Faculty of Science

Lecture 13: (Partial) Parameter regions for multistationarity

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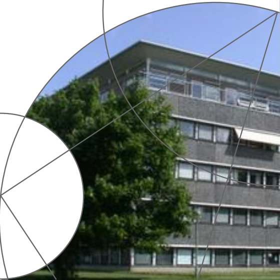


Sometimes partial answers are more informative

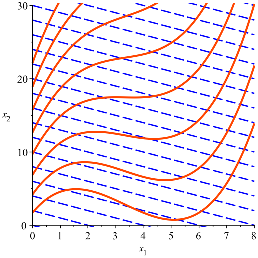
Find projections of the parameter region of multistationarity into subsets of parameters.

Some partial answers (employing polyhedral geometry techniques):

- Partial parameter regions on the reaction rate constants κ – NOW
- Partial parameter regions involving total amounts T and some κ (Bihan, Dickenstein, Giaroli). – SHORTLY
- Partial parameter regions on only T for systems where $N(\kappa \circ x^B) = 0$ in $\mathbb{R}^n_{>0}$ admits a monomial parametrization (Conradi, Iosif, Kahle).

κ enables multistationarity if there exists T such that $\#C_{\kappa,T} \geq 2$.

What values of κ enable multistationarity?



Recall the theorem

Theorem. Consider a network such that assumptions (A) and (B) hold.

Fix κ. Assume a positive parametrization exists. There exists a (computable) polynomial $p_\kappa(x)$ such that

(A) Uniqueness. If

$$\operatorname{sign}(p_\kappa(x)) = + \quad \text{for all positive } x,$$

then $\#C_{\kappa,T} = 1$ for all T.

(B) Multistationarity. If

$$\operatorname{sign}(p_\kappa(x^*)) = - \quad \text{for some positive } x^*,$$

then $\#C_{\kappa,T} \geq 2$ for some T.

Example: Hybrid two-component system

If $\text{sign}(p_\kappa(x)) = +$ for all positive x, then $\#C_{\kappa,T} = 1$ for all T.

If $\text{sign}(p_\kappa(x^*)) = -$ for one positive x^*, then $\#C_{\kappa,T} \geq 2$ for some T.

$$\mathrm{HK_{00}} \xrightarrow{\kappa_1} \mathrm{HK_{p0}} \xrightarrow{\kappa_2} \mathrm{HK_{0p}} \xrightarrow{\kappa_3} \mathrm{HK_{pp}}$$
$$\mathrm{HK_{0p}} + \mathrm{Htp} \xrightarrow{\kappa_4} \mathrm{HK_{00}} + \mathrm{Htp_p}$$
$$\mathrm{HK_{pp}} + \mathrm{Htp} \xrightarrow{\kappa_5} \mathrm{HK_{p0}} + \mathrm{Htp_p}$$
$$\mathrm{Htp_p} \xrightarrow{\kappa_6} \mathrm{Htp}$$

$$p_\kappa(x) = \kappa_1\kappa_2\kappa_3\kappa_6 + (\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^2 + \kappa_2\kappa_4\kappa_5^2\left(\frac{\kappa_1}{\kappa_3} - 1\right)x_4x_5^2 + 2\kappa_1\kappa_2\kappa_4\kappa_5 x_4x_5 + (\kappa_2+\kappa_3)\kappa_1\kappa_5\kappa_6 x_5 + \kappa_1\kappa_2\kappa_3\kappa_5 x_4$$

- If $\kappa_1 \geq \kappa_3$: sign$=+$ for all $x_4, x_5 > 0$. Hence $\#C_{\kappa,T} = 1$ for all T.
- If $\kappa_1 < \kappa_3$, let $x_i = \xi$ and ξ be arbitrarily large. Then sign$=-$. Hence $\#C_{\kappa,T} \geq 2$ for some T.

κ enables multistationarity for some total amount $T \quad \Leftrightarrow \quad \kappa_1 < \kappa_3$

Original problem of multistationarity: Understand for what κ, T, the system

$$N(\kappa \circ x^B) = 0, \qquad Wx = T$$

has at least two positive solutions.

New problem: For which κ does it hold

$$p_\kappa(x^*) < 0, \qquad \text{for some positive } x^*?$$

We deal now with the question of deciding whether a polynomial is non-negative over the positive orthant.

Did we gain anything? Use of polyhedral geometry techniques

Recall: Signs and the Newton polytope

Multivariate polynomial $f(x) = \sum_{v\in\mathbb{N}^n} \alpha_v x^v$.

The Newton polytope $\mathcal{N}(f)$ of f is the convex hull of the exponents $v \in \mathbb{N}^n$ for which $\alpha_v \neq 0$.

Proposition: Given a face τ of the Newton polytope, let f_τ be the restriction of f to the monomials supported in the face.

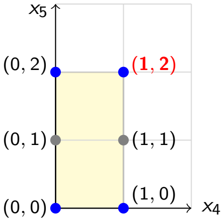
For any $y^* \in \mathbb{R}^n_{>0}$ there exists $x^* \in \mathbb{R}^n_{>0}$ such that

$$\mathrm{sign}(f(x^*)) = \mathrm{sign}(f_\tau(y^*)).$$

In particular: for every vertex v of $\mathcal{N}(f)$, there exists $x^* \in \mathbb{R}^n_{>0}$ such that

$$\mathrm{sign}(f(x^*)) = \mathrm{sign}(\alpha_v).$$

$$\begin{aligned} p(x) = {} & \kappa_1\kappa_2\kappa_3\kappa_6 \\ & + (\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^2 \\ & + \kappa_2\kappa_4\kappa_5^2\left(\frac{\kappa_1}{\kappa_3} - 1\right) x_4 x_5^2 \\ & + 2\kappa_1\kappa_2\kappa_4\kappa_5 x_4 x_5 \\ & + (\kappa_2+\kappa_3)\kappa_1\kappa_5\kappa_6 x_5 \\ & + \kappa_1\kappa_2\kappa_3\kappa_5 x_4 \end{aligned}$$



This often works!

This method works for numerous networks!

- With a positive parametrization: find parameter regions
- With convex parameters: decide multistationarity

Gene regulatory network

If $\text{sign}(p_\kappa(x)) = +$ for all positive x, then $\#C_{\kappa,T} = 1$ for all T.

If $\text{sign}(p_\kappa(x^*)) = -$ for one positive x^*, then $\#C_{\kappa,T} \geq 2$ for some T.

$$X_1 + X_1 \xrightarrow{\kappa_1} P_1 \qquad P_1 \xrightarrow{\kappa_3} 0 \qquad X_2 + P_1 \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} Y_1 \qquad X_1 + Y_2 \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} Y_3$$

$$X_2 + X_2 \xrightarrow{\kappa_2} P_2 \qquad P_2 \xrightarrow{\kappa_4} 0 \qquad 2P_2 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} Y_2$$

The sign of $p_\kappa(x)$ agrees with the sign of:

$$q_\kappa(x) = -\kappa_2\kappa_7\kappa_9 x_4^2 x_5 + \kappa_4\kappa_7\kappa_9 x_4^3 + \kappa_2\kappa_8\kappa_{10} x_5 + \kappa_4\kappa_8\kappa_{10} x_4$$

Can this polynomial be negative?

YES, $x_4^2 x_5$ corresponds to a vertex of the Newton polytope.

All κ enable multistationarity for some T

Disclaimer: This network is not conservative, but satisfies a milder condition (dissipativity) under which the theorem applies as well.

Signs and the Newton polytope

Dual phosphorylation cycle (the *model model*)

$$A + K \rightleftharpoons AK \xrightarrow{k_1} A_p + K \rightleftharpoons A_pK \xrightarrow{k_2} A_{pp} + K$$

$$A_{pp} + F \rightleftharpoons A_{pp}F \xrightarrow{k_4} A_p + F \rightleftharpoons A_pF \xrightarrow{k_3} A + F$$

$K_1, K_2, K_3, K_4 > 0$ Michaelis-Menten constants (depending on κ).

$$\begin{aligned}
p_\kappa(x) = {} & K_2^2K_4k_1^2k_2(k_1k_4 - k_2k_3)x_1^4x_3^2 + K_1K_2^2K_4k_1^2k_3k_2^2x_1^4x_3 \\
& + K_1K_2K_3k_1k_3k_4(k_1k_4 - k_2k_3)x_1^3x_2^2x_3 + K_2^2K_3k_1^2k_4(k_1k_4 - k_2k_3)x_1^3x_2x_3^2 \\
& + 2\,K_1K_2K_3K_4k_1^2k_3k_2k_4x_1^3x_2x_3 + K_1K_2K_3k_1k_3k_4(k_1k_4 - k_2k_3)x_1^2x_2^3x_3 \\
& + (K_1^2K_2K_3k_1k_3^2k_4(k_2 + k_4)x_1^2x_2^3 + K_1K_2K_3k_1k_3k_4(k_1k_4 - k_2k_3)x_1^2x_2^2x_3^2 \\
& + K_1K_2K_3k_1k_3k_4((K_2 + K_3)k_1k_4 - (K_1 + K_4)k_2k_3)x_1^2x_2^2x_3 \\
& + K_1^2K_2K_3K_4k_1k_2k_3^2k_4x_1^2x_2^2 + K_1^2K_3^2k_3^2k_4^2(k_1 + k_3)x_1x_2^4 + 2K_1^2K_2K_3k_1k_3^2k_4^2x_1x_2^3x_3 \\
& + K_1^2K_2K_3^2k_1k_3^2k_4^2x_1x_2^3 + K_1^2K_3^2k_3^3k_4^2x_2^4x_3 + K_1^3K_3^2k_3^3k_4^2x_2^4
\end{aligned}$$

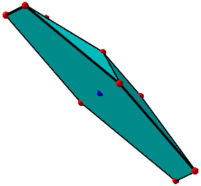
$$b_1(\kappa) = k_1k_4 - k_2k_3, \qquad b_2(\kappa) = k_1k_4(K_2 + K_3) - k_2k_3(K_1 + K_4)$$

$$b_1(\kappa) = k_1k_4 - k_2k_3, \qquad b_2(\kappa) = k_1k_4(K_2+K_3) - k_2k_3(K_1+K_4)$$

- $b_1(\kappa) \geq 0$ and $b_2(\kappa) \geq 0 \quad \Rightarrow \quad p_\kappa(x) > 0 \quad \Rightarrow \quad \#C_{\kappa,T} = 1$ for all T.
- $b_1(\kappa)$ corresponds to a vertex of the Newton polytope. Hence

$$b_1(\kappa) < 0 \quad \Rightarrow \quad p_\kappa(x) < 0 \text{ for some } x \quad \Rightarrow \quad \#C_{\kappa,T} \geq 2 \text{ for some } T.$$

- $b_2(\kappa)$ does not correspond to a vertex. What happens when $b_2(\kappa) < 0$ and $b_1(\kappa) \geq 0$?

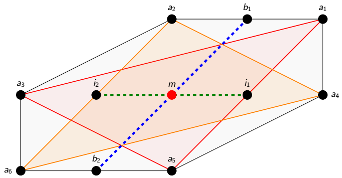


Conradi, Mincheva (2015)

New inequalities

Both situations occur when

$$b_1(\kappa) = k_1 k_4 - k_2 k_3 \geq 0,$$
$$b_2(\kappa) = k_1 k_4(K_2 + K_3) - k_2 k_3(K_1 + K_4) < 0$$



Using circuit numbers and the decomposition:

- If
$$-b_2(\kappa) \leq 3(\alpha_{a_1}\alpha_{a_3}\alpha_{a_5})^{\frac{1}{3}} + 3(\alpha_{a_2}\alpha_{a_4}\alpha_{a_6})^{\frac{1}{3}} + 2(\alpha_{b_1}\alpha_{b_2})^{\frac{1}{2}} + 2(\alpha_{i_1}\alpha_{i_2})^{\frac{1}{2}},$$
then $p_\kappa(x) > 0$ for all positive x, and hence κ does not enable multistationarity.
- There exist κ that enable multistationarity. (Requires that exactly one of K_1 or K_4 are large enough.)
- The region where multistationarity is enabled and the region where it is not, are both connected.

Feliu, Kaihnsa, de Wolff, Yürück (2020), JDDE
Feliu, Kaihnsa, de Wolff, Yürück (2023), SIAM Appl Dyn Sys

Appendix: computational approach

To work with the theorem, do as follows:

- Use N and B to find a matrix of conservation laws W, and the generators of $\ker(N) \cap \mathbb{R}^n_{\geq 0}$. Write the generators as columns of a matrix E. Decide whether the network is conservative and has no relevant boundary steady states.
- Construct the matrix $M(\lambda, h)$ consisting of the rows of W and the rows of $N' \operatorname{diag}(E\lambda) B^\top \operatorname{diag}(h)$, with N' of full rank such that $\ker N' = \ker N$. Choose the right order!
- Find the determinant of $M(\lambda, h)$ and check the sign of the coefficients:
  - If all positive, then monostationarity.
  - If coefficients of both sign, construct the Newton Polytope P of $\det(M(\lambda, h))$ by finding the exponent vectors of $\det(M(\lambda, h))$. Find the vertices of P. Check for each of them the sign of the coefficient. If one of the coefficients is negative, then $\det(M(\lambda, h))$ attains negative values and the network admits multistationarity.
- To find parameter regions, we need to find a parametrization of the positive steady state variety and evaluate the determinant of the relevant Jacobian matrix to that. Study the signs as above by viewing the polynomial as a polynomial in the variables of the parametrization.