

BE 150 Spring 2018

Homework #7

Due at the start of lecture, May 23, 2018.

Problem 7.1 (Controlling p53 levels, 70 pts).

In class (lecture 16), we discussed the work from Galit Lahav's lab in which they investigated how temporal dynamics of p53 controls cell fate in MCF-7 cells. Naturally, p53 levels oscillate upon exposure to stress due to γ radiation. To instead study how cells respond to sustained levels of p53, the authors controlled p53 levels using the drug Nutlin-3. To do this, they devised a program for adjusting Nutlin-3 levels in the cell culture that would keep the p53 levels at a constant high level. They based this program on a mathematical model of the p53 circuit (shown in Fig. 1) that they developed and parametrized in an earlier paper (Batchelor, et al., *Molecular Cell*, **30**, 277–289, 2008).

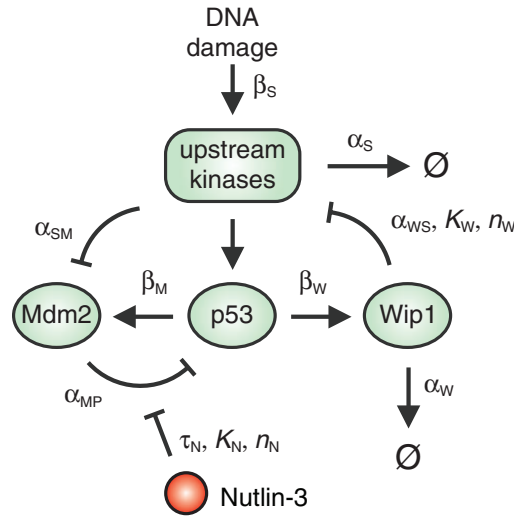


Figure 1: The p53 regulatory circuit. Taken from Purvis, et al., *Science*, **336**, 1440–1444, 2012.

The p53 levels oscillate due to a delays in the autoinhibitory loops mediated by Mdm2 and Wip1. The dynamical equations for this circuit, as presented in the paper, are

$$\frac{dP_i}{dt} = \beta_P - \frac{\alpha_{MP_i} M P_i}{1 + (N(t - \tau_N)/K)^{n_N}} - \beta_{SP} P_i \frac{(S/T_S)^{n_S}}{1 + (S/T_S)^{n_S}} - \alpha_{P_i} P_i, \quad (7.1)$$

$$\frac{dP_a}{dt} = \beta_{SP} P_i \frac{(S/T_S)^{n_S}}{1 + (S/T_S)^{n_S}} - \frac{\alpha_{MP_a} M P_a}{1 + (N(t - \tau_N)/K)^{n_N}}, \quad (7.2)$$

$$\frac{dM}{dt} = \beta_M P_a(t - \tau_M) + \beta_{M_i} - \alpha_{SM} S M - \alpha_M M, \quad (7.3)$$

$$\frac{dW}{dt} = \beta_w P_a(t - \tau_w) - \alpha_w W, \quad (7.4)$$

$$\frac{dS}{dt} = \beta_s \theta(t) - \alpha_{ws} S \frac{(W/T_w)^{n_w}}{1 + (W/T_w)^{n_w}} - \alpha_s S. \quad (7.5)$$

Here, P_i and P_a denote the concentrations of inactive and active p53, respectively. M and W are respectively the concentrations of Mdm2 and Wip1. The concentration of the DNA damage signal is denoted as S . Finally, N is the externally imposed concentration of Nutlin-3. The function $\theta(t)$ is the Heaviside function. The parameters for the model are given on the last page of this problem set in a convenient format for copying and pasting. Before proceeding, take a moment and make sure you understand the physical meaning of each term in the equations.

- a) Solve the equations numerically with $N = 0$. Plot the solution along with the experimental measurements from the Purvis, et al. paper, given below.

time (hr)	relative total p53 conc.
0	0.13
1	0.69
2	1.00
3	0.87
4	0.60
5	0.35
6	0.34
7	0.54
8	0.61
12	0.43

This helps verify that the model gives results similar to what you would observe experimentally.

- b) Come up with a program for controlling the Nutlin-3 concentration so as to bring the total p53 level to a sustained value similar to that of its maximum value during oscillations in the absence of Nutlin-3. I.e., choose a function $N(t)$ to give a sustained level of p53 that is approximately unity (in the units specified by the parameter values). You might want to consider experimental constraints, for example that you might want to have only a few steps where the Nutlin-3 concentrations are adjusted to ease experimentation. Show a plot verifying that your scheme works.

Problem 7.2 (Ruling out oscillations, 30 pts).

This problem is based on problem 3.6 of Del Vecchio and Murray. There are fifteen circuits in Fig. 2. Use the Bendixson criterion to identify circuits that cannot give sus-

tained oscillations. *Hint:* Read the [relevant section of the lecture 18 notes](#) to learn about the Bendixson criterion.

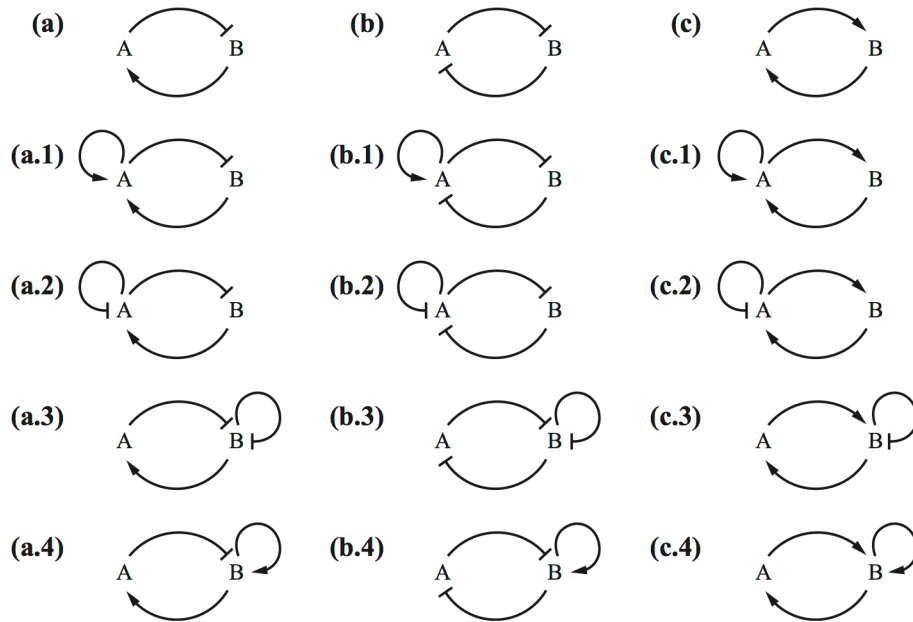


Figure 2: A collection of two-gene circuits. Take from Del Vecchio and Murray, *Biomolecular Feedback Systems*, Princeton University Press, 2015.

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alpha_MPi = 5
alpha_Pi = 2
alpha_MPa = 1.4
alpha_SM = 0.5
alpha_M = 1
alpha_W = 0.7
alpha_WS = 50
alpha_S = 7.5
beta_P = 0.9
beta_SP = 10
beta_M = 0.9
beta_Mi = 0.2
beta_W = 0.25
beta_S = 10
tau_N = 0.4      # hours
tau_M = 0.7      # hours
tau_W = 1.25     # hours
K = 2.3          # μM
n_N = 3.3
n_S = 4
n_W = 4
T_W = 0.2
T_S = 1
```