Multistationarity in the space of total concentrations for systems that admit a monomial parametrization

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• For the 2−site phosphorylation multistationarity is possible if and only if the concentration of the substrate is larger than either the concentration of the kinase or of the phosphatase. (Theorem 1)

• For toric systems multistationarity is scale invariant in the space of total concentrations. (Theorem 2)

An introductory example

$$3X_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} 2X_1 + X_2$$

$$X_1 + X_2 \xrightarrow{k_3} 2X_2$$

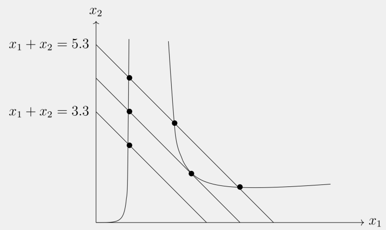
$$X_2 \xrightarrow{k_4} X_1$$

Dynamics:

$$\begin{aligned} \dot{x}_1 &= -\,k_1x_1^3 + k_2x_1^2x_2 - k_3x_1x_2 + k_4x_2 \\ \dot{x}_2 &= k_1x_1^3 - k_2x_1^2x_2 + k_3x_1x_2 - k_4x_2. \end{aligned}$$

Conservation relation:

$$x_1 + x_2 = c.$$



Problem. *Classify* <u>*parameters*</u> *with respect to multistationarity.*

Discriminant:

$$\begin{aligned} &k_2^2k_3^2c^4 - 4k_2^3k_4c^4 - 4k_1k_3^3c^3 - 2k_2k_3^3c^3 \\ &+18k_1k_2k_3k_4c^3 + 8k_2^2k_3k_4c^3 + k_3^4c^2 + 6k_1k_3^2k_4c^2 \\ &-2k_2k_3^2k_4c^2 - 27k_1^2k_4^2c^2 - 36k_1k_2k_4^2c^2 - 8k_2^2k_4^2c^2 \\ &-2k_3^3k_4c + 6k_1k_3k_4^2c + 8k_2k_3k_4^2c + k_3^2k_4^2 - 4k_1k_4^3 \\ &-4k_2k_4^3 = 0 \end{aligned}$$

Phosphorylations

$$A + K \underset{k_2}{\overset{k_1}{\rightleftarrows}} AK \xrightarrow{k_3} A_p + K \underset{k_5}{\overset{k_4}{\rightleftarrows}} A_pK \xrightarrow{k_6} A_{pp} + K$$

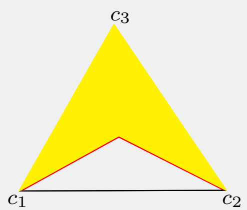
$$A_{pp} + P \underset{k_8}{\overset{k_7}{\rightleftarrows}} A_{pp}P \xrightarrow{k_9} A_p + P \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} A_pP \xrightarrow{k_{12}} A + P$$

Conservation relations:

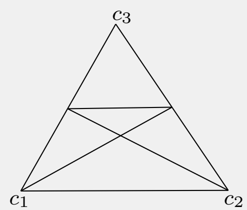
$$[K] + [AK] + [A_pK] = c_1, \quad [P] + [A_pP] + [A_{pp}P] = c_2,$$
$$[A] + [A_p] + [A_{pp}] + [AK] + [A_pK] + [A_pP] + [A_{pp}P] = c_3.$$

Theorem 1 (Bihan, Dickenstein, Giaroli; Conradi, I., Kahle) *Generically, in the space of total concentrations c_1, c_2, and c_3 of the previous network multistationarity is possible if and only if*

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



Multistationarity



Chamber decomposition

Multistationarity in the space of total concentrations

• Total concentrations are experimentally more accessible than rate constants.

Problem. *Classify* <u>*total concentrations*</u> *with respect to multistationarity.*

• Rate constants are easy to eliminate for (positive) toric systems.

Systems with positive toric steady states

Definition. *Dynamical systems with positive toric steady states are systems whose positive equilibria are parametrized by monomials.*

Example. Take the following network:

$$X_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X_2$$

As $I = \langle k_1x_1 - k_2x_2 \rangle$, for $k \in \mathbb{R}^2_{>0}$, we get

$$\mathbb{V}(I) \cap \mathbb{R}^2_{>0} = \operatorname{im} \begin{pmatrix} \mathbb{R}_{>0} & \to & \mathbb{R}^2_{>0} \\ t & \mapsto & (t, \frac{k_1}{k_2}t) \end{pmatrix}$$

Theorem 2 (Conradi, I., Kahle). *In the space of total concentrations of a system with positive toric steady states the multistationarity locus is a cone with the origin removed.*

Publications and References

[1] Alexandru Iosif. *Algebraic Methods for the Study of Multistationarity in Mass-Action Networks.* PhD thesis, Otto-von-Guericke-Universität Magdeburg, 2019.

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[3] Frédéric Bihan, Alicia Dickenstein, and Magalí Giaroli. Lower bounds for positive roots and regions of multistationarity in chemical reaction networks. *preprint, arXiv:1807.05157*, 2018.

[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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