An Efficient Way of Understanding the Maximum Number of Steady-State Solutions for Chemical Reaction Networks

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Abstract

Many chemical processes can be modeled mathematically by chemical reaction networks. A chemical reaction network can give some ordinary differential equations that model the concentrations of the chemical species as time varies and conservation laws that constrain the total concentrations. Under mild hypotheses, this resulting system is a polynomial system. We can use this acquired system to solve for steady states of the network by setting the equations equal to zero and finding the values of the variables. For a generic polynomial system, the number of nonzero complex solutions is called the mixed volume. Since the concentrations of chemicals can only be described as positive real numbers, we are interested in the instances when the mixed volume equals to the maximum number of positive real solutions, because this would allow us to efficiently compute the maximum number of steady states of a network. In this paper, we classify the monomolecular networks whose maximum number of steady states is equal to the mixed volume of the corresponding polynomial system. We also give examples of networks with more species that have the same property.

Keywords: Chemical reaction network, mixed volume, positive steady states.

1 Introduction

The concern of this work is to identify the properties of chemical reaction networks that have mixed volume equal to the maximum number of positive steady states (for any choice of rate constants and total concentrations). A *chemical reaction network* is defined by a reaction network where some species or complexes of chemicals reacts in order to produce some species or complexes. In other words, Angeli [2] describes a chemical reaction network by a collection of reactions as given in (1) where the k_i and k_l are called *reaction rate constants*, the A_j are called *reactant species*, the B_m are called *product species*, and $I, J, L, M \in \mathbb{N}$.

$$\sum_{(i,j)=(1,1)}^{(I,J)} k_i A_j \longrightarrow \sum_{(l,m)=(1,1)}^{(L,M)} k_l B_m \tag{1}$$

Chemical reaction network theory helps solve problems in biochemistry and molecular biology by the use of applied mathematics [2]. The steady-state solutions for the system of differential equations derived from the network can be interpreted as the species concentrations at which the network reaches equilibrium. The existing method for calculating the maximum number of steady states in a chemical reaction network is time consuming [3]. Solving the polynomial systems derived from the networks over the set of nonzero complex numbers gives an upper bound on the positive real solutions, and the number of nonzero complex solutions to a polynomial system is called its *mixed volume* [11]. Obatake, Shiu, Tang and Torres in [10] first introduced the notion of mixed volume for chemical reaction networks as an efficient bound on the number of steady-state solutions of the network.

We say that a chemical reaction network is *equatorial* when its mixed volume is equal to the maximum number positive steady states of the network for any choice of rate constants and total concentrations. While many chemical reaction networks are not equatorial, we show that there exist some equatorial networks. In terms of looking for the number of steady states, Joshi and Shiu in [9] have classified the small chemical reaction networks that have multiple steady states. Also, Obatake et. al in [10] looked at mixed volume of ERK regulation networks. However, the instances when a chemical reaction network is equatorial has not been looked at yet. Furthermore, if we know the properties of the equatorial networks we can just calculate the mixed volume which is faster than trying to find out the maximum number of steady states. In Section 2, we give some background information, definitions and theorems. In Section 3, we classify the mixed volume of monomolecular networks, identify the equatorial monomolecular networks and give examples of equatiorial bimolecular networks. In Section 4, we discuss our results and upcoming possible concerns related to the topics of mixed volume and positive steady state of the network.

2 Background

In this section we give some definitions, and illustrate the definitions through an example. Assume the following chemical reaction network:

$$\begin{aligned} 2A+B &\xrightarrow{k_1} A+2B \\ 2A+2B &\xrightarrow{k_2} 3A+B \end{aligned}$$

Figure 1: A chemical reaction network

Here, the variables A, B are chemical species and the k_is are the reaction rate constants. The different complexes in this network are $2A+B$, $A+2B$, $2A+2B$. We will always assume that the concentrations of A, B and the reaction rate constants k_i are positive real numbers.

As time varies, the ODEs we get from the network in Figure 1 are:

$$\frac{da}{dt} = -k_1 a^2 b + k_2 a^2 b^2,$$
$$\frac{db}{dt} = k_1 a^2 b - k_2 a^2 b^2.$$

The conservation law that constrains the system by constant $T > 0$ is:

$$a + b = T.$$

Now that we have all of the equations from the network, we define the augmented polynomial system defining the network. The *augmented polynomial system* is achieved by replacing one of the ODEs by the conservation law, and setting the remaining ODEs to zero. The augmented polynomial system we get for the network in Figure 1, obtained by replacing $\frac{db}{dt}$ by the conservation law, is:

$$\begin{aligned} -k_1 a^2 b + k_2 a^2 b^2 &= 0 \\ a + b &= T \end{aligned} \tag{2}$$

Remark. In the case of monomolecular networks, there is no conservation law. In this case, the augmented polynomial system is obtained by setting the ODE equal to zero, and we refer to this polynomial as the *simplified polynomial* for the network.

The Newton polytope P_j of a polynomial is the convex hull of the exponent vectors v_i of the species variables in the polynomial system which in [11] is generally described as:

$$\mathrm{Newt}(P_j) = \mathrm{Conv}\{v_1, v_2, \ldots, v_n\}. \tag{3}$$

The Newton polytopes derived from the augmented system in (2) are:

$$\begin{aligned} \mathrm{Newt}(P_1) &= \mathrm{Conv}\{\begin{pmatrix}2\\1\end{pmatrix}, \begin{pmatrix}2\\2\end{pmatrix}\} \\ \mathrm{Newt}(P_2) &= \mathrm{Conv}\{\begin{pmatrix}1\\0\end{pmatrix}, \begin{pmatrix}0\\1\end{pmatrix}, \begin{pmatrix}0\\0\end{pmatrix}\} \end{aligned} \tag{4}$$

The Minkowski sum of two polytopes is the convex hull of the set of pairwise sums of the points in each of the polytopes [11]:

$$\mathrm{Mink}(P_1, P_2) = \{p_1 + p_2 \mid p_1 \in P_1, p_2 \in P_2\}. \tag{5}$$

The Minkowski sum derived from the Newton polytopes in Equations (4) is:

$$\mathrm{Mink}(P_1, P_2) = \mathrm{Conv}\{\begin{pmatrix}3\\1\end{pmatrix}, \begin{pmatrix}2\\1\end{pmatrix}, \begin{pmatrix}3\\2\end{pmatrix}, \begin{pmatrix}2\\3\end{pmatrix}, \begin{pmatrix}2\\2\end{pmatrix}\}. \tag{6}$$

The mixed volume is calculated by taking the volumes of Newton polytopes and Minkowski sums, which according to Sturmfels [11], is given by Equation (7).

$$\mathrm{MV}(P_1, P_2, \dots P_n) = \sum_{J \subseteq \{1,2,\dots,n\}} (-1)^{n-\#J} \mathrm{Vol}\left(\sum_{j\in J} P_j\right). \tag{7}$$

In our case, the P_j represent the Newton polytopes derived from the augmented polynomial system. The mixed volume for the augmented system (2) is

$$\begin{aligned}\mathrm{MV}(P_1, P_2) &= (-1)^2\mathrm{Vol}(\mathrm{Mink}(P_1, P_2)) + (-1)^1(\mathrm{Vol}(\mathrm{Newt}(P_1)) + \mathrm{Vol}(\mathrm{Newt}(P_2)))\\ &= \frac{3}{2} - (0 + 1/2)\\ &= 1.\end{aligned}$$

We interchangeably use Equation (7) and `Macaulay2` to compute the mixed volume, whichever is efficient. An example code for computing mixed volume for a network with 5 species is given in Appendix A.

In order to know how many positive solutions there are we have to solve for the variables in the augmented system by setting some values of k_i and T. For the system in (2), assume $k_1 = 1$, $k_2 = 0.5$, and $T = 1$ and by substituting these values, the solutions we get for a and b are given by:

$$\begin{aligned}-0.5a^2b + a^2b^2 &= 0,\\ a^2b(-0.5 + b) &= 0,\\ b &= 0.5.\end{aligned}$$

By substituting the value of b into the conservation law,

$$\begin{aligned}a &= 1 - 0.5,\\ a &= 0.5.\end{aligned}$$

Thus, for this choice of rate constants and total concentration, there is exactly one positive steady state $(a, b) = (0.5, 0.5)$. However, the augmented polynomial system does not always have a straightforward solution. Sometimes we can reduce the system to a univariate polynomial by substitutions. In the next section we will show that when the reduced polynomial system is univariate, we can utilize Theorem 1 and Theorem 2 to calculate the mixed volume and maximum number of positive real solutions for such systems.

Theorem 1. *(Fundamental Theorem of Algebra [1]) The number of solution to a polynomial system equals to the highest degree of the polynomial*

Theorem 2. *(Descartes' Rule of Signs [9]) For a univariate polynomial, the number of positive real solutions is at most the number of sign changes.*

To apply Descartes' rule of signs, the polynomial has to be written with terms in decreasing degree or increasing degree.

3 Results

In this section we classify the equatorial monomolecular networks and answer questions about whether an equatorial network remains equatorial when it is made fully reversible.

3.1 Equatorial monomolecular chemical reaction networks

As stated earlier, the mixed volume and the maximum number of steady states of networks with one species can be inferred from the ODE by applying Theorems 1 and 2. We make this explicit in Theorem 3.

Theorem 3. *For a polynomial derived from a monomolecular chemical reaction network, let* $n_r > n_1$*, where* $n_1 \in \mathbb{Z}_{\geq 0}$ *denotes the smallest coefficient in any of the reactant complexes and* $n_r \in \mathbb{N}$ *denotes the largest coefficient in any of the reactant complexes. Then the mixed volume of the network is* $n_r - n_1$*.*

Proof. Assume a monomolecular chemical reaction network with A as the chemical species in each of the complexes consisting of the r reactions

$$n_i\mathrm{A} \xrightarrow{k_i} m_i\mathrm{A}$$

where $i = 1, \ldots, r$. Without loss of generality, assume $n_r > n_i$ for all $i \neq r$ and $n_1 < n_i$ for all $i \neq 1$.

The ODE we get from this network is given by,

$$\frac{da}{dt} = \pm k_r(m_r - n_r)a^{n_r} \pm \cdots \pm k_i(m_i - n_i)a^{n_i} \pm \cdots \pm k_1(m_1 - n_1)a^{n_1}.$$

Let C_i denote the coefficient of a^{n_i}. Then the ODE becomes

$$\frac{da}{dt} = C_r a^{n_r} + \cdots + C_1 a^{n_1},$$

and the solutions can be achieved by setting this ODE equal to zero and solving for a. Note that the highest degree term has degree n_r and the lowest degree term has degree n_1. By Theorem 1, there are n_r complex solutions to the polynomial (counted with multiplicity). Simplifying the polynomial equation, we get

$$a^{n_1}(C_r a^{n_r - n_1} + \cdots + C_1) = 0$$

which implies that $a = 0$ is a solution with multiplicity n_1 and there are $n_r - n_1$ nonzero complex solutions for generic C_i. Thus, the mixed volume for the network is $n_r - n_1$. □

The mixed volume gives the upper bound on the number of nonzero complex solutions but since we are looking for equatorial networks we now investigate the number of positive real solutions for monomolecular networks.

Example 4. Consider the following network:

$$\mathrm{A} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 0 \xrightarrow{k_3} 2\mathrm{A} \xrightarrow{k_4} 3\mathrm{A}$$

We will show that the defining polynomial for this network has alternating signs. In this network we have a birth, a leak, some positive rate constants k_i. The polynomial that defines the steady states of this network is,

$$(k_1 + 2k_3) - k_2 a + k_4 a^2 = 0$$

The number of sign changes in this polynomial is 2 and so according to Theorem 2, the number of positive real solutions is at most 2. Note that since the values of k_i are positive real numbers, the number of sign changes will be unaffected no matter the choice of k_i. Furthermore, it can be observed that the coefficients of a are independent of each other such that any choice k_i's would not impact coefficients in a different term which as a result tells us that maximum number of steady state is 2. For example, if $k_1 = 0.5,\ k_2 = 2,\ k_3 = 0.25,\ k_4 = 1$, then when solving for a the polynomial would be

$$a^2 - 2a + (0.5 + 2(0.25)) = 0.$$

Then, we have $a = 1$ with multiplicity 2. Note that since k_i's are arbitrary, the steady state solutions to this system are not unique. For example, if we substitute $k_1 = 1, k_2 = 3, k_3 = 1, k_4 = 1$, then

$$\begin{gathered} a^2 - 3a + 2 = 0 \\ (a-1)(a-2) = 0 \\ a = \{1, 2\} \end{gathered}$$

Thus, the maximum number of positive steady states is $|\{1, 2\}| = 2$.

In the previous example, we saw that for a univariate polynomial we could choose rate constants such that the number of positive solutions was equal to the number of sign changes. We generalize this example to more general monomolecular networks now.

Theorem 5. *In a simplified polynomial of monomolecular network, if the number of sign changes in the polynomial equals mixed volume, then the network is equatorial.*

Proof. To generalize Example 4, suppose we have $r \in \mathbb{N}$ reactions in a monomolecular network where the simplified polynomial has alternating sign. As in the proof of Theorem 3 we write the polynomial as

$$C_r a^{n_r} + \cdots + C_1 a^{n_1} = 0.$$

Here $\mathrm{sign}(C_i C_{i+1}) = -1$ for all $i = 1, \ldots, r-1$ since, by hypothesis, the simplified polynomial has alternating signs. By Theorem 3, the mixed volume is $n_r - n_1$. Since, by hypothesis, the number of sign changes is $n_r - n_1$ and the choice of C_i are independent in each of the terms, by Theorem 2, the maximum number of positive steady states is $n_r - n_1$. $\square$

3.2 How does reversing reactions affect equatorial networks?

In the beginning of our research, we asked,

Question 6. Let N be an irreversible equatorial network. Let $\hat{N}$ be the fully reversible network obtained from N by adding all reverse reactions. Is $\hat{N}$ equatorial?

While it may be true in some cases, it is not true in general. We investigate Question 6 for monomolecular and bimolecular networks.

3.2.1 Monomolecular networks

The following monomolecular network shows that the answer to Question 6 is no.

$$2\mathrm{A} \xrightarrow{k_1} \mathrm{A} \xrightarrow{k_2} 3\mathrm{A} \xrightarrow{k_3} 5\mathrm{A}$$

Figure 2: One species irreversible network that is equatorial

Example 7. The ODE and simplified polynomial we get from this reaction network is given by,

$$2k_3a^3 - k_1a^2 + 2k_2a = 0$$

If we substitute $k_1 = 3,\ k_2 = 1,\ k_3 = 0.5$ we get

$$a = \{0, 2, 1\}$$

Thus, the mixed volume is equal to the maximum number of positive steady states. However, if the network is made fully reversible, then we have,

$$2\mathrm{A} \underset{k_4}{\overset{k_1}{\rightleftharpoons}} \mathrm{A} \underset{k_5}{\overset{k_2}{\rightleftharpoons}} 3\mathrm{A} \underset{k_6}{\overset{k_3}{\rightleftharpoons}} 5\mathrm{A}$$

Figure 3: Fully reversible network created from Figure 2

The ODE and the simplified polynomial equation for the network in Figure 3 are,

$$\frac{dA}{dt} = -k_1a^2 + k_4a + 2k_2a - 2k_5a^3 + 2k_3a^3 - 2k_6a^5$$

$$-2k_6a^5 + (2k_3 - 2k_5)a^3 - k_1a^2 + (k_4 + 2k_2)a = 0$$

We simplify the equation here to see the possible sign changes that happen in the polynomial. By Theorem 3, the mixed volume is 4 but the number of sign changes we can have at most is 3 even if $2k_3 > 2k_5$. This proves that the network $\hat{N}$ does not remain equatorial when the reverse reactions are added N.

However, does this trend hold true in more than one species case? We discuss it in Section 3.2.2.

3.2.2 Bimolecular networks

There exists an irreversible bimolecular network with two reactions that is equatorial, but when we make this network fully reversible, the property is lost.

$$\begin{aligned} 2\mathrm{A} + 2\mathrm{B} &\xrightarrow{k_1} \mathrm{A} + \mathrm{B} \\ \mathrm{A} + 2\mathrm{B} &\xrightarrow{k_2} 2\mathrm{A} + 3\mathrm{B} \end{aligned}$$

Figure 4: An irreversible equatorial bimolecular network N

Example 8. The augmented polynomial system we get from this network is

$$\begin{aligned} -k_1 a^2 b^2 + k_2 a b^2 &= 0 \\ a - b &= T \end{aligned}$$

Its mixed volume is equal to 1 and by solving for a and b in the system, we get that the maximum number of positive solutions is 1: one of the possible positive solutions is $(a, b) = (4, 1)$ (when $k_1 = 0.25$ and $k_2 = 1$, and $T = 3$).

Then, when we make the network fully reversible, we get the network in Figure 5.

$$\begin{aligned} 2\mathrm{A} + 2\mathrm{B} &\underset{k_3}{\overset{k_1}{\rightleftharpoons}} \mathrm{A} + \mathrm{B} \\ \mathrm{A} + 2\mathrm{B} &\underset{k_4}{\overset{k_2}{\rightleftharpoons}} 2\mathrm{A} + 3\mathrm{B} \end{aligned}$$

Figure 5: Fully reversible network for $\hat{N}$ that illustrates Question 6 is not necessarily true

The fully reversible network $\hat{N}$ has the following augmented polynomial system,

$$\begin{aligned} -k_1 a^2 b^2 + k_2 a b^2 + k_3 a b - k_4 a^2 b^3 &= 0 \\ a - b &= T. \end{aligned}$$

This polynomial system has mixed volume equal to 3, but the number of positive solutions is at most 1. Thus, adding reverse reactions to the equatorial network in Figure 4 results in the network Figure 5 which is not equatorial.

Remark. Note that the reactant species B is constant in each of the reactants of the network in Figure 4. This helps us to reduce the polynomial system to a univariate polynomial (by solving the conservation law for one of the variables and then substituting into the other polynomial) where the coefficients are not dependent on each other. Then, Theorem 5 illustrates that the number of positive solutions to system is computed using only the resulting univariate polynomial.

4 Discussions and further research

As we saw in Section 3, when reverse reactions are added to a irreversible equatorial network the new network is not necessarily equatorial. However, in the following strongly connected network equatoriality is preserved when reverse reactions are added.

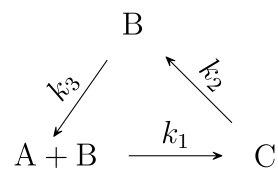

Figure 6: Strongly connected equatorial network

The mixed volume for this network is 1, and so is the maximum number of positive steady states. For choice of constant values $k_1 = 1,\ k_2 = 1,\ k_3 = 1,$ and $T = 1$ the solution is $(a, b, c) = (1,\ 0.5,\ 0, 5)$. When the reverse reactions are added to make the network fully reversible, the mixed volume is still 1 and the positive solution is $(a, b, c) = (1,\ 0.5,\ 0.5)$ for the same choices of constants. Thus, we conjecture the following.

Conjecture 9. *If a strongly connected network is equatorial, then its fully reversible network is also equatorial.*

The following questions are directed towards finding equatorial networks. First, in light of the irreversible equatorial network in Example 8, we ask the following:

Question 10. Is there any multimolecular irreversible network where each of the species in the reactant complexes is not constant but the network is equatorial?

Question 11. Assume an irreversible network that is not equatorial, would adding reverse reaction(s) make it equatorial?

We give evidence that investigates Questions 10 and 11 in Appendix A.2.

In Theorem 5, we gave a classification of equatorial monomolecular networks. Although the maximum number of steady states can be easily identified in the monomolecular network, the equations get complicated when there are multiple species due to the increase of the coefficient dependence. Furthermore, we cannot always reduce the analysis to univariate polynomials in general.

Question 12. Is there any other efficient way to solve the augmented polynomial system that would illustrate the maximum number of positive steady states?

Coming up, it would better to get better understanding of solving multivariate polynomial system when we manipulate the values of the parameters. Also, the code can be developed further which would take only take the reaction network as input and produce the mixed volume and the maximum number positive real solutions.

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Appendix A Code

A.1 Code to compute the mixed volume of a network

This example code can be modified to any chemical reaction networks that has at least 2 species.

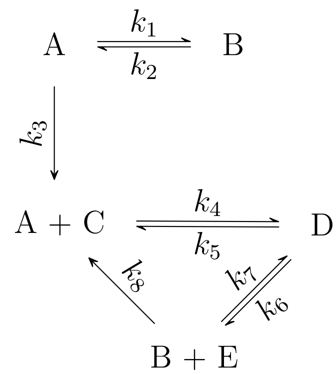

Figure 7: An example network for code

Here is the Macaulay2 code used to mixed volume of the chemical reaction network in Figure 7 and the possible nonzero complex solutions for its augmented polynomial system:

```
loadPackage("PHCpack") --package for computing mixed volume
R=CC[a,b,c,d,e]; --ring for the polynomial system
-- we enter all the values of k_i and T as 1
f1=-1*a+1*b-1*a*c+1*d+1*b*e; --diff. eq. for a
f2=1*a-1*b+1*d-1*b*e-1*b*e; --diff. eq. for b
f3=1*a-1*a*c+1*d+1*b*e; --diff. eq. for c
f4=1*a*c-1*d-1*d+1*b*e; --diff. eq. for d
f5=1*d-1*b*e-1*b*e; --diff. eq. for e
C1=a+b+d-1; --conservation law
--one of the ODEs of either a,b,or d should be replaced by the conservation law
mixedVolume({f2,f3,f4,f5,C1},StartSystem=>true)
--mixed volume calculated by replacing C1 for diff. eq. of a.
--it solves the system with some arbitrary nonzero complex k_i
--the output is of the form (mixed volume, start system, nonzero complex solutions)
(1, {(.265348 + .964153*ii)b*e + (- .639258 + .768993*ii)a,
(.777534 -.628841*ii)b*e + (.775023 - .631933*ii)b, (.0924633 + .995716*ii)a*c
+(.919193 + .393808*ii)a, (- .139833 - .990175*ii)b*e + (.991269 -.131854*ii)d,
(- .132379 + .991199*ii)a + .787578 - .616215*ii}, {{.71505+.699073*ii,
-.168577+.985689*ii, -.477112+.878842*ii,.987646+.1567*ii, -.999992+.003984*ii}})
```

A.2 An example of an irreversible network that is not equatorial

Question 10, asks about irreversible networks with more than one species where no single species is constant throughout all reactant complexes. The following is an example of such a network that is **not** equatorial.

$$
\begin{array}{lcl}
\mathrm{A}+2\mathrm{B} & \xrightarrow{k_1} & 3\mathrm{B} \\
3\mathrm{A}+\mathrm{B} & \xrightarrow{k_2} & 4\mathrm{A}
\end{array}
$$

Figure 8: A non-equatorial network N

Notice that the two reactant complexes are $A + 2B$ and $3A + B$, and that neither A nor B is constant in these reactant complexes. The augmented polynomial system we get from the network is,

$$
\begin{aligned}
k_1ab^2 - k_2a^3b &= 0 \\
a + b &= T.
\end{aligned}
$$

The mixed volume for this system is 2 and maximum number of positive solutions is 1. We can show that one positive solution exists for some choice of k_i and T: assuming $k_1 = 0.1,\ k_2 = 10,\ T = 1$ produces

$$(a, b) \in \{(-0.370156, 1.37016),\ (0, 1),\ (0.270156, 0.729844),\ (1, 0)\}.$$

$$
\begin{array}{lcl}
\mathrm{A}+2\mathrm{B} & \underset{k_2}{\overset{k_1}{\rightleftharpoons}} & 3\mathrm{B} \\
3\mathrm{A}+\mathrm{B} & \underset{k_4}{\overset{k_3}{\rightleftharpoons}} & 4\mathrm{A}
\end{array}
$$

Figure 9: Fully reversible non-equatorial network $\hat{N}$

If we make the network fully reversible, the network still has the property that no species is constant throughout all reactant complexes. This fully reversible network has mixed volume 4. However, the maximum number of positive real solutions is still 1, which gives evidence related to Question 11. In particular, this is an example where making a non-equatorial network fully reversible does not increase the likelihood of the new network being equatorial.