

Synthetic Biology

Assignment #01

Stephanie Fingerhuth, Lorenzo Gatti

Saturday 24th March, 2012**0.1 The model**

The model for a two protein network can be given by the system of equations:

$$\frac{dx}{dt} = f(y) - d_1x \quad (0.1a)$$

$$\frac{dy}{dt} = g(x) - d_2y \quad (0.1b)$$

where x and y are the concentration of the two proteins, f and g are “repression functions” and d_1, d_2 are positive constant describing the protein decay.

$$f(y) = \frac{k_1}{1 + [Y]^n} \quad (0.2a)$$

$$g(x) = \frac{k_2}{1 + [X]} \quad (0.2b)$$

The level of repression of $[X]$ in a “mixed” circuit model is described by a Hill function [Cherry and Adler, 2000], which models cooperativity of binding between two different molecular species. Cooperativity magnitude is described by the Hill coefficient n . Using the conditions for a change in the number of steady states derived from nullclines analysis:

$$d_1[X] = \frac{k_1}{1 + [Y]^n} * \frac{1}{d_1} = \frac{k'_1}{1 + [Y]^n} \quad (0.3a)$$

$$y_1 = \sqrt[n]{\frac{k'_1}{d_1[X]} - 1} \quad (0.3b)$$

$$d_2[Y] = \frac{k_2}{1 + [X]} * \frac{1}{d_2} = \frac{k'_2}{1 + [X]} \quad (0.3c)$$

$$y_2 = \frac{k'_2}{1 + [X]} \quad (0.3d)$$

with $k'_1 = \frac{k_1}{d_1}$ and $k'_2 = \frac{k_2}{d_2}$.

The equations 0.3a and 0.3d are solved as functions of $f(x)$ in the form $y = f(x)$.

0.2 Nullcline plots

The analysis performed in graphs 0.1 shows the existence of multiple steady states depending on which parameters are chosen. Multiple steady states are the necessary condition to have a switch. The purpose of the switch is to obtain a consisting change in the concentration of a certain protein. The graph 0.1b shows transverse nullclines.

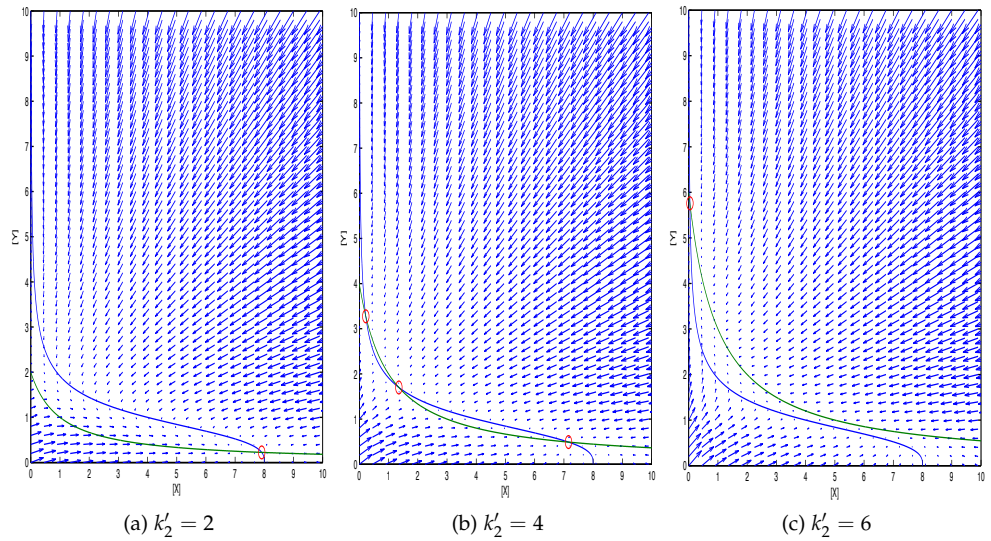


Figure 0.1: Nullclines plots for the parametres $n = 3$, $k'_1 = 8$, $k'_2 = \{2, 4, 6\}$

Intersection of functions lines are circled in red. These points represent the steady state at different values of the parameter k_2 . In the graph 0.1a we can distinguish only one point at high concentration of protein Y as well as in the graph 0.1c where the steady state is reached at high concentration of X. The major difference is visible in the graph 0.1b where we clearly confirm a possible switch, due to the presence of three steady state points.

0.3 Analytic expressions for k'_1 and k'_2

According to Matlab *solve* function for the equations:

$$e1 : x = \frac{k'_1}{(1+y^3)} \quad (0.4a)$$

$$e2 : y = \frac{k_2}{(1+x)} \quad (0.4b)$$

$$e3 : \delta\left(\frac{k_1}{(1+y^3)}, y\right) * \delta\left(\frac{k_2}{(1+x)}, x\right) = 1 \quad (0.4c)$$

we retrieve three solutions:

$$k'_1 = \frac{(3 * x^2)}{(2 * x - 1)} \quad (0.5a)$$

$$k'_2 = \left(\frac{(x+1)}{(2 * x - 1)}\right)^{\frac{1}{3}} * (x+1) \quad (0.5b)$$

$$y = \left(\frac{(x+1)}{(2 * x - 1)}\right)^{\frac{1}{3}} \quad (0.5c)$$

0.4 Bifurcation diagram

In bifurcation diagram the region delimited by the graph is the bistable region. Only in this region switches are possible. From this diagram one can see clearly that $k'_2 = 2$ is completely outside the bistable region, whereas $k'_2 = 4$ lies inside. This corresponds to the nullclines analyses in plot 0.1. There we could find a possible switch for $k'_2 = 4$ but not for $k'_2 = 2$. Even though $k'_2 = 6$ seems to be in the bistable region here, we can see from graph 0.1c that there are no possible switches.

0.5 synthbio_script_01.m

```
1 #####
2 ## Synth Bio Project 01 ##
3 #####
4 %# Author: Stephanie Fingerhuth, Lorenzo Gatti
5 %# Date: 09-Mar-2012 v.0.0.1
6 %# Update: 10-Mar-2012 v.0.1.1
7 %# Usage:
8 %# Parametres:
9 %# Output:
10 %#
11 %# TODO: Add comments [DONE]
12 %#
13 #####
14
15 #####
16 % Problem [B]
17 #####
18 % Solving equation with given parametres:
19 % n=3, k1p = 8; k2p = {2,4,6}
20
21 % Initialization of variables
22 n = 3;
23 k1 = 8;
24 k2 = [2 4 6];
25 x_val = [0:0.01:10];
26
27 % Defining the range of X and Y
28
29 [vf_x, vf_y] = meshgrid(0:0.45:15,0:0.20:10);
30
31 % Plotting solutions on a graph
32 for i=1:length(k2)
33
34     % Plotting the vector field
35     quiver(vf_x, vf_y,dx(k1, n, vf_x, vf_y), dy(k2(i), vf_x, vf_y), 2);
36
37     hold on;
38
39     % Find intersection points for the defined functions (X,Y)
40     [xi, yi] = polyxpoly(x_val, nx(k1, n, x_val), x_val, ny(x_val, k2(i)));
41
42     % Plotting the nulclines
43     plot(x_val, nx(k1, n, x_val), x_val, ny(x_val, k2(i)));
44
45     % Plot intersection of graphs
46     plot(xi, yi, 'or', 'MarkerSize',10);
47
48     xlabel('X');
49     ylabel('Y');
50
51     % Setting the new axis
52     axis([0 max(x_val) 0 10]);
53
54     hold off;
55
56     % Export graph in a pdf file
57     print('-dpdf', ['plot_B' num2str(i)]);
58 end
59
60 #####
61 % Problem [C]
62 #####
63
64 % Defining the equations to solve
65
66 e1 = 'x_0=k1/(1+y^3)';
67 e2 = 'y_0=k2/(1+x)';
68 e3 = 'diff(k1/(1+y^3),y)*diff(k2/(1+x),x)_0=1';
69
70 % Solving system of equations
71
72 S = solve(e1, e2, e3, 'y', 'k1', 'k2');
```

```

73 |
74 | % Retriving first solution for each variable
75 |
76 | k1 = S.k1(1);
77 | k2 = S.k2(1);
78 | y = S.y(1);
79 |
80 | % Defining the range of X
81 |
82 | x = [0:0.01:5];
83 |
84 | % Solve the equations in the range of x
85 |
86 | k1_solv = x.*subs(k1);
87 | k2_solv = x.*subs(k2);
88 |
89 | #####
90 | % Problem [D]
91 | #####
92 |
93 | % Plotting of the solutions from the previous step
94 |
95 | plot(k1_solv, k2_solv);
96 | xlabel(' [k1] ');
97 | ylabel(' [k2] ');
98 |
99 | % Setting the new axis
100 |
101 | axis([0 max(k1_solv) 0 max(k2_solv)]);
102 |
103 | % Export graph in a pdf file
104 | print('-dpdf', 'plot_D0');

```

Listing 1: ./synthbio_script.01.m

0.6 dx.m

```

1 | function [ dx ] = dx( k1, n, x, y )
2 |
3 |     dx = (k1./(1+(y.^n))) - x;
4 |
5 | end

```

Listing 2: ./dx.m

0.7 dy.m

```

1 | function [ dy ] = dy( k2, x, y )
2 |
3 |     dy = (k2./(1+x))-y;
4 |
5 | end

```

Listing 3: ./dy.m

0.8 nx.m

```

1 |
2 | function [ y ] = nx( k1, n, x )
3 |
4 |     y = nthroot((k1-x)./x, n);
5 |
6 | end

```

Listing 4: ./nx.m

0.9 ny.m

```
1 function [ y ] = ny( x, k2 )  
2  
3     y = k2./(1+x);  
4  
5 end
```

Listing 5: ./ny.m

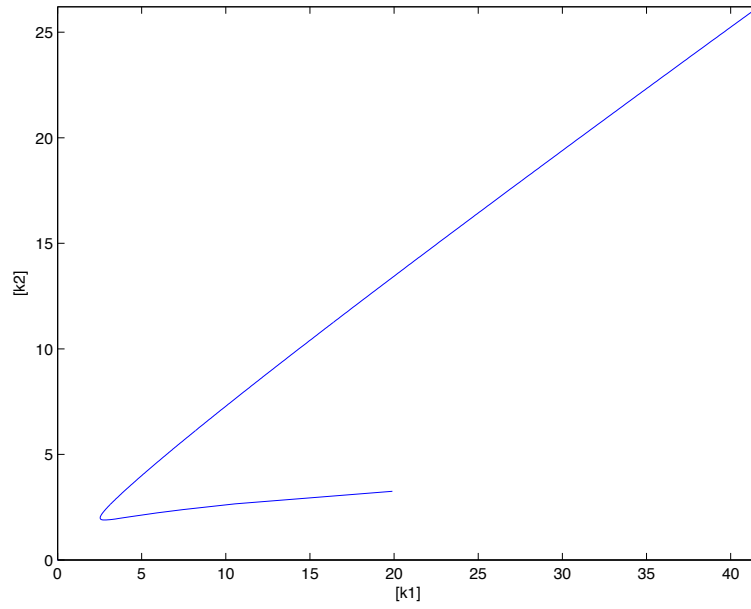


Figure 0.2: Values of the parameter k'_1 and k'_2 needed for a working switch for particular values of the exponent n in the Hill function.

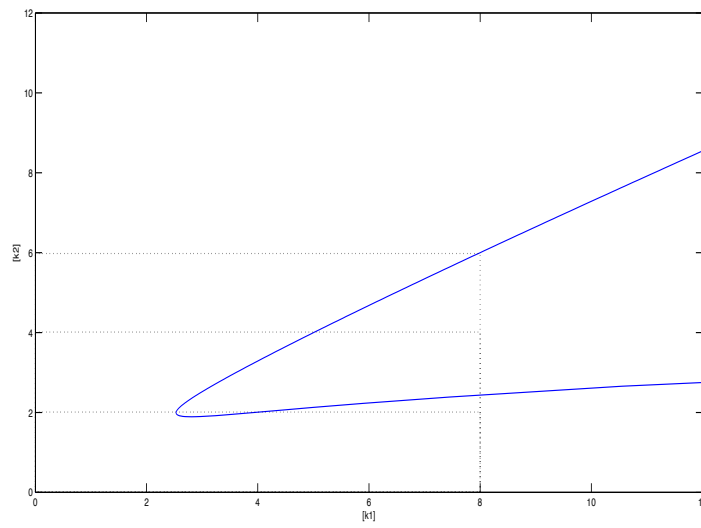


Figure 0.3: Values of the parameter k'_1 and k'_2 needed for a working switch for particular values of the exponent n in the Hill function.

Bibliography

Joshua L Cherry and Frederick R Adler. How to make a biological switch. *Journal of Theoretical Biology*, 203(2):117 – 133, 2000. ISSN 0022-5193. doi: 10.1006/jtbi.2000.1068. URL <http://www.sciencedirect.com/science/article/pii/S0022519300910683>.