

Algebraic Methods for the Study of Multistationarity in Mass-Action Networks

MathCoRe Research Project of Alexandru Iosif

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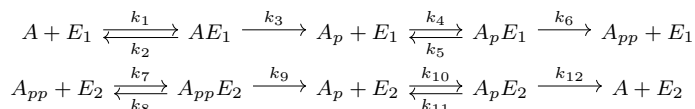
Summary

The subject of this project is Algebraic Systems Biology with focus on detecting multistationarity in mass-action networks. The main contributions of this work can be divided into three parts. First, we develop the theory of multistationarity for mass-action networks whose positive steady states admit a monomial parameterization and we apply this theory to the well-known sequential and distributive phosphorylation networks. Second, we prove that mass-action networks with the isolation property have toric positive steady states. Finally, we introduce a new discriminant, the Sturm discriminant, which is suitable for the study of parametric families of polynomial systems with positive roots.

Mass-action networks

- The Theory of Chemical Reaction Networks started to develop early in the 1970s (mainly by Feinberg, Horn, Jackson, and collaborators).
- One of the main application of this theory is Systems Biology.

Example. The following is the 2-site phosphorylation:



Assumption: *The dynamics is encoded in the network.*

Mass-action hypothesis: *Usually it is assumed that the speed of a reaction is directly proportional to the concentration of reactants.*

- The dynamics of a mass-action network is given by ODEs with polynomial right hand side: $\dot{x}_i = P_i(k, x) \in \mathbb{R}[k][x]$, $i \in [n]$.
- Often these dynamical systems have linear conservation laws.

Example: For the 2-site phosphorylation let x_1 denote the concentration of A , x_2 of E_1 , etc. There are three conserved quantities:

$$\begin{aligned} x_2 + x_3 + x_5 &= c_1, & x_7 + x_8 + x_9 &= c_2, \\ x_1 + x_3 + x_4 + x_5 + x_6 + x_8 + x_9 &= c_3. \end{aligned}$$

Relation to Complexity Reduction

- Often one does not try to solve these dynamical systems, but rather pick a more modest objective. For example, equilibria contain information about long-term behaviour and different modi operandi.
- In particular, one is frequently interested in the existence of multiple equilibria (multistationarity).

Problem: *Decide whether there exist values of the conserved quantities that enable multiple positive equilibria.*

- While in general this can be a hard problem, biochemical networks have special combinatorial properties. For example, in 2017 Millán et al. proved that many biochemical networks have toric equilibria.
- From a computational and mathematical point of view, toric equilibria are interesting, as they admit monomial parameterizations.

Publications and References

- [1] Frédéric Bihan, Alicia Dickenstein, and Magalf Giaroli. Lower bounds for positive roots and regions of multistationarity in chemical reaction networks. *preprint*, arXiv:1807.05157, 2018.
- [2] Carsten Conradi, Alexandru Iosif, and Thomas Kahle. Multistationarity in the space of total concentrations for systems that admit a monomial parametrization. *preprint*, arXiv:1810.08152, 2019.
- [3] Carsten Conradi and Dietrich Flockerzi. Multistationarity in mass action networks with applications to ERK activation. *J. Math. Bio.*, 65(1):107–156, 2012.

Dynamical systems with positive toric steady states

Theorem (Conradi, I., Kahle)

In the space of conserved quantities of a system with positive toric steady states the multistationarity locus is a cone missing the origin.

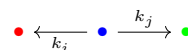
Theorem (Bihan, Dickenstein, Giaroli; Conradi, I., Kahle)

Generically, in the space of conserved quantities c_1 , c_2 , and c_3 of the 2-site phosphorylation multistationarity is possible if and only if $c_2 < c_3$ or $c_1 < c_3$.

Idea of the proof: The “if” part was proved by Bihan et al. The “only if” part was proved in Mathematica; previous to computations, a dimension reduction was done by means of monomial parameterizations.

Dynamical systems with the isolation property

- The pair $\{i, j\}$, $i < j$, is called a doubling set whenever



- Doubling sets induce a **clustering** of the reactions.

Definition (local version of: 2011; Conradi and Flockerzi)

For a fixed k , a system has the isolation property if coordinates of the nonnegative kernel of the stoichiometric matrix indexed by different clusters have disjoint supports.

Theorem (Conradi, I., Kahle)

The positive equilibria of a system with the isolation property are toric.

Sturm discriminants

- Biochemical networks are often large and measurement data is noisy. Hence this data can be encoded in a set of parameters. Discriminants offer a way to classify the parameters with respect to some property.

Definition Let $R = \mathbb{R}[t_1, \dots, t_m]$, $\mathbb{K} = \mathbb{R}(t_1, \dots, t_m)$, and $p \in R[x]$. The Sturm discriminant $\Delta_S(p)$ of $p \in R[x]$ is the polynomial obtained by multiplying the numerators and denominators of the leading coefficients and nonzero constant terms of elements of $s(p)$. Connected components of $\mathbb{R}^m \setminus \mathbb{V}(\Delta_S(p))$ are called cells of the discriminant.

Theorem (I.)

For $a \in \mathbb{R}^m$, let p_a denote the specialization of p to $t = a$. If $p(0) \neq 0$ and a and b are contained in a common cell of $\mathbb{V}(\Delta_S(p))$, then p_a and p_b have the same number of distinct positive roots.

- [4] Mercedes Pérez Millán and Alicia Dickenstein. The structure of MESSI biological systems. *SIAM Journal on Applied Dynamical Systems*, 17(2):1650–1682, 2018.

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