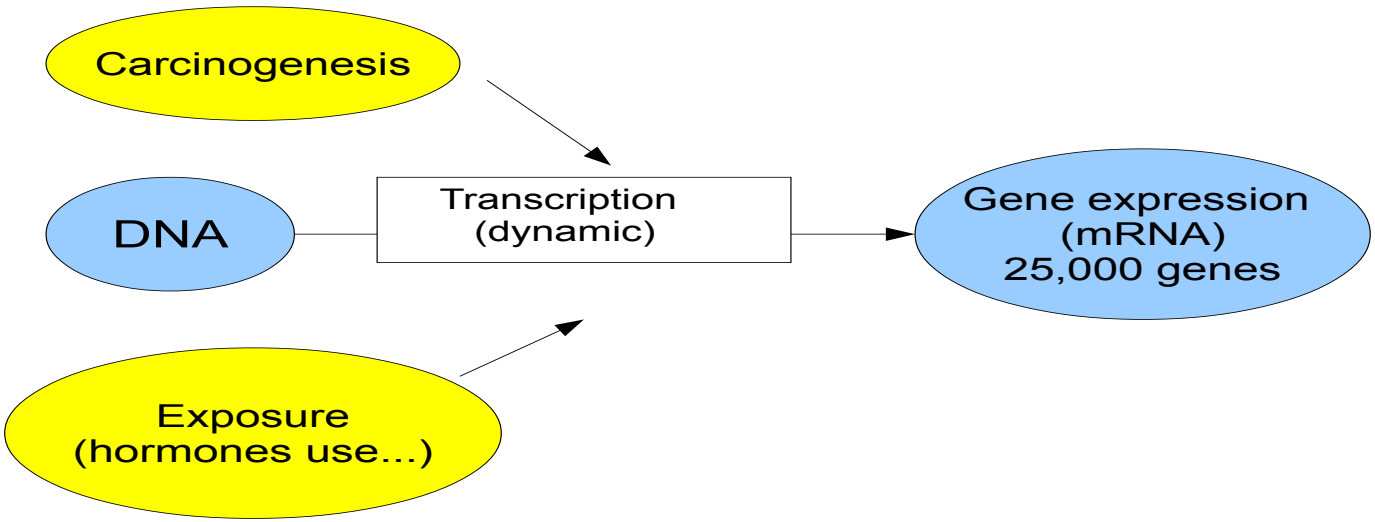

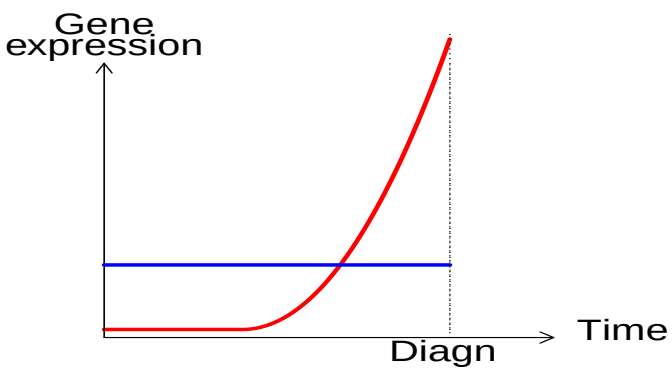

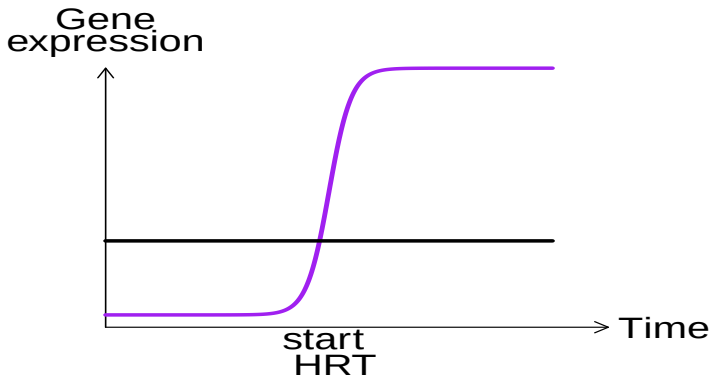

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— gene non involved

— gene linked to HRT
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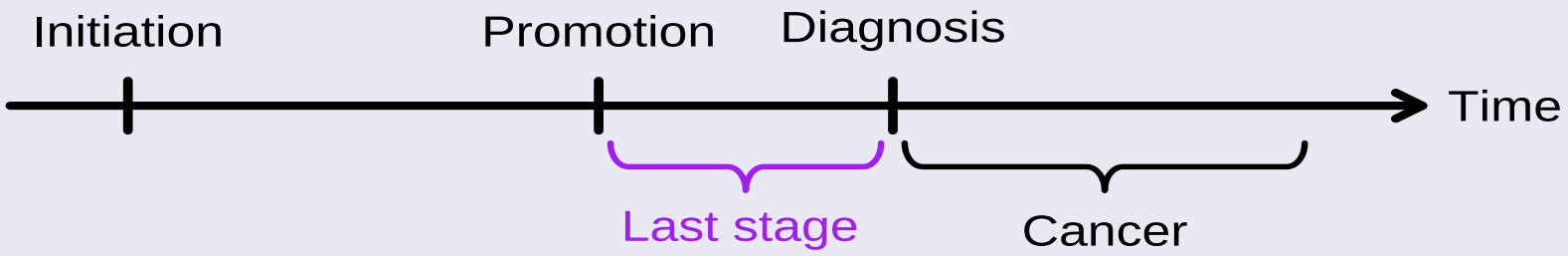
Multi-stage model and gene expression



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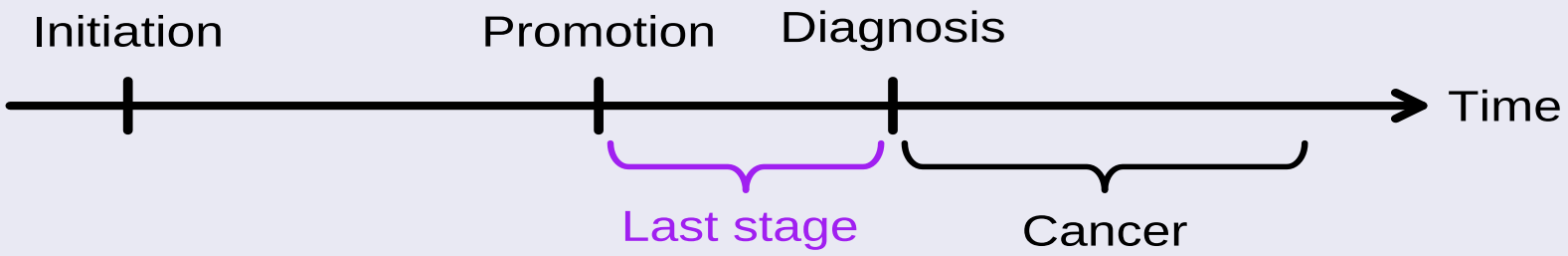
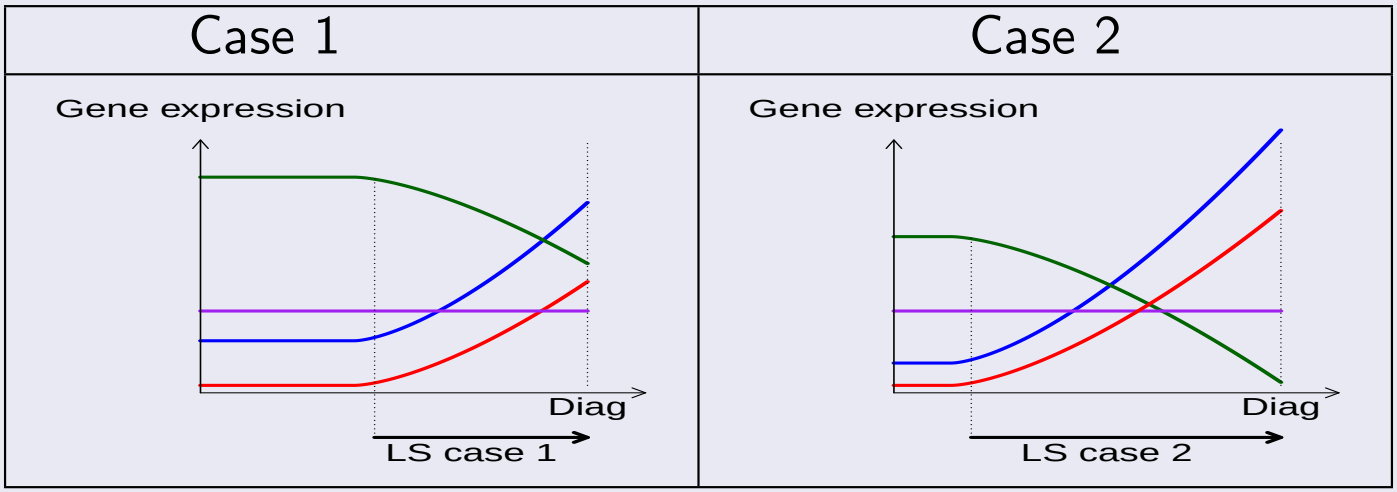


Multi-stage model and gene expression

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



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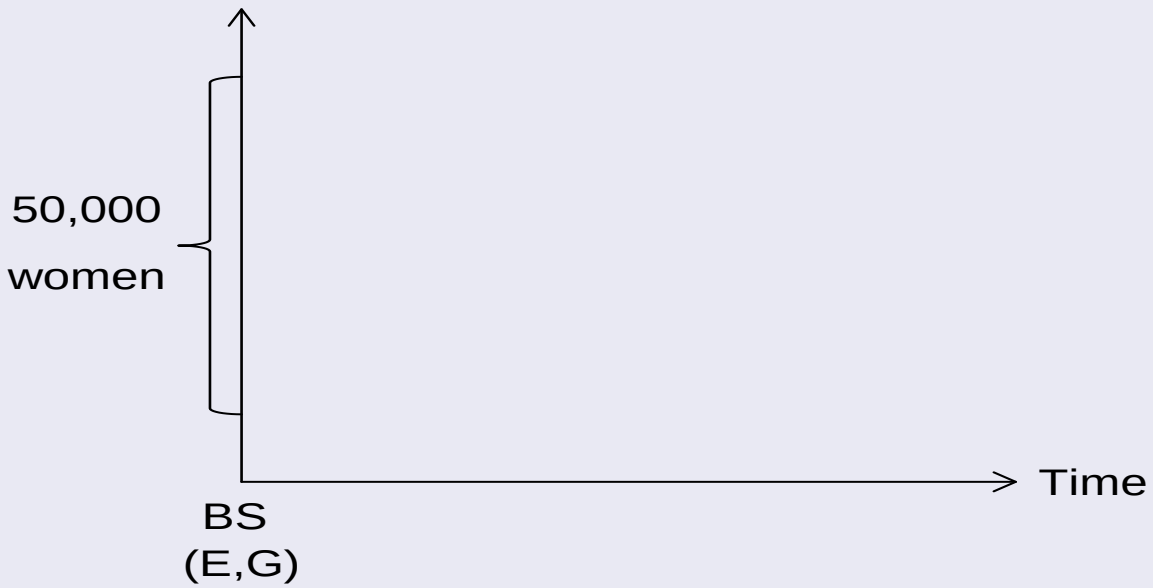
2 The NOWAC data

3 The latent variable statistical model

The NOWAC cohort

Cohort of 50,000 women



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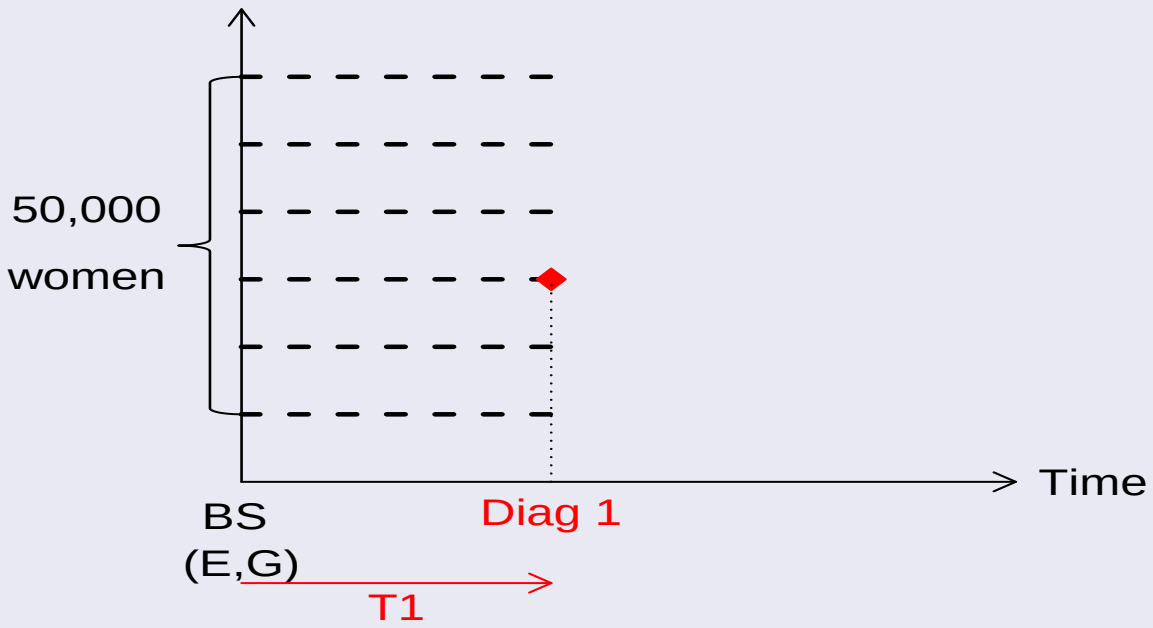

◆: case

●: control

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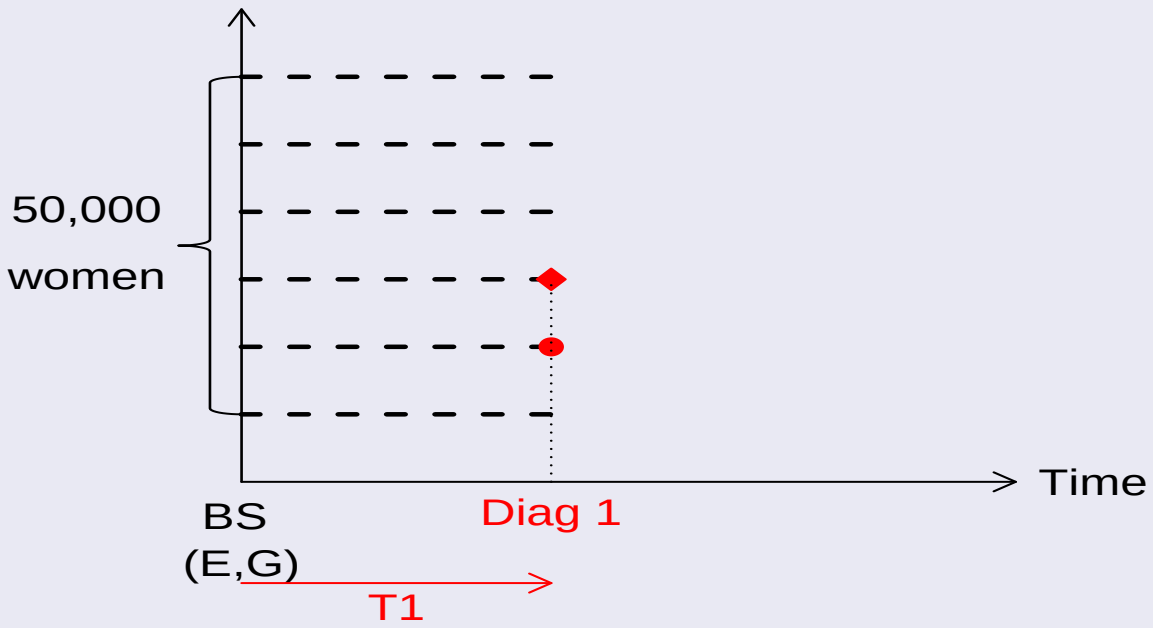

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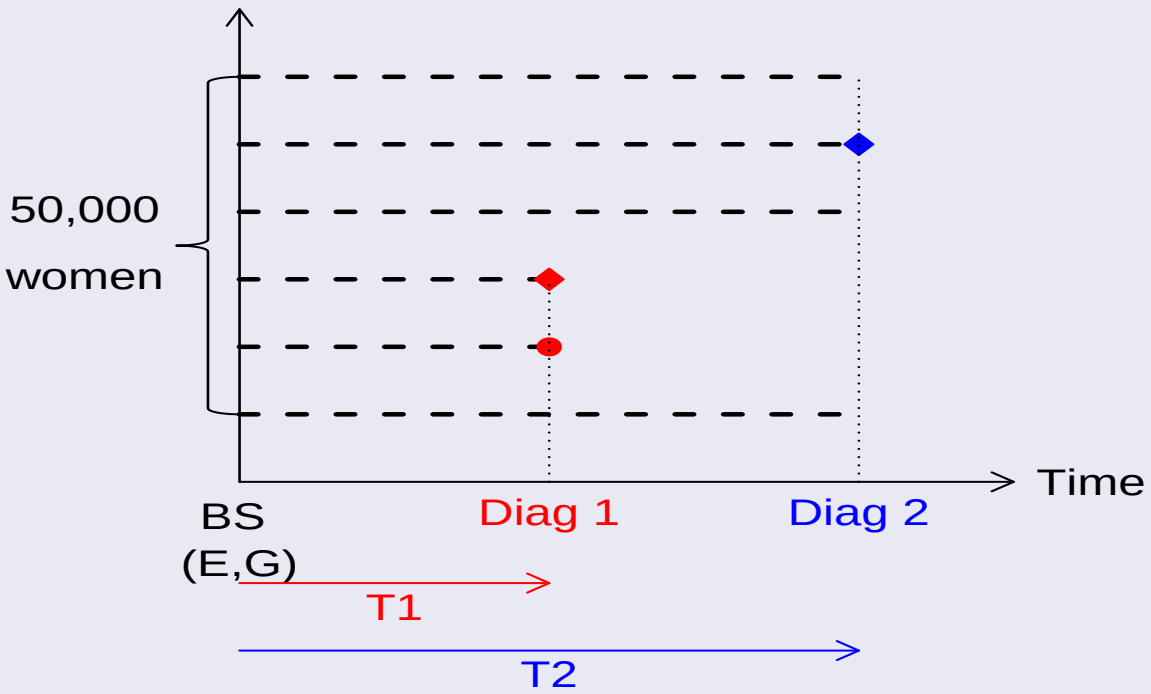

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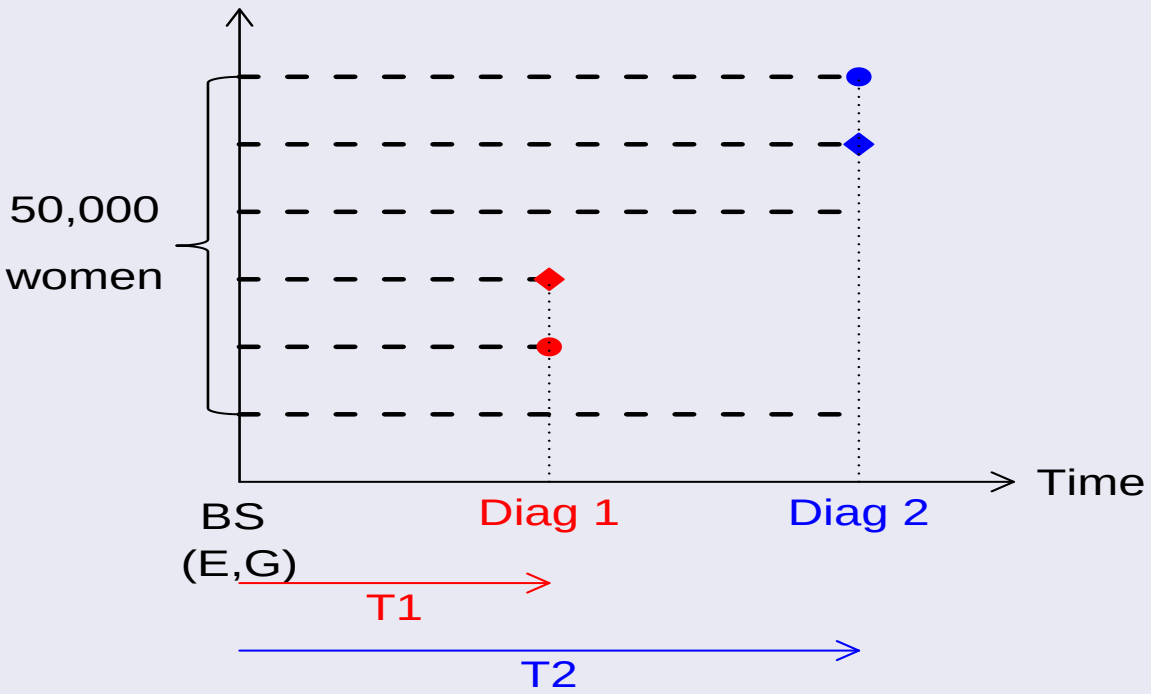

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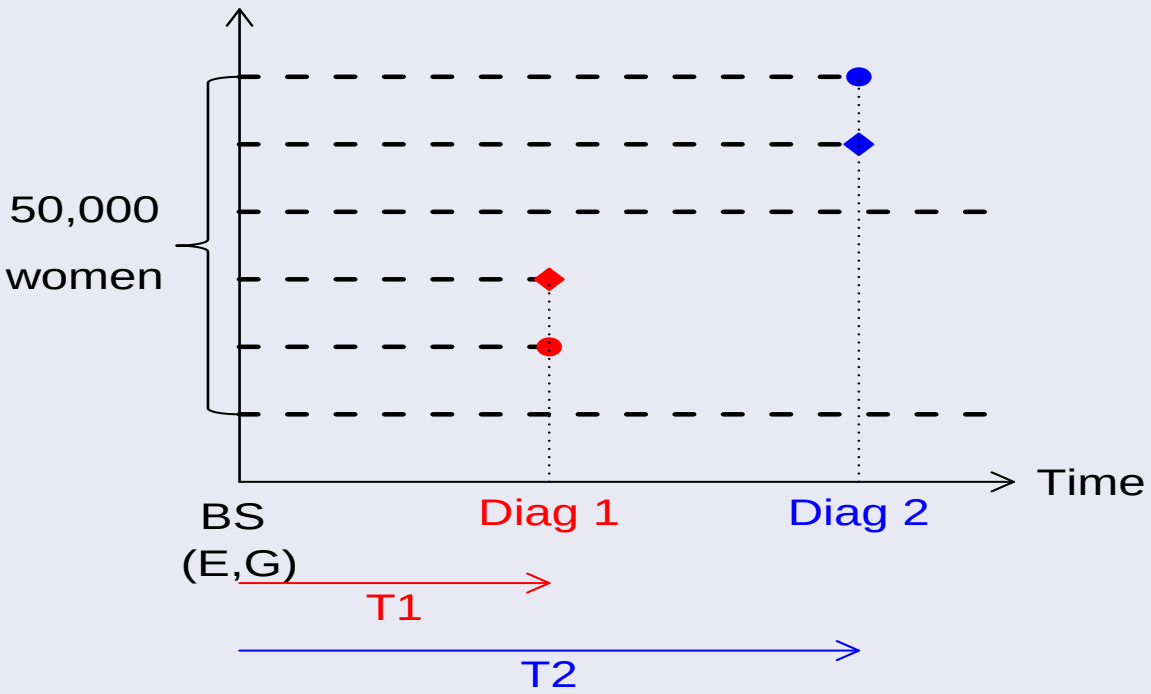

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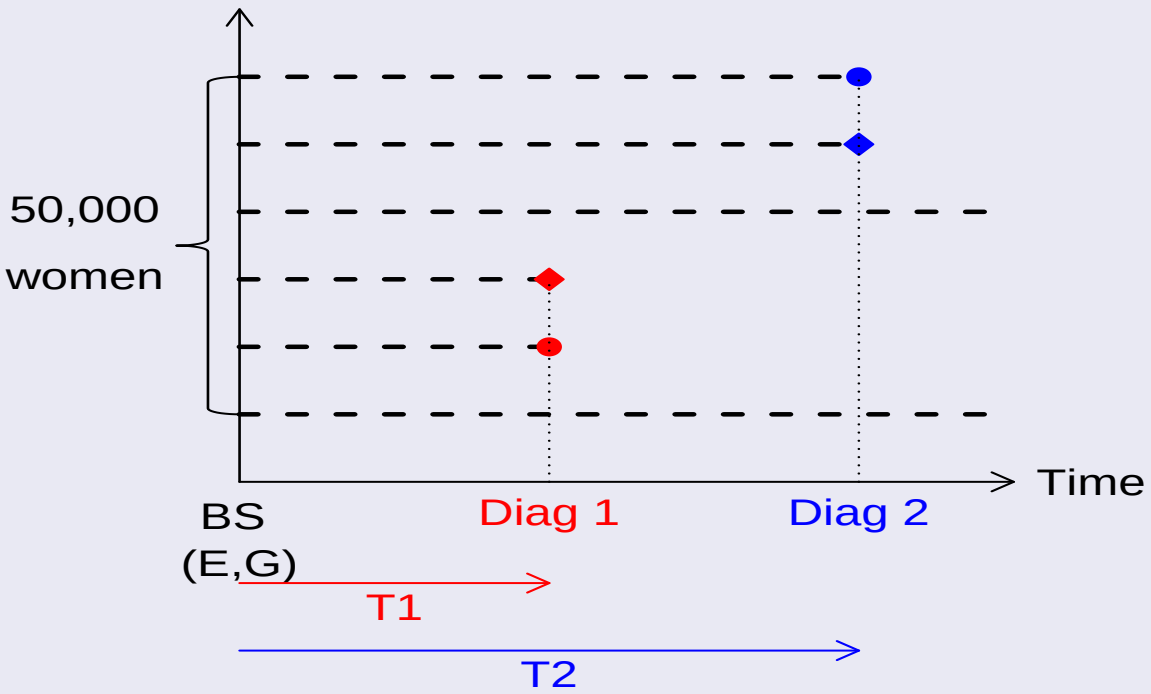

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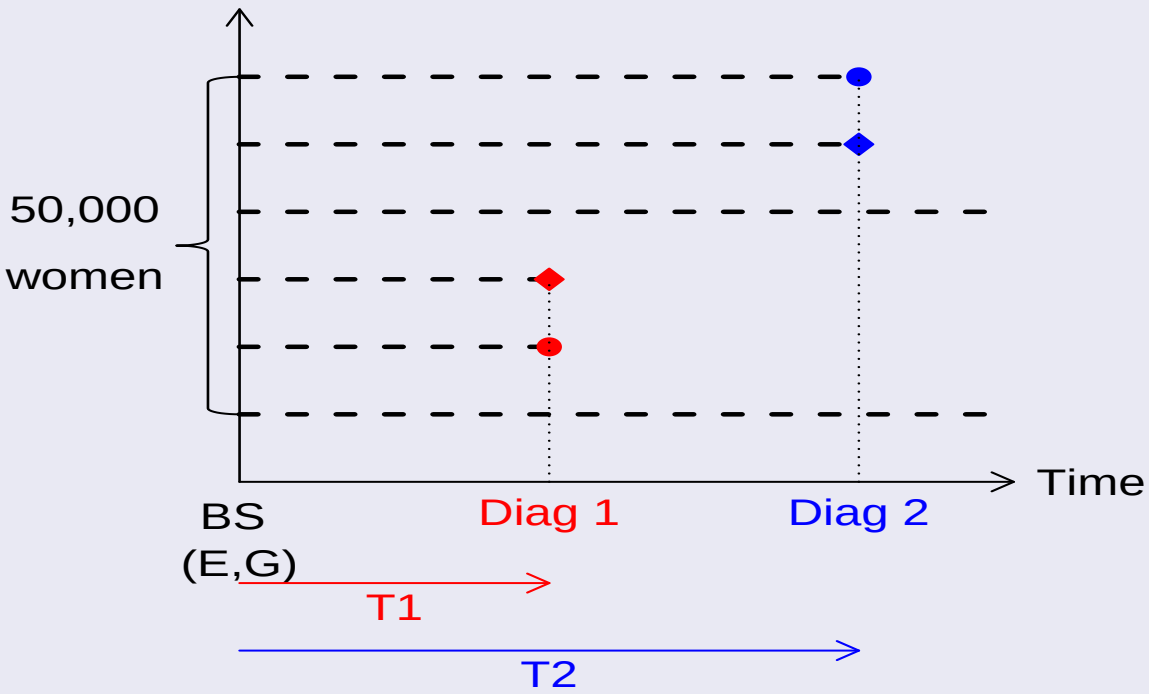

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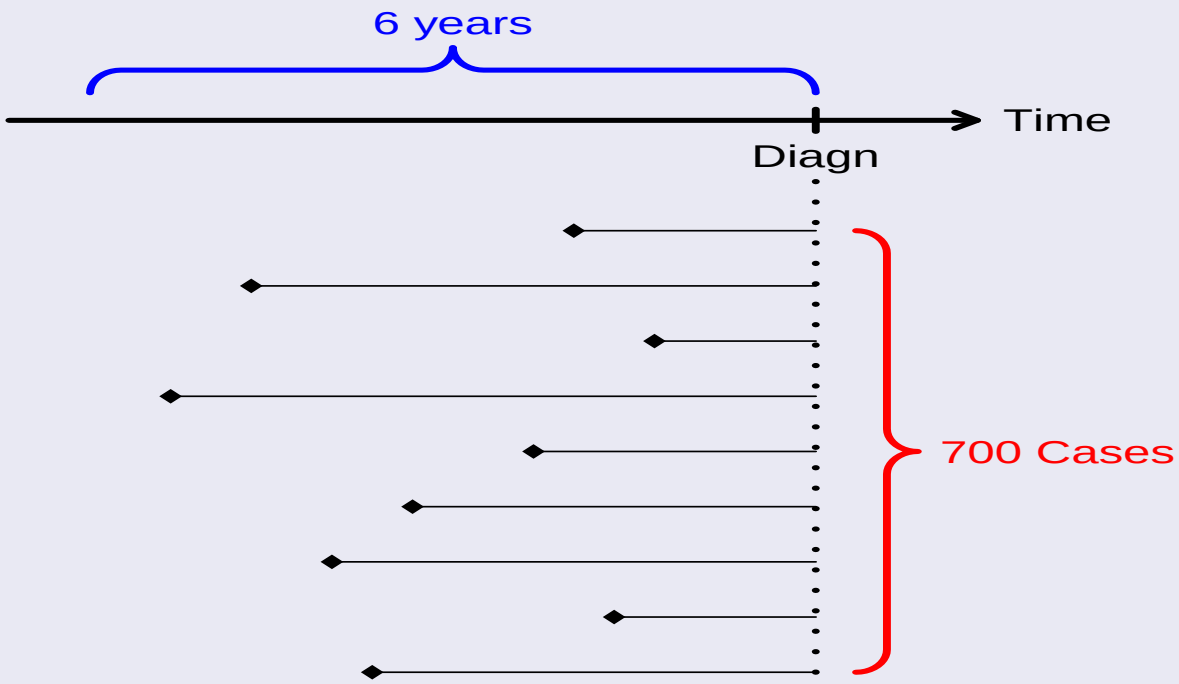
For each case-control pair:

- $(E^{\text{case}}, E^{\text{ctl}})$ = 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.



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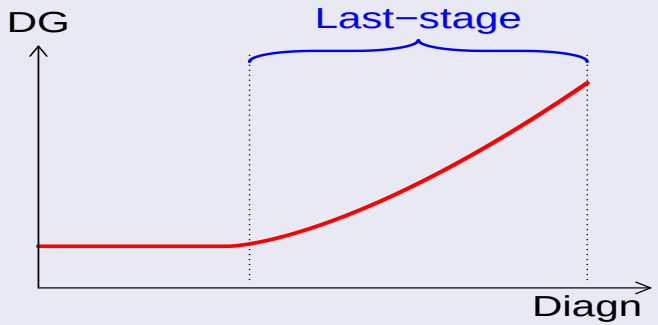
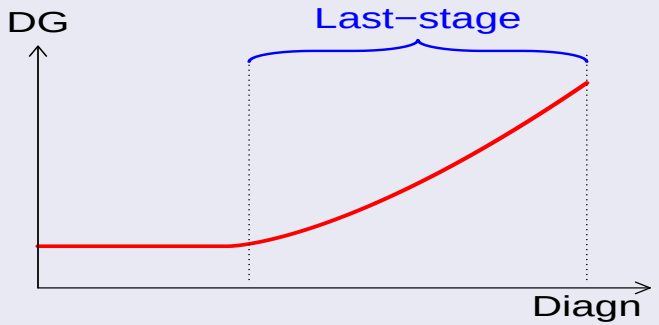
The latent last-stage statistical model

Gene expression





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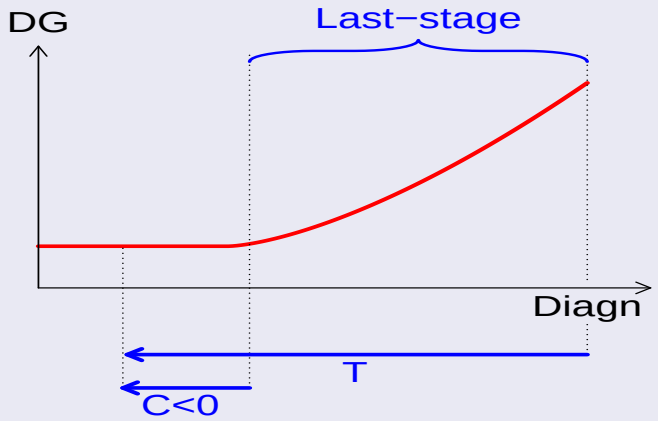

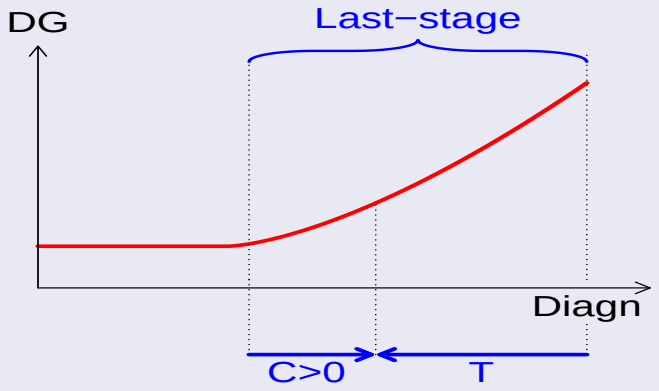

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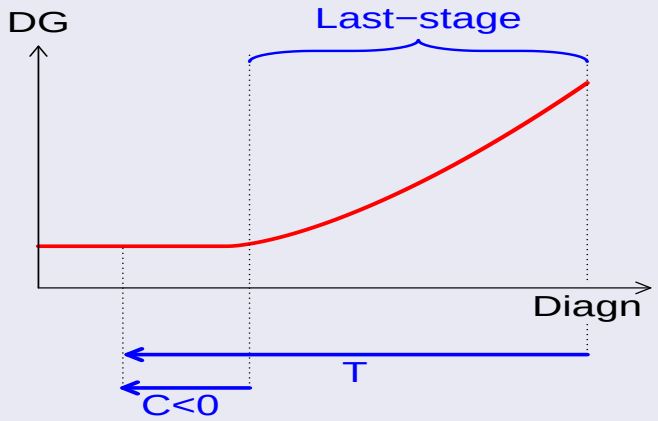

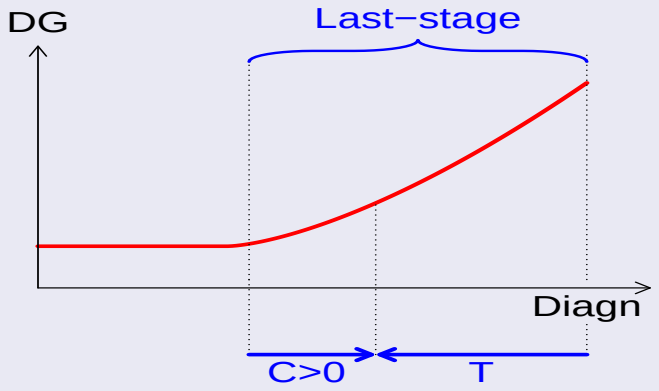

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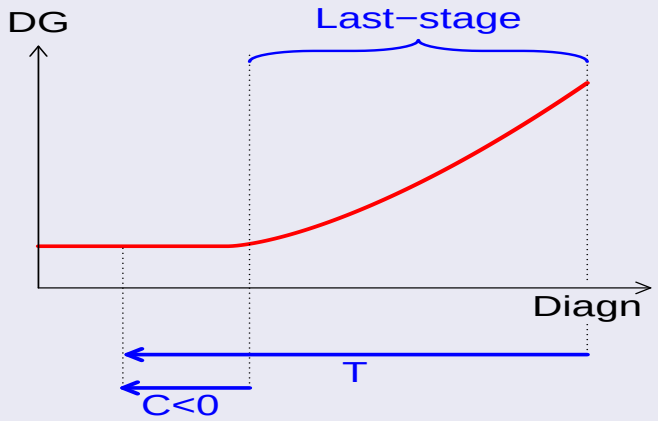

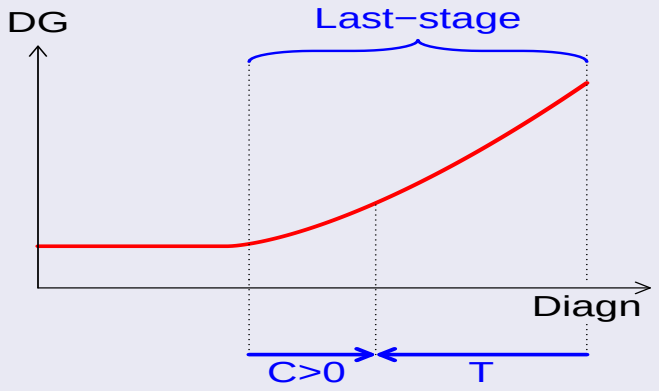

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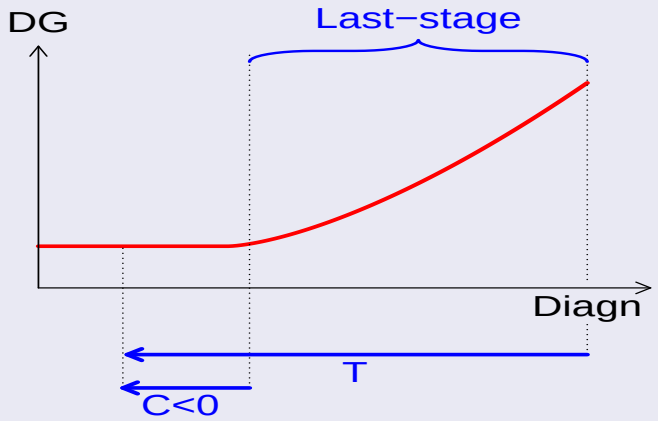

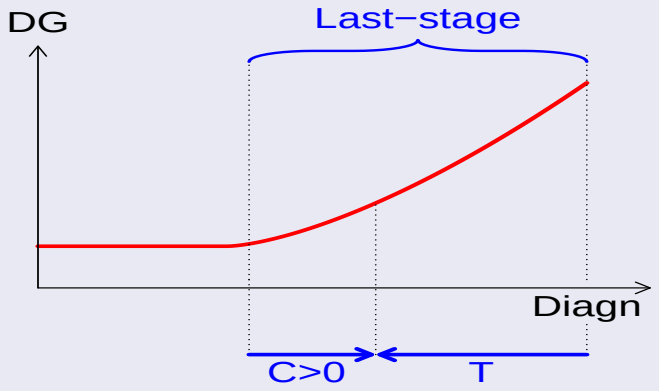

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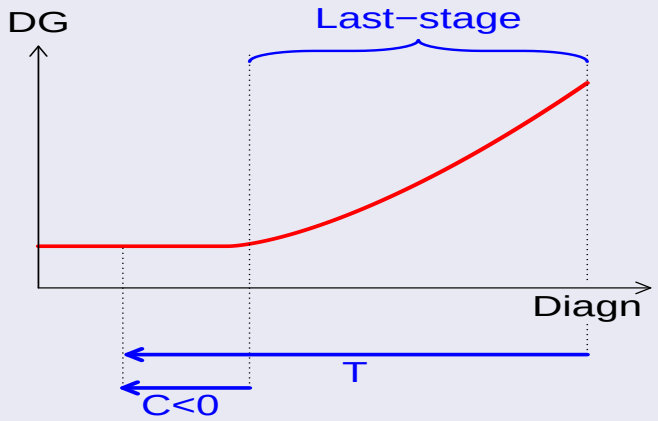

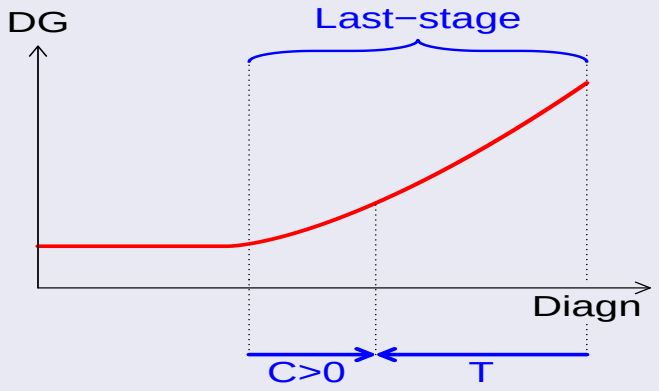

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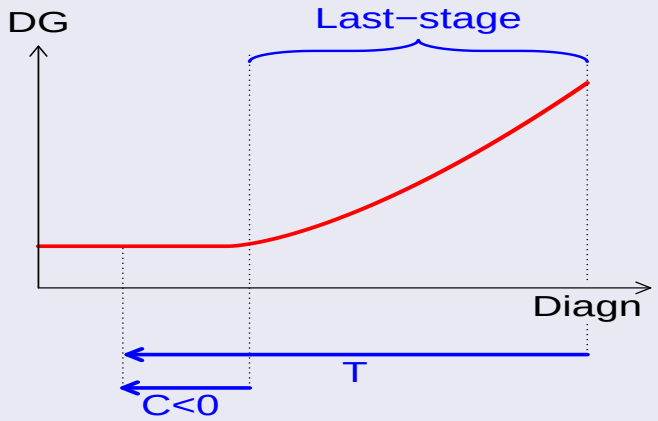

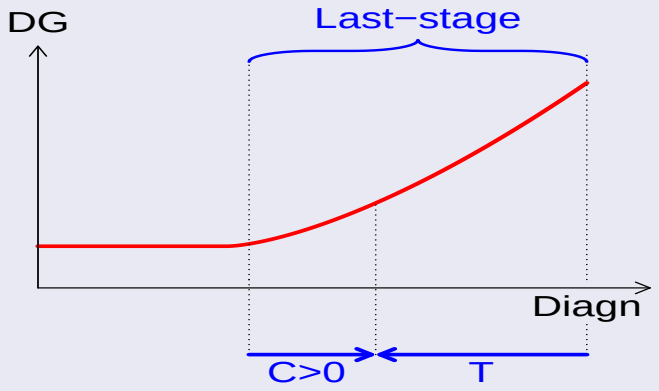

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Last-stage length

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

Estimation of the model

- Algorithm SEM (Simulated Expectation Maximization)
- Validation on simulated data

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Primary goals

- Detect genes involved in the last stage (multiple testing).
- Estimate the distribution of the last stage depending on the exposures.

Further developments

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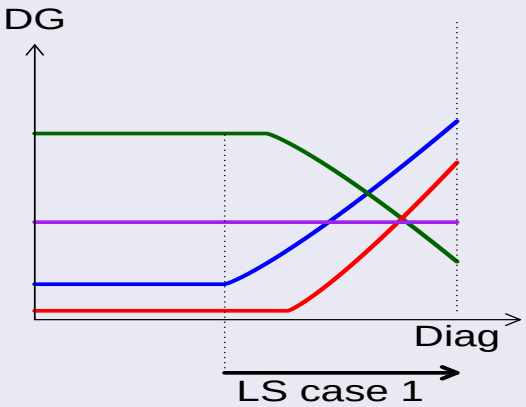

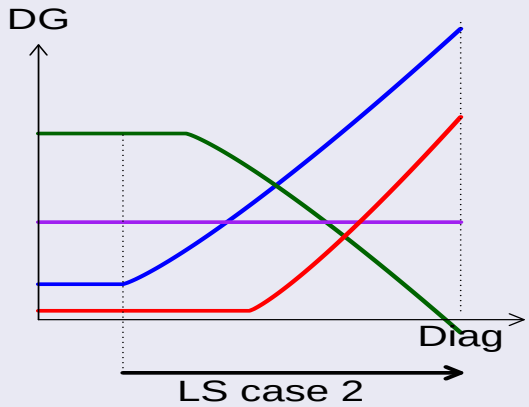

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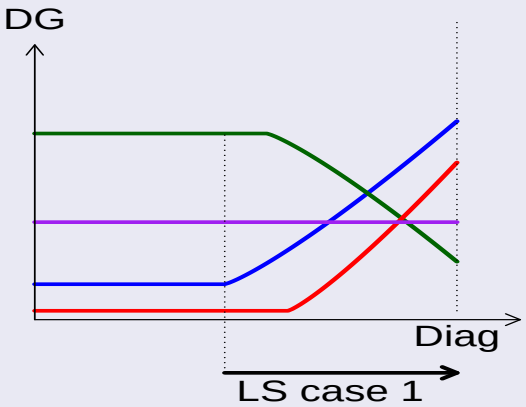
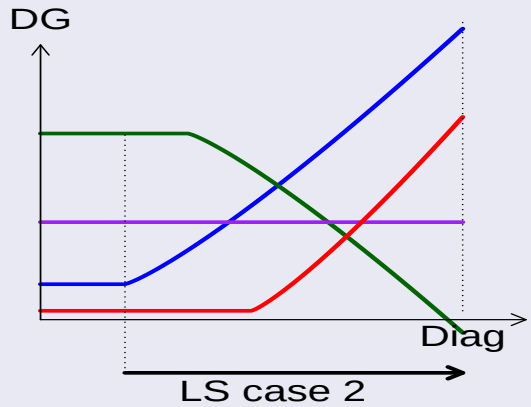


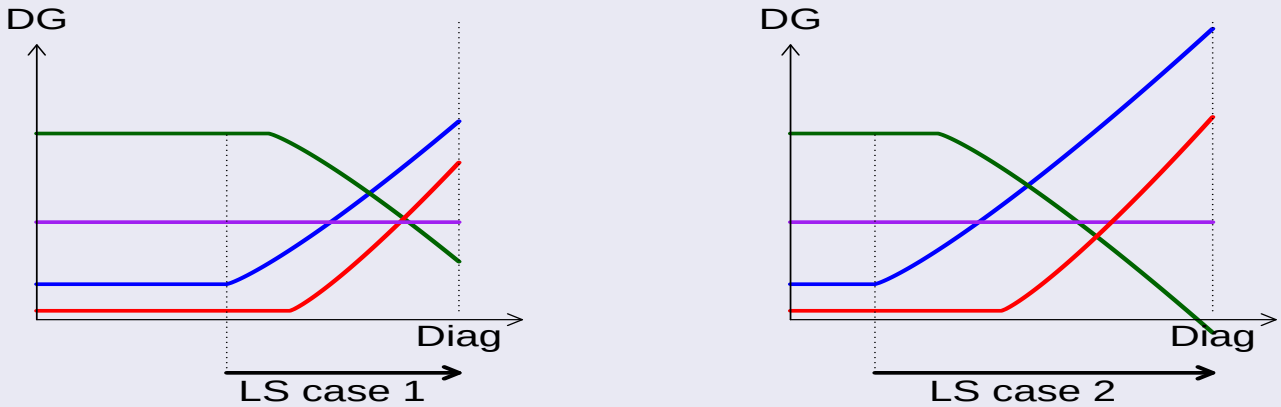


- Cross-effect Time/Exposure (Cancer driven by exposure).

Further developments

Modeling of $P[DG|C, DE]$

- Alternative parametrization of time dependence.
- Interval between between beginning of last stage and gene expression changes.



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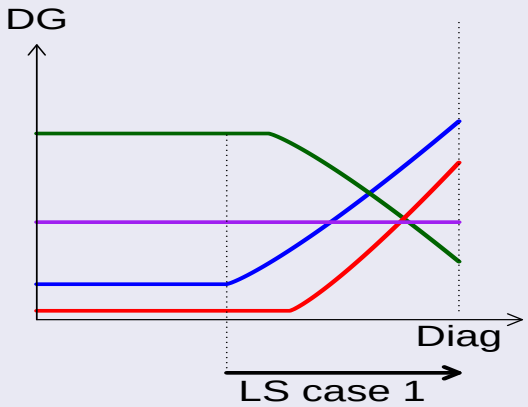

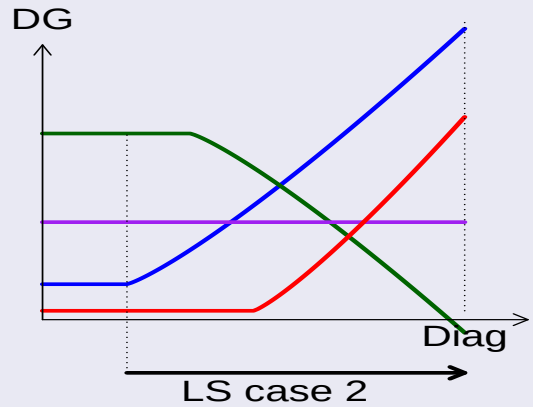

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Subgroups

Further developments

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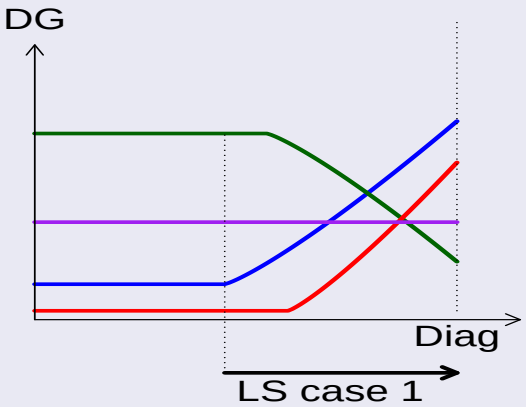

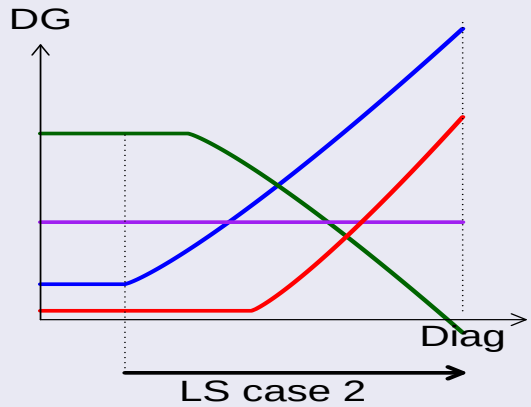

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Further developments

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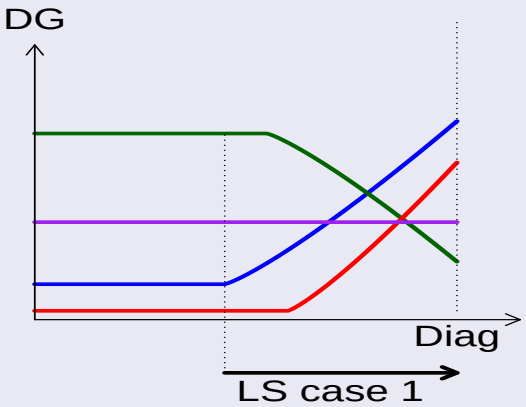

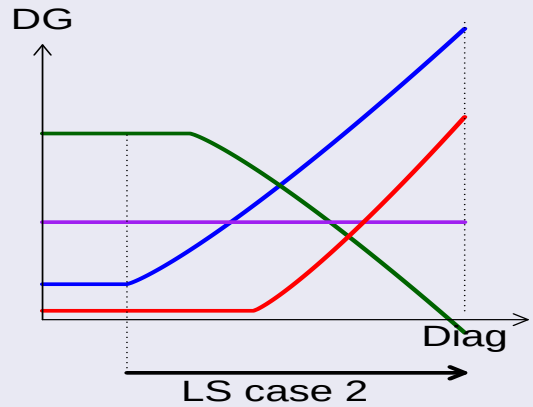

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Subgroups

- Classification by exposure/type of cancer
- Stratification/hierarchical model.

Conclusion

- Goal: study gene expression through the multi-stage model of carcinogenesis.
- Conceptual model based on biological modeling
- Good results on simulations but require development to be applied on experimental data.