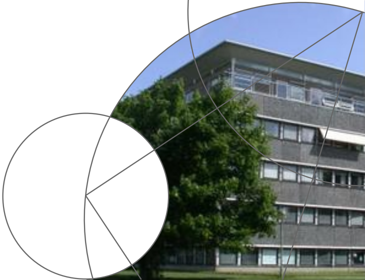
Faculty of Science

Monomial parametrizations for the steady states of Chemical Reaction Networks

Elisenda Feliu (join with Oskar Henriksson)

Work in progress

Department of Mathematical Sciences
University of Copenhagen



Bonn, March 2022

Setting

- Reaction network:

$$X_1 \xrightarrow{\kappa_1} X_2 \qquad 2X_2 \xrightarrow{\kappa_2} 2X_1 \qquad X_1 + X_2 \xrightarrow{\kappa_3} 2X_2$$

- Dynamical system: (x_i = concentration of species X_i)

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -1 & 2 & -1 \\ 1 & -2 & 1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix},$$

$$\dot{x} = N(\kappa \circ x^B), \quad x \in \mathbb{R}^n_{\geq 0}, \quad B, N \in \mathbb{R}^{n \times r}, \quad \kappa \in \mathbb{R}^r_{>0}$$

N = stoichiometric matrix, $\kappa_j > 0$ reaction rate constant, $(\kappa \circ x^B)$ mass-action kinetics.

- Stoichiometric compatibility classes:

$$x_1 + x_2 = c, \qquad Wx = c, \qquad x \in \mathbb{R}^n_{\geq 0}$$

W = matrix with rows a basis of the left kernel of N, $\ker(N^T) = \operatorname{Im}(N)^\perp$.

($W\dot{x} = 0$ and trajectories are confined to $Wx = c$, with c depending on the initial condition.)

- Multistationarity: More than one steady state (solution to $N(\kappa \circ x^B) = 0$) in some stoichiometric compatibility class.

Monomial parametrizations

Consider the set of steady states

$$V_\kappa = \{x \in \mathbb{R}^n_{>0} \mid N(\kappa \circ x^B) = 0\}, \qquad N \in \mathbb{R}^{n\times r}, B \in \mathbb{R}^{n\times r}.$$

Question: Does V_κ admit a monomial parametrization for all κ, with the same exponent matrix $A \in \mathbb{Z}^{d\times n}$?

$$V_\kappa = x^*_\kappa \circ X_A := \{x^*_\kappa \circ t^A \mid t \in \mathbb{R}^d_{>0}\},$$

where

$$(t^A)_j = \prod_{i=1}^{d} t_i^{a_{ij}}, \qquad x^*_\kappa \in V_\kappa.$$

Equivalently:
If we let $V_{\kappa,\mathbb{C}}$ denote the complex variety defined by the steady state equations, we want to determine when $V_{\kappa,\mathbb{C}}$ has only one irreducible component intersecting $\mathbb{R}^n_{>0}$, which is toric (defined by binomial equations).

Example

The IDHKP-IDH system in bacterial cells from Shinar-Feinberg:

$$X_1 + X_2 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_3 \xrightarrow{\kappa_3} X_1 + X_4 \qquad X_3 + X_4 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} X_5 \xrightarrow{\kappa_6} X_3 + X_2$$

We have

$$N = \begin{bmatrix} -1 & 1 & 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 & 1 \\ 1 & -1 & -1 & -1 & 1 & 1 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \end{bmatrix}.$$

Monomial parametrization:

$$x_1 = t_1, \quad x_2 = t_2, \quad x_3 = \frac{\kappa_1}{\kappa_3 + \kappa_2} t_1\, t_2, \quad x_4 = \frac{\kappa_3(\kappa_6 + \kappa_5)}{\kappa_6 \kappa_4}, \quad x_5 = \frac{\kappa_1 \kappa_3}{\kappa_6(\kappa_3 + \kappa_2)} t_1\, t_2.$$

So

$$A = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 & 1 \end{bmatrix}.$$

Steady states and monomial parametrizations

Question: Does V_κ admit a monomial parametrization for all κ, with the same exponent matrix $A \in \mathbb{Z}^{d\times n}$?

$$V_\kappa = x^*_\kappa \circ X_A := \{x^*_\kappa \circ t^A \mid t \in \mathbb{R}^d_{>0}\}$$

Basic examples: complex balancing for deficiency zero networks, networks in the deficiency one theorem.

Reason:

- It is useful to have parametrizations, and monomial parametrizations are easy.
- Knowing A, even if x^*_κ is not known, allows to decide upon multistationarity (Conradi, Dickenstein, Pérez-Millán, Shiu).
- Varieties defined by monomial parametrizations are "nice" (toric varieties: dimension, nonsingularity...).
- For such varieties, total amounts can be scaled and multistationarity is preserved (Conradi, Kahle).
- (...)

Mathematical and computational methods

Does V_κ admit a monomial parametrization for all κ, with the same exponent matrix $A \in \mathbb{Z}^{d\times n}$?

$$V_\kappa = x^*_\kappa \circ X_A := \{x^*_\kappa \circ t^A \mid t \in \mathbb{R}^d_{>0}\}$$

- Find the irreducible components of V_κ, decide which ones intersect $\mathbb{R}^n_{>0}$, decide toricity by finding a Gröbner basis of the defining ideal: if it consists of binomials, then the monomial parametrization exists.

  In practice:

- Find a Gröbner basis of the steady state ideal, and see whether it consists of binomials. This implies the monomial parametrization exists over $V_{\kappa,\mathbb{C}}$ (only sufficient condition).

  Working with κ is not straightforward (comprehensive Gröbner bases, etc...)

- Some works look at specific families and check whether binomials arise from linear operations.
- Phrase as a quantifier elimination problem (people in the audience can tell you about that...).

Today: Exploit the structure of the system.
Our systems are not generic and we want toricity for all κ.

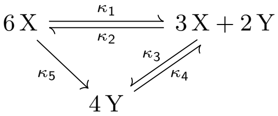
Note: As only the row space of N matters for

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

I'll often replace N by one of maximal rank, and denote it by N.

$$N \in \mathbb{R}^{n \times r} \qquad \rightarrow \qquad N \in \mathbb{R}^{s \times r}$$

Triangle network



The steady states are the zeros of

$$f_\kappa = \kappa_1 x_1^6 - \kappa_2 x_1^3 x_2^2 + \kappa_3 x_1^3 x_2^2 - \kappa_4 x_2^4 + 2\kappa_5 x_1^6.$$

So

$$N = \begin{bmatrix} 1 & -1 & 1 & -1 & 2 \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} 6 & 3 & 3 & 0 & 6 \\ 0 & 2 & 2 & 4 & 0 \end{bmatrix}.$$

It holds

$$V_\kappa = \{(t^2, \alpha t^3) \mid t \in \mathbb{R}_{>0}\},$$

where α is the unique positive root of the polynomial $-(\kappa_1 + 2\kappa_5) + (\kappa_2 - \kappa_3)y^2 + \kappa_4 y^4$.

In this example, the ideal $\langle f_\kappa \rangle$ is only binomial when $\kappa_2 = \kappa_3$.

Necessary condition: invariance under the action X_A

Theorem. (Feliu, Henriksson) Let $V_\kappa = \{x \in \mathbb{R}^n_{>0} | \; N(\kappa \circ x^B) = 0\}$ with $N \in \mathbb{R}^{n\times r}, B \in \mathbb{R}^{n\times r}$. Let $A \in \mathbb{Z}^{d\times n}$.
The following are equivalent:

- $x^* \circ X_A \subseteq V_\kappa$ for all $\kappa \in \mathbb{R}^r_{>0}$ and $x^* \in V_\kappa$.
- For every extreme ray w of $\ker(N) \cap \mathbb{R}^r_{\geq 0}$ and every $i, j \in \operatorname{supp}(w)$, it holds that

$$\operatorname{col}_i(AB) = \operatorname{col}_j(AB)$$

In the IDHKP-IDH system: extreme rays of $\ker(N) \cap \mathbb{R}^r_{\geq 0}$:

$$(1,0,1,1,0,1), \quad (0,0,0,1,1,0), \quad (1,1,0,0,0,0)$$

We have:

$$AB = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 & 1 \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix},$$

The theorem holds: V_κ is invariant by the action by X_A.

In practice: detecting invariance

Theorem. (Feliu, Henriksson) Let $A \in \mathbb{Z}^{d\times n}$. The following are equivalent:

(i) $V_\kappa \circ X_A \subseteq V_\kappa$ for all $\kappa \in \mathbb{R}^r_{>0}$.

(ii) For every extreme ray w of $\ker(N) \cap \mathbb{R}^r_{\geq 0}$ and every $i,j \in \mathrm{supp}(w)$, it holds that

$$\mathrm{col}_i(AB) = \mathrm{col}_j(AB)$$

When (ii) holds, V_κ is a union of cosets of X_A.

Approach:

- Find the extreme rays and partition the set $\{1,\dots,n\}$ accordingly.
- Consider a symbolic matrix A and impose (ii) on AB. This gives a linear system.
- Solve the system to find A of maximal rank.

In practice: detecting invariance

- Find the extreme rays and partition the set $\{1, \ldots, n\}$ accordingly.
- Consider a symbolic matrix A and impose (ii) on AB. This gives a linear system.
- Solve the system to find A of maximal rank.

In the IDHKP-IDH system: extreme rays of $\ker(N) \cap \mathbb{R}^r_{\geq 0}$:

$$(1,0,1,1,0,1), \quad (0,0,0,1,1,0), \quad (1,1,0,0,0,0).$$

All columns of AB need to be equal.

This gives the system

$$\begin{bmatrix} a_{1,1}+a_{1,2} & a_{1,3} & a_{1,3} & a_{1,3}+a_{1,4} & a_{1,5} & a_{1,5} \\ a_{2,1}+a_{2,2} & a_{2,3} & a_{2,3} & a_{2,3}+a_{2,4} & a_{2,5} & a_{2,5} \end{bmatrix} = \begin{bmatrix} c_{1,1} & c_{1,1} & c_{1,1} & c_{1,1} & c_{1,1} & c_{1,1} \\ c_{2,1} & c_{2,1} & c_{2,1} & c_{2,1} & c_{2,1} & c_{2,1} \end{bmatrix}$$

One solution is

$$A = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 & 1 \end{bmatrix}.$$

This approach always returns a matrix A

Consider the network

$$\begin{aligned} \mathrm{HK_{00}} &\to \mathrm{HK_{p0}} \to \mathrm{HK_{0p}} \to \mathrm{HK_{pp}} \\ \mathrm{HK_{0p}} + \mathrm{RR} &\to \mathrm{HK_{00}} + \mathrm{RR_p} \\ \mathrm{HK_{pp}} + \mathrm{RR} &\to \mathrm{HK_{p0}} + \mathrm{RR_p} \\ \mathrm{RR_p} &\to \mathrm{RR} \end{aligned}$$

We apply the algorithm and obtain:

$$A = \begin{bmatrix} 1 & 1 & 1 & 1 & 0 & 1 \end{bmatrix}$$

of rank 1, while the steady state variety has dimension 2. There is no monomial parametrization.

Missing:

- Determine the dimension of V_κ.
- If dimensions match, then V_κ is a finite union of cosets of the form $x^*_\kappa \circ X_A$

Counting components

Well-known result going back to Feinberg, Horn, Jackson:

Let $A \in \mathbb{Z}^{d\times n}$ and $x^* \in \mathbb{R}^n_{>0}$. Then it holds that

$$\#((x^* \circ X_A) \cap (\ker(A) + x_0)) = 1 \qquad \text{for all } x_0 \in \mathbb{R}^n_{>0}\,.$$

$\#(V_\kappa \cap (\ker(A) + x_0))$ gives the number of cosets of the form $x^* \circ X_A$ whose union is V_κ.

Result. (Feliu, Henriksson) Let $A \in \mathbb{Z}^{d\times n}$. Assume

(i) $V_\kappa \circ X_A \subseteq V_\kappa$ for all $\kappa \in \mathbb{R}^r_{>0}$.

(ii) $\#(V_\kappa \cap (\ker(A) + x_0)) = 1$ for all $x_0 \in \mathbb{R}^n_{>0}$ and $\kappa \in \mathbb{R}^r_{>0}$.

Then

$$V_\kappa = x^*_\kappa \circ X_A$$

for any $x^*_\kappa \in V_\kappa$.

Checking (ii): the literature on multistationarity has been addressing a similar problem for many years!!

$$\#(V_\kappa \cap (S + x_0)).$$

Injectivity

Injectivity criterion. (Feliu, Wiuf, 2013) Let $f_\kappa = N\,\mathrm{diag}(\kappa)x^B$, with $N \in \mathbb{R}^{s\times r}$, $B \in \mathbb{R}^{n\times r}$, and let $A \in \mathbb{R}^{(n-s)\times n}$. The following conditions are equivalent:
(inj) f_κ is injective on $(\ker(A) + x_0) \cap \mathbb{R}^n_{>0}$ for all $x_0 \in \mathbb{R}^n_{>0}$ and $\kappa \in \mathbb{R}^r_{>0}$.
(det) The determinant of

$$M_{\mu,\alpha} := \begin{bmatrix} A \\ N\,\mathrm{diag}(\mu)B^t\,\mathrm{diag}(\alpha) \end{bmatrix}$$

is a nonzero polynomial in $\mathbb{R}[\mu,\alpha]$, with all nonzero coefficients having the same sign.

In the IDHKP-IDH system:

$$\det(M_{\mu,\alpha}) = -\alpha_1\alpha_3\alpha_4\mu_1\mu_3\mu_4 - \alpha_1\alpha_4\alpha_5\mu_1\mu_4\mu_6 \\ - \alpha_2\alpha_3\alpha_4\mu_1\mu_3\mu_4 - \alpha_2\alpha_4\alpha_5\mu_1\mu_4\mu_6 - \mu_2\alpha_3\mu_6\alpha_5\mu_4\alpha_4 - \mu_3\alpha_3\mu_6\alpha_5\mu_4\alpha_4.$$

As (det) holds, so does (inj), and $\#(V_\kappa \cap (\ker(A) + x_0)) \leq 1$ for all $x_0 \in \mathbb{R}^n_{>0}$ and $\kappa \in \mathbb{R}^r_{>0}$.

As we had invariance, the system admits a monomial parametrization with the matrix A we found, if we can show nonemptiness of V_κ.

Dimension

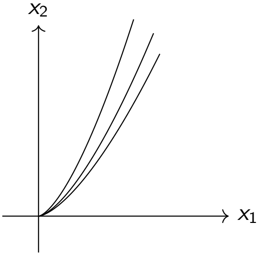
With

$$N = \begin{bmatrix} -6 & -3 & 6 & 3 \\ 4 & 2 & -4 & -2 \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} 9 & 3 & 0 & 6 \\ 0 & 4 & 6 & 2 \end{bmatrix},$$

the set V_κ satisfies the invariance condition with

$$A = \begin{bmatrix} 2 & 3 \end{bmatrix}$$

but there are more than one component for some κ:



To conclude that V_κ is a finite union of components admitting a monomial parametrization with the same exponent matrix, we need to know the dimension of V_κ.

Dimension and non-degeneracy

Non-degeneracy. Let $f_\kappa = N\,\mathrm{diag}(\kappa)x^B$, with $N \in \mathbb{R}^{s\times r}, B \in \mathbb{R}^{n\times r}$, and let $A \in \mathbb{R}^{(n-s)\times n}$. Let $E = \begin{bmatrix} E_1 & \cdots & E_\ell \end{bmatrix}$, where $E_1, \dots, E_\ell$ are the extreme rays of the convex polyhedral cone $\ker(N) \cap \mathbb{R}^r_{\geq 0}$.

Then

$$\{J_{f_\kappa}(x^*) \mid x^* \in V_\kappa, \kappa \in \mathbb{R}^r_{>0}\} = \{N\,\mathrm{diag}(E\lambda)\,B^t\,\mathrm{diag}(h) \mid \lambda \in \mathbb{R}^\ell_{\geq 0}, E\lambda \in \mathbb{R}^r_{>0}, h \in \mathbb{R}^n_{>0}\}\,.$$

The $s \times s$ minors of $N\,\mathrm{diag}(E\lambda)\,B^t\,\mathrm{diag}(h)$ are polynomials in $\mathbb{R}[\lambda, h]$. If at least one of these minors is nonzero for all $\lambda \in \mathbb{R}^\ell_{\geq 0}$ and all $h \in \mathbb{R}^n_{>0}$, then all points in V_κ are non-degenerate, and hence

$$\dim V_\kappa = n - s.$$

Emptiness

The results are non-informative, if we do not verify that V_κ is nonempty.

- If $\ker(N) \cap \mathbb{R}^r_{>0} \neq \emptyset$, then V_κ is nonempty for some κ.
- We can directly check whether $V_\kappa \neq \emptyset$ symbolically by writing

$$N \operatorname{diag}(\kappa) x^B = \Sigma_\kappa x^Y,$$

  impose $x^Y \in \ker(N) \cap \mathbb{R}^r_{>0}$, and apply logarithms.
- Quantifier elimination (Reduce).

Computational workflow to determine monomial parametrizations

- Find extreme rays of the flux cone $\ker(N) \cap \mathbb{R}^r_{\geq 0}$.
- Find the maximally fine partition of $\{1, \dots, r\}$ that is compatible with the structure of $\ker(N) \cap \mathbb{R}^r_{>0}$.
- Form symbolic $d \times n$ matrix A, and find expression for AB. Impose equality of columns according to the partition, and solve for A.
- If there is a solution with $\mathrm{rk}(A) = n - s$: V_κ may have toric components wrt A.
  - If we have injectivity wrt $\ker(A)$:
    For all κ, we have $V_\kappa = \varnothing$ or V_κ toric wrt A. Check nonemptiness.
  - If we have non-degeneracy for all (most) κ: Conclude finitely many toric components for all κ.
- If $\mathrm{rk}(A) < n - s$ for all solutions A:
  Rule out toric components if non-degeneracy check holds.

Note: this procedure returns A, but not necessarily a base point x^*_κ.

ODEbase - Mass-action models with steady states and $r \leq 100$

ID	n	r	d	Max rk(A)	Injectivity wrt ker(A)	Non-degeneracy	Binomial Gröbner basis	Toric components
2	13	34	2	1	–	–	–	✗
11	22	30	7	7	✓	✓	✓	1
26	11	16	3	2	–	–	–	✗
28	16	27	3	2	–	–	–	✗
30	18	32	3	2	–	–	–	✗
38	17	20	7	7	✓	✓	✓	1
57	6	10	1	1	✓	✓	✓	1
60	4	6	1	1	✓	✓	✓	1
85	17	34	5	1	–	–	–	✗
92	4	6	2	1	–	–	–	✗
200	22	46	7	1	–	–	–	✗
405	6	8	2	1	–	–	–	✗
413	5	9	1	0	–	–	–	✗
430	27	44	6	5	–	–	–	✗
431	27	44	6	2	–	–	–	✗
486	2	2	1	1	✓	✓	✓	1
487	6	6	3	3	✓	✓	✓	1
500	14	36	2	1	–	–	–	✗
629	5	4	3	3	✓	✓	✓	1
637	12	35	3	0	–	–	–	✗
647	11	11	5	4	–	–	–	✗
692	8	10	3	3	✓	✓	✓	1
854	4	7	1	1	✓	✓	✓	1
871	8	17	1	0	–	–	–	✗

ODEbase - Non-mass-action models with steady states and $r \leq 100$

ID	n	r	d	Max rk(A)	Injectivity wrt ker(A)	Non-degeneracy	Binomial Gröbner basis	$\lvert V_{\kappa}/X_A^+ \rvert$
2	13	34	2	1	✗			
4	5	7	2	2	✓	✓	✓	1
6	4	3	2	2	✓	✓	✗	1
9	26	30	11	11	✓	✓	✓	1
10	8	10	3	3	✓	✓	✓	1
11	22	30	7	7	✓	✓	✓	1
23	13	22	3	3	✓	✓	✓	1
24	3	4	1	1	✓	✓	✓	1
26	11	16	3	2	✗	✓	✗	∞
27	5	4	3	3	✓	✓	✓	1
28	16	27	3	2	✗	✓	✗	∞
29	6	7	3	3	✓	✓	✓	1
⋮								
704	17	33	2	2	✓	✓	✓	$\leqslant 1^*$
715	5	11	1	1	✓	✓	✓	1
720	9	25	1	1	✓	✓	✗	$\leqslant 1$
730	45	108	1	1	✓	✓	✓	1
757	10	18	3	3	✓	✓	✓	1
767	3	5	1	1	✓	✓	✓	1
810	14	53	1	1	✓	✓	✓	1
812	6	9	2	2	✓	✓	✓	$\leqslant 1^*$
823	16	20	6	6	✓	✓	✓	1
824	2	3	1	1	✓	✓	✓	1
832	20	29	7	5	✗	✓	✗	∞
835	55	74	23	23		✓	✓	$< \infty$
837	8	17	1	1	✓	✓	✓	1
842	21	26	10	7	✗	✓	✗	∞
853	9	21	1	1	✓	✓	✓	1
854	4	7	1	1	✓	✓	✓	1

Thank you for
your attention