A Case Study on the Parametric Occurrence of Multiple Steady States

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ACA, Kassel, 2016

Motivation

- *Bistability*— or more generally *multistationarity*—has important consequences on the capacity of *signaling pathways* to process biological signals.
- *Algorithmically* the task is to find the *positive real solutions of a parameterized system* of *polynomial* or *rational systems*.
  - 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.
- Problem: *High computation complexity* of problem [Grigoriev and Vorobjov, 1988] and *dimensionality of typical systems*.

Motivation

- 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*.
    - 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.
- Considerable work using Feinberg's *chemical reaction network theory (CRNT)*.
- 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 [Conradi et al., 2008, Pérez Millán and Turjanski, 2015, Johnston, 2014] and to [Joshi and Shiu, 2015] for a survey.

Motivation

- However, given a bistable mechanism it is important to compute the *bistability domains* in *parameter space*.
  - 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.
- For this purpose the work of [Paris et al., 2005] is relevant: they used symbolic computation tools to determine the *number of steady states* and their *stability* of several systems—and they reported results up to a *5-dimensional system* using specified parameter values.

Our Case Study

- We use an *11-dimensional model* of a mitogen-activated protein kinases *(MAPK)* cascade [Markevich et al., 2004] as a case study.

  - To investigate properties of the system and
  - algorithmic methods towards the goal of *semi-algebraic descriptions of parameter regions* for which *multiple positive steady states exist*.

- The model of the MAPK cascade we are investigating can be found in the Biomodels database [Li et al., 2010] 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:

ODE system of MAPK (BIOMOD026)

$$\dot{x_1} = k_2 x_6 + k_{15} x_{11} - k_1 x_1 x_4 - k_{16} x_1 x_5$$

$$\dot{x_2} = k_3 x_6 + k_5 x_7 + k_{10} x_9 + k_{13} x_{10} - x_2 x_5 (k_{11} + k_{12}) - k_4 x_2 x_4$$

$$\dot{x_3} = k_6 x_7 + k_8 x_8 - k_7 x_3 x_5$$

$$\dot{x_4} = x_6 (k_2 + k_3) + x_7 (k_5 + k_6) - k_1 x_1 x_4 - k_4 x_2 x_4$$

$$\dot{x_5} = k_8 x_8 + k_{10} x_9 + k_{13} x_{10} + k_{15} x_{11} - x_2 x_5 (k_{11} + k_{12})$$
$$\quad - k_7 x_3 x_5 - k_{16} x_1 x_5$$

$$\dot{x_6} = k_1 x_1 x_4 - x_6 (k_2 + k_3)$$

$$\dot{x_7} = k_4 x_2 x_4 - x_7 (k_5 + k_6)$$

$$\dot{x_8} = k_7 x_3 x_5 - x_8 (k_8 + k_9)$$

$$\dot{x_9} = k_9 x_8 - k_{10} x_9 + k_{11} x_2 x_5$$

$$\dot{x_{10}} = k_{12} x_2 x_5 - x_{10} (k_{13} + k_{14})$$

$$\dot{x_{11}} = k_{14} x_{10} - k_{15} x_{11} + k_{16} x_1 x_5$$

Conservation constraints

Using the left-null space of the stoichiometric matrix under positive conditions as conservation constraint [Famili and Palsson, 2003] we obtain the following *three linear conservation constraints*:

$$
\begin{aligned}
x_5 - k_{17} + x_8 + x_9 + x_{10} + x_{11} &= 0, \\
x_4 - k_{18} + x_6 + x_7 &= 0, \\
x_1 - k_{19} + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} &= 0,
\end{aligned}
$$

where k_{17}, k_{18}, k_{19} are new constants computed from the initial data.

A first computational attempt

- The polynomial system *without the conservation laws* can be *solved fully parametrically* by Maple.
  - In less than *1 second of computation time*.
  - Complex solutions can be expressed using three transcendental bases.
- But for multistationarity one has to determine whether there are *multiple positive real solutions obeying the conservation constraints.*
- Substituting the solutions into the conservations constraints yielded a three dimensional polynomial system
  - From which one variable could be eliminated rather easily.
  - A second variable could be eliminated using resultants.
  - But the obtained parametric polynomial withstood the attempt to determine parametric multiple solutions.
  - Also using other symbolic techniques on the level of two remaining polynomials turned out to be *not simpler* than directly working on the *original system*.

Non-parametric computations

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

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

Using the *homotopy solver Bertini* [Bates et al.,] we obtained the following results using for k_{19} different parameter values found in the literature:

- For the parameter values as above and $k_{19} = 500$ we obtained 6 solutions,
    - of which 3 were positive real solutions.
- For $k_{19} = 200$, a single positive solutions was obtained.

Parametric computations

- Our focus to analyze the system for multiple positive steady states is on methods based on *real quantifier elimination*,
  - which can *directly deal with the quest of multiple positive real solutions* even in the *presence of parameters*.
  - Although the method can handle arbitrary numbers of parameters in principle, only up to one parameter will has been left free to come up with feasible computations.

Parametric computations

Using a combination of Redlog
[Dolzmann and Sturm, 1997, Dolzmann et al., 2004] and Qepcad B
[Brown, 2003] we have obtained the following results (using the
estimates for the parameters except of k_{19} as above):

1. For all positive choices of k_{19}—extending to infinity—there is at least one positive solution for $(x_1, \ldots, x_{11})$.

2. There is a breaking point β around $k_{19} = 409.253$ where the system changes its qualitative behavior. We have exactly computed β as a real algebraic number. For $k_{19} < \beta$ there is exactly one positive solution for $(x_1, \ldots, x_{11})$. For $k_{19} > \beta$ there are at least 3 and at most 3^{11} positive solutions for $(x_1, \ldots, x_{11})$.

The overall computation time for this parametric analysis has been
less than 5 minutes.

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Determining the Stability of the Fixed Points

- For the numeric approximations of the fixed points we numerically computed the eigenvalues of the Jacobian using Maple.
- For $k_{19} = 200$ the single positive fixed point could be shown to be stable in this way.
- For $k_{19} = 500$ one of the three positive fixed points could be shown to be unstable whereas two could be shown to be stable.
    - Hence for $k_{19} = 500$ the system is indeed bistable.
- A verification of the stability of the fixed points using the exact real algebraic numbers and the Routh-Hurwitz criterion seems to be out of range of current methods for this example.

Conclusion and Future Work

- Although the goal of *semi-algebraic description* of the range of several parameters yielding bistable behavior could not be achieved for the *11-dimensional system*, which was used for the case study, our case study shows that *one is not too far off*.
- As there are *many very relevant systems* having *dimensions between 10 and 20* it seems to be worth the effort to *enhance the algorithmic methods* and to come up with improved implementations of them to solve this very important applications problem for symbolic computation.

Conclusion and Future Work

- In addition to improving the *real quantifier elimination methods*, which can deal with the question of *positive real solutions in a parametric way directly*, using methods that *deal with complex solutions first* (such as *Gröbner bases* or *regular chain methods*) are a topic of future research.
  - A challenge for the latter methods are the parametric determination of the positive real solutions out of the descriptions of the complex solutions.

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