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:

$$A + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} AE_1 \xrightarrow{k_3} A_p + E_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} A_pE_1 \xrightarrow{k_6} A_{pp} + E_1$$

$$A_{pp} + E_2 \underset{k_8}{\overset{k_7}{\rightleftarrows}} A_{pp}E_2 \xrightarrow{k_9} A_p + E_2 \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} A_pE_2 \xrightarrow{k_{12}} A + E_2$$

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:

$$x_2 + x_3 + x_5 = c_1, \quad x_7 + x_8 + x_9 = c_2,$$
$$x_1 + x_3 + x_4 + x_5 + x_6 + x_8 + x_9 = c_3.$$

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.

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

$$c_2 < c_3 \text{ or } c_1 < c_3.$$

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 $R = \mathbb{R}[t_1, \ldots, t_m]$, $\mathbb{K} = \mathbb{R}(t_1, \ldots, t_m)$, 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.

Publications and References

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