Gene Regulatory Networks for Cellular Differentiation - a Random Boolean Network Approach

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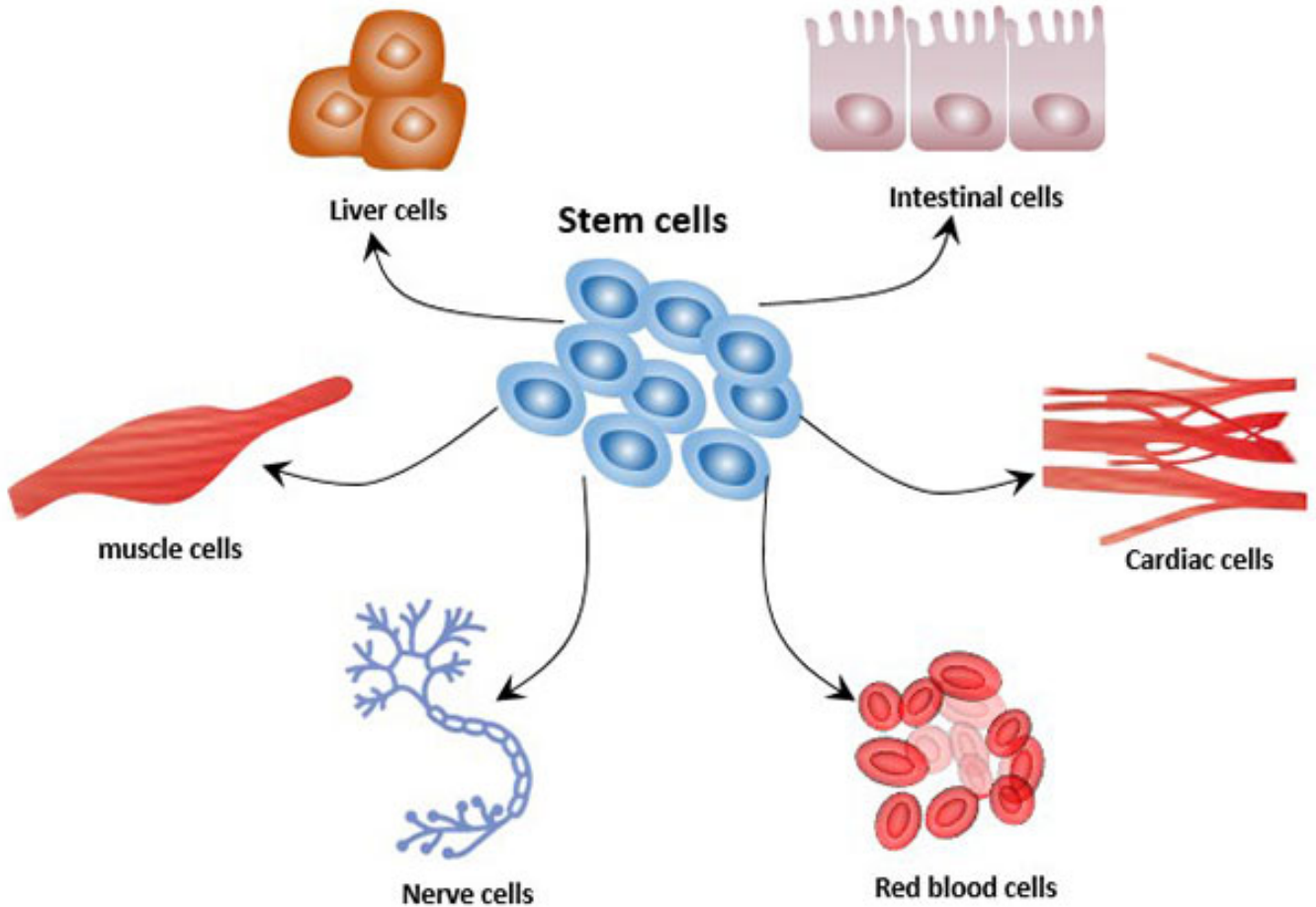
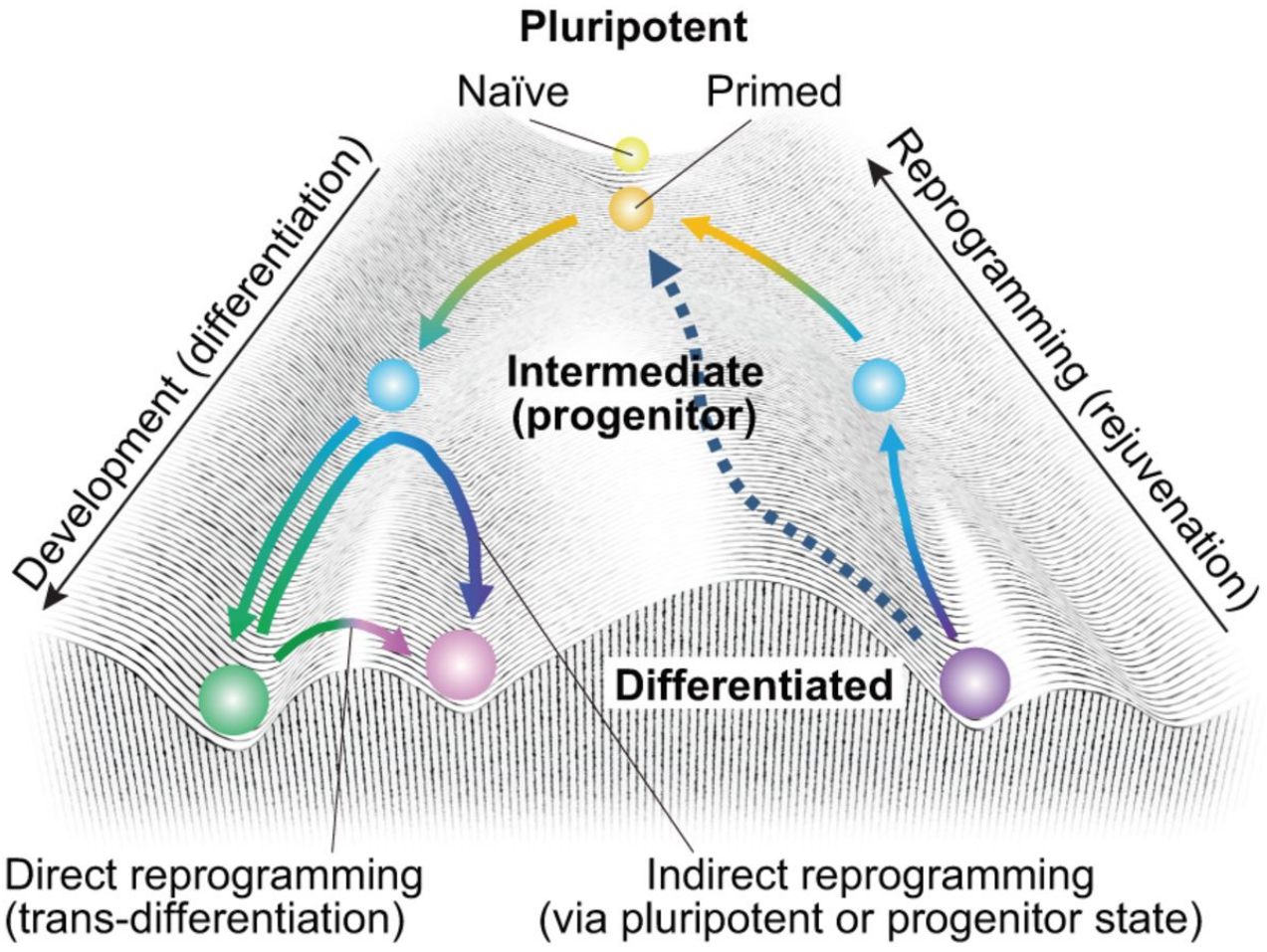
Introduction

Cellular Differentiation

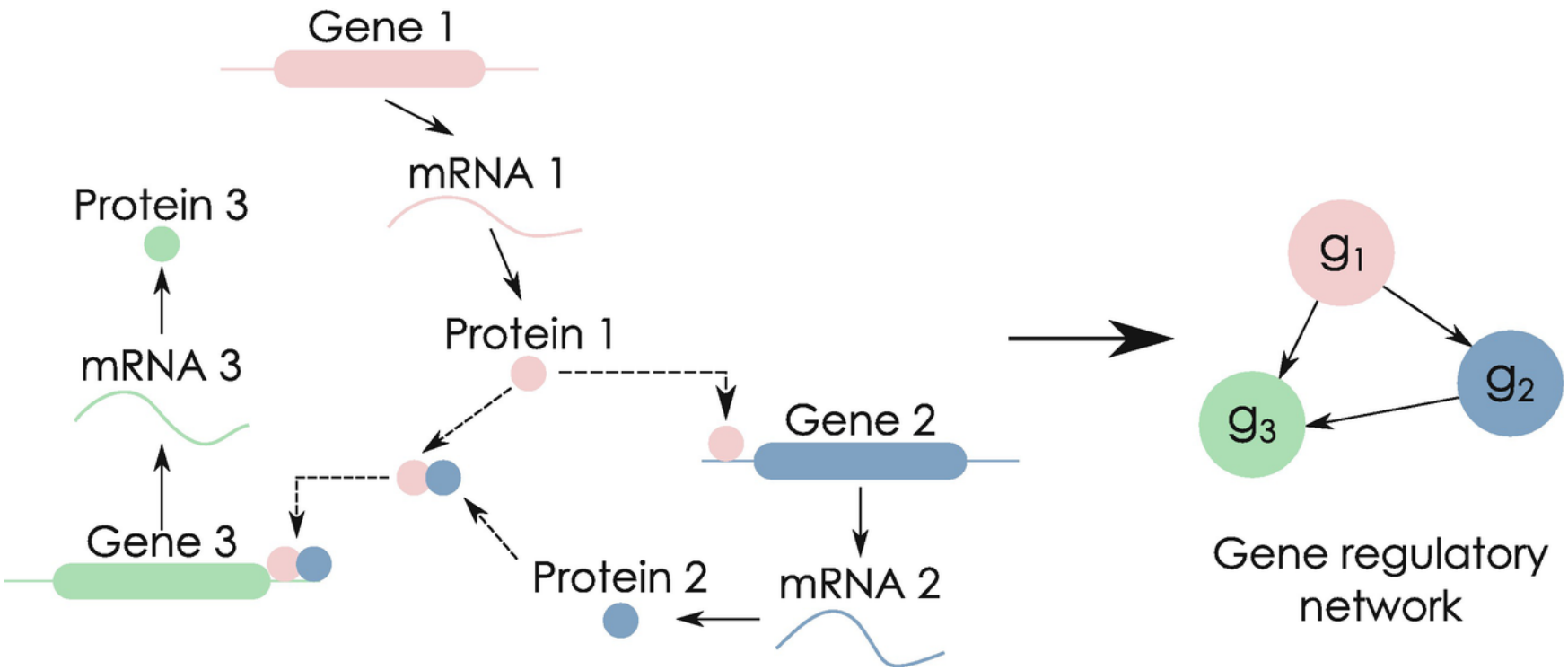


Fitness Landscape



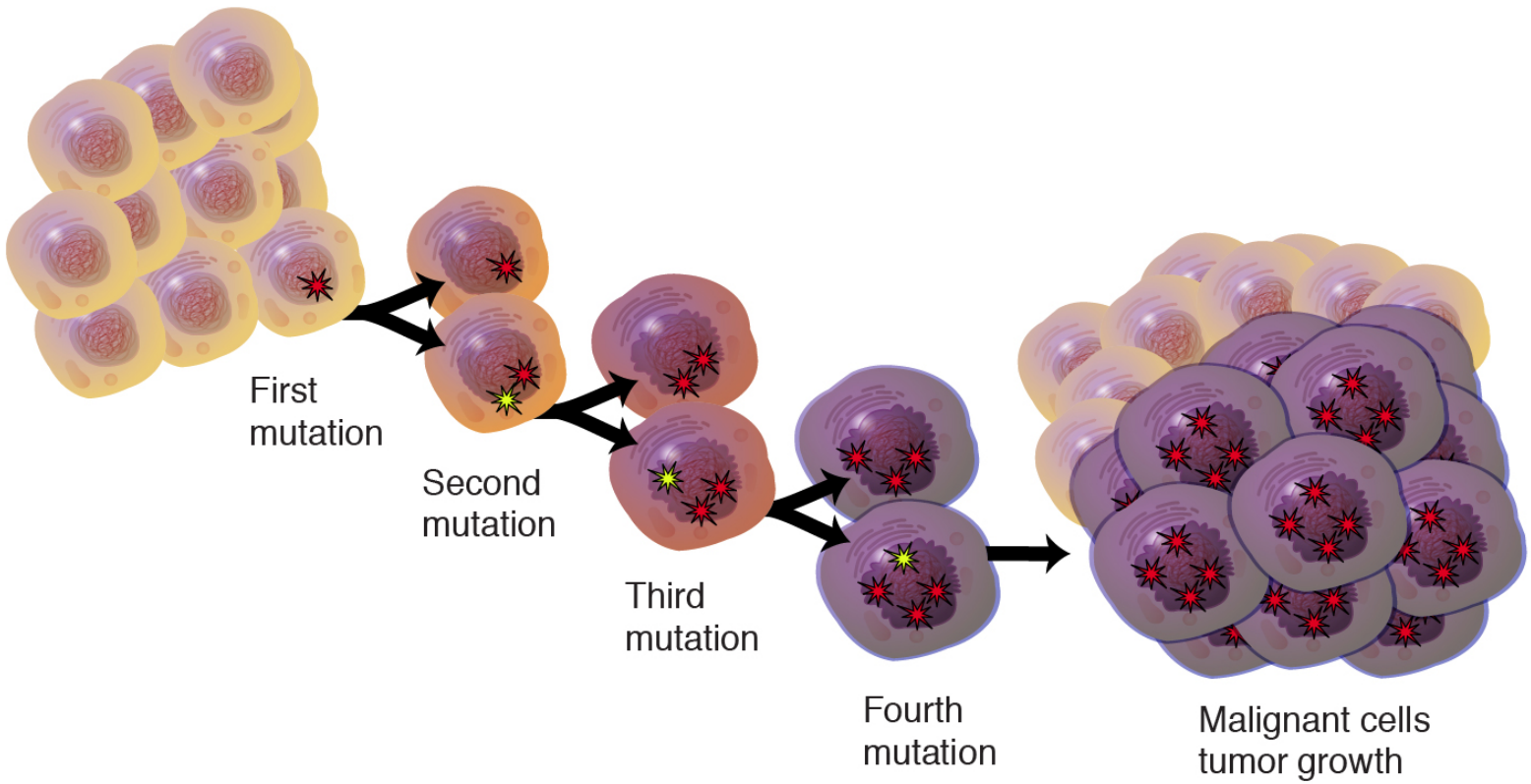
Gene Regulatory Networks

Cellular differentiation and other mechanisms in cell dynamics are governed by the gene regulatory networks (GRN)



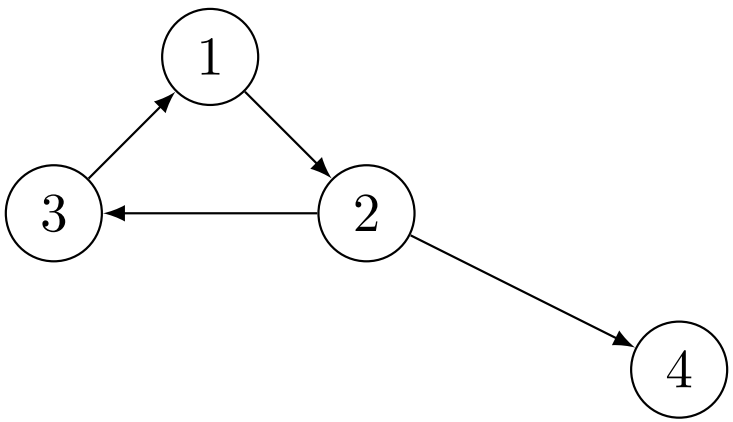
Mutation

Studies confirmed that during the process of GRN we can have mutations in the networks which cause the birth of cancer cells



Modelling GRN - Random Boolean Networks

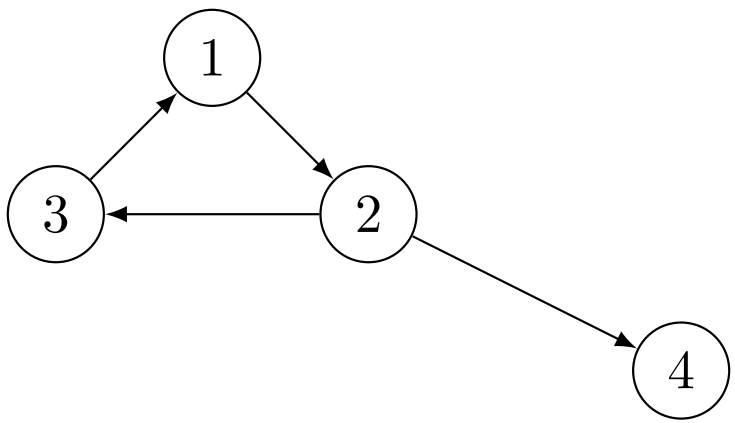
Stuart Kauffman proposed to model GRN using Random Boolean Networks (RBN) which are networks in which each gene is a node in a directed graph and can be "on" or "off", so we have that each node σ_i can have values 0 or 1.



RBN Dynamics

The evolution of the state of each node $\sigma_i(t)$ is given by a Boolean function $\Lambda_i(\sigma_{i_1}, ..., \sigma_{i_k})$ of K parameters, which are the incoming links from the other nodes in the network:

$$\sigma_i(t+1) = \Lambda_i(\sigma_{i_1}(t), ...\sigma_{i_k}(t))$$



RBN Dynamics

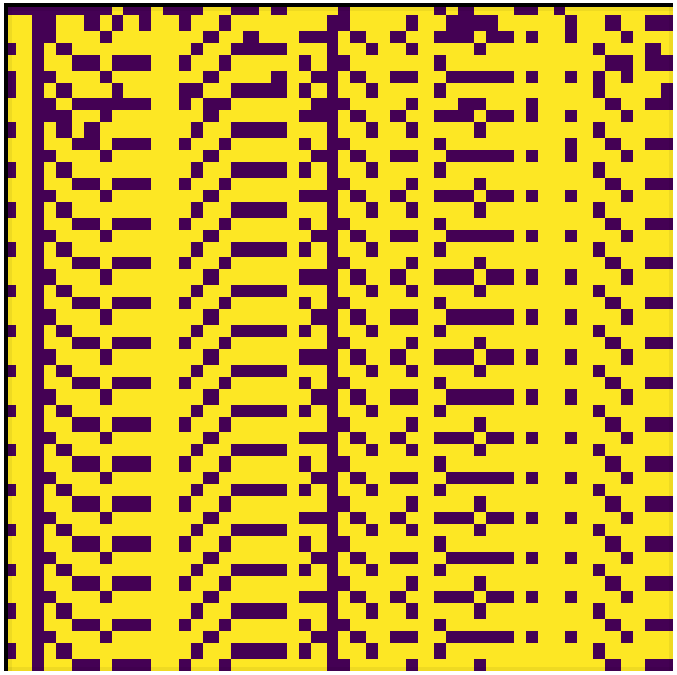


Figure: Example of a RBN with $N = 50$ and $K = 1$.

State space

For example we can consider an evolution of the network with number of nodes $N = 4$ in this form:

$$1111 \to 0011 \to 0100 \to 1111$$

If we interpret the bit sequence characterizing the state of the network as a number in binary notation, the sequence of states can also be written as

$$15 \to 3 \to 4 \to 15$$

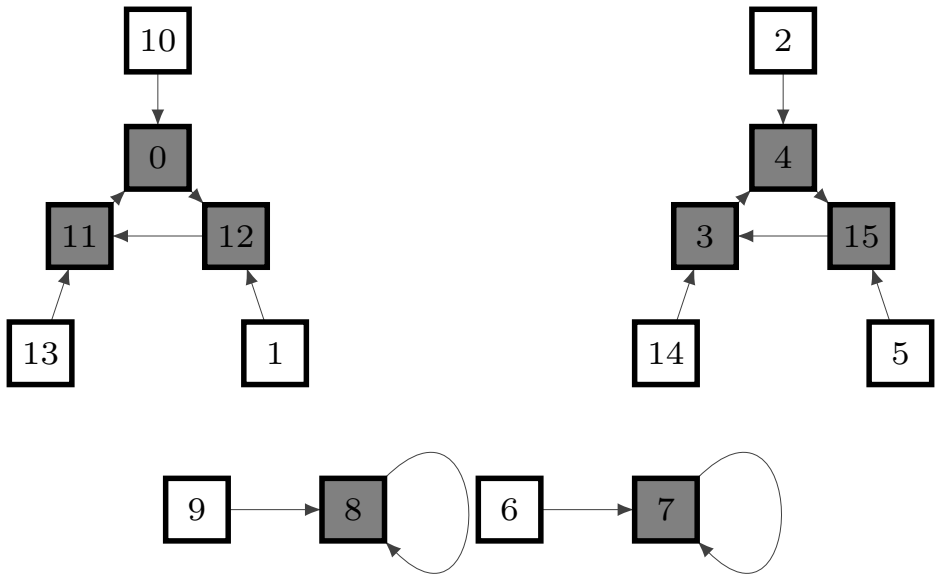
Since the update rule is deterministic, the same state must always be followed by the same next state:

$$15 \to 3 \to 4 \to 15 \to 3 \to 4 \to 15 \to \ldots$$

So starting from some initial state, the network performs a trajectory in state space and eventually arrives on a periodic sequence, called *attractor*

Attractors

Now, we can represent the different configurations in a network:



Perturbations

Flipping a bit:

$$1100 \rightarrow 1110$$

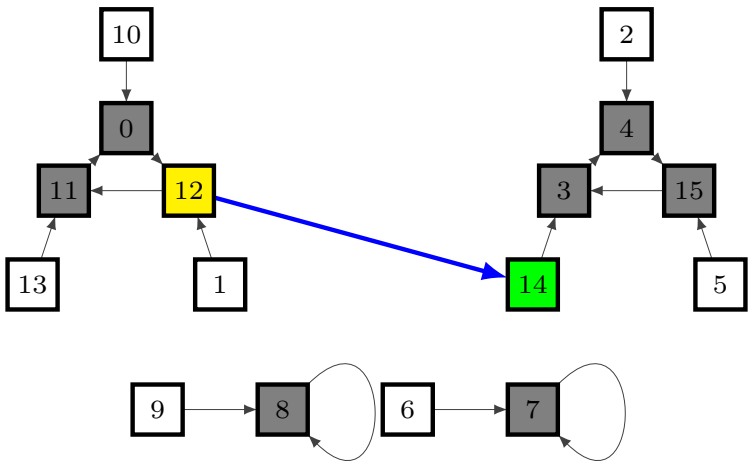


Figure: Jump from one attractor to another one in the state space

Attractors

We can construct the network of the attractors, where the links connect different attractor after a perturbation:

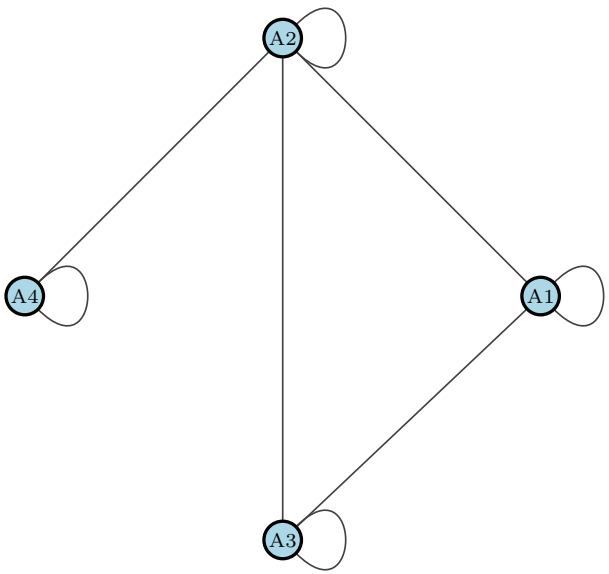
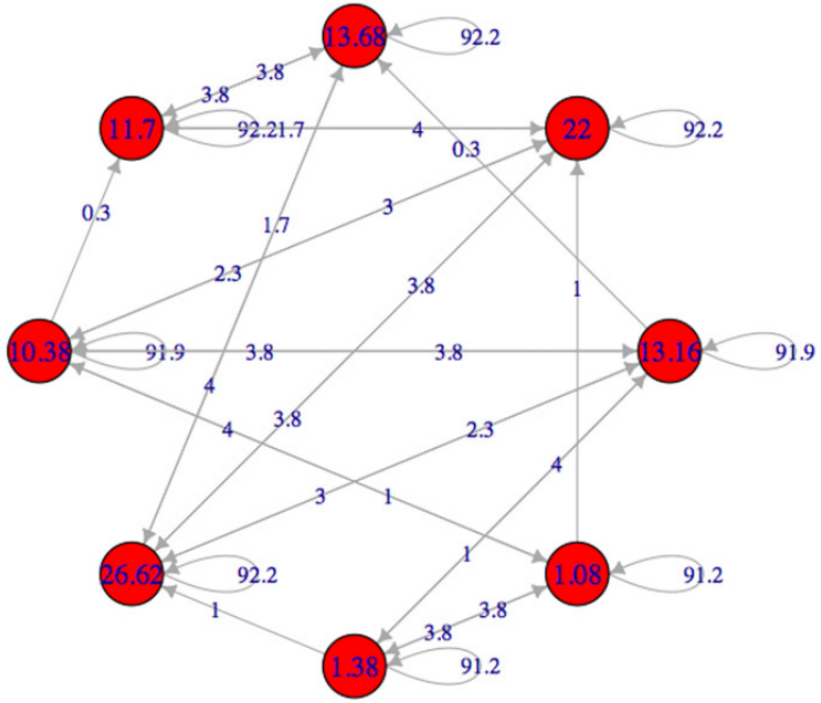


Figure: Network of attractors of a RBN

Stochastic process



From the network of the attractors, we can analyze the different frequencies of transtion between an attractor from another one, and build a stochastic process.

Conclusions

From this model, we can associate different attractors to different type of cells, and in particular cancer cell can be considered as little attractors in the network.
So the aim of this thesis work is to build a stochastic process and a random walk on a network of attractors of a RBN.