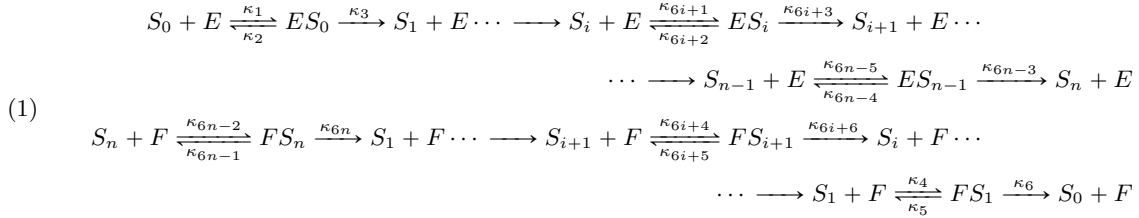# EXTENDED ABSTRACT - MULTISTATIONARITY IN $n-$SITE PHOSPHORYLATION

ELISENDA FELIU, NIDHI KAIHNSA, TIMO DE WOLFF, AND OGUZHAN YÜRÜK

1. Introduction

The process of phosphorylation and dephosphorylation is a crucial chemical reaction network, which plays an important role in cell signaling [3, 8, 9, 12]. We consider a *protein S* with n phosphorylation sites, whose phosphorylation and dephosphorylation are respectively regulated by the enzymes *kinase E* and *phosphatase F*. Following the notation in [1], the reaction network that governs the n-site phosphorylation cycle is:

$$
\begin{aligned}
& S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \cdots \longrightarrow S_i + E \underset{\kappa_{6i+2}}{\overset{\kappa_{6i+1}}{\rightleftharpoons}} ES_i \xrightarrow{\kappa_{6i+3}} S_{i+1} + E \cdots \\
& \hspace{5cm} \cdots \longrightarrow S_{n-1} + E \underset{\kappa_{6n-4}}{\overset{\kappa_{6n-5}}{\rightleftharpoons}} ES_{n-1} \xrightarrow{\kappa_{6n-3}} S_n + E \\
& S_n + F \underset{\kappa_{6n-1}}{\overset{\kappa_{6n-2}}{\rightleftharpoons}} FS_n \xrightarrow{\kappa_{6n}} S_1 + F \cdots \longrightarrow S_{i+1} + F \underset{\kappa_{6i+5}}{\overset{\kappa_{6i+4}}{\rightleftharpoons}} FS_{i+1} \xrightarrow{\kappa_{6i+6}} S_i + F \cdots \\
& \hspace{5cm} \cdots \longrightarrow S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F
\end{aligned}
\tag{1}
$$

where S_i denotes the protein S after i phosphorylation steps. We denote the concentration of the reactants in network (1) as $e = [E]$, $f = [F]$, $s_i = [S_i]$ for $i = 0, \ldots, n$ and $u_i = [FS_{i+1}]$, $y_i = [ES_i]$ for $i = 0, \ldots, n-1$. Under the mass-action assumption, the ODE system governing the evolution of the concentration of the species in time is as follows:

$$
\begin{aligned}
& \frac{de}{dt} = -\sum_{i=0}^{n-1} \kappa_{6i+1} s_i e + \sum_{i=0}^{n-1} \kappa_{6i+1}(\kappa_{6i+2} + \kappa_{6i+3}) y_i, \quad \frac{df}{dt} = -\sum_{i=0}^{n-1} \kappa_{6i+4} s_{i+1} f + \sum_{i=0}^{n-1} (\kappa_{6i+5} + \kappa_{6i+6}) u_i, \\
& \frac{ds_i}{dt} = \kappa_{6i-3} y_{i-1} - \kappa_{6i+1} s_i e + \kappa_{6i+2} y_i + \kappa_{6i+6} u_i - \kappa_{6i-2} s_i f + \kappa_{6i-1} u_{i-1}, \qquad \text{for } i = 0, \ldots, n, \\
& \frac{dy_i}{dt} = \kappa_{6i+1} s_i e - (\kappa_{6i+2} + \kappa_{6i+3}) y_i, \quad \frac{du_i}{dt} = \kappa_{6i+4} s_{i+1} f - (\kappa_{6i+5} + \kappa_{6i+6}) u_i \qquad \text{for } i = 0, \ldots, n-1,
\end{aligned}
\tag{2}
$$

with the agreement that $\kappa_j = 0$ if $j > 6n$ or $j < 0$. Each solution trajectory is confined in the subspace given by the *conservation laws*

$$
e + \sum_{i=0}^{n-1} y_i = E_{\text{tot}}, \quad f + \sum_{i=0}^{n-1} u_i = F_{\text{tot}}, \quad s_0 + \sum_{i=1}^{n} s_i + \sum_{i=0}^{n-1} y_i + \sum_{i=0}^{n-1} u_i = S_{\text{tot}}.
\tag{3}
$$

where $E_{\text{tot}}, F_{\text{tot}}$ and S_{tot} correspond to the total amounts of phosphatase, kinase and the protein S in the system. The intersection of one such level set with the non-negative orthant is called a *stoichiometric compatibility class*. The *steady states* of the system are found by setting the left-hand side of (2) to zero. We refer the reader to [5] or [6] for more information on chemical reaction network theory.

Following the notation in [1], we consider the set of parameters $K_i = \frac{\kappa_{6i+1}}{\kappa_{6i+2} + \kappa_{6i+3}}$ and $L_i = \frac{\kappa_{6i+4}}{\kappa_{6i+5} + \kappa_{6i+6}}$ for $i = 0, \ldots, n-1$, which correspond to the inverses of the *Michaelis-Menten constants* (see e.g.[11, Chapter 10]) of the (de)phosphorylation events, and define $T_i = \prod_{j=0}^{j=i} \frac{\kappa_{6j+3} K_j}{\kappa_{6j+6} L_j}$ for $i = 0, \ldots, n-1$ with the convention $T_{-1} = 1$. Then, the solution to the system given by the last $3n$ steady state equations in the variables s_{i+1}, y_i, u_i for $i = 0, \ldots, n-1$ is

$$
s_{i+1} = T_i e^{i+1} f^{-(i+1)} s_0 \qquad y_i = K_i T_{i-1} e^{i+1} f^{-i} s_0 \qquad u_i = L_i T_i e^{i+1} f^{-i} s_0.
\tag{4}
$$

This gives rise to a parametrization of the set of positive steady states in the variables e, f, s_0,

$$
\varphi_\kappa \colon \mathbb{R}^3_{>0} \quad \rightarrow \quad \mathbb{R}^{3n+3}_{>0},
\tag{5}
$$

that is, the image of φ_κ is precisely the set of positive steady states. We consider the polynomial function given by the right-hand side of (2), and by replacing its first three entries with the left-hand side of (3) we construct the polynomial function

$$(6) \qquad \psi_\kappa \colon \mathbb{R}^{3n+3} \longrightarrow \mathbb{R}^{3n+3},$$

whose image is the set if positive steady states in the compatibility class given by $E_{\text{tot}}, F_{\text{tot}}$ and S_{tot}.

If, for a given vector of reaction rate constants κ, there exist positive E_{tot}, F_{tot}, and S_{tot} such that some stoichoimetric compatibility class has at least two positive steady states, then we say that κ *enables multistationarity*. If this is not the case, then κ is said to *preclude multistationarity*.

In this work, we first point out that the monostationarity of the system can be verified by checking the nonnegativity of a particular real polynomial as given in Theorem 3.3. Furthermore, we give a sufficient condition for multistationarity for n-site phosphorylation in Theorem 4.1. We introduce a general construction for sufficient symbolic monostationarity conditions in Remark 4.3. Moreover, in Theorem 4.4, we present an effective method for checking monostationarity if κ is given explicitly.

2. A Polynomial for Multistationarity

We follow the approach in [7], and reduce the problem of detecting multistationarity to the study of the signs a multivariate rational function. We apply Theorem 1 in [4], and obtain the following result:

Proposition 2.1. *Let* $\kappa \in \mathbb{R}_{>0}^{6n}$, ψ_κ *be the polynomial function defined in* (6) *and* φ_κ *the parametrization of the set of positive steady states from* (5). *Define the following rational function*

$$q_\kappa(e, f, s_0) := (-1)^{3n} \det J_{\psi_\kappa}(\varphi_\kappa(e, f, s_0)).$$

Then it holds that:

(i) *If* $q_\kappa(e, f, s_0) > 0$ *for all* $(e, f, s_0) \in \mathbb{R}_{>0}^3$, *then* κ *precludes multistationarity.*
(ii) *If* $q_\kappa(e^*, f^*, s_0^*) < 0$ *for some* $(e^*, f^*, s_0^*) \in \mathbb{R}_{>0}^3$, *then* κ *enables multistationarity. In this case the stoichiometric compatibility class containing* $\varphi_\kappa(e^*, f^*, s_0^*)$ *contains at least two positive steady states.*

Based on Proposition 2.1, we study the signs q_κ attains on the positive orthant to determine the set of reaction rate constants that enable multistationarity. To this end, we first reduce the computation of the determinant of a matrix of size $3n + 3$, to the computation of the determinant of a matrix of size 3. Let Φ be the linear map given by the left-hand side of (3).

Proposition 2.2. *For any* $\kappa \in \mathbb{R}_{>0}^{6n}$ *and* $(e, f, s_0) \in \mathbb{R}_{>0}^3$, *the sign of* $q_\kappa(e, f, s_0)$ *agrees with the sign of*

$$\det J_{\Phi \circ \varphi_\kappa}(e, f, s_0).$$

In view of Proposition 2.1 and 2.2, multistationarity is determined by considering the sign of the determinant of the Jacobian of $\Phi \circ \varphi_\kappa$. Hence, $\Phi \circ \varphi_\kappa$ depends on κ through the assembled parameters K_i, L_i, T_i, and the determinant of its Jacobian agrees with the determinant of the following matrix:

$$(7) \quad J := \begin{bmatrix} 1 + \sum_{i=0}^{n-1}(i+1)\,a_i\,x_2^i x_3 & -\sum_{i=0}^{n-1} i\,a_i\,x_2^{i+1}x_3 & \sum_{i=0}^{n-1} a_i\,x_1 x_2^i \\ \sum_{i=0}^{n-1}(i+1)\,b_i\,x_2^i x_3 & 1 - \sum_{i=0}^{n-1} i\,b_i\,x_2^{i+1}x_3 & \sum_{i=0}^{n-1} b_i\,x_1 x_2^i \\ -1 + \sum_{i=0}^{n-1}(i+1)\,c_i\,x_1^{-1}x_2^{i+1}x_3 & -1 - \sum_{i=0}^{n-1}(i+1)\,c_i\,x_1^{-1}x_2^{i+2}x_3 & 1 + \sum_{i=0}^{n-1} c_i\,x_2^{i+1} \end{bmatrix},$$

where a_i, b_i, and c_i corresponds to $K_i T_{i-1}, L_i T_i, T_i$ for $i = 0, \dots, n-1$ respectively, and $x_1 = e$, $x_2 = \frac{e}{f}$, and $x_3 = s_0$. The determinant of (7) is a polynomial in x_1, x_2, x_3 with coefficients depending on a_i, b_i, c_i. From Proposition 2.1 and Proposition 2.2, we see that the region of multistationarity is described by the nonnegativity of the polynomial $p_\eta(x_1, x_2, x_3) := \det J$.

Proposition 2.3. *Let* $\kappa \in \mathbb{R}_{>0}^{6n}$, *consider the corresponding parameter vector* η *and the polynomial* $p_\eta(x_1, x_2, x_3) := \det J$ *for* J *given in* (7). *Then:*

(i) *If* $p_\eta(x_1, x_2, x_3) > 0$ *for all* $(x_1, x_2, x_3) \in \mathbb{R}_{>0}^3$, *then* κ *precludes multistationarity.*
(ii) *If* $p_\eta(x_1^*, x_2^*, x_3^*) < 0$ *for some* $(x_1^*, x_2^*, x_3^*) \in \mathbb{R}_{>0}^3$, *then* κ *enables multistationarity, and the stoichiometric compatibility class containing* $\varphi_\kappa(x_1^*, x_1^* x_2^*, x_3^*)$ *contains at least two positive steady states.*

3. Newton Polytope and Positivity

To analyze the possible signs that $p_\eta(x_1, x_2, x_3)$ attains over the positive orthant, we study its Newton polytope, which we denote by $N(p_\eta)$. We note that p_η is linear in x_1, and hence can be expressed as

$$p_\eta(x_1, x_2, x_3) = P_0(x_2, x_3) + x_1 P_1(x_2, x_3).$$

Therefore, each exponent vector in $N(P_0)$ either belong to $N(p_\eta) \cap \{x \in \mathbb{N}^3 : x_1 = 0\} = \{0\} \times N(P_0)$ or $N(p_\eta) \cap \{x \in \mathbb{N}^3 : x_1 = 1\} = \{1\} \times N(P_1)$.

Theorem 3.1. *For any n, the set of vertices of the Newton polytope $N(p_\eta)$ of the polynomial p_η consists of the following* 10 *points:*

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

Sketch of Proof: It is sufficient to determine the vertices of $N(P_0)$ and $N(P_1)$. P_0 is quadratic in x_3, and it can be expressed as $P_0(x_2, x_3) = A_2(x_2)x_3^2 + A_{10}(x_2)x_3 + A_{00}(x_2)$ for

$$(8) \quad A_2(x_2) = \left(1 + \sum_{i=0}^{n-1} c_i x_2^{i+1}\right)\left(\sum_{\ell=1}^{2n-2} \sum_{i+j=\ell} (i-j)\, a_i\, b_j\, x_2^{\ell+1}\right), \qquad A_{00}(x_2) = 1 + \sum_{i=0}^{n-1} c_i x_2^{i+1},$$

$$A_{10}(x_2) = \sum_{\ell=0}^{n-1}(\ell+1)\, a_\ell\, x_2^\ell - \sum_{\ell=0}^{n-1}\ell\, b_\ell\, x_2^{\ell+1} + \sum_{\ell=0}^{2n-2}\sum_{i+j=\ell}(j+1-i)\, b_i\, c_j\, x_2^{\ell+2} + \sum_{\ell=1}^{2n-2}\sum_{i+j=\ell}(i-j)\, a_i\, c_j\, x_2^{\ell+1}.$$

The vertices of $N(P_0)$ are located along the lines $L_i := \{x_3 = i\}$, for $i = 0, 1, 2$, in the (x_2, x_3)-plane, and correspond to the highest and lowest exponents of the polynomials given in (8). Therefore, the set of vertices of $N(P_0)$ is contained in $S_1 = \big\{(0,0), (n,0), (0,1), (2n,1), (2,2), (3n-2,2)\big\}$. To show that this is exactly the set of vertices of $N(P_0)$, it is enough to verify that the vertices on L_1 do not lie in the convex hull of the other four points in S_1. This is easily checked by considering the relative position of $(0,1)$ with respect to the line joining $(0,0)$ and $(2,2)$ and similarly, that of $(2n,1)$ with respect to the line joining $(n,0)$ and $(3n-2,2)$. Therefore, the Newton polytope $N(P_0)$ is the hexagon with vertex set S_1. P_0 is linear in x_3, and it can be expressed as $P_1(x_2, x_3) = A_{11}(x_2)x_3 + A_{01}(x_2)$ for

$$(9) \qquad A_{11}(x_2) = (1 + x_2)\left(\sum_{\ell=1}^{2n-2}\sum_{i+j=\ell}(j-i)a_j\, b_i\, x_2^\ell\right), \qquad A_{01}(x_2) = \sum_{i=0}^{n-1}(a_i + b_i)x_2^i$$

Following a similar argument, we see that the vertices of $N(P_1)$ are $S_2 = \big\{(0,0), (n-1,0), (1,1), (2n-2,1)\big\}$. Thus, we conclude that the set of vertices of $N(p_\eta)$ is

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

$\square$

Remark 3.2. In the full article, we present the H-description of the Newton polytope $N(p_\eta)$, and we show that it has 18 edges and 10 facets.

Newton polytopes of a polynomial can be used to determine properties of a polynomial, in particular, its positivity. In what follows, we use a well known result stating that if a polynomial P with Newton polytope $N(P)$ is restricted to the polynomial P_F with support contained in a face F of $N(P)$, then any sign which is attained by P_F is also attained by P, see [7, Proposition 2.3]. In particular, if the coefficient of the monomial supported at one of the vertices is negative, then there exists some $x \in \mathbb{R}^n_{>0}$ such that the polynomial is negative at x.

Theorem 3.3. *Fix $\eta \in \mathbb{R}^{4n}_{>0}$.*
- *The polynomial p_η attains a negative value over $\mathbb{R}^3_{>0}$ if and only if P_0 attains negative values over $\mathbb{R}^2_{>0}$.*
- *η enables multistationarity if and only if p_η attains negative values over $\mathbb{R}^3_{>0}$ (equivalently P_0 attains negative values over $\mathbb{R}^2_{>0}$).*

Sketch of Proof. By inspecting the coefficients of $A_*(x_2)$, we conclude that only A_2, A_{10}, and A_{11} have negative coefficients. Furthermore, for a fixed $x_2 > 0$, we observe that $A_2(x_2)$ is positive if and only if $A_{11}(x_2)$ is positive, since both A_2 and A_{11} are positive multiples of $\left(\sum_{\ell=1}^{2n-2}\sum_{i+j=\ell}(j-i)a_j\, b_i\, x_2^\ell\right)$. $\square$

By Theorem 3.3, multistationarity is completely characterized by the sign of P_0 over $\mathbb{R}^2_{>0}$. We rewrite the polynomial as P_η, to indicate dependence on the parameter vector:

$$(10) \qquad P_\eta(x_2, x_3) = A_2(x_2)x_3^2 + A_{10}(x_2)x_3 + A_{00}(x_2).$$

This is a polynomial in two variables x_2 and x_3. If $A_2(x_2) < 0$, then P_η attains also negative values.

4. Region of Multistationarity and its Connectedness

We investigate the nonnegativity of the polynomial to describe subsets in the parameter region that enable or preclude monostationarity. In order to do so, we utilize circuit polynomials, which are originally defined in [10], to find symbolic nonnegativity conditions.

Theorem 4.1. *If η is such that $\kappa_3\kappa_{12} - \kappa_6\kappa_9 < 0$ or $\kappa_{6n-9}\kappa_{6n} - \kappa_{6n-3}\kappa_{6n-6} < 0$, then η enables multistationarity.*

Sketch of Proof. The term that decides the sign of $A_2(x_2)$ is

$$(11) \qquad \sum_{i+j=\ell} (i-j)\,a_i\,b_j\,x_2^{\ell+1} = \sum_{\substack{i>j \\ i+j=\ell}} (i-j)(a_ib_j - a_jb_i)x_2^{\ell+1}.$$

For $i, j < n$, we have $a_ib_j - a_jb_i = T_{i-1}T_{j-1}K_iK_j\left(\frac{\kappa_{6j+3}}{\kappa_{6j+6}} - \frac{\kappa_{6i+3}}{\kappa_{6i+6}}\right)$. Therefore, the signs of the coefficients of $A_2(x_2)$ are decided by the signs of the minors of the following matrix:

$$(12) \qquad M_\kappa = \begin{bmatrix} \kappa_3 & \kappa_9 & \ldots & \kappa_{6n-3} \\ \kappa_6 & \kappa_{12} & \ldots & \kappa_{6n} \end{bmatrix}$$

Note that the two expressions in Theorem 4.1 are the first and last maximal minors of matrix M_κ. $\square$

Proposition 4.2. *Let $a_{i+1}b_i - a_ib_{i+1} > 0$ for all $i \in \{0, \ldots, n-1\}$. Then, all 2 by 2 minors of M_κ are positive, and $A_2(x_2)$ is nonnegative.*

For a given choice of parameters η that satisfies the conditions of Proposition 4.2, the only exponents of $P_\eta(x_2, x_3)$ with negative coefficients are

$$(13) \qquad A_- := \{(2,1), (3,1), \ldots, (2n-2, 1)\}.$$

If $n = 2$, then A_- consists of a single element, and M_κ has a unique 2 by 2 minor given by $\kappa_3\kappa_{12} - \kappa_6\kappa_9$. If $\kappa_3\kappa_{12} - \kappa_6\kappa_9 > 0$, then the nonnegativity of $P_\eta(x_2, x_3)$ only depends on the coefficient of the single exponent in A_-. In [7, Theorem 3.5], authors provide a symbolic sufficient condition for monostationarity using sums of nonnegative circuit (SONC) polynomials. We further point out that $P_\eta(x_2, x_3)$ is nonnegative if and only if it is a SONC polynomial due to [13, Theorem 3.11] when $n = 2$. For $n > 2$, one can extend the the previous approach of decomposing the polynomial $P_\eta(x_2, x_3)$ into circuit polynomials, and then write a nonnegativity condition for each circuit polynomial.

Remark 4.3. For $n \geqslant 2$, each exponent in A_- is contained in both of the simplices given by $\Delta_1 = \{(0,0), (2,2), (2n,1)\}$ and $\Delta_2 = \{(0,1), (n,0), (3n-2, 2)\}$. One can form $2n - 3$ circuit polynomials from each one of Δ_1 and Δ_2, by dividing the coefficients of each exponent in $\mathrm{Vert}(N(P_0))$ equally into $2n - 3$ circuits. This yields two conditions for each exponent in A_-, which arise from the nonnegativity condition for circuit polynomials (see [10, Theorem 3.8]) of the polynomials that we consider for each element of A_-.

The approach given in Remark 4.3 can be improved by considering the other elements of the support that are known to have positive coefficients. But it is not evident how to choose circuits optimally involving these extra exponents for general n. However, if the vector of reaction rate parameters η is fixed from the beginning, then one can give a lower bound for $P_\eta(x_2, x_3)$ by solving a relative entropy program. Relative entropy programs are a class of convex problems, which can be solved effectively to a desired accuracy via interior point methods, see e.g. [2].

Theorem 4.4. *For any n, given a fixed κ such that the conditions of Proposition 4.2 hold, one can find a non-decreasing sequence of lower bounds for P_η by solving a relative entropy program at each step.*

Furthermore, in the full article, we investigate the connectivity of the multistationarity region given by $X := \left\{\eta = (\kappa_3, \kappa_6, \ldots, \kappa_{6n}, K_0, \ldots, K_{n-1}, L_0, \ldots, L_{n-1}) \in \mathbb{R}^{4n}_{>0} : \eta \text{ enables multistationarity}\right\}$.

Theorem 4.5. *The region X of multistationarity and the region $\mathbb{R}^{4n}_{>0} \backslash X$ of monostationarity is path connected for all n.*

References

[1] F. Bihan, A. Dickenstein, and Giaroli M. Lower bounds for positive roots and regions of multistationarity in chemical reaction networks. *J. Algebra*, 542:367–411, 2020.

[2] V. Chandrasekaran and P. Shah. Relative entropy optimization and its applications. *Mathematical Programming*, 161(1-2):1–32, 2017.

[3] P. Cohen. The structure and regulation of protein phosphatases. *Annu. Rev. Biochem.*, 58:453–508, Jan 1989.

[4] C. Conradi, E. Feliu, M. Mincheva, and C. Wiuf. Identifying parameter regions for multistationarity. *PLoS Comput. Biol.*, 13(10):e1005751, 2017.

[5] A. Dickenstein. Biochemical reaction networks: An invitation for algebraic geometers. In *Mathematical congress of the Americas*, volume 656, pages 65–83. Contemp. Math, 2016.

[6] M. Feinberg. *Foundations of Chemical Reaction Network Theory.* Springer International Publishing, 2019.

[7] E. Feliu, N. Kaihnsa, T. de Wolff, and O. Yuruk. The Kinetic Space of Multistationarity in Dual Phosphorylation. *J Dyn Diff Equat*, 2020.

[8] J. Hell and A. D. Rendall. Dynamical features of the map kinase cascade. In Cham Springer, editor, *Modeling Cellular Systems*, volume 11. 2017.

[9] C. Y. Huang and J. E. Ferrell. Ultrasensitivity in the mitogen-activated protein kinase cascade. *Proc. Natl. Acad. Sci. U.S.A.*, 93:10078–10083, 1996.

[10] S. Iliman and T. de Wolff. Amoebas, nonnegative polynomials and sums of squares supported on circuits. *Res. Math. Sci.*, 3(9), 2016.

[11] K.J. Laidler. *Physical Chemistry with Biological Applications.* Benjamin/Cummings Pub. Co., 1978.

[12] L. Qiao, R. B. Nachbar, I. G. Kevrekidis, and S. Y. Shvartsman. Bistability and oscillations in the Huang-Ferrell model of MAPK signaling. *PLoS Comput. Biol.*, 3(9):1819–1826, 2007.

[13] J. Wang. Nonnegative polynomials and circuit polynomials. *arXiv:1804.09455*, 2018.

Elisenda Feliu, Department of Mathematical Sciences, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark. efeliu@math.ku.dk

Nidhi Kaihnsa, Division of Applied Mathematics, Brown University, 182 George Street, Providence, RI, 02912. nidhi_kaihnsa@brown.edu

Timo de Wolff, Institute of Analysis and Algebra, TU Braunschweig, Universitätsplatz 2, 38106 Braunschweig, Germany. t.de-wolff@tu-braunschweig.de

Oguzhan Yürük, Technische Universität Berlin, Institut für Mathematik, Strasse des 17. Juni 136, 10623 Berlin, Germany. yuruk@math.tu-berlin.de