A Case Study on the Parametric Occurrence of Multiple Steady States

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Bistability— or more generally multistationarity—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 [19]. 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 [14]. 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 [10] 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 [9, 5]. 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 [4, 16, 11] and to [12] 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. For this purpose the work of Wang and Xia [15] 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—but their method is extensible to parametric questions. However, we are not aware of work on higher-dimensional systems for this context.

In this paper we use an 11-dimensional model of a mitogen-activated protein kinases (MAPK) cascade [14] 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 MapK Network and the Arising System of Polynomials. The model of the MAPK cascade we are investigating can be found in the Biomodels database [13] 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:

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

Using the left-null space of the stoichiometric matrix under positive conditions as conservation constraint [8] 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.

Computing complex solutions using homotopy solvers We estimate all parameters except k_{19} with values from Biomodels database as follows:

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

Using the homotopy solver Bertini [1] 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.

Determination of Parametric Multiple Steady States. Our focus to analyze the system for multiple positive steady states is on methods based on real quantifier elimination, which directly can 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 one parameter has been left free to come up with feasible computations.

Using a combination of Redlog [7, 17, 18, 6] and Qepcad B [3] 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 les than 5 minutes.

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, whereas 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 some 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. 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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References

[1] D. J. Bates, J. D. Hauenstein, A. J. Sommese, and C. W. Wampler. Bertini: Software for numerical algebraic geometry. Available at bertini.nd.edu with permanent doi:

dx.doi.org/10.7274/R0H41PB5.

[2] U. S. Bhalla and R. Iyengar. Emergent properties of networks of biological signaling pathways. *Science*, 283(5400):381–387, 1999.

[3] C. W. Brown. QEPCAD B: a program for computing with semi-algebraic sets using CADs. *ACM SIGSAM Bulletin*, 37(4):97–108, 2003.

[4] C. Conradi, D. Flockerzi, and J. Raisch. Multistationarity in the activation of a MAPK: parametrizing the relevant region in parameter space. *Math. Biosci.*, 211(1):105–31, jan 2008.

[5] G. Craciun, A. Dickenstein, A. Shiu, and B. Sturmfels. Toric dynamical systems. *Journal of Symbolic Computation*, 44(11):1551–1565, 2009.

[6] A. Dolzmann, A. Seidl, and T. Sturm. Efficient projection orders for CAD. In J. Gutierrez, editor, *Proceedings of the 2004 International Symposium on Symbolic and Algebraic Computation (ISSAC 2004)*, pages 111–118. ACM Press, New York, NY, July 2004.

[7] A. Dolzmann and T. Sturm. Redlog: Computer algebra meets computer logic. *ACM SIGSAM Bulletin*, 31(2):2–9, June 1997.

[8] I. Famili and B. Ø. Palsson. The convex basis of the left null space of the stoichiometric matrix leads to the definition of metabolically meaningful pools. *Biophys. J.*, 85(1):16–26, 2003.

[9] M. Feinberg. Stability of complex isothermal reactors–I. the deficiency zero and deficiency one theorems. *Chemical Engineering Science*, 42(10):2229–2268, 1987.

[10] D. Grigoriev and N. N. Vorobjov. Solving systems of polynomial inequalities in subexponential time. *Journal of Symbolic Computation*, 5(1-2):37–64, Feb. 1988.

[11] M. Johnston. A note on" MAPK networks and their capacity for multistationarity due to toric steady states". *arXiv Prepr. arXiv1407.5651*, pages 1–13, 2014.

[12] B. Joshi and A. Shiu. A Survey of Methods for Deciding Whether a Reaction Network is Multistationary. *Math. Model. Nat. Phenom.*, 10(5):47–67, aug 2015.

[13] C. Li, M. Donizelli, N. Rodriguez, H. Dharuri, L. Endler, V. Chelliah, L. Li, E. He, A. Henry, M. I. Stefan, J. L. Snoep, M. Hucka, N. Le Novère, and C. Laibe. BioModels database: An enhanced, curated and annotated resource for published quantitative kinetic models. *BMC Systems Biology*, 4:92, Jan. 2010.

[14] N. I. Markevich, J. B. Hoek, and B. N. Kholodenko. Signaling switches and bistability arising from multisite phosphorylation in protein kinase cascades. *J. Cell Biol.*, 164(3):353–359, 2004.

[15] F. Paris, D. Wang, and B. Xia. Stability analysis of biological systems with real solution classification. In *ISSAC '05 Proc. 2005 Int. Symp. Symb. Algebr. Comput.*, pages 354–361, Beijing, China, 2005. ACM.

[16] M. Pérez Millán and A. G. Turjanski. MAPK's networks and their capacity for multistationarity due to toric steady states. *Math. Biosci.*, 262:125–37, 2015.

[17] A. Seidl. *Cylindrical Decomposition Under Application-Oriented Paradigms*. PhD thesis, Universität Passau, 94030 Passau, Germany, Mar. 2006.

[18] A. Seidl and T. Sturm. A generic projection operator for partial cylindrical algebraic decomposition. In R. Sendra, editor, *Proceedings of the 2003 International Symposium on Symbolic and Algebraic Computation (ISSAC 03), Philadelphia, Pennsylvania*, pages 240–247. ACM Press, New York, NY, 2003.

[19] G. Weng, U. S. Bhalla, and R. Iyengar. Complexity in biological signaling systems. *Science*, 284(5411):92–6, 1999.