# Symbolic Nonnegativity Certification for Identifying Multistationarity in CRN

Oguzhan Yürük

joint with Elisenda Feliu, Nidhi Kaihnsa, Timo de Wolff

MEGA 2021

TU Berlin

June 8, 2021

# Outline

# Polynomial Nonnegativity

Let $A \subset \mathbb{N}^n$ be a finite set of lattice points, and consider the set of real polynomials supported on $A$:

# Polynomial Nonnegativity

Let $A \subset \mathbb{N}^n$ be a finite set of lattice points, and consider the set of real polynomials supported on $A$:

$$\mathbb{R}[A] := \left\{ f(\boldsymbol{x}) = \sum_{\boldsymbol{\alpha} \in A_f} f_{\boldsymbol{\alpha}} \boldsymbol{x}^{\boldsymbol{\alpha}} \;\middle|\; A_f \subseteq A \text{ and } f_{\boldsymbol{\alpha}} \in \mathbb{R} \right\} \rightsquigarrow \begin{array}{l} \boldsymbol{x}^{\boldsymbol{\alpha}} := \prod_{i=1}^{n} x_i^{\alpha_i} \\ A_f := \left\{ \boldsymbol{\alpha} \in \mathbb{N}^n \mid f_{\boldsymbol{\alpha}} \neq 0 \right\} \text{(support)} \\ \mathcal{N}(f) := \operatorname{conv}(A_f) \subset \mathbb{R}^n \text{(Newton Polytope)} \end{array}$$

# Polynomial Nonnegativity

Let $A \subset \mathbb{N}^n$ be a finite set of lattice points, and consider the set of real polynomials supported on $A$:

$$\mathbb{R}[A] := \left\{ f(\boldsymbol{x}) = \sum_{\boldsymbol{\alpha} \in A_f} f_{\boldsymbol{\alpha}} \boldsymbol{x}^{\boldsymbol{\alpha}} \;\middle|\; A_f \subseteq A \text{ and } f_{\boldsymbol{\alpha}} \in \mathbb{R} \right\} \rightsquigarrow$$

$\boldsymbol{x}^{\boldsymbol{\alpha}} := \prod_{i=1}^{n} x_i^{\alpha_i}$

$A_f := \{\boldsymbol{\alpha} \in \mathbb{N}^n \mid f_{\boldsymbol{\alpha}} \neq 0\}$ (support)

$\mathcal{N}(f) := \text{conv}(A_f) \subset \mathbb{R}^n$ (Newton Polytope)

**Definition**

A polynomial $f \in \mathbb{R}[A]$ is called nonnegative, if $f(\boldsymbol{x}) \geq 0$ for all $\boldsymbol{x} \in \mathbb{R}^n$.

# Polynomial Nonnegativity

Let $A \subset \mathbb{N}^n$ be a finite set of lattice points, and consider the set of real polynomials supported on $A$:

$$\mathbb{R}[A] := \left\{ f(\boldsymbol{x}) = \sum_{\boldsymbol{\alpha} \in A_f} f_{\boldsymbol{\alpha}} \boldsymbol{x}^{\boldsymbol{\alpha}} \;\middle|\; A_f \subseteq A \text{ and } f_{\boldsymbol{\alpha}} \in \mathbb{R} \right\} \rightsquigarrow \begin{array}{l} \boldsymbol{x}^{\boldsymbol{\alpha}} := \prod_{i=1}^n x_i^{\alpha_i} \\ A_f := \{\boldsymbol{\alpha} \in \mathbb{N}^n \mid f_{\boldsymbol{\alpha}} \neq 0\} \text{(support)} \\ \mathcal{N}(f) := \operatorname{conv}(A_f) \subset \mathbb{R}^n \text{(Newton Polytope)} \end{array}$$

**Definition**

A polynomial $f \in \mathbb{R}[A]$ is called nonnegative, if $f(\boldsymbol{x}) \geq 0$ for all $\boldsymbol{x} \in \mathbb{R}^n$.

- Nonnegativity of polynomials is studied clasically, see e.g., [Hil88].
- It is a significant notion in polynomial optimization, see e.g., [BPT12, Las10, DKdW18, CS16].
- It has practical applications in scientific research, see e.g., [FKdWY20].

# Circuit Polynomials

In general, it is (NP) hard to check if a polynomial $f \in \mathbb{R}[\boldsymbol{x}]$ is nonnegative.

# Circuit Polynomials

In general, it is (NP) hard to check if a polynomial $f \in \mathbb{R}[\boldsymbol{x}]$ is nonnegative.

Idea: Exploit the AM-GM inequality to certify nonnegativity [Hur91, Mot67, Rez89, IdW16].

In general, it is (NP) hard to check if a polynomial $f \in \mathbb{R}[\mathbf{x}]$ is nonnegative.

Idea: Exploit the AM-GM inequality to certify nonnegativity [Hur91, Mot67, Rez89, IdW16].

For any nonnegative real numbers $p_1, \ldots, p_n \in \mathbb{R}_{\geq 0}$,

$$\sum_{i=1}^{n} p_i \geq n \left( \prod_{i=1}^{n} p_i \right)^{\frac{1}{n}}$$

$$\rightsquigarrow M(x,y) = \underbrace{x^4y^2}_{p_1} + \underbrace{x^2y^4}_{p_2} + \underbrace{1}_{p_3} - 3x^2y^2 \geq 0$$

.

In general, it is (NP) hard to check if a polynomial $f \in \mathbb{R}[\boldsymbol{x}]$ is nonnegative.

Idea: Exploit the AM-GM inequality to certify nonnegativity [Hur91, Mot67, Rez89, IdW16].

For any nonnegative real numbers $p_1, \ldots, p_n \in \mathbb{R}_{\geq 0}$,

$$\sum_{i=1}^{n} p_i \geq n \left( \prod_{i=1}^{n} p_i \right)^{\frac{1}{n}}$$

$$\rightsquigarrow M(x, y) = \underbrace{x^4 y^2}_{p_1} + \underbrace{x^2 y^4}_{p_2} + \underbrace{1}_{p_3} - 3x^2 y^2 \geq 0$$

.

# Circuit Polynomials

In general, it is (NP) hard to check if a polynomial $f \in \mathbb{R}[\boldsymbol{x}]$ is nonnegative.

Idea: Exploit the AM-GM inequality to certify nonnegativity [Hur91, Mot67, Rez89, IdW16].

For any nonnegative real numbers $p_1, \ldots, p_n \in \mathbb{R}_{\geq 0}$,

$$\sum_{i=1}^{n} p_i \geq n \left( \prod_{i=1}^{n} p_i \right)^{\frac{1}{n}}$$

$$\rightsquigarrow M(x,y) = \underbrace{x^4y^2}_{p_1} + \underbrace{x^2y^4}_{p_2} + \underbrace{1}_{p_3} - 3x^2y^2 \geq 0$$

.

**Definition (Circuit Polynomial)**

A polynomial $p(\boldsymbol{x}) = \sum_{j=0}^{n} p_{\alpha(j)} \boldsymbol{x}^{\boldsymbol{\alpha(j)}} + p_\beta x^{\boldsymbol{\beta}} \in \mathbb{R}[\boldsymbol{x}]$ is called a circuit polynomial if

(1) $A_p = \Delta \cup \{\boldsymbol{\beta}\}$, where $\Delta = \{\boldsymbol{\alpha(0)}, \ldots, \boldsymbol{\alpha(n)}\} \subset (2\mathbb{N})^n$ is an affine independent, and lattice point $\boldsymbol{\beta} \in \text{conv}(\Delta) \cap \mathbb{N}^n$,

(2) $p_{\boldsymbol{\alpha(j)}} > 0$ for each $\boldsymbol{\alpha(j)} \in \Delta$.

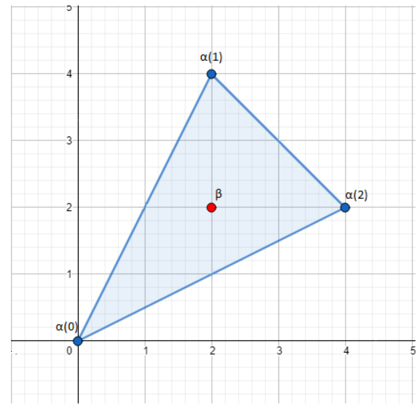
The circuit number $\Theta_p$ associated to $p(\boldsymbol{x})$ is $\Theta_p := \prod \left( \frac{p_{\alpha(j)}}{\lambda_j^{(\beta)}} \right)^{\lambda_j^{(\beta)}}$, where $\boldsymbol{\lambda}^{(\boldsymbol{\beta})} = (\lambda_0^{(\boldsymbol{\beta})}, \ldots, \lambda_n^{(\boldsymbol{\beta})})$ is the Barycentric coordinates of $\boldsymbol{\beta}$ w.r.t. $\Delta$.

# An Example

# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

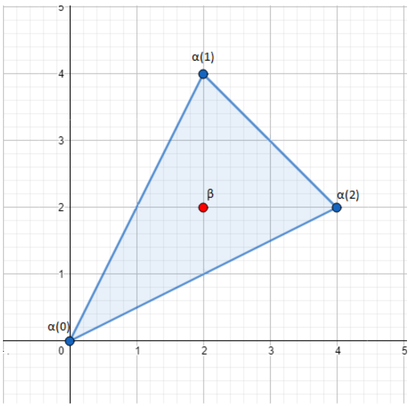


# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x, y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\boldsymbol{\beta})} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$

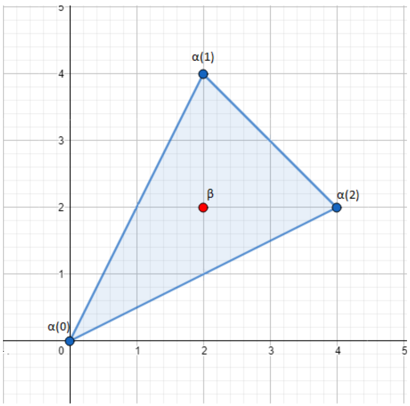


# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\boldsymbol{\beta})} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$

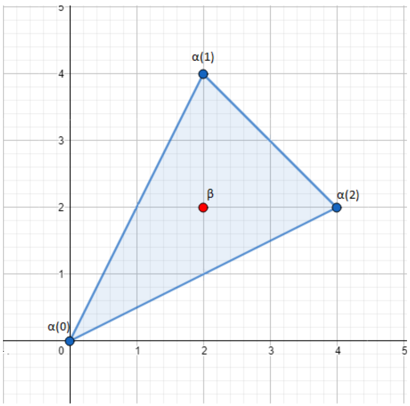


# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\boldsymbol{\beta})} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$

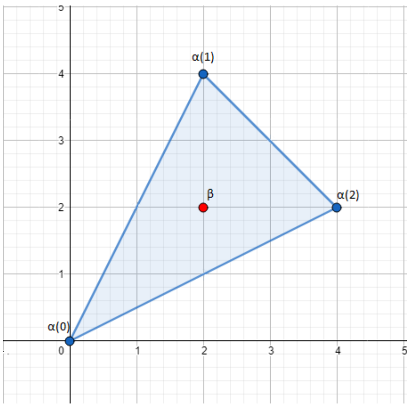


# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\boldsymbol{\beta})} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$

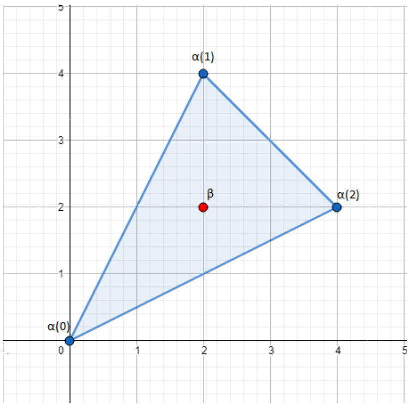


# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\beta)} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$




**Theorem (de Wolff and Iliman, 2016 [IdW16])**

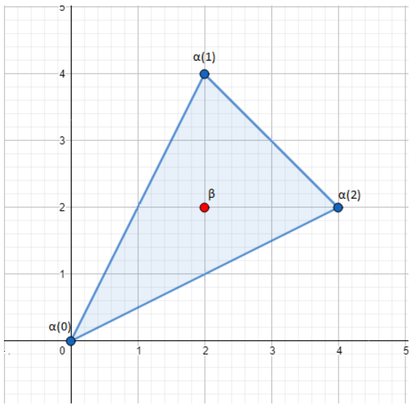
*A circuit polynomial $p(\boldsymbol{x})$ is nonnegative iff $|p_\beta| \leq \Theta_p$ and $\beta \notin (2\mathbb{N})^n$ or $p_\beta \geq -\Theta_p$ and $\beta \in (2\mathbb{N})^n$.*

# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\beta)} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$




**Theorem (de Wolff and Iliman, 2016 [IdW16])**

*A circuit polynomial $p(\mathbf{x})$ is nonnegative iff $|p_\beta| \le \Theta_p$ and $\beta \notin (2\mathbb{N})^n$ or $p_\beta \ge -\Theta_p$ and $\beta \in (2\mathbb{N})^n$.*

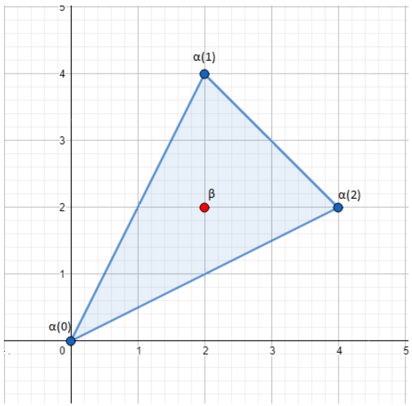
If we fix the coefficients $M_{(4,2)} = M_{(2,4)} = M_{(0,0)} = 1$ of $M$, then $M(x,y)$ is nonnegative $\iff M_{(2,2)} \ge -\Theta_M = -3$

# An Example

**Example (Motzkin Polynomial [Mot67], 1967)**

$$M(x,y) = x^4y^2 + x^2y^4 + 1 - 3x^2y^2$$

$$\boldsymbol{\lambda}^{(\beta)} = \left(\tfrac{1}{3}, \tfrac{1}{3}, \tfrac{1}{3}\right) \rightsquigarrow \Theta_M = \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} \left(\frac{1}{\frac{1}{3}}\right)^{\frac{1}{3}} = 3$$




**Theorem (de Wolff and Iliman, 2016 [IdW16])**

*A circuit polynomial $p(\mathbf{x})$ is nonnegative iff $|p_\beta| \le \Theta_p$ and $\beta \notin (2\mathbb{N})^n$ or $p_\beta \ge -\Theta_p$ and $\beta \in (2\mathbb{N})^n$.*

If $M_{(i,j)}$ are parameterized, then we get a symbolic condition for nonnegativity in terms of the parameters.

# Chemical Reaction Networks

Reaction network $\xrightarrow{\text{Mass Action Kinetics}}$ $\dot{x} = N v_\kappa(x)$

# Chemical Reaction Networks

Reaction network — Mass Action Kinetics → $\dot{x} = N v_\kappa(x)$

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

$\rightsquigarrow$

$$\dot{x}_1 = -\kappa_1 x_1 + 2\kappa_2 x_2^2 - \kappa_3 x_1 x_2$$
$$\dot{x}_2 = \kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_3 x_1 x_2$$

# Chemical Reaction Networks

**Reaction network** ⇢ Mass Action Kinetics ⇢ $\dot{x} = Nv_\kappa(x)$

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

$\rightsquigarrow$

$$\dot{x}_1 = -\kappa_1 x_1 + 2\kappa_2 x_2^2 - \kappa_3 x_1 x_2$$
$$\dot{x}_2 = \kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_3 x_1 x_2$$

$\rightsquigarrow$

$$\dot{\boldsymbol{x}} = \begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & 2 & -1 \\ 1 & -2 & 1 \end{bmatrix}}_{N} \underbrace{\begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix}}_{v_\kappa(x)}$$

# Chemical Reaction Networks

Reaction network

Mass Action Kinetics

$\dot{x} = N v_\kappa(x)$

$$\sum_{i=1}^{n} a_{i,1} X_i \xrightarrow{\kappa_1} \sum_{i=1}^{n} b_{i,1} X_i$$

$$\vdots \qquad \vdots \qquad \vdots$$

$$\sum_{i=1}^{n} a_{i,\ell} X_i \xrightarrow{\kappa_\ell} \sum_{i=1}^{n} b_{i,\ell} X_i$$

# Chemical Reaction Networks

Reaction network

Mass Action Kinetics

$$\dot{x} = N v_\kappa(x)$$

$$\sum_{i=1}^{n} a_{i,1} X_i \xrightarrow{\kappa_1} \sum_{i=1}^{n} b_{i,1} X_i$$

$$\vdots$$

$$\sum_{i=1}^{n} a_{i,\ell} X_i \xrightarrow{\kappa_\ell} \sum_{i=1}^{n} b_{i,\ell} X_i$$

$$\rightsquigarrow$$

$$\dot{x}_1 = \kappa_1 (b_{1,1} - a_{1,1}) \boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \dots + \kappa_\ell (b_{1,\ell} - a_{1,\ell}) \boldsymbol{x}^{\boldsymbol{a}_{i,\ell}}$$

$$\dot{x}_n = \kappa_1 (b_{n,1} - a_{n,1}) \boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \dots + \kappa_\ell (b_{n,\ell} - a_{n,\ell}) \boldsymbol{x}^{\boldsymbol{a}_{i,\ell}}$$

# Chemical Reaction Networks

Reaction network $\dashrightarrow$ Mass Action Kinetics $\dashrightarrow$ $\dot{x} = Nv_\kappa(x)$

$$\sum_{i=1}^{n} a_{i,1}X_i \xrightarrow{\kappa_1} \sum_{i=1}^{n} b_{i,1}X_i$$
$$\vdots$$
$$\sum_{i=1}^{n} a_{i,\ell}X_i \xrightarrow{\kappa_\ell} \sum_{i=1}^{n} b_{i,\ell}X_i$$

$\rightsquigarrow$

$$\dot{x}_1 = \kappa_1(b_{1,1} - a_{1,1})\boldsymbol{x}^{\boldsymbol{a_{i,1}}} + \dots + \kappa_\ell(b_{1,\ell} - a_{1,\ell})\boldsymbol{x}^{\boldsymbol{a_{i,\ell}}}$$
$$\dot{x}_n = \kappa_1(b_{n,1} - a_{n,1})\boldsymbol{x}^{\boldsymbol{a_{i,1}}} + \dots + \kappa_\ell(b_{n,\ell} - a_{n,\ell})\boldsymbol{x}^{\boldsymbol{a_{i,\ell}}}$$

$\rightsquigarrow$ $\dot{\boldsymbol{x}} = N \cdot \boldsymbol{v}_{\boldsymbol{\kappa}}(\boldsymbol{x})$

Stoichiometric Matrix $\rightsquigarrow N$
Sto. Subspace $\rightsquigarrow S :=$ column span of $N$
Vector of Reaction Rates $\rightsquigarrow v_{\boldsymbol{\kappa}}(\boldsymbol{x})$
Steady States $\rightsquigarrow V := \left\{\boldsymbol{x} \in \mathbb{R}^n_{\geq} \middle| Nv_{\boldsymbol{\kappa}}(\boldsymbol{x}) = \mathbf{0}\right\}$
Sto. Compatibility Class $\rightsquigarrow \boldsymbol{x}(\mathbf{0}) + S$

# Chemical Reaction Networks

Reaction network — Mass Action Kinetics → $\dot{x} = Nv_\kappa(x)$

$$\sum_{i=1}^n a_{i,1}X_i \xrightarrow{\kappa_1} \sum_{i=1}^n b_{i,1}X_i$$

$$\vdots$$

$$\sum_{i=1}^n a_{i,\ell}X_i \xrightarrow{\kappa_\ell} \sum_{i=1}^n b_{i,\ell}X_i$$

$\rightsquigarrow$

$$\dot{x}_1 = \kappa_1(b_{1,1} - a_{1,1})\boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \dots + \kappa_\ell(b_{1,\ell} - a_{1,\ell})\boldsymbol{x}^{\boldsymbol{a}_{i,\ell}}$$

$$\vdots$$

$$\dot{x}_n = \kappa_1(b_{n,1} - a_{n,1})\boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \dots + \kappa_\ell(b_{n,\ell} - a_{n,\ell})\boldsymbol{x}^{\boldsymbol{a}_{i,\ell}}$$

$\rightsquigarrow$ $\dot{\boldsymbol{x}} = N \cdot \boldsymbol{v}_{\boldsymbol{\kappa}}(\boldsymbol{x})$

Stoichiometric Matrix $\rightsquigarrow N$
Sto. Subspace $\rightsquigarrow S :=$ column span of $N$
Vector of Reaction Rates $\rightsquigarrow v_{\boldsymbol{\kappa}}(\boldsymbol{x})$
Steady States $\rightsquigarrow V := \left\{\boldsymbol{x} \in \mathbb{R}^n_{\geq} \middle| \, Nv_{\boldsymbol{\kappa}}(\boldsymbol{x}) = \boldsymbol{0}\right\}$
Sto. Compatibility Class $\rightsquigarrow \boldsymbol{x}(\boldsymbol{0}) + S$

$\longrightarrow$ Each solution trajectory of the ODE given by the starting point $\boldsymbol{x}(\boldsymbol{0})$, is confined to the affine space $\boldsymbol{x}(\boldsymbol{0}) + S \subset \mathbb{R}^2$ .

$\longrightarrow$ For a full rank row reduced matrix $W \in \mathbb{Z}^{(n-\text{rank}(N))\times n}$ such that $WN = \boldsymbol{0}$, $W\boldsymbol{x} = \boldsymbol{c} := W\boldsymbol{x}(\boldsymbol{0})$ for all $\boldsymbol{x} \in \boldsymbol{x}(\boldsymbol{0}) + S$.

$\longrightarrow$ $\boldsymbol{x}(\boldsymbol{0}) + S \rightsquigarrow \mathcal{P}_c := \{\boldsymbol{x} \in \mathbb{R}^n_{>0} | W\boldsymbol{x} = \boldsymbol{c}\}$ for some $\boldsymbol{c} \in \mathbb{R}^{n-\text{rank}(N)}$

# Chemical Reaction Networks

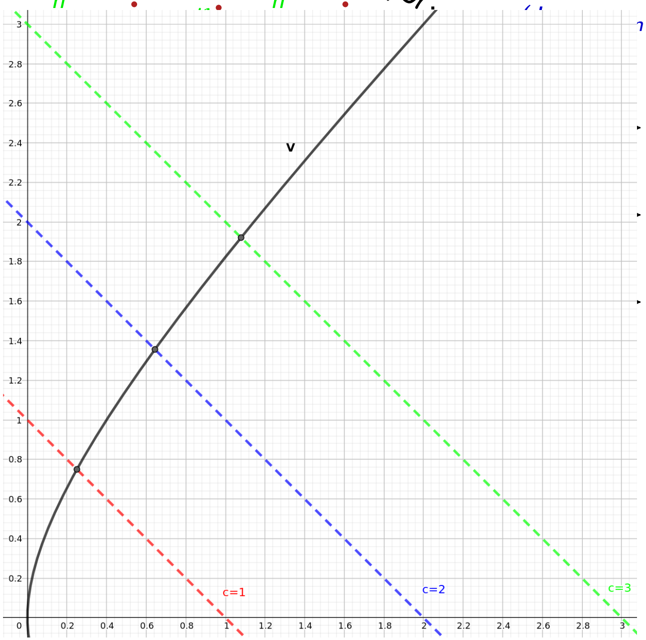
Reaction network - - - Mass Action Kinetics - - -> $\dot{x} = N v_\kappa(x)$

$$\sum_{i=1}^{n} a_{i,1} X_i \xrightarrow{\kappa_1} \sum_{i=1}^{n} b_{i,1} X_i$$

$$\vdots$$

$$\rightsquigarrow \dot{x}_1 = \kappa_1(b_{1,1} - a_{1,1})\boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \dots + \kappa_\ell(b_{1,\ell} - a_{1,\ell})\boldsymbol{x}^{\boldsymbol{a}_{i,\ell}}$$

$$\dots{}_{,1})\boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \dots + \kappa_\ell(b_{n,\ell} - a_{n,\ell})\boldsymbol{x}^{\boldsymbol{a}_{i,\ell}} \rightsquigarrow \dot{\boldsymbol{x}} = N \cdot \boldsymbol{v}_{\boldsymbol{\kappa}}(\boldsymbol{x})$$




- Each solution trajectory of the ODE given by the starting point $\boldsymbol{x}(0)$, is confined to the affine space $\boldsymbol{x}(0) + S \subset \mathbb{R}^2$ .
- For a full rank row reduced matrix $W \in \mathbb{Z}^{(n-\mathrm{rank}(N))\times n}$ such that $WN = \mathbf{0}$, $W\boldsymbol{x} = \boldsymbol{c} := W\boldsymbol{x}(0)$ for all $\boldsymbol{x} \in \boldsymbol{x}(0) + S$.
- $\boldsymbol{x}(0) + S \rightsquigarrow \mathcal{P}_c := \{\boldsymbol{x} \in \mathbb{R}^n_{>0} | W\boldsymbol{x} = \boldsymbol{c}\}$ for some $\boldsymbol{c} \in \mathbb{R}^{n-\mathrm{rank}(N)}$

- Recall the toy example:

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

- $V = \left\{\boldsymbol{x} \in \mathbb{R}^2_{>0} \middle| -\kappa_1 x_1 + 2\kappa_2 x_2^2 - \kappa_3 x_1 x_2 = 0\right\}$
- $W = [1\ 1] \rightsquigarrow \mathcal{P}_c = \left\{\boldsymbol{x} \in \mathbb{R}^2_{>0} \middle| x_1 + x_2 = c\right\}$ for some $c \in \mathbb{R}$.

# Chemical Reaction Networks

Reaction network $\dashrightarrow$ Mass Action Kinetics $\dot{x} = Nv_\kappa(x)$

$$\sum_{i=1}^{n} a_{i,1}X_i \xrightarrow{\kappa_1} \sum_{i=1}^{n} b_{i,1}X_i \qquad \vdots \qquad \sum_{i=1}^{n} a_{i,\ell}X_i \xrightarrow{\kappa_\ell} \sum_{i=1}^{n} b_{i,\ell}X_i$$

$$\rightsquigarrow \begin{array}{l} \dot{x}_1 = \kappa_1(b_{1,1} - a_{1,1})\boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \ldots + \kappa_\ell(b_{1,\ell} - a_{1,\ell})\boldsymbol{x}^{\boldsymbol{a}_{i,\ell}} \\ \vdots \\ \dot{x}_n = \kappa_1(b_{n,1} - a_{n,1})\boldsymbol{x}^{\boldsymbol{a}_{i,1}} + \ldots + \kappa_\ell(b_{n,\ell} - a_{n,\ell})\boldsymbol{x}^{\boldsymbol{a}_{i,\ell}} \end{array} \rightsquigarrow \dot{\boldsymbol{x}} = N \cdot \boldsymbol{v}_{\boldsymbol{\kappa}}(\boldsymbol{x})$$

Stoichiometric Matrix $\rightsquigarrow N$
Sto. Subspace $\rightsquigarrow S :=$ column span of $N$
Vector of Reaction Rates $\rightsquigarrow v_{\boldsymbol{\kappa}}(\boldsymbol{x})$
Steady States $\rightsquigarrow V := \{\boldsymbol{x} \in \mathbb{R}^n_{\geq} \mid Nv_{\boldsymbol{\kappa}}(\boldsymbol{x}) = \boldsymbol{0}\}$
Sto. Compatibility Class $\rightsquigarrow \boldsymbol{x}(\boldsymbol{0}) + S$

$\longrightarrow$ Each solution trajectory of the ODE given by the starting point $\boldsymbol{x}(\boldsymbol{0})$, is confined to the affine space $\boldsymbol{x}(\boldsymbol{0}) + S \subset \mathbb{R}^2$ .

$\longrightarrow$ For a full rank row reduced matrix $W \in \mathbb{Z}^{(n-\text{rank}(N))\times n}$ such that $WN = \boldsymbol{0}$, $W\boldsymbol{x} = \boldsymbol{c} := W\boldsymbol{x}(\boldsymbol{0})$ for all $\boldsymbol{x} \in \boldsymbol{x}(\boldsymbol{0}) + S$.

$\longrightarrow$ $\boldsymbol{x}(\boldsymbol{0}) + S \rightsquigarrow \mathcal{P}_c := \{\boldsymbol{x} \in \mathbb{R}^n_{>0} | W\boldsymbol{x} = \boldsymbol{c}\}$ for some $\boldsymbol{c} \in \mathbb{R}^{n-\text{rank}(N)}$

Let $C_{\kappa,c} := \{\boldsymbol{x} \in \mathbb{R}^n_{>0}$ such that $Nv_\kappa(\boldsymbol{x}) = 0$ and $W\boldsymbol{x} = \boldsymbol{c}\}$ for a given network with stoichiometric matrix $N$

- If $|C_{\kappa,c}| = 1$ for all $\boldsymbol{\kappa} \in \mathbb{R}^\ell_{>0}$ and $\boldsymbol{c} \in \mathbb{R}^{n-\text{rank}(N)}$ $\longrightarrow$ the system precludes multistationarity.
- If $|C_{\kappa,c}| > 1$ for some $\boldsymbol{\kappa} \in \mathbb{R}^\ell_{>0}$ and $\boldsymbol{c} \in \mathbb{R}^{n-\text{rank}(N)}$ $\longrightarrow$ the system enables multistationarity.

# $n$-site Phosphorylation

$$
\begin{array}{l}
S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \rightleftharpoons \cdots \longrightarrow S_{n-1} + E \underset{\kappa_{6n-4}}{\overset{\kappa_{6n-5}}{\rightleftharpoons}} ES_{n-1} \xrightarrow{\kappa_{6n-3}} S_n + E \\
S_n + F \underset{\kappa_{6n-1}}{\overset{\kappa_{6n-2}}{\rightleftharpoons}} FS_n \xrightarrow{\kappa_{6n}} S_1 + F \rightleftharpoons \cdots \cdots \longrightarrow S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F
\end{array} \tag{1}
$$


[Biochemical Reaction Networks: An Invitation to Algebraic Geometers, Alicia Dickenstein]

# Identifying Multistationarity

**Theorem ([CFMW17] 2017, Feliu-Kaihnsa-de Wolff- Y. 2021)**

*Let $\boldsymbol{\kappa} \in \mathbb{R}^{6n}_{>0}$ be a vector of reaction rate constants for the n-site phosphorylation cycle. There exists a polynomial $p(x_1, x_2, x_3)$ whose coefficients are parameterized by $\boldsymbol{\kappa}$ and variables are given as $x_1 = [E] + \sum_{i=0}^{n-1}[ES_i]$, $x_2 = [F] + \sum_{i=0}^{n-1}[FS_i]$, $x_3 = \sum_{i=0}^{n}[S_i] + \sum_{i=0}^{n-1}[ES_i] + [FS_i]$ such that*

- *if $p(\boldsymbol{x}) > 0$ for all $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, then $\boldsymbol{\kappa}$ precludes multistationarity, and*
- *if $p(\boldsymbol{x}) < 0$ for some $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, then $\boldsymbol{\kappa}$ enables multistationarity.*

# Identifying Multistationarity

**Theorem ([CFMW17] 2017, Feliu-Kaihnsa-de Wolff- Y. 2021)**

*Let $\boldsymbol{\kappa} \in \mathbb{R}^{6n}_{>0}$ be a vector of reaction rate constants for the n-site phosphorylation cycle. There exists a polynomial $p(x_1, x_2, x_3)$ whose coefficients are parameterized by $\boldsymbol{\kappa}$ and variables are given as $x_1 = [E] + \sum_{i=0}^{n-1}[ES_i]$, $x_2 = [F] + \sum_{i=0}^{n-1}[FS_i]$, $x_3 = \sum_{i=0}^{n}[S_i] + \sum_{i=0}^{n-1}[ES_i] + [FS_i]$ such that*

- *if $p(\boldsymbol{x}) > 0$ for all $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, then $\boldsymbol{\kappa}$ precludes multistationarity, and*
- *if $p(\boldsymbol{x}) < 0$ for some $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, then $\boldsymbol{\kappa}$ enables multistationarity.*

The polynomial $p$ is given by $\det(J)$, where

$$J := \begin{bmatrix} 1 + \sum_{i=0}^{n-1} (i+1)\, a_i\, x_2^i x_3 & -\sum_{i=0}^{n-1} i\, a_i\, x_2^{i+1} x_3 & \sum_{i=0}^{n-1} a_i\, x_1 x_2^i \\ \sum_{i=0}^{n-1} (i+1)\, b_i\, x_2^i x_3 & 1 - \sum_{i=0}^{n-1} i\, b_i\, x_2^{i+1} x_3 & \sum_{i=0}^{n-1} b_i\, x_1 x_2^i \\ -1 + \sum_{i=0}^{n-1} (i+1)\, c_i\, x_1^{-1} x_2^{i+1} x_3 & -1 - \sum_{i=0}^{n-1} (i+1)\, c_i\, x_1^{-1} x_2^{i+2} x_3 & 1 + \sum_{i=0}^{n-1} c_i\, x_2^{i+1} \end{bmatrix}$$

# Identifying Multistationarity

**Theorem ([CFMW17] 2017, Feliu-Kaihnsa-de Wolff- Y. 2021)**

*Let $\boldsymbol{\kappa} \in \mathbb{R}^{6n}_{>0}$ be a vector of reaction rate constants for the n-site phosphorylation cycle. There exists a polynomial $p(x_1, x_2, x_3)$ whose coefficients are parameterized by $\boldsymbol{\kappa}$ and variables are given as $x_1 = [E] + \sum_{i=0}^{n-1}[ES_i]$, $x_2 = [F] + \sum_{i=0}^{n-1}[FS_i]$, $x_3 = \sum_{i=0}^{n}[S_i] + \sum_{i=0}^{n-1}[ES_i] + [FS_i]$ such that*

- *if $p(\boldsymbol{x}) > 0$ for all $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, then $\boldsymbol{\kappa}$ precludes multistationarity, and*
- *if $p(\boldsymbol{x}) < 0$ for some $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, then $\boldsymbol{\kappa}$ enables multistationarity.*

**2-site (De-)Phosphorylation Cycle**

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

$$S_2 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} FS_2 \xrightarrow{\kappa_{12}} S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F$$

# Identifying Multistationarity

**Theorem ([CFMW17] 2017, Feliu-Kaihnsa-de Wolff- Y. 2021)**

*Let* $\boldsymbol{\kappa} \in \mathbb{R}^{6n}_{>0}$ *be a vector of reaction rate constants for the n-site phosphorylation cycle. There exists a polynomial* $p(x_1, x_2, x_3)$ *whose coefficients are parameterized by* $\boldsymbol{\kappa}$ *and variables are given as* $x_1 = [E] + \sum_{i=0}^{n-1}[ES_i]$, $x_2 = [F] + \sum_{i=0}^{n-1}[FS_i]$, $x_3 = \sum_{i=0}^{n}[S_i] + \sum_{i=0}^{n-1}[ES_i] + [FS_i]$ *such that*

- *if* $p(\boldsymbol{x}) > 0$ *for all* $\boldsymbol{x} \in \mathbb{R}^3_{>0}$*, then* $\boldsymbol{\kappa}$ *precludes multistationarity, and*
- *if* $p(\boldsymbol{x}) < 0$ *for some* $\boldsymbol{x} \in \mathbb{R}^3_{>0}$*, then* $\boldsymbol{\kappa}$ *enables multistationarity.*

**2-site (De-)Phosphorylation Cycle**

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

$$S_2 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} FS_2 \xrightarrow{\kappa_{12}} S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F$$

$K_i := \frac{\kappa_{6i+1}}{\kappa_{6i+2}+\kappa_{6i+3}}$, $L_i := \frac{\kappa_{6i+4}}{\kappa_{6i+5}+\kappa_{6i+6}}$, for $i = 0, \dots, n-1$

$K_i^{-1}, L_i^{-1} \rightsquigarrow$ Michaelis-Menten constants

$$T_i := \frac{\kappa_{6j+3} K_j}{\kappa_{6j+6} L_j} \text{ for } i = 0, \dots, n-1, \text{ and } T_{-1} := 0$$

$a_i := K_i T_{i-1}$, $b_i := L_i T_i$, $c_i := T_i$ for $i = 0, \dots, n-1$

# Identifying Multistationarity

**Theorem ([CFMW17] 2017, Feliu-Kaihnsa-de Wolff- Y. 2021)**

*Let* $\boldsymbol{\kappa} \in \mathbb{R}^{6n}_{>0}$ *be a vector of reaction rate constants for the n-site phosphorylation cycle. There exists a polynomial* $p(x_1, x_2, x_3)$ *whose coefficients are parameterized by* $\boldsymbol{\kappa}$ *and variables are given as* $x_1 = [E] + \sum_{i=0}^{n-1}[ES_i]$, $x_2 = [F] + \sum_{i=0}^{n-1}[FS_i]$, $x_3 = \sum_{i=0}^{n}[S_i] + \sum_{i=0}^{n-1}[ES_i] + [FS_i]$ *such that*

- *if* $p(\boldsymbol{x}) > 0$ *for all* $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, *then* $\boldsymbol{\kappa}$ *precludes multistationarity, and*
- *if* $p(\boldsymbol{x}) < 0$ *for some* $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, *then* $\boldsymbol{\kappa}$ *enables multistationarity.*

**2-site (De-)Phosphorylation Cycle**

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

$$S_2 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} FS_2 \xrightarrow{\kappa_{12}} S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F$$

$$K_i := \frac{\kappa_{6i+1}}{\kappa_{6i+2}+\kappa_{6i+3}},\ L_i := \frac{\kappa_{6i+4}}{\kappa_{6i+5}+\kappa_{6i+6}},\ \text{for } i = 0, \ldots, n-1$$

$K_i^{-1}, L_i^{-1} \rightsquigarrow$ Michaelis-Menten constants

$$T_i := \frac{\kappa_{6j+3}K_j}{\kappa_{6j+6}L_j}\ \text{ for } i = 0, \ldots, n-1, \text{ and } T_{-1} := 0$$

$a_i := K_i T_{i-1}$, $b_i := L_i T_i$, $c_i := T_i$ for $i = 0, \ldots, n-1$

$$p(\boldsymbol{x}) = 1 + (-a_0 b_1 + a_1 b_0) x_1 x_2^2 x_3 + (-a_0 b_1 + a_1 b_0) x_1 x_2 x_3 + (a_1 + b_1) x_1 x_2 + (a_0 + b_0) x_1 + c_1 (-a_0 b_1 + a_1 b_0) x_2^4 x_3^2 + b_1 c_1 x_2^4 x_3 + 2 b_0 c_1 x_2^3 x_3 + c_0 (-a_0 b_1 + a_1 b_0) x_2^3 x_3^2 + (-a_0 b_1 + a_1 b_0) x_2^2 x_3^2 + (-a_0 c_1 + a_1 c_0 + b_0 c_0 - b_1) x_2^2 x_3 + c_1 x_2^2 + 2 a_1 x_2 x_3 + c_0 x_2 + a_0 x_3$$

# Identifying Multistationarity

**Theorem ([CFMW17] 2017, Feliu-Kaihnsa-de Wolff- Y. 2021)**

*Let* $\boldsymbol{\kappa} \in \mathbb{R}^{6n}_{>0}$ *be a vector of reaction rate constants for the n-site phosphorylation cycle. There exists a polynomial* $p(x_1, x_2, x_3)$ *whose coefficients are parameterized by* $\boldsymbol{\kappa}$ *and variables are given as* $x_1 = [E] + \sum_{i=0}^{n-1}[ES_i]$, $x_2 = [F] + \sum_{i=0}^{n-1}[FS_i]$, $x_3 = \sum_{i=0}^{n}[S_i] + \sum_{i=0}^{n-1}[ES_i] + [FS_i]$ *such that*

- *if* $p(\boldsymbol{x}) > 0$ *for all* $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, *then* $\boldsymbol{\kappa}$ *precludes multistationarity, and*
- *if* $p(\boldsymbol{x}) < 0$ *for some* $\boldsymbol{x} \in \mathbb{R}^3_{>0}$, *then* $\boldsymbol{\kappa}$ *enables multistationarity.*

**2-site (De-)Phosphorylation Cycle**

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

$$S_2 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} FS_2 \xrightarrow{\kappa_{12}} S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F$$

$K_i := \frac{\kappa_{6i+1}}{\kappa_{6i+2}+\kappa_{6i+3}}$, $L_i := \frac{\kappa_{6i+4}}{\kappa_{6i+5}+\kappa_{6i+6}}$, for $i = 0, \ldots, n-1$

$K_i^{-1}, L_i^{-1} \rightsquigarrow$ Michaelis-Menten constants

$T_i := \frac{\kappa_{6j+3} K_j}{\kappa_{6j+6} L_j}$ for $i = 0, \ldots, n-1$, and $T_{-1} := 0$

$a_i := K_i T_{i-1}$, $b_i := L_i T_i$, $c_i := T_i$ for $i = 0, \ldots, n-1$

$$p(\boldsymbol{x}) = 1 + (-a_0 b_1 + a_1 b_0) x_1 x_2^2 x_3 + (-a_0 b_1 + a_1 b_0) x_1 x_2 x_3 + (a_1 + b_1) x_1 x_2 + (a_0 + b_0) x_1 + c_1 (-a_0 b_1 + a_1 b_0) x_2^4 x_3^2 + b_1 c_1 x_2^4 x_3 + 2 b_0 c_1 x_2^3 x_3 + c_0 (-a_0 b_1 + a_1 b_0) x_2^3 x_3^2 + (-a_0 b_1 + a_1 b_0) x_2^2 x_3^2 + (-a_0 c_1 + a_1 c_0 + b_0 c_0 - b_1) x_2^2 x_3 + c_1 x_2^2 + 2 a_1 x_2 x_3 + c_0 x_2 + a_0 x_3$$

Conradi,Mincheva (2019) [CM14]: If $a_1 b_0 - a_0 b_1 < 0$, then the system precludes multistationarity as $p(\boldsymbol{x})$ can be negative.

# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\boldsymbol{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\boldsymbol{x})$ be the restriction of $p(\boldsymbol{x})$ to the monomials supported in the face.*

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

$$\operatorname{sign}(p(\boldsymbol{y}^*)) = \operatorname{sign}(p_\tau(\boldsymbol{x}^*)).$$

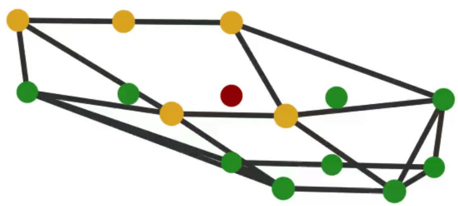
# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\boldsymbol{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\boldsymbol{x})$ be the restriction of $p(\boldsymbol{x})$ to the monomials supported in the face.*

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

$$\operatorname{sign}(p(\boldsymbol{y}^*)) = \operatorname{sign}(p_\tau(\boldsymbol{x}^*)).$$



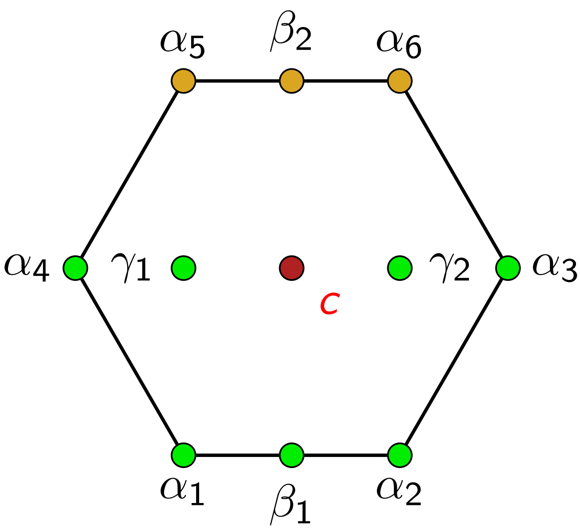
# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\mathbf{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\mathbf{x})$ be the restriction of $p(\mathbf{x})$ to the monomials supported in the face.*

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

$$\mathrm{sign}(p(\mathbf{y}^*)) = \mathrm{sign}(p_\tau(\mathbf{x}^*)).$$




Assume that $a_1 b_0 - a_0 b_1 > 0$, and consider
$p_\tau \in \mathbb{R}[A_p] \rightsquigarrow$ the restriction of $p$ to the hexagonal face of $\mathcal{N}(p)$

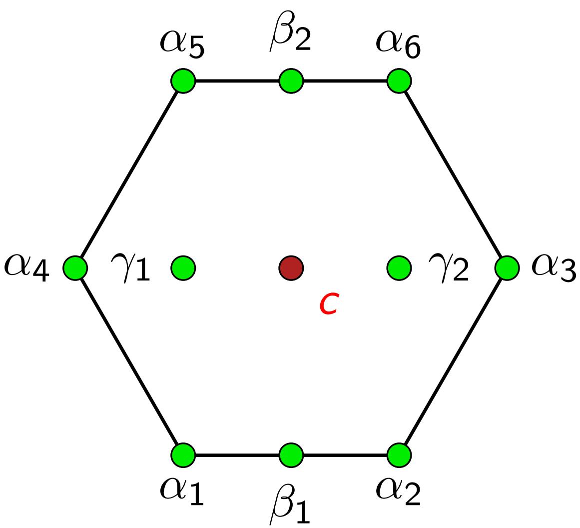
# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\mathbf{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\mathbf{x})$ be the restriction of $p(\mathbf{x})$ to the monomials supported in the face.*

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

$$\operatorname{sign}(p(\mathbf{y}^*)) = \operatorname{sign}(p_\tau(\mathbf{x}^*)).$$




Assume that $a_1 b_0 - a_0 b_1 > 0$, and consider
$p_\mathcal{T} \in \mathbb{R}[A_p] \rightsquigarrow$ the restriction of $p$ to the hexagonal face of $\mathcal{N}(p)$

Kaihnsa, Feliu, de Wolff, Y. (2020) [FKdWY20]:

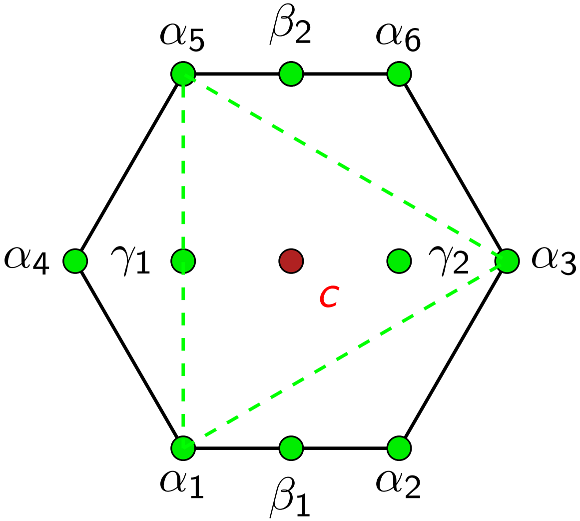
- Find a symbolic nonnegativity condition for $p_\mathcal{T}$ in terms of its coefficients via circuit polynomials.

**Lemma**

*Let $p \in \mathbb{R}[\mathbf{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\mathbf{x})$ be the restriction of $p(\mathbf{x})$ to the monomials supported in the face.*

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

$$\mathrm{sign}(p(\mathbf{y}^*)) = \mathrm{sign}(p_\tau(\mathbf{x}^*)).$$




Assume that $a_1 b_0 - a_0 b_1 > 0$, and consider
$p_\tau \in \mathbb{R}[A_p] \rightsquigarrow$ the restriction of $p$ to the hexagonal face of $\mathcal{N}(p)$

Kaihnsa, Feliu, de Wolff, Y. (2020) [FKdWY20]:

- Find a symbolic nonnegativity condition for $p_\tau$ in terms of its coefficients via circuit polynomials.

  $\alpha_1, \alpha_3, \alpha_5, c \rightsquigarrow \Theta_1 = 3(p_{\alpha_1} p_{\alpha_3} p_{\alpha_5})^{\frac{1}{3}} \rightsquigarrow -p_c \le \Theta_1$

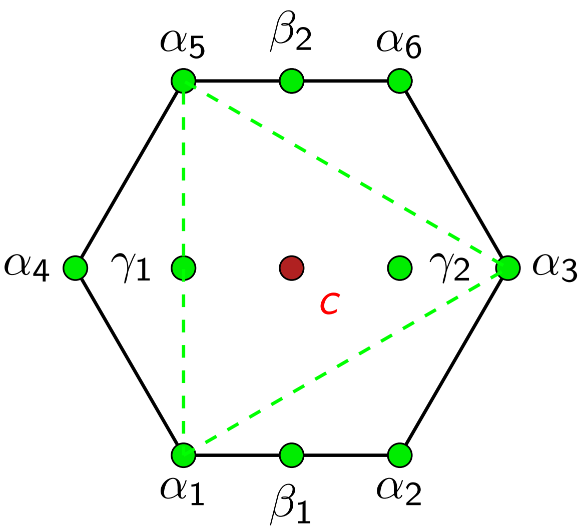
# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\mathbf{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\mathbf{x})$ be the restriction of $p(\mathbf{x})$ to the monomials supported in the face.*

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

$$\operatorname{sign}(p(\mathbf{y}^*)) = \operatorname{sign}(p_\tau(\mathbf{x}^*)).$$




Assume that $a_1 b_0 - a_0 b_1 > 0$, and consider $p_\tau \in \mathbb{R}[A_p] \rightsquigarrow$ the restriction of $p$ to the hexagonal face of $\mathcal{N}(p)$

Kaihnsa, Feliu, de Wolff, Y. (2020) [FKdWY20]:

- Find a symbolic nonnegativity condition for $p_\tau$ in terms of its coefficients via circuit polynomials.

  $\alpha_1, \alpha_3, \alpha_5, c \rightsquigarrow \Theta_1 = 3(p_{\alpha_1} p_{\alpha_3} p_{\alpha_5})^{\frac{1}{3}} \rightsquigarrow -p_c \leq \Theta_1$

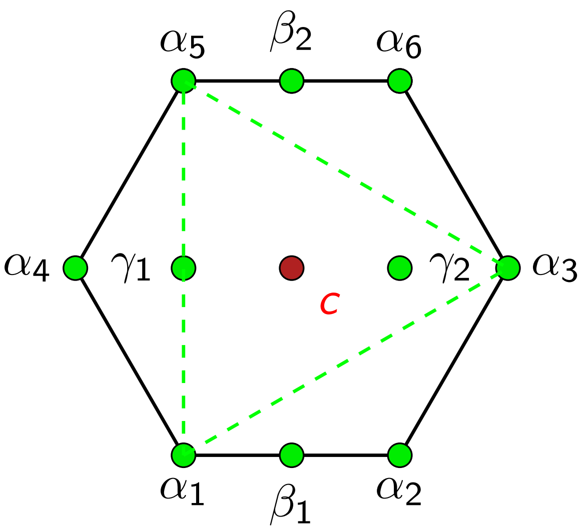
# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\mathbf{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\mathbf{x})$ be the restriction of $p(\mathbf{x})$ to the monomials supported in the face.*

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

$$\operatorname{sign}(p(\mathbf{y}^*)) = \operatorname{sign}(p_\tau(\mathbf{x}^*)).$$




Assume that $a_1 b_0 - a_0 b_1 > 0$, and consider $p_\tau \in \mathbb{R}[A_p] \rightsquigarrow$ the restriction of $p$ to the hexagonal face of $\mathcal{N}(p)$

Kaihnsa, Feliu, de Wolff, Y. (2020) [FKdWY20]:

- Find a symbolic nonnegativity condition for $p_\tau$ in terms of its coefficients via circuit polynomials.

  $\alpha_1, \alpha_3, \alpha_5, c \rightsquigarrow \Theta_1 = 3(p_{\alpha_1} p_{\alpha_3} p_{\alpha_5})^{\frac{1}{3}} \rightsquigarrow -p_c \leq \Theta_1$
- Parameterization of the boundary between mono and multistationarity regions for 2-site phosphorylation.

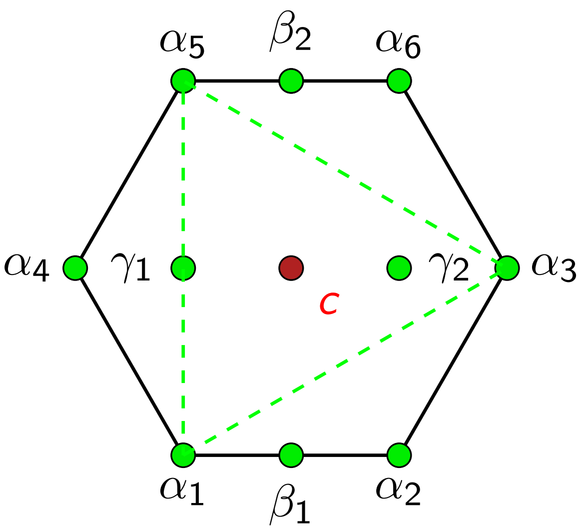
# Reduction Lemma

**Lemma**

*Let $p \in \mathbb{R}[\mathbf{x}]$ be a multivariate polynomial. Given a face $\tau$ of $\mathcal{N}(p)$, let $p_\tau(\mathbf{x})$ be the restriction of $p(\mathbf{x})$ to the monomials supported in the face.*

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

$$\mathrm{sign}(p(\mathbf{y}^*)) = \mathrm{sign}(p_\tau(\mathbf{x}^*)).$$




Assume that $a_1 b_0 - a_0 b_1 > 0$, and consider $p_\tau \in \mathbb{R}[A_p] \rightsquigarrow$ the restriction of $p$ to the hexagonal face of $\mathcal{N}(p)$

Kaihnsa, Feliu, de Wolff, Y. (2020) [FKdWY20]:

- Find a symbolic nonnegativity condition for $p_\tau$ in terms of its coefficients via circuit polynomials.

  $\alpha_1, \alpha_3, \alpha_5, c \rightsquigarrow \Theta_1 = 3(p_{\alpha_1} p_{\alpha_3} p_{\alpha_5})^{\frac{1}{3}} \rightsquigarrow -p_c \leq \Theta_1$
- Parameterization of the boundary between mono and multistationarity regions for 2-site phosphorylation.
- Connectivity of mono and multistationarity regions.

# The Newton Polytope for $n$-site

**Theorem (Feliu, Kaihnsa, de Wolff, Y. 2021+)**

*For any $n$, the set of vertices of the Newton polytope $N(p_\eta)$ of the polynomial $p_\eta$ consists of the following* 10 *points:*

$$\{(0,0,0),(0,n,0),(0,0,1),(0,2n,1),(0,2,2),(0,3n-2,2),(1,0,0),(1,n-1,0),(1,1,1),(1,2n-2,1)\}.$$

# The Newton Polytope for $n$-site

**Theorem (Feliu, Kaihnsa, de Wolff, Y. 2021+)**

*For any $n$, the set of vertices of the Newton polytope $N(p_\eta)$ of the polynomial $p_\eta$ consists of the following 10 points:*

$$\{(0,0,0),(0,n,0),(0,0,1),(0,2n,1),(0,2,2),(0,3n-2,2),(1,0,0),(1,n-1,0),(1,1,1),(1,2n-2,1)\}\,.$$

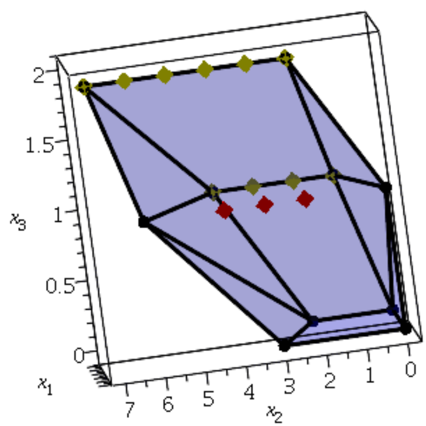
Proof Idea: $p_\eta$ is of degree 2 in the variable $x_3$. Compute the contribution of each polygonal sections $P_i := \{(x_1,x_2,x_3) \in N(p_\eta) \mid x_3 = i\}$ for $i = 0,1,2$, and reconstruct the vertices from these sections.

# The Newton Polytope for $n$-site

**Theorem (Feliu, Kaihnsa, de Wolff, Y. 2021+)**

*For any $n$, the set of vertices of the Newton polytope $N(p_\eta)$ of the polynomial $p_\eta$ consists of the following 10 points:*

$$\{(0,0,0),(0,n,0),(0,0,1),(0,2n,1),(0,2,2),(0,3n-2,2),(1,0,0),(1,n-1,0),(1,1,1),(1,2n-2,1)\}\,.$$



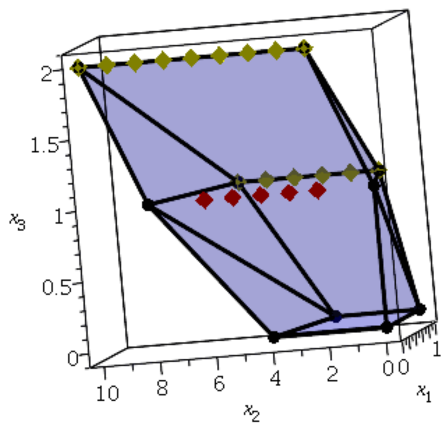

$\longrightarrow$ 3-site

# The Newton Polytope for $n$-site

**Theorem (Feliu, Kaihnsa, de Wolff, Y. 2021+)**

*For any $n$, the set of vertices of the Newton polytope $N(p_\eta)$ of the polynomial $p_\eta$ consists of the following 10 points:*

$$\{(0,0,0),(0,n,0),(0,0,1),(0,2n,1),(0,2,2),(0,3n-2,2),(1,0,0),(1,n-1,0),(1,1,1),(1,2n-2,1)\}\,.$$

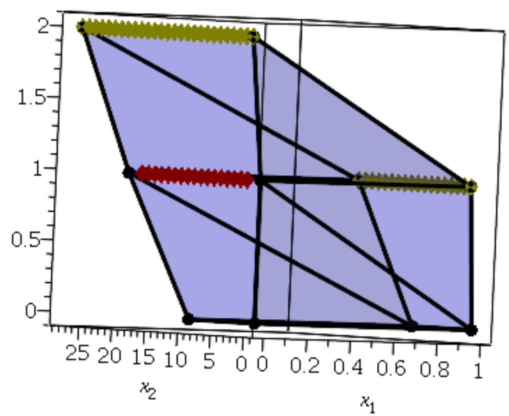



$\longrightarrow$ 4-site

# The Newton Polytope for $n$-site

Let $M_\kappa := \begin{bmatrix} \kappa_3 & \kappa_9 & \cdots & \kappa_{6n-3} \\ \kappa_6 & \kappa_{12} & \cdots & \kappa_{6n} \end{bmatrix}$.

Sign of each yellow point $\rightsquigarrow$ sign of $\kappa_{6i+3}\kappa_{6j+6} - \kappa_{6i+6}\kappa_{6j+3}$ for some $i, j \in \{0, \ldots, n-1\}$



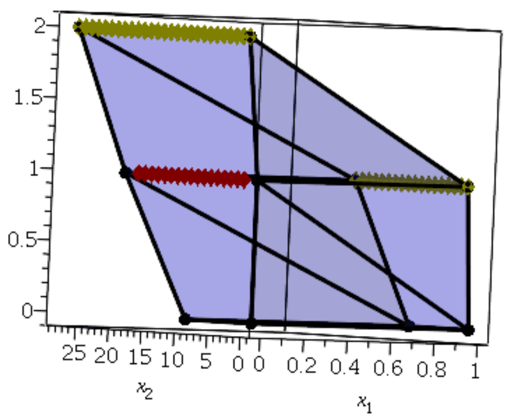

$\longrightarrow$ 10-site

# The Newton Polytope for $n$-site

Let $M_\kappa := \begin{bmatrix} \kappa_3 & \kappa_9 & \cdots & \kappa_{6n-3} \\ \kappa_6 & \kappa_{12} & \cdots & \kappa_{6n} \end{bmatrix}$.

Sign of each yellow point $\rightsquigarrow$ sign of $\kappa_{6i+3}\kappa_{6j+6} - \kappa_{6i+6}\kappa_{6j+3}$ for some $i, j \in \{0, \ldots, n-1\}$

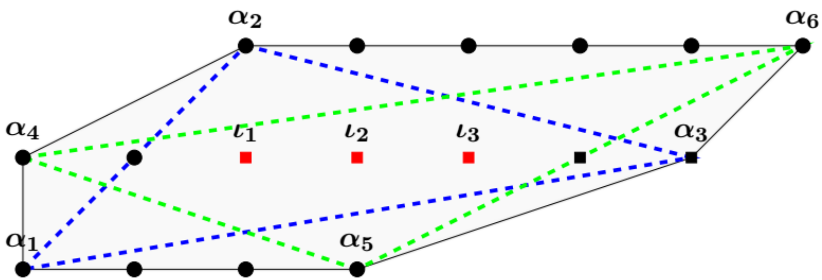
If $\kappa_{6i+3}\kappa_{6i+12} - \kappa_{6i+6}\kappa_{6i+9} > 0$ for all $i$, then it is enough to consider the restriction of $p$ to the hexagonal face.



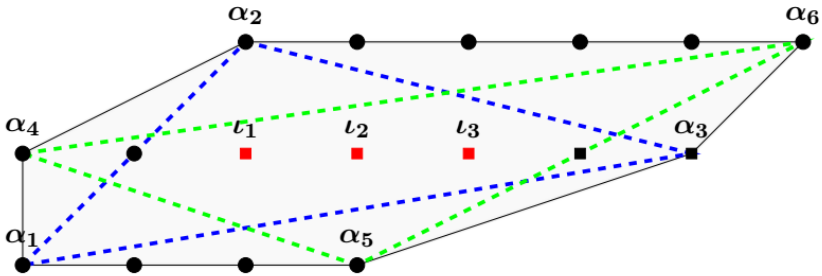

$\longrightarrow$ 10-site

# Circuit Covers

FIn 3-site, consider the hexagonal face, and six circuits defined by two triangles and three red points.



FIn 3-site, consider the hexagonal face, and six circuits defined by two triangles and three red points.



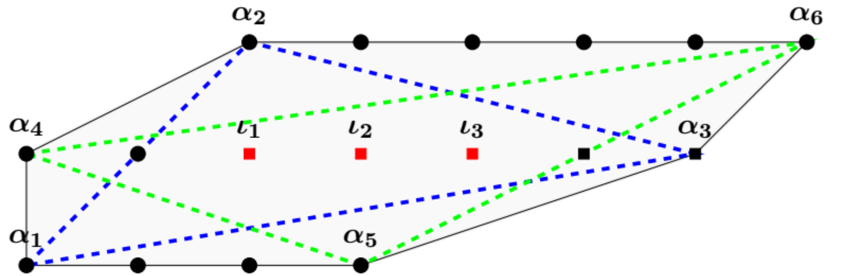

We define three circuit polynomials for each triangle, and distribute the coefficient of $p$ at each $\boldsymbol{\alpha_i}$ evenly to these circuit polynomials. For example, for $\iota_1$ we have the polynomials

$$C_{\Delta_1}^{\iota_1} := \mathrm{coef}(p, \boldsymbol{\alpha_1})\boldsymbol{x}^{\boldsymbol{\alpha_1}} + \mathrm{coef}(p, \boldsymbol{\alpha_2})\boldsymbol{x}^{\boldsymbol{\alpha_2}} + \mathrm{coef}(p, \boldsymbol{\alpha_3})\boldsymbol{x}^{\boldsymbol{\alpha_3}} + c_{1,\boldsymbol{\alpha_1}}\boldsymbol{x}^{\boldsymbol{\iota_1}}$$

We write the circuit conditions corresponding to $C_{\Delta_1}^{\iota_1}$ and $C_{\Delta_2}^{\iota_1}$:

$$\Theta_1^{\Delta_1} = \left(\frac{1}{4}\right)^{\frac{4}{10}} \left(\frac{a_1 b_0 - a_0 b_1}{4}\right)^{\frac{4}{10}} \left(\frac{b_2 c_2}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right), \quad \Theta_1^{\Delta_2} = \left(\frac{a_0}{8}\right)^{\frac{6}{10}} \left(\frac{c_2}{2}\right)^{\frac{2}{10}} \left(\frac{c_2(a_2 b_1 - a_1 b_2)}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right),$$

FIn 3-site, consider the hexagonal face, and six circuits defined by two triangles and three red points.




We define three circuit polynomials for each triangle, and distribute the coefficient of $p$ at each $\boldsymbol{\alpha_i}$ evenly to these circuit polynomials. For example, for $\iota_1$ we have the polynomials

$$C_{\Delta_1}^{\iota_1} := \operatorname{coef}(p, \boldsymbol{\alpha_1})\boldsymbol{x}^{\boldsymbol{\alpha_1}} + \operatorname{coef}(p, \boldsymbol{\alpha_2})\boldsymbol{x}^{\boldsymbol{\alpha_2}} + \operatorname{coef}(p, \boldsymbol{\alpha_3})\boldsymbol{x}^{\boldsymbol{\alpha_3}} + c_{1,\boldsymbol{\alpha_1}}\boldsymbol{x}^{\boldsymbol{\iota_1}}$$

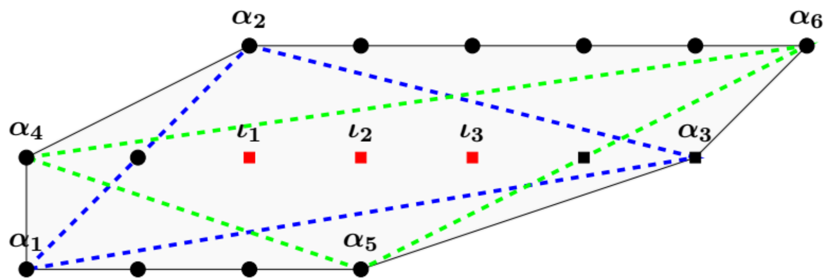
We write the circuit conditions corresponding to $C_{\Delta_1}^{\iota_1}$ and $C_{\Delta_2}^{\iota_1}$:

$$\Theta_1^{\Delta_1} = \left(\frac{1}{4}\right)^{\frac{4}{10}} \left(\frac{a_1 b_0 - a_0 b_1}{4}\right)^{\frac{4}{10}} \left(\frac{b_2 c_2}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right), \quad \Theta_1^{\Delta_2} = \left(\frac{a_0}{8}\right)^{\frac{6}{10}} \left(\frac{c_2}{2}\right)^{\frac{2}{10}} \left(\frac{c_2(a_2 b_1 - a_1 b_2)}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right),$$

If $\operatorname{coef}(P, \boldsymbol{\iota_i}) \geq -\Theta_i^{\Delta_1} - \Theta_i^{\Delta_2}$, then one can distribute $\operatorname{coef}(P, \boldsymbol{\iota_i})$ into $C_{\Delta_1}^{\iota_1}$ and $C_{\Delta_2}^{\iota_1}$ so that both of them are nonnegative.

# Circuit Covers

FIn 3-site, consider the hexagonal face, and six circuits defined by two triangles and three red points.




We define three circuit polynomials for each triangle, and distribute the coefficient of $p$ at each $\boldsymbol{\alpha_i}$ evenly to these circuit polynomials. For example, for $\iota_1$ we have the polynomials

$$C_{\Delta_1}^{\iota 1} := \operatorname{coef}(p, \boldsymbol{\alpha_1})\boldsymbol{x}^{\boldsymbol{\alpha 1}} + \operatorname{coef}(p, \boldsymbol{\alpha_2})\boldsymbol{x}^{\boldsymbol{\alpha 2}} + \operatorname{coef}(p, \boldsymbol{\alpha_3})\boldsymbol{x}^{\boldsymbol{\alpha 3}} + c_{1,\boldsymbol{\alpha_1}}\boldsymbol{x}^{\boldsymbol{\iota 1}}$$

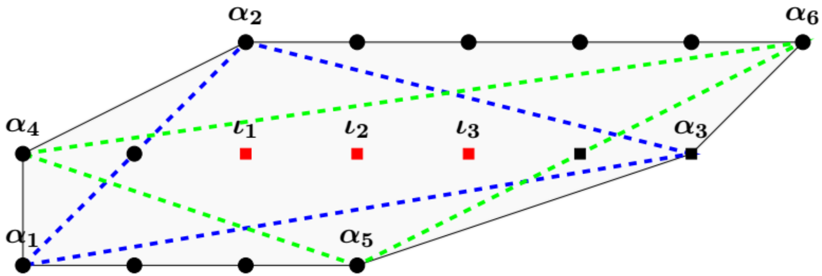
We write the circuit conditions corresponding to $C_{\Delta_1}^{\iota 1}$ and $C_{\Delta_2}^{\iota 1}$:

$$\Theta_1^{\Delta_1} = \left(\frac{1}{4}\right)^{\frac{4}{10}} \left(\frac{a_1 b_0 - a_0 b_1}{4}\right)^{\frac{4}{10}} \left(\frac{b_2 c_2}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right), \quad \Theta_1^{\Delta_2} = \left(\frac{a_0}{8}\right)^{\frac{6}{10}} \left(\frac{c_2}{2}\right)^{\frac{2}{10}} \left(\frac{c_2(a_2 b_1 - a_1 b_2)}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right),$$

If $\operatorname{coef}(P, \boldsymbol{\iota_i}) \geq -\Theta_i^{\Delta_1} - \Theta_i^{\Delta_2}$, then one can distribute $\operatorname{coef}(P, \boldsymbol{\iota_i})$ into $C_{\Delta_1}^{\iota 1}$ and $C_{\Delta_2}^{\iota 1}$ so that both of them are nonnegative.

$$R_i := \{\boldsymbol{\kappa} \in \mathbb{R}_{>0}^{6n} \mid \operatorname{coef}(P, \boldsymbol{\iota_i}) \geq -\Theta_i^{\Delta_1} - \Theta_i^{\Delta_2}\}$$

FIn 3-site, consider the hexagonal face, and six circuits defined by two triangles and three red points.




We define three circuit polynomials for each triangle, and distribute the coefficient of $p$ at each $\boldsymbol{\alpha_i}$ evenly to these circuit polynomials. For example, for $\iota_1$ we have the polynomials

$$C_{\Delta_1}^{\boldsymbol{\iota_1}} := \mathrm{coef}(p, \boldsymbol{\alpha_1})\boldsymbol{x}^{\boldsymbol{\alpha_1}} + \mathrm{coef}(p, \boldsymbol{\alpha_2})\boldsymbol{x}^{\boldsymbol{\alpha_2}} + \mathrm{coef}(p, \boldsymbol{\alpha_3})\boldsymbol{x}^{\boldsymbol{\alpha_3}} + c_{1,\boldsymbol{\alpha_1}}\boldsymbol{x}^{\boldsymbol{\iota_1}}$$

We write the circuit conditions corresponding to $C_{\Delta_1}^{\boldsymbol{\iota_1}}$ and $C_{\Delta_2}^{\boldsymbol{\iota_1}}$:

$$\Theta_1^{\Delta_1} = \left(\frac{1}{4}\right)^{\frac{4}{10}} \left(\frac{a_1 b_0 - a_0 b_1}{4}\right)^{\frac{4}{10}} \left(\frac{b_2 c_2}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right), \quad \Theta_1^{\Delta_2} = \left(\frac{a_0}{8}\right)^{\frac{6}{10}} \left(\frac{c_2}{2}\right)^{\frac{2}{10}} \left(\frac{c_2(a_2 b_1 - a_1 b_2)}{2}\right)^{\frac{2}{10}} \left(\frac{10}{3}\right),$$

If $\mathrm{coef}(P, \boldsymbol{\iota_i}) \geq -\Theta_i^{\Delta_1} - \Theta_i^{\Delta_2}$, then one can distribute $\mathrm{coef}(P, \boldsymbol{\iota_i})$ into $C_{\Delta_1}^{\boldsymbol{\iota_1}}$ and $C_{\Delta_2}^{\boldsymbol{\iota_1}}$ so that both of them are nonnegative.

$$R_i := \{\boldsymbol{\kappa} \in \mathbb{R}_{>0}^{6n} \mid \mathrm{coef}(P, \boldsymbol{\iota_i}) \geq -\Theta_i^{\Delta_1} - \Theta_i^{\Delta_2}\}$$

Feliu, Kaihnsa, de Wolff, Y.(2021+): For $n$-site,

- $2n - 3$ points with (possibly) negative signs
- $R_i \neq \varnothing$, for $i \in \{1, \ldots, 2n-3\}$
- $\bigcap_{i=1}^{2n-3} R_i \neq \varnothing$

# Concluding Remarks

Further remarks about ongoing work:

- $\longrightarrow$ Inequalities that define $R_i$ can be improved by considering additional circuit polynomials constructed from the remaining positive points in the hexagonal face.
- $\longrightarrow$ Connectivity of the multi/monostationarity regions are also investigated.

# Concluding Remarks

Further remarks about ongoing work:

⟶ Inequalities that define $R_i$ can be improved by considering additional circuit polynomials constructed from the remaining positive points in the hexagonal face.

⟶ Connectivity of the multi/monostationarity regions are also investigated.

Remarks about possible follow up works:

⟶ Describe the region of multi/mono stationarity for $n$-site under different conditions on the minors of $M_\kappa = \begin{bmatrix} \kappa_3 & \kappa_9 & \cdots & \kappa_{6n-3} \\ \kappa_6 & \kappa_{12} & \cdots & \kappa_{6n} \end{bmatrix}$.

⟶ Consider other such chemical reaction networks, and study the polynomial whose sign is associated to multi/monostationarity using similar techniques.

⟶ Similar symbolic nonnegativity certification techniques can further be applied to other important problems in CRNT, e.g., Routh-Hurwitz criterion for determining the Hopf bifurcations [TF20, CMS19].

Thank you for your attention

# References I


- G. Blekherman, P.A. Parrilo, and R.R. Thomas, *Semidefinite optimization and convex algebraic geometry*, Society for Industrial and Applied Mathematics, 2012.
- C. Conradi, E. Feliu, M. Mincheva, and C. Wiuf, *Identifying parameter regions for multistationarity*, PLoS computational biology **13** (2017), no. 10, e1005751.
- C. Conradi and M. Mincheva, *Catalytic constants enable the emergence of bistability in dual phosphorylation*, Journal of The Royal Society Interface **11** (2014), no. 95, 20140158.
- C. Conradi, M. Mincheva, and A. Shiu, *Emergence of oscillations in a mixed-mechanism phosphorylation system*, Bulletin of mathematical biology **81** (2019), no. 6, 1829–1852.

# References II

V. Chandrasekaran and P. Shah, *Relative entropy relaxations for signomial optimization*, SIAM Journal on Optimization **26** (2016), no. 2, 1147–1173.

M. Dressler, A. Kurpisz, and T. de Wolff, *Optimization over the boolean hypercube via sums of nonnegative circuit polynomials*, 43rd International Symposium on Mathematical Foundations of Computer Science (MFCS 2018), vol. 117, Schloss Dagstuhl-Leibniz-Zentrum für Informatik, 2018, p. 82.

E. Feliu, N. Kaihnsa, T. de Wolff, and O. Yürük, *The kinetic space of multistationarity in dual phosphorylation*, Journal of Dynamics and Differential Equations (2020).

D. Hilbert, *Über die darstellung definiter formen als summe von formenquadraten*, Mathematische Annalen **32** (1888), no. 3, 342–350.

# References III


- A. Hurwitz, *Ueber den Vergleich des arithmetischen und des geometrischen Mittels.*, Journal für die reine und angewandte Mathematik **108** (1891), 266–268.
- S. Iliman and T. de Wolff, *Amoebas, nonnegative polynomials and sums of squares supported on circuits*, Research in the Mathematical Sciences **3** (2016), no. 9, 1–35.
- J.B. Lasserre, *Moments, positive polynomials and their applications*, vol. 1, World Scientific, 2010.
- T.S. Motzkin, *The arithmetic-geometric inequality*, Inequalities: Proceedings, Volume 1, Academic Press, 1967, pp. 203–224.
- B. Reznick, *Forms derived from the arithmetic-geometric inequality*, Mathematische Annalen **283** (1989), no. 3, 431–464.

# References IV


A. Torres and F. Feliu, *Symbolic proof of bistability in reaction networks*, 2020.