Lab Course: Modelling and Simulation (SS-2016, LSI) 5th – 15th September 2016: Part 3

Background

Bistability has important consequences on the capacity of signaling pathways to process biological signals. Bistable switches can act as memory circuits storing the information needed for later stages of processing [13]. The response of bistable signaling pathways show hysteresis, namely dynamic and static lags between input and output. Because of hysteresis, one can have in the same time sharp, all or nothing response and protection against chatter noise.

Bistability of signaling usually occurs as a result of activation of upstream signaling proteins by downstream components [2]. A different mechanism for producing bistability in signaling pathways was proposed by Kholodenko [11]. In this mechanism the cause of bistability are multiple phosphorylation/dephosphorylation cycles that share enzymes. A simple, two steps phosphorylation/dephosphorylation cycle is capable of ultrasensitivity, a form of all or nothing response with no hysteresis (Goldbeter-Koshland mechanism). In multiple phosphorylation/dephosphorylation cycles, enzyme sharing provides competitive interactions and positive feedback that ultimately leads to bistability.

Algorithmically the task is to find the positive real solutions of a parameterized system of polynomial or rational systems, since the dynamics of the network is given by polynomial systems—arising from mass action kinetics—or rational functions—arising in signaling networks when some some intermediates of the reaction mechanisms are reduced. Due to the high computational complexity of this task [7] considerable work has been done to use specific properties of networks and to investigate the potential of bistability (or more general, multistationarity) of a biological network out of the network structure and only to determine whether there exist certain rate constants such that there are multiple steady states instead of coming up with a semi-algebraic description of the range of parameters yielding this property. These approaches can be traced back to the origins of Feinberg's *chemical reaction network theory* (CRNT) whose main result is that networks of deficiency 0 have a unique positive steady state for all rate constants [6, 4]. For clever ways to use CRNT and other graph theoretic methods to determine in contrast the potential of multiple positive steady states we refer to [3, 12, 8] and to [9] for a survey.

However, given a bistable mechanism it is important to compute the

bistability domains in parameter space, namely the parameter values for which there are more than one stable steady states. The size of bistability domains gives the spread of the hysteresis and quantifies the robustness of the switches.

In the following assignment you shall use an 11-dimensional model of a mitogen-activated protein kinases (MAPK) cascade [11] to compute for fixed parameters – or for one non-fixed parameter – to compute regions of bistability.

The MapK Network and the Arising System of Polynomials

The model of the MAPK cascade we are investigating can be found in the Biomodels database [10] as number 26 and is given by the following set of differential equations. We have renamed the species names into $x_1, \ldots, x_{11}$ and the rate constants into $k_1, \ldots, k_{16}$ to facilitate reading:

$$
\begin{aligned}
\dot{x_1} &= k_2x_6 + k_{15}x_{11} - k_1x_1x_4 - k_{16}x_1x_5 \\
\dot{x_2} &= k_3x_6 + k_5x_7 + k_{10}x_9 + k_{13}x_{10} - x_2x_5(k_{11} + k_{12}) - k_4x_2x_4 \\
\dot{x_3} &= k_6x_7 + k_8x_8 - k_7x_3x_5 \\
\dot{x_4} &= x_6(k_2 + k_3) + x_7(k_5 + k_6) - k_1x_1x_4 - k_4x_2x_4 \\
\dot{x_5} &= k_8x_8 + k_{10}x_9 + k_{13}x_{10} + k_{15}x_{11} - x_2x_5(k_{11} + k_{12}) - k_7x_3x_5 - k_{16}x_1x_5 \\
\dot{x_6} &= k_1x_1x_4 - x_6(k_2 + k_3) \\
\dot{x_7} &= k_4x_2x_4 - x_7(k_5 + k_6) \\
\dot{x_8} &= k_7x_3x_5 - x_8(k_8 + k_9) \\
\dot{x_9} &= k_9x_8 - k_{10}x_9 + k_{11}x_2x_5 \\
\dot{x_{10}} &= k_{12}x_2x_5 - x_{10}(k_{13} + k_{14}) \\
\dot{x_{11}} &= k_{14}x_{10} - k_{15}x_{11} + k_{16}x_1x_5
\end{aligned}
$$

In the Biomodels database estimates for parameters are given as follows:

$$
\begin{aligned}
&k_1 = 0.02, \quad k_4 = 0.032, \quad k_7 = 0.045, \quad k_9 = 0.092, \quad k_{15} = 0.086, \\
&k_2 = 1, \quad k_3 = 0.01, \quad k_5 = 1, \quad k_6 = 15, \quad k_8 = 1, \\
&k_{10} = 1, \quad k_{11} = 0.01, \quad k_{12} = 0.01, \quad k_{14} = 0.5, \quad k_{13} = 1, \\
&k_{16} = 0.0011.
\end{aligned}
$$

Task 7

Perform numeric simulations using the given parameter values and various initial values fulfilling the following conditions:

$$\begin{aligned} x_5 + x_8 + x_9 + x_{10} + x_{11} &= 100, \\ x_4 + x_6 + x_7 &= 50, \\ x_1 + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} &= 200, \end{aligned}$$

Do the trajectories converge to the same value for all those initial values? Do the values of the following sums stay constant?

1. $x_1 + x_2 + x_3 + x_4 + x_5$
2. $x_5 + x_8 + x_9 + x_{10} + x_{11}$
3. $x_4 + x_6 + x_7$
4. $x_1 + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11}$
5. $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11}$

Task 8

Perform similar computations as in Task 7, but now the initial values should obey

$$\begin{aligned} x_5 + x_8 + x_9 + x_{10} + x_{11} &= 100, \\ x_4 + x_6 + x_7 &= 50, \\ x_1 + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} &= \mathbf{500}, \end{aligned}$$

Task 8

Using the left-null space of the stoichiometric matrix under positive conditions as conservation constraint [5] we obtain the following three linear conservation constraints:

$$\begin{aligned} x_5 + x_8 + x_9 + x_{10} + x_{11} &= k_{17}, \\ x_4 + x_6 + x_7 &= k_{18}, , \\ x_1 + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} &= k_{19}, , \end{aligned}$$

The following equation system computes the fixed points of the vector field supplemented with three conservation laws.

$$\begin{aligned}
k_2x_6 + k_{15}x_{11} - k_1x_1x_4 - k_{16}x_1x_5 &= 0 \wedge \\
k_3x_6 + k_5x_7 + k_{10}x_9 + k_{13}x_{10} - x_2x_5(k_{11} + k_{12}) - k_4x_2x_4 &= 0 \wedge \\
k_6x_7 + k_8x_8 - k_7x_3x_5 &= 0 \wedge \\
x_6(k_2 + k_3) + x_7(k_5 + k_6) - k_1x_1x_4 - k_4x_2x_4 &= 0 \wedge \\
k_8x_8 + k_{10}x_9 + k_{13}x_{10} + k_{15}x_{11} - x_2x_5(k_{11} + k_{12}) - k_7x_3x_5 - k_{16}x_1x_5 &= 0 \wedge \\
k_1x_1x_4 - x_6(k_2 + k_3) &= 0 \wedge \\
k_4x_2x_4 - x_7(k_5 + k_6) &= 0 \wedge \\
k_7x_3x_5 - x_8(k_8 + k_9) &= 0 \wedge \\
k_9x_8 - k_{10}x_9 + k_{11}x_2x_5 &= 0 \wedge \\
k_{12}x_2x_5 - x_{10}(k_{13} + k_{14}) &= 0 \wedge \\
k_{14}x_{10} - k_{15}x_{11} + k_{16}x_1x_5 &= 0 \wedge \\
x_5 - k_{17} + x_8 + x_9 + x_{10} + x_{11} &= 0 \wedge \\
x_4 - k_{18} + x_6 + x_7 &= 0 \wedge \\
x_1 - k_{19} + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} &= 0.
\end{aligned}$$

We estimate all parameters except k_{19} with values from Biomodels database as follows:

$$\begin{array}{lllll}
k_1 = 0.02, & k_4 = 0.032, & k_7 = 0.045, & k_9 = 0.092, & k_{15} = 0.086, \\
k_2 = 1, & k_3 = 0.01, & k_5 = 1, & k_6 = 15, & k_8 = 1, \\
k_{10} = 1, & k_{11} = 0.01, & k_{12} = 0.01, & k_{14} = 0.5, & k_{13} = 1, \\
k_{16} = 0.0011, & k_{17} = 100, & k_{18} = 50. & &
\end{array}$$

We are going to consider two fixed values for k_{19}, viz. $k_{19} = 200$ and $k_{19} = 500$.

1. Use the homotopy solver Bertini [1] to obtain the solutions for the given cases.

2. Determine the number of positive real solutions.

Task 9

Perform the computations of Task 8 for varying values of $k_{19} \in [200, 500]$.

Determine approximately (by bisecting values up to one digit of occuracy) the value of k_{19} at which the system changes its behavior (from a single fixed point to 3 fixed points).

Task 10

This task is splitted over the groups.

Take your favorite parameter k_f.

1. Search the literature for values of k_f.
2. Systematically determine the number of positive real solutions of the system, in which $k_{19} = 200, 500$, all other parameters (except k_f) have the values given above, and k_f is varied by two orders of magnitudes around the value given above.

References

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