

Analyzing Multistationarity in Chemical Reaction Networks using the Determinant Optimization Method

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Abstract

Multistationary chemical networks are a subject of interest to scientists and mathematicians alike. While some criteria for multistationarity have been given, explicitly solving for these rates and concentrations is nontrivial. We use an existence proof to describe a method that allows us to find multiple steady states of a system given that satisfies the conditions described by Craciun and Feinberg [2]. Using this method we give closed forms for the rates and steady-state concentrations of the particular sequestration network $\tilde{K}_{m,n}$. Furthermore, our results allow us to prove that the steady states are non-degenerate when $n = 3$, thereby resolving one case of the conjecture stated by Shiu and Joshi [4]. Additionally, we show for the first time how this method can give rise to a degenerate steady state.

1 Introduction

Many scientists and mathematicians would like to know which chemical reaction networks exhibit *multistationarity*, i.e. if they have the potential to exhibit two or more steady state concentrations with the same reaction rates. One result that can help answer this question is due to Joshi & Shiu [4]: if a chemical reaction network has an “embedded” subnetwork that can exhibit multistationarity, then the entire reaction network also has the potential to exhibit multistationarity under certain hypotheses. Therefore we are interested in cataloguing the multistationary networks that do not have embedded multistationary networks, because all larger multistationary networks would contain at least one embedded multistationary subnetwork from the catalogue. Toward that end, [4] named a certain infinite family of chemical reaction networks $\tilde{K}_{m,n}$ to be of particular interest among networks that include inflow and outflow reactions. This family is minimal, in that it has no embedded subnetworks that exhibit multistationarity.

Using the determinant optimization method [3], [2], Joshi & Shiu [4] proved

that $\tilde{K}_{m,n}$ has the potential to exhibit multistationarity for integers $m \geq 2$ and odd integers $n \geq 3$. They conjectured that furthermore $\tilde{K}_{m,n}$ has the potential for multiple *non-degenerate* steady states, informally the “friendly” type of steady states. If this conjecture is true, then $\tilde{K}_{m,n}$ would be the first infinite family of chemical reaction networks with inflow and outflow reactions that is at-most bimolecular, minimal, and has the potential to exhibit multiple *non-degenerate* steady states. Because trimolecular reactions are rather uncommon in chemistry, and $\tilde{K}_{m,n}$ contains networks that are at most *bimolecular*, this family of networks is of particular interest in chemical applications.

Analyzing the degeneracy of steady states in $\tilde{K}_{m,n}$, we prove the case that $\tilde{K}_{m,3}$ has the potential to exhibit multiple nondegenerate steady state equilibria for all $m \geq 2$. Furthermore, we use our analysis to show examples of when the determinant optimization method outlined in [2] produces degenerate steady states in Section 3.1.

To accomplish this, we need more information than the *existence* of steady states; we must have the closed form of the rates and concentrations themselves. Toward that end, we use a refinement of the determinant optimization method in [2] to generate new closed forms for the reaction rates and concentrations for the system, $\tilde{K}_{m,n}$.

Recognizing the usefulness of generating a closed form for the rates and concentrations for any chemical reaction system satisfying the hypotheses of [2], we outline the steps we took with enough generality to be used in other contexts. While this process may not generate a closed form for every chemical reaction system, we describe step-by-step how to implement the determinant optimization method of [2] to obtain explicit steady state rates and concentrations in Section 3.

2 Background

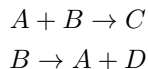
We will begin this section by introducing the notation used to describe chemical reaction networks. Then, we proceed to describe what *mass action kinetics* systems are and how we use them. Finally, we conclude by introducing the main object of our paper, the network $\tilde{K}_{m,n}$.

Definition 1. A chemical reaction network $G = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ consists of three finite sets:

1. a set of species \mathcal{S} , which contains all distinct elements that take part in any of the reactions.
2. a set \mathcal{C} of complexes, which contains all the distinct linear combinations of the elements in \mathcal{S} . And,

3. a set $\mathcal{R} \subseteq \mathcal{C} \times \mathcal{C}$ of reactions, which indicates which complexes are involved in each of the reactions.

Example Consider the following chemical reaction network:



The sets that describe this network, namely \mathcal{S} , \mathcal{C} , and \mathcal{R} are defined as follows

1. The set of species $\mathcal{S} = \{A, B, C, D\}$.
2. The set of complexes $\mathcal{C} = \{A + B, C, B, A + D\}$. Note, for this case, that B is part of two interactions, one where it interacts with A and another one, where it interacts by itself. Hence, B appears twice in \mathcal{C} as part of two distinct complexes.
3. The set of reactions $\mathcal{R} = \{(A + B, C), (B, A + D)\}$.

Moving on, any reaction network $G = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is contained in the *fully open extension network* \tilde{G} obtained by including all inflow and outflow reactions. i.e.

$$\tilde{G} := \{\mathcal{S}, \mathcal{C} \cup \mathcal{S} \cup \{0\}, \mathcal{R} \cup \{X_i \leftrightarrow 0\}_{X_i \in \mathcal{S}}\} \quad (1)$$

In other words, the fully open extension of any network is obtained by adding the reactions for all species X in the set \mathcal{S} :



We should note that as the reactions take place, the concentrations of the species will change, unless we are at an equilibrium state. To study such changes, we make use of *mass-action kinetics* to define a system of ordinary differential equations that describes how these concentrations will change with respect to time. To this end, we introduce the following terms: the *stoichiometric matrix* Γ and the *reactant vector* $R(x)$. We should note that $R(x)$ is a vector function of the species vector \mathbf{x} .

Definition 2. The stoichiometric matrix Γ is the $|\mathcal{S}| \times |\mathcal{R}|$ matrix whose k^{th} column is the vector $y_j - y_i$ of the k^{th} reaction $y_i \rightarrow y_j$.

Definition 3. The reactant vector $R(x) \in \mathbb{R}^{|\mathcal{R}|}$ is the vector whose k^{th} entry represents the k^{th} reactant complex:

$$\alpha_1 X_1 + \alpha_2 X_2 + \dots + \alpha_{|\mathcal{S}|} X_{|\mathcal{S}|}$$

as the product:

$$r_k X_1^{\alpha_1} X_2^{\alpha_2} \dots X_{|\mathcal{S}|}^{\alpha_{|\mathcal{S}|}} \quad (2)$$

where $r_k \in \mathbb{R}^+$ is the reaction rate of the k^{th} reaction.

Having defined the stoichiometric matrix and the reactant vector, we are ready to define the *reaction kinetics system* of a chemical reaction network as follows:

Definition 4. *The mass-action kinetics system of a network G is given by the system of ordinary differential equations:*

$$\frac{d\mathbf{x}}{dt} = \Gamma \cdot R(\mathbf{x}) \quad (3)$$

We proceed to show an example of how to construct the mass-action kinetics system.

Example Consider the following network:



The network describes how one molecule of A binds with two molecules of B at a rate r to produce two molecules of A . Since we have 3 species and only one reaction, our stoichiometric matrix Γ will have dimensions 2×1 while $R(x)$ will be a 1-dimensional vector.

Now, we represent the complex $A + 2B$ as the vector $\begin{pmatrix} 1 \\ 2 \end{pmatrix}$, and in the same manner we represent the complex $2A$ as the vector $\begin{pmatrix} 2 \\ 0 \end{pmatrix}$. Following Definition 2 we construct Γ as the matrix:

$$\Gamma = \begin{bmatrix} 1 \\ -2 \end{bmatrix}$$

Now we proceed to construct the vector $R(x)$. We start by turning the reactant complex $A + 2B$ into the product $A \cdot B^2$. Hence

$$R(x) = (rAB^2)$$

And finally we define the reaction kinetics system by multiplying Γ and $R(x)$. In this example we arrive at:

$$\frac{d\mathbf{x}}{dt} = \begin{bmatrix} 1 \\ -2 \end{bmatrix} \cdot (rAB^2) = \begin{bmatrix} rAB^2 \\ -2rAB^2 \end{bmatrix}$$

Or, using an equivalent notation:

$$\begin{aligned} \frac{dA}{dt} &= rAB^2 \\ \frac{dB}{dt} &= -2rAB^2 \end{aligned}$$

which is our mass action kinetics system.

An important characteristic of mass action kinetic system is that they may or may not have the capacity to admit *steady states*. Which are formally defined as follows:

Definition 5. A steady state is a vector $\mathbf{x} \in \mathbb{R}_{>0}^{|\mathcal{S}|}$ such that $\Gamma \cdot R(\mathbf{x}) = 0$.

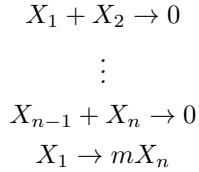
Remark A network that is extended to include inflow and outflow reactions and has the capacity to admit more than one steady state is said to be *multistationary*. In order to admit more than one steady state, there must exist two distinct concentrations $\mathbf{x}^*, \mathbf{x}^\#$ such that $\Gamma \cdot R(\mathbf{x}) = 0$ for both concentrations and a fixed set of reaction rates.

Furthermore, we can characterize a steady state as *non-degenerate* if it satisfies the following condition:

Definition 6. A steady state $\mathbf{x}^* \in \mathbb{R}_{>0}^{|\mathcal{S}|}$ is non-degenerate if $\text{im}(df(\mathbf{x}^*)) = \text{im}(\Gamma)$. Where $df(\mathbf{x}^*)$ denotes the Jacobian of the reaction kinetics system at \mathbf{x}^* .

Now we are ready to introduce the main object of our paper, which is the *fully open extension* of the network $K_{m,n}$.

Definition 7. For positive integers $n \geq 2$, $m \geq 1$ we define the sequestration network $K_{m,n}$ of order n and production factor m to be:



We obtain the fully open extension of $K_{m,n}$ by adjoining the inflow and outflow rates as stated in (1). It has already been shown by Shiu and Joshi in [4] that this network $\tilde{K}_{m,n}$ is multistationary, i.e. it has more than one positive steady state solution for integers $m \geq 2$, and odd integers $n \geq 3$. But the following remains unsolved.

Conjecture 1 (Joshi & Shiu [4]). For positive integers $n \geq 2$ and $m \geq 2$, if n is odd, then $\tilde{K}_{m,n}$ admits multiple nondegenerate steady states.

We wish to attack this problem by showing that $\text{Im}(df(\mathbf{x}^*)) = \text{Im}(\Gamma)$. Or, since Γ is full rank, the problem reduces to showing that $\det(df(\mathbf{x}^*)) \neq 0$ for both positive steady state solutions $\mathbf{x}^*, \mathbf{x}^\#$.

Note that the corresponding stoichiometric matrix of our network is:

$$\Gamma = \begin{bmatrix} -1 & 0 & 0 & \dots & 0 & -1 & & \\ -1 & -1 & 0 & \dots & 0 & 0 & & \\ 0 & -1 & -1 & \dots & \vdots & \vdots & -I^n, & I^n \\ 0 & 0 & -1 & \ddots & \vdots & \vdots & & \\ \vdots & \vdots & \vdots & \ddots & -1 & 0 & & \\ 0 & 0 & 0 & \dots & -1 & m, & & \end{bmatrix} \quad (4)$$

where I^n is the identity matrix, and the first $n-1$ columns describe the reactions $X_{i-1} + X_i \rightarrow 0$, the n^{th} column describes $X_1 \rightarrow mX_n$. Because each of these reactions $1, \dots, n$ involve more than one species, they are referred to as *internal*, or *true* reactions. The $n+1$ through $2n$ entries describe the *outflow* reactions, and the $2n+1$ through $3n$ entries describe *inflow* reactions. In the general case, we refer to internal, outflow, and inflow reactions as \mathcal{R}_T , \mathcal{R}_O , and \mathcal{R}_I respectively. Similarly, our flow vector is given by,

$$R(\mathbf{x}) = \begin{bmatrix} r_1 x_1 x_2 \\ r_2 x_2 x_3 \\ \vdots \\ r_{n-1} x_{n-1} x_n \\ r_n x_1 \\ r_{n+1} x_1 \\ r_{n+1} x_1 \\ \vdots \\ r_{2n} x_n \\ r_{2n+1} \\ \vdots \\ r_{3n} \end{bmatrix} \quad (5)$$

where the $r_i \in \mathbb{R}_+$ are the flowrate constants and the $x_i \in \mathbb{R}_+$ are the concentrations of each species. Each ODE is of the form,

$$\begin{aligned} \dot{x}_1 &= -r_1 x_1 x_2 - r_n x_1 - r_{n+1} x_1 + r_{2n+1} \\ \dot{x}_i &= -r_{i-1} x_{i-1} x_i - r_i x_i x_{i+1} - r_{n+1} x_i + r_{2n+i} \quad \forall i \in \{2, 3, \dots, n-1\} \\ \dot{x}_n &= -r_{n-1} x_{n-1} x_n + m r_n x_1 + r_{2n} x_n + r_{3n}. \end{aligned} \quad (6)$$

Thus the Jacobian, $df(\mathbf{x})$ is given by

$$\begin{bmatrix} -r_1 x_2 - r_n - r_{n+1} & -r_1 x_1 & 0 & \dots & 0 & 0 \\ -r_1 x_2 & -r_1 x_1 - r_2 x_3 - r_{n+2} & -r_2 x_2 & \dots & \vdots & \vdots \\ 0 & -r_2 x_3 & -r_2 x_2 - r_3 x_4 - r_{n+3} & \ddots & 0 & 0 \\ 0 & 0 & -r_3 x_4 & \ddots & -r_{n-2} x_{n-2} & 0 \\ \vdots & \vdots & \vdots & \ddots & -r_{n-2} x_{n-2} - r_{n-1} x_n - r_{2n-1} & -r_{n-1} x_{n-1} \\ m r_n & 0 & 0 & \dots & -r_{n-1} x_n & -r_{n-1} x_{n-1} - r_{2n} \end{bmatrix} \quad (7)$$

or, for completeness, each entry is defined by,

$$\begin{aligned}
df(\mathbf{x})_{(1,1)} &= -r_1 x_2 - r_n - r_{n+1} \\
df(\mathbf{x})_{(1,2)} &= -r_1 x_1 \\
df(\mathbf{x})_{(i,i-1)} &= -r_{i-1} x_i \quad \forall i \in \{2, 3, \dots, n-1\} \\
df(\mathbf{x})_{(i,i)} &= -r_{i-1} x_{i-1} - r_i x_{i+1} - r_{n+i} \\
df(\mathbf{x})_{(i,i+1)} &= -r_i x_i \\
df(\mathbf{x})_{(n,1)} &= m r_n \\
df(\mathbf{x})_{(n,n-1)} &= -r_{n-1} x_n \\
df(\mathbf{x})_{(n,n)} &= -r_{n-1} x_{n-1} - r_{2n}
\end{aligned} \tag{8}$$

3 The Determinant Optimization Method for Constructing Multiple Steady States

The *determinant optimization method* is a method of finding whether or not a chemical reaction system has the capability of producing multiple steady states [3], [2]. In many applications, it might be useful to study the explicit steady state rates and concentrations. However, there is currently no closed form to generate an instance of these steady states rates and concentrations. Here we outline the steps necessary to “back-track” from satisfaction of determinant optimization method’s hypothesis to arrive at the steady state rates and concentrations for any given system. While our process does not necessarily generate closed form rates and concentrations for every chemical reaction system satisfying the hypotheses of determinant optimization method, we outline the general steps necessary to construct the steady states for any system.

Furthermore, from the above section we know that the steady state flow rates and concentrations of $\tilde{K}_{m,n}$ exist. As an example of this process, we develop a method for explicitly producing a closed form for the steady state concentrations and rate constants for the network $\tilde{K}_{m,n}$. This closed form could be used to make significant progress towards Conjecture 6.10 of [4]. The determinant optimization method’s hypothesis is given by,

$$(I) \det(y_1, y_2, \dots, y_n) \cdot \det((y_1 - y'_1), (y_2 - y'_2), \dots, (y_n - y'_n)) < 0.$$

(II) There exists a vector $\tilde{\eta} \in \mathbb{R}_+^k$ such that $\sum_{i=1}^k \tilde{\eta}_i (y_i - y'_i) \in \mathbb{R}_+^n$, where $(y_i - y'_i)$ is the negation of the i^{th} column in $\Gamma(x)$.

Example Condition (I) was proven for $\tilde{K}_{m,n}$ in Lemma 6.7 of [4]. Likewise, [4] also proved (II) is easily doable by using the first n columns (i.e. $n = k$), letting the $(n-1)^{th}$ entry of $\tilde{\eta}$ be $(m+1)$ and letting all other entries be 1.

The first step is to extend $\tilde{\eta}$ to a vector describing all internal and outflow reactions of the system, η^- . This vector η^- must have certain properties, which we can ensure by letting $\eta_i^- = \lambda \tilde{\eta}_i$ for some large λ on all reaction indices where $\tilde{\eta}_i$ is defined.

For all other reactions we let $\eta_i^- = \epsilon$, for sufficiently small ϵ .

Example We define, for our network, η^- be defined as follows:

$$\eta_i^- = \begin{cases} \lambda & \text{for } 1 \leq i \leq n-2 \text{ and } i = n \\ (m+1)\lambda & \text{for } i = n-1 \\ \epsilon & \text{for } n+1 \leq i \leq 2n \end{cases} \quad (9)$$

Note: At any later point in this paper, an entry of any η vector represents an entry in $R(x)$, i.e. the product of a flow rate and concentrations.

The second step, is to define a linear transformation T_η originally defined in [2] by,

$$T_\eta(\delta) = \sum_{y \rightarrow y' \in \mathcal{R}_T \cup \mathcal{R}_O} \eta_{y \rightarrow y'}(y \cdot \delta)(y - y') \quad (10)$$

It was shown by [2] that a proper choice of λ and ϵ , along with property (I) allows us to say that the determinant $\det(T_{\eta^-})$, is negative.

Example In our case, T_η strongly resembles the Jacobian matrix:

$$\begin{bmatrix} \eta_1 + \eta_n + \eta_{n+1} & \eta_1 & 0 & \cdots & 0 \\ \eta_1 & \eta_1 + \eta_2 + \eta_{n+2} & \eta_2 & \cdots & 0 \\ 0 & \eta_2 & \eta_2 + \eta_3 + \eta_{n+3} & \eta_3 & \cdots 0 \\ \vdots & 0 & \ddots & \ddots & \ddots \\ 0 & \vdots & \cdots & \eta_{n-2} + \eta_{n-1} + \eta_{2n-1} & \eta_{n-1} \\ -m\eta_3 & 0 & \cdots & \eta_{n-1} & \eta_{n-1} + \eta_{2n} \end{bmatrix} \quad (11)$$

Notice that $T_\eta = df(\mathbf{x})$ if all concentrations x_i are equal to 1 and η_i equal the rate r_i .

The third step is to generate a vector $\eta^0 \in \mathbb{R}_+^{|\mathcal{R}_T \cup \mathcal{R}_O|}$ such that the determinant of T_{η^0} is zero. The proof shows the existence of an η^+ such that $\det(T_{\eta^+}) > 0$. By the IVT, we know there exists such an η^0 . However, the mechanics of the proof really only require two properties of η^0 :

$$(I') \det(T_{\eta^0}) = 0$$

$$(II') \sum_{i=1}^{|\mathcal{R}_T \cup \mathcal{R}_O|} \eta_i^0 (y_i - y'_i) \in \mathbb{R}_+^{|\mathcal{S}|}.$$

The IVT approach essentially creates η^+ by defining a sufficiently large scalar λ^+ , and small scalar ϵ^+ such that

$$\eta_{y \rightarrow y'}^+ = \begin{cases} \lambda^+ & \text{for all reactions } y \rightarrow y' \in \mathcal{R}_O \\ \epsilon^+ & \text{for all reactions } y \rightarrow y' \in \mathcal{R}_I. \end{cases}$$

It was proven by Lemma 3.3 in [2] that with proper choice of λ^+ and ϵ^+ , one can show $\det(T_{\eta^+}) > 0$.

We also found that, if a strictly positive column vector $(y_i - y'_i)$ corresponding to the i^{th} reaction exists in the internal and outflow reactions, then properties (I') and (II') might be satisfied relatively easily. Since property (I') is only one equation, it

can be satisfied by allowing one free variable from our vector η^0 . If we let the entry η_i^0 (corresponding to the same i^{th} reaction) be free and fix $\eta_j^0 = \eta_j^-$ for $j \neq i$, then we can guarantee the satisfaction of (I') by algebraically solving for η_i^0 . In solving for η_i^0 , we hope that it is positive (recall η^0 must be a strictly positive vector). Unfortunately, this process is not guaranteed to work for every chemical reaction system. However, if this holds, property (II') is immediately satisfied since $(y_i - y'_i)$ and η_i^0 are positive and no other summands in (II') were changed.

Example We see that that property (II') can be satisfied by letting η^0 be identical to η^- , with the modification that we let the entry η_{2n}^0 be any positive value that satisfies (I') (note: all inflow/outflow reactions are indexed $1, 2, \dots, 2n$). Since the linear combination (II') is satisfied for η^- , it remains satisfied as long as $\eta_{2n}^0 > 0$. Furthermore, since (I') only requires we satisfy one equation, allowing one free variable is sufficient. Thus, we will let $\eta_1^0, \dots, \eta_{2n-1}^0$ take the same values as $\eta_1^-, \dots, \eta_{2n-1}^-$ and solve for the free variable η_{2n}^0 in $\det(T_{\eta^0}) = 0$. After substituting the values of η^0 , we have

$$T_{\eta^0} = \begin{bmatrix} 2\lambda + \epsilon & \lambda & 0 & \cdots & 0 \\ \lambda & 2\lambda + \epsilon & \lambda & \cdots & 0 \\ 0 & \lambda & 2\lambda + \epsilon & \lambda & \cdots & 0 \\ \vdots & 0 & \ddots & \ddots & \ddots & \ddots \\ 0 & \vdots & \cdots & \lambda + \lambda(m+1) + \epsilon & \lambda(m+1) \\ -m\lambda & 0 & \cdots & \lambda(m+1) & \lambda(m+1) + \eta_{2n}^0 \end{bmatrix}. \quad (12)$$

Expanding (12) along the bottom row, we see the determinant of T_{η^0} in the following recursive form,

$$\det(T_{\eta^0}) = -m(m+1)\lambda^n - \lambda^2(m+1)^2\mathfrak{T}_{n-2} + (\lambda(m+1) + \eta_{2n}^0)\mathfrak{T}_{n-1}, \quad (13)$$

where \mathfrak{T}_i is the determinant of the $i \times i$ tridiagonal matrix located in the upper left part of T_{η^0} . The determinant of tridiagonal matrices can be solved recursively [1]. In this case, it is easy to verify

$$\begin{aligned} \mathfrak{T}_{i+2} &= (2\lambda + \epsilon)\mathfrak{T}_{i+1} - \lambda^2\mathfrak{T}_i \\ \mathfrak{T}_0 &= 1 \\ \mathfrak{T}_1 &= 2\lambda + \epsilon, \end{aligned} \quad (14)$$

is true for entries of T_η independent of m , i.e. this works for $i \leq (n-2)$. Notice that \mathfrak{T}_{n-1} must be treated separately, because the $(n-1)^{st}$ row contains η_{n-1}^0 , which is a function of m . Using standard methods we can get the generating function of the recurrence.

$$\mathfrak{T}_i = \frac{1}{2^{i+1}c_1} * (-c_2(c_2 - c_1)^i + c_1(c_2 - c_1)^i + c_2(c_1 + c_2)^i + c_1(c_1 + c_2)^i) \quad (15)$$

where $c_1 = (\epsilon)^{\frac{1}{2}}(\epsilon + 4\lambda)^{\frac{1}{2}}$ and $c_2 = \epsilon + 2\lambda$. Notice here that \mathfrak{T}_i is always positive for sufficiently small ϵ . A formula for \mathfrak{T}_{n-1} is given using the formula for tridiagonal matrixes [1],

$$\mathfrak{T}_{n-1} = \mathfrak{T}_{n-2}(\lambda(m+2) + \epsilon) - \lambda^2\mathfrak{T}_{n-3} \quad (16)$$

With this recurrence solved, we derive an explicit function for η_{2n}^0 from (13) in terms of m, λ , and ϵ :

$$\begin{aligned}\eta_{2n}^0 &= \frac{m(m+1)\lambda^n}{\Upsilon_{n-1}} + \lambda^2(m+1)^2 \frac{\Upsilon_{n-2}}{\Upsilon_{n-1}} - \lambda(m+1) \\ &= \frac{(m+1)(m\lambda^n + \lambda(m+1)\Upsilon_{n-2})}{(\lambda(m+2) + \epsilon)\Upsilon_{n-2} - \lambda^2\Upsilon_{n-3}} - \lambda(m+1)\end{aligned}\quad (17)$$

Claim: $\eta_{2n}^0 > 0$ for sufficiently large λ and sufficiently small ϵ .

Proof. One can see that as $m \rightarrow \infty$, η_{2n}^0 is eventually positive. It is easy to verify for a given n , but we have not proven it in the general case. \square

The fourth step is to find some $\delta \neq 0$ in the nullspace of T_{η^0} ; i.e. some δ such that

$$T_{\eta^0} \cdot \delta = 0 \quad (18)$$

Note that the nullspace of T_{η^0} is non trivial, since $\det(T_{\eta^0}) = 0$. Thus such a vector δ must exist.

Example Here, we find a vector in the nullspace of (12). Furthermore, because our upper-left submatrix is tridiagonal, we can prove that the dimension of the nullspace is equal to 1 for any n .

Proof. It suffices to show that the rank of T_{η^0} is equal to $n - 1$. Then, the result follows from the rank-nullity theorem.

We proceed by showing that the first $n - 1$ rows of T_{η^0} are linearly independent. Assume, to the contrary, that they are not linearly independent and there is a non-trivial linear combination of the first $n - 1$ rows of T_{η^0} that adds to 0. Note that among the first $n - 1$ rows only the last one contains an entry in the last column, namely η_{n-1}^0 . Since $\eta_{n-1}^0 \neq 0$ the corresponding scalar of the $n - 1$ row should be 0, thus, annihilating the entire row. In the same manner, the corresponding scalar for the $n - 2$ row would be equal to 0. Repeating the process shows that the only linear combination that adds to 0 is the trivial one, thus, arriving at a contradiction. \square

As a corollary of the previous result we can get the basis of the nullspace of T_{η^0} from the first $n - 1$ rows. We proceed by defining δ as:

$$\delta = \begin{pmatrix} \delta_1 \\ \vdots \\ \delta_n \end{pmatrix} \quad (19)$$

Then, the first $n - 1$ entries of δ are given recursively as follows (we introduce δ_0 for the sake of the recurrence):

$$\delta_0 = 0 \quad (20)$$

$$\delta_1 = \delta_1 \quad (21)$$

$$\delta_k = \frac{-(2\lambda + \epsilon)}{\lambda} \delta_{k-1} - \delta_{k-2} \text{ for } 2 \leq k \leq n - 1 \quad (22)$$

$$\delta_n = \frac{-(\lambda(m+2) + \epsilon)}{\lambda(m+1)} \delta_{n-1} - \frac{1}{m+1} \delta_{n-2} \quad (23)$$

Again, using standard techniques for analyzing recurrence, we can find the generating function for any of the first $n - 1$ entries of δ .

$$\delta_k = \delta_1 \lambda \cdot \frac{(\sqrt{4\lambda\epsilon + \epsilon^2} - (2\lambda + \epsilon))^k - (-\sqrt{4\lambda\epsilon + \epsilon^2} - (2\lambda + \epsilon))^k}{2^k \lambda^k \sqrt{4\lambda\epsilon + \epsilon^2}} \quad (24)$$

The final step is to use δ to define all internal and outflow rate constants,

$$r_{y_i \rightarrow y'_i} = \frac{\langle y_i, \delta \rangle}{e^{\langle y_i, \delta \rangle} - 1} \quad \forall y_i \rightarrow y'_i \in \mathcal{R}_O \cup \mathcal{R}_I \quad (25)$$

and concentrations,

$$\mathbf{x}^* = (1, 1, \dots, 1) \quad (26)$$

$$\mathbf{x}^\# = (e^{\delta_1}, e^{\delta_2}, \dots, e^{\delta_{|S|}}). \quad (27)$$

Now that all other rates and concentrations have been determined, the inflow rates for each species can be solved from that species' ODE. This is easily doable, because each inflow rate only appears once in each ODE.

Note: As a method of double-checking if this process was done correctly, one can check that the inflow rates are all positive.

Theorem 1. *For all m, n , let δ be defined as in (18)-(24). Then, for the reaction system defined by the fully open sequestration network $\tilde{K}_{m,n}$ and for the rate constants r_i defined as follows,*

$$r_i = \frac{\langle y_i, \delta \rangle}{e^{\langle y_i, \delta \rangle} - 1} \eta_i^0 \quad \forall i \in \{1, 2, \dots, 2n\} \quad (28)$$

$$r_{2n+1} = r_1 + r_n + r_{n+1} \quad (29)$$

$$r_{2n+i} = r_{i-1} + r_i + r_{n+i} \quad \forall 2 \leq i \leq n-1 \quad (30)$$

$$r_{3n} = r_{n-1} + r_{2n} - mr_n \quad (31)$$

the concentrations,

$$\mathbf{x}^* = (1, 1, \dots, 1) \quad (32)$$

$$\mathbf{x}^\# = (e^{\delta_1}, e^{\delta_2}, \dots, e^{\delta_n}). \quad (33)$$

are both positive steady state vectors.

By the proof outlined in [2], these will always satisfy the equation ,

$$\Gamma \cdot R(\mathbf{x}^*) = \Gamma \cdot R(\mathbf{x}^\#) = \mathbf{0}.$$

The main contribution of this theorem is generating the closed form of reaction constants and concentrations for the system $\tilde{K}_{m,n}$.

3.1 An example of Degeneracy using Determinant Optimization Method

One may wonder whether or not the determinant optimization method has the potential to create degenerate steady state equilibria. The answer is yes.

If we study $\tilde{K}_{2,3}$ then one may arrive at values of $\lambda = 1$ and $\epsilon = 0.124296$ using

determinant optimization method. These values create a vector η^- satisfying the hypothesis of Theorem 4.1 of [2], thus showing that this system has the potential for steady state equilibria with these values of λ and ϵ . Following the steps before, one can find that the concentration given by (32) is degenerate. This result was discovered by fixing $\lambda = 1$ and allowing δ and all rates r to be functions of both m and ϵ . As ϵ varied, several roots were found. $m = 2$ was the smallest case of degeneracy.

4 The $\tilde{K}_{m,3}$ case

Here we discuss the case when we fix $n = 3$ and let m be any integer ≥ 3 . Here we will be following the recipe outlined in [2] to find our rate constants $r \in \mathbb{R}_+^{2n}$ and steady state concentrations $\mathbf{x}^*, \mathbf{x}^\#$. We then prove nondegeneracy of $\mathbf{x}^*, \mathbf{x}^\#$ by showing the image of the Jacobian matrix is equal to the image of Γ for both steady states. As stated earlier, since Γ is full rank, the problem reduces to showing $\det(df(\mathbf{x})) \neq 0$ for integer values of m . The Jacobian matrix when $n = 3$ is given by,

$$df = \begin{bmatrix} r_1x_2 + r_n + r_{n+1} & r_1x_1 & 0 \\ r_1x_2 & r_1x_1 + r_2x_3 + r_5 & r_2x_2 \\ -mr_n & r_2x_3 & r_2x_3 - r_6 \end{bmatrix}. \quad (34)$$

We begin solving for our rates and concentrations using the method outlined in section 3. First, we create a vector $\eta^- \in \mathbb{R}_+^{2n}$ such that $\sum_{i=1}^{2n} \eta_i^-(y_i - y'_i) \in \mathbb{R}_+^{2n}$. As mentioned in [4], we simply let $\eta^- = (\lambda, \lambda(m+1), \lambda, \epsilon, \epsilon, \epsilon)$.

Graphical tests have shown for this case, $\lambda = 1, \epsilon = 0.1$ work sufficiently well. By Theorem 4.1 in [2] we know we can now solve for an η^0 such that the determinant of

$$T_\eta = \begin{bmatrix} \eta_1 + \eta_3 + \eta_4 & \eta_1 & 0 \\ \eta_1 & \eta_1 + \eta_2 + \eta_5 & \eta_2 \\ -m\eta_3 & \eta_2 & \eta_2 + \eta_6 \end{bmatrix} \quad (35)$$

is zero. One can simply let $\eta_1^0, \dots, \eta_5^0$ stay the same as η^- and solve for η_6 . Substituting and solving for η_6 we have:

$$\eta_6 = \frac{m^2 - 0.31m - 1.31}{2.1m + 3.41} \quad (36)$$

when $\lambda = 1$ and $\epsilon = 0.1$. Solving for the nullspace vector δ , we let $\delta_1 = 1$ and solve for the rest:

$$\delta = \begin{pmatrix} 1 \\ -2.1 \\ \frac{2.1m+3.41}{m+1} \end{pmatrix} \quad (37)$$

Armed with our delta vector, we use (28) and (1) to get our inflow/outflow rates and concentrations:

$$\begin{aligned} r_1 &= \frac{-1.1}{e^{-1.1}-1} \approx 1.65 & r_2 &= \frac{1.31}{\frac{1.31}{e^{m+1}}-1} & r_3 &= \frac{1}{e-1} \approx .58 \\ r_4 &= \frac{.1}{e-1} \approx .06 & r_5 &= \frac{-2.1}{e^{-2.1}-1} \approx .24 & r_6 &= \frac{m-1.31}{\frac{2.1m+3.41}{e^{\frac{m+1}{m+1}}}-1} \end{aligned} \quad (38)$$

$$\begin{aligned} \mathbf{x}^* &= (1, 1, 1) \\ \mathbf{x}^\# &= (e, e^{-2.1}, e^{\frac{2.1m+3.41}{m+1}}). \end{aligned} \quad (39)$$

Note that only $\mathbf{x}_3^\#$, r_2 and r_6 depend on m . Taking the Jacobian for both of our steady state solutions, we have

$$\det(f(\mathbf{x}^*)) = r_2 r_1 r_3 m - (r_2 + r_6)(r_1 r_3 + r_1 r_4 + r_1 r_5 + r_3 r_5 + r_4 r_5) - r_2 r_6 (r_1 + r_3 + r_4) \quad (40)$$

$$\det(f(\mathbf{x}^\#)) = r_2 x_2 ((r_1 x_2 + r_3 + r_4)(r_2 x_3) + r_1 x_1 m r_3) - (r_2 x_2 + r_6)(r_1 x_2 + r_3 + r_4)(r_1 x_1 + r_2 x_3 + r_5) + (r_2 x_2 + r_6)(r_1 x_1 r_1 x_2) \quad (41)$$

From this point on we make use of a slight abuse of notation, defining $x_i = \mathbf{x}_i^\#$, since $\mathbf{x}_1^* = 1$.

4.1 Proving non-degeneracy of steady states for the network $\tilde{K}_{m,3}$

The graph of the Jacobian at x^* (40), suggests that it increases quadratically as a function of m . In order to prove this is nonzero for integer values of $m \geq 2$, we will bound (40) below with a quadratic function. This bound is obtained by relying on a series of inequalities. Similarly, the determinant of the Jacobian at $x^\#$, (41), appears to be decreasing quadratically, so we will bound (41) above with another quadratic function. Using these bounds, we then conclude that (40) and (41) are strictly positive and negative (respectively) after certain cutoff points of m , effectively showing non-degeneracy of both steady states beyond the cutoffs. Afterwards, we offer numerical evidence to show (40) and (41) are nonzero for integer values of m between the 2 and the cutoff points. We begin by presenting our series of inequalities.

Remark (Bounds on $\mathbf{x}_3^\#(m) = x_3(m)$)

It can easily be shown that $e^{\frac{2.1m+3.41}{m+1}}$ is a decreasing function for positive m , and its lower bound is $e^{2.1}$. Its upper bound will be conveniently chosen for some value y which yields the best bound on our Jacobian.

$$e^{\frac{2.1y+3.41}{y+1}} \geq x_3 = e^{\frac{2.1m+3.41}{m+1}} > e^{2.1} \quad \forall m \geq y \quad (42)$$

The proofs of the following Lemmas 1 and 2 are reserved for the Appendix A.

Lemma 1 (Bounds on r_2). *When $\lambda = 1, \epsilon = 0.1$, the function $r_2(m)$ is bounded by,*

$$m + 1 > r_2 \geq m \quad \forall m \geq 2.$$

Lemma 2 (Bounds on $r_6(m)$). *When $\lambda = 1, \epsilon = 0.1$, the function $r_2(m)$ is bounded by,*

$$0.14m > r_6 > 0.13m - 0.5$$

where the upper bound holds for $m \geq 2$, and the lower bound holds for $m \geq 20$

We should note that the inflow rates of the species are always positive. Note that by construction

$$\begin{aligned} r_7 &= r_1 + r_3 + r_4 > 0 \\ r_8 &= r_1 + r_2 + r_5 > 0 \end{aligned}$$

We provide a proof to show $r_9 > 0$

Proof.

$$\begin{aligned} r_9 &= r_2 + r_6 - mr_3 \\ &= \frac{1.31}{e^{\frac{1.31}{m+1}} - 1} + \frac{m - 1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1} - \frac{m}{e - 1} \\ &> \frac{1.31}{e^{\frac{1.31}{m+1}} - 1} - \frac{m}{e - 1} \end{aligned}$$

Then, by Lemma 1, we have

$$\frac{1.31}{e^{\frac{1.31}{m+1}} - 1} - \frac{m}{e - 1} > m - \frac{m}{e - 1} > 0$$

□

It follows that all rates and concentrations for the case $n = 3$ are positive. We summarize this section's results in the following theorem.

Theorem 2 (Non-degeneracy of steady states for $\tilde{K}_{m,3}$). *If one uses the determinant optimization method with $\lambda = 1$ and $\epsilon = 0.1$, the system $\tilde{K}_{m,3}$ has the capacity to admit multiple non-degenerate steady state equilibria.*

Proof. We generate our rates and concentrations as in Theorem 2. By using our bound on $x_3(m)$, namely (42) along with Lemmas 1 and 2, we can bound $\det(df(\mathbf{x}^*))$ as in (40) from below by underestimating positive terms and overestimating negative terms. Our bound is given by,

$$\begin{aligned} \det(df(\mathbf{x}^*)) &> m^2 r_1 r_3 - \\ &\quad ((m+1) + 0.14m)(r_1 r_3 + r_1 r_4 + r_1 r_5 + r_3 r_5 + r_4 r_5) - \\ &\quad (x+1)(0.14x)(r_1 + r_3 + r_4). \end{aligned} \quad (43)$$

Noting that all other terms are constants, we see

$$\begin{aligned} \det(df(\mathbf{x}^*)) &> m^2(0.95) - ((m+1) + 0.14m)1.61 - (x+1)(0.14x)2.29. \quad (44) \\ &> 0.6294m^2 - 2.156m - 1.61 \quad (45) \end{aligned}$$

It is easy to show that the righthand side of (45) is always positive for integers $m > 4$. Since (40) is always greater than this positive quadratic function, it is nonzero for all $m > 4$. Hence, \mathbf{x}^* is a non-degenerate steady-state for all integer values of $m > 4$. In Table 1 we will see how $\det(df(\mathbf{x}^*)) \neq 0$ for $2 \leq m \leq 4$.

Now we proceed to give a bound for $\det(df(\mathbf{x}^\#))$. Recall from (41) that

$$\begin{aligned} \det(df(\mathbf{x}^\#)) &= r_2 x_2 ((r_1 x_2 + r_3 + r_4)(r_2 x_3) + r_1 x_1 m r_3) - \\ &\quad (r_2 x_2 + r_6)(r_1 x_2 + r_3 + r_4)(r_1 x_1 + r_2 x_3 + r_5) + \\ &\quad (r_2 x_2 + r_6)(r_1 x_1 r_1 x_2). \end{aligned}$$

This time we bound the determinant from above by using Lemmas 1, 2 along with our bound on x_3 as in (42). In order to bound from above, we overestimate positive terms of the determinant and we underestimate negative terms. Our bound is given by,

$$\det(df(x^\#)) < (m+1)x_2((r_1x_2 + r_3 + r_4)((m+1)x_3) + r_1x_1mr_3) - \\ (mx_2 + (.13m - .5))(r_1x_2 + r_3 + r_4)(r_1x_1 + mx_3 + r_5) + \\ ((m+1)x_2 + .14m)(r_1x_1r_1x_2).$$

Note that since we used the lower bound of r_6 , we will need to numerically check all values of the second determinant (41) for $2 \leq m \leq 20$.

In the same manner as the other case, we approximate all of the constants to get

$$\det(df(x^\#)) < (m+1).13(.85)((m+1)8.7) + 2.61m) - \\ (.25m - .5)(.84)(4.72 + 8.16m) + \\ (.13(m+1) + .14m)(.91).$$

Finally, by simplifying the previous result we get,

$$\det(df(x^\#)) < -0.41295m^2 + 4.9437m + 3.06205. \quad (46)$$

It's easy to show that (46) is not zero for $m > 20$. For $2 \leq m \leq 20$ we refer to the table below (Table 1). This proves that $\det(df(x^\#)) \neq 0$ for all $m \geq 2$.

m	2	3	4	5	6	7	8	9	10	
$\det(df(x^\#))$	-1.063	-3.811	-7.85	-13.19	-19.8	-27.71	-36.89	-47.36	-59.11	
$\det(df(x^*))$	0.336	2.784	6.525							
m	11	12	13	14	15	16	17	18	19	20
$\det(df(x^\#))$	-72.14	-86.4	-102	-118.9	-137.1	-156.5	-177.2	-199.2	-222.5	-247.1

Table 1: Values of the determinants of the Jacobian matrices at all values of m before the proven bounds. No values are zero, thus these steady states are non-degenerate for every $m \geq 2$.

Using the bounds (45), (46), and Table 1, we have effectively shown that $\tilde{K}_{m,3}$ has the potential for multiple *non-degenerate* steady state equilibria for all integer values $m \geq 2$. \square

5 Nondegeneracy of $\tilde{K}_{m,n}$ for small values

Using our process for generating rates, from Theorem 1, we have shown the determinant of the Jacobian matrix is nonzero for integers $m \in [2, 5]$ and odd integers n between 3 and 11. Thanks to Theorem 4.5 from [4], if these small reactions are embedded subnetworks of a given chemical reaction network, then under certain hypotheses the network has also the potential to admit multiple *nondegenerate* steady state equilibria. As mentioned in the introduction, bimolecular reactions are particularly interesting because they are very common in chemistry. The bimolecular reactions in $\tilde{K}_{m,n}$ are precisely the cases $\tilde{K}_{2,n}$, where the n^{th} reaction is $X_1 \rightarrow 2X_n$. In Table 2, determinants of the Jacobians are shown to be nonzero for both steady states in these bimolecular systems with small values of n . Graphical plots of these determinants for $m \leq 5$ are shown in Appendix B.

n	5	7	9	11
$\det(df(\mathbf{x}^\#))$	-1.16315	-0.609136	-0.275949	-0.11463
$\det(df(\mathbf{x}^*))$	1.9424	1.80639	1.5354	1.20022

Table 2: Displaying that bimolecular ($m = 2$) reactions for small n have the potential for multiple nondegenerate equilibria, where x^* is the 1s concentration defined in (32) and $x^\#$ defined in (33). The values were determined using $\delta_1 = 1$, $\lambda = 1$, and $\epsilon = 0.001$ which satisfies all necessary hypotheses.

6 Discussion

As stated in the introduction, showing that a network is multistationary is not easy in the general case. And even when we can characterize a chemical reaction network as multistationary, there is no general technique to show that it will admit multiple *non-degenerate* steady states. In this paper we were able to analyze two of steady points of the chemical reaction network $\tilde{K}_{m,n}$ after finding a closed form for them. And although the general case of the conjecture remains unsolved, we believe that our technique is a step forward towards finally solving it. With this in mind, here are some final thoughts

Some future directions towards solving the conjecture are:

1. make use of the closed formulas given in this paper to analyze the general case
2. perhaps an easier step is to fix m and work with general n .

Looking at another direction it might be also useful to:

1. find an alternate method to get closed forms for the steady states of a chemical reaction network
2. find different criteria to characterize steady states as non degenerate

We conclude by saying that the ultimate goal is to find a more general technique to characterize steady state points of a chemical reaction network as non degenerate. And to this end, we are in the need of more criteria to be developed.

Appendix

Here we give the proofs of Lemma 1 and 2

Lemma 1 (Bounds on r_2). *When $\lambda = 1$, and $\epsilon = 0.1$, the function $r_2(m)$ is bounded by,*

$$m + 1 > r_2(m) = \frac{1.31}{e^{\frac{1.31}{m+1}} - 1} \geq m \quad \forall m \geq 2.$$

Proof. Recall $r_2 = \frac{1.31}{e^{\frac{1.31}{m+1}} - 1}$. The upper bound is given by first observing that

$$\log \left(\left(1 + \frac{1.31}{m+1} \right)^{m+1} \right) < \log(e^{1.31}) \leq 1.31 \quad \forall m \geq 0$$

since $\lim_{x \rightarrow \infty} (1 + \frac{y}{x})^x$ converges to e^y from below for positive values of y . Then we see

$$\begin{aligned} 1.31 &> \log \left(\left(1 + \frac{1.31}{m+1} \right)^{m+1} \right) \\ &> \log \left(\left(\frac{m+2.31}{m+1} \right)^{m+1} \right), \end{aligned}$$

which implies

$$\begin{aligned} \frac{1.31}{m+1} &> \log \left(\frac{m+2.31}{m+1} \right) \\ \implies e^{\frac{1.31}{m+1}} &> \frac{m+2.31}{m+1} \\ \implies e^{\frac{1.31}{m+1}}(m+1) - (m+1) &> 1.31 \\ \implies m+1 &> \frac{1.31}{e^{\frac{1.31}{m+1}} - 1} = r_2(m) \quad \forall m \geq 2. \end{aligned}$$

Notice that our claim, $\frac{1.31}{e^{\frac{1.31}{m+1}} - 1} > m$, is equivalent to the statement,

$$\frac{m+1.31}{m} > e^{\frac{1.31}{m+1}}.$$

We make use of the change of variables, $z = \frac{1}{m}$, $a = 1.31$. Note that, because of this change of variables, we only consider $0 < z \leq \frac{1}{2}$. Taking the log, we see our claim is also equivalent to,

$$\log(1+az) > \frac{a}{z^{-1}+1} = \frac{az}{1+z}.$$

We will show that $\log(1+az) - \frac{az}{1+z} \geq 0$. Next, define b such that $1-b = a-1$. Notice, $1 > b > \frac{1}{2} > (a-1)$. Next, notice that

$$\log(1+az) - \frac{az}{1+z} = \int_0^{az} \left(\frac{1}{1+t} - \frac{1}{1+z} \right) dt$$

$$\int_0^{az} \left(\frac{1}{1+t} - \frac{1}{1+z} \right) dt = \int_0^{bz} \frac{z-t}{(1+z)(1+t)} dt + \int_{bz}^z \left(\frac{1}{1+t} - \frac{1}{1+z} \right) dt + \int_z^{az} \frac{z-t}{(1+z)(1+t)} dt$$

Then the second integral is bounded below by 0, and other integrals are bounded by

$$\int_0^{bz} \frac{z-t}{(1+z)(1+t)} dt \geq \frac{(1-b)z^2b}{(z+1)^2}$$

and

$$\int_z^{az} \frac{z-t}{(1+z)(1+t)} dt \geq \frac{-(a-1)^2z^2}{(z+1)^2}.$$

Recalling that $(1-b) = (a-1)$ and $b \geq (a-1)$, we see $\frac{(1-b)z^2b}{(z+1)^2}$ outweighs $\frac{-(a-1)^2z^2}{(z+1)^2}$, thus we have

$$\log(1+az) - \frac{az}{1+z} = \int_0^{az} \left(\frac{1}{1+t} - \frac{1}{1+z} \right) dt \geq 0$$

□

Lemma 2(Bounds on $r_6(m)$) *When $\lambda = 1$, and $\epsilon = 0.1$, the function $r_6(m)$ is bounded by,*

$$0.14m > r_6(m) = \frac{m - 1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1} > 0.13m - 0.5$$

where the upper bound holds for $m \geq 2$, and the lower bound holds for $m \geq 20$

Proof. Recall $r_6 = \frac{m-1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1}$. We first show the proof of the upper bound.

Notice by (42), $(e^{\frac{2.1m+3.41}{m+1}} - 1) > 0$ for $m \geq 2$. Thus we can see that

$$\frac{m - 1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1} < 0.14m$$

is equivalent to the statement,

$$-1.31 < m(0.14e^{\frac{2.1m+3.41}{m+1}} - 1.14),$$

which is true whenever $(0.14e^{\frac{2.1m+3.41}{m+1}} - 1.14) > 0$. Since log is an increasing function, we can algebraically manipulate the expression $0.14e^{\frac{2.1m+3.41}{m+1}} > 1.14$ to see

$$2.1m + 3.41 > (m + 1) \log\left(\frac{1.14}{0.14}\right) > 2.09(m + 1).$$

which is true for all m satisfying $.01m > -1.32 \implies m \geq -132$. So this inequality is true for all $m \geq 2$.

Next, we will show $r_6 = \frac{m-1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1} \geq 0.13m - 0.5$ for $m \geq 20$. By clearing the denominator and gathering exponential terms on the righthand side, we see that the above equation is equivalent to the claim,

$$1.13m - 1.81 \geq e^{\frac{2.1m+3.41}{m+1}} (0.13m - 0.5).$$

Since $e^{\frac{2.1m+3.41}{m+1}}$ is a decreasing function for positive values of m , we see that

$$1.13m - 1.81 \geq 8.692(0.13m - 0.5) > e^{\frac{2.1(20)+3.41}{(20)+1}} (0.13m - 0.5) \geq e^{\frac{2.1m+3.41}{m+1}} (0.13m - 0.5).$$

holds for $m \geq 20$. However, the leftmost inequality is equivalent to the statement, $.00004m \geq -2.536$, which is true. \square

Appendix B

Here we present the graphs of the determinant of the Jacobian evaluated at the steady states x^* and $x^\#$ of $K_{m,n}$ for $n \leq 11$ as functions of m . The steady states (x^* and $x^\#$) are obtained using the method described in Section 3.

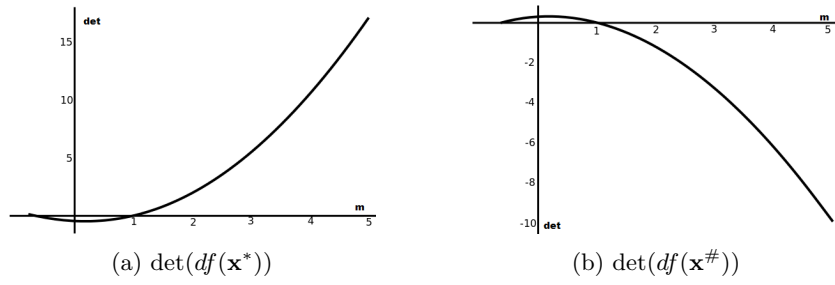


Figure 1: $\tilde{K}_{m,5}$

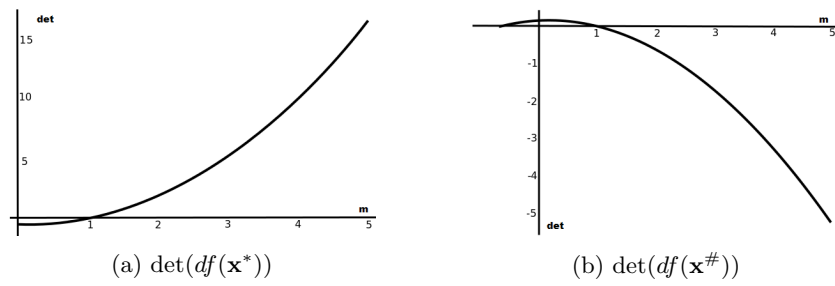


Figure 2: $\tilde{K}_{m,7}$

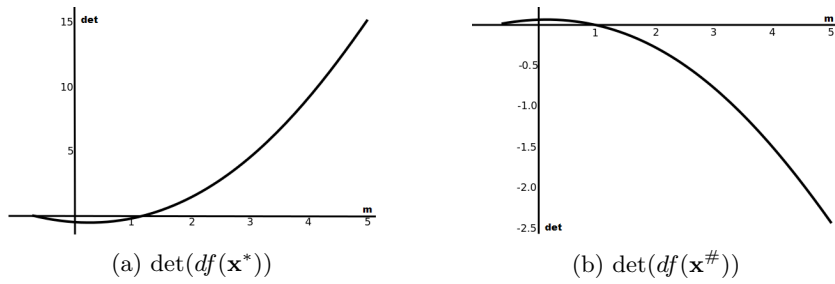


Figure 3: $\tilde{K}_{m,9}$

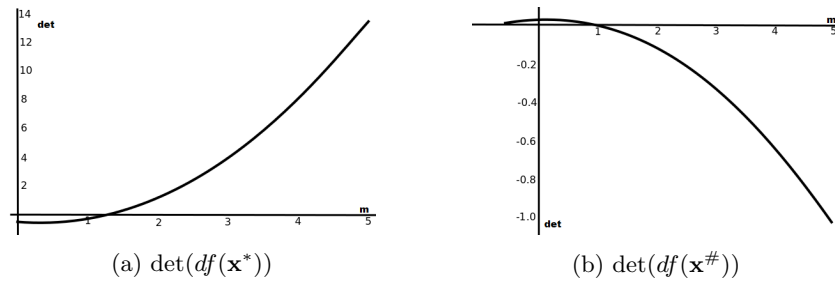


Figure 4: $\tilde{K}_{m,11}$

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