Steady state degree and mixed volume of chemical reaction networks

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September 17, 2019

Abstract
The steady-state degree of a chemical reaction network is the number of complex steady-states, which is a measure of the algebraic complexity of solving the steady-state system. In general, the steady-state degree may be difficult to compute. Here, we give an upper bound to the steady-state degree of a reaction network by utilizing the underlying polyhedral geometry associated with the corresponding polynomial system. We focus on three case studies of infinite families of networks, each generated by joining smaller networks to create larger ones. For each family, we state results on the steady-state degree or give an upper bound in terms of the mixed volume of the corresponding polynomial system.

1 Introduction
Chemical reaction networks, under the assumption of mass-action kinetics, are deterministic polynomial systems commonly used in systems biology to model mechanisms such as inter- and intracellular signaling. In this paper, we study the Newton polytopes of the steady-state system of several reaction networks. The geometry of these polytopes can inform us about the steady-state degree of the network, and consequently, the algebraic complexity of exploring regions of multistationarity.

One way to evaluate whether a given reaction network is an appropriate model for a biological process is to consider its capacity for multiple positive real steady-states. If a reaction network has this capacity, we call the network *multistationary*. Multistationarity for reaction networks with mass-action kinetics has been extensively studied (see [JS15]) with algebraic methods playing a key role [Dic16].

Once multistationarity is established, then bounds on the number of real positive steady-states [BDG18] [FH18] [MFR+16] [OSTT19] and the regions of multistationarity can be explored [CFMW17] [CIK18] [GBD18] [GHR16] [OMBA12]. One method...
to explore regions of multistationarity, which is used in [GHRS16] and [CIK18], is to sample parameters in a systematic way and repeatedly solve the steady-state system. The steady-state system of a reaction network is the parameterized polynomial system formed by the steady-state equations and the conservation equations. Solving steady-state systems can be done numerically using solvers based on polynomial homotopy continuation such as Bertini [BHSW13], PHCpack [Ver99], and HOM-4-PS2 [LLT08]. Such solvers will return all complex solutions, and so a final step requires filtering for real, positive solutions. We call the number of complex steady-states for generic rate constants and initial conditions the steady-state degree of a chemical reaction network. The steady-state degree is not only a bound on the number of real, positive steady-states, but is also a measure of the algebraic complexity of solving the steady-state system for a given reaction network. The steady-state degree is similar to the maximum likelihood degree studied in algebraic statistics [CHKS06] and the Euclidean distance degree studied in optimization [DHO+16]; the former is a measure of the algebraic complexity of maximum likelihood estimation and the latter is a measure of the algebraic complexity of minimizing the distance between a point and a variety. From the viewpoint of using numerical algebraic geometry to explore regions of multistationarity, the steady-state degree is the number of paths that need to be tracked when using a parameter-homotopy to solve the steady-state system and can serve as a stopping criterion for monodromy-based solvers, such as the one described in [DHJ+18].

Using the steady-state degree as motivation, in this paper we study the polyhedral geometry associated to the steady-state and conservation equations. In many cases, particularly when there are many variables involved, the steady-state degree of a family of networks can be difficult to establish. However, we can provide an upper bound by the Bézout bound and the mixed volume of the polynomial system arising from the chemical reaction network. As an example, the mixed volume was used to bound the steady-state degree of a model of ERK regulation in [OSTT19]. In this paper, we explore the mixed volumes of reaction networks further, giving formulas for three families of networks. In particular, we study the combinatorics of the Newton polytopes and their Minkowski sums that arise for three infinite families of networks.

The three infinite families of chemical reaction networks that we study are constructed by successively building on smaller networks to create larger ones. The base network for each family is: the cell death model from [HH10], the Edelstein network [MFPLV10], and the one-site phosphorylation cycle (see for example, motif (a) in [FW12]). For each network, we compute the mixed volume and steady-state degree of the networks using various techniques such as explicit computation, reducing to semi-mixed and unmixed volume computation [Che17], and in the case of a randomized system, constructing a unimodular triangulation. Each of these examples illustrate a different relationship between the steady-state degree and the mixed volume of the the steady-state system. For the first family, based on a cluster model for
cell death, we see that that the steady-state degree is actually slightly larger than the mixed volume, due to the presence of boundary steady-states. In the second family, based on the Edelstein model, the mixed volume and steady-state degree agree. While in the third family, multisite distributive phosphorylation, we see that the mixed volume is quadratic in the number of sites, while the steady-state degree is linear in the number of sites.

The most significant of these three case studies is the exploration of the multisite distributive phosphorylation system in Section 3.3. The \( n \)-site distributive phosphorylation system can be obtained by successively gluing together \( n \) copies of the one-site phosphorylation cycle [GHMS18]. The regions of multistationarity of this network have been well-studied (e.g. see [BDG18], [CIK18], [HFC13]) in the field of chemical reaction network theory. In addition, the authors of [WS08] show that the steady-state degree of the \( n \)-site system is \( 2n + 1 \) and the number of real positive solutions is bounded above by \( 2n - 1 \), while the authors of [FHC14] show that the \( 2n - 1 \) bound can be achieved. In Section 3.3, we give the mixed volume of the randomized steady-state system of \( n \)-site distributive phosphorylation. This requires computing the normalized volume of a \( 3n + 3 \) dimensional \( 0-1 \) polytope with \( 5n + 4 \) vertices and \( 3n + 7 \) facets. At the end of Section 3.3 we show that this polytope of interest is the matching polytope of a graph.

The paper is organized as follows. In Section 2, we give the necessary background, definitions, and motivation. In Section 3, we systematically explore each of the three families of networks.

2 Background & motivation

A chemical reaction network \( \mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}) \) is a triple where \( \mathcal{S} = \{A_1, A_2, \ldots, A_n\} \) is a set of \( n \) chemical species, \( \mathcal{C} = \{y_1, y_2, \ldots, y_p\} \) is a set of \( p \) complexes (finite nonnegative-integer combinations of the species), and \( \mathcal{R} = \{y_i \rightarrow y_j \mid y_i, y_j \in \mathcal{C}\} \) is a set of \( r \) reactions.

Each complex in \( \mathcal{C} \) can be written in the form \( y_{i1}A_1 + y_{i2}A_2 + \cdots + y_{in}A_n \) where \( y_{ij} \in \mathbb{Z}_{\geq 0} \), and thus, we will view the elements of \( \mathcal{C} \) as vectors in \( \mathbb{Z}_{\geq 0}^n \), i.e. \( y_i = (y_{i1}, y_{i2}, \ldots, y_{in}) \). Additionally, to each complex of the chemical reaction network, we associate a monomial \( x^{y_i} = x_{A_1}^{y_{i1}}x_{A_2}^{y_{i2}}\cdots x_{A_n}^{y_{in}} \) where \( x_{A_i} = x_{A_i}(t) \) represents the concentration for species \( A_i \) with respect to time. For example, for the reaction \( A + B \rightarrow 4B + C \), the monomials corresponding to the reactant \( A + B \) and the product \( 4B + C \) are \( x_A x_B \) and \( x_B^4 x_C \), respectively, with exponent vectors \( y_1 = (1, 1, 0) \) and \( y_2 = (4, 0, 1) \).

Let \( y_i \rightarrow y_j \) be the reaction from the \( i \)-th to the \( j \)-th complex. To each reaction we associate a reaction vector \( y_j - y_i \) that gives the net change in each species due to the reaction. Moreover, each reaction has an associated positive reaction rate constant
Given a chemical reaction network \((S, C, R)\) and a choice of \(k_{ij} \in \mathbb{R}^r_> 0\) the system of polynomial ordinary differential equations under the assumption of mass-action kinetics is

\[
\frac{dx}{dt} = \sum_{y_i \to y_j \in R} k_{ij}x^y_i(y_j - y_i) =: f(x), \quad x \in \mathbb{R}^n.
\]  

(1)

Setting the left-hand side of the ODEs above equal to zero gives us a set of polynomial equations that we call the steady-state equations.

The stoichiometric subspace associated with the chemical reaction network \(N = (S, C, R)\) is a vector subspace of \(\mathbb{R}^n\) spanned by the reaction vectors \(y_j - y_i\), denoted by

\[
S_N := \mathbb{R}\{y_j - y_i \mid y_i \to y_j \in R\}.
\]  

(2)

Given initial conditions \(c \in \mathbb{R}^n\), the stoichiometric compatibility class is the affine space \(S_N + c\), and the conservation equations of \(N\) are the set of linear equations defining \(S_N + c\).

In this paper, we are concerned with the parameterized system of equations formed by the steady-state and conservation equations, which we call the steady-state system, we view the polynomials of the steady-state system as polynomials in the ring \(\mathbb{Q}(k, c)[x_1, \ldots, x_n]\). When the solution set of this polynomial system is zero-dimensional for generic parameters \(k\) and \(c\), we define the number of complex solutions to the system for generic parameters as the steady-state degree of \(N\), where we distinguish boundary steady-states as complex solutions \(x \in \mathbb{C}^n\) such that \(x_i = 0\), for one or more \(i = 1, \ldots, n\).

The steady-state degree can be computed symbolically (using Gröbner bases) or numerically (using polynomial homotopy continuation), however, both these methods become computationally expensive when a large number of species are involved. In such cases we would like to know an upper bound on the degree. Two such bounds are the Bézout bound and the Bernlhein-Kushnirenko-Khovanskii (BKK) bound. Given a zero-dimensional polynomial system \(P = (f_1, \ldots, f_m)\) with \(f_i \in \mathbb{Q}[x_1, \ldots, x_n]\), the Bézout bound on the number of solutions in \(\mathbb{C}^n\) is the product of the degrees of all the polynomials in the system. The BKK bound on the number of solutions in \((\mathbb{C}^*)^n\) is the mixed volume of \(P\), which requires \(P\) to be a square system, i.e., a system of \(n\) equations in \(n\) variables, in this case, \(m = n\). The mixed volume of \(P\) is the mixed volume of the Newton polytopes of \(f_1, \ldots, f_n\), i.e., it is the coefficient of the term \(\lambda_1 \cdots \lambda_n\) in the expansion of \(\text{vol}(\lambda_1 \text{Newt}(f_1) + \cdots + \lambda_n \text{Newt}(f_n))\). Chen provides sufficient conditions under which the mixed volume of the Newton polytopes is the normalized volume of the convex hull of their union. We state these results below and reference them later in this note.

**Theorem 2.1.** [Che17] For finite sets \(S_1, \ldots, S_n \subset \mathbb{Q}^n\), let \(\bar{S} = S_1 \cup \cdots \cup S_n\). If for every proper positive dimensional face \(F\) of \(\text{conv}(\bar{S})\) we have \(F \cap S_i \neq \emptyset\) for each \(i = 1, \ldots, n\) then \(\text{MV}(\text{conv} S_1, \ldots, \text{conv} S_n) = n! \text{vol}_n(\text{conv}(\bar{S}))\).
Theorem 2.2. [Che17] Given $n$ nonempty finite sets $S_1, \ldots, S_n \subset \mathbb{Q}^n$, let $\tilde{S} = S_1 \cup \cdots \cup S_n$. If every positive dimensional face $F$ of $\text{conv}(\tilde{S})$ satisfies one of the following conditions:

(i) $F \cap S_i \neq \emptyset$ for all $i \in \{1, \ldots, n\}$;

(ii) $F \cap S_i$ is a singleton for some $i \in \{1, \ldots, n\}$;

(iii) For each $i \in I := \{i \mid F \cap S_i \neq \emptyset\}$, $F \cap S_i$ is contained in a common coordinate subspace of dimension $|I|$, and the projection of $F$ to this subspace is of dimension less than $|I|$;

then $\text{MV}(\text{conv} \, S_1, \ldots, \text{conv} \, S_n) = n! \, \text{vol}_n(\text{conv}(\tilde{S}))$.

Corollary 2.3. [Che17] Given nonempty finite set $S_{i,j} \subset \mathbb{Q}^n$ for $i = 1, \ldots, m$ and $j = 1, \ldots, k_i$ with $k_i \in \mathbb{Z}^+$ and $k_1 + \cdots + k_m = n$, let $Q_{i,j} = \text{conv}(S_{i,j})$, $\tilde{S}_i = \bigcup_{j=1}^{k_i} S_{i,j}$, and $\tilde{Q}_i = \text{conv}(\tilde{S}_i)$. If for each $i$, every positive dimensional face of $\tilde{Q}_i$ intersecting $S_{i,j}$, for some $j$, on at least two points also intersects all $S_{i,1}, \ldots, S_{i,k}$, then

$$\text{MV}(Q_{1,1}, \ldots, Q_{m,k_m}) = \text{MV}(\underbrace{\tilde{Q}_1, \ldots, \tilde{Q}_1, \ldots, \tilde{Q}_1}_{k_1}, \ldots, \underbrace{\tilde{Q}_m, \ldots, \tilde{Q}_m}_{k_m}).$$

In this collection of case studies, for each family of networks, we give the steady-state degree, the Bézout bound, and the mixed volume of the steady-state systems employing these results and other standard techniques.

3 Three families of networks

In what follows, we investigate three infinite families of reaction networks. The second two families result from successively joining, or gluing, smaller networks to form a larger network as defined in [GHMS18].

The first two families in this study showcase different methods that can be used to understand the steady-state degree, while the third family, multitesite distributive sequential phosphorylation, requires more sophisticated methods. In particular, in the third case study, we describe the polytope $Q_n$ obtained by taking the convex hull of the exponent vectors of the support of the system. We compute the normalized volume of $Q_n$, which bounds the number of non-boundary steady-states. This computation is done by first establishing the $\mathcal{H}$-representation of $Q_n$ and then explicitly constructing a regular unimodular triangulation of $Q_n$. 

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3.1 Cell death model

The first case study is a model representing the cell death mechanism as described in [HH10]. We consider these cluster-stabilization reactions involving unstable and stable open receptors, where each network of the family has two species: Y and Z, the unstable and stable receptors, respectively. The nth reaction network in this family, denoted CD\textsubscript{n}, has n complexes \( C_i \) of the form \( C_i = (n - i)Y + iZ \), with \( i = 1, \ldots, n \), and \( n(n - 1)/2 \) reactions \( C_i \xrightarrow{k_{i,j}} C_j \) such that \( i < j \). The polynomial system associated to \( CD_n \) consists of one linear conservation equation in the variables \( x_Y \) and \( x_Z \) and their initial conditions \( c = (c_Y, c_Z) \) and two steady-state equations, one for each species. Specifically, the polynomial system of interest is

\[
\begin{align*}
&f_1 = x_Y + x_Z - c_Y - c_Z \\
&f_2 = \dot{x}_Y = - \sum_{i,j,i \neq j}^n (j - i)k_{i,j}x_Y^i x_Z^{n-j} \\
&f_3 = \dot{x}_Z = \sum_{i,j,i \neq j}^n (j - i)k_{i,j}x_Y^i x_Z^{n-j}.
\end{align*}
\]

(3)

Since \( \dot{x}_Z = -\dot{x}_Y \), there is only one unique steady-state equation of degree \( n \). In this example, both the Bézout and BKK bounds are linear in \( n \), with the BKK bound being slightly lower. In Proposition 3.4 we show that the steady-state degree, including boundary solutions, is given by the Bézout bound; see Remark 3.5.

Example 3.1. For \( n = 4 \), the cell death model has two species, four complexes, and six reactions. Figure 1 shows the reaction graph for this model. The polynomial system for \( CD_4 \) consists of one conservation equation and two steady-state equations,
Figure 2: Newton polytopes for the polynomials corresponding to $CD_4$ in Example 3.1.

Figure 3: Minkowski sum of the Newton polytopes for the system in Example 3.1.

as displayed below.

\[
\begin{align*}
  f_1 &= xY + xZ - cY - cZ \\
  f_2 &= xY = -k_{0,1}x^3YxZ - 2k_{0,2}x^3YxZ - 3k_{0,3}x^3YxZ \\
        &\quad - k_{1,2}x^2Yx^2Z - 2k_{1,3}x^2Yx^2Z - k_{2,3}xYx^3Z \\
  f_3 &= xZ = k_{0,1}x^3YxZ + 3k_{0,2}x^3YxZ + 2k_{0,3}x^3YxZ \\
        &\quad + k_{1,2}x^2Yx^2Z + 2k_{1,3}x^2Yx^2Z + k_{2,3}xYx^3Z.
\end{align*}
\]

Observe that $f_3 = -f_2$, hence we have a square system in two variables. \(\triangle\)

**Proposition 3.2.** The Bézout bound for the chemical reaction network $CD_n$ is $n$.

**Proof.** The Bézout bound can be seen from the system (3) – there are always three equations, one linear and two of degree $n$. However, the two degree $n$ equations are identical, hence we have two equations and the Bézout bound is $n$. \(\square\)

**Proposition 3.3.** The polynomial system corresponding to the chemical reaction network $CD_n$ has mixed volume $n - 2$.

The proof of this result requires a direct computation of the mixed volume of the system. There are two Newton polytopes for any $n$, one of which is a line segment. Hence, the computation is straightforward. Recall that the mixed volume of $m$ polytopes $Q_1, \ldots, Q_m \subset \mathbb{R}^n$ is $\text{MV}(Q_1, \ldots, Q_m)$, which is the coefficient of $\lambda_1\lambda_2\cdots\lambda_m$ in the expansion of $\text{vol}_n(\lambda_1Q_1 + \lambda_2Q_2 + \cdots + \lambda_mQ_m)$, with $\lambda_i \geq 0$.

**Proof.** Consider the system (3) for a network of type $CD_n$ for some $n > 1$. As discussed earlier, we can consider only the first two polynomials $f_1$ and $f_2$, whose Newton polytopes in $\mathbb{R}^2$ are

\[
\begin{align*}
  N_1 &= \text{conv}((1, 0), (0, 1), (0, 0)) \\
  N_2 &= \text{conv}((1, n - 1), (2, n - 2), \ldots, (n - 2, 2), (n - 1, 1))
\end{align*}
\]

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Note that $N_1$ is a triangle of area $\frac{1}{2}$ and $N_2$ is a line of length $\sqrt{2}(n-2)$. In this case, the mixed volume of (3) is the coefficient of $\lambda_1\lambda_2$ in the following expansion

$$
\text{vol}_2(\lambda_1 N_1 + \lambda_2 N_2) = \text{vol}_2(N_1)\lambda_1^2 + 2\text{vol}_2(N_1, N_2)\lambda_1\lambda_2 \\
+ \text{vol}_2(N_2)\lambda_2^2, \quad \lambda_1, \lambda_2 \geq 0,
$$

implying that

$$
\text{vol}_2(N_1, N_2) = \frac{1}{2}(\text{vol}_2(N_1 + N_2) - (\text{vol}_2(N_1) + \text{vol}_2(N_2))).
$$

Since $N_1$ is an equilateral right triangle of side length one, we have that $\text{vol}_2(N_1) = \frac{1}{2}$, and because $N_2$ is a line, it follows that $\text{vol}_2(N_2) = 0$. The polytope $N_1 + N_2$ is the Minkowski sum of the two Newton polytopes $N_1$ and $N_2$, that is $N_1 + N_2 = \text{conv}(\{a + b \mid a \in N_1, b \in N_2\})$. The Minkowski sum of a line segment and an equilateral right triangle is a trapezoid, as shown in Figure 3 for $n = 4$. The two bases of the trapezoid have length $\sqrt{2}(n-2)$ and $\sqrt{2}(n-1)$, and the height of the trapezoid is $\frac{1}{\sqrt{2}}$. Hence, the area of $N_1 + N_2$ is

$$
\text{vol}_2(N_1 + N_2) = \sqrt{2}(2n-3) \cdot \frac{1}{\sqrt{2}} = \frac{2n-3}{2},
$$

and from (7) we have that $\text{vol}_2(N_1, N_2) = \frac{n-2}{2}$. Thus, the coefficient of $\lambda_1\lambda_2$ in (6) is $n-2$, which is precisely $\text{MV}(N_1, N_2)$.

**Proposition 3.4.** For the chemical reaction network $CD_n$ there are $n$ steady states, including two boundary steady-states.

**Proof.** Based on the discussion following (3), we wish to solve a square polynomial system in two variables with one linear equation and one equation of degree $n$. This is easily done with elimination. Using the linear conservation equation, we can express one of the indeterminates, say $x_Z$, in terms of $x_Y$, that is $x_Z = c_Y - c_Z - x_Y$. Observe that we can factor out $x_Yx_Z$ in $\dot{x}_Y$, and substitute the expression for $x_Z$. This results in two boundary solutions of the form $(x_Z, y_Z) = (0, c_Y - c_Z), (c_Y - c_Z, 0)$, and $n-2$ complex solutions in $(\mathbb{C}^*)^2$. Hence, there are $n$ steady-states, including the boundary steady-states. \qed

**Remark 3.5.** Based on Proposition 3.4, there are more steady-states than the mixed volume predicts. This is not contradictory, since the mixed volume gives a bound on the solutions in the torus $(\mathbb{C}^*)^n$, while the steady-state degree counts all solutions of the polynomial system. When there are boundary steady-states, i.e., solutions with some zero entries, the steady-state degree may be larger than the mixed volume.
3.2 Edelstein model

The Edelstein model was proposed by B. Edelstein in 1970 [Ede70]. It is known to exhibit multiple real, positive steady states [MFPLV10] and thus is an example of a multistationary network. We study the behavior of the steady-state degree of the network after gluing \( n \) copies of the Edelstein model over shared complexes (see [GHMS18] for more details on gluing); we denote the new network \( E_n \). This model is of particular interest, because although the Bézout bound is exponential in the number of species, the mixed volume bound is constant and is achieved for all \( n \).

To construct \( E_n \), we start with the Edelstein model \( E_1 \) itself: \( \{ A \rightleftharpoons 2A, A + B \rightleftharpoons B_1 \rightleftharpoons B \} \). Then beginning at \( i = 2 \) and continuing until \( i = n \), each step is defined by adding one new species \( B_i \) and four reactions gluing over the complexes \( A + B \) and \( B \).

For instance, for \( n = 2 \), the network \( E_2 \) would have the form: \( \{ A \rightleftharpoons 2A, A + B \rightleftharpoons B_1 \rightleftharpoons B, A + B \rightleftharpoons B_2 \rightleftharpoons B \} \). In general, the \( n \)th reaction network in this family has \( n + 2 \) species, \( n + 4 \) complexes, and \( 4n + 2 \) reactions. The corresponding polynomial system consists of one conservation equation and \( n + 2 \) differential equations:

\[
\begin{align*}
    f_1 &= x_B - c_B + \sum_{i=1}^{n} (x_{B_i} - c_{B_i}) \\
    f_2 &= -k_{10}x_A^2 - (k_{23} + k_{25} + \cdots + k_{2,n+3})x_Ax_B + k_{01}x_A + k_{32}x_{B_1} \\
        &\quad + k_{52}x_{B_2} + \cdots + k_{n+3,2}x_{B_n} \\
    f_3 &= -(k_{23} + k_{25} + \cdots + k_{2,n+3})x_Ax_B - (k_{43} + k_{45} + \cdots + k_{4,n+3})x_B \\
        &\quad + (k_{32} + k_{34})x_{B_1} + \cdots + (k_{n+3,2} + k_{n+3,4})x_{B_n} \\
    f_4 &= k_{23}x_Ax_B + k_{43}x_B - (k_{32} + k_{34})x_{B_1} \\
        &\quad \vdots \\
    f_{n+3} &= k_{2,n+3}x_Ax_B + k_{4,n+3}x_B - (k_{n+3,2} + k_{n+3,4})x_{B_n}.
\end{align*}
\]

Observe that only \( n + 1 \) of the differential equations are unique as there is a linear dependence between \( f_3, \ldots, f_{n+3} \), namely \( f_3 = -\sum_{i=4}^{n+3} f_i \). Despite the exponential Bézout bound shown in Proposition 3.6, it turns out that the mixed volume of the polynomial system (9) is constant and it is achieved as the steady-state degree.

**Proposition 3.6.** The chemical reaction network \( E_n \) has a Bézout bound of \( 2^{n+1} \).

**Proof.** There are \( n + 3 \) equations in the system, where one equation is linear and the rest \( n + 2 \) are quadratic. Since \( f_3 = -\sum_{i=4}^{n+3} f_i \), we can drop the polynomial \( f_3 \) and we are left with \( n + 1 \) quadratic equations. This gives us a Bézout bound of \( 2^{n+1} \).

**Proposition 3.7.** The mixed volume of the polynomial system corresponding to \( E_n \) is 3.
Example 3.8. Before we give a proof to Proposition 3.7 we give details for \( n = 1 \). The polynomial system for \( E_1 \) is

\[
\begin{align*}
    f_1 &= x_B + x_{B_1} - c_B - c_{B_1} \\
    f_2 &= \dot{x}_A = -k_{1,0}x_A^2 + k_{0,1}x_A - k_{2,3}x_A x_B + k_{3,2}x_{B_1} \\
    f_3 &= \dot{x}_B = -k_{2,3}x_A x_B + k_{3,2}x_{B_1} + k_{3,4}x_{B_1} - k_{4,3}x_B \\
    f_4 &= \dot{x}_{B_1} = k_{2,3}x_A x_B - k_{3,2}x_{B_1} - k_{3,4}x_{B_1} + k_{4,3}x_B.
\end{align*}
\]  

(10)

Let \( S_i \) be the support of \( f_i \), \( i = 1, \ldots, 4 \), and \( Q_i = \text{conv}(S_i) \), where \( f_4 = -f_3 \), so we consider only \( f_3 \). For ease of notation we write 101 for \((1, 0, 1)\). Then, the supports of the three polynomials are

\[
\begin{align*}
    S_1 &= \{000, 010, 001\} \\
    S_2 &= \{200, 110, 100, 001\} \\
    S_3 &= \{110, 010, 001\}.
\end{align*}
\]  

(11)

Let \( S = S_1 \cup S_2 \cup S_3 \), and \( Q = \text{conv}(S) \), see Figure 5. We will show that the collection of sets in (11) satisfies the hypothesis of [Che17, Theorem 2]. Let \( F \) be a facet of \( Q \), which is a pyramid with a trapezoidal base. If \( F \) is one of the lateral facets, then \( F \) contains 001 which is a member of each set \( S_i \), \( i = 1, 2, 3 \). If \( F \) is the base of the pyramid, then \( F \cap S_i \neq \emptyset \), \( i = 1, 2, 3 \), since \( F \) contains at least two elements from each set \( S_i \). If \( F \) is an edge containing 001, then \( F \cap S_i \neq \emptyset \), \( i = 1, 2, 3 \). The edges containing 001 are the lateral edges. We now consider the four edges of the base of \( Q \). In the case when \( F = \text{conv}(110, 010) \), we have that \( F \cap S_i \neq \emptyset \) for all \( i \). Otherwise, when \( F \) is one of the other three edges, condition (B) of [Che17, Theorem 2] is satisfied, since for at least one \( i = 1, 2, 3 \), \( F \cap S_i \) is a singleton. Hence, each face of \( Q \) satisfies either condition (A) or (B) of [Che17, Theorem 2] and therefore the mixed volume of the system in (10) is the same as the normalized volume of the convex hull of the union of the Newton polytopes of the corresponding system. That is

\[
\text{MV}(Q_1, Q_2, Q_3) = 3! \text{vol}_3(Q).
\]  

(12)

The Euclidean volume of \( Q \) is the number of simplices contained in a unimodular regular triangulation of \( Q \), times the normalized volume of a unimodular three-dimensional simplex, which is \( 1/3! \). To see the triangulation, first we note that \( Q \) is a pyramid with a trapezoidal base. This base has a unimodular triangulation containing three simplices, see Figure 4. To construct \( Q \) we simply add the vertex 001 and cone over the existing simplices, see Figure 5. Hence, there are 3 simplices, each with volume \( 1/3! \). By (12) we have that

\[
\text{MV}(Q_1, Q_2, Q_3) = 3! \cdot 3 \cdot \frac{1}{3!} = 3.
\]  

\( \triangle \)  

(13)
To prove Proposition 3.7, we use results from [Che17] to compute the mixed volume of the polynomial system in (9). Consider (9) and let $S_i = \text{Newt}(f_i)$. We relabel the polynomials $f_i$ by omitting $f_3$ and letting $f_j = f_{i-1}$ for $i \geq 4$. Let $Q_i = \text{conv}(S_i), i \in \{1, \ldots, n+2\}$, and for $n \geq 2$ let $\tilde{S} = S_3 \cup \cdots \cup S_{n+2}, \tilde{Q} = \text{conv}(\tilde{S})$, and $Q = \text{conv}(S_\cup)$, where $S_\cup = \bigcup_{i=1}^{n+2} S_i$.

**Lemma 3.9.** Let $n \geq 2$ and consider the chemical reaction network $E_n$ and the corresponding polynomial system (9). Then

$$\text{MV}(Q_1, \ldots, Q_{n+2}) = (n + 2)! \text{vol}_{n+2}(Q). \quad (14)$$

**Proof.** The mixed volume computation in this case can be reduced to a semi-mixed volume computation, where some of the polytopes are identical. First, we want to show that

$$\text{MV}(Q_1, \ldots, Q_{n+2}) = \text{MV}(Q_1, Q_2, \underbrace{\tilde{Q}, \ldots, \tilde{Q}}_n).$$

Let the indeterminates of (9) be ordered lexicographically: $x_A, x_B, x_{B_1}, \ldots, x_{B_n}$, and let $e_i$ be the corresponding exponent vector for each monomial. We write $e_0$ for the zero vector in $\mathbb{R}^{n+2}$ and $e_{ij}$ for $e_i + e_j$, where $i, j \in \{A, B, B_1, \ldots, B_n\}$. After the aforementioned relabeling the supports of the $f_i$s, $i \in \{1, \ldots, n+2\}$, in (9) are

$$S_1 = \{e_0, e_B, e_{B_1}, \ldots, e_{B_n}\}$$
\[ S_2 = \{ 2e_A, e_{AB}, e_A, e_{B_1}, \ldots, e_{B_n} \} \]
\[ S_3 = \{ e_{AB}, e_B, e_{B_1} \} \]
\[ \vdots \]
\[ S_{n+2} = \{ e_{AB}, e_B, e_{B_n} \}. \]

Observe that \( S_3, \ldots, S_{n+2} \) differ by one element only, hence, they meet the criterion in [Che17, Corollary 1] implying that
\[ \text{MV}(Q_1, \ldots, Q_{n+2}) = \text{MV}(Q_1, Q_2, \underbrace{\tilde{Q}, \ldots, \tilde{Q}}_{n}). \]  

Now, the mixed volume of the system with support (15) is the same as the mixed volume of the system below.

\[ \tilde{S}_1 = \{ e_0, e_B, e_{B_1}, \ldots, e_{B_n} \} \]
\[ \tilde{S}_2 = \{ 2e_A, e_A, e_{AB}, e_{B_1}, \ldots, e_{B_n} \} \]
\[ \tilde{S}_j = \{ e_{AB}, e_B, e_{B_1}, \ldots, e_{B_n} \}, j = 3, \ldots, n+2 \]

We want to show that the collection of \( \tilde{S}_i, i \in \{ 1, \ldots, n+2 \} \), satisfies the hypothesis of [Che17, Theorem 2]. Let \( F \) be a positive dimensional face of \( Q \). If any of the vertices of \( F \) are in \( S \cap = \bigcap_{i=1}^{n+2} S_i \) then \( F \cap \tilde{S}_i \neq \emptyset \) for all \( i \in \{ 1, \ldots, n+2 \} \). In this case, \( F \) satisfies Theorem 2.2(i). Suppose that none of the vertices of \( F \) are in \( S \cap \). Then they must be in the set difference \( D = S \cup \setminus S \cap = \{ e_0, e_B, 2e_A, e_A, e_{AB} \} \). Note that \( e_A \in D \) is in the interior of the edge \( \{ e_0, 2e_A \} \), so it is not a vertex. Suppose that the vertices of \( F \) are all of \( D - \{ e_A \} \). Then \( F \cap \tilde{S}_i \neq \emptyset \) for all \( i \), and we are in case (i) of Theorem 2.2. If the vertices of \( F \) is a smaller subset of \( D - \{ e_A \} \), then \( F \) must be an edge. There are four such edges, and for each one of them, either \( F \cap \tilde{S}_i \neq \emptyset \) for all \( i \), or for some \( j \) we have that \( F \cap \tilde{S}_j \) is a singleton. In this case we meet condition (ii) of the theorem. Hence, we have that
\[ \text{MV}(Q_1, \ldots, Q_{n+2}) = (n+2)! \text{vol}_{n+2}(Q). \]  

\( \square \)  

Proof of Proposition 3.7. To compute the volume of \( Q \) we construct a unimodular triangulation. Recall that the Euclidean volume of an \( n \)-dimensional unimodular simplex is \( \frac{1}{n!} \). The vertices of \( Q \) are \( \{ e_0, 2e_A, e_{AB}, e_B, e_{B_i} \} \) where \( i = 1, \ldots, n \). Note that all \( e_j, j \in \{ A, B, B_i \} \) are the \( \{ 0,1 \} \) unit vectors in \( \mathbb{R}^{n+2} \), and that vectors \( e_{B_i} \) are linearly independent. This means that we can work with the polytope \( P = \text{conv}(e_0, 2e_A, e_{AB}, e_B) \subset \mathbb{R}^2 \). After constructing a unimodular triangulation of \( P \) we cone over it with each of the vertices \( e_{B_i}, i \in \{ 1, \ldots, n \} \). This process preserves unimodularity.
As shown in Figure 4, $P$ is a trapezoid consisting of three unimodular simplices, each with area $\frac{1}{2!} = \frac{1}{2}$. In particular, we have

\[
\begin{align*}
\sigma_1 &= \text{conv}(00, 10, 01) \\
\sigma_2 &= \text{conv}(10, 01, 11) \\
\sigma_3 &= \text{conv}(10, 20, 11).
\end{align*}
\] (19)

As we cone over the existing triangulation with each $e_{B_i}$, the number of simplices remains the same; see Figure 5 for example. Thus, $Q$ has three $(n + 2)$-dimensional simplices, each with volume $\frac{1}{(n+2)!}$. Hence, by Lemma 3.9 it follows that

\[
\text{MV}(Q_1, \ldots, Q_{n+2}) = (n + 2)! \text{vol}_{n+2}(Q) = (n + 2)! \frac{3}{(n + 2)!} = 3. \quad \square
\] (20)

Proposition 3.10. The steady-state degree of the chemical reaction network $E_n$ is 3.

Proof. We use elimination to reduce the system to a univariate cubic polynomial in $x_A$; the elimination algorithm is easy to see for $E_1$. The corresponding system (10) contains four polynomials in three variables with $f_4 = -f_3$, so we can reduce the system to three polynomials by forgetting $f_4$. Using $f_1$, we solve for $x_{B_i}$ as a linear expression in $x_B$. Subtracting $f_3$ from $f_2$ and substituting for $x_{B_i}$ in the difference, we can solve for $x_B$, and in turn for $x_{B_1}$, as a quadratic in $x_A$. Lastly, substituting for all variables in terms of $x_A$ in $f_2$ results in a univariate cubic polynomial in $x_A$. Hence, there are exactly three equilibrium solutions to (10).

The polynomial system for $n \geq 2$ has the general form of 9. Similarly to the first case, using equations $f_4, \ldots, f_{n+3}$, for each $i = 1, \ldots, n$ we can express $x_{B_i}$ as a bilinear expression in $x_A$ and $x_B$. These expressions can then be substituted in $f_1$, from where we can solve for $x_B$ (and respectively all $x_{B_i}$) as a rational expression in terms of $x_A$, with a quadratic numerator and a linear denominator in $x_A$. These operations are defined, since we assume that the collection of $k_{ij}$s is generic, and hence, no linear combination is zero; moreover we assume that $x_A$ is nonzero. Substituting the rational expressions for $x_B$ and $x_{B_i}$ into $f_2$ and clearing the denominators results in a univariate cubic polynomial in $x_A$. Hence, there are three solutions to the system, i.e., the steady-state degree is 3. This result along with Proposition 3.7 shows that the BKK bound is tight for all $n$. \qed

3.3 One-site phosphorylation cycle

The last family of networks we study is based on the one-site phosphorylation cycle, a mechanism that plays a role in the activation and deactivation of proteins. In particular, we look at the reaction network $PC_n$ obtained by gluing $n$ one-site distributive phosphorylation cycles over complexes. As an example, when two one-site distributive
phosphorylation cycles are glued in this way, we obtain a two-site phosphorylation cycle [FW12].

The one-site distributive phosphorylation cycle consists of six species, six complexes, and six reactions: \( \{ S_0 + E \rightleftharpoons X_1 \rightarrow S_1 + E, S_1 + F \rightleftharpoons Y_1 \rightarrow S_0 + F \} \). The second copy of the one-site phosphorylation cycle will have the form \( \{ S_1 + E \rightleftharpoons X_2 \rightarrow S_2 + E, S_2 + F \rightleftharpoons Y_2 \rightarrow S_1 + F \} \) where all species with index \( i \) are replaced by the same type of species with index \( i + 1 \), e.g., \( S_1 \) is replaced by \( S_2 \). We glue over the common complexes \( S_1 + E \) and \( S_1 + F \). For \( n \) copies of the cycle, we have \( 3n + 3 \) species, \( 4n + 2 \) complexes, and \( 6n \) reactions. The reaction network \( PC_4 \) is shown in Figure 6. The corresponding polynomial system consists of three conservation equations and \( 3n + 1 \) distinct differential equations up to sign. The three conservation equations are

\[
\begin{align*}
f_1 &= x_E - c_E + \sum_{i=1}^{n} (x_{X_i} - c_{X_i}) \\
\kappa_x &= x_F - c_F + \sum_{i=1}^{n} (x_{Y_i} - c_{Y_i})
\end{align*}
\]
and the $3n + 1$ distinct differential equations for $n \geq 2$ are

\[
\begin{align*}
  f_3 &= \sum_{i=0}^{n} (x_{S_i} - c_{S_i}) - (x_E - c_E) - (x_F - c_F),
  \\
  f_4 &= \dot{x}_{S_0} = -k_{01}x_{S_0}x_E + k_{10}x_{X_1} + k_{45}x_{Y_1}, \\
  f_5 &= \dot{x}_{S_p} = -k_{26}x_{S_p}x_E - k_{34}x_{S_1}x_F + k_{12}x_{X_1} + k_{43}x_{Y_1} + k_{62}x_{X_2} + k_{93}x_{Y_2}, \\
  f_{j+4} &= \dot{x}_{S_j} = -k_{4j+1}x_{S_j}x_F + k_{4j-2}x_{A_j-1}x_{X_j} + k_{4j+1,4}x_{Y_j} - k_{4j-1,4}x_{S_j}x_E \\
  &\quad + k_{4j+2}x_{A_j-1}x_{X_{j+1}} + k_{4j+5}x_{Y_{j+1}}, \quad j = 2, \ldots, n-1 \\
  f_{n+4} &= \dot{x}_{S_n} = -k_{4n,4n+1}x_{S_n}x_F + k_{4n-2,4n-1}x_{X_n} + k_{4n+1,4n}x_{Y_n} \\
  f_{n+5} &= \dot{x}_{X_1} = k_{01}x_{S_0}x_E - (k_{10} + k_{12})x_{X_1} \\
  f_{n+6} &= \dot{x}_{X_2} = k_{26}x_{S_1}x_E - (k_{62} + k_{97})x_{X_2} \\
  f_{n+j+4} &= \dot{x}_{X_j} = k_{4j-5,4j-2}x_{S_{j-1}}x_E - (k_{4j-2,4j-5} + k_{4j-2,4j-1})x_{X_j}, \quad j = 3, \ldots, n \\
  f_{2n+5} &= \dot{x}_{Y_1} = k_{34}x_{S_1}x_F - (k_{43} + k_{45})x_{Y_1} \\
  f_{2n+6} &= \dot{x}_{Y_2} = k_{89}x_{S_1}x_F - (k_{93} + k_{98})x_{Y_2} \\
  f_{2n+j+4} &= \dot{x}_{Y_j} = k_{4j+1,4}x_{S_j}x_F - (k_{4j+1,4}(j-1) + k_{4j+1,4})x_{Y_j}, \quad j = 3, \ldots, n.
\end{align*}
\]

The full list of steady-state equations includes $\dot{x}_E = -\sum_i \dot{x}_{X_i}$ and $\dot{x}_F = -\sum_i \dot{x}_{Y_i}$, which we disregard, since they are linear combinations of other polynomials from the system. Let $\tilde{P}_n$ be the polynomial system for the reaction network $PC_n$ consisting of the $3n + 4$ equations from (21) and (22) set equal to zero. The following result assumes that the steady-state ideal is zero-dimensional, which follows from [WS08] where the authors show that the steady-state degree of $PC_n$ is $2n + 1$.

**Proposition 3.11.** The Bézout bound for the reaction network $PC_n$ is $2^{3n+1}$.

**Proof.** Note that each of the $3n + 1$ polynomial ODEs in (22) is quadratic, and each of the three conservation equations in (21) is linear. Hence, the Bézout bound for the system $\tilde{P}_n$ is $2^{3n+1}$. 

\[\square\]

The mixed volume of the polynomial system $\tilde{P}_n$ provides a tighter bound on the steady-state degree of $PC_n$. However, since $\tilde{P}_n$ is overdetermined, we instead consider the randomized system $P_n = M \cdot \tilde{P}_n$, where $M \in \mathbb{C}^{(3n+3)\times(3n+4)}$ is a generic matrix. The system $P_n$ is a square system with $3n + 3$ equations where each polynomial is a linear combination of the polynomials $f_i$, $i = 1, \ldots, 3n + 4$.

For the remainder of this section we work with the system $P_n$ where each polynomial has support $S_n = \bigcup_{i=1}^{3n+4} S_i$ for $S_i = \text{supp}(f_i)$, $i = 1, \ldots, 3n + 4$. Let $Q_n = \text{conv}(S_n)$ be the Newton polytope of each polynomial of $P_n$. This leads to the main theorem of this section.
Theorem 3.12. Let $P_n$ be the randomized polynomial system for the reaction network $PC_n$. Then,

$$MV(Q_n, \ldots, Q_n, 0, \ldots, 0) = (3n + 3)! \text{vol}_{3n+3}(Q_n) = \frac{(n + 1)(n + 4)}{2} - 1. \quad (23)$$

The first equality of (23) follows from the definition of mixed volume in the special case when all polytopes are identical. To prove the second equality we construct a triangulation $T_n$ of the polytope $Q_n$. Provided $T_n$ is unimodular, i.e., all simplices are unimodular, the normalized Euclidean volume of $Q_n$ is the number of simplices in $T_n$. First we give a description of the vertices of $Q_n$, followed by a hyperplane representation of $Q_n$, which aids in the construction of the triangulation $T_n$ with the desired number of simplices. We illustrate Theorem 3.12 with an example for $n = 1$.

Example 3.13. The reaction network for $n = 1$ is $\{S_0 + E \rightarrow X_1 \rightarrow S_1 + E, S_1 + F \rightarrow Y_1 \rightarrow S_0 + F\}$, and the corresponding polynomial system $P_1$ is

$$
\begin{align*}
  f_1 &= x_E + x_{X_1} - c_E - c_{X_1} \\
  f_2 &= x_F + x_{Y_1} - c_F - c_{Y_1} \\
  f_3 &= x_{S_0} + x_{S_1} - x_E - x_F - c_{S_0} - c_{S_1} + c_E + c_F \\
  f_4 &= -k_{01} x_{S_0} x_E + k_{10} x_{X_1} + k_{45} x_{Y_1} \\
  f_5 &= -k_{34} x_{S_1} x_F + k_{12} x_{X_1} + k_{43} x_{Y_1} \\
  f_6 &= k_{01} x_{S_0} x_E - (k_{10} + k_{12}) x_{X_1} \\
  f_7 &= k_{34} x_{S_1} x_F - (k_{43} + k_{45}) x_{Y_1}.
\end{align*}
$$

We take generic parameters $k_{ij}$ and consider the randomized system $P_1$ with six equations in six variables with the following order: $x_{S_0}, x_E, x_{X_1}, x_{S_1}, x_F, x_{Y_1}$. Each polynomial in $P_1$ has the same support, namely

$$S_1 = \left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \ldots, \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix} \right\} = \{e_0, e_1, \ldots, e_6, e_{12}, e_{45}\}.$$

For $Q_1 = \text{conv}(S_1) \subseteq \mathbb{R}^6$, the mixed volume for the system $P_1$ is

$$MV(Q_1, \ldots, Q_1) = 6! \text{vol}_6(Q_1).$$

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Observe that $e_3$ and $e_6$ are linearly independent from the rest of the vertices as vectors. In order to simplify computations, we will project away $e_3$ and $e_6$ and relabel the vertices. We will study the new polytope $K_1 = \text{conv}(V_1)$ in $\mathbb{R}^4$ where

$$V_1 = \left\{ \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 0 \\ 1 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 0 \\ 1 \end{pmatrix} \right\} = \{v_0, v_1, \ldots, v_4, v_{12}, v_{34}\}.$$

Then we will cone over the triangulation of $K_1$ with $e_3$ and then $e_6$ to recover $Q_1$. To compute the volume of $K_1$ we construct a placing triangulation $T_1$, which is unimodular; see the proof of Lemma 3.16 and [DL10, GOT17] for more details.

We begin the triangulation by placing the first five vertices $v_0, \ldots, v_4$, which form a standard simplex in $\mathbb{R}^4$. Let $\sigma_1 = \text{conv}(v_0, \ldots, v_4)$. Next we place the vertex $v_{12}$. Note that $v_{12} \not\in \sigma_1$, but it is in the affine hull of $\sigma_1$. We consider the facets of $\sigma_1$ visible from $v_{12}$, where the only such facet is $F_1 = \text{conv}(v_1, \ldots, v_4)$ since all other facets lie on the coordinate hyperplanes. We cone over $F_1$ with $v_{12}$ and obtain the simplex $\sigma_2 = \text{conv}(v_1, \ldots, v_4, v_{12})$. Lastly, we place $v_{34}$ and observe that $v_{34}$ is not in the convex hull of $\{v_0, v_1, \ldots, v_4, v_{12}\}$ but it is in their affine hull. None of the facets of $\sigma_1$ are visible from $v_{34}$, but two of the facets of $\sigma_2$ are visible: $F_{21} = \text{conv}(v_1, v_3, v_4, v_{12})$ and $F_{22} = \text{conv}(v_2, v_3, v_4, v_{12})$. We cone over each one with $v_{34}$ constructing two more simplices: $\sigma_3 = \text{conv}(F_{21} \cup \{v_{34}\})$ and $\sigma_4 = \text{conv}(F_{22} \cup \{v_{34}\})$. The collection $T_1 = \bigcup_{i=1}^4 \sigma_i$ is a triangulation of $K_1$ by construction. Moreover, by a similar proof as the one for Lemma 3.16, $T_1$ is a unimodular triangulation.

To construct a triangulation of $Q_1$, we embed $K_1$ in $\mathbb{R}^6$ and then we cone over each $\sigma_i$ with $e_3$ and then $e_6$. This gives $T_1 = \bigcup_{i=1}^4 s_i$, where

$$s_1 = \text{conv}(e_0, \ldots, e_6),$$
$$s_2 = \text{conv}(e_1, \ldots, e_6, e_{12}),$$
$$s_3 = \text{conv}(e_1, e_3, e_4, e_5, e_6, e_{12}, e_{45}),$$
$$s_4 = \text{conv}(e_2, e_3, e_4, e_5, e_6, e_{12}, e_{45}).$$

The triangulation $T_1$ remains unimodular, hence the normalized Euclidean volume of each simplex is $1/6!$, and

$$\text{MV}(Q_1, \ldots, Q_4) = 6! \cdot \text{vol}_6(Q_1) = 6! \cdot \frac{1}{6!} = 4 = \frac{(n + 1)(n + 4)}{2} - 1. \quad \triangle$$

Now let consider the general case where the dimension of the ambient space of $Q_n$ is $3n + 3$. Let $e_i \in \mathbb{R}^{3n+3}$ represent the $i$th standard unit vector, $e_0$ be the zero vector, and $e_{ij} = e_i + e_j$. For $1 \leq i \leq d$, the vector $e_i$ is the exponent vector of $i$th indeterminate in the following ordered list $(x_{s_0}, x_E, x_X, x_{S_1}, x_F, x_{Y_1}, x_{X_j}, x_{S_j}, x_{Y_j})_{j=2}^n$. 

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of size $3n + 3$. For $n = 1$ and $n = 2$ the vertices of $Q_1$ and $Q_2$ are given by the vector configurations $e_0, e_1, \ldots, e_6, e_{12}, e_{45}$ and $e_0, e_1, \ldots, e_9, e_{12}, e_{24}, e_{45}, e_{58}$, respectively. Going from the $(j - 1)$-site phosphorylation network to the $j$-site phosphorylation network ($j \geq 2$), we gain three new steady-state equations and five new monomials: $x_{X_j}, x_{S_j}, y_j, x_{S_{j-1}} , x_E, x_{S_j}, x_F$. Hence, for $n \geq 3$ the vertices of $Q_n$ are given by the $5n + 4$ vectors of dimension $3n + 3$ in the configuration

$$V_n = \{e_0, e_1, \ldots, e_{3n+3}, e_{12}, e_{24}, e_{28}, \ldots, e_{2,3n-7}, e_{2,3n-4}, e_{45}, e_{58}, \ldots, e_{5,3n-1}, e_{5,3n+2}\}.$$  

(25)

Proposition 3.14. Let $Q_n$ be the Newton polytope of each polynomial in the system $P_n$ for $n \geq 2$. The $\mathcal{H}$-representation of $Q_n$ is given by

$$1 - x_1 - x_3 - x_4 - \sum_{i=6}^{3n+3} x_i \geq 0$$

$$1 - x_1 - x_3 - x_5 - \sum_{i=2}^{n} (x_{3i} + x_{3i+1}) - x_{3n+3} \geq 0$$

$$1 - x_2 - x_3 - x_5 - \sum_{i=2}^{n} (x_{3i} + x_{3i+1}) - x_{3n+3} \geq 0$$

$$1 - x_2 - x_3 - \sum_{i=2}^{n} (x_{3i} + x_{3i+1}) - x_{3n+2} - x_{3n+3} \geq 0$$

$$x_i \geq 0, \ i = 1, \ldots, 3n + 3.$$  

Proof. Let $Q_n^H$ be the polytope defined by (26). We aim to show that $Q_n$ and $Q_n^H$ coincide. Note that each coordinate $x_i, i \in \{1, \ldots, 3n + 3\}$ is bounded in $Q_n^H$; in particular, $0 \leq x_i \leq 1$. Otherwise, if $x_i > 1$ (or $x_i < 0$) at least one of the multivariate (resp. univariate) inequalities will be violated. It remains to show that the vertex sets of $Q_n$ and $Q_n^H$ coincide. Observe that none of the inequalities in (26) can be obtained by taking positive linear combinations of the remaining inequalities, implying that (26) is an irredundant description of $Q_n^H$, hence each inequality defines a distinct facet [Zie95].

A vertex of the polytope $Q_n^H$ must be in the intersection of at least $3n + 3$ hyperplanes described in (26). Hence, a vertex must satisfy a subsystem of (26) of size at least $(3n + 3) \times (3n + 3)$ at equality. We begin by considering subsets of $3n + 3$ inequalities whose corresponding linear systems are consistent.

First, consider all $3n+3$ univariate equations and set $x_i = 0$ for all $i = 1, \ldots, 3n+3$; this yields the origin $e_0$ as a vertex of $Q_n^H$. Next, select $3n+2$ variables $x_i$ set equal to zero and one of the four multivariate equations. Note that some of these combinations will result in an inconsistent system. Those yielding a consistent system will have a
solution with each coordinate zero except one of the $x_i$s, which will be 1; there are $3n+3$ distinct choices for the nonzero $x_i$. These choices yield the vertices $e_1, \ldots, e_{3n+3}$. Thus far we have found $3n + 4$ vertices of $Q_n^H$ and each is also a vertex of $Q_n$.

Continuing in the same manner, we now choose $3n + 1$ variables $x_i$ set equal to zero and two of the four multivariate equations. Each of the nonzero variables must take the value 1. Otherwise we would have $0 < x_i, x_j < 1$, where $i \neq j$, implying that they appear together in both multivariate equations. In this case, each multivariate equation is reduced to $1 - x_i - x_j = 0$. However, this system yields a positive-dimensional face of $Q_n^H$ and hence does not describe a vertex. Thus, both nonzero variables must be 1, and they cannot appear in the same multivariate equation. Independent of the choice of the two multivariate equations, the pair $\{x_i, x_j\}$ will be a subset of the variables in the symmetric difference of their supports. In particular, there are $2n$ distinct such choices: \{x_1, x_2\}, \{x_2, x_4\}, \{x_4, x_5\}, \{x_2, x_{3j+2}\}, \{x_5, x_{3k+2}\}$, for $2 \leq j \leq n-1, 2 \leq k \leq n$. These combinations yield the $2n$ vertices $e_{12}, e_{24}, e_{28}, e_{2,11}, \ldots, e_{2,3n-1}, e_{45}, e_{58}, \ldots, e_{5,3n+2}$. Together with the previously found $3n + 4$ vertices, we have a total of $5n + 4$ vertices of $Q_n^H$, which are exactly the vertices of $Q_n$ shown in (25). It remains to show that $Q_n^H$ does not have any more vertices.

Suppose that $Q_n^H$ has a vertex $q \not\in V_n$. Then, since we considered all vertices of $Q_n^H$ with zero, one, or two nonzero entries, $q$ must have more than two nonzero entries. Now suppose that for distinct $i, j,$ and $k$, the entries $q_i, q_j$, and $q_k$ are all nonzero, and the remaining $3n$ entries of $q$ are zero. Note that $q_i, q_j,$ and $q_k$ must have value 1, otherwise $q$ cannot satisfy a zero-dimensional system constructed from the inequalities in (26). Since $q_i = q_j = q_k$, the variables $x_i, x_j,$ and $x_k$ cannot appear in the same inequality. But there is no possible choice for three such variables, implying it is also not possible to have more than three nonzero variables. Therefore, we have found all vertices of $Q_n^H$; in particular, they coincide with the vertex representation of $Q_n$, hence $Q_n^H = Q_n$. \hfill \Box

Now we will compute the normalized Euclidean volume of $Q_n$ by constructing a unimodular triangulation. Let $d_n = n + 3$. Similar to Example 3.13 we can reduce $Q_n$ to a lower-dimensional polytope $K_n \subset \mathbb{R}^{d_n}$ by projecting down $2n$ dimensions corresponding to the vectors $e_3, e_6, e_{3j+1},$ and $e_{3j+3}, 2 \leq j \leq n$. These are the exponent vectors of the monomials $x_{X_j}$ and $x_{Y_j}$. To avoid ambiguity of notation, we relabel the standard unit vectors and their sums after the projection (e.g. $v_1$ will be the 1st standard unit vector in $\mathbb{R}^{d_n}$ and $v_{12} = v_1 + v_2$), so $K_n = \textrm{conv}(V_n)$ where $|V_n| = 3n + 4$ and

$$V_n = \{v_0, v_1, \ldots, v_d, v_{12}, v_{23}, v_{25}, \ldots, v_{2,d_n-1}, v_{34}, v_{45}, \ldots, v_{4,d_n}\}. \quad (27)$$

Following the ideas of Example 3.13, we construct a placing triangulation $T_n$ of $K_n$. Then we cone over $T_n$ with the $2n$ remaining unit vectors from $V_n$ to recover a unimodular triangulation of $Q_n$. 

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We will construct $\mathcal{T}_n$ by successively placing vertices. After placing each vertex, we will need information about the convex hull of the vertices already placed. The following lemma describes these intermediate polytopes and is used in the construction of $\mathcal{T}_n$. The proofs are omitted as they follow the same process and reasoning as the proof of Proposition 3.14.

**Lemma 3.15.** Let $d_n = n + 3$. For each $n$, let $K'_{n-1}$ be the embedding of $K_{n-1}$ in $\mathbb{R}^{d_n}$. Let $K_n^* = \text{conv}(K'_{n-1} \cup \{v_{d_n}\})$ and $\tilde{K}_n = \text{conv}(K_n^* \cup \{v_{2,d_n-1}\})$. Then:

1. The $\mathcal{H}$-representation of $K^*_n$ is

\[1 - x_1 - x_3 - \sum_{j=2}^{n} x_{d_j} \geq 0\]

\[1 - x_1 - x_4 - x_{d_n} \geq 0\] (28)

\[1 - x_2 - x_4 - x_{d_n} \geq 0\]

\[1 - x_2 - x_{d_n-1} - x_{d_n} \geq 0\]

\[x_i \geq 0, i = 1, \ldots, d_n = n + 3.\]

2. The $\mathcal{H}$-representation of $\tilde{K}_n$ is

\[1 - x_1 - x_3 - \sum_{j=2}^{n} x_{d_j} \geq 0\] (29)

\[1 - x_1 - x_4 - x_{d_n} \geq 0\] (30)

\[1 - x_2 - x_4 - x_{d_n} \geq 0\] (31)

\[x_i \geq 0, i = 1, \ldots, d_n.\] (32)

**Lemma 3.16.** Let $n \geq 2$ and $d_j = j + 3, j \leq n$. Let $\mathcal{T}_1$ be the triangulation of $K_1$ as described in Example 3.13. Let $\mathcal{T}_n$ be the placing triangulation obtained from $\mathcal{T}_{n-1}$ by coning over the $k_{n-1}$ simplices of $\mathcal{T}_{n-1}$ with apex $v_{d_n}$ and placing $v_{2,d_n-1}$ and $v_{4,d_n}$, in that order. The simplices obtained by placing $v_{2,d_n-1}$ and $v_{4,d_n}$ are

\[\sigma_{k_{n-1}+1} = \text{conv}(v_2, v_{d_n-1}, v_{d_n}, v_{12}, v_{23}, v_{25}, \ldots, v_{2,d_n-1}, v_{4,d_n-1})\]

\[\sigma_{k_{n-1}+2} = \text{conv}(v_1, v_4, v_{d_n}, v_{12}, v_{34}, v_{45}, \ldots, v_{4,d_n})\]

\[\sigma_{k_{n-1}+3} = \text{conv}(v_2, v_4, v_{d_n}, v_{12}, v_{23}, v_{25}, \ldots, v_{2,d_n-1}, v_{4,d_n})\]

\[\sigma_{k_{n-1}+4} = \text{conv}(v_2, v_{d_n}, v_{12}, v_{23}, v_{34}, v_{45}, \ldots, v_{4,d_n})\]

\[\sigma_{k_{n-1}+5} = \sigma_{k_{n-1}+4} \setminus \{v_{34}\} \cup \{v_{25}\}\] (33)

\[\vdots\]

\[\sigma_{k_{n-1}+d_{n-1}} = \sigma_{k_{n-1}+d_{n-1}-1} \setminus \{v_{4,d_n-1}\} \cup \{v_{2,d_n-1}\}\]

Furthermore, $\mathcal{T}_n$ has $k_n = 4 + \sum_{j=2}^{n-1} d_j$ simplices and is unimodular.
Proof. The triangulation $\mathcal{T}_n$ is obtained inductively beginning with the explicit construction of $\mathcal{T}_1$ in Example 3.13 containing $k_1 = 4$ unimodular simplices. Suppose the triangulation $\mathcal{T}_{n-1}$ has been constructed by successively placing vertices as described in the statement of the lemma. Furthermore, assume $\mathcal{T}_{n-1}$ contains $k_{n-1} = 4 + \sum_{j=2}^{n-2} d_j$ unimodular simplices as described in (33). We embed $K_{n-1}$ and its triangulation $\mathcal{T}_{n-1}$ into $\mathbb{R}^{d_n}$ and place the vertices (i) $v_{d_n}$, (ii) $v_{2,d_n-1}$, and (iii) $v_{4,d_n}$ as follows.

(i) Placing $v_{d_n}$: Placing $v_{d_n}$ increases the dimension of the polytope $K_{n-1}$ by one from $d_{n-1}$ to $d_n$. We cone over all simplices of $\mathcal{T}_{n-1}$ with $v_{d_n}$ and obtain the first $k_{n-1}$ simplices of $\mathcal{T}_n$. The resulting polytope is $K_n^*$ and its facet defining inequalities are given in (28).

(ii) Placing $v_{2,d_n-1}$: Consider the facet defining inequalities of $K_n^*$ in (28). Note that the hyperplane $1 - x_2 - x_{d_n-1} - x_{d_n} = 0$ is the only one separating $v_{2,d_n-1}$ and $K_n^*$. Facets of $K_n^*$ contained in this hyperplane will be visible from $v_{2,d_n-1}$.

The facet $F_{2,d_n-1,d_n} = \text{conv}(v_2, v_{d_n-1}, v_{d_n}, v_{12}, v_{23}, v_{25}, \ldots, v_{2,d_n-2}, v_{4,d_n-1})$, containing $d_n$ vertices and hence it is a simplex of dimension $d_{n-1}$. Coning over $F_{2,d_n-1,d_n}$ with $v_{2,d_n-1}$ yields the $d_n$-dimensional simplex $\sigma_{k_{n-1}+1}$. The resulting polytope after placing $v_{2,d_n-1}$ is $\tilde{K}_n$ whose facet defining inequalities are given in (29) – (32).

(iii) Placing $v_{4,d_n}$: We aim to show that in this step we add $d_n - 1$ new simplices. Investigating the facet defining inequalities of $\tilde{K}_n$, we note that there are two hyperplanes separating $v_{4,d_n}$ from $\tilde{K}_n$, namely (30) and (31) containing the respective facets

$$F_{1,4,d_n} = \text{conv}(v_1, v_4, v_{d_n}, v_{12}, v_{34}, v_{45}, \ldots, v_{4,d_n-1})$$

$$F_{2,4,d_n} = \text{conv}(v_2, v_4, v_{d_n}, v_{12}, v_{23}, v_{25}, \ldots, v_{2,d_n-1}, v_{34}, v_{45}, \ldots, v_{4,d_n-1}).$$

Note that $F_{1,4,d_n}$ is a $d_{n-1}$-dimensional simplex, so coning over it with $v_{4,d_n}$ results in the $d_n$-dimensional simplex $\sigma_{k_{n-1}+2}$.

The facet $F_{2,4,d_n}$ lies in the facet defining hyperplane $1 - x_2 - x_4 - x_{d_n} = 0$; it has $2d_n - 2$ vertices and a unimodular triangulation induced by the triangulation of $\tilde{K}_n$. In particular, the simplices in the triangulation of $F_{2,4,d_n}$ are $\sigma_{k_{n-2}+3} \setminus \{v_{d_n-1}\} \cup \{v_{d_n}\}, \ldots, \sigma_{k_{n-2}+d_n-2} \setminus \{v_{d_n-1}\} \cup \{v_{d_n}\}, \sigma_{k_{n-1}+1} \setminus \{v_{d_n-1}\}$. These $d_{n-1}$ dimensional simplices are obtained by considering the intersection of the simplices $\sigma_{k_{n-2}+1} \cup \{v_{d_n}\}, \ldots, \sigma_{k_{n-2}+d_n-2} \cup \{v_{d_n}\}, \sigma_{k_{n-1}+1}, \sigma_{k_{n-1}+2}$ of $\tilde{K}_n$ with the hyperplane $1 - x_2 - x_4 - x_{d_n} = 0$; note that we do not need to consider the remaining simplices of $\tilde{K}_n$, since each intersection with $F_{2,4,d_n}$ is necessarily of dimension less than $d_{n-1}$. 

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We cone over the triangulation of $F_{2,4,d_n}$ with $v_{4,d_n}$ and obtain the $d_n - 2 - 1 = d_n - 3$ simplices $\sigma_{k_n-1+3}, \ldots, \sigma_{k_n-1+d_n-1}$. Hence, we have a total of

$$k_n = k_{n-1} + 2 + (d_n - 3) = k_{n-1} + d_{n-1} = 4 + \sum_{j=2}^{n-1} d_j$$

simplices in $\mathcal{T}_n$.

Finally, we show that the placing triangulation $\mathcal{T}_n$ is unimodular. The polytope $K_n$ is a $d_n$-dimensional compressed polytope [DL10], implying that all of its pulling triangulations are unimodular. A placing triangulation is equivalent to a pushing triangulation. The latter is a regular triangulation with a lifting vector of heights $\omega : J \to \mathbb{R}$, where $J$ is the set of labels on $V_n$ with respect to some order. Reversing the order of the labels of $V_n$ and the heights of the weight vector $\omega$ makes the pushing triangulation into a pulling triangulation [GOT17, DL10]. Hence, $\mathcal{T}_n$ as constructed is a regular unimodular triangulation.

**Proof of Theorem 3.12.** The first equality in (23) follows from the definition of mixed volume in the special case when all polytopes are identical. We aim to obtain a unimodular triangulation of $Q_n$. By Lemma 3.16 $K_n$ has a triangulation $\mathcal{T}_n$ with

$$4 + \sum_{i=1}^{n-1} d_i = 4 + \sum_{i=1}^{n-1} i + 3 = \frac{(n+4)(n+1)}{2} - 1$$

simplices. To achieve a unimodular triangulation of $Q_n$, we cone over the triangulation $\mathcal{T}_n$ in the $2n$ originally-collapsed dimensions, which preserves the number of simplices. The polytope $Q_n$ has dimension $3n + 3$, hence the normalized Euclidean volume of each full dimensional unimodular simplex is $\frac{1}{(3n+3)!}$. The second equality of (23) now follows.

The mixed volume for the randomized system of $PC_n$ is quadratic in $n$, which is a tighter bound than the exponential Bézout bound. Nonetheless, it is still significantly higher than the steady-state degree of the ideal. The authors of [WS08] show that steady-state degree of $PC_n$ is $2n + 1$ and they also give a lower bound to the number of positive steady states. In [FHC14], the authors show that the latter number can be achieved.

**Theorem 3.17.** [WS08] The steady-state degree of the chemical reaction network $PC_n$ is $2n + 1$ with at most $2n - 1$ positive steady states.

Our exploration of $Q_n$ reveals that Newton polytopes of steady-state equations are interesting combinatorially on their own. Indeed, we finish our discussion of $Q_n$ by showing that it is a matching polytope of a graph.
Let $G_n$ be the multigraph on $n + 3$ vertices with $d = 3n + 3$ edges, such that $G_n$ contains one four-cycle, $n - 1$ edges incident with one node of the four-cycle, say $s_1$, and $2n$ parallel edges connecting $s_1$ diagonally with $s_3$. See Figure 8 for example. Each edge of $G_n$ represents a species of $PC_n$.

The matching polytope of the graph $G_n$ is the convex hull of the incidence vectors of all matchings of $G_n$, i.e.,

$$P_{MA}(G_n) = \text{conv}\{\chi^M | M \text{ is a matching of } G_n\}.$$ 

A matching of $G_n$ is a subset of edges $M \subseteq E(G_n)$ such that each vertex is incident with no more than one edge of $M$. The incidence vector $\chi^M \in \{0, 1\}^{|E(G_n)|}$ of a matching $M$ is

$$\chi^M_t = \begin{cases} 
1, & t \in M, \\
0, & \text{otherwise.}
\end{cases}$$

Each matching of the graph $G_n$, equivalently each vertex of $P_{MA}(G_n)$, corresponds to the support of a monomial in the dynamical polynomial system $P_n$ of §3.3.

**Proposition 3.18.** The polytope $Q_n$ is the matching polytope of the graph $G_n$ described above, i.e., $Q_n = P_{MA}(G_n)$.

**Proof.** The incidence vector of a matching of $G_n$ containing only one edge $t_i$ coincides with the standard vector $e_i$ with entry 1 in the $i$th position. A matching of $G_n$ can contain at most two edges, and each pair is either of the form $M_j = \{t_2, t_j\}$, $j = 1, 4, 8, 11, \ldots, 3n - 1$ or of the form $M_\ell = \{t_5, t_\ell\}$, $\ell = 4, 8, 11, \ldots, 3n - 1, 3n + 2$. Note that the incidence vectors of the matchings of type $M_j$ and $M_\ell$ can be represented as $e_{2,j}$ or $e_{5,\ell}$ for $\ell, j$ as specified above. Hence, the vertices of the matching polytope of $G_n$ are the same as the vertices of $Q_n$ as given in (25), implying the two polytopes coincide. \qed
Let $\tilde{G}_n$ be the simple graph arising from $G_n$ by deleting the $2n$ parallel edges $t_{3i}, t_{3i+1}, 1 \leq i \leq n$ and relabeling the remaining edges. Then $\tilde{G}_n$ is the graph on $n + 3$ vertices and $n + 3$ edges.

**Proposition 3.19.** The polytope $K_n$ is the matching polytope for $\tilde{G}_n$, i.e., $K_n = P_{\text{MA}}(\tilde{G}_n)$.

**Proof.** Similarly to the proof of Proposition 3.18, we will show that the vertices of $K_n$ and $P_{\text{MA}}(\tilde{G}_n)$ are the same. Note that the matching for $\tilde{G}_n$ will be a subset of the matching of $G_n$. In particular, there will be $2n$ fewer singleton matchings resulting from the deletion of the $2n$ parallel edges. No two-edge matching will be lost in the construction of $\tilde{G}_n$ from $G_n$. All single edge matchings correspond to the standard vectors $e_i$ for $1 \leq i \leq n + 3$, with $e_0$ representing the empty matching. As in the proof of Proposition 3.18, we have two-edge matchings of types $M_{j'}$ and $M_{\ell'}$ for $j' = 1, 3, 5, 6, \ldots, n - 1$ and $\ell' = 3, 5, 6, \ldots, n$ corresponding to the vertices $v_{2j'}$ and $v_{4\ell'}$ from the vertex representation of $K_n$ given in (27). Hence, $K_n = P_{\text{MA}}(\tilde{G}_n)$. □

4 Acknowledgements

Elizabeth Gross was supported by NSF DMS-1620109. Cvetelina Hill was partially supported by NSF DMS-1600569. Additionally, this material is based upon work supported by the National Science Foundation under Grant No. DMS-1439786 while the authors were in residence at the Institute for Computational and Experimental Research in Mathematics in Providence, RI, during the Fall 2018 semester.

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