Modeling Cell Fate

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Exercise Sheet 3

Due: Jun 16, 2015 10:00 am

Submission

- You are advised to work in groups of two people. If necessary, we will suggest teammates.
- Submit your solutions on paper at the beginning of the lecture in the lecture hall or in Room 3.02, both E2 1. Alternatively you may send an email with a single PDF attachment to maryam.nazarieh@bioinformatik.uni-saarland.de. Late submissions will not be considered.
- Do not forget to mention your names/matriculation numbers.
- Discussion of this exercise will be on Tuesday, Jun 23th at 12:45 in the lecture room (E2 1 007).

Exercise 3.1: A Two-ODE System (50 points)

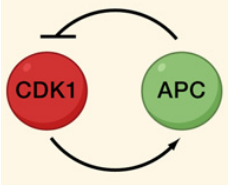

Figure 1: Schematic of the Two-ODE model.

The ODE for CDK1 is defined as:

$$\frac{dCDK1}{dt} = \alpha_1 - \beta_1.CDK1.\frac{APC^{n1}}{K_1^{n_1} + APC1^{n_1}}$$

In words, CDK1 is activated by a constant rate of cyclin synthesis (α_1), while its inactivation by APC is described by a Hill function. The inactivation rate is proportional to the concentration of CDK1 times a Hill function of APC.
The ODE for APC activation is:

$$\frac{dAPC}{dt} = \alpha_2.(1 - APC)\frac{CDK^{n_2}}{K2^{n_2} + CDK1^{n_2}} - \beta_2.APC$$

For APC, the activation by CDK is proportional to the concentration of inactive APC (assuming that the total concentration of active and inactive APC is constant) times a Hill function of CDK1 while the rate of inactivation of APC is described by simple mass action kinetics.

(a) Implement the model in Python (or similar). Start with all concentrations = 0 and simulate with $t = [0; 25]$. Use the following parameters.

- $\alpha_1 = 0.1$

- $\alpha_2 = \beta_1 = 3$
- $\beta_2 = 1$
- $K_1 = K_2 = 0.5$
- $n_1 = n_2 = 8$

(b) Plot both the CDK1 and APC activity against time. Explain the oscillation (if any) and the behaviour.

(c) Investigate the oscillation behaviour by plotting the concentration of CDK1 against APC. Also, plot the nullcline curves, i.e. plot the steady state concentration of CDK1 with fixed APC using the interval [0;1] and vice versa. Those curves describe the concentration change if there was no regulation of APC by CDK1 (and vice versa, see Figure2). Show the ranges for x,y = CDK1, APC between [0;1]. Explain your findings.

(d) Repeat the previous steps with different concentrations for APC and CDK. Explain your conclusions.

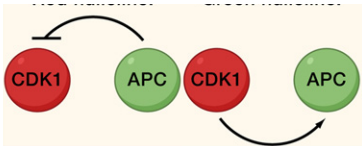

Figure 2: The nullcline models

Exercise 3.2: Boolean Network (50 points)

In the following, we consider the yeast cell cycle network described in Orlando et al: Global control of cell-cycle transcription by coupled CDK and network oscillators. Nature 453, 2008.
The statements describe the dependencies of the network:

- MBF is activated by CLN3.
- If CLN3 or MBF is transcribed and at least one of the inhibitors YOX1 and YHP1 is inactive, SBF is active.
- YOX1 is active if both its transcription factors MBF and SBF are present. The same applies to HCM1.
- YHP1 can be activated independently by MBF and SBF.
- SBF and HCM1 jointly activate SFF.
- ACE2 require SFF to be active. The same applies to SWI5.
- CLN3 requires the presence of SWI5 and ACE2 and the inactivity of at least one of the inhibitors YOX1 and YHP1 to be activated.

(a) Construct a Boolean network (conditional tables) from these statements and save it to a file boolean_nw.txt. Load the network into BoolNet using the function loadNetwork and visualize its wiring with plotNetworkWiring(). (BoolNet is an R package that provides tools for assembling, analyzing and visualizing synchronous and asynchronous Boolean networks as well as probabilistic Boolean networks.)

(b) Plot the trajectory starting from (MBF, CLN3, YOX1, YHP1, SBF, HCM1, SFF, ACE2, SWI5) = (0,1,1,1,1,1,1,1,1) for next two state transitions. (solve on paper)

Have fun!