ETH

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Synthetic Biology

Assignment #01

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0.1 The model

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

$$\frac{dx}{dt} = f(y) - d_1 x \tag{0.1a}$$

$$\frac{dy}{dt} = g(x) - d_2 y \tag{0.1b}$$

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.

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

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

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:

$$d_1[X] = \frac{k_1}{1 + [Y]^n} * \frac{1}{d_1} = \frac{k_1'}{1 + [Y]^n} \tag{0.3a}$$

$$y_1 = \sqrt[n]{\frac{k_1'}{d_1[X]} - 1} \tag{0.3b}$$

$$d_2[Y] = \frac{k_2}{1 + [X]} * \frac{1}{d_2} = \frac{k_2'}{1 + [X]^n} \tag{0.3c}$$

$$y_2 = \frac{k_2'}{1 + [X]} \tag{0.3d}$$

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.
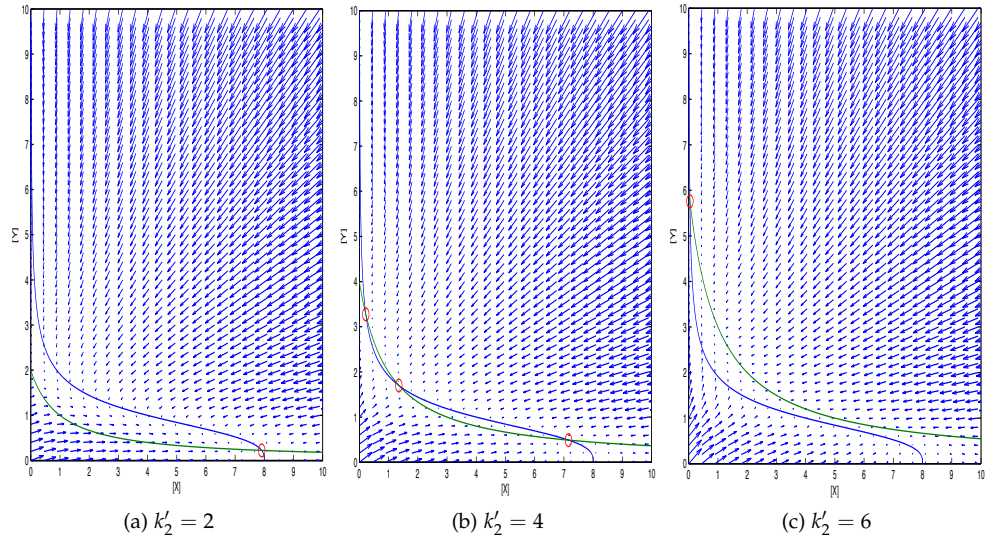

(a) $k_2' = 2$ (b) $k_2' = 4$ (c) $k_2' = 6$

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:

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

$$e2 : y = \frac{k2}{(1+x)} \tag{0.4b}$$

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

we retrieve three solutions:

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

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

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

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.

3

0.5 synthbio_script_01.m

```matlab
%###########################################################
%## Synth Bio Project 01 ##
%###########################################################
%# Author: Stephanie Fingerhuth, Lorenzo Gatti
%# Date: 09-Mar-2012  v.0.0.1
%# Update: 10-Mar-2012 v.0.1.1
%# Usage:
%# Parametres:
%# Output:
%#
%# TODO: Add comments [DONE]
%#
%###########################################################

%######################################
% Problem [B]
%######################################
% Solving equation with given parametres:
% n=3, k1p = 8; k2p = {2,4,6}

% Initialization of variables
n = 3;
k1 = 8;
k2 = [2 4 6];
x_val = [0:0.01:10];

% Defining the range of X and Y

[vf_x, vf_y] = meshgrid(0:0.45:15,0:0.20:10);

% Plotting solutions on a graph
for i=1:length(k2)

    % Plotting the vector field
    quiver(vf_x, vf_y,dx(k1, n, vf_x, vf_y), dy(k2(i), vf_x, vf_y), 2);

    hold on;

    % Find intersection points for the defined functions (X,Y)
    [xi, yi] = polyxpoly(x_val, nx(k1, n, x_val), x_val, ny(x_val, k2(i)));

    % Plotting the nulclines
    plot(x_val, nx(k1, n, x_val), x_val, ny(x_val, k2(i)));

    % Plot intersection of graphs
    plot(xi, yi, 'or', 'MarkerSize',10);

    xlabel('[X]');
    ylabel('[Y]');

    % Setting the new axis
    axis([0 max(x_val) 0 10]);

    hold off;

    % Export graph in a pdf file
    print('-dpdf', ['plot_B' num2str(i)]);
end

%######################################
% Problem [C]
%######################################

% Defining the equations to solve

e1 = 'x␣=␣k1/(1+y^3)';
e2 = 'y␣=␣k2/(1+x)';
e3 = 'diff(k1/(1+y^3),␣y)*diff(k2/(1+x),x)␣=1';

% Solving system of equations

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
```

0.9 ny.m

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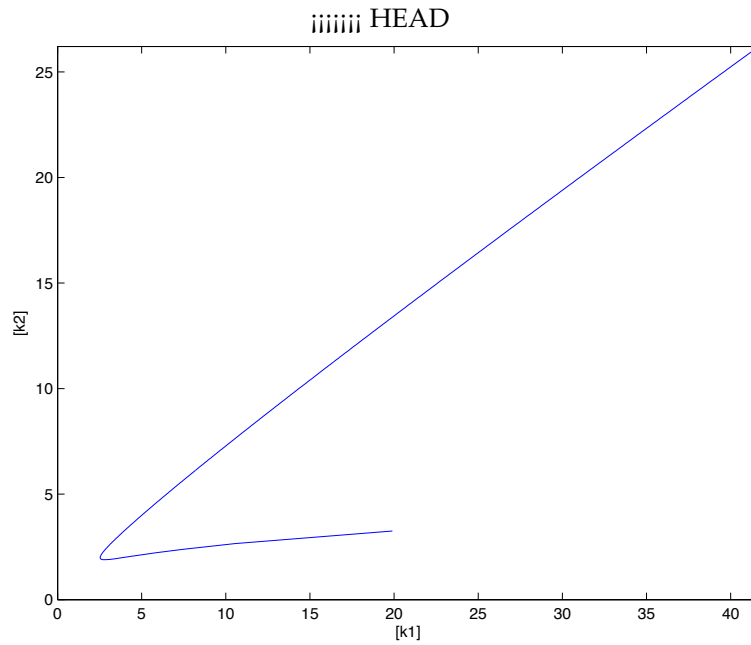
Listing 5: ./ny.m

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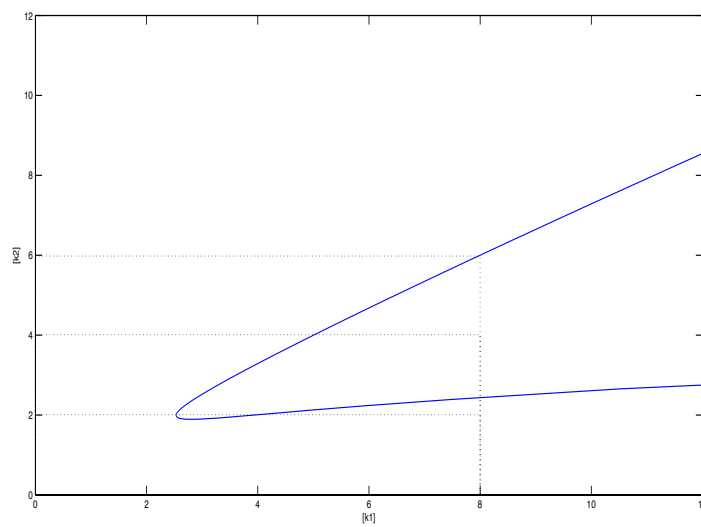
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Figure 0.3: Values of the parameter k'_1 and k'_2 needed for a working switch for particular values of the exponent n in the Hill function.

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.