

# **Longitudinal modeling of omics data from HPV-induced transformation**

# Contributors

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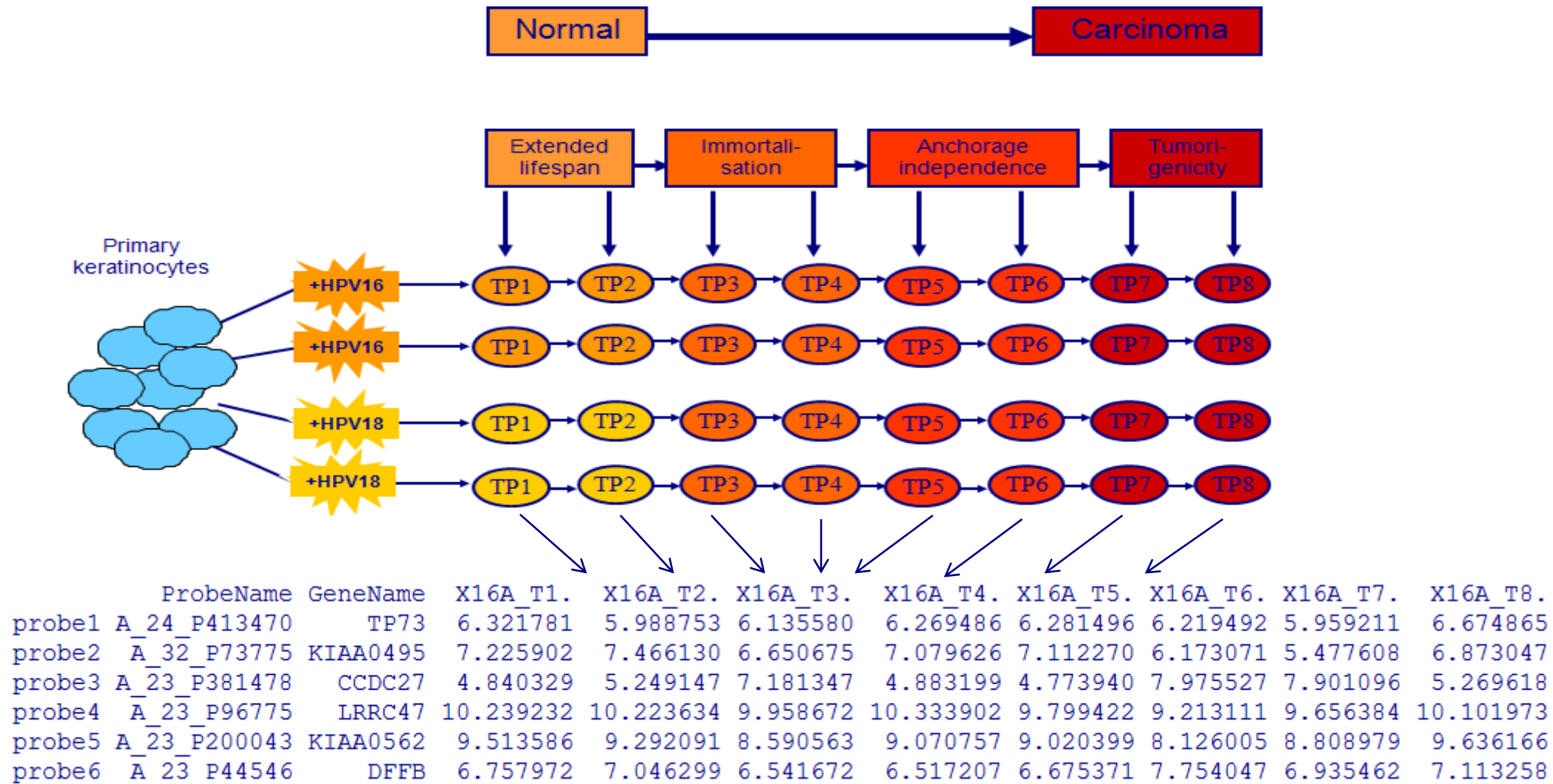
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- Renske Steenbergen
- Peter Snijders

# Cervical cancer study

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- Second most common cancer in women worldwide.
- Caused by HPV virus, in 70% cases HPV16 and HPV18.
- Cell line model – in vitro model system of HPV-induced transformation.
- Integration – high-throughput multi level molecular data sets.
- Aim: reconstruct temporal interaction among the genes.

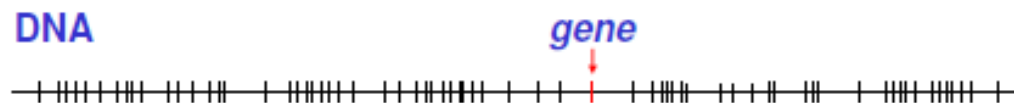
# Time-course experiment



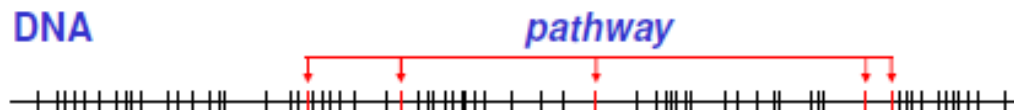
Measured expression of 27637 mRNAs

# Statistical unit

- Gene – measured part of the genome



- Pathway – group of genes which work together

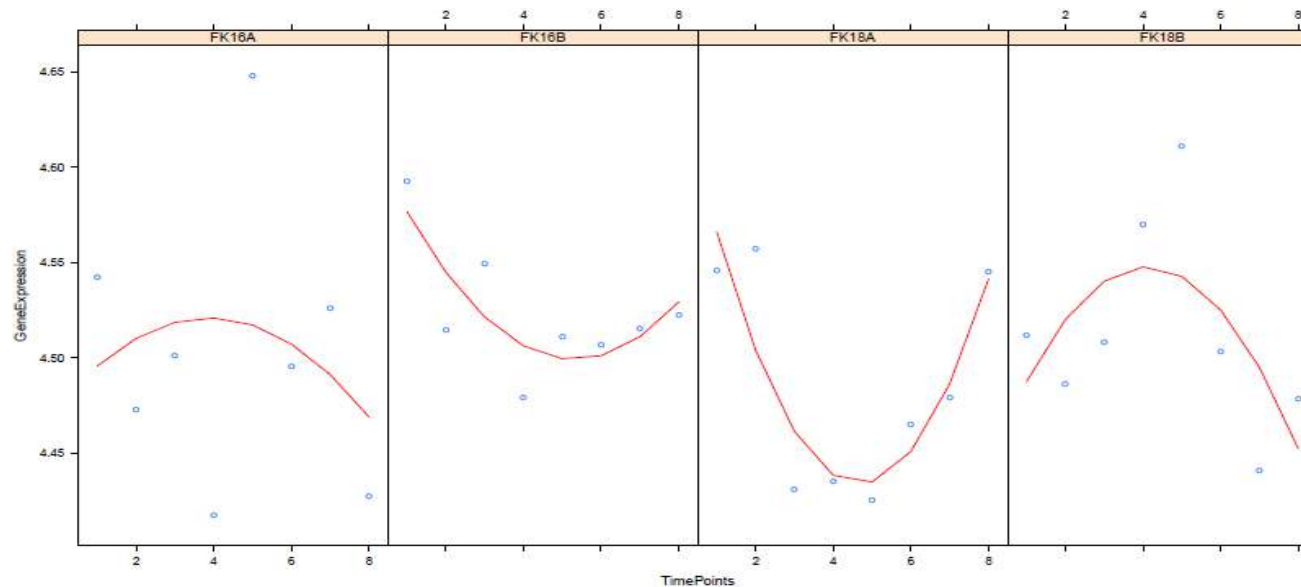


# Model

$$GE = CL + \text{Time}$$

fixed (cell line) effect

random (splines) effect

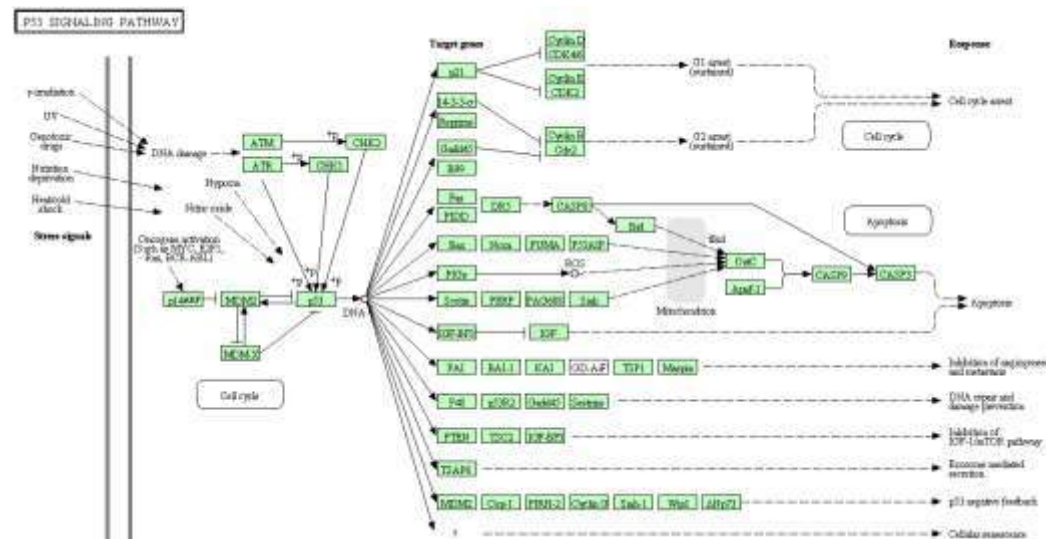


3642 significant mRNAs

(concordant change in expression in at least 3 cell lines)

# Pathways

- Pathway are defined using repositories: **KEGG**, **GO**, **Reactome**...



- Problems with repositories:
  - Incomplete
  - Mostly well-known pathways
  - Loosely defined
- Goal: using our data to reconstruct the p 53 signaling pathway

# Data, model and network

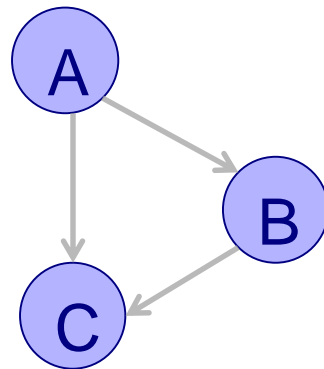
- Pathway can be represented by graph or network



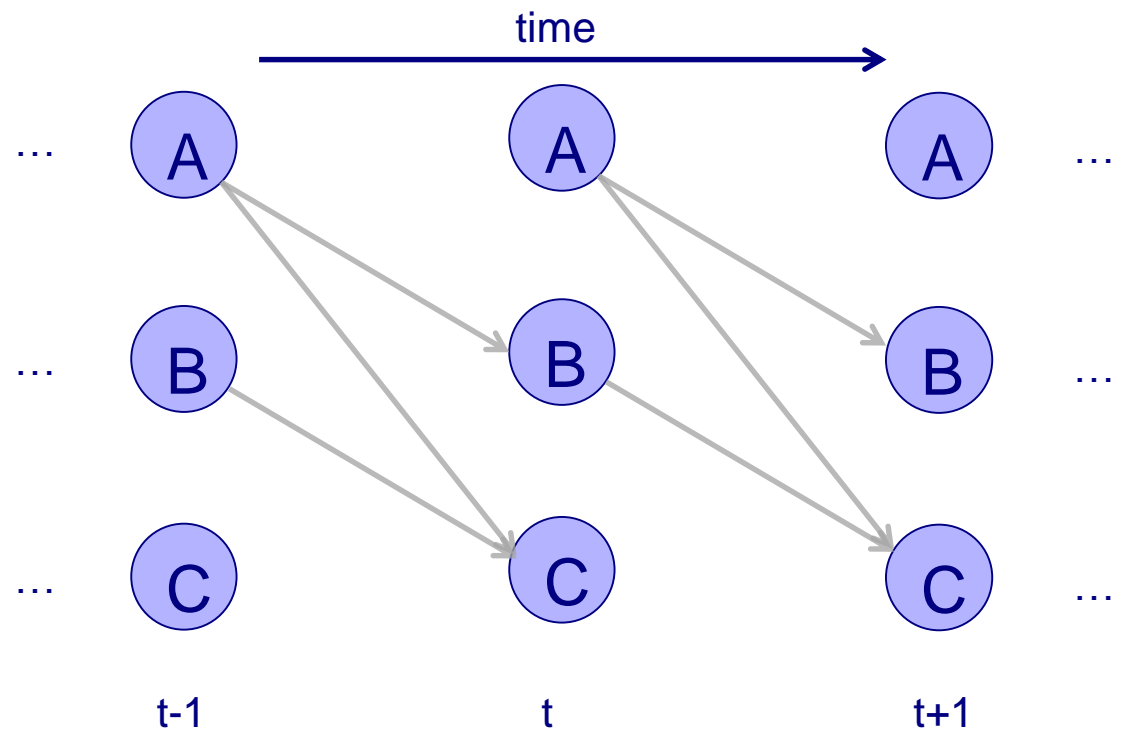
node or vertex, indicate a gene



Edge or arrow, indicating an interaction between two genes



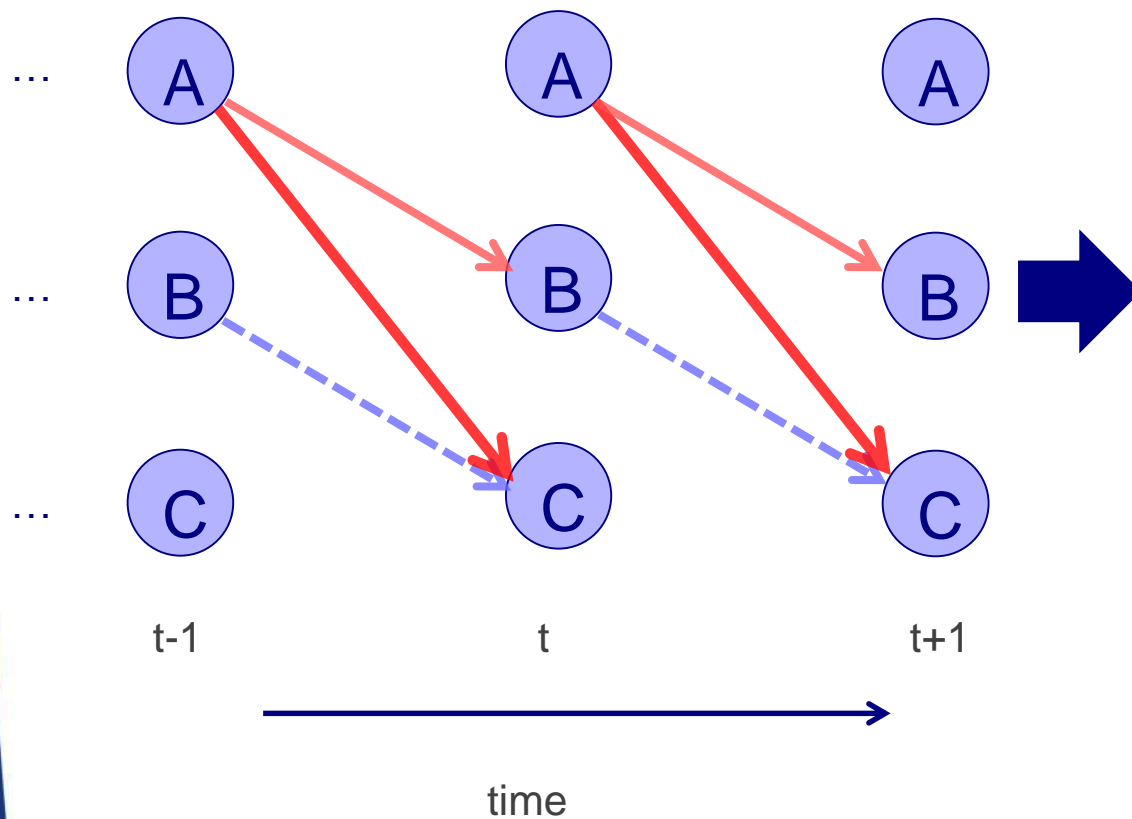
Feed-forward loop



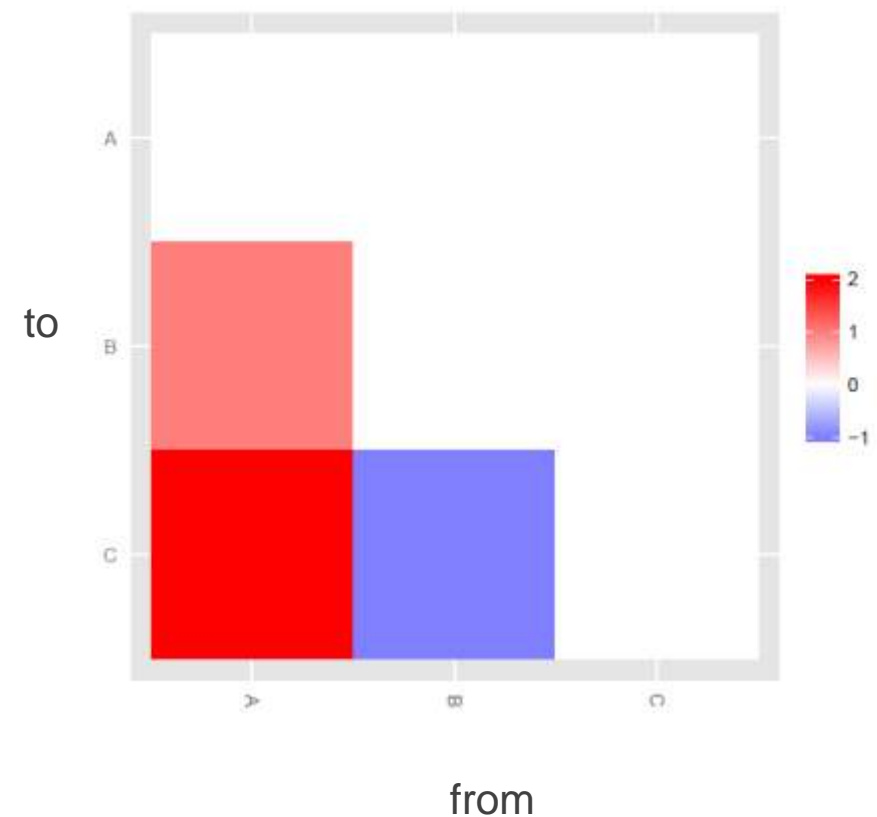
Feed-forward loop (unrolled)



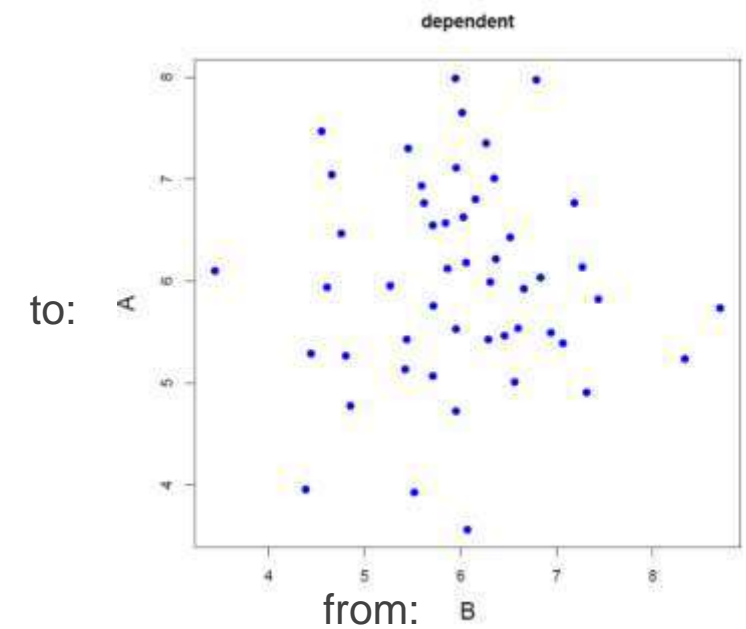
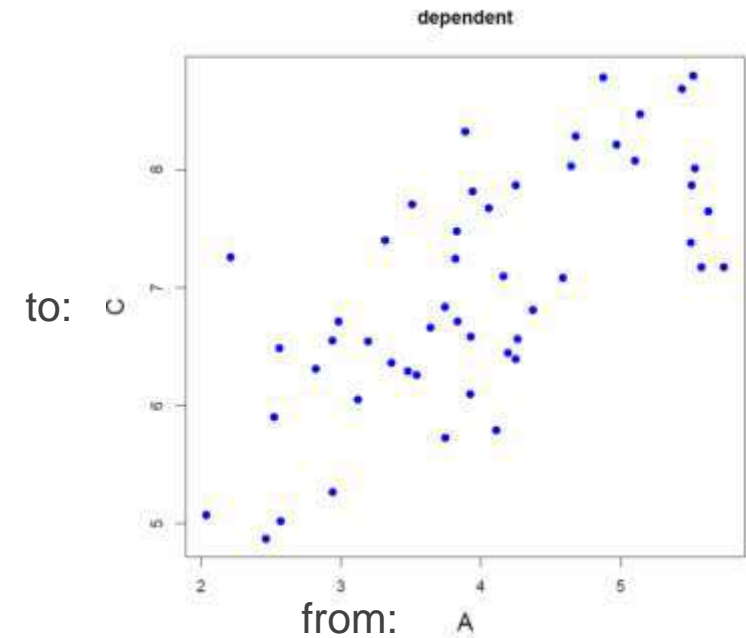
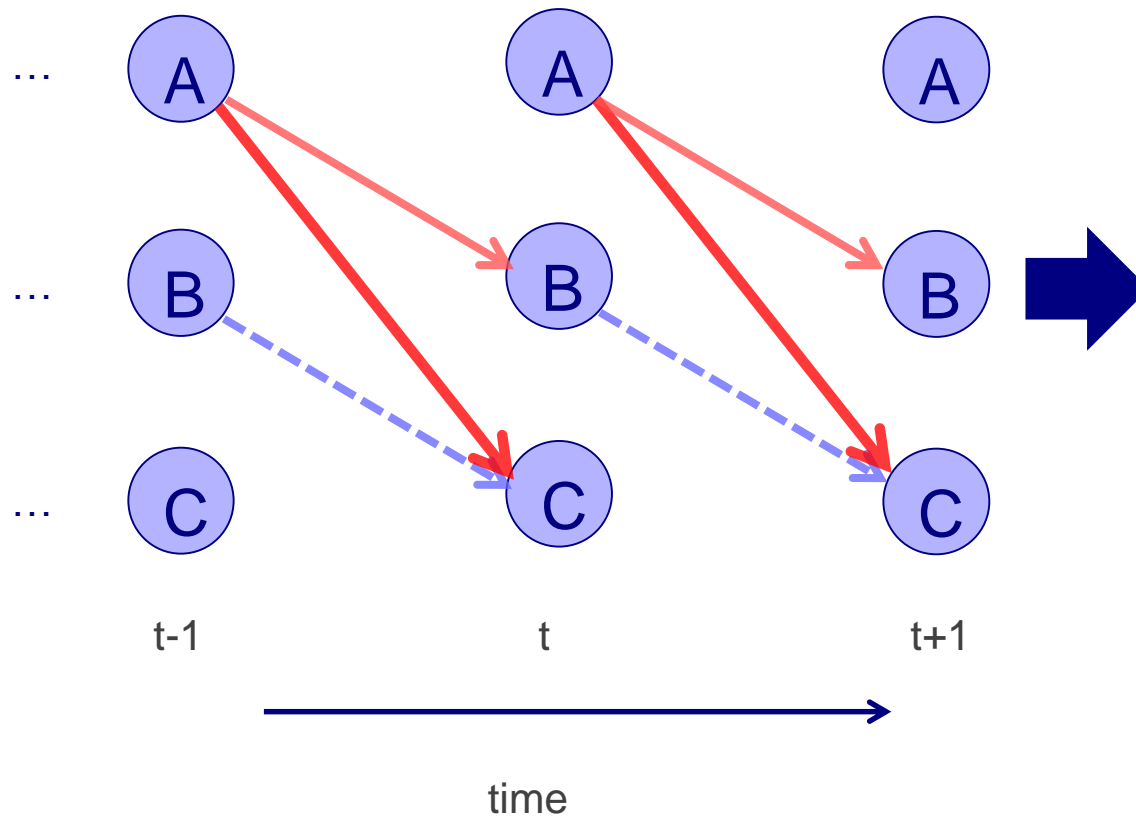
# Network and model



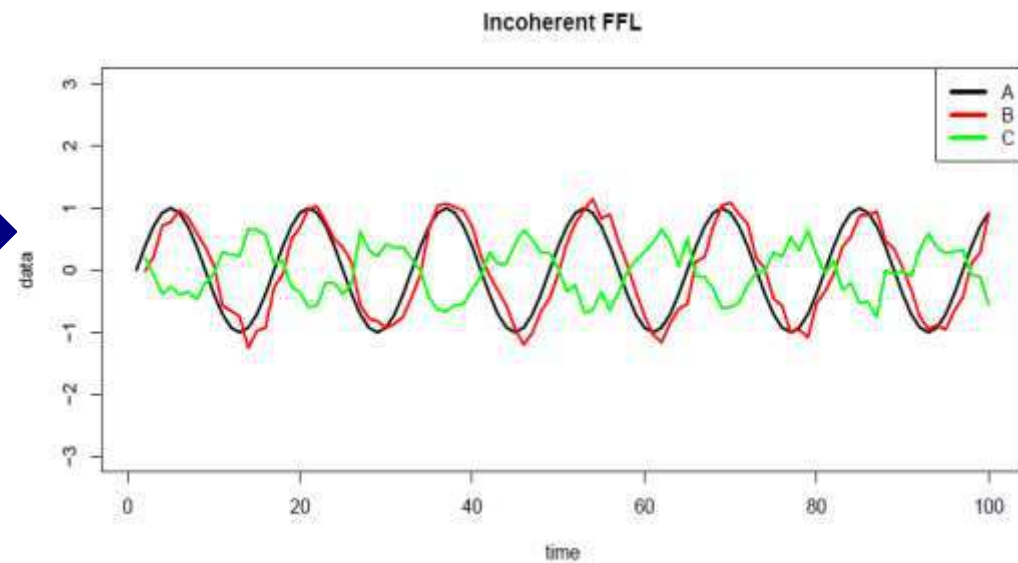
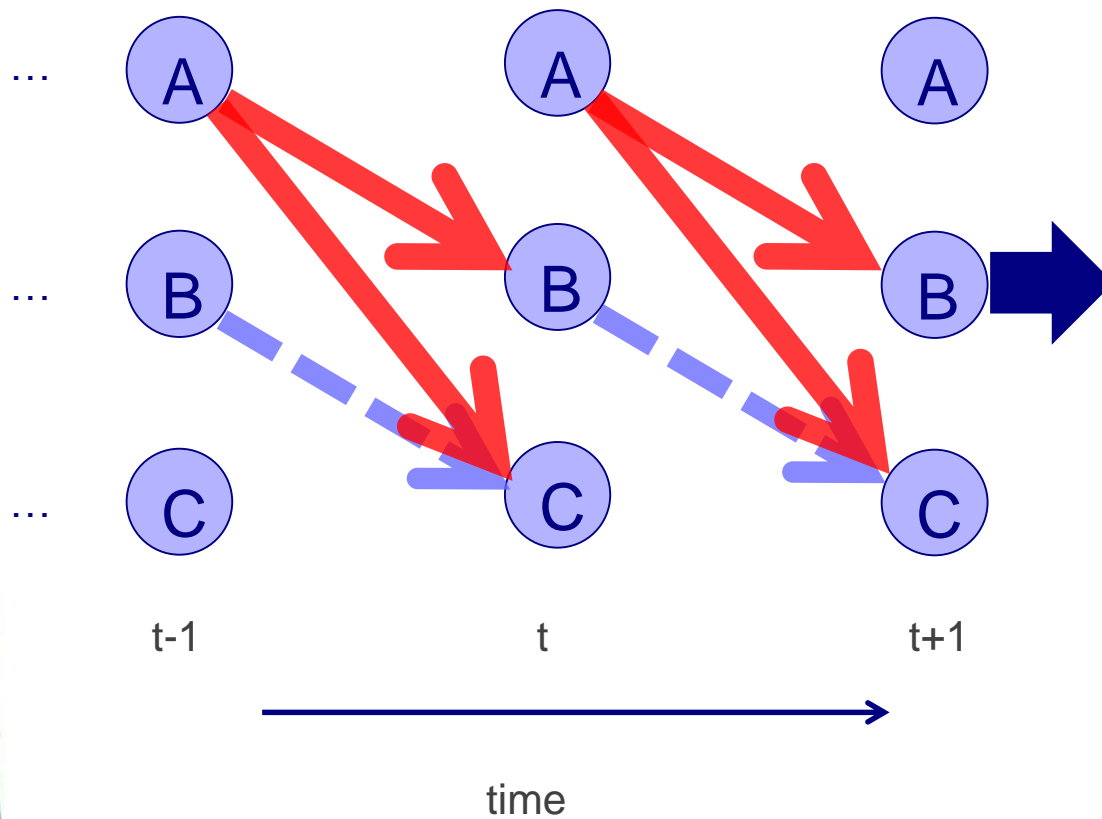
$$\begin{aligned} A_t &= +\varepsilon_{A,t} \\ B_t &= A_{t-1} + \varepsilon_{B,t} \\ C_t &= 2A_{t-1} - B_{t-1} + \varepsilon_{C,t} \end{aligned}$$



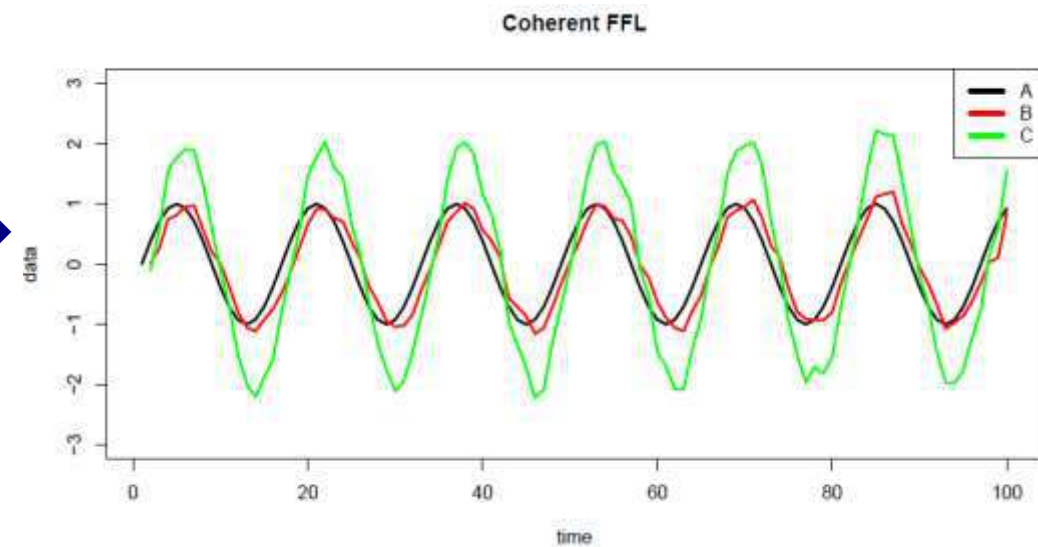
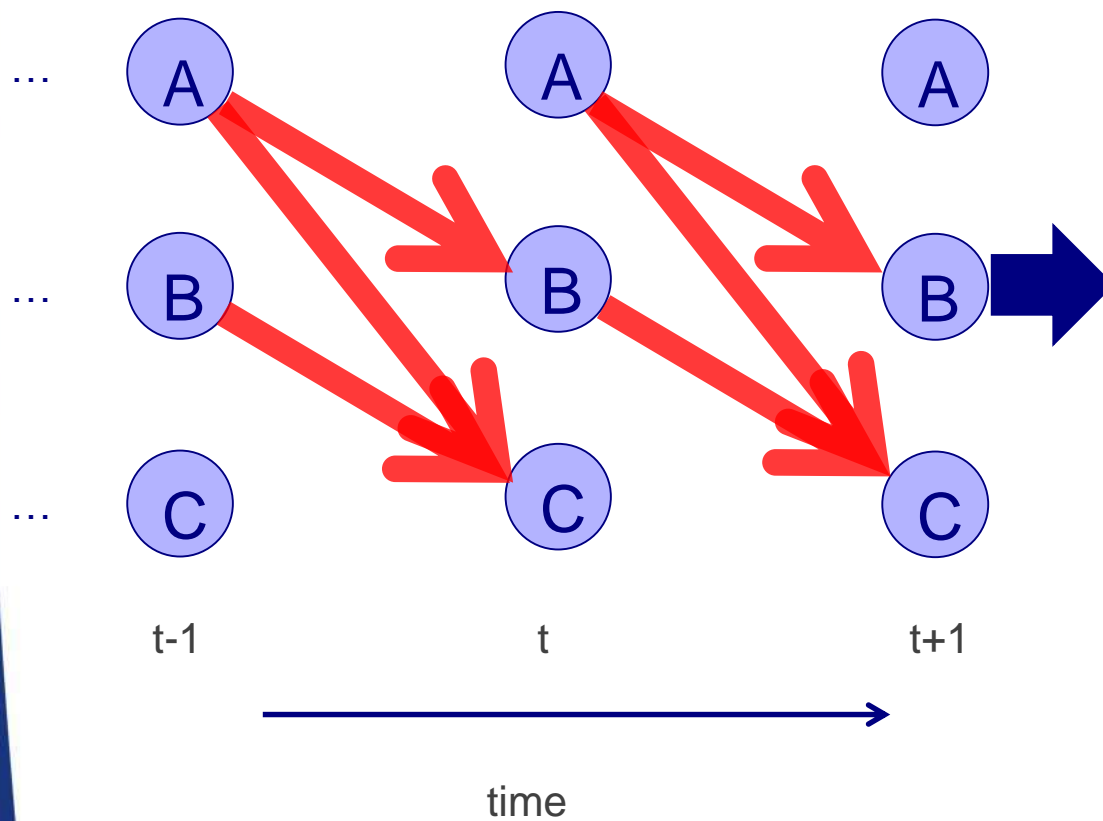
# Network and data



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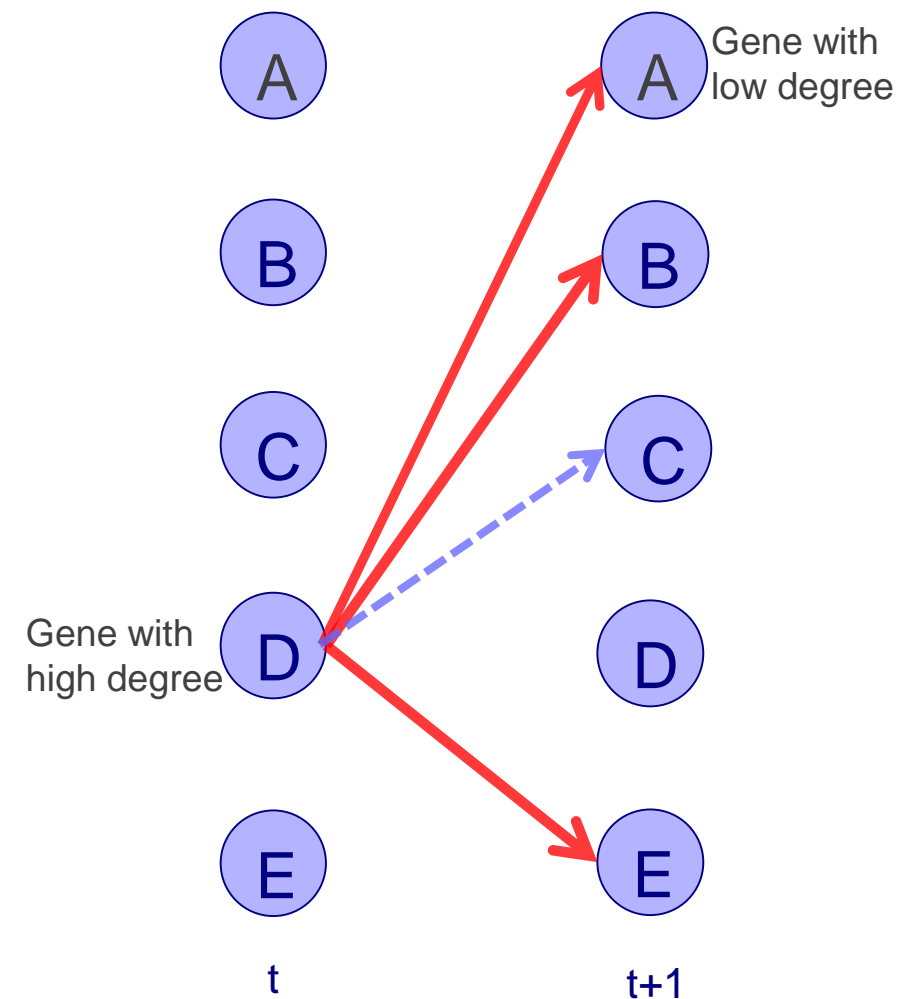
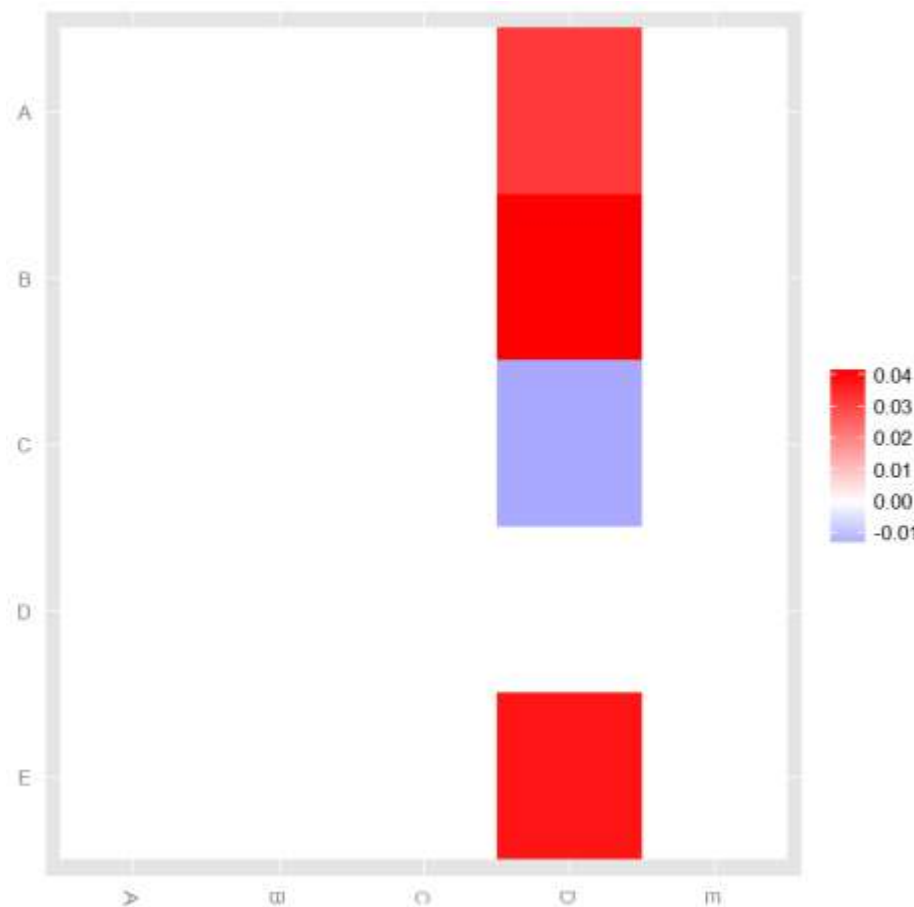


# Network and data

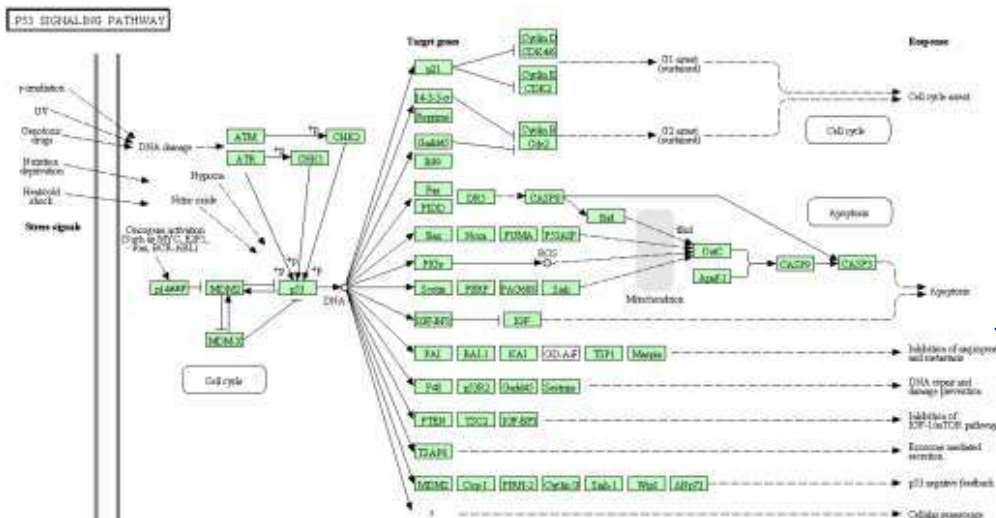
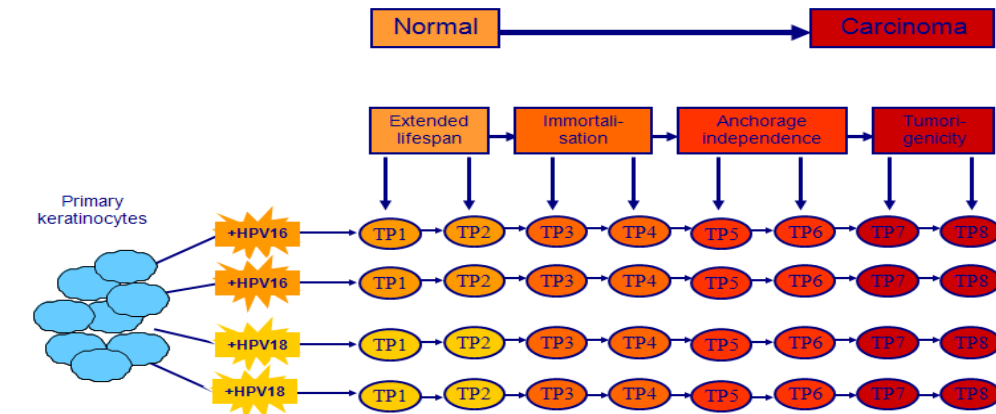


# Hub genes - model and network

- Hub – gene with many connections (disease genes)



# Real data and network



|           |           |
|-----------|-----------|
| CDK6      | CDK6      |
| THBS1     | THBS1     |
| CCNE2     | CCNE2     |
| TP53      | TP53      |
| PMAIP1    | PMAIP1    |
| IGFBP3    | IGFBP3    |
| IGF1      | IGF1      |
| SIH1      | SIH1      |
| ZMAT3     | ZMAT3     |
| SERPINE1  | SERPINE1  |
| CDKN2A    | CDKN2A    |
| SES3      | SES3      |
| CDKN1A    | CDKN1A    |
| CCND2     | CCND2     |
| RPRM      | RPRM      |
| BBC3      | BBC3      |
| GADD45G   | GADD45G   |
| TP73      | TP73      |
| SES1      | SES1      |
| SES2      | SES2      |
| PERP      | PERP      |
| TP53AIP1  | TP53AIP1  |
| PTEN      | PTEN      |
| SFN       | SFN       |
| CCNB3     | CCNB3     |
| BID       | BID       |
| EI24      | EI24      |
| CCNG1     | CCNG1     |
| RRM2      | RRM2      |
| STEAP3    | STEAP3    |
| CASP8     | CASP8     |
| ATR       | ATR       |
| ATM       | ATM       |
| FAS       | FAS       |
| CCNG2     | CCNG2     |
| CCNE1     | CCNE1     |
| CCND3     | CCND3     |
| TNFRSF10B | TNFRSF10B |
| RFWD2     | RFWD2     |
| SHISA5    | SHISA5    |
| GADD45B   | GADD45B   |
| APAF1     | APAF1     |

???

64 mRNAs mapped to p53 signalling pathway

(28% of genes with significant time effect)

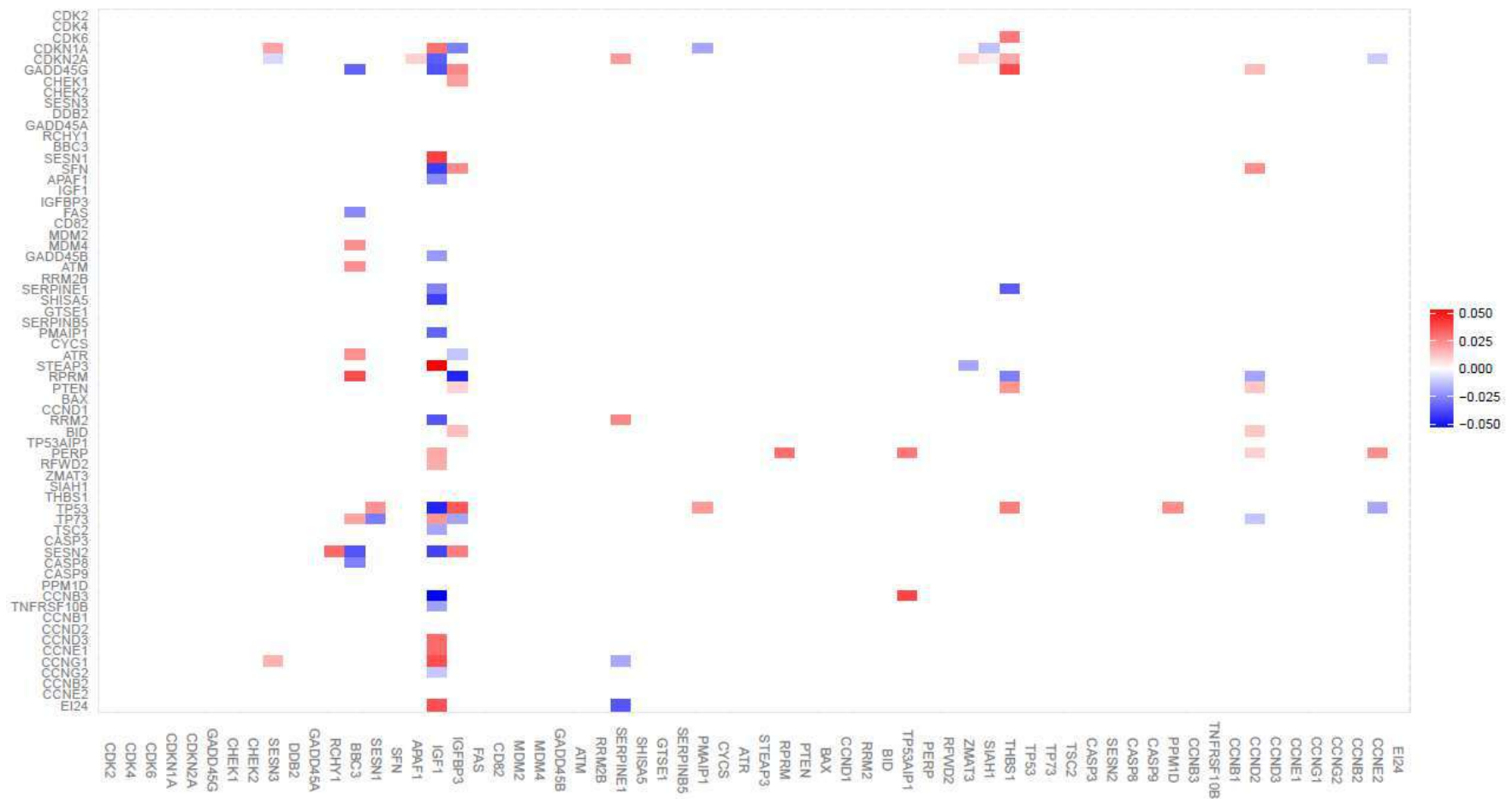
t

t+1

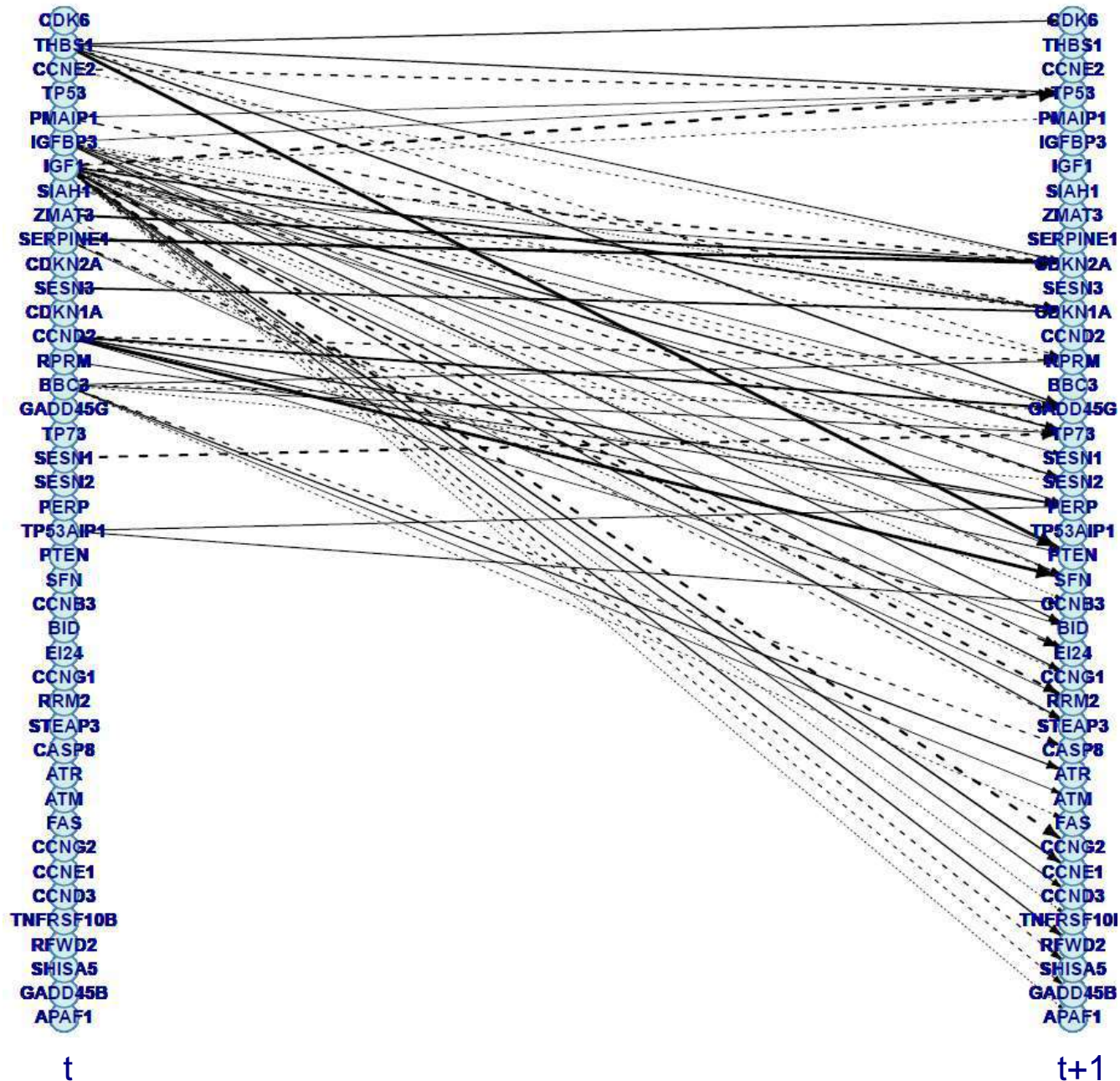


# Model parameters

- Each spot in the heatmap represents significant interaction between two genes



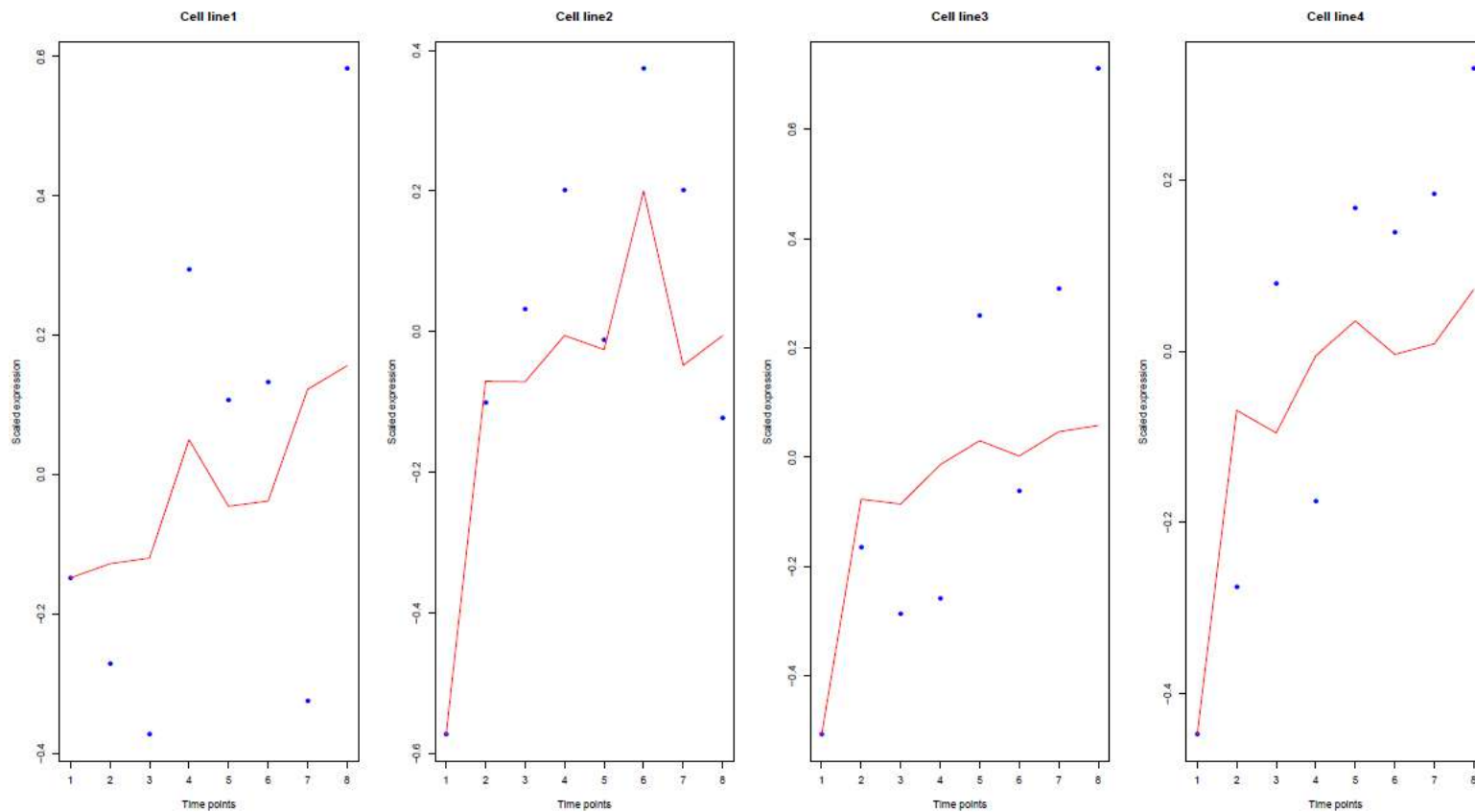
# Network





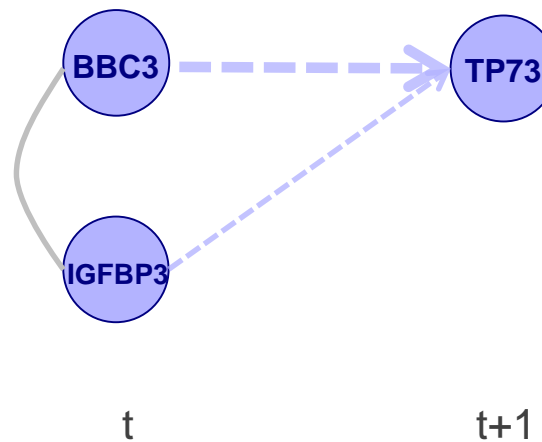
# Model fit

- Fit of the TP73 gene

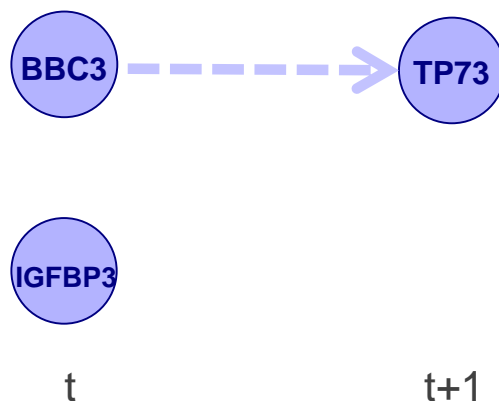


# Path decomposition

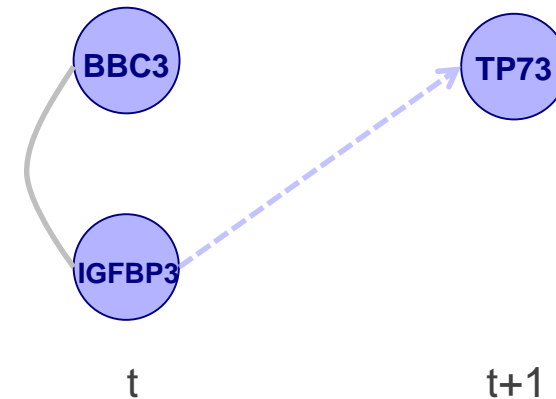
Contribution between BBC3 and TP73: -0.003168001



Contribution path 1: -0.002483485

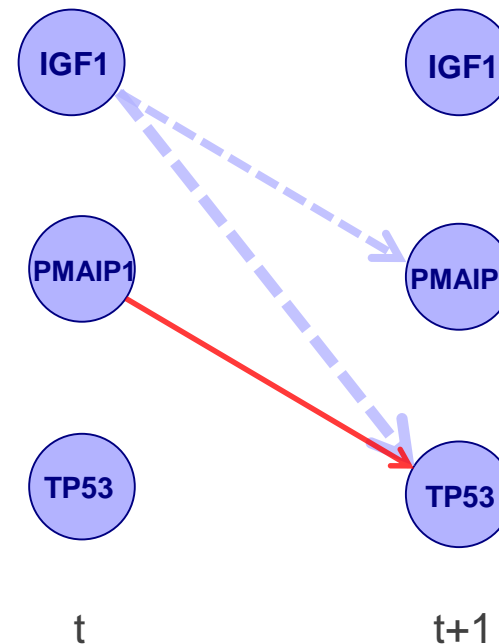
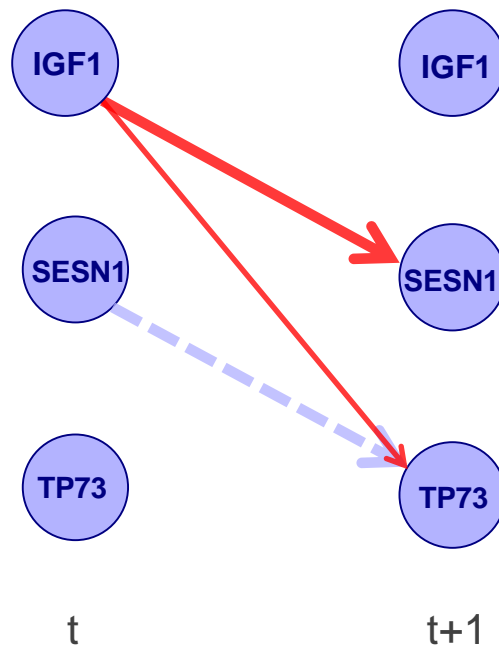


Contribution paths 2: -0.0006845158



# Motifs

- Framework in which particular function is achieved efficiently
- Carry out specific dynamic function
- Deregulation lead to cancer formation



# Summary

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- Identification of temporal differential gene expression for mRNA data (method is extended for DNA copy number and miRNA gene expression).
- Reconstruction of the temporal interaction between genes
- Path decomposition
- Future plans: reconstruction of the temporal interaction including DNA copy number and miRNA gene expression data.

**Thank you for your  
attention!**

# Network and data

