EVOLUTION AND CONTROLLABILITY OF CANCER NETWORKS: A BOOLEAN PERSPECTIVE

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IMB

Controllability of Systems

A dynamic system is controllable if it can be moved from an initial state to a desired final state by application of suitable inputs.

E.g. Controlling this car using steering wheel, accelerators, brakes and gears.

Structural Controllability of a Network

Factors contributing to controllability arranged as a network.

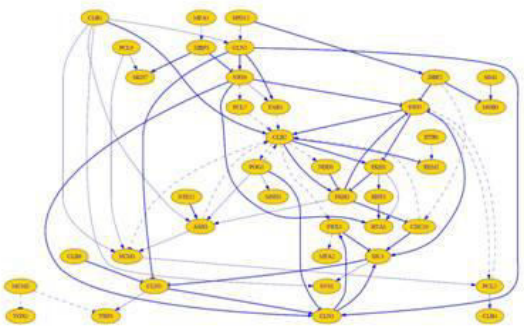
Structural controllability of the network through *input* nodes.

Usually the goal is to identify input nodes – *driver* nodes.

Structural Controllability of Real-world Networks

[Liu et al., *Nature* 2011]

Used a maximal-matching approach to identify the *minimum* dumber of drivers. Nodes not matched are the *driver nodes*.



Gene Regulatory Network

Large number of drivers.

Implications in identifying drug targets.

World Wide Web network

Few number of drivers.

A few individuals could bring down the WWW.

Social Network

Few number of drivers.

A few individuals could influence social connections.

Liu YY, Slotine JJ, Barabasi AL: Controllability of complex networks, *Nature* 2011

CONTROLLABILITY OF CANCER NETWORKS

Cancer: a robust dynamic system

- Cancer forms a robust system [Kitano 2004]
  - Capable of maintaining stable functioning (cell sustenance and proliferation) despite perturbations.

- Cancer forms a dynamic system
  - Progresses as stages over time with increasing aggressiveness and worsening prognosis – localized or *in situ,* regional spread, distant spread or metastasis.

Kitano H, Cancer as a robust system: implications for anticancer therapy, *Nature Reviews Cancer* 2004.

Controllability of cancer networks

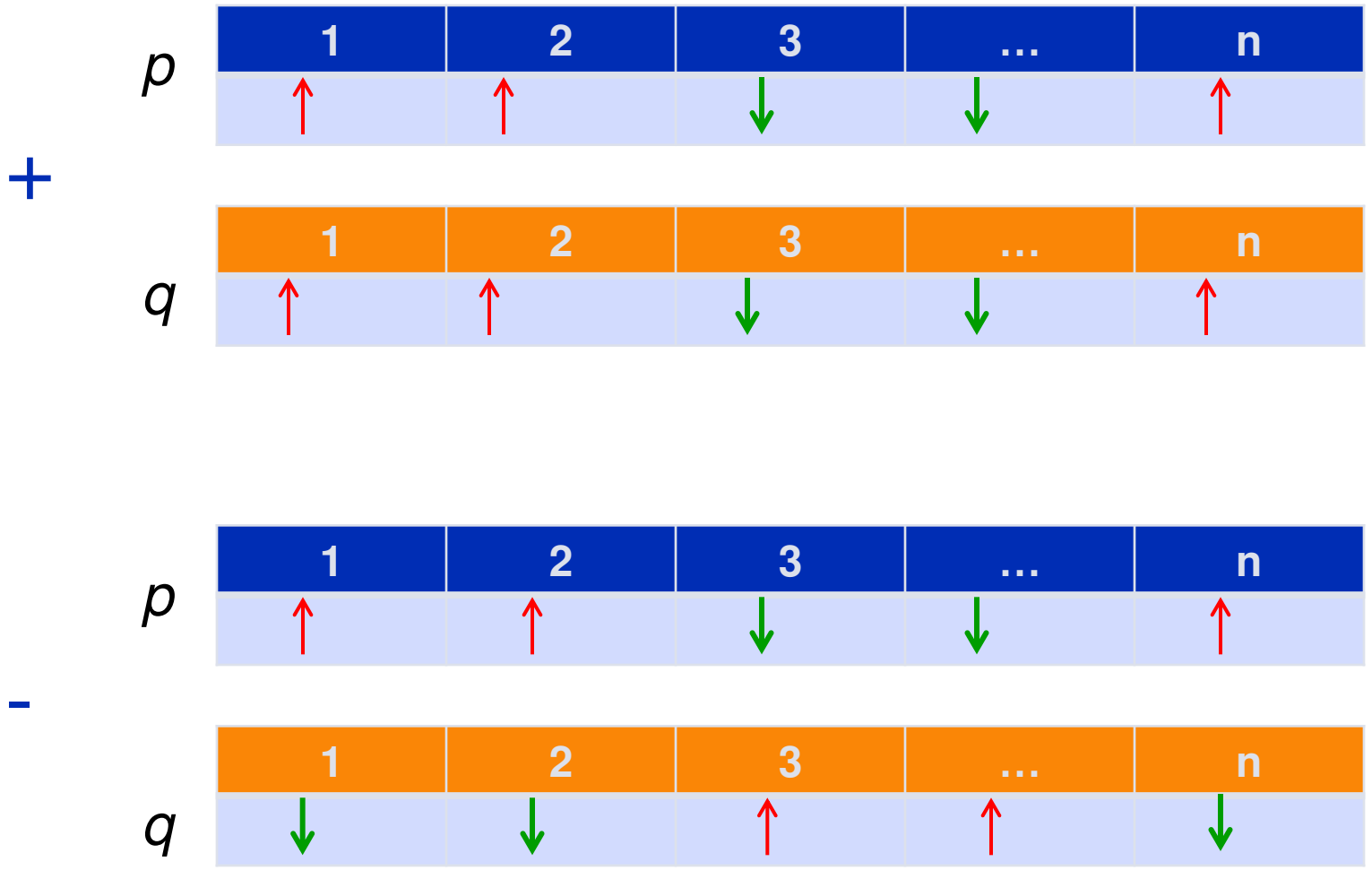
- Cancer network
  - A network of factors contributing to the robustness and dynamics of the cancer system
  - One obvious thing is the molecular network – of gene regulatory or protein-protein interaction

- Driver nodes
  - Nodes controlling the *transition* of the cancer network over time
  - Critical to identify "soft-points" to break the robustness of cancer

A novel Boolean model for controllability of cancer networks

BOOLSPACE

Gene co-expression across samples



Now see this…

When the Boolean logic is SATISFIED, the relationships reflect gene co-expression patterns.

p	*q*	XNOR
0	0	1
0	1	0
1	0	0
1	1	1

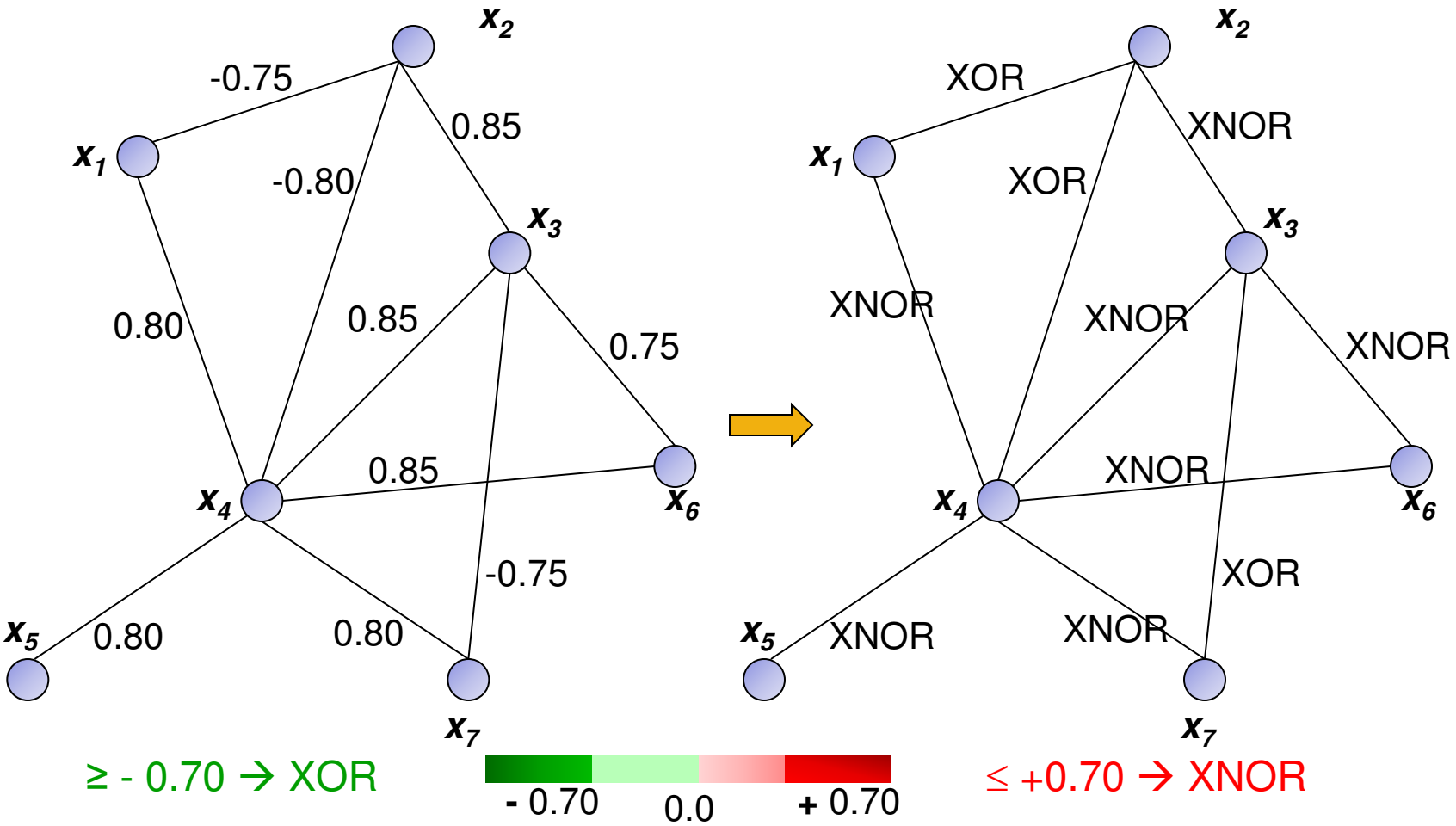
+

p	*q*	XOR
0	0	0
0	1	1
1	0	1
1	1	0

-

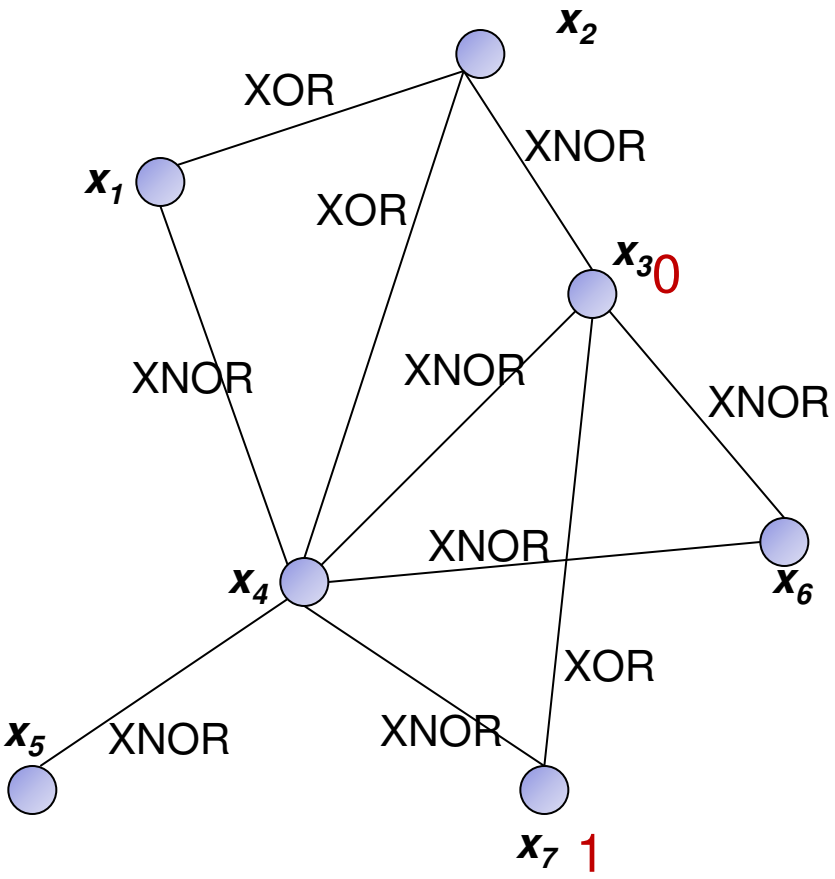
Boolean modeling of the cancer network

A novel way to integrate PPI and gene-expression datasets



Boolean modeling of cancer network

Satisfying the Boolean network

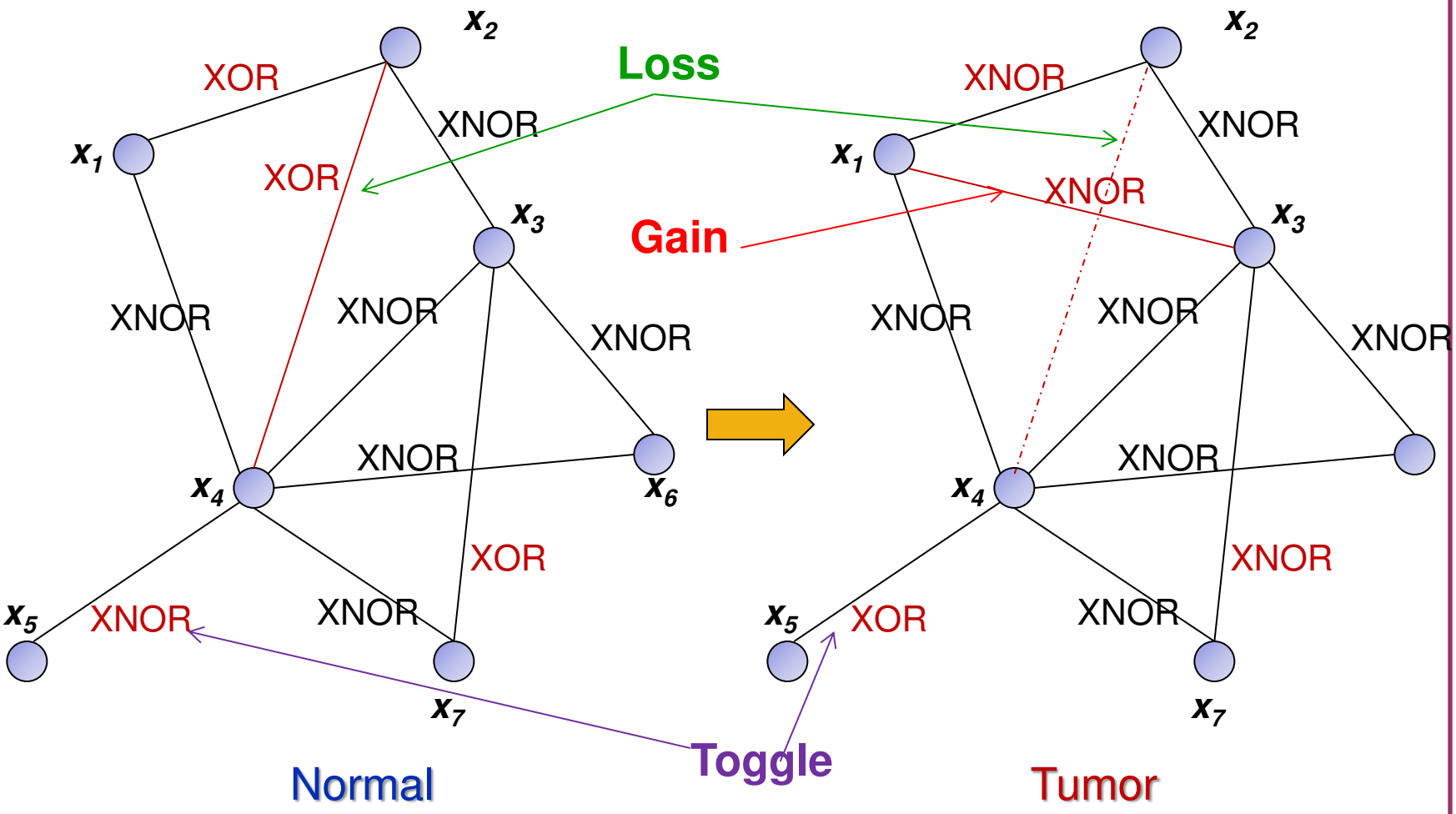


x_1	x_2	x_3	…	x_7
1	0	0	…	1

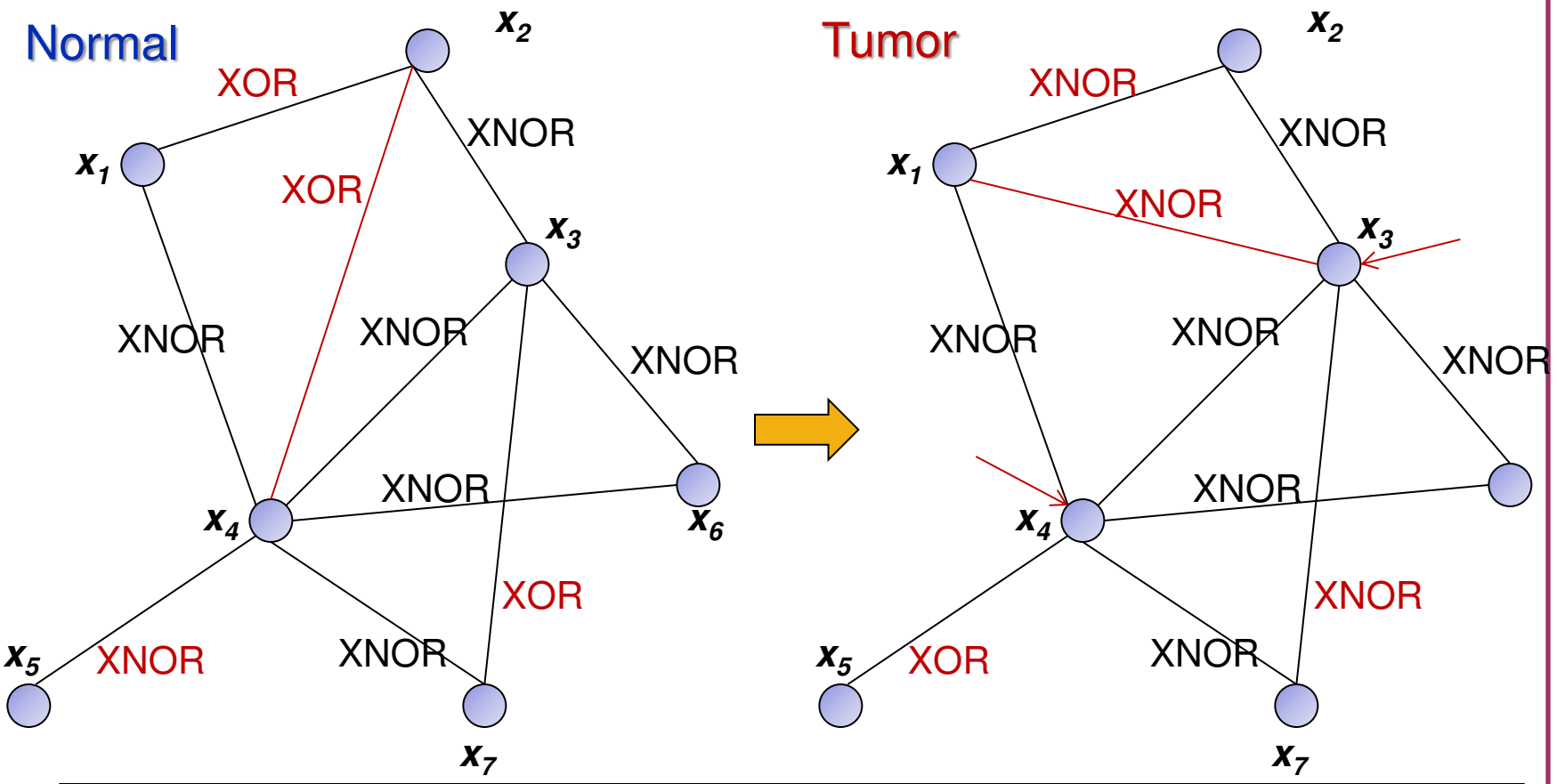
In an XOR-XNOR network, polynomial number of SAT assignments.
In a general network, O(2^n) possible assignments.
We pick the one with minimum 1's.

Boolean modeling of cancer network

Capturing rewiring between conditions



Which genes are "flipped" as a result?



Genes that need to be flipped to re-satisfy the network form the driver genes

x_1	x_3	x_4	…	x_7
1	0	1	…	1

x_1	x_3	x_4	…	x_7
1	1	0	…	1

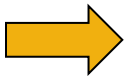
Which set of genes to flip?

Our hypothesis:

The *minimum* set of genes to be flipped to re-satisfy the network form the driver genes.

x_1	x_3	x_4	…	x_7
1	0	1	…	1

Normal



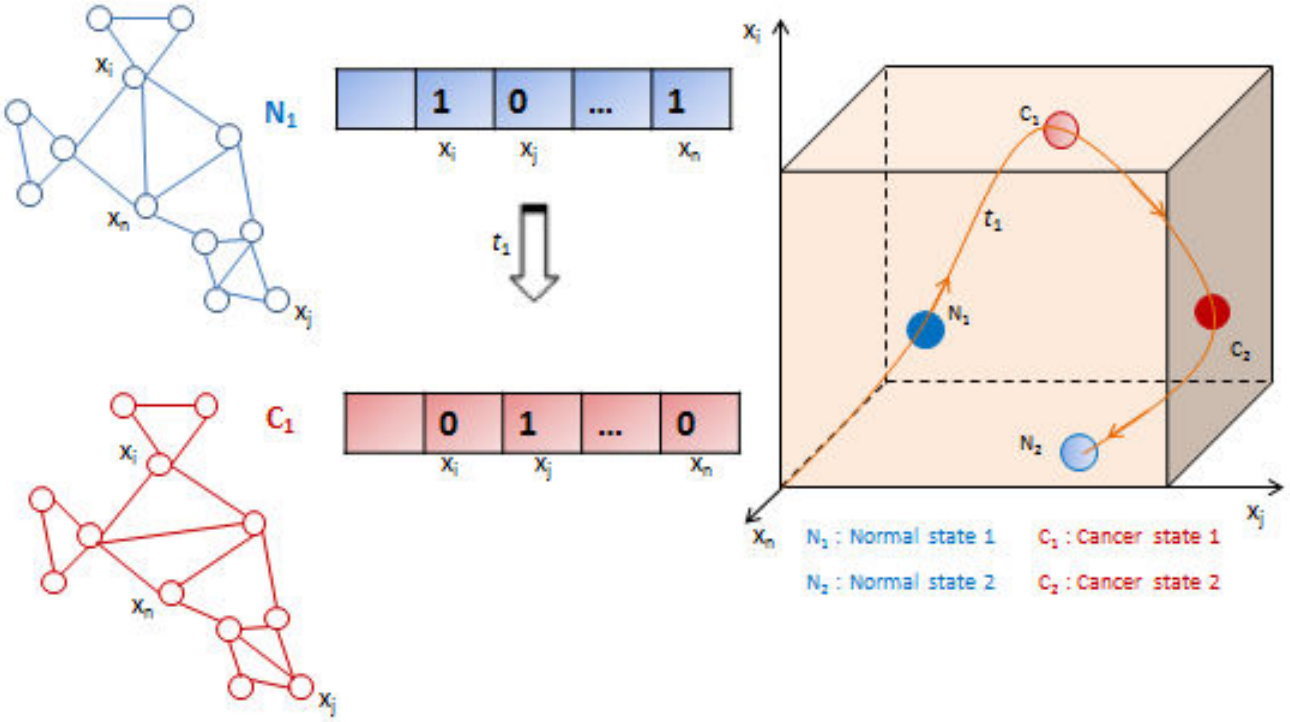
x_1	x_3	x_4	…	x_7
1	1	0	…	1

Tumor

Defines a “distance” between the two conditions (Hamming distance)

Modeling the cancer state space

- Cancer state space – the state space of cancer containing different stages/forms of cancer over time.
- Modeled as the state space of molecular networks over time.



QUICKLY SOME RESULTS

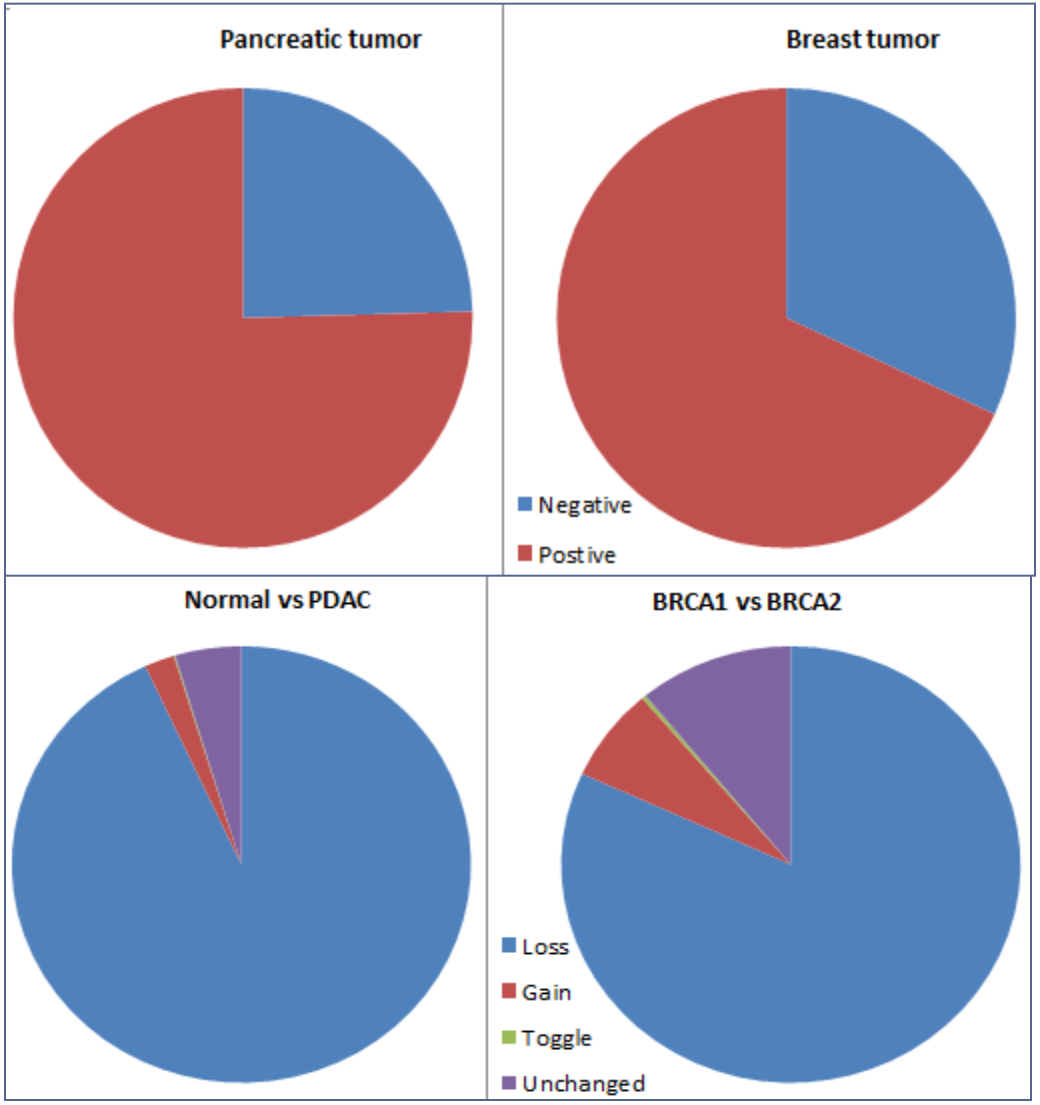
Three case studies

- Pancreatic normal vs tumour
  - Pancreatic ductal adenocarcinoma (PDAC)
- Two familial breast tumours
  - BRCA1 and BRCA2 tumours
- Post traumatic spinal cord injury in rats
  - 0hr, 4hrs, 72hrs, 7days and 28days

The PPI and gene-expression datasets

- Human PPI network
  - 5824 proteins and 29600 interactions (d_avg = 10.16)
- Mammalian PPI network (mouse and rat)
  - 1146 proteins and 3215 interactions (d_avg = 5.61)
- Gene expression samples
  - 39 normal-PDAC matched samples
  - 19 BRCA1- and 30 BRCA2-tumour samples
  - At least 15 samples per time point in spinal-cord injury: 0hr, 4hr, 72hr, 7d and 28d.

Analysis of network edits between conditions



Normal vs PDAC

-- significant loss in interactions

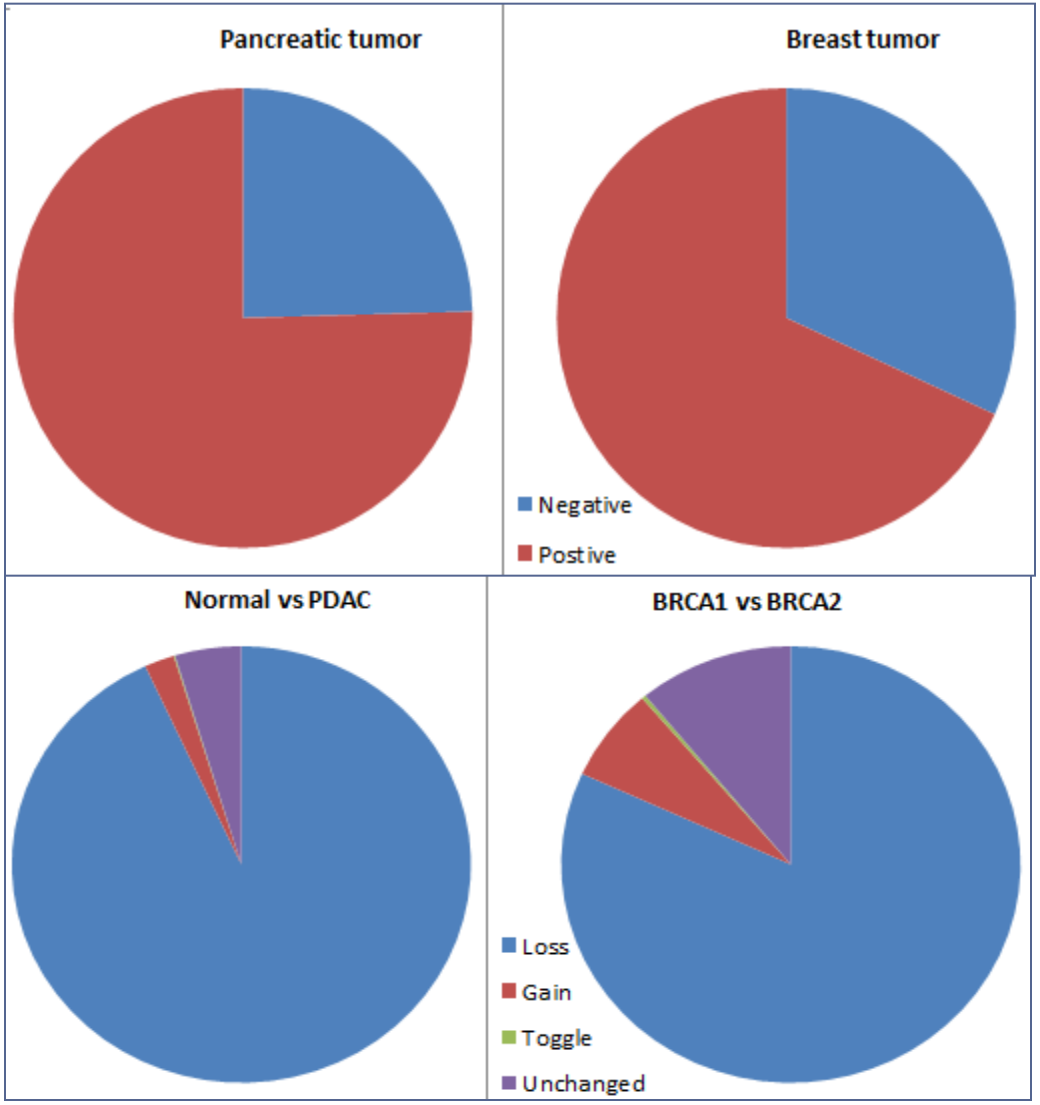
-- indicates loss in cellular machinery

BRCA1 vs BRCA2

-- loss as well as gain.

-- does this indicate that rewiring as a basis for heterogeneity among the two breast tumors.

Analysis of network edits between conditions



Enriched significantly ($p < 0.001$) for DNA damage repair and Cell cycle pathways.

Pancreatic:

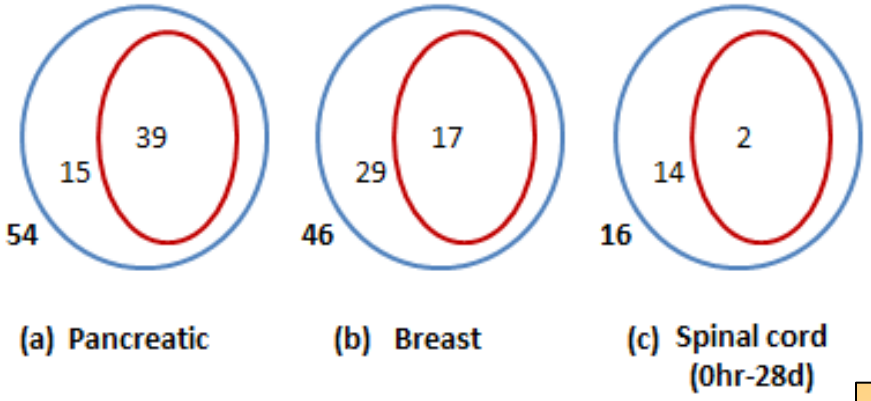
TGFβ, Wnt signalling, Cell cycle -- strongly implicated in pancreatic tumors.

Breast:

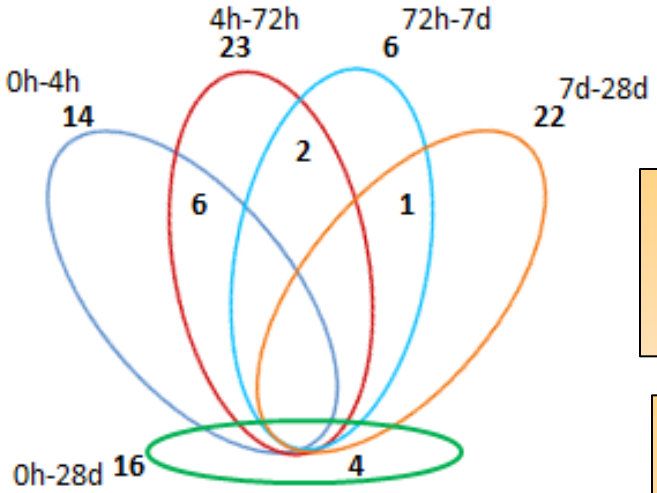
Homologous recombination, Cell cycle

-- HR houses BRCA1/BRCA2

Analysis of genes flipped between conditions



(a) Pancreatic (b) Breast (c) Spinal cord (0hr-28d)



(d) Spinal cord (trajectory)

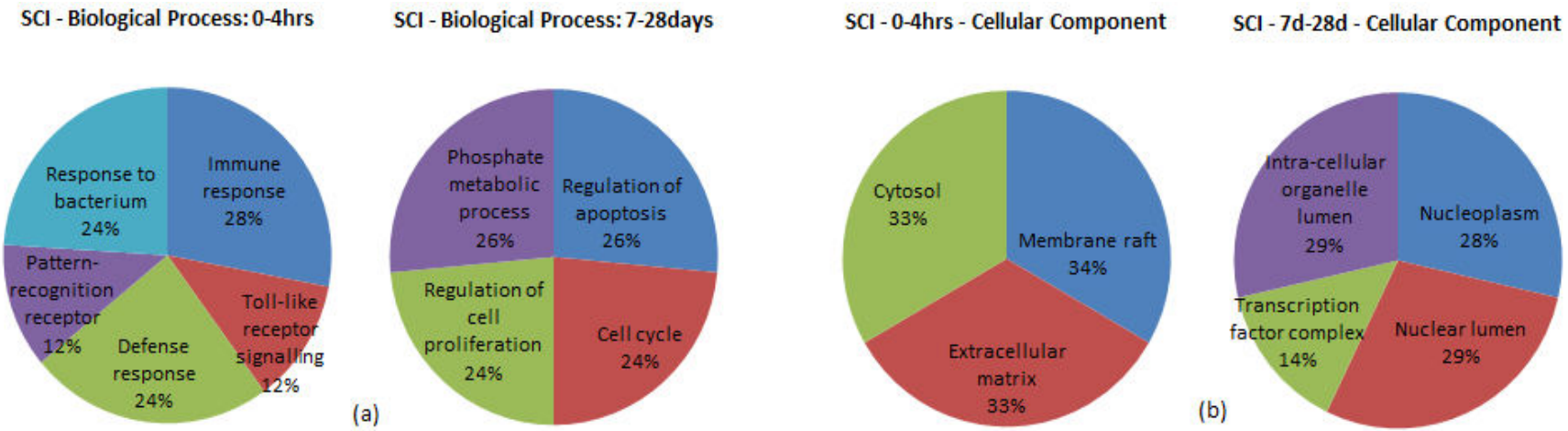
Many of the flipped genes are in fact differentially co-expressed with key genes involved in tumors.

1.Different set of genes flipped at different stages of SCI.

2. Many cell cycle progression genes involved in SCI

3. Considerable overlap between pancreatic tumour and SCI genes.

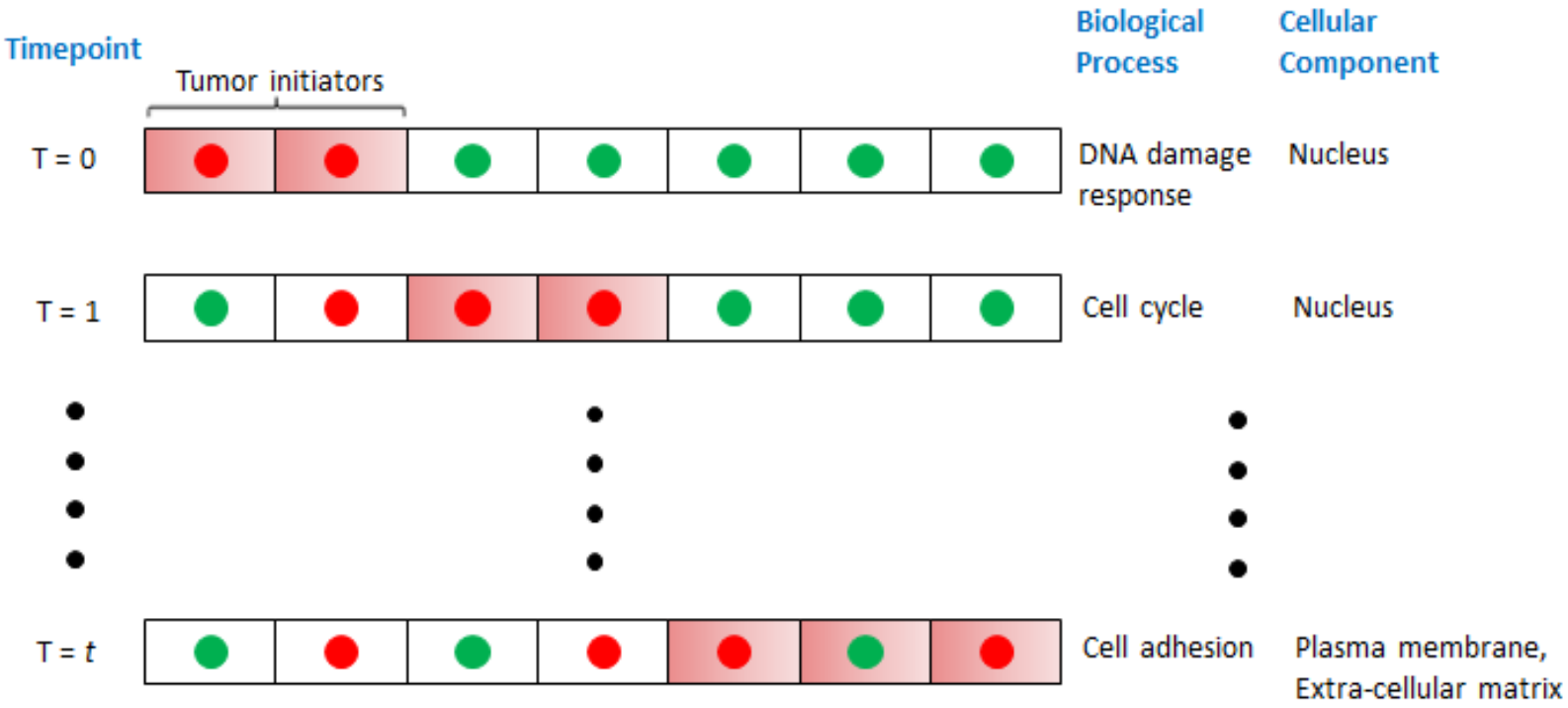
Biological Process and Cellular Component across time in spinal cord injury



The enrichment for genes during **initial** and **final** stages are **strikingly different**. Initial stages mainly in *defence/immune response*, final stages in *cell cycle progression*.

Our Hypothesis:

"Passing the baton" among driver genes

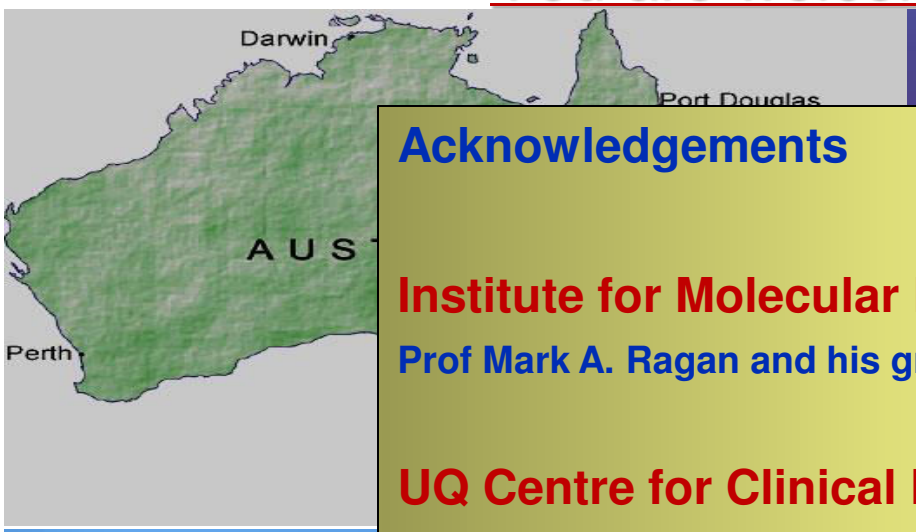


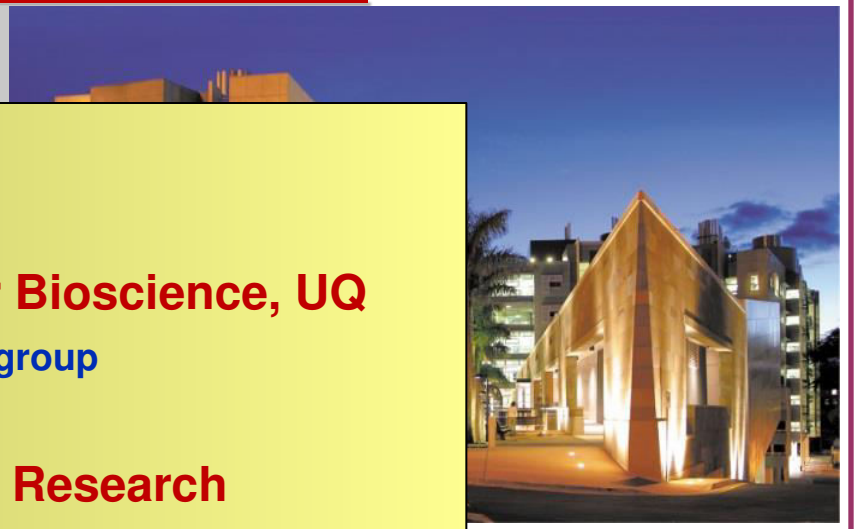
Contributes to the robustness of cancer

Targeted therapy should involve knowledge of timepoint/stage.

Thank You…

You are welcome to visit….





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