Modelling cell differentiation using stochastic dynamical systems on graphs

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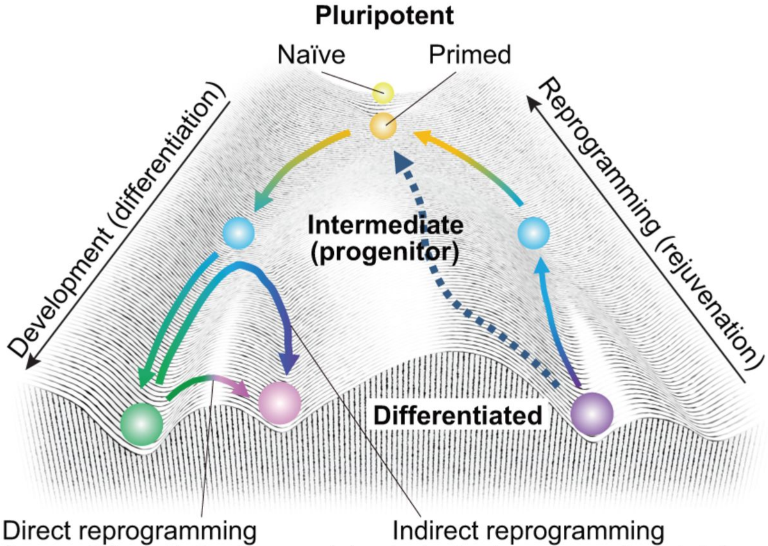
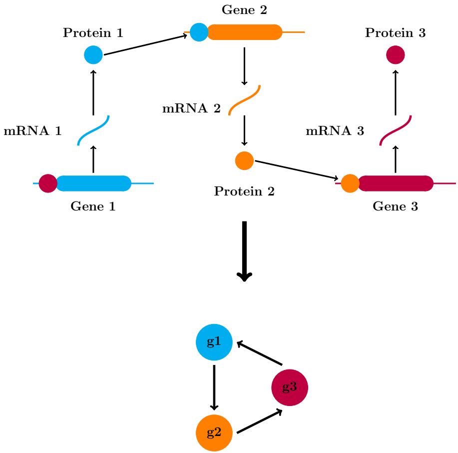
Waddington potential



Introduction - Gene Regulatory Networks

Gene Regulatory Networks for cell differentiation



Random Boolean Networks

Random Boolean Networks are networks in which each node can have only the values 0 or 1:

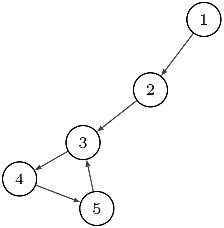
$$\sigma_i(t) \in \{0, 1\}$$

And the discrete evolution of the network is given by:

$$\sigma_i(t+1) = \Phi_i(\sigma(t)) = \Theta\left(\sum_j A_{ij}\sigma_j(t)\right)$$

where A is the connectivity matrix and $\Theta(x)$ is the Heaviside function.

Random Boolean Networks

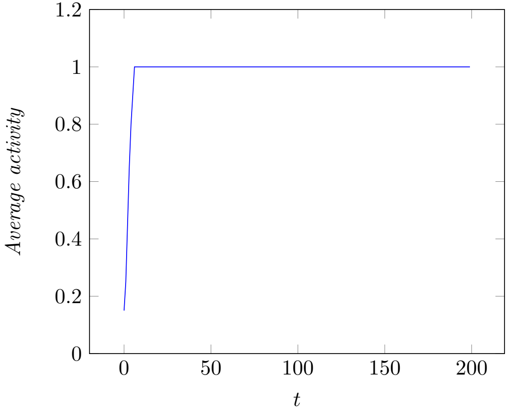


The connectivity matrix A of this network will be constructed as follows:

$$A = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

The model - Deterministic Evolution

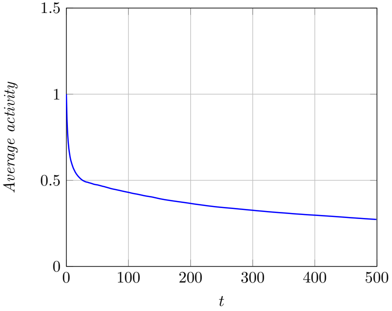
Deterministic evolution of the activity:



Discrete evolution

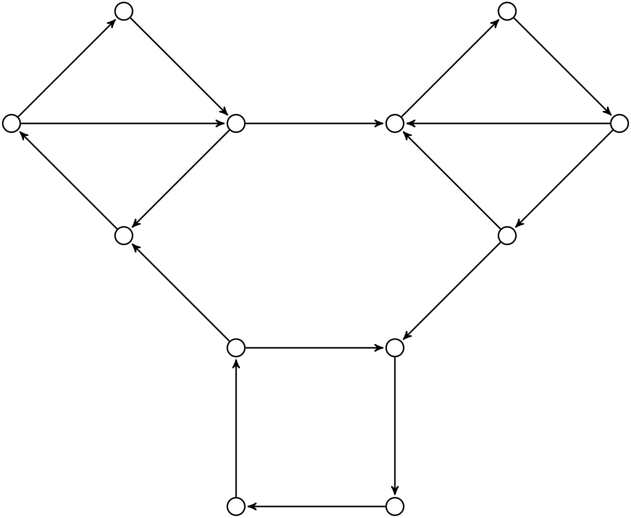
The system is deterministic, but during the evolution we can add noise to the system:

1. internal noise, which hinibits the activation of the nodes
2. envinromental noise, which can activate some nodes in the network



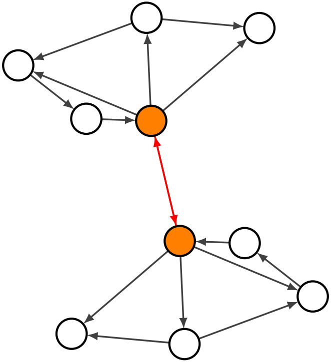
The model - Multiple cluster networks

We can construct networks with multiple clusters



The model - Double-cluster networks

In this work we consider networks made by two clusters which hinibit each other: A subnetwork hinibits the other:

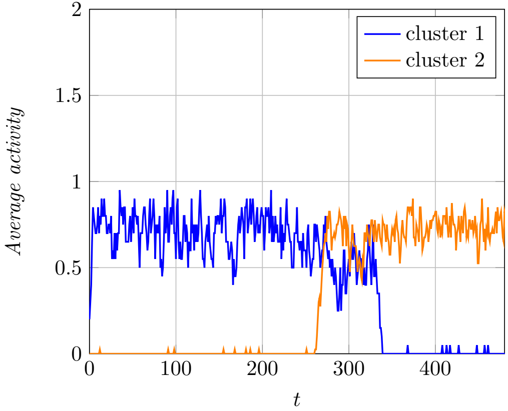


The two clusters are connected by negative links.

Double-cluster networks

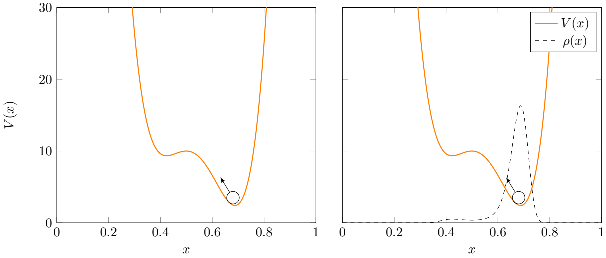
We can introduce a metadynamics where $\nu_k(t)$ is the state of the k subnetwork and we have a relation

$$\nu_k(t + \Delta t) - \nu_k(t) = \phi(\nu_k(t)) - \gamma\left(H_{kj}\nu_j(t)\right)$$



Kramer Transition Rate Theory

$$dx = -V'(x)dt + \sqrt{2T}dw_t$$



$$k_{a\to c} \simeq \frac{\omega_a \omega_b}{2\pi} e^{\frac{V_b - V_a}{T}}$$

So the log of transition rates gives us an estimate for the potential $V(x)$.

The model related to Kramer Theory

Given an ensemble of double-cluster networks, we can make an estimate for a double well potential: The local minima of the potential are the stationary states of the two clusters of the networs. We expect that the potential V depends on the size and on the number of links per node:

$$V = V(N, K)$$

Ensemble

To measure the activity transition, we can define the total activity of the network:

$$I(t) = \nu_2(t) - \nu_1(t)$$

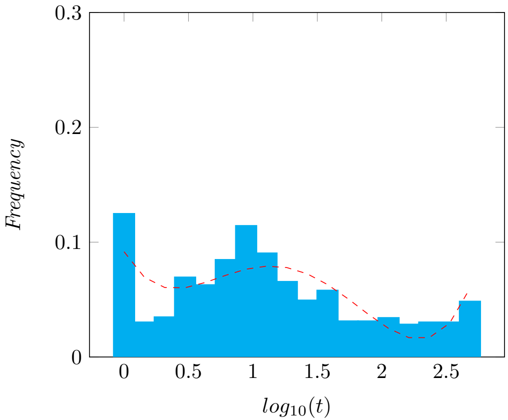
with $\nu_k(t) \in [0, 1]$ and $I(t) \in [-1, 1]$. Starting from an initial condition in which only the second cluster is active:

$$\rho_0(I) = \delta(I - 1)$$

Every time the activity passes from one cluster to the other, we register the time of transition.

Evolution of the system

Transition times



The histogram of transition rates (in logarithmic scale) shows a possible form of the potential for the double-cluster networks.