Comparisons of Ramp Functions and Michaelis-Menten Functions in Biochemical Dynamical Systems

by

Skye Dore-Hall
MSc, University of Victoria, 2021
BSc (Honours), Kwantlen Polytechnic University, 2018

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Supervisory Committee

Dr. Roderick Edwards, Supervisor
Department of Mathematics and Statistics

Dr. Junling Ma, Departmental Member
Department of Mathematics and Statistics

Dr. Stephanie Willerth, Outside Member
Department of Mechanical Engineering

Abstract

Analysis of nonlinear dynamical systems, such as those modeled using Michaelis-Menten kinetics, can be difficult. Thus, it is natural to consider whether such systems can be simplified in a way that facilitates analysis while preserving qualitative behaviour. Previously, we showed that when the Michaelis-Menten terms in a model of plant metabolism are replaced by piecewise linear approximations called *ramp functions*, the qualitative behaviour of the model is maintained. We then defined a limited class of systems containing ramp functions called *biochemical ramp systems* and studied their properties, including the existence and stability of equilibria and global flow.

Here, we expand on our previous work by reforming the definition of a biochemical ramp system to describe a wider class of systems. We study the properties of several types of biochemical ramp systems that were previously not covered by the definition, and show that their qualitative behaviour is similar to that of their Michaelis-Menten counterparts. We then introduce concepts from chemical reaction network theory, such as the Deficiency Zero and Deficiency One Theorems, and explain how they are applicable to the analysis of biochemical ramp functions, but cannot be applied to the corresponding Michaelis-Menten systems. In the last chapter, we show that when ramp functions are used in systems that do not fall under the expanded definition of a biochemical ramp system, there can be qualitative differences in behaviour between these ramp systems and their Michaelis-Menten counterparts. We end with a look at periodic behaviour in ramp systems by studying a version of the Lotka-Volterra predator-prey model containing ramp functions.

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Dedicated to my parents and sister

In loving memory of my grandparents:
Barbara $\sim$ Walter $\sim$ Frances $\sim$ Peter

Introduction

An enzymatic reaction, in which a substrate is converted into a product with the aid of an enzyme catalyst, is commonly modeled using *Michaelis-Menten* kinetics. Under this model of enzyme kinetics, pioneered by Leonor Michaelis and Maud Menten with their 1913 paper [15], the rate at which the substrate is converted into the product is given by

$$\frac{Vs}{\theta + s},$$

where s is the substrate concentration and V and θ are positive constants; specifically, V represents the maximum reaction rate while θ is the substrate concentration at which half of this maximum is achieved [16].

An example of a Michaelis-Menten system is the model of phenylalanine metabolism in plants developed by Adams, Ehlting, and Edwards in [1]. Two versions of the model, which we will refer to as the *Adams model*, were considered: one that included the *Shikimate Ester Loop* (SEL), a series of several reactions, and one that did not include the SEL. Without the SEL, the Adams model is described by the system of three equations

$$\begin{aligned} \dot{x}_1 &= a_0 - \frac{a_1 x_1}{K_1 + x_1} \\ \dot{x}_2 &= \frac{a_1 x_1}{K_1 + x_1} - \frac{a_3 x_2}{K_3^2 + x_2} - \frac{a_5 x_2}{K_5 + x_2} \\ \dot{x}_3 &= \frac{a_3 x_2}{K_3^2 + x_2} - \frac{a_4 x_3}{K_4 + x_3}, \end{aligned} \tag{1}$$

where $a_0 \geq 0$ is the rate at which shikimate, a phenylalanine precursor, is synthesized by the plant, and x_1, x_2, and x_3 represent the concentrations of plastidial shikimate, phenylalanine, and caffeoyl-shikimate respectively. As mentioned above, the parameters in the Michaelis-Menten terms are positive.

The Adams model with the SEL contains four variables in [1]; however, below we present a three-variable version of the model studied in [5, 6] that we will reference throughout this work:

$$\begin{aligned} \dot{y} &= a_0 - \frac{a_1 y}{K_1 + y} - \frac{a_3 x_2 y}{(K_3^2 + x_2)(K_3^3 + y)} + \frac{a_4 x_3}{K_4 + x_3} \\ \dot{x}_2 &= \frac{a_1 y}{K_1 + y} - \frac{a_3 x_2 y}{(K_3^2 + x_2)(K_3^3 + y)} - \frac{a_5 x_2}{K_5 + x_2} \\ \dot{x}_3 &= \frac{a_3 x_2 y}{(K_3^2 + x_2)(K_3^3 + y)} - \frac{a_4 x_3}{K_4 + x_3}. \end{aligned} \tag{2}$$

Here, y is the combined concentration of plastidial and cytosolic shikimate. Note that in the parameters K_3^2 and K_3^3, the superscripts are indices, not exponents.

Analysis of the Adams model in [1] focused on two mechanisms by which phenylalanine is prioritized for use in primary metabolism (protein synthesis) over use in the secondary

monolignol metabolic pathway in trees, which is involved in wood formation, when shikimate synthesis is low. The two mechanisms considered were the presence of the SEL and threshold separation, in which the threshold constant associated with the secondary metabolic pathway (K_3^2) is larger than that of the primary pathway (K_5), i.e. it is more difficult for phenylalanine to enter the secondary pathway.

Adams et al. showed that in the version of the model with the SEL, primary metabolism is always prioritized over secondary metabolism when shikimate availability is poor, regardless of threshold constants; thus, the SEL effects a form of metabolic regulation, which was named the *Precursor Shutoff Valve* (PSV) in [1]. In the model without the SEL, this prioritization of primary metabolism occurs only when the threshold constant associated with the secondary metabolic pathway is two orders of magnitude greater than that of the primary metabolic pathway.

Since Michaelis-Menten terms are non-linear, it can be difficult to analyze systems such as the Adams model. Hence, it is natural to consider whether Michaelis-Menten systems can be simplified to facilitate analysis. One approach is to replace the Michaelis-Menten terms with piecewise linear approximations, which was done by Edwards and Wood with the Adams model in [7]. There, the Michaelis-Menten terms were replaced with step functions. However, analysis revealed qualitative differences between the step function model and the original Michaelis-Menten model, in that the SEL does not effect PSV-type regulation on its own in the step function model; that is, there is no prioritization of primary metabolism in the step function model with the SEL when the threshold constant associated with the primary pathway is equal to that of the secondary pathway.

In [5, 6], the Michaelis-Menten terms in the Adams model were replaced by piecewise linear approximations called *ramp functions*. Such a function, which approximates a Michaelis-Menten function $M : [0, \infty) \to [0, 1)$ of the form

$$M(x) = \frac{x}{\theta + x},$$

is defined as follows:

Definition 0.0.1. [*Ramp Function*]
Let $\theta > 0$. Then, we define the ramp function $r : [0, \infty) \to [0, 1]$ by

$$r(x) = \begin{cases} \dfrac{x}{2\theta}, & 0 \leq x < 2\theta \\ 1, & x \geq 2\theta. \end{cases}$$

The piece of the ramp function defined by $r(x) = \dfrac{x}{2\theta}$ is called the *ramp region* while the $r(x) = 1$ piece is the *saturated region*. The constant 2θ, the x value at which the function switches from the ramp to the saturated region, is the *threshold* of the function. With this definition, the functions $M(x)$ and $r(x)$ have the following properties in common:

$$M(0) = r(0) = 0, \qquad M(\theta) = r(\theta) = 1/2, \qquad \lim_{x\to\infty} M(x) = \lim_{x\to\infty} r(x) = 1$$

A graph of $M(x)$ and $r(x)$ is shown in Figure 0.0.1 below.

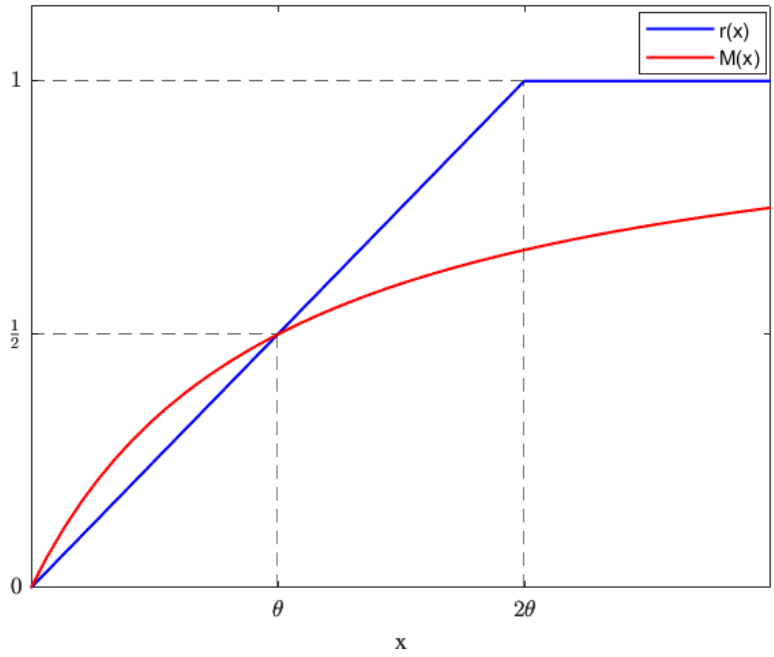


Figure 0.0.1: Graph of the Michaelis-Menten function $M(x)$ (red) and the ramp function $r(x)$ (blue) with key input and output values labeled.

Note that the above definition of ramp functions is not unique; other definitions of ramp functions, often including three or more pieces, have been used for piecewise approximations of various non-linear functions. For instance, see [17] for a definition of ramp functions that approximate sigmoid functions in gene networks and [23] for ramp functions used as activation functions in neural networks.

With Definition 0.0.1, in [5, 6] the Michaelis-Menten terms in systems (1) and (2) were replaced by the ramp functions

$$r_i(x) = \begin{cases} \dfrac{x}{2K_i}, & 0 \le x < 2K_i \\ 1, & x \ge 2K_i \end{cases}$$

$$r_3^j(x) = \begin{cases} \dfrac{x}{2K_3^j}, & 0 \le x < 2K_3^j \\ 1, & x \ge 2K_3^j \end{cases},$$

where $i = 1, 4, 5$ and $j = 2, 3$. Thus, system (1), the Adams model without the SEL, became the ramp system

$$\begin{aligned}
\dot{x}_1 &= a_0 - a_1 r_1(x_1) \\
\dot{x}_2 &= a_1 r_1(x_1) - a_3 r_3^2(x_2) - a_5 r_5(x_2) \\
\dot{x}_3 &= a_3 r_3^2(x_2) - a_4 r_4(x_3),
\end{aligned} \tag{3}$$

while system (2) with the SEL became

$$\begin{aligned}
\dot{y} &= a_0 - a_1 r_1(y) - a_3 r_3^2(x_2) r_3^3(y) + a_4 r_4(x_3) \\
\dot{x}_2 &= a_1 r_1(y) - a_3 r_3^2(x_2) r_3^3(y) - a_5 r_5(x_2) \\
\dot{x}_3 &= a_3 r_3^2(x_2) r_3^3(y) - a_4 r_4(x_3).
\end{aligned} \tag{4}$$

Analysis in [5, 6] showed that the Adams model with ramp functions behaves qualitatively the same as the original Michaelis-Menten model; that is, in system (4) with the SEL, primary metabolism is prioritized under low shikimate conditions regardless of threshold constants, but in system (3) without the SEL, this prioritization is seen only when the threshold constant of the secondary pathway is sufficiently large.

The shared qualitative behaviour of the Michaelis-Menten and ramp function versions of the Adams model suggests that ramp functions could be used to study the dynamics of other, more complex Michaelis-Menten systems, which would otherwise be difficult to analyze. Consequently, it is worth studying the properties of general systems with ramp functions. This was done in [5], where a class of ramp systems called *biochemical ramp systems* was studied.

Biochemical ramp systems were defined in [5] based on the fact that when every ramp function is in its ramp region — a situation referred to as being in the *all ramp region* — systems (3) and (4) are *mass action*. Much research has been done on mass action systems and their properties; see sources such as [9] for key results.

Under mass action kinetics, the rates at which the concentrations of chemicals species change over time are proportional to the concentration of the reactants. For instance, in

$$\begin{aligned}
\dot{y} &= a_0 - \frac{a_1}{2K_1} y - \frac{a_3}{4K_3^2 K_3^3} x_2 y + \frac{a_4}{2K_4} x_3 \\
\dot{x}_2 &= \frac{a_1}{2K_1} y - \frac{a_3}{4K_3^2 K_3^3} x_2 y - \frac{a_5}{2K_5} x_2 \\
\dot{x}_3 &= \frac{a_3}{4K_3^2 K_3^3} x_2 y - \frac{a_4}{2K_4} x_3,
\end{aligned} \tag{5}$$

which is system (4) when in the all ramp region, the $\pm\frac{a_1}{2K_1} y$ terms derive from a reaction of the form $Y \xrightarrow{k} X_2$, in which species Y, which has concentration y, is converted to species X_2 at rate $k > 0$; here, $k = a_1/2K_1$. Similarly, the $\pm\frac{a_4}{2K_4} x_3$ terms derive from the reaction $X_3 \xrightarrow{k} Y$ with $k = a_4/2K_4$.

The lone $-\dfrac{a_5}{2K_5}x_2$ term in the $\dot{x_2}$ equation in (5) comes from a reaction of the form $X_2 \xrightarrow{k} 0$; here, the *zero complex* 0 is not a chemical species, but rather is used to indicate pathways of inflow or outflow. Thus, the reaction $X_2 \xrightarrow{k} 0$ says that X_2 leaves the system at rate $k = a_5/2K_5$. Similarly, the a_0 (if strictly positive) in the $\dot{y}$ equation can be described by the reaction $0 \xrightarrow{a_0} Y$, in which Y enters the system at a constant rate.

Finally, the $\pm\dfrac{a_3}{4K_3^2K_3^3}x_2y$ terms in (5) derive from the reaction $X_2 + Y \xrightarrow{k} X_3$, in which both X_2 and Y react at rate $k = \dfrac{a_3}{4K_3^2K_3^3}$ to form X_3.

Reactions of the form $A \xrightarrow{k} B$, $A \xrightarrow{k} 0$, and $0 \xrightarrow{k} A$ are referred to as *single reactant and product* (SRP) reactions in [5], due to the presence of at most one species on each side of the reaction, and a system of differential equations derived from at least one such reaction is said to contain *SRP terms*. The reaction $A + B \xrightarrow{k} C$ is called a *combining* reaction and contributes a *combining term* to the corresponding set of differential equations.

Despite not appearing in the Adams model, reactions of the form $A \xrightarrow{k} B + C$, in which species A splits into two new species B and C, were also considered in [5]; these *dissociation* reactions produce *dissociation terms* in the associated system of differential equations. Note that in the reaction types described here, A, B, and C are assumed to be distinct species.

A system with ramp functions was defined in [5] as being a biochemical ramp system if, when in the all ramp region, it was a mass action system derived solely from reactions of the SRP, combining, and dissociation types. Analysis of these systems included determining eigenvalues of their Jacobian matrices; deriving necessary and sufficient conditions for the existence of equilibria; and establishing parameter conditions for unbounded flow in two-variable systems containing only SRP terms (*SRP systems*).

While [5] provided notable results for general biochemical ramp systems, the scope was rather limited. There are many reaction types outside the three mentioned above that were not considered. Additionally, most results only apply to systems in which each variable has exactly one associated ramp function. This means that in order to apply the results to a system like (3), in which both r_3^2 and r_5 are functions of x_2, the thresholds of the two ramp functions must be assumed to be equal, i.e $K_3^2 = K_5$.

Another limitation is that aside from the Adams model analysis, the qualitative behaviour of ramp systems was not compared to that of their Michaelis-Menten counterparts in [5]. Hence, it is not known whether replacing Michaelis-Menten functions with ramp functions will preserve system properties in general or only under certain circumstances.

Here, one of our main goals is to build on the work of [5] by expanding the existing theory to cover a wider variety of systems with ramp functions. We will consider systems with terms derived from reactions not of the SRP, combining, or dissociation types, and will study ramp functions in contexts not considered previously, such as in oscillatory systems and as compositions with other functions. We will begin building theory on systems in which a variable is associated with multiple ramp functions. Where possible, we will also

analyze the corresponding Michaelis-Menten systems in an effort to ascertain under which circumstances qualitative behaviour is preserved when switching to ramp functions.

Additionally, we will discuss an advantage of using ramp functions over Michaelis-Menten functions in dynamical systems: the ability to apply deficiency theorems. The most well-known deficiency result, the Deficiency Zero Theorem, which was developed in 1972 with the seminal papers [8, 11, 12] of Feinberg, Horn, and Jackson, provides conditions for the existence of an asymptotically stable positive equilibrium point in mass action systems; this theorem can thus be applied to ramp systems in the all ramp region, but not to their Michaelis-Menten counterparts. We will explain deficiency theory more in-depth near the end of this work.

This dissertation is structured as follows:

- **Chapter 1** provides results and definitions that will be useful throughout this work. In particular, we redefine the concept of a biochemical ramp system to include a wider range of systems. Key linear algebra results from [5] are provided, along with progress on several linear algebra conjectures proposed in [5].

- **Chapter 2** provides equilibria and stability results for biochemical ramp systems in which a variable can have more than one associated ramp function, with a focus on SRP systems and systems with one combining term. With this, we are able to fully characterize the existence of equilibria in systems (3) and (4), the Adams model without and with the SEL respectively, even when ramp functions of the same variable have unequal thresholds. Where possible, in this chapter we will also compare the qualitative behaviour of ramp systems to their Michaelis-Menten counterparts.

- **Chapter 3** analyzes biochemical ramp systems that, when in the all ramp region, are not derived solely from reactions of the SRP, combining, and dissociation types; specifically, we consider systems with terms derived from reactions of the form $X+Y \to Z+W$, $X+Y \to 2X$, and $mX \to Y$. Several results regarding the eigenvalues of the corresponding Jacobian matrices of these systems are provided. As in Chapter 2, we also compare the qualitative behaviour of the ramp systems to their Michaelis-Menten counterparts.

- **Chapter 4** formally introduces the concept of chemical reaction networks and their associated properties. In particular, we define the *deficiency* of a network and explain how the Deficiency Zero and Deficiency One Theorems can be applied to the analysis of biochemical ramp systems. We also provide results regarding the deficiency of a few classes of networks, focusing on characterizing when the addition of a new reaction will result in the network's deficiency changing.

- **Chapter 5** contains results that do not fit elsewhere in this work. We first consider the use of ramp functions in contexts other than biochemical ramp systems. Specifically, we examine systems with ramp functions composed with other functions, and *mixed*

systems in which variables can appear both as inputs of ramp functions and in non-ramp terms. We compare the behaviour of these systems to their Michaelis-Menten counterparts, and show that there can be differences in behaviour in certain circumstances. Finally, we consider the Lotka-Volterra model and show that closed orbits are still possible after replacing the mass action terms with ramp or Michaelis-Menten functions.

Chapter 1

Preliminaries

1.1 Useful Definitions and Theorems

We begin here by presenting some definitions and results that will be useful throughout this work.

1.1.1 Redefining Biochemical Ramp Systems

As mentioned in the Introduction, the definition of a biochemical ramp system in [5] was restricted to systems that, when in the all ramp region, were mass action systems derived from chemical reactions of the single reactant and product (SRP), combining, and dissociation types. Our first goal here is to expand this definition to include all systems that are mass action when in the all ramp region.

The differential equations of a mass action system will always be polynomials, but not every system of polynomials is a mass action system derived from a set of chemical reactions. To determine when a system of polynomial differential equations is mass action, we will use the *Hungarian Lemma* proven by Hárs and Tóth in [10], as stated in [4]:

Lemma 1.1.1. (*Hungarian Lemma*) Consider the n-variable system of differential equations

$$\begin{aligned} \dot{x_1} &= f_1(x_1, x_2, \dots x_n) \\ \dot{x_2} &= f_2(x_1, x_2, \dots x_n) \\ &\vdots \\ \dot{x_n} &= f_n(x_1, x_2, \dots x_n), \end{aligned} \tag{1.1}$$

where the f_i are polynomials. System (1.1) is mass action if and only if $\forall i$, whenever $\dot{x_i}$ contains a term with a negative coefficient, the degree of x_i in that term is positive.

The presence of a negative term in the equation corresponding to species X in a mass action system indicates the net loss of X as a result of a chemical reaction. Thus, Lemma 1.1.1 says that in order for a species to be lost, it must have been used as a reactant.

Below, we present our updated definition of a biochemical ramp system. Like in [5], our definition requires that variables only appear in ramp functions, and not on their own or as part of other functions. Additionally, the input of any ramp function in the system must be a single variable and not a combination of multiple variables or another function; thus, terms such as $r(x)r(y)$ and $[r(x)]^3$ are allowed, but terms such as $r(x^2)$, $r(\sin(x))$, and $r(x+y)$ are not. This latter assumption was implicitly assumed in [5] but not officially stated.

Definition 1.1.2. [*Biochemical Ramp System*]
Suppose that

$$\begin{aligned} \dot{x_1} &= f_1(x_1, x_2, \dots x_n) \\ \dot{x_2} &= f_2(x_1, x_2, \dots x_n) \\ &\vdots \\ \dot{x_n} &= f_n(x_1, x_2, \dots x_n), \end{aligned} \tag{1.2}$$

is an n-variable system of differential equations in which the f_i contain ramp functions. Then, (1.2) is a biochemical ramp system if and only if all of the following hold:

a.) $\forall i$ if x_i appears in one or more f_j, it always does so as the input of a ramp function

b.) If r is a ramp function appearing in some f_i, the input of r is x_j for some j.

c.) When in the all ramp region, system (1.2) is mass action in terms of Lemma 1.1.1

We end this section with examples of systems that do and do not satisfy Definition 1.1.2. In each system below, ramp function r_i has threshold $2\theta_i$.

Example 1.1.3. The system

$$\begin{aligned} \dot{x} &= -2r_1(x) - r_2(y) + r_3(x) \\ \dot{y} &= 2r_1(x) + 3 \end{aligned}$$

does not satisfy Definition 1.1.2. In the all ramp region, the system becomes

$$\begin{aligned} \dot{x} &= -\frac{x_1}{\theta_1} - \frac{y}{2\theta_2} + \frac{x}{2\theta_3} \\ \dot{y} &= \frac{x_1}{\theta_1} + 3, \end{aligned}$$

which does not satisfy Lemma 1.1.1 because the $\dot{x}$ equation contains the term $-\dfrac{y}{2\theta_2}$, which does not include the variable x.

Example 1.1.4. The system

$$\begin{aligned}\dot{x} &= -3r_1(x) + x^2y^7 + \cos(x)\\ \dot{y} &= 3r_1(x) - 5r_2(y)\\ \dot{z} &= r_3(2z^4)\end{aligned}$$

is not a biochemical ramp system as x and y appear outside ramp functions in the $x^2y^7 + \cos(x)$ term, and the input of r_3 is $2z^4$ and not just z.

Example 1.1.5. The system

$$\begin{aligned}\dot{x} &= -2[r_1(x)]^2 - r_2(x)r_3(y) + r_4(z)\\ \dot{y} &= -r_2(x)r_3(y) + r_4(z)\\ \dot{z} &= -r_4(z) + 1.5\end{aligned}$$

satisfies Definition 1.1.2 and is thus a biochemical ramp system. In the all ramp region, the equations are

$$\begin{aligned}\dot{x} &= -2\frac{x^2}{(2\theta_1)^2} - \frac{xy}{4\theta_2\theta_3} + \frac{z}{2\theta_4}\\ \dot{y} &= -\frac{xy}{4\theta_2\theta_3} + \frac{z}{2\theta_4}\\ \dot{z} &= -\frac{z}{2\theta_4} + 1.5,\end{aligned}$$

which derive from the reactions $2X \xrightarrow{k_1} 0$, $X + Y \xrightarrow{k_2} 0$, $Z \xrightarrow{k_3} X + Y$, and $0 \xrightarrow{1.5} Z$ with $k_1 = (2\theta_1)^{-2}$, $k_2 = (4\theta_1\theta_2)^{-1}$, and $k_3 = (2\theta_4)^{-1}$. Note that the extra 2 in front of the x^2 term in the $\dot{x}$ equation comes from the fact that the reaction $2X \to 0$ results in the loss of two molecules of species X.

1.1.2 SRP Matrices and Their Properties

In [5], the Jacobian matrix of a mass action system containing only SRP terms was called a *single reactant and product (SRP) matrix*. These matrices have a particular structure, based on the fact that the reaction $X_i \xrightarrow{k} X_j$ produces a $-k$ term in the ith diagonal entry in the Jacobian and a $+k$ in the jth entry of the same column, while the reaction $X_i \xrightarrow{k} 0$ only produces a $-k$ on the diagonal (the third SRP reaction type, $0 \xrightarrow{k} X$, does not contribute to the Jacobian as the derivative of a constant is zero). This structure is characterized in the following definition from [5]:

Definition 1.1.6. [*SRP Matrix*]
An $n \times n$ matrix of the form

$$\begin{bmatrix} -a_{11} & a_{12} & a_{13} & \dots & a_{1n} \\ a_{21} & -a_{22} & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}$$

is an SRP matrix if and only if

a.) $a_{ij} \geq 0 \quad \forall i, j, \quad$ and

b.) $\sum_{j \neq i} a_{ji} \leq a_{ii} \quad \forall i.$

The following theorem presents several useful properties of SRP matrices, which were proven in [5]:

Theorem 1.1.7. *Consider an $n \times n$ SRP matrix A as defined in Definition 1.1.6. If λ is an eigenvalue of A, then both of the following hold:*

a.) $\mathfrak{Re}(\lambda) \leq 0$

b.) $\mathfrak{Re}(\lambda) = 0 \implies \lambda = 0$

Denote the (i, j) cofactor of A by C_{ij}. If A is invertible, then we have the following:

c.) All entries of A^{-1} are non-positive

d.) If n is even, $det(A) > 0$ and $C_{ij} \leq 0 \quad \forall i, j$

e.) If n is odd, $det(A) < 0$ and $C_{ij} \geq 0 \quad \forall i, j$

The eigenvalue results in Theorem 1.1.7 follow from the *Gershgorin Circle Theorem* applied to columns (see, for instance, [21]). We state this theorem below for a general complex matrix.

Theorem 1.1.8. ***(Gershgorin).*** *Let $A = [a_{ij}] \in \mathbb{C}^{n \times n}$ be an $n \times n$ matrix with complex entries. Define the Gershgorin disk associated with the i-th column of A as*

$$D_i(A) \ = \ \{z \in \mathbb{C} : |z - a_{ii}| \ \leq \ \rho_i(A)\},$$

where

$$\rho_i(A) \ = \ \sum_{j \neq i} |a_{ji}|.$$

If λ is an eigenvalue of A, then

$$\lambda \in \bigcup_{i=1}^{n} D_i(A).$$

Thus, Gershgorin's theorem states that the eigenvalues of a matrix are located in disks on the complex plane, where each disk is centered at a diagonal entry of the matrix and has a radius equal to the sum of the absolute values of the off-diagonal entries from the same column. In the case of an SRP matrix, the two conditions given in Definition 1.1.6 ensure that the ith disk is centered at the non-positive real number $-a_{ii}$ and has a radius that cannot exceed a_{ii}; hence, each disk is restricted to the left side of the complex plane and can touch the imaginary axis only at the origin.

The preceding paragraph gives us the following result on the eigenvalues of real matrices with a column structure similar to that of SRP matrices:

Proposition 1.1.9. Let $A = [a_{ij}] \in \mathbb{R}^{n\times n}$ be an $n \times n$ real matrix. Suppose that $\forall i$, the ith column of A satisfies both of the following:

a.) $a_{ii} \leq 0$

b.) $\sum_{j\neq i} |a_{ji}| \leq |a_{ii}|$

Then if λ is an eigenvalue of A, $\mathfrak{Re}(\lambda) \leq 0$.

We will make use of Proposition 1.1.9 later in this chapter.

1.1.3 Matrices with One Combining Term

Another class of matrices covered in [5] was the Jacobian matrices of mass action systems derived from exactly one reaction of the form $X + Y \to Z$ and an arbitrary number of SRP reactions; these matrices are thus referred to as *matrices with one combining term*. It was assumed that, without loss of generality, the single combining reaction was of the form $X_1 + X_2 \to X_3$, in which the first two species in the system combine to form the third.

The reaction $X_1 + X_2 \xrightarrow{k} X_3$ gives rise to the mass action system

$$\begin{aligned} \dot{x_1} &= -kx_1x_2 \\ \dot{x_2} &= -kx_1x_2 \\ \dot{x_3} &= kx_1x_2, \end{aligned}$$

which has Jacobian

$$\begin{bmatrix} -kx_2^* & -kx_1^* & 0 \\ -kx_2^* & -kx_1^* & 0 \\ kx_2^* & kx_1^* & 0 \end{bmatrix} \tag{1.3}$$

when evaluated at an equilibrium point. Like in [5], here we will assume that x_1^* and x_2^* are positive equilibrium values, making the terms kx_1^* and kx_2^* strictly positive. As a result, we formally define a matrix with one combining term as follows:

Definition 1.1.10. [*Matrix with One Combining Term*]
Let A' be an $n \times n$ matrix for $n \geq 3$. Then, A' is a matrix with one combining term if and only if it can be written in the form

$$A' = A + M,$$

where A is an SRP matrix and

$$M = \begin{bmatrix} -c & -d & 0 & 0 & \dots & 0 \\ -c & -d & 0 & 0 & \dots & 0 \\ c & d & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 \end{bmatrix},$$

with c and d both positive.

Hence, a matrix with one combining term is any matrix that can be written as the sum of an SRP matrix and an $n \times n$ matrix whose upper 3×2 block resembles the first two columns of (1.3) and has zeros in all other entries. A few results regarding the properties of matrices with one combining term were proven in [5], which we present in the theorem below.

Theorem 1.1.11. *Let $A' = A + M$ be a matrix with one combining term as described in Definition 1.1.10 with eigenvalue λ. Then we have the following:*

a.) If A is invertible, then so is A'

b.) If $\lambda \in \mathbb{R}$, then $\lambda \leq 0$

c.) If A' is 3×3, then $\mathfrak{Re}(\lambda) \leq 0$.

1.2 Progress on Linear Algebra Conjectures

Three linear algebra conjectures were posed in [5] regarding the properties of the Jacobian matrices of mass action systems with SRP, combining, and dissociation terms. This section is dedicated to providing results on these conjectures, starting with one that we will prove in full.

1.2.1 Eigenvectors of Singular SRP Matrices

Conjecture 3 in [5] hypothesized that singular SRP matrices have a non-negative eigenvector corresponding to the eigenvalue 0. We prove this conjecture in the proposition below. Note that a similar result for related classes of matrices, such as singular, irreducible M-matrices, is already known; see, for instance, [2].

Proposition 1.2.1. Let

$$A = \begin{bmatrix} -a_{11} & a_{12} & a_{13} & \dots & a_{1n} \\ a_{21} & -a_{22} & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}$$

be an $n \times n$ singular SRP matrix. Then, A has an eigenvector

$$v = \begin{bmatrix} v_1 & v_2 & \dots & v_n \end{bmatrix}^T$$

corresponding to the eigenvalue $\lambda = 0$ such that $v \geq 0$ componentwise.

Proof. Suppose that v has a mix of positive and negative components; WLOG suppose the first k components $v_1, v_2, \dots, v_k$ are negative and $v_{k+1}, \dots, v_n$ are non-negative with at least one strictly positive. We will show that in this case, A will have a structure such that we can change the signs of the first k components of v and still have an eigenvector corresponding to 0.

The first k equations of $Av = 0$ are

$$\begin{aligned} -a_{11}v_1 + a_{12}v_2 + \cdots + a_{1k}v_k + a_{1k+1}v_{k+1} + \cdots + a_{1n}v_n &= 0 \\ a_{21}v_1 - a_{22}v_2 + \cdots + a_{2k}v_k + a_{2k+1}v_{k+1} + \cdots + a_{2n}v_n &= 0 \\ &\vdots \\ a_{k1}v_1 + a_{k2}v_2 + \cdots - a_{kk}v_k + a_{kk+1}v_{k+1} + \cdots + a_{kn}v_n &= 0. \end{aligned} \tag{1.4}$$

Adding these equations, we get

$$\sum_{j=1}^{n}\left(\Big(\sum_{i=1}^{k} a_{ij}\Big)v_j\right) \;=\; 0 \tag{1.5}$$

where, for $j \leq k$,

$$\sum_{i=1}^{k} a_{ij} \;=\; a_{1j} + \cdots + a_{j-1j} - a_{jj} + a_{j+1j} + \cdots + a_{kj}.$$

The left hand side of (1.5) is the sum of n terms of the form $\Big(\sum_{i=1}^{k} a_{ij}\Big)v_j$, which are all non-negative:

- For $j \leq k$, the sum $\sum_{i=1}^{k} a_{ij}$ includes the diagonal entry of the jth column, and is thus non-positive by Definition 1.1.6. Then, we know $v_j < 0$ by assumption, and thus $\Big(\sum_{i=1}^{k} a_{ij}\Big)v_j \geq 0$.

- For $j > k$, the sum $\sum_{i=1}^{k} a_{ij}$ does not include the diagonal entry of the jth column, and is thus non-negative. The value v_j is also assumed to be non-negative in this case, and hence $\Big(\sum_{i=1}^{k} a_{ij}\Big)v_j \geq 0$.

Thus, in order for equation (1.5) to hold, each $\Big(\sum_{i=1}^{k} a_{ij}\Big)v_j$ term must equal zero. For $j \leq k$, this implies that $\sum_{i=1}^{k} a_{ij} = 0$ because $v_j < 0$. This then implies that the lower lower left $(n-k) \times k$ submatrix of A,

$$\begin{bmatrix} a_{k+11} & a_{k+12} & \dots & a_{k+1k} \\ a_{k+21} & a_{k+22} & \dots & a_{k+2k} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & a_{nk} \end{bmatrix},$$

must be the zero matrix; if at least one entry was positive, then the corresponding column sum in A would be positive, contradicting Definition 1.1.6. Then, the final $n-k$ equations of $Av = 0$ do not depend on $v_1, \dots, v_k$:

$$\begin{aligned} -a_{k+1k+1}v_{k+1} + a_{k+1k+2}v_{k+2} + \cdots + a_{k+1n}v_n &= 0 \\ a_{k+2k+1}v_{k+1} - a_{k+2k+2}v_{k+2} + \cdots + a_{k+2n}v_n &= 0 \\ &\vdots \\ a_{nk+1}v_{k+1} + a_{nk+2}v_{k+2} + \cdots - a_{nn}v_n &= 0 \end{aligned} \tag{1.6}$$

Adding these equations up, the left hand side is the sum of $n-k$ terms of the form $\Big(\sum_{i=k+1}^{n} a_{ij}\Big)v_j$, each of which is non-positive; here $j > k$ means that $v_j \geq 0$ and $\sum_{i=k+1}^{n} a_{ij} \leq 0$ as the diagonal entry $-a_{jj}$ is included. As the right hand side is zero, each $\Big(\sum_{i=k+1}^{n} a_{ij}\Big)v_j$ must be zero, which gives two possibilities for each j:

- $v_j = 0$, or
- $\sum_{i=k+1}^{n} a_{ij} = 0$

The latter case above implies that the first k elements of column j of A must all equal zero as the full column sum must be non-positive. In either case, the result is that in (1.4), the terms corresponding to the last $n-k$ columns are zero, and thus only the terms with $v_1, \ldots, v_k$ appear.

Hence, if we flip the signs of $v_1, v_2, \ldots, v_k$ to positive, then we still have an eigenvector of A corresponding to the eigenvalue 0; the first k equations (1.4) of $Av = 0$ are still satisfied since the terms containing $v_{k+1}, \ldots v_n$ were already zero, and the final $n-k$ equations in (1.6) do not depend on $v_1, \ldots, v_k$. Hence, we have found a non-negative eigenvector. □

Proposition 1.2.1 is useful for finding equilibria of certain mass action systems. For instance, in a system of the form

$$\begin{bmatrix} \dot{x_1} \\ \dot{x_2} \\ \vdots \\ \dot{x_n} \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & \ldots & a_{1n} \\ a_{21} & -a_{22} & \ldots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \ldots & -a_{nn} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix},$$

where the $n \times n$ matrix A on the right hand side is a singular SRP matrix, finding an equilibrium point at which not every variable is zero is equivalent to finding an eigenvector of A corresponding to the eigenvalue 0. Since the variables in mass action systems typically represent quantities such as concentrations, we want each variable to be non-negative at equilibrium; Proposition 1.2.1 guarantees the existence of such an equilibrium, in particular one in which at least one variable is strictly positive.

1.2.2 Eigenvalues of Matrices with One Combining Term

If A' is a matrix satisfying Definition 1.1.10, then by Theorem 1.1.11 we have that any real eigenvalue of A' is non-positive, and that if A' is of size 3×3, then the real part of any eigenvalue is non-positive. **Conjecture 1** from [5] posits that we can say something even stronger: *any* eigenvalue λ of a matrix with one combining term of *any* size satisfies $\mathfrak{Re}(\lambda) \leq 0$.

While we do not currently have a full proof of the conjecture, in the following propositions we will prove the result for a few special cases.

Proposition 1.2.2. Consider a matrix A' satisfying Definition 1.1.10 such that A' has the form

$$a.) \begin{bmatrix} -a_{11}-c & a_{12}-d & 0 & 0 & \dots & 0 \\ a_{21}-c & -a_{22}-d & 0 & 0 & \dots & 0 \\ a_{31}+c & a_{32}+d & -a_{33} & a_{34} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix} \text{ or}$$

$$b.) \begin{bmatrix} -a_{11}-c & a_{12}-d & a_{13} & a_{14} & \dots & a_{1n} \\ a_{21}-c & -a_{22}-d & a_{23} & a_{24} & \dots & a_{2n} \\ a_{31}+c & a_{32}+d & -a_{33} & a_{34} & \dots & a_{3n} \\ 0 & 0 & 0 & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & a_{n4} & \dots & -a_{nn} \end{bmatrix}.$$

If λ is an eigenvalue of A', then $\mathfrak{Re}(\lambda) \leq 0$.

Proof. First, suppose A' is of form a.). Then, since all entries in the upper right $2 \times (n-2)$ block are zero, the eigenvalues of A' are the eigenvalues of the $(n-2) \times (n-2)$ SRP matrix

$$\begin{bmatrix} -a_{33} & a_{34} & \dots & a_{3n} \\ a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix},$$

all of which have non-positive real part by Theorem 1.1.7, together with the eigenvalues of

$$\begin{bmatrix} -a_{11}-c & a_{12}-d \\ a_{21}-c & -a_{22}-d \end{bmatrix}.$$

The diagonal entries of this 2×2 matrix are negative, and we have $|a_{11} + c| \geq |a_{21} - c|$ and $|a_{22} + d| \geq |a_{12} - d|$ because $a_{11} \geq a_{21}$ and $a_{22} \geq a_{12}$ by definition of an SRP matrix. Hence, by Proposition 1.1.9, both eigenvalues of this matrix have non-positive real part.

If A' is of form b.), then the lower left $(n-3) \times 3$ block is all zeros. The eigenvalues of A' are thus the eigenvalues of the SRP matrix

$$\begin{bmatrix} -a_{44} & a_{45} & \dots & a_{4n} \\ a_{54} & -a_{55} & \dots & a_{5n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n4} & a_{n5} & \dots & -a_{nn} \end{bmatrix}$$

along with the three eigenvalues of the 3×3 matrix with one combining term

$$\begin{bmatrix} -a_{11} - c & a_{12} - d & a_{13} \\ a_{21} - c & -a_{22} - d & a_{23} \\ a_{31} + c & a_{32} + d & -a_{33} \end{bmatrix},$$

which all have non-positive real part by Theorem 1.1.11. □

Proposition 1.2.3. Suppose that

$$A' = \begin{bmatrix} -a_{11} - c & a_{12} - d & a_{13} & a_{14} & \dots & a_{1n} \\ a_{21} - c & -a_{22} - d & a_{23} & a_{24} & \dots & a_{2n} \\ a_{31} + c & a_{32} + d & -a_{33} & a_{34} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix},$$

is a matrix satisfying Definition 1.1.10 in which

$$\begin{aligned} a_{11} + c &\geq |a_{21} - c| + a_{31} + c + a_{41} + \cdots + a_{n1} \\ a_{22} + d &\geq |a_{12} - d| + a_{32} + d + a_{42} + \cdots + a_{n2} \end{aligned}$$

both hold. Then if λ is an eigenvalue of A', $\mathfrak{Re}(\lambda) \leq 0$.

Proof. The given inequalities imply that the first two columns of A' satisfy points a.) and b.) of Proposition 1.1.9. The third through nth columns also satisfy a.) and b.) as they are of the SRP type. Hence, all eigenvalues of A' must have non-positive real part by Proposition 1.1.9. □

Proposition 1.2.4. Let A' be a matrix satisfying Definition 1.1.10 of the form

$$\begin{bmatrix} -a_{11}-c & -d & a_{13} & a_{14} & \dots & a_{1n} \\ -c & -a_{22}-d & a_{23} & a_{24} & \dots & a_{2n} \\ c & d & -a_{33} & a_{34} & \dots & a_{3n} \\ 0 & 0 & a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix}.$$

If λ is an eigenvalue of A', then $\mathfrak{Re}(\lambda) \leq 0$.

Proof. We know from Theorem 1.1.11 that any real eigenvalue of A' is non-positive. Hence, it suffices to prove the conclusion holds for complex eigenvalues.

By contradiction, suppose A' has the complex conjugate pair of eigenvalues $a \pm bi$, where a and b are both positive. We consider the transpose of A',

$$(A')^T = \begin{bmatrix} -a_{11}-c & -c & c & 0 & \dots & 0 \\ -d & -a_{22}-d & d & 0 & \dots & 0 \\ a_{13} & a_{23} & -a_{33} & a_{43} & \dots & a_{n3} \\ a_{14} & a_{24} & a_{34} & -a_{44} & \dots & a_{n4} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{1n} & a_{2n} & a_{3n} & a_{4n} & \dots & -a_{nn} \end{bmatrix}.$$

Let w be an eigenvector of $(A')^T$ corresponding to $a+bi$, with jth component $w_j = v_j + u_j i$. Choose w such that each component satisfies $|w_j| \leq 1$, and there is at least one component that equals 1. Note that only the first or second components of w can equal 1; if $w_j = 1$ for $j > 2$, the real part of the jth equation of $(A')^T w = (a+bi)w$ would be

$$-a_{jj} + \sum_{k \neq j} a_{kj} v_k = a > 0,$$

but the fact that $|v_k| \leq 1$ and $\sum_{k \neq j} a_{kj} \leq a_{jj}$ by Definition 1.1.6 implies the left hand side cannot be positive.

WLOG, suppose $w_1 = 1$. Then, the real part of the first equation of $(A')^T w = (a+bi)w$ is

$$\begin{aligned} -a_{11} - c - cv_2 + cv_3 &= a \\ \implies c(v_3 - v_2 - 1) &= a + a_{11} > 0. \end{aligned}$$

In order for the left hand side to be positive, it must be the case that $v_3 > v_2 + 1$. As v_2 and v_3 have absolute value at most 1, this implies that $v_2 < 0$ and $v_3 > 0$. Then, the imaginary part of the first equation is

$$-cu_2 + cu_3 = c(u_3 - u_2) = b > 0,$$

and so we must have $u_3 - u_2 > 0$.

Next, we consider the second equation of $(A')^T w = (a+bi)w$. The imaginary part satisfies

$$\begin{aligned} -(a_{22}+d)u_2 + du_3 &= au_2 + bv_2 \\ \implies d(u_3 - u_2) &= (a + a_{22})u_2 + bv_2. \end{aligned}$$

We know from above that $d(u_3 - u_2) > 0$, and hence the right hand side here must also be positive. Given that $v_2 < 0$, this is only possible if $u_2 > 0$. The real part of the second equation is then

$$\begin{aligned} -d - (a_{22}+d)v_2 + dv_3 &= av_2 - bu_2 \\ \implies d(v_3 - v_2 - 1) &= (a + a_{22})v_2 - bu_2. \end{aligned}$$

Since $v_2 < 0$ and $u_2 > 0$, we have that $(a + a_{22})v_2 - bu_2 < 0$. Hence, the left hand side must also be negative, implying that $v_3 < v_2 + 1$. However, this is a contradiction as we showed that $v_3 > v_2 + 1$ above.

Thus, we must conclude that $a + bi$ with $a > 0$ cannot be an eigenvalue of A'. □

Proposition 1.2.5. Let A' be a matrix satisfying Definition 1.1.10 of the form

$$\begin{bmatrix} -a_{11} - c & a_{12} - d & 0 & a_{14} & \dots & a_{1n} \\ a_{21} - c & -a_{22} - d & 0 & a_{24} & \dots & a_{2n} \\ a_{31} + c & a_{32} + d & -a_{33} & a_{34} & \dots & a_{3n} \\ a_{41} & a_{42} & 0 & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & 0 & a_{n4} & \dots & -a_{nn} \end{bmatrix},$$

where

$$a_{11} > \sum_{i \neq 1} a_{i1}, \quad a_{22} > \sum_{i \neq 2} a_{i2},$$

and all entries in column 3 are zero except possibly a_{33}. Then, if λ is an eigenvalue of A', $\mathfrak{Re}(\lambda) \leq 0$.

Proof. We will make use of the concept of matrix similarity. Our matrix A' is similar to $B = SA'S^{-1}$, where S is an invertible $n \times n$ matrix, which means A' and B have the same eigenvalues. Here, we will choose our S to be the diagonal matrix

$$S = \begin{bmatrix} 1 & 0 & 0 & 0 & \dots & 0 \\ 0 & 1 & 0 & 0 & \dots & 0 \\ 0 & 0 & 1/m & 0 & \dots & 0 \\ 0 & 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 1 \end{bmatrix}, \text{ with } S^{-1} = \begin{bmatrix} 1 & 0 & 0 & 0 & \dots & 0 \\ 0 & 1 & 0 & 0 & \dots & 0 \\ 0 & 0 & m & 0 & \dots & 0 \\ 0 & 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 1 \end{bmatrix},$$

where $m > 0$. Then, $B = SA'S^{-1}$ is A' with row 3 multiplied by $1/m$ and column 3 multiplied by m:

$$B = \begin{bmatrix} -a_{11} - c & a_{12} - d & 0 & a_{14} & \dots & a_{1n} \\ a_{21} - c & -a_{22} - d & 0 & a_{24} & \dots & a_{2n} \\ (a_{31} + c)/m & (a_{32} + d)/m & -a_{33} & a_{34}/m & \dots & a_{3n}/m \\ a_{41} & a_{42} & 0 & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & 0 & a_{n4} & \dots & -a_{nn} \end{bmatrix}$$

The third column of B is the same as that of A', and its corresponding Gershgorin disk contains only the non-positive number $-a_{33}$. If $m > 1$, then the fourth through nth columns of B are of the SRP type like in A', and hence their corresponding Gershgorin disks also contain only complex numbers with non-positive real part.

Hence, if we can show there is an $m > 1$ such that the Gersgorin disks corresponding to the first and second columns of B fall on the left hand side of the complex plane, then Proposition 1.1.9 applies and we have proven the result.

For the first column of B, we thus want to find an m such that

$$|a_{21} - c| + \frac{a_{31} + c}{m} + \sum_{i=4}^{n} a_{i1} \leq a_{11} + c.$$

There are a couple of cases to consider. First, suppose that $|a_{21} - c| = a_{21} - c$. Then, using the given assumption $a_{11} > \sum_{i \neq 1} a_{i1}$, we have for $m > 1$

$$\begin{aligned} a_{21} - c + \frac{a_{31} + c}{m} + \sum_{i=4}^{n} a_{i1} &\leq \sum_{i \neq 1} a_{i1} + c\Big(\frac{1}{m} - 1\Big) \\ &< a_{11} + c\Big(\frac{1}{m} - 1\Big) \\ &< a_{11} + c. \end{aligned}$$

Thus, in this case choosing $m > 1$ gets us the desired result.

Next, we consider the case in which $|a_{21} - c| = c - a_{21}$. We will break this down into two

subcases:

1.) *If $a_{21} > 0$:* Here, we will use the fact that

$$a_{21} + a_{31} + \ldots a_{n1} \ < \ a_{11}$$

implies

$$-a_{21} + a_{31} + \cdots + a_{n1} \ < \ a_{11} - 2a_{21}.$$

We then have that

$$\begin{aligned} c - a_{21} + \frac{a_{31} + c}{m} + \sum_{i=4}^{n} a_{i1} \ &\leq -a_{21} + a_{31} + \cdots + a_{n1} + c\Big(\frac{1}{m} + 1\Big) \\ &< \ a_{11} - 2a_{21} + c\Big(\frac{1}{m} + 1\Big) \end{aligned}$$

if $m > 1$. Note that at $m = \dfrac{c}{2a_{21}}$,

$$a_{11} - 2a_{21} + c\Big(\frac{1}{m} + 1\Big) \ = \ a_{11} + c,$$

and this equality becomes a strict inequality as m increases further. Hence, choosing $m > \max\left\{1, \dfrac{c}{2a_{21}}\right\}$ establishes the desired inequality.

2.) *If $a_{21} = 0$:* The assumption $\displaystyle\sum_{i \neq 1} a_{i1} < a_{11}$ means there exists an $0 < \epsilon \leq a_{11}$ such that $\displaystyle\sum_{i \neq 1} a_{i1} = a_{11} - \epsilon$. Then for $m > 1$,

$$\begin{aligned} c + \frac{a_{31} + c}{m} + \sum_{i=4}^{n} a_{i1} \ &\leq \sum_{i \neq 1} a_{i1} + c\Big(\frac{1}{m} + 1\Big) \\ &= \ a_{11} - \epsilon + c\Big(\frac{1}{m} + 1\Big). \end{aligned}$$

We want to find a value of m such that $a_{11} - \epsilon + c\Big(\dfrac{1}{m} + 1\Big) \leq a_{11} + c$. We get that

$$\begin{aligned} a_{11} - \epsilon + c\Big(\frac{1}{m} + 1\Big) \ &\leq \ a_{11} + c \\ \iff c/m \ &\leq \ \epsilon \\ \iff c/\epsilon \ &\leq \ m \end{aligned}$$

Hence, choosing $m > \max\{1, c/\epsilon\}$ will produce the desired inequality.

Thus, in each case there exists an $m = m' > 1$ such that

$$|a_{21} - c| + \frac{a_{31} + c}{m'} + \sum_{i=4}^{n} a_{i1} \leq a_{11} + c$$

holds. For the second column, by the same process as above we can find an $m = m'' > 1$ such that

$$|a_{12} - d| + \frac{a_{32} + d}{m''} + \sum_{i=4}^{n} a_{i2} \leq a_{22} + d.$$

Then, choosing $m = \max\{m', m''\}$ will ensure that the Gershgorin disks associated with columns 1 and 2 of B do not overlap the right hand side of the complex plane, and thus Proposition 1.1.9 applies. □

1.2.3 Inverses of Dissociation Matrices

A *dissociation matrix* as considered in [5] is the Jacobian of a mass action system containing at least one dissociation term derived from a reaction of the form $X \to Y + Z$, along with an arbitrary number of SRP terms. The following result was proven in [5] regarding the inverse of a dissociation matrix:

Theorem 1.2.6. *Let A be an invertible dissociation matrix. All entries of A^{-1} are non-positive if and only if for every eigenvalue λ of A, $\mathfrak{Re}(\lambda) < 0$.*

Theorem 1.2.6 tells us that if an invertible dissociation matrix has an eigenvalue with positive real part, then at least one entry of A^{-1} is positive. **Conjecture 2** from [5] posits that a stronger conclusion holds: *all* entries of A^{-1} will be non-negative in this case. Here, we will prove that this conjecture holds for the 3×3 case, but is not true in general for larger matrices.

For the proof of the 3×3 case, we will use the following proposition:

Proposition 1.2.7. Let A be an invertible 3×3 dissociation matrix. Then, the non-zero entries of A^{-1} all have the same sign as the determinant of A.

Proof. Note that the dissociation reaction $X_j \xrightarrow{k} X_i + X_\ell$ will affect the jth column of the Jacobian, with a $-k$ term in the diagonal entry and a $+k$ in both the ith and ℓth entries. A 3×3 matrix can contain at most three dissociation terms, one in each column, derived from the reactions $X_1 \xrightarrow{b} X_2 + X_3$, $X_2 \xrightarrow{c} X_1 + X_3$, and $X_3 \xrightarrow{d} X_1 + X_2$. We will first consider the case in which A has all three of these dissociation terms, meaning that when combined with an arbitrary number of SRP terms, A has the form

$$\begin{bmatrix} -a_{11} - b & a_{12} + c & a_{13} + d \\ a_{21} + b & -a_{22} - c & a_{23} + d \\ a_{31} + b & a_{32} + c & -a_{33} - d \end{bmatrix},$$

where b, c, and d are positive and the a_{ij} form an SRP matrix. We show that the cofactors of this matrix are non-negative. Expanding along column 1, we have that

$$\begin{aligned} C_{11} &= (-a_{22}-c)(-a_{33}-d)-(a_{32}+c)(a_{23}+d) \\ &= a_{22}a_{33}-a_{23}a_{32}+(a_{22}-a_{32})d+(a_{33}-a_{23})c \\ &\geq 0, \end{aligned}$$

using the fact that an SRP matrix satisfies $a_{22} \geq a_{32}$ and $a_{33} \geq a_{23}$. For C_{21} and C_{31}, we get that

$$\begin{aligned} C_{21} &= -[(a_{12}+c)(-a_{33}-d)-(a_{32}+c)(a_{13}+d)] \\ &= (a_{12}+c)(a_{33}+d)+(a_{32}+c)(a_{13}+d) \end{aligned}$$

and

$$\begin{aligned} C_{31} &= (a_{12}+c)(a_{23}+d)-(-a_{22}-c)(a_{13}+d) \\ &= (a_{12}+c)(a_{23}+d)+(a_{22}+c)(a_{13}+d), \end{aligned}$$

both of which are non-negative.

The calculations for the other C_{ij} are similar. Hence, each cofactor satisfies $C_{ij} \geq 0$. Then, in A^{-1} each entry has the form $C_{ij}/\det(A)$; hence, any entry with $C_{ij} > 0$ will have the same sign as the determinant of A.

For matrices with only 1 or 2 dissociation terms, we still have that $C_{ij} \geq 0$; setting at least one of b, c, or d equal to zero will not change the sign of the cofactor calculations. Thus, the sign of the entries of A^{-1} will still depend on the sign of $\det(A)$. □

We can now prove **Conjecture 2** from [5] for the 3×3 case:

Proposition 1.2.8. Let A be an invertible 3×3 dissociation matrix and suppose A has an eigenvalue with a positive real part. Then, all entries of A^{-1} are non-negative.

Proof. By Proposition 1.2.7, all non-zero entries of A^{-1} will have the same sign. Since A has an eigenvalue whose real part is positive, Theorem 1.2.6 says that A^{-1} must have at least one positive entry. Thus, all non-zero entries of A^{-1} are positive, and hence $A^{-1} \geq 0$ entrywise. □

Similar to Proposition 1.2.1, the results of Proposition 1.2.8 have implications for equilibria in certain mass action systems. Unlike Proposition 1.2.1, however, Proposition 1.2.8 can instead tell us when a system *cannot* have an equilibrium point at which all variables are non-negative. For instance, consider a system of the form

$$\begin{bmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{bmatrix} = \begin{bmatrix} -a_{11}-b & a_{12}+c & a_{13}+d \\ a_{21}+b & -a_{22}-c & a_{23}+d \\ a_{31}+b & a_{32}+c & -a_{33}-d \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \\ z_0 \end{bmatrix}, \tag{1.7}$$

where

- The 3×3 matrix A on the right hand side is a dissociation matrix (i.e. at least one of b, c, and d is strictly positive), invertible, and has at least one eigenvalue with positive real part.

- The constant vector on the right hand side is non-negative entrywise, and positive entries are obtained from the reactions $0 \xrightarrow{x_0} X$, $0 \xrightarrow{y_0} Y$, and $0 \xrightarrow{z_0} Z$.

The unique equilibrium point of (1.7) is given by

$$\begin{bmatrix} x^* \\ y^* \\ z^* \end{bmatrix} = - \begin{bmatrix} -a_{11} - b & a_{12} + c & a_{13} + d \\ a_{21} + b & -a_{22} - c & a_{23} + d \\ a_{31} + b & a_{32} + c & -a_{33} - d \end{bmatrix}^{-1} \begin{bmatrix} x_0 \\ y_0 \\ z_0 \end{bmatrix}.$$

By Proposition 1.2.8, the inverse matrix A^{-1} has only non-negative entries, and thus $-A^{-1} \leq 0$ entrywise. But since x_0, y_0, and z_0 are non-negative, this means the equilibrium solution is non-positive. Given that A^{-1} is invertible, and thus cannot have a row or column of zeros, the equilibrium point is non-negative if and only if $(x_0, y_0, z_0)^T$ is the zero vector, producing an equilibrium point at the origin. Otherwise, at least one of x^*, y^*, and z^* will be strictly negative.

Thus, Proposition 1.2.8 allows us to characterize the biochemically relevant (i.e. non-negative) equilibria of system (1.7): no such equilibria exist if the constant vector has a positive entry, and a unique such equilibrium occurs at the origin if and only if all three of x_0, y_0, and z_0 are zero.

The conclusion of Proposition 1.2.8 does not necessarily hold for dissociation matrices of size 4×4 or higher. For instance, consider the block matrix

$$\begin{bmatrix} -9 & 7 & 4 & 0 & 0 \\ 6 & -8 & 3 & 0 & 0 \\ 5 & 1 & -9 & 0 & 0 \\ 0 & 0 & 0 & -2 & 0 \\ 0 & 0 & 0 & 1 & -3 \end{bmatrix} \tag{1.8}$$

which is an invertible dissociation matrix; it can be written as

$$\begin{bmatrix} -9 & 7 & 4 & 0 & 0 \\ 6 & -8 & 3 & 0 & 0 \\ 5 & 1 & -9 & 0 & 0 \\ 0 & 0 & 0 & -2 & 0 \\ 0 & 0 & 0 & 1 & -3 \end{bmatrix} = \begin{bmatrix} -5 & 7 & 4 & 0 & 0 \\ 2 & -8 & 3 & 0 & 0 \\ 1 & 1 & -9 & 0 & 0 \\ 0 & 0 & 0 & -2 & 0 \\ 0 & 0 & 0 & 1 & -3 \end{bmatrix} + \begin{bmatrix} -4 & 0 & 0 & 0 & 0 \\ 4 & 0 & 0 & 0 & 0 \\ 4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

the sum of an SRP matrix and the Jacobian of the mass action system corresponding to the dissociation reaction $X_1 \xrightarrow{4} X_2 + X_3$. Matrix (1.8) has a positive eigenvalue $\lambda \approx 0.27507$ and inverse

$$\begin{bmatrix} -9 & 7 & 4 & 0 & 0 \\ 6 & -8 & 3 & 0 & 0 \\ 5 & 1 & -9 & 0 & 0 \\ 0 & 0 & 0 & -2 & 0 \\ 0 & 0 & 0 & 1 & -3 \end{bmatrix}^{-1} = \begin{bmatrix} 3/2 & 67/46 & 53/46 & 0 & 0 \\ 3/2 & 61/46 & 51/46 & 0 & 0 \\ 1 & 22/23 & 15/23 & 0 & 0 \\ 0 & 0 & 0 & -1/2 & 0 \\ 0 & 0 & 0 & -1/6 & -1/3 \end{bmatrix},$$

which has a mix of positive and negative entries.

In general, for size $n \geq 4$ any block matrix of the form

$$M = \begin{bmatrix} D & 0 \\ C & S \end{bmatrix},$$

where D is a 3×3 invertible dissociation matrix with at least one eigenvalue with positive real part, S is an $(n-3) \times (n-3)$ invertible SRP matrix, and the $(n-3) \times 3$ block C is chosen such that M is a dissociation matrix overall, will be a counterexample to **Conjecture 2** from [5]. Matrix M has inverse

$$M^{-1} = \begin{bmatrix} D^{-1} & 0 \\ -S^{-1}CD^{-1} & S^{-1} \end{bmatrix},$$

where D^{-1} will have at least one positive entry by Theorem Theorem 1.2.6 and Proposition 1.2.8, while S^{-1} will have at least one negative entry by Theorem 1.1.7.

Chapter 2

Systems with Multiple Thresholds Per Variable

2.1 Single-Variable Systems

We begin here by considering biochemical ramp systems in a single variable x, in which x is the input of multiple ramp functions. Our focus will be on systems that, when in the all ramp region, are mass action systems derived from reactions in which only one chemical species is involved; since this chapter will focus on systems with SRP and combining reactions, the only reactions that fit this description are those of the form $X \to 0$ and $0 \to X$.

Note that as we have done previously, throughout this chapter we will use X, Y, Z, etc. to denote chemical species, with their respective concentrations being given by x, y, z, etc.

2.1.1 Systems with Two Thresholds

We start by considering simple systems of the form

$$\dot{x} = -br_1(x) - cr_2(x) + a_0, \tag{2.1}$$

where $b, c > 0$, $a_0 \geq 0$, and r_1 and r_2 are ramp functions as defined in Definition 0.0.1 with thresholds $2\theta_1$ and $2\theta_2$ respectively. WLOG, we will assume that $\theta_1 < \theta_2$.

In the all ramp region, system (2.1) has the form

$$\dot{x} = -\frac{bx}{2\theta_1} - \frac{cx}{2\theta_2} + a_0. \tag{2.2}$$

The two negative terms derive from the reactions $X \xrightarrow{k_1} 0$ and $X \xrightarrow{k_2} 0$, where $k_1 = b/2\theta_1$ and $k_2 = c/2\theta_2$. If $k_1 \neq k_2$, these two reactions represent species X leaving the system via two distinct routes at differing rates; biologically, we can think of these as two different enzyme-mediated reactions through which X is consumed. In the special case $k_1 = k_2 = k$, the negative terms can be combined into one $-2kx$ term deriving from the reaction $X \xrightarrow{2k} 0$.

If the constant term is positive, it comes from the reaction $0 \xrightarrow{a_0} X$, representing X being produced at a constant rate.

Our goal for this section is to characterize the equilibria of system (2.1). Phase space for system (2.1) can be divided into three regions: the all ramp region (2.2), which spans all x values satisfying $0 \leq x < 2\theta_1$; the region where r_1 (but not r_2) is saturated ($2\theta_1 \leq x < 2\theta_2$), and the region in which both ramp functions are saturated ($x \geq 2\theta_2$). We will consider the dynamics in each of these regions.

In the all ramp region, setting the right hand side of (2.2) equal to zero gives the unique solution

$$x^* = \frac{2a_0\theta_1\theta_2}{b\theta_2 + c\theta_1}.$$

This value exists in the all ramp region if and only if

$$x^* \leq 2\theta_1 \iff a_0 < b + c\frac{\theta_1}{\theta_2}.$$

Next, when $2\theta_1 \leq x < 2\theta_2$, the function r_1 is saturated and equal to 1, while r_2 is still in its ramp region. System (2.1) thus becomes

$$\dot{x} = -b - \frac{cx}{2\theta_2} + a_0,$$

with the unique equilibrium

$$x^* = \frac{2\theta_2(a_0 - b)}{c}.$$

This equilibrium satisfies $2\theta_1 \leq x < 2\theta_2$ if and only if

$$b + c\frac{\theta_1}{\theta_2} \leq a_0 < b + c.$$

Finally, both r_1 and r_2 are in their saturated regions when $x \geq 2\theta_2$. System (2.1) is then described by the equation

$$\dot{x} = -b - c + a_0.$$

Every $x^* \geq 2\theta_2$ is an equilibrium point in this region if and only if $a_0 = b + c$.

Now, we will consider stability of equilibria. When system (2.1) has a unique equilibrium x^* — which can happen in only the $x \leq 2\theta_1$ and $2\theta_1 \leq x < 2\theta_2$ cases — the sole eigenvalue of the 1×1 Jacobian of the system at this equilibrium is negative, equal to either $-\left(\frac{b}{2\theta_1} + \frac{c}{2\theta_2}\right)$ or $-\frac{c}{2\theta_2}$. Thus, the equilibrium is asymptotically stable.

In fact, flow in system (2.1) will always be toward the unique equilibrium:

- If $x^* = 0$, then $a_0 = 0$, and hence the right hand side of (2.1) is negative for any $x > 0$.
- If x^* is positive, then $\dot{x} > 0$ for $x < x^*$ and $\dot{x} < 0$ for $x > x^*$.

In either case, global flow is directed toward x^*, and thus x^* is globally stable.

Next, system (2.1) can have a line of equilibria given by $x^* \geq 2\theta_2$ in the special case $a_0 = b + c$. The eigenvalue of the Jacobian in this case will be zero; however, we will still have stability in this case: for $x < 2\theta_2$, the $\dot{x}$ equation will be positive, since $r_2(x) < 1$ implies the ramp function terms will be strictly less than $b + c$. Hence, when $x < 2\theta_2$ flow will be toward the equilibrium at $x^* = 2\theta_2$, while the system will remain at equilibrium for any $x \geq 2\theta_2$.

Thus, if at least one equilibrium point exists, flow in system (2.1) will be toward such a point. We will now consider flow when the system does not have any equilibria; based on our work above, this happens if and only if $a_0 > b + c$. In this case, we have that

$$\begin{aligned} \dot{x} &= -br_1(x) - cr_2(x) + a_0 \\ &> -br_1(x) - cr_2(x) + b + c \\ &= b(1 - r_1(x)) + c(1 - r_2(x)) \\ &\geq 0 \end{aligned}$$

for all values of x, so we will have unbounded behaviour.

Our results here are summarized in the theorem below.

Theorem 2.1.1. *Consider a system of form* (2.1).

1.) *The system has at least one equilibrium point if and only if* $a_0 \leq b + c$. *Equilibria are given by*

$$x^* \begin{cases} = \dfrac{2a_0\theta_1\theta_2}{b\theta_2 + c\theta_1}, & 0 \leq a_0 < b + c\dfrac{\theta_1}{\theta_2} \\ = \dfrac{2\theta_2(a_0 - b)}{c}, & b + c\dfrac{\theta_1}{\theta_2} \leq a_0 < b + c \\ \geq 2\theta_2, & a_0 = b + c \end{cases}$$

2.) *If the system has at least one equilibrium, then flow is bounded and is toward an equilibrium point.*

3.) *If* $a_0 > b + c$, *then the system has no equilibria and flow is unbounded.*

2.1.1.1 Comparisons to Michaelis-Menten

Here, we will compare the behaviour of system (2.1) to that of the corresponding Michaelis-Menten system

$$\dot{x} = -\frac{bx}{\theta_1 + x} - \frac{cx}{\theta_2 + x} + a_0. \tag{2.3}$$

Equilibria in system (2.3) are possible if and only if $a_0 < b + c$. As the Michaelis-Menten term $\frac{x}{\theta + x}$ is always strictly less than 1, if $a_0 \geq b + c$ we have that

$$\begin{aligned}
\dot{x} &= -\frac{bx}{\theta_1 + x} - \frac{cx}{\theta_2 + x} + a_0 \\
&\geq -\frac{bx}{\theta_1 + x} - \frac{cx}{\theta_2 + x} + b + c \\
&= b\Big(1 - \frac{x}{\theta_1 + x}\Big) + c\Big(1 - \frac{x}{\theta_2 + x}\Big) \\
&> 0
\end{aligned}$$

for any $x \geq 0$. Hence, no non-negative equilibria are possible in this case and x will grow to infinity over time.

For $a_0 < b + c$, equilibria of (2.3) are the solutions to

$$(b + c - a_0)x^2 + [b\theta_2 + c\theta_1 - a_0(\theta_1 + \theta_2)]x - a_0\theta_1\theta_2 = 0.$$

The discriminant of this quadratic is

$$\Delta = [b\theta_2 + c\theta_1 - a_0(\theta_1 + \theta_2)]^2 + 4a_0\theta_1\theta_2(b + c - a_0),$$

which cannot be negative under the assumption $a_0 < b + c$. In fact, Δ will always be strictly positive under this assumption; $\Delta = 0$ if and only if both terms in the sum equal zero, but $4a_0\theta_1\theta_2(b + c - a_0) = 0$ implies $a_0 = 0$, which then implies

$$[b\theta_2 + c\theta_1 - a_0(\theta_1 + \theta_2)]^2 = [b\theta_2 + c\theta_1]^2,$$

which is positive. Hence, the quadratic will always have real roots, with the positive root from the quadratic formula giving a non-negative equilibrium:

$$x^* = \frac{a_0(\theta_1 + \theta_2) - (b\theta_2 + c\theta_1) + \sqrt{\Delta}}{2(b + c - a_0)}. \tag{2.4}$$

Note that $x^* = 0$ if and only if $a_0 = 0$, and is strictly positive otherwise.

One should also note that we will never get a second non-negative equilibrium by taking the negative root in the quadratic formula. Letting

$$B = b\theta_2 + c\theta_1 - a_0(\theta_1 + \theta_2),$$

the condition $a_0 < b + c$ gives us that

$$\Delta = B^2 + 4a_0\theta_1\theta_2(b + c - a_0) \geq B^2.$$

Hence, the denominator of the negative root solution,

$$-B - \sqrt{\Delta},$$

is non-positive. If $-B < 0$, the denominator is always strictly negative. If $-B \geq 0$, then the denominator equals zero if and only if $\Delta = B^2$. However, this equality holds if and only if $a_0 = 0$, in which case we have

$$B \;=\; b\theta_2 + c\theta_1,$$

which is positive, contradicting that $-B \geq 0$. Thus, taking the negative root from the quadratic formula will not result in an additional non-negative equilibrium for system (2.3).

The sole eigenvalue of system (2.3) evaluated at the x^* given in (2.4) is

$$-\left(\frac{b\theta_1}{(\theta_1 + x^*)^2} + \frac{c\theta_2}{(\theta_2 + x^*)^2}\right),$$

which is always negative; hence, x^* is asymptotically stable. Global stability of x^* for $x \geq 0$ follows from the same reasoning used for the unique equilibrium of ramp system (2.1): if $x^* = 0$, then $\dot{x} < 0$ for all $x > 0$, and if $x^* > 0$, then $\dot{x} > 0$ for $x < x^*$ and $\dot{x} < 0$ for $x > x^*$. Thus, global flow is toward x^* for non-negative values of x.

Thus, ramp system (2.1) and Michaelis-Menten system (2.3) display qualitatively similar behaviour: when $a_0 < b + c$, both systems have a unique globally stable non-negative equilibrium, but unbounded flow occurs in both systems when $a_0 > b + c$. There is a slight difference in behaviour only for the special case $a_0 = b + c$: system (2.1) has a line of stable equilibria in this case, while system (2.3) has no equilibria and flow is unbounded. This result is a consequence of using ramp functions, stemming from the fact that a ramp function can have the value 1 as an output, while the corresponding Michaelis-Menten function cannot.

Now, we will examine the quantitative behaviour of ramp system (2.1) compared to Michaelis-Menten system (2.3) by graphing the non-negative equilibrium x^* — unique for both systems except in the special case $a_0 = b+c$ for the ramp system — as a function of a_0. The graph is presented in Figure 2.1.1 below, using the equilibrium values given in Theorem 2.1.1 for system (2.1) and in (2.4) for system (2.3).

From Figure 2.1.1, x^* is similar in value between the two systems for relatively small a_0, but then the Michaelis-Menten equilibrium quickly pulls away. In fact, the Michaelis-Menten equilibrium given in (2.4) approaches infinity as a_0 approaches $b+c$ from below: the denominator of x^* approaches zero from above, while the numerator approaches the positive value

$$b\theta_1 + c\theta_2 + \sqrt{(-b\theta_1 - c\theta_2)^2} \;=\; 2(b\theta_1 + c\theta_2).$$

Meanwhile, the x^* value for the ramp system is bounded when $a_0 < b + c$, always being less than $2\theta_2$. When $a_0 = b + c$, every $x^* \geq 2\theta_2$ is an equilibrium, giving us the vertical line shown in Figure 2.1.1; this is analogous to the behaviour seen in the Michaelis-Menten system as a approached $b+c$. However, this is a special case involving an equality condition on the parameters; we will usually be working with the $a_0 < b + c$ case.

Thus, there is a quantitative difference in the $a_0 < b + c$ case, which is when the two

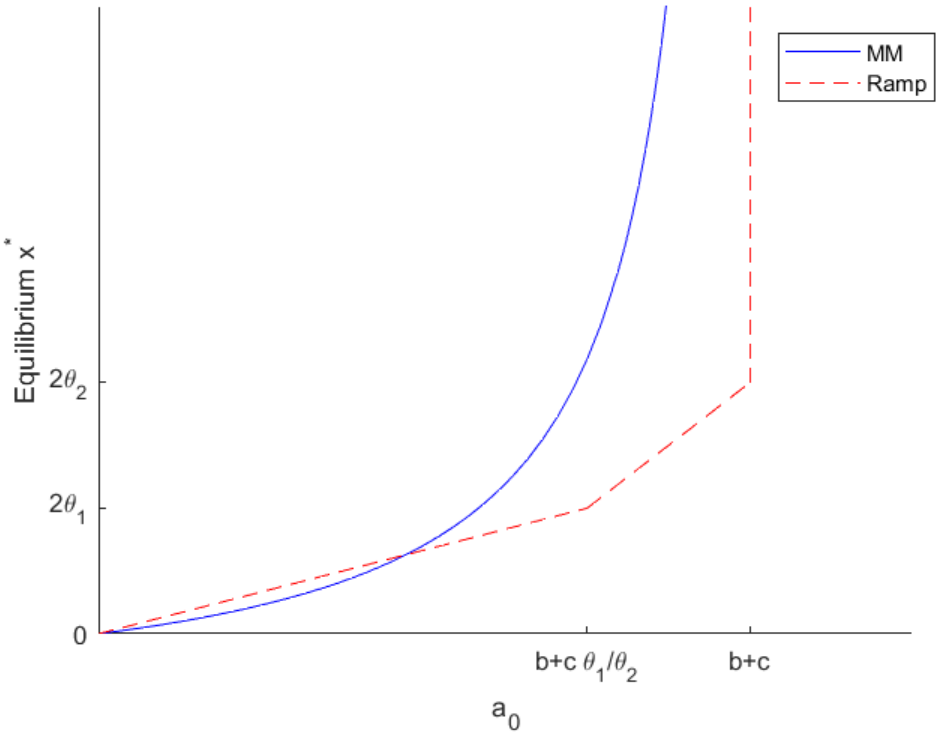


Figure 2.1.1: Equilibrium x^* of ramp system (2.1) (red dashed line) and Michaelis-Menten system (2.3) (solid blue line) as a function of a_0. Parameters are $\theta_2 = 2$ and $b, c, \theta_1 = 1$.

systems have a unique equilibrium x^*: this equilibrium is always less than $2\theta_2$ in ramp system (2.1) when this condition on parameters holds, but in the Michaelis-Menten system (2.3), the value of x^* grows without bound as a_0 approached $b + c$.

2.1.2 Systems with n Thresholds

Now, we will extend our results on system (2.1) to single variable systems with an arbitrary number of thresholds. These systems have the form

$$\dot{x} \;=\; -b_1 r_1(x) - b_2 r_2(x) - \cdots - b_n r_n(x) + a_0, \tag{2.5}$$

with $a_0 \geq 0$ and each $b_i > 0$. Ramp function r_i has threshold $2\theta_i$ and we will assume WLOG that

$$\theta_1 < \theta_2 < \cdots < \theta_{n-1} < \theta_n.$$

When looking at equilibria in system (2.5), there will be $n + 1$ regions of phase space to consider: the all ramp region ($x < 2\theta_1$); the region in which all n ramp functions are saturated ($x \geq 2\theta_n$); and $n - 1$ regions in which x is between consecutive thresholds ($2\theta_k \leq x < 2\theta_{k+1}$

for $k = 1, 2, \ldots, n-1$).

In the all ramp region, system (2.5) has the form

$$\dot{x} = -\frac{b_1 x}{2\theta_1} - \frac{b_2 x}{2\theta_2} - \cdots - \frac{b_n x}{2\theta_n} + a_0.$$

The unique equilibrium in this region is given by

$$\begin{aligned} x^* &= a_0 \left[\frac{b_1}{2\theta_1} + \frac{b_2}{2\theta_2} + \cdots + \frac{b_n}{2\theta_n} \right]^{-1} \\ &= a_0 \left[\sum_{i=1}^{n} \frac{b_i}{2\theta_i} \right]^{-1} \end{aligned}$$

if and only if $x^* < 2\theta_1$, i.e.

$$\begin{aligned} a_0 &< b_1 + b_2 \frac{\theta_1}{\theta_2} + b_3 \frac{\theta_1}{\theta_3} + \cdots + b_n \frac{\theta_1}{\theta_n} \\ &= \sum_{i=1}^{n} \frac{b_i \theta_1}{\theta_i} \end{aligned}$$

Next, we consider the case in which $2\theta_k \leq x < 2\theta_{k+1}$ for some $k = 1, 2, \ldots, n-1$. In such a region, the first k ramp functions are saturated, while the the remaining $n-k$ ramp functions are still in their ramp regions. Thus, system (2.5) becomes

$$\dot{x} = -b_1 - b_2 - \cdots - b_k - \frac{b_{k+1} x}{2\theta_{k+1}} - \frac{b_{k+2} x}{2\theta_{k+2}} - \cdots - \frac{b_n x}{2\theta_n} + a_0.$$

The sole equilibrium in this region is then

$$\begin{aligned} x^* &= (a_0 - b_1 - b_2 - \cdots - b_k) \left[\frac{b_{k+1}}{2\theta_{k+1}} + \frac{b_{k+2}}{2\theta_{k+2}} + \cdots + \frac{b_n}{2\theta_n} \right]^{-1} \\ &= \left(a_0 - \sum_{i=1}^{k} b_i \right) \left[\sum_{j=k+1}^{n} \frac{b_j}{2\theta_j} \right]^{-1}. \end{aligned}$$

We need this equilibrium to satisfy $2\theta_k \leq x^* < 2\theta_{k+1}$. The lower bound here gives us that

$$\begin{aligned} a_0 &\geq b_1 + b_2 + \ldots b_k + 2\theta_k \left[\frac{b_{k+1}}{2\theta_{k+1}} + \frac{b_{k+2}}{2\theta_{k+2}} + \cdots + \frac{b_n}{2\theta_n} \right] \\ &= \sum_{i=1}^{k} b_i + \sum_{j=k+1}^{n} \frac{b_j \theta_k}{\theta_j}, \end{aligned}$$

while from the upper bound, we have

$$a_0 \;<\; b_1 + b_2 + \ldots b_k + 2\theta_{k+1}\left[\frac{b_{k+1}}{2\theta_{k+1}} + \frac{b_{k+2}}{2\theta_{k+2}} + \cdots + \frac{b_n}{2\theta_n}\right]$$

$$= \sum_{i=1}^{k} b_i + \sum_{j=k+1}^{n} \frac{b_j\theta_{k+1}}{\theta_j}.$$

Thus, we will have $2\theta_k \leq x^* < 2\theta_{k+1}$ if and only if

$$\sum_{i=1}^{k} b_i + \sum_{j=k+1}^{n} \frac{b_j\theta_k}{\theta_j} \;\leq\; a_0 \;<\; \sum_{i=1}^{k} b_i + \sum_{j=k+1}^{n} \frac{b_j\theta_{k+1}}{\theta_j}.$$

Finally, when $x \geq 2\theta_n$, system (2.5) is simply

$$\dot{x} \;=\; -b_1 - b_2 - \cdots - b_n + a_0,$$

and every $x^* \geq 2\theta_n$ will be an equilibrium point if and only if $a_0 = \sum_{i=1}^{n} b_i$.

If system (2.5) has an equilibrium, it will be stable; the work showing this is similar to what we did with the two-threshold system (2.1) using the sign of $\dot{x}$. When the equilibrium x^* is unique, global flow will be directed toward it. In the special case where every $x^* \geq 2\theta_n$ is an equilibrium, flow will be toward the point $x^* = 2\theta_n$ when $x < 2\theta_n$.

When $a_0 > \sum_{i=1}^{n} b_i$, system (2.5) satisfies

$$\begin{aligned}
\dot{x} \;&=\; -b_1 r_1(x) - b_2 r_2(x) - \cdots - b_n r_n(x) + a_0 \\
&>\; -b_1 r_1(x) - b_2 r_2(x) - \cdots - b_n r_n(x) + \sum_{i=1}^{n} b_i \\
&=\; \sum_{i=1}^{n} b_i[1 - r_i(x)] \\
&\geq\; 0
\end{aligned}$$

for all x. As a result, there will be no equilibria and flow is unbounded.

Our results for system (2.5) are summarized in the following theorem:

Theorem 2.1.2. *Consider a system of form* (2.5).

1.) *The system has at least one equilibrium point if and only if* $a_0 \leq \sum_{i=1}^{n} b_i$. *Equilibria are given by*

$$x^* \begin{cases} = a_0 \left[\sum_{i=1}^{n} \frac{b_i}{2\theta_i} \right]^{-1}, & 0 \le a_0 < \sum_{i=1}^{n} \frac{b_i \theta_1}{\theta_i} \\ = \left(a_0 - \sum_{i=1}^{k} b_i \right) \left[\sum_{j=k+1}^{n} \frac{b_j}{2\theta_j} \right]^{-1}, & L_k \le a_0 < U_k \\ \ge 2\theta_n, & a_0 = \sum_{i=1}^{n} b_i \end{cases}$$

where $k = 1, 2, \ldots, n-1$ *and*

$$L_k = \sum_{i=1}^{k} b_i + \sum_{j=k+1}^{n} \frac{b_j \theta_k}{\theta_j}$$

$$U_k = \sum_{i=1}^{k} b_i + \sum_{j=k+1}^{n} \frac{b_j \theta_{k+1}}{\theta_j}$$

2.) *If the system has at least one equilibrium, then flow is bounded and is toward an equilibrium point.*

3.) *If* $a_0 > \sum_{i=1}^{n} b_i$, *then the system has no equilibria and flow is unbounded.*

2.1.2.1 Comparisons to Michaelis-Menten

As we did in the two threshold case, we will compare the qualitative behaviour of the ramp system (2.5) with n thresholds to that of the corresponding Michaelis-Menten system

$$\dot{x} = -\frac{b_1 x}{\theta_1 + x} - \frac{b_2 x}{\theta_2 + x} - \cdots - \frac{b_n x}{\theta_n + x} + a_0. \tag{2.6}$$

System (2.6) admits a non-negative equilibrium point if and only if $a_0 < \sum_{i=1}^{n} b_i$. When $a_0 \ge \sum_{i=1}^{n} b_i$, flow is unbounded for $x \ge 0$ as $\dot{x}$ will always be positive:

$$\dot{x} = -\sum_{i=1}^{n} \frac{b_i x}{\theta_i + x} + a_0$$

$$\ge -\sum_{i=1}^{n} \frac{b_i x}{\theta_i + x} + \sum_{i=1}^{n} b_i$$

$$= \sum_{i=1}^{n} b_i \Big(1 - \frac{x}{\theta_i + x}\Big)$$
$$> 0.$$

If $a_0 = 0$, then system (2.6) has an equilibrium at the origin. For the $0 < a_0 < \sum_{i=1}^{n} b_i$ case, we will show that (2.6) will have a non-negative equilibrium by looking at the sign of $\dot{x}$. As a_0 is positive in this case, $\dot{x}$ will be positive at $x = 0$. Next, the condition $a_0 < \sum_{i=1}^{n} b_i$ means that there exists an $\epsilon \in \Big(0, \sum_{i=1}^{n} b_i\Big)$ such that $a_0 = \sum_{i=1}^{n} b_i - \epsilon$. The ith Michaelis-Menten function

$$M_i(x) = \frac{b_i x}{\theta_i + x}$$

from (2.6) is continuous, strictly increasing, and can take any value in $[0, b_i)$ when $x \geq 0$; hence, there exists an $x = x_i$ such that $M_i(x_i) > b_i - \epsilon/n$.

Then, at $x = \max_i\{x_i\} = x'$ we have that

$$\begin{aligned}
\dot{x} &= -\sum_{i=1}^{n} \frac{b_i x'}{\theta_i + x'} + \sum_{i=1}^{n} b_i - \epsilon \\
&< \sum_{i=1}^{n} \Big(\frac{\epsilon}{n} - b_i\Big) + \sum_{i=1}^{n} b_i - \epsilon \\
&= 0.
\end{aligned}$$

Hence, the right hand side of (2.6) eventually switches from positive to negative on the interval $[0, \infty)$. As the Michaelis-Menten terms are continuous on this interval, this implies there must be an $x^* \in [0, \infty)$ at which $\dot{x}$ equals zero; this x^* is thus an equilibrium of the system.

Any non-negative equilibrium of (2.6) will be unique. The derivative of the right hand side is

$$-\sum_{i=1}^{n} \frac{b_i \theta_i}{(\theta_i + x)^2},$$

which is always negative; hence, $\dot{x}$ is strictly decreasing for $x \geq 0$ and equals zero at one one point in this range.

The fact that the derivative of the right hand side of (2.6) is negative also implies that a non-negative equilibrium x^* is asymptotically stable. As we saw with the two threshold case, global flow will be toward x^* for $x \geq 0$; $\dot{x}$ is positive when $x < x^*$ and negative when $x > x^*$.

Thus, as was seen in the two threshold case, the qualitative behaviour of ramp system (2.5) and Michaelis-Menten system (2.6) is identical for almost every a_0 value: both system admit a unique globally stable non-negative equilibrium point when $a_0 < \sum_{i=1}^{n} b_i$, and display unbounded behaviour when $a_0 > \sum_{i=1}^{n}$. Again, the only difference in behaviour occurs in the special case $a_0 = \sum_{i=1}^{n} b_i$, where (2.5) has a line of equilibria due to the presence of ramp functions over Michaelis-Menten terms.

2.2 A Class of Two-Variable Systems

We now move on to considering systems of two variables. In particular, here we will analyze systems of the form

$$\begin{aligned} \dot{x} &= -ar_1(x) - br_2(x) + x_0 \\ \dot{y} &= ar_1(x) - cr_3(y) + y_0, \end{aligned} \tag{2.7}$$

where r_1 and r_2 have thresholds $2\theta_1$ and $2\theta_2$ respectively, with $\theta_1 \neq \theta_2$. The function r_3 has threshold $2\theta_3$. The parameters a, b, and c are positive while x_0 and y_0 are non-negative.

In the all ramp region, this system becomes

$$\begin{aligned} \dot{x} &= -\frac{ax}{2\theta_1} - \frac{bx}{2\theta_2} + x_0 \\ \dot{y} &= \frac{ax}{2\theta_1} - \frac{cy}{2\theta_3} + y_0, \end{aligned} \tag{2.8}$$

the mass action system corresponding to the reactions

$$X \xrightarrow{k_1} Y \quad X \xrightarrow{k_2} 0 \quad Y \xrightarrow{k_3} 0$$

$$0 \xrightarrow{x_0} X \quad 0 \xrightarrow{y_0} Y$$

with

$$k_1 = \frac{a}{2\theta_1}, \quad k_2 = \frac{b}{2\theta_2}, \quad k_3 = \frac{c}{2\theta_3}.$$

Biologically, these reactions describe a system in which two species X and Y are each produced at a constant rate, species X is transformed into Y via an enzyme-mediated reaction, and both species are lost as a result of other enzymatic reactions.

We want to study under what parameter conditions system (2.7) has an equilibrium in the all ramp region. Additionally, we will consider the case in which an equilibrium exists

when x falls between the thresholds $2\theta_1$ and $2\theta_2$; both the $\theta_1 < \theta_2$ and $\theta_2 < \theta_1$ cases will be considered.

2.2.1 All Ramp Region

From the $\dot{x}$ equation in (2.8), we have that

$$x^* = \frac{2\theta_1\theta_2 x_0}{a\theta_2 + b\theta_1}$$

at equilibrium. This value falls in the all ramp region if and only if $x^* < \min\{2\theta_1, 2\theta_2\}$. Equivalently, using our expression for x^* above, this condition can be written as

$$x_0 < \min\left\{a + \frac{b\theta_1}{\theta_2}, \frac{a\theta_2}{\theta_1} + b\right\}.$$

Then, for y^* we have

$$\begin{aligned} y^* &= \frac{a\theta_3}{c\theta_1}x^* + \frac{2\theta_3 y_0}{c} \\ &= \frac{2a\theta_2\theta_3 x_0}{c(a\theta_2 + b\theta_1)} + \frac{2\theta_3 y_0}{c}. \end{aligned}$$

This value falls in the ramp region for y if and only if $y^* < 2\theta_3$, i.e. $\frac{a}{2\theta_1}x^* + y_0 < c$ or equivalently,

$$\frac{a\theta_2 x_0}{a\theta_2 + b\theta_1} + y_0 < c.$$

Now, we consider stability and flow in the all ramp region. The Jacobian of (2.8) is triangular with two negative eigenvalues, $-\frac{aX}{2\theta_1} - \frac{bX}{2\theta_2}$ and $-\frac{cY}{2\theta_3}$, and hence the equilibrium point in this region is asymptotically stable. For flow, we have six regions of phase space to consider; x can be below both, in between, or above both thresholds, while y is either below or above its threshold $2\theta_3$.

The x nullcline of (2.8) is the vertical line

$$x = \frac{2\theta_1\theta_2 x_0}{a\theta_2 + b\theta_1}.$$

The $\dot{x}$ equation in (2.7) is positive for x values located to the left of this line, and negative for x values to the right of this line. Note that this line is not contained to just the all ramp region; it extends into the box in which $x < \min\{2\theta_1, 2\theta_2\}$ and $y \geq 2\theta_3$ (i.e. where the function $r_3(y)$ is saturated, but $r_1(x)$ and $r_2(x)$ are both still in their ramp regions).

The y nullcline is given by

$$y = \frac{a\theta_3}{c\theta_1}x + \frac{2\theta_3 y_0}{c}$$

in the all ramp region. This line eventually enters another region of phase space, but which one depends on parameters. In general, the y nullcline of system (2.7) is

$$r_3(y) \;=\; \frac{a}{c} r_1(x) + \frac{y_0}{c}.$$

If $c < a + y_0$, then the y nullcline passes through a point in which $r_3(y) = 1$ before it reaches a point with $r_1(x) = 1$. In this case, the y nullcline becomes the line

$$\begin{aligned} 1 \;&=\; \frac{a}{c} \cdot \frac{x}{2\theta_1} + \frac{y_0}{c} \\ \Longrightarrow\; x \;&=\; \frac{2(c - y_0)\theta_1}{a} \end{aligned}$$

for $y \geq 2\theta_3$. Meanwhile, if $c > a + y_0$ the function $r_1(x)$ will saturate first, resulting in the y nullcline becoming

$$\begin{aligned} \frac{y}{2\theta_3} \;&=\; \frac{a}{c} + \frac{y_0}{c} \\ \Longrightarrow\; y \;&=\; \frac{2(a + y_0)\theta_3}{c} \end{aligned}$$

for $x \geq 2\theta_1$. Finally, $c = a + y_0$ is the special case in which $(r_1(x), r_3(y)) = (1, 1)$ falls on the y nullcline, resulting in the nullcline extending into region(s) of phase space in which $y \geq 2\theta_3$ and $x \geq 2\theta_1$.

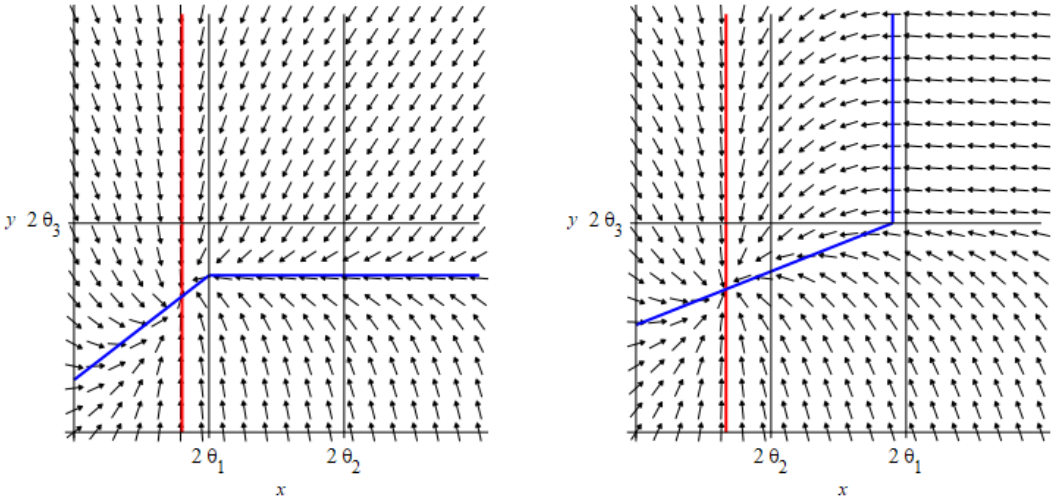
The $\dot{y}$ equation in (2.7) is positive at points that fall below or to the right of the y nullcline and negative at points located above or to the left. This, combined with the sign pattern of $\dot{x}$ described above, results in a flow pattern in system (2.7) in which global flow is directed toward the unique equilibrium in the all ramp region. A couple of vector fields showing this flow pattern are provided in Figure 2.2.1, representing both the $\theta_1 < \theta_2$ and $\theta_2 < \theta_1$ cases, as well as showing two possibilities for the regions of phase space the y nullcline can be located in.

2.2.2 The $2\theta_1 \leq x < 2\theta_2$ Case

Now, we will determine under what parameter conditions system (2.7) has equilibria when x is between its two thresholds, starting with the $\theta_1 < \theta_2$ case. Like in the previous section, we will assume y is below its threshold $2\theta_3$. When $2\theta_1 \leq x < 2\theta_2$ and $y < 2\theta_3$, the function $r_1(x)$ is saturated at 1 and system (2.7) has the form

$$\begin{aligned} \dot{x} \;&=\; -a - \frac{bx}{2\theta_2} + x_0 \\ \dot{y} \;&=\; a - \frac{cy}{2\theta_3} + y_0. \end{aligned} \tag{2.9}$$

Setting the $\dot{x}$ equation in (2.9) equal to zero, we get that $x^* = \dfrac{2(x_0 - a)\theta_2}{b}$. This value



(a) $\theta_1 < \theta_2$ (b) $\theta_2 < \theta_1$

Figure 2.2.1: Flow in system (2.7) when an equilibrium exists in the all ramp region. The x nullcline is shown in red while the y nullcline is shown in blue.

falls within the desired bounds for x if and only if

$$2\theta_1 \leq \frac{2(x_0 - a)\theta_2}{b} < 2\theta_2$$

$$\iff a + \frac{b\theta_1}{\theta_2} \leq x_0 < a + b.$$

From $\dot{y} = 0$, we get that $y^* = \dfrac{2(a + y_0)\theta_3}{c}$, which satisfies $y^* < 2\theta_3$ if and only if $a + y_0 < c$.

The Jacobian of (2.9) has the two negative eigenvalues $-\dfrac{b}{2\theta_2}$ and $-\dfrac{c}{2\theta_3}$, implying that the equilibrium point found above is asymptotically stable. As $2\theta_1 \leq x^* < 2\theta_2$, the x nullcline of system (2.7) is

$$x = \frac{2(x_0 - a)\theta_2}{b},$$

which spans two boxes of phase space: the one defined by $2\theta_1 \leq x < 2\theta_2$ and $y < 2\theta_3$ along with the one defined by $2\theta_1 \leq x < 2\theta_2$ and $y \geq 2\theta_3$. Note that as the equilibrium value of x falls in between the two thresholds in this case, system (2.7) no longer has an x nullcline in the all ramp region. The $\dot{x}$ equation is positive for $x < x^*$ and negative for $x > x^*$.

The y nullcline is similar to what was discussed in the previous section. It starts in the all ramp region as the line

$$y = \frac{a\theta_3}{c\theta_1}x + \frac{2\theta_3 y_0}{c},$$

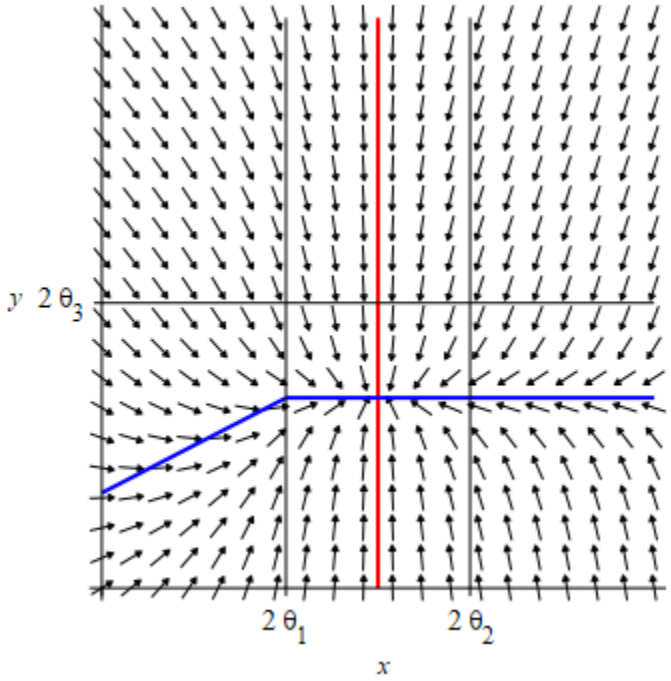


Figure 2.2.2: Flow in system (2.7) when there is an equilibrium satisfying $2\theta_1 \leq x^* < 2\theta_2$ and $y^* < 2\theta_3$. The x nullcline is shown in red while the y nullcline is shown in blue.

and eventually enters another region of phase space. As we have the condition $c > a + y_0$ for the existence of y^* in system (2.9), the y nullcline becomes

$$y = \frac{2(a + y_0)\theta_3}{c}$$

for $x \geq 2\theta_1$. Thus, the y nullcline will resemble the one shown in Figure 2.2.1(a). As mentioned in the previous section, the $\dot{y}$ equation in (2.7) will be positive at points located below or to the right of the y nullcline and negative at points located above or to the left.

As a result, when system (2.7) has an equilibrium satisfying $2\theta_1 \leq x^* < 2\theta_2$ and $y^* < 2\theta_3$, global flow will be toward this equilibrium point. The vector field for this case is shown in Figure 2.2.2.

2.2.3 The $2\theta_2 \leq x < 2\theta_1$ Case

Finally, we consider the case in which $\theta_2 < \theta_1$. We want to know when system (2.7) has an equilibrium satisfying $2\theta_2 \leq x^* < 2\theta_1$ and $y^* < 2\theta_3$. Under these variable bounds, (2.7) has the form

$$\begin{aligned} \dot{x} &= -\frac{ax}{2\theta_1} - b + x_0 \\ \dot{y} &= \frac{ax}{2\theta_1} - \frac{cy}{2\theta_3} + y_0. \end{aligned} \tag{2.10}$$

System (2.10) has the unique equilibrium point

$$\begin{aligned} x^* &= \frac{2(x_0 - b)\theta_1}{a} \\ y^* &= \frac{2(x_0 + y_0 - b)\theta_3}{c} \end{aligned}$$

if and only if

$$\frac{\theta_2 a}{\theta_1} + b \leq x_0 < a + b$$

$$x_0 + y_0 < c + b$$

both hold. Stability and flow is similar to the previous two cases: the Jacobian of (2.10) has two negative eigenvalues, $-\frac{a}{2\theta_1}$ and $-\frac{c}{2\theta_3}$, and global flow is toward the equilibrium point. The x nullcline in this case is given by

$$x = \frac{2(x_0 - b)\theta_1}{a}.$$

Meanwhile, the y nullcline once again begins as the line

$$y = \frac{a\theta_3}{c\theta_1}x + \frac{2\theta_3 y_0}{c}$$

in the all ramp region and the box in which $2\theta_2 \leq x < 2\theta_1$ and $y < 2\theta_3$, and eventually extends into another region of phase space; as discussed in the section on the all ramp region, which region the y nullcline enters depends on whether the parameter c is less than, greater than, or equal to $a + y_0$. The vector field for this case is displayed in Figure 2.2.3 below.

2.2.4 Other Cases and Summary

So far, our work has considered equilibria in system (2.7) when $x < \max\{2\theta_1, 2\theta_2\}$ and $y < 2\theta_3$; as we have seen, we always have a unique equilibrium when these conditions hold. Now, we will briefly cover the existence of equilibria when one or both variables are above all of their associated thresholds, which will allow system (2.7) to have lines of equilibria.

When $x \geq \max\{2\theta_1, 2\theta_2\}$, the $\dot{x}$ equation from (2.7) becomes

$$\dot{x} = -a - b + x_0.$$

This gives us a line of equilibrium values for x, $x^* \geq \max\{2\theta_1, 2\theta_2\}$, if and only if $x_0 = a + b$. The $\dot{y}$ equation in this case is

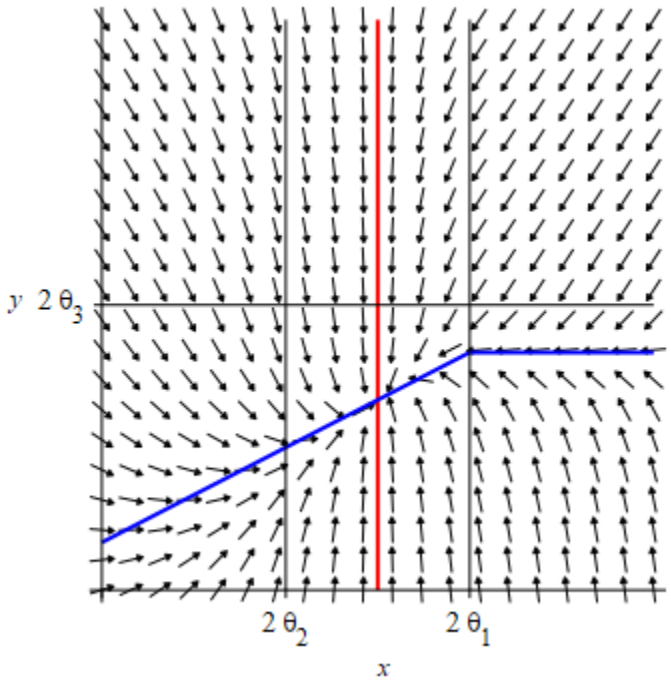


Figure 2.2.3: Flow in system (2.7) when there is an equilibrium satisfying $2\theta_2 \leq x^* < 2\theta_1$ and $y^* < 2\theta_3$. The x nullcline is shown in red while the y nullcline is shown in blue.

$$\dot{y} \;=\; a - cr_3(y) + y_0,$$

and thus the equilibrium value(s) of y satisfy

$$r_3(y^*) \;=\; \frac{a + y_0}{c}$$

if and only if $a + y_0 \leq c$. Here, $a + y_0 < c$ gives us the unique value $y^* = \dfrac{2(a + y_0)\theta_3}{c}$, while the $a + y_0 = c$ case corresponds to $r_3(y^*) = 1$, giving us the line of equilibrium values $y^* \geq 2\theta_3$.

The previous paragraph describes equilibria in system (2.7) when both variables are above all their thresholds or when just x is. The case in which y is above threshold and x is below at least one threshold is similar. When $y \geq 2\theta_3$, the $\dot{y}$ equation from (2.7) is given by

$$\dot{y} \;=\; ar_1(x) - c + y_0.$$

Assuming there is an x^* such that $\dot{x} = 0$, we will have $y^* \geq 2\theta_3$ if and only if $c = ar_1(x^*) + y_0$.

Next, we will consider the qualitative behaviour of system (2.7) when it has no equilibria at all. Our analysis has shown that there is at least one x^* at which $\dot{x} = 0$ if and only if $x_0 \leq a + b$. If $x_0 > a + b$, then the $\dot{x}$ equation from (2.7) will satisfy

$$\dot{x} \;=\; -ar_1(x) - br_2(x) + x_0$$

$$\begin{aligned} &> -ar_1(x) - br_2(x) + a + b \\ &= a[1 - r_1(x)] + b[1 - r_2(x)] \\ &\geq 0, \end{aligned}$$

and thus x will grow without bound.

If there exists an x^* at which $\dot{x} = 0$, then the $\dot{y}$ equation

$$\dot{y} = ar_1(x) - cr_3(y) + y_0$$

has the equilibrium solution $r_3(y^*) = \dfrac{ar_1(x^*) + y_0}{c}$ if and only if $ar_1(x^*) + y_0 \leq c$. If we have $ar_1(x^*) + y_0 > c$, then on the x nullcline

$$\begin{aligned} \dot{y} &= ar_1(x^*) - cr_3(y) + y_0 \\ &> ar_1(x^*) - [ar_1(x^*) + y_0]r_3(y) + y_0 \\ &= ar_1(x^*)[1 - r_3(y)] + y_0[1 - r_3(y)] \\ &\geq 0, \end{aligned}$$

and hence flow is straight upward. Thus, if system (2.7) does not have equilibria, flow will be unbounded.

Our analysis of system (2.7) is summarized in the following theorem:

Theorem 2.2.1. *Consider a system of form* (2.7).

1.) *There is at least one value $x = x^*$ at which the $\dot{x}$ equation in* (2.7) *equals zero if and only if $x_0 \leq a + b$. If such an x^* exists, there is at least one $y = y^*$ at which $\dot{y} = 0$ if and only if $ar_1(x^*) + y_0 \leq c$.*

2.) *The cases $x_0 < a + b$ and $ar_1(x^*) + y_0 < c$ correspond to a unique equilibrium point (x^*, y^*) in which $x^* < \max\{2\theta_1, 2\theta_2\}$ and $y^* < 2\theta_3$. There are three possibilities for this unique equilibrium depending on whether x is below or in between its thresholds, and which threshold is larger:*

   a.) *System* (2.7) *has an equilibrium in the all ramp region ($x < \min\{2\theta_1, 2\theta_2\}$, $y < 2\theta_3$) at*

$$\begin{aligned} x^* &= \frac{2\theta_1\theta_2 x_0}{a\theta_2 + b\theta_1} \\ y^* &= \frac{2a\theta_2\theta_3 x_0}{c(a\theta_2 + b\theta_1)} + \frac{2\theta_3 y_0}{c} \end{aligned}$$

   if and only if

$$x_0 < \min\left\{a + \frac{b\theta_1}{\theta_2}, \frac{a\theta_2}{\theta_1} + b\right\}$$

$$\frac{a\theta_2 x_0}{a\theta_2 + b\theta_1} + y_0 \ < \ c$$

both hold.

b.) System (2.7) has the equilibrium

$$x^* \ = \ \frac{2(x_0 - a)\theta_2}{b}$$

$$y^* \ = \ \frac{2(a + y_0)\theta_3}{c}$$

satisfying $2\theta_1 \leq x^* < 2\theta_2$ *and* $y^* < 2\theta_3$ *if and only if*

$$a + \frac{b\theta_1}{\theta_2} \ \leq x_0 \ < \ a + b$$

$$a + y_0 \ < \ c$$

both hold.

c.) System (2.7) has the equilibrium

$$x^* \ = \ \frac{2(x_0 - b)\theta_1}{a}$$

$$y^* \ = \ \frac{2(x_0 + y_0 - b)\theta_3}{c}$$

satisfying $2\theta_2 \leq x^* < 2\theta_1$ *and* $y^* < 2\theta_3$ *if and only if*

$$\frac{\theta_2 a}{\theta_1} + b \ \leq x_0 \ < \ a + b$$

$$x_0 + y_0 \ < \ c + b$$

both hold.

3.) *If system (2.7) has a unique equilibrium point, then global flow is toward this equilibrium.*

4.) *If system (2.7) has no equilibria, flow is unbounded.*

2.2.5 Comparisons to Michaelis-Menten

Now, we will examine how the qualitative behaviour of ramp system (2.7) compares to the corresponding Michaelis-Menten system

$$\begin{aligned} \dot{x} &= -\frac{ax}{\theta_1 + x} - \frac{bx}{\theta_2 + x} + x_0 \\ \dot{y} &= \frac{ax}{\theta_1 + x} - \frac{cy}{\theta_3 + y} + y_0. \end{aligned} \tag{2.11}$$

Here, we will find parameter conditions for system (2.11) to have non-negative equilibria. First, $\dot{x} = 0$ will have a solution if and only if $x_0 < a + b$; if $x_0 \geq a + b$, then, since the Michaelis-Menten terms $\frac{x}{\theta_1 + x}$ and $\frac{x}{\theta_2 + x}$ are each strictly less than 1 for non-negative values of x, the $\dot{x}$ equation will always be positive for $x \geq 0$.

If $x_0 < a + b$, then from $\dot{x} = 0$ we have that the equilibrium value of x must satisfy

$$(a + b - x_0)x^2 + (a\theta_2 + b\theta_1 - x_0[\theta_1 + \theta_2])x - x_0\theta_1\theta_2 = 0.$$

As we saw with system (2.3), this quadratic has only one non-negative root, obtained from taking the positive root in the quadratic formula. Hence, we have that

$$x^* = \frac{-B + \sqrt{B^2 + 4(x_0\theta_1\theta_2)(a + b - x_0)}}{2(a + b - x_0)}, \tag{2.12}$$

where $B = a\theta_2 + b\theta_1 - x_0[\theta_1 + \theta_2]$.

Then, the equilibrium value for y^* must satisfy

$$\frac{cy^*}{\theta_3 + y^*} = y_0 + aM_1(x^*),$$

where $M_1(x) = \frac{x}{\theta_1 + x}$ and x^* is from (2.12). This then gives us that

$$\begin{aligned} y^* &= \frac{\theta_3(y_0 + aM_1(x^*))}{c - y_0 - aM_1(x^*)} \\ &= \frac{\theta_1\theta_3 y_0 + \theta_3(y_0 + a)x^*}{(c - y_0)\theta_1 + (c - y_0 - a)x^*}. \end{aligned} \tag{2.13}$$

This value for y^* is defined and non-negative if and only if $c > y_0 + aM_1(x^*)$. Note that if $c \leq y_0 + aM_1(x^*)$, then along the x nullcline we have

$$\begin{aligned} \dot{y} &= aM_1(x^*) - \frac{cy}{\theta_3 + y} + y_0 \\ &\geq aM_1(x^*) - \frac{[y_0 + aM_1(x^*)]y}{\theta_3 + y} + y_0 \\ &= aM_1(x^*)\Big(1 - \frac{y}{\theta_3 + y}\Big) + y_0\Big(1 - \frac{y}{\theta_3 + y}\Big) \\ &> 0, \end{aligned}$$

and hence flow is straight upward.

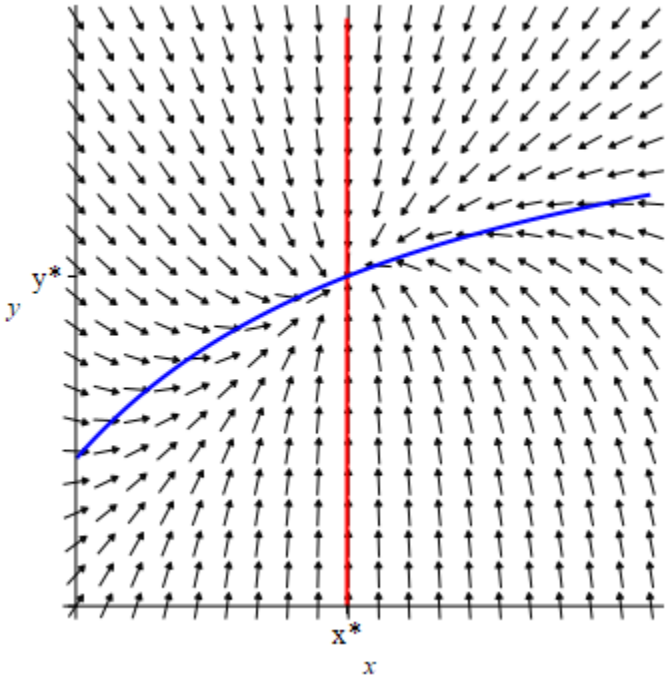


Figure 2.2.4: Flow in system (2.11) in the first quadrant when the equilibrium point $(x^*, y^*) = ((2.12), (2.13))$ exists. The x nullcline is shown in red while the y nullcline is shown in blue.

Thus, Michaelis-Menten system (2.11) has the unique non-negative equilibrium $(x^*, y^*) = ((2.12), (2.13))$ if and only if the conditions $x_0 < a + b$ and $c > y_0 + aM_1(x^*)$ hold. The Jacobian of (2.11) is triangular with negative diagonal entries, and hence this equilibrium is asymptotically stable. Global flow in the first quadrant will be toward this unique equilibrium point; the $\dot{x}$ equation is positive for x values to the left of the x nullcline

$$x = \frac{-B + \sqrt{B^2 + 4(x_0\theta_1\theta_2)(a + b - x_0)}}{2(a + b - x_0)},$$

and negative for x values to the right of this line, while $\dot{y}$ is positive for y values below the y nullcline

$$y = \frac{\theta_1\theta_3 y_0 + \theta_3(y_0 + a)x}{(c - y_0)\theta_1 + (c - y_0 - a)x},$$

and negative at y values that fall above this line. Figure 2.2.4 shows the vector field for system (2.11) in the first quadrant when there is an equilibrium point.

In summary, ramp system (2.7) and Michaelis-Menten system (2.11) display qualitatively similar behaviour:

- The conditions for the existence of non-negative equilibria are analogous: $x_0 \leq a + b$ and $ar_1(x^*) + y_0 \leq c$ for the ramp system, and $x_0 < a + b$ and $y_0 + aM_1(x^*) < c$ for

the Michaelis-Menten system. The conditions for the Michaelis-Menten system always result in a unique non-negative equilibrium, while the ramp system will also have a unique equilibrium if both inequalities are strict; the equality conditions for the ramp system correspond to special cases in which the system has a line of equilibria resulting from the use of ramp functions.

- In both systems, if a unique non-negative equilibrium exists, flow is toward that equilibrium in the first quadrant.
- Both systems display unbounded behaviour if no equilibria exist.

2.3 SRP Systems in n Variables

The ramp systems (2.1), (2.5), and (2.7) we have analyzed so far in this chapter are SRP systems in one or two variables. In this section, we will study general n-variable SRP systems with multiple thresholds per variable, with a focusing on finding equilibria in these systems.

2.3.1 A Linear Algebra Approach to Finding Equilibria

The third chapter of [5] focused on determining parameter conditions under which n-variable SRP systems with a single ramp function associated with each variable had equilibria, with emphasis on equilibria in the all ramp region. These SRP systems had the form

$$\begin{bmatrix} \dot{x_1} \\ \dot{x_2} \\ \vdots \\ \dot{x_n} \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & -a_{22} & \dots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(x_1) \\ r_2(x_2) \\ \vdots \\ r_n(x_n) \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ \vdots \\ x_{n_0} \end{bmatrix},$$

where the $n \times n$ matrix is an SRP matrix, and the $x_{i_0} \geq 0$ represent possible reactions of the form $0 \xrightarrow{x_{i_0}} X_i$.

The equilibria results presented on these systems in [5] used techniques from linear algebra. Here, we will apply similar linear algebra techniques to determine when equilibria exist in SRP systems with multiple thresholds allowed per variable. In general, when an SRP system is in the all ramp region, it has the form

$$\begin{bmatrix} \dot{x_1} \\ \dot{x_2} \\ \vdots \\ \dot{x_n} \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & -a_{22} & \dots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ \vdots \\ x_{n_0} \end{bmatrix}, \tag{2.14}$$

which can be more compactly written as

$$\dot{\vec{x}} \;=\; A\vec{x} + \vec{x_0},$$

where the $n \times n$ matrix A is still an SRP matrix; in fact, it is the Jacobian of the system in the all ramp region.

As an example, the all ramp region equations for system (2.7) were given in (2.8) as

$$\begin{aligned} \dot{x} \;&=\; -\frac{ax}{2\theta_1} - \frac{bx}{2\theta_2} + x_0 \\ \dot{y} \;&=\; \frac{ax}{2\theta_1} - \frac{cy}{2\theta_3} + y_0, \end{aligned}$$

which can be written in the matrix and vector form (2.14) as

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -\dfrac{a}{2\theta_1} - \dfrac{b}{2\theta_2} & 0 \\ \dfrac{a}{2\theta_1} & -\dfrac{c}{2\theta_3} \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix}.$$

Below, we present several results regarding equilibria in systems that have form (2.14) when in the all ramp region. These results are similar to those presented in [5], but with $r(x) < 1$ conditions replaced with $x < m$, where m is the smallest threshold associated with variable x.

Proposition 2.3.1. Consider a biochemical ramp system that has form (2.14) when in the all ramp region. Suppose the ith variable x_i has α_i distinct thresholds $2\theta_{1i}, 2\theta_{2i}, \ldots, 2\theta_{\alpha_i i}$, and let $m_i = \min\{2\theta_{1i}, 2\theta_{2i}, \ldots, 2\theta_{\alpha_i i}\}$. Then, if A is invertible, (2.14) has an equilibrium in the all ramp region if and only if for all i,

$$\frac{\sum_{j=1}^{n} C_{ji} x_{j_0}}{-\det(A)} \;<\; m_i,$$

where the C_{ji} are cofactors of A. Additionally, if this equilibrium exists, it is unique.

Proof. Equilibria of (2.14) are given by $\vec{x^*} = -A^{-1}\vec{x_0}$. Note that every component of $\vec{x^*}$ is non-negative as by Theorem 1.1.7, all entries of A^{-1} are non-positive. The ith component is

$$\begin{aligned} x_i^* \;&=\; \frac{C_{1i}x_{1_0} + C_{2i}x_{2_0} + \cdots + C_{ni}x_{n_0}}{-\det(A)} \\ &=\; \frac{\sum_{j=1}^{n} C_{ji} x_{j_0}}{-\det(A)}, \end{aligned}$$

which falls in the all ramp region for x_i if and only if it is strictly less than m_i. If we have $x_i^* < m_i$ for all i, then $\vec{x^*}$ is the only equilibrium point of the system, since A being invertible means that $A\vec{x^*} = -\vec{x_0}$ has a unique solution. □

Proposition 2.3.2. Consider a biochemical ramp system that has form (2.14) when in the all ramp region. If $\vec{x_0} = 0$, then the system has at least one equilibrium in the all ramp region. If A is not invertible, there are infinitely many such equilibria.

Proof. With $\vec{x_0} = 0$, equilibria are solutions to $A\vec{x^*} = 0$, which always has at least the origin as a solution.

By Proposition 1.2.1, a singular SRP matrix has an eigenvector with non-negative components. Hence, $A\vec{x^*} = 0$ has a non-negative solution aside from the origin, and we can find infinitely many such eigenvectors in the all ramp region by multiplying the eigenvector by sufficiently small positive scalars. □

Proposition 2.3.3. Consider a biochemical ramp system that has form (2.14) when in the all ramp region. If the system has an equilibrium in the all ramp region, then for all i we have $x_{i_0} \leq m_i a_{ii}$, where m_i is the smallest threshold associated with x_i. If $a_{ii} \neq 0$, this inequality is strict.

Proof. Suppose (2.14) has an equilibrium $\vec{x^*}$ with $x_i^* < m_i$ for all i. By contradiction, suppose $x_{i_0} > m_i a_{ii}$ for some i. Then at equilibrium,

$$\begin{aligned} \dot{x_i} &= -a_{11}x_1^* + \sum_{j\neq 1} a_{ji}x_j^* + x_{i_0} \\ &> a_{11}[m_i - x_i^*] + \sum_{j\neq 1} a_{ji}x_j^* \\ &\geq 0, \end{aligned}$$

a contradiction. If a_{ii} is not zero, then $a_{ii}[m_i - x_i^*]$ is strictly positive, and thus the $x_{i_0} = m_i a_{ii}$ case cannot hold. □

2.3.1.1 Adams Model

The ramp function version of the Adams model of plant metabolism without the SEL was given in (3) as

$$\begin{aligned} \dot{x_1} &= a_0 - a_1 r_1(x_1) \\ \dot{x_2} &= a_1 r_1(x_1) - a_3 r_3^2(x_2) - a_5 r_5(x_2) \\ \dot{x_3} &= a_3 r_3^2(x_2) - a_4 r_4(x_3). \end{aligned}$$

This is an SRP system that has form (2.14) when in the all ramp region. The variable x_2 in this system has two associated ramp functions, r_3^2 and r_5, with thresholds $2K_3^2$ and $2K_5$ respectively. The linear algebra approach used in Chapter 3 of [5] to find all ramp region equilibria in SRP systems could only be applied to the Adams model when $K_3^2 = K_5$. However, our work in this section now allows us to find equilibria even when these parameters are not equal.

In the all ramp region, system (3) becomes

$$\dot{x_1} = a_0 - \frac{a_1 x_1}{2K_1}$$

$$\begin{aligned}\dot{x_2} &= \frac{a_1 x_1}{2K_1} - \frac{a_3 x_2}{2K_3^2} - \frac{a_5 x_2}{2K_5} \\ \dot{x_3} &= \frac{a_3 x_2}{2K_3^2} - \frac{a_4 x_3}{2K_4},\end{aligned}$$

which can be written in form (2.14) as

$$\begin{bmatrix}\dot{x_1} \\ \dot{x_2} \\ \dot{x_3}\end{bmatrix} = \begin{bmatrix}-\frac{a_1}{2K_1} & 0 & 0 \\ \frac{a_1}{2K_1} & -\left(\frac{a_3}{2K_3^2} + \frac{a_5}{2K_5}\right) & 0 \\ 0 & \frac{a_3}{2K_3^2} & -\frac{a_4}{2K_4}\end{bmatrix}\begin{bmatrix}x_1 \\ x_2 \\ x_3\end{bmatrix} + \begin{bmatrix}a_0 \\ 0 \\ 0\end{bmatrix}.$$

The 3×3 matrix is invertible with

$$\begin{bmatrix}-\frac{a_1}{2K_1} & 0 & 0 \\ \frac{a_1}{2K_1} & -\left(\frac{a_3}{2K_3^2} + \frac{a_5}{2K_5}\right) & 0 \\ 0 & \frac{a_3}{2K_3^2} & -\frac{a_4}{2K_4}\end{bmatrix}^{-1} = \begin{bmatrix}-\frac{2K_1}{a_1} & 0 & 0 \\ -\frac{2K_3^2 K_5}{a_3 K_5 + a_5 K_3^2} & -\frac{2K_3^2 K_5}{a_3 K_5 + a_5 K_3^2} & 0 \\ -\frac{2a_3 K_4 K_5}{a_4(a_3 K_5 + a_5 K_3^2)} & -\frac{2a_3 K_4 K_5}{a_4(a_3 K_5 + a_5 K_3^2)} & -\frac{2K_4}{a_4}\end{bmatrix}.$$

Thus, we have that

$$\begin{aligned}\begin{bmatrix}x_1^* \\ x_2^* \\ x_3^*\end{bmatrix} &= \begin{bmatrix}-\frac{2K_1}{a_1} & 0 & 0 \\ -\frac{2K_3^2 K_5}{a_3 K_5 + a_5 K_3^2} & -\frac{2K_3^2 K_5}{a_3 K_5 + a_5 K_3^2} & 0 \\ -\frac{2a_3 K_4 K_5}{a_4(a_3 K_5 + a_5 K_3^2)} & -\frac{2a_3 K_4 K_5}{a_4(a_3 K_5 + a_5 K_3^2)} & -\frac{2K_4}{a_4}\end{bmatrix}\begin{bmatrix}-a_0 \\ 0 \\ 0\end{bmatrix} \\ &= \begin{bmatrix}\frac{2a_0 K_1}{a_1} \\ \frac{2a_0 K_3^2 K_5}{a_3 K_5 + a_5 K_3^2} \\ \frac{2a_0 a_3 K_4 K_5}{a_4(a_3 K_5 + a_5 K_3^2)}\end{bmatrix},\end{aligned}$$

which falls in the all ramp region if and only if

$$x_1^* < 2K_1 \qquad x_2^* < \min\{2K_3^2, 2K_5\} \qquad x_3^* < 2K_4$$

all hold, or equivalently, if and only if

$$a_0 < \min\left\{a_1,\ \frac{a_3K_5 + a_5K_3^2}{K_3^2},\ \frac{a_3K_5 + a_5K_3^2}{K_5},\ \frac{a_4(a_3K_5 + a_5K_3^2)}{a_3K_5}\right\}.$$

2.3.2 A Class of Systems

We saw that the two-variable ramp system (2.7), when in the all ramp region, resembles as mass action system derived from the reactions $X \to Y$, $X \leftrightharpoons 0$, and $Y \leftrightharpoons 0$, where $X \leftrightharpoons 0$ represents the two reactions $X \to 0$ and $0 \to X$. Here, we will expand this to a series of reactions in n variables. In particular, our n-variable system in the all ramp region will be derived from a mass action system consisting of the chain of reactions $X_1 \to X_2 \to \cdots \to X_n$ along with $X_i \leftrightharpoons 0$ for all i. With ramp functions, this gives us the following system of differential equations:

$$\begin{aligned}
\dot{x}_1 &= -a_1 r_{1_1}(x_1) - b_1 r_{2_1}(x_1) + x_{1_0} \\
\dot{x}_2 &= a_1 r_{1_1}(x_1) - a_2 r_{1_2}(x_2) - b_2 r_{2_2}(x_2) + x_{2_0} \\
&\vdots \\
\dot{x}_m &= a_{m-1} r_{1_{m-1}}(x_{m-1}) - a_m r_{1_m}(x_m) - b_m r_{2_m}(x_m) + x_{m_0} \\
&\vdots \\
\dot{x}_n &= a_{n-1} r_{1_{n-1}}(x_{n-1}) - c r_3(x_n) + x_{n_0}
\end{aligned} \tag{2.15}$$

Here, $2 \leq m \leq n-1$ and the a_i and b_i are positive constants. We will assume the x_{i_0} are non-negative; if some $x_{i_0} = 0$, then the reaction $0 \xrightarrow{x_0} X_i$ is not present. Ramp function r_{1_i} has threshold $2\theta_{1_i}$ and r_{2_i} has threshold $2\theta_{2_i}$. The variable x_n only has one associated ramp function, r_3, which has threshold $2\theta_3$.

We will determine under what parameter conditions system (2.15) has equilibria. In particular, we will find equilibria for which each variable is below at least one of its thresholds; we will not cover the special case in which both ramp functions associated with a particular variable are saturated at 1. To reduce the number of cases to consider, we will assume that for $i = 1, 2, \ldots, n-1$, $\theta_{1_i} < \theta_{2_i}$. Thus, we will be concerned with equilibria in which each x_i at equilibrium satisfies $x_i^* < 2\theta_{2_i}$ for $i < n$ and x_n^* satisfies $x_n^* < 2\theta_3$.

For $\dot{x}_1$ in (2.15), the equilibrium solution for x_1^* is similar to what we saw for x^* in the two-variable system (2.7). When $x_1 < 2\theta_{1_1} < 2\theta_{2_1}$, we get

$$x_1^* = \frac{2\theta_{1_1}\theta_{2_1}x_{1_0}}{a_1\theta_{2_1} + b_1\theta_{1_1}}$$

if and only if $x_{1_0} < a_1 + b_1\dfrac{\theta_{1_1}}{\theta_{2_1}}$. If $2\theta_{1_1} \leq x_1 < 2\theta_{2_1}$, we have that

$$x_1^* = \frac{2(x_{1_0} - a_1)\theta_{2_1}}{b_1}$$

if and only if $a_1 + b_1\dfrac{\theta_{1_1}}{\theta_{2_1}} \leq x_{1_0} < a_1 + b_1$.

Next, we will look at $\dot{x}_m$ for $m \in \{2, 3, \ldots, n-1\}$. First, suppose that $x^*_{m-1} < 2\theta_{2_{m-1}}$ exists; we will solve for x^*_m in terms of x^*_{m-1}. When $x_m < 2\theta_{1_m} < 2\theta_{2_m}$, x^*_m is the solution to

$$a_{m-1}r_{1_{m-1}}(x^*_{m-1}) - \frac{a_m x^*_m}{2\theta_{1_m}} - \frac{b_m x^*_m}{2\theta_{2_m}} + x_{m_0} \;=\; 0,$$

which is

$$x^*_m \;=\; \frac{2[x_{m_0} + a_{m-1}r_{1_{m-1}}(x^*_{m-1})]\theta_{1_m}\theta_{2_m}}{a_m\theta_{2_m} + b_m\theta_{1_m}}$$

if and only if

$$x_{m_0} + a_{m-1}r_{1_{m-1}}(x^*_{m-1}) \;<\; a_m + b_m\frac{\theta_{1_m}}{\theta_{2_m}}.$$

Then, for $2\theta_{1_m} \leq x_m < 2\theta_{2_m}$, we have

$$a_{m-1}r_{1_{m-1}}(x^*_{m-1}) - a_m - \frac{b_m x^*_m}{2\theta_{2_m}} + x_{m_0} \;=\; 0$$

$$\Longrightarrow\; x^*_m \;=\; \frac{2[x_{m_0} + a_{m-1}r_{1_{m-1}}(x^*_{m-1}) - a_m]\theta_{2_m}}{b_m}$$

if and only if

$$a_m + b_m\frac{\theta_{1_m}}{\theta_{2_m}} \leq x_{m_0} + a_{m-1}r_{1_{m-1}}(x^*_{m-1}) \;<\; a_m + b_m.$$

Finally, we look at $\dot{x}_n$. If $x^*_{n-1} < 2\theta_{2_{n-1}}$ exists, then for $x_n < 2\theta_3$ we have

$$a_{n-1}r_{1_{n-1}}(x^*_{n-1}) - \frac{cx^*_n}{2\theta_3} + x_{n_0} \;=\; 0$$

$$\Longrightarrow\; x^*_n \;=\; \frac{2[x_{n_0} + a_{n-1}r_{1_{n-1}}(x^*_{n-1})]\theta_3}{c}$$

if and only if

$$x_{n_0} + a_{n-1}r_{1_{n-1}}(x^*_{n-1}) \;<\; c.$$

Our work here has shown that if system (2.15) has an equilibrium such that $x^*_i < 2\theta_{2_i}$ for $i < n$ and $x^*_n < 2\theta_3$, it will be unique. Additionally, it will be asymptotically stable; the Jacobian of (2.15) at the equilibrium will be triangular with negative entries on the diagonal.

It can also been seen that such an equilibrium point will be globally stable. The $\dot{x}_1$ equation in (2.15) is functionally identical to the $\dot{x}$ equation in (2.7), and our analysis of the latter showed that when x^* was below at least one of its thresholds, flow in the x direction was always toward the x nullcline. Hence, if $x^*_1 < 2\theta_{2_1}$ exists, x_1 will approach x^*_1 over time.

Once x_1 has reached its equilibrium value, the $\dot{x}_2$ equation in(2.15) is positive when

$$a_2 r_{1_2}(x_2) + b_2 r_{2_2}(x_2) \;<\; a_1 r_{1_1}(x_1^*) + x_{2_0},$$

and negative when

$$a_2 r_{1_2}(x_2) + b_2 r_{2_2}(x_2) \;>\; a_1 r_{1_1}(x_1^*) + x_{2_0}.$$

Hence, x_2 will approach x_2^* over time. The $2 < m \leq n-1$ case is similar; x_m will approach the equilibrium value x_m^*. Finally, the $\dot{x}_n$ equation has the same form as the $\dot{y}$ equation from (2.7); hence, with x_{n-1}^* existing x_n will tend toward x_n^* over time.

2.3.2.1 Comparisons to Michaelis-Menten

The Michaelis-Menten system corresponding to ramp system (2.15) is

$$\begin{aligned}
\dot{x}_1 &= -a_1 M_{1_1}(x_1) - b_1 M_{2_1}(x_1) + x_{1_0} \\
\dot{x}_2 &= a_1 M_{1_1}(x_1) - a_2 M_{1_2}(x_2) - b_2 M_{2_2}(x_2) + x_{2_0} \\
&\vdots \\
\dot{x}_m &= a_{m-1} M_{1_{m-1}}(x_{m-1}) - a_m M_{1_m}(x_m) - b_m M_{2_m}(x_m) + x_{m_0} \\
&\vdots \\
\dot{x}_n &= a_{n-1} M_{1_{n-1}}(x_{n-1}) - c M_3(x_n) + x_{n_0},
\end{aligned} \tag{2.16}$$

where $M_{k_i}(x_i) = \dfrac{x_i}{\theta_{k_i} + x_i}$ for $k = 1, 2$ and $i \leq n-1$, and $M_3(x_n) = \dfrac{x_n}{\theta_3 + x_n}$.

We will determine when system (2.16) has an equilibrium point at which all variables are non-negative. The $\dot{x}_1$ equation above has the same form as the $\dot{x}$ equation from system (2.11), so x_1^* will have a form similar to the x^* value given in (2.12). Thus, $\dot{x_1} = 0$ has a single non-negative solution,

$$x_1^* \;=\; \frac{-B + \sqrt{B^2 + 4(x_{1_0}\theta_{1_1}\theta_{2_1})(a_1 + b_1 - x_{1_0})}}{2(a_1 + b_1 - x_{1_0})},$$

where $B = a_1\theta_{2_1} + b_1\theta_{1_1} - x_{1_0}[\theta_{1_1} + \theta_{2_1}]$, if and only if $x_{1_0} < a_1 + b_1$.

Next, if x_{m-1}^* exists for $2 \leq m \leq n-1$ then from $\dot{x}_m = 0$ we get that $x_m = x_m^*$ is the solution to

$$(a_m + b_m - K_m)x_m^2 + B_m x_m - K_m\theta_{1_m}\theta_{2_m} \;=\; 0$$

where

$$\begin{aligned}
K_m &= a_{m-1} M_{1_{m-1}}(x_{m-1}^*) + x_{m_0} \\
B_m &= a_m\theta_{2_m} + b_m\theta_{1_m} - K_m(\theta_{1_m} + \theta_{2_m}).
\end{aligned}$$

The coefficients of this quadratic are similar to those of the quadratic we examined when determining x^* for system (2.11); as a result, we will once again have only one non-negative solution, obtained by taking the positive root in the quadratic formula:

$$x_m^* = \frac{-B_m + \sqrt{B_m^2 + 4K_m\theta_{1_m}\theta_{2_m}(a_m + b_m - K_m)}}{2(a_m + b_m - K_m)}$$

This value for x_m^* exists if and only if $K_m < a_m + b_m$; if this inequality does not hold, then $\dot{x}_m$ will always be positive at $x_{m-1} = x_{m-1}^*$ for $x_m \geq 0$.

For x_n, the $\dot{x}_n$ equation in (2.16) has the same form as the $\dot{y}$ equation from (2.11). Hence, the equilibrium value for x_n is similar to the y^* given in (2.13), being equal to

$$\begin{aligned} x_n^* &= \frac{\theta_3(x_{n_0} + aM_{1_{n-1}}(x_{n-1}^*))}{c - x_{n_0} - aM_{1_{n-1}}(x_{n-1}^*)} \\ &= \frac{\theta_{1_{n-1}}\theta_3 x_{n_0} + \theta_3(x_{n_0} + a_{n-1})x_{n-1}^*}{(c - x_{n_0})\theta_{1_{n-1}} + (c - x_{n_0} - a_{n-1})x_{n-1}^*}, \end{aligned}$$

which is defined and non-negative if and only if $c > x_{n_0} + aM_{1_{n-1}}(x_{n-1}^*)$.

Thus, if system (2.16) has a non-negative equilibrium, it is unique. When this equilibrium exists, flow and stability is similar to what was seen in ramp system (2.15); the Jacobian at the equilibrium is triangular with all negative eigenvalues, and global flow in the first quadrant is toward the equilibrium.

Hence, ramp system (2.15) and Michaelis-Menten system (2.16) display qualitatively similar behaviour when their unique non-negative equilibrium exists:

- The necessary and sufficient parameter conditions for the existence of the equilibrium point is analogous between the two systems. In ramp system (2.15), an equilibrium point with $x_i^* < 2\theta_{2_i}$ and $x_n^* < 2\theta_3$ exists if and only if

$$\begin{aligned} x_{1_0} &< a_1 + b_1 \\ x_{m_0} + a_{m-1}r_{1_{m-1}}(x_{m-1}^*) &< a_m + b_m \\ x_{n_0} + a_{n-1}r_{1_{n-1}}(x_{n-1}^*) &< c \end{aligned}$$

  all hold. In system (2.16), the equivalent conditions for the existence of a non-negative equilibrium are

$$\begin{aligned} x_{1_0} &< a_1 + b_1 \\ K_m &< a_m + b_m \\ x_{n_0} + a_{n-1}M_{1_{n-1}}(x_{n-1}^*) &< c, \end{aligned}$$

  where $K_m = x_{m_0} + a_{m-1}M_{1_{m-1}}(x_{m-1}^*)$.

- The Jacobian evaluated at this equilibrium has solely negative eigenvalues.

- Global flow in the first quadrant is toward the equilibrium point.

2.4 Invertible Systems with One Combining Term

Chapter 4 of [5] studied a class of systems known as *invertible systems with one combining term*. These were ramp systems that, when in the all ramp region, were mass action systems derived from exactly one reaction of the form $X + Y \to Z$ and an arbitrary number of SRP terms. These systems had the general form

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \vdots \\ \dot{x}_n \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & a_{13} & a_{14} & \dots & a_{1n} \\ a_{21} & -a_{22} & a_{23} & a_{24} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & a_{34} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(x_1) \\ r_2(x_2) \\ r_3(x_3) \\ r_4(x_4) \\ \vdots \\ r_n(x_n) \end{bmatrix} + \begin{bmatrix} -kr_1(x_1)r_2(x_2) \\ -kr_1(x_1)r_2(x_2) \\ kr_1(x_1)r_2(x_2) \\ 0 \\ \vdots \\ 0 \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ x_{3_0} \\ x_{4_0} \\ \vdots \\ x_{n_0} \end{bmatrix},$$

or more compactly,

$$\dot{\vec{x}} \;=\; A\vec{r} + \vec{k} + \vec{x_0}, \tag{2.17}$$

where

- A is an invertible $n \times n$ SRP matrix with $n \geq 3$
- $\vec{r}$ is the vector of ramp functions, where function r_i has threshold $2\theta_i$.
- $\vec{k}$ is the combining term vector, with $k > 0$. Note that only the first three components of this vector are non-zero because it was assumed, WLOG, that the sole combining term derived from the reaction $X_1 + X_2 \to X_3$ involving the first three chemical species.
- $\vec{x_0}$ is the vector of constant input terms, with $x_{i_0} \geq 0$ for each i, representing possible SRP reactions of the form $0 \to x_{i_0} X_i$.

Analysis of system (2.17) in [5] focused on solving for an equilibrium point in the all ramp region and determining under which parameter conditions such an equilibrium exists. Note, however, that system (2.17) only describes systems in which each variable is associated with a single ramp function, which limited the scope of the analysis. This limitation is noteworthy as the analysis in [5] was motivated by the Adams model with the SEL, which from (4) consists of the equations

$$\dot{y} \;=\; a_0 - a_1 r_1(y) - a_3 r_3^2(x_2) r_3^3(y) + a_4 r_4(x_3)$$

$$\begin{aligned}\dot{x_2} &= a_1 r_1(y) - a_3 r_3^2(x_2) r_3^3(y) - a_5 r_5(x_2)\\ \dot{x_3} &= a_3 r_3^2(x_2) r_3^3(y) - a_4 r_4(x_3),\end{aligned}$$

and can also be written in the form

$$\begin{bmatrix}\dot{y}\\ \dot{x}_2\\ \dot{x}_3\end{bmatrix} = \begin{bmatrix}-a_1 & 0 & a_4\\ a_1 & -a_5 & 0\\ 0 & 0 & -a_4\end{bmatrix}\begin{bmatrix}r_1(y)\\ r_5(x_2)\\ r_4(x_3)\end{bmatrix} + \begin{bmatrix}-a_3 r_3^3(y) r_3^2(x_2)\\ -a_3 r_3^3(y) r_3^2(x_2)\\ a_3 r_3^3(y) r_3^2(x_2)\end{bmatrix} + \begin{bmatrix}a_0\\ 0\\ 0\end{bmatrix}. \tag{2.18}$$

Hence, the Adams model with the SEL has almost the same form as (2.17), except the variables y and x_2 each have two associated ramp functions; the results presented in [5] could thus only be applied to the Adams model in the special case that r_1 and r_3^3 had equal thresholds, as did r_5 and r_3^2.

Our goal in this section is to extend the theory developed in Chapter 4 of [5] to cover invertible systems with one combining term like (2.18). That is, systems in which the the first two variables each have two associated ramp functions. We will start, however, by summarizing key results on system (2.17); see Chapter 4 of [5] for the full derivation and a more detailed explanation.

2.4.1 Summary of Previous Results

Equilibria in system (2.17) satisfy

$$A\vec{r} + \vec{k} + \vec{x_0} = 0,$$

or equivalently, since A is invertible,

$$\vec{r} + A^{-1}\vec{k} = -A^{-1}\vec{x_0}.$$

From here, two sets of quantities were defined in [5]: first $S_1, S_2, \ldots, S_n$ as

$$-A^{-1}\vec{x_0} = [S_1,\ S_2,\ \ldots,\ S_n]^T, \tag{2.19}$$

and $D_1, D_2, \ldots, D_n$ as

$$D_i = \frac{C_{3i} - C_{1i} - C_{2i}}{\det(A)} \quad \forall i, \tag{2.20}$$

where the C_{ji} are cofactors of A. Note that D_i appears in the ith component of $A^{-1}k$, which is $kr_1(x_1^*)r_2(x_2^*)D_i$. As A is an SRP matrix, the S_i are all non-negative by Theorem 1.1.7. While **Theorem 40** of [5] established that D_1 and D_2 are always non-negative, no such restriction exists on D_i for $i \geq 3$.

The analysis in [5] culminated in **Theorem 41**, which provided the values of the ramp functions at the unique equilibrium in the all ramp region, as well as necessary and sufficient conditions for the existence of this equilibrium. We restate this as Theorem 2.4.1 below.

Theorem 2.4.1. *Consider a system of form (2.17). Define S_i and D_i for all i as in (2.19) and (2.20) respectively, and let $b = 1 + kD_1S_2 - kD_2S_1$. Then, the unique equilibrium point*

$$r_1(x_1^*) = \begin{cases} \dfrac{S_1}{1+kD_1S_2}, & D_2 = 0 \\ \dfrac{-b+\sqrt{b^2+4kD_2S_1}}{2kD_2}, & D_2 > 0, \end{cases}$$

$$r_2(x_2^*) = \begin{cases} \dfrac{S_2}{1+kD_2S_1}, & D_1 = 0 \\ \dfrac{b-2+\sqrt{b^2+4kD_2S_1}}{2kD_1}, & D_1 > 0, \end{cases}$$

$$r_i(x_i^*) = S_i - kr_1(x_1^*)r_2(x_2^*)D_i \qquad \forall i \geq 3$$

falls in the all ramp region if and only if all of the following hold:

$$S_1 < 1 + \frac{kD_1S_2}{1+kD_2}, \qquad S_2 < 1 + \frac{kD_2S_1}{1+kD_1},$$

$$\max\{0, kr_1(x_1^*)r_2(x_2^*)D_i\} \leq S_i < 1 + kr_1(x_1^*)r_2(x_2^*)D_i \quad \forall i \geq 3$$

2.4.2 Two Thresholds for x_1 and x_2

We will now focus on systems resembling the Adams model (2.18); that is, systems of the form

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \vdots \\ \dot{x}_n \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & a_{13} & a_{14} & \dots & a_{1n} \\ a_{21} & -a_{22} & a_{23} & a_{24} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & a_{34} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(x_1) \\ r_2(x_2) \\ r_3(x_3) \\ r_4(x_4) \\ \vdots \\ r_n(x_n) \end{bmatrix} + \begin{bmatrix} -kr_{11}(x_1)r_{22}(x_2) \\ -kr_{11}(x_1)r_{22}(x_2) \\ kr_{11}(x_1)r_{22}(x_2) \\ 0 \\ \vdots \\ 0 \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ x_{3_0} \\ x_{4_0} \\ \vdots \\ x_{n_0} \end{bmatrix},$$

where the $n \times n$ matrix is an invertible SRP matrix, each r_i has threshold $2\theta_i$, and r_{ii} for $i = 1, 2$ has threshold $2\theta_{ii}$. Thus, x_1 has two associated ramp functions with thresholds $2\theta_1$ and $2\theta_{11}$, and similarly x_2 has thresholds $2\theta_2$ and $2\theta_{22}$. We assume that θ_1 and θ_{11} are not necessarily equal to each other, nor are θ_2 and θ_{22}.

In the all ramp region, the above system becomes

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \vdots \\ \dot{x}_n \end{bmatrix} = \begin{bmatrix} -\frac{a_{11}}{2\theta_1} & \frac{a_{12}}{2\theta_2} & \frac{a_{13}}{2\theta_3} & \frac{a_{14}}{2\theta_4} & \cdots & \frac{a_{1n}}{2\theta_n} \\ \frac{a_{21}}{2\theta_1} & -\frac{a_{22}}{2\theta_2} & \frac{a_{23}}{2\theta_3} & \frac{a_{24}}{2\theta_4} & \cdots & \frac{a_{2n}}{2\theta_n} \\ \frac{a_{31}}{2\theta_1} & \frac{a_{32}}{2\theta_2} & -\frac{a_{33}}{2\theta_3} & \frac{a_{34}}{2\theta_4} & \cdots & \frac{a_{3n}}{2\theta_n} \\ \frac{a_{41}}{2\theta_1} & \frac{a_{42}}{2\theta_2} & \frac{a_{43}}{2\theta_3} & -\frac{a_{44}}{2\theta_4} & \cdots & \frac{a_{4n}}{2\theta_n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \frac{a_{n1}}{2\theta_1} & \frac{a_{n2}}{2\theta_2} & \frac{a_{n3}}{2\theta_3} & \frac{a_{n4}}{2\theta_4} & \cdots & -\frac{a_{nn}}{2\theta_n} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ \vdots \\ x_n \end{bmatrix} + \frac{k}{4\theta_{11}\theta_{22}} \begin{bmatrix} -x_1x_2 \\ -x_1x_2 \\ x_1x_2 \\ 0 \\ \vdots \\ 0 \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ x_{3_0} \\ x_{4_0} \\ \vdots \\ x_{n_0} \end{bmatrix}.$$

This can then be written compactly as

$$\dot{\vec{x}} \;=\; B\vec{x} + \vec{\kappa} + \vec{x_0}, \tag{2.21}$$

where we note that

- B is still an invertible SRP matrix, since it is obtained by multiplying each column of an invertible SRP matrix by a positive scalar.
- $\vec{\kappa}$ is the combining term vector, and we will let $\kappa = \dfrac{k}{4\theta_{11}\theta_{22}}$.

We want to determine when system (2.21) has an equilibrium. Note that system (2.21) has the same form as system (2.17), just with every instance of $r(x)$ replaced with x. Thus, equilibrium values for (2.21) will take the same general form as those listed in Theorem 2.4.1, just written in terms of the x_i instead of $r_i(x_i)$. The conditions on parameters for existence of an equilibrium in the all ramp region will have to be re-derived, however, due to x_1 and x_2 now having two thresholds.

With B and κ in (2.21) being non-identical to their counterparts A and k in (2.17), we will rename the quantities S_i and D_i defined in (2.19) and (2.20) to T_i and E_i respectively. These are defined as follows:

$$-B^{-1}\vec{x_0} \;=\; [T_1,\, T_2,\, \ldots,\, T_n]^T, \tag{2.22}$$

and

$$E_i \;=\; \frac{C_{3i} - C_{1i} - C_{2i}}{\det(B)} \quad \forall i, \tag{2.23}$$

where the C_{ji} are cofactors of B. Note that the T_i are all non-negative as the inverse of an SRP matrix has non-positive entries, so all entries of $-B^{-1}$ are non-negative. Additionally,

by **Theorem 40** of [5], E_1 and E_2 are non-negative like their counterparts D_1 and D_2, but the other E_i do not have this restriction. Similar to the D_i, the T_i are derived from the ith component of $B^{-1}\vec{\kappa}$, which is $\kappa x_1^* x_2^* E_i$.

Next, the quantity b from Theorem 2.4.1 can then be renamed c, with

$$c \;=\; 1 + \kappa E_1 T_2 - \kappa E_2 T_1.$$

Thus, the equilibrium point in the all ramp region for system (2.21) will be given by

$$x_1^* \;=\; \begin{cases} \dfrac{T_1}{1+\kappa E_1 T_2}, & E_2 \;=\; 0 \\ \dfrac{-c+\sqrt{c^2+4\kappa E_2 T_1}}{2\kappa E_2}, & E_2 \;>\; 0, \end{cases}$$

$$x_2^* \;=\; \begin{cases} \dfrac{T_2}{1+\kappa E_2 T_1}, & E_1 \;=\; 0 \\ \dfrac{c-2+\sqrt{c^2+4\kappa E_2 T_1}}{2\kappa E_1}, & E_1 \;>\; 0, \end{cases}$$

$$x_i^* \;=\; T_i - \kappa x_1^* x_2^* E_i \qquad\qquad \forall i \geq 3$$

Now, we will determine under what conditions these equilibrium values actually fall in the all ramp region, starting with x_1^*. First, let $m_1 = \min\{2\theta_1, 2\theta_{11}\}$. In the $E_2 = 0$ case, we have $x_1^* < m_1$ if and only if $T_1 < m_1(1+\kappa E_1 T_2)$. For the $E_2 \neq 0$ case, if $x_1^* < m_1$, then

$$\begin{aligned} &\frac{-c+\sqrt{c^2+4\kappa E_2 T_1}}{2\kappa E_2} \;<\; m_1 \\ \Longrightarrow\;& \sqrt{c^2+4\kappa E_2 T_1} \;<\; 2m_1\kappa E_2 + c \\ \Longrightarrow\;& c^2 + 4\kappa E_2 T_1 \;<\; (2m_1\kappa E_2)^2 + 4m_1\kappa E_2 c + c^2 \\ \Longrightarrow\;& 4\kappa E_2 T_1 \;<\; 4m_1\kappa E_2(m_1\kappa E_2 + c) \\ \Longrightarrow\;& T_1 \;<\; m_1^2\kappa E_2 + cm_1 \\ &\qquad = \; m_1^2\kappa E_2 + m_1(1+\kappa E_1 T_2 - \kappa E_2 T_1) \\ \Longrightarrow\;& T_1(1+m_1\kappa E_2) \;<\; m_1 + m_1^2\kappa E_2 + m_1\kappa E_1 T_2 \\ &\qquad\qquad = \; m_1(1+m_1\kappa E_2) + m_1\kappa E_1 T_2 \\ \Longrightarrow\;& T_1 \;<\; m_1 + \frac{m_1\kappa E_1 T_2}{1+m_1\kappa E_2}. \end{aligned}$$

Thus, $x_1^* < m_1$ in the $E_2 > 0$ case implies that $T_1 < m_1 + \dfrac{m_1\kappa E_1 T_2}{1+m_1\kappa E_2}$. The reverse implication can be shown by following the above steps from the bottom to the top. Note

that assuming the upper bound on T_1, we will not have trouble taking a square root at the $c^2 + 4\kappa E_2 T_1 < (2m_1\kappa E_2)^2 + 4m_1\kappa E_2 c + c^2$ step as $2m_1\kappa E_2 + c$ is positive:

$$\begin{aligned}
2m_1\kappa E_2 + c &= 2m_1\kappa E_2 + 1 + \kappa E_1 T_2 - \kappa E_2 T_1 \\
&> 2m_1\kappa E_2 + 1 + \kappa E_1 T_2 - \kappa E_2\Big(m_1 + \frac{m_1\kappa E_1 T_2}{1 + m_1\kappa E_2}\Big) \\
&= m_1\kappa E_2 + 1 + \kappa E_1 T_2 - \frac{m_1\kappa^2 E_1 E_2 T_2}{1 + m_1\kappa E_2} \\
&= \frac{(1 + m_1\kappa E_2)^2 + (\kappa E_1 T_2)(1 + m_1\kappa E_2) - m_1\kappa^2 E_1 E_2 T_2}{1 + m_1\kappa E_2} \\
&= \frac{(1 + m_1\kappa E_2)^2 + \kappa E_1 T_2}{1 + m_1\kappa E_2} \\
&> 0
\end{aligned}$$

Additionally, when E_2 is set to zero, $T_1 < m_1 + \dfrac{m_1\kappa E_1 T_2}{1 + m_1\kappa E_2}$ becomes $T_1 < m_1(1 + \kappa E_1 T_2)$, the condition we had in the $E_2 = 0$ case. Hence, we can say that x_1^* falls in the all ramp region if and only if $T_1 < m_1 + \dfrac{m_1\kappa E_1 T_2}{1 + m_1\kappa E_2}$ regardless of which case we are in.

For x_2^*, let $m_2 = \min\{2\theta_2, 2\theta_{22}\}$. Finding conditions on parameters in which $x_2^* < m_2$ is similar to the x_1^* case; in the end, we find that $x_2^* < m_2$ if and only if $T_2 < m_2 + \dfrac{m_2\kappa E_2 T_1}{1 + m_2\kappa E_1}$.

For $i \geq 3$, we need to ensure both that $x_i^* = T_i - \kappa x_1^* x_2^* E_i$ is less than $2\theta_i$ and that it is non-negative, since there is no restriction on the sign of E_i in this case. Hence, we have that $0 \leq x_i^* < 2\theta_i$ if and only if $\max\{0, \kappa x_1^* x_2^* E_i\} \leq T_i < 2\theta_i + \kappa x_1^* x_2^* E_i$.

Thus, we have the following theorem regarding equilibria in system (2.21):

Theorem 2.4.2. *Consider a biochemical ramp system that, when in the all ramp region, has form (2.21). Define T_i and E_i as in (2.22) and (2.23) respectively. Let $c = 1 + \kappa E_1 T_2 - \kappa E_2 T_1$, $m_1 = \min\{2\theta_1, 2\theta_{11}\}$, and $m_2 = \min\{2\theta_2, 2\theta_{22}\}$. Then, the system has the unique equilibrium point*

$$x_1^* = \begin{cases} \dfrac{T_1}{1 + \kappa E_1 T_2}, & E_2 = 0 \\ \dfrac{-c + \sqrt{c^2 + 4\kappa E_2 T_1}}{2\kappa E_2}, & E_2 > 0, \end{cases}$$

$$x_2^* = \begin{cases} \dfrac{T_2}{1+\kappa E_2 T_1}, & E_1 = 0 \\ \dfrac{c-2+\sqrt{c^2+4\kappa E_2 T_1}}{2\kappa E_1}, & E_1 > 0, \end{cases}$$

$$x_i^* = T_i - \kappa x_1^* x_2^* E_i \qquad \forall i \geq 3$$

in the all ramp region if and only if all of the following hold:

$$T_1 < m_1 + \frac{m_1\kappa E_1 T_2}{1+m_1\kappa E_2}, \qquad T_2 < m_2 + \frac{m_2\kappa E_2 T_1}{1+m_2\kappa E_1},$$
$$\max\{0, \kappa x_1^* x_2^* E_i\} \leq T_i < 2\theta_i + \kappa x_1^* x_2^* E_i \quad \forall i \geq 3$$

2.4.2.1 Adams Model

We will use the results given in Theorem 2.4.2 to determine when the Adams model (2.18) with the SEL has an equilibrium in the all ramp region. The system, when in the all ramp region, can be written in form (2.21) as

$$\begin{bmatrix} \dot{y} \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -\frac{a_1}{2K_1} & 0 & \frac{a_4}{2K_4} \\ \frac{a_1}{2K_1} & -\frac{a_5}{2K_5} & 0 \\ 0 & 0 & -\frac{a_4}{2K_4} \end{bmatrix} \begin{bmatrix} y \\ x_2 \\ x_3 \end{bmatrix} + \frac{a_3}{4K_3^2K_3^3} \begin{bmatrix} -yx_2 \\ -yx_2 \\ yx_2 \end{bmatrix} + \begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix},$$

with $\kappa = \dfrac{a_3}{4K_3^2K_3^3}$. The 3×3 matrix is invertible with

$$\begin{bmatrix} -\frac{a_1}{2K_1} & 0 & \frac{a_4}{2K_4} \\ \frac{a_1}{2K_1} & -\frac{a_5}{2K_5} & 0 \\ 0 & 0 & -\frac{a_4}{2K_4} \end{bmatrix}^{-1} = \begin{bmatrix} -\frac{2K_1}{a_1} & 0 & -\frac{2K_1}{a_1} \\ -\frac{2K_5}{a_5} & -\frac{2K_5}{a_5} & -\frac{2K_5}{a_5} \\ 0 & 0 & -\frac{2K_4}{a_4} \end{bmatrix},$$

which we will use to put the system in the form $\vec{x}+B^{-1}\vec{\kappa} = -B^{-1}\vec{x_0}$ so that we can determine the T_i and E_i. We get that

$$\begin{bmatrix} y \\ x_2 \\ x_3 \end{bmatrix} + \frac{a_3 y x_2}{4K_3^2K_3^3} \begin{bmatrix} 0 \\ \frac{2K_5}{a_5} \\ -\frac{2K_4}{a_4} \end{bmatrix} = \begin{bmatrix} \frac{2a_0K_1}{a_1} \\ \frac{2a_0K_5}{a_5} \\ 0 \end{bmatrix}$$

From here, the T_i and E_i are

$$\begin{aligned} E_1 &= 0 & T_1 &= 2a_0K_1/a_1 \\ E_2 &= 2K_5/a_5 & T_2 &= 2a_0K_5/a_5 \\ E_3 &= -2K_4/a_4 & T_3 &= 0. \end{aligned}$$

Next, we can determine the values the variables take at the equilibrium in the all ramp region using the formulas given in Theorem 2.4.2. With $E_1 = 0$, we have that

$$c = 1 - \kappa E_2 T_1$$

and

$$\sqrt{c^2 + 4\kappa E_2 T_1} = 1 + \kappa E_2 T_1.$$

The equilibrium in the all ramp region is then

$$\begin{aligned} y^* &= \frac{-c + \sqrt{c^2 + 4\kappa E_2 T_1}}{2\kappa E_2} \\ &= \frac{\kappa E_2 T_1 - 1 + 1 + \kappa E_2 T_1}{2\kappa E_2} \\ &= T_1 \\ &= \frac{2a_0K_1}{a_1}, \end{aligned}$$

$$\begin{aligned} x_2^* &= \frac{T_2}{1 + \kappa E_2 T_1} \\ &= \frac{2a_0K_5/a_5}{1 + \frac{a_3}{4K_3^2K_3^3} \cdot \frac{2K_5}{a_5} \cdot \frac{2a_0K_1}{a_1}} \\ &= \frac{2a_0K_5}{a_5 + \frac{a_0a_3K_1K_5}{a_1K_3^2K_3^3}} \\ &= \frac{2a_0a_1K_3^2K_3^3K_5}{a_1a_5K_3^2K_3^3 + a_0a_3K_1K_5}, \end{aligned}$$

$$\begin{aligned} x_3^* &= T_3 - \kappa y^* x_2^* E_3 \\ &= \frac{a_3}{4K_3^2K_3^3} \cdot \frac{2a_0K_1}{a_1} \cdot \frac{2a_0a_1K_3^2K_3^3K_5}{a_1a_5K_3^2K_3^3 + a_0a_3K_1K_5} \cdot \frac{2K_4}{a_4} \end{aligned}$$

$$= \frac{2a_0^2 a_3 K_1 K_4 K_5}{a_4(a_0 a_3 K_1 K_5 + a_1 a_5 K_3^2 K_3^3)}.$$

Now, we determine the necessary and sufficient parameter conditions for the existence of this equilibrium. With $m_1 = \min\{2K_1, 2K_3^3\}$ and $m_2 = \min\{2K_3^2, 2K_5\}$, these conditions are

$$T_1 < m_1 + \frac{m_1 \kappa E_1 T_2}{1 + m_1 \kappa E_2} \iff a_0 < \frac{m_1 a_1}{2K_1}$$

$$T_2 < m_2 + \frac{m_2 \kappa E_2 T_1}{1 + m_2 \kappa E_1} \iff \frac{2a_0 a_1 K_3^2 K_3^3 K_5}{m_2(a_0 a_3 K_1 K_5 + a_1 a_5 K_3^2 K_3^3)} < 1$$

$$\max\{0, \kappa x_1^* x_2^* E_3\} \leq T_3 < 2K_4 + \kappa x_1^* x_2^* E_3 \iff \frac{a_0^2 a_3 K_1 K_5}{a_4(a_0 a_3 K_1 K_5 + a_1 a_5 K_3^2 K_3^3)} < 1.$$

Chapter 3

New Reaction Types

3.1 Double Combining Reactions

In this chapter, we will analyze biochemical ramp systems that, when in the all ramp region, have mass action terms derived from reactions that are not of the SRP, combining, or dissociation types. We begin with reactions of the form $A + B \to C + D$, in which two chemical species A and B react to form two new species C and D. Such reactions are commonly seen in chemistry; for instance,

$$\mathrm{AgNO_3} + \mathrm{KCl} \longrightarrow \mathrm{AgCl} + \mathrm{KNO_3}$$

is the reaction in which silver nitrate ($\mathrm{AgNO_3}$) and potassium chloride (KCl) react to form silver chloride (AgCl) and potassium nitrate ($\mathrm{KNO_3}$) [24]. This is a reaction of the form $A + B \to C + D$ with $A = \mathrm{AgNO_3}$, $B = \mathrm{KCl}$, $C = \mathrm{AgCl}$, and $D = \mathrm{KNO_3}$.

We will refer to reactions of the form $A + B \to C + D$ as *double combining reactions*. A mass action system derived from at least one such reaction is said to contain *double combining terms*, as is the Jacobian of the system evaluated at a positive equilibrium point.

3.1.1 Systems with One Double Combining Term

We will first consider n-variable systems containing exactly one double combining term when in the all ramp region; WLOG, we will assume the double combining term derives from a reaction of the form $X_1 + X_2 \to X_3 + X_4$, involving the first four variables. Additionally, we will allow the systems to contain an arbitrary number of SRP terms. The variables x_1 and x_2 will have two associated thresholds, while the other variables will only have one each. Thus, the systems we will be studying have the general form

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \\ \dot{x}_5 \\ \vdots \\ \dot{x}_n \end{bmatrix} = A\vec{r} + \begin{bmatrix} -kr_{11}(x_1)r_{22}(x_2) \\ -kr_{11}(x_1)r_{22}(x_2) \\ kr_{11}(x_1)r_{22}(x_2) \\ kr_{11}(x_1)r_{22}(x_2) \\ 0 \\ \vdots \\ 0 \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ x_{3_0} \\ x_{4_0} \\ x_{5_0} \\ \vdots \\ x_{n_0} \end{bmatrix}, \tag{3.1}$$

where

- The $n \times n$ matrix

$$A = \begin{bmatrix} -a_{11} & a_{12} & a_{13} & \dots & a_{1n} \\ a_{21} & -a_{22} & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}$$

  is an SRP matrix.

- $\vec{r} = \begin{bmatrix} r_1(x_1) & r_2(x_2) & \dots & r_n(x_n) \end{bmatrix}^T$ is the vector of ramp functions corresponding to the SRP terms. Ramp function r_i has threshold $2\theta_i$.

- The reaction $X_1 + X_2 \to X_3 + X_4$ is represented by the $\pm kr_{11}(x_1)r_{22}(x_2)$ terms in the first four equations, with $k > 0$. Ramp function r_{ii} has threshold $2\theta_{ii}$, which is not necessarily equal to $2\theta_i$ for $i = 1, 2$.

- The x_{i_0} are non-negative If an x_{i_0} is positive, it is the rate constant for the reaction $0 \xrightarrow{x_{i_0}} X_i$.

We will present a couple of properties of systems of form (3.1). First, we have the following regarding parameter conditions necessary for the existence of an equilibrium point in the all ramp region:

Proposition 3.1.1. Consider a system of form (3.1). Suppose the system has an equilibrium point in the all ramp region. Then, the following hold:

a.) $x_{1_0} < a_{11} + k$ and $x_{2_0} < a_{22} + k$.

b.) For $i \geq 3$, $x_{i_0} \leq a_{ii}$. If $a_{ii} \neq 0$, this inequality is strict.

c.) If all column sums of A are zero, then $x_{i_0} = 0$ for all i.

Proof. We assume system (3.1) has an equilibrium point $(x_1^*, x_2^*, \ldots, x_n^*)$ such that

$$\begin{aligned} x_1^* &< \min\{2\theta_1, 2\theta_{11}\} \\ x_2^* &< \min\{2\theta_2, 2\theta_{22}\} \\ x_i^* &< 2\theta_i, \quad i \geq 3. \end{aligned}$$

For *a.*), we will use the fact that $k > 0$ and the ramp functions are strictly less than 1 at the equilibrium values. If $x_{1_0} \geq a_{11} + k$, then at equilibrium we have

$$\begin{aligned} \dot{x_1} &= -a_{11} r_1(x_1^*) - k r_{11}(x_1^*) r_{22}(x_2^*) + \sum_{i \neq 1} a_{1i} r_i(x_i^*) + x_{1_0} \\ &\geq a_{11}[1 - r_1(x_1^*)] + k[1 - r_{11}(x_1^*) r_{22}(x_2^*)] + \sum_{i \neq 1} a_{1i} r_i(x_i^*) \\ &> 0, \end{aligned}$$

contradicting that $\dot{x} = 0$. The condition on x_{2_0} is similar.

Part *b.*) is also similar. If we have $x_{i_0} > a_{ii}$ for some $i \geq 3$, then at equilibrium

$$\begin{aligned} \dot{x_i} &= -a_{ii} r_1(x_i^*) + \sum_{j \neq i} a_{ij} r_j(x_j^*) + x_{i_0} \\ &> a_{ii}[1 - r_1(x_i^*)] + \sum_{j \neq i} a_{ij} r_j(x_j^*) \\ &\geq 0, \end{aligned}$$

a contradiction. If $a_{ii} \neq 0$, then the term $a_{ii}[1 - r_1(x_i^*)]$ is strictly positive, and thus $x_{i_0} = a_{ii}$ implies $\dot{x_i} > 0$ at equilibrium, another contradiction.

For *c.*), if all column sums of A are zero, then at equilibrium we have

$$\sum_{i=1}^{n} \dot{x_i} = \sum_{i=1}^{n} x_{i_0} = 0.$$

Since the x_{i_0} are all non-negative, this condition holds if and only if all of them are zero. □

We also have the following parameter conditions sufficient for global flow to be toward the all ramp region:

Proposition 3.1.2. Consider a system of form (3.1). If the conditions

$$a_{ii} > \max\left\{ \sum_{j \neq i} a_{ij} + x_{i_0}, \frac{\theta_i}{\theta_{ii}} \Big(\sum_{j \neq i} a_{ij} + x_{i_0} \Big) \right\}, \quad i = 1, 2$$

$$a_{\ell\ell} \;>\; \sum_{j\neq\ell} a_{\ell j} + k + x_{\ell_0}, \quad \ell = 3, 4$$

$$a_{mm} \;>\; \sum_{j\neq m} a_{mj} + x_{m_0}, \quad m \geq 5$$

then global flow in the system is toward the all ramp region.

Proof. Our goal will be to show that when the given parameter conditions hold, each $\dot{x}_i$ equation is negative when x_i is at or above its smallest associated threshold. Thus, if a variable takes on a value outside the all ramp region, it will decrease and eventually fall below all of its thresholds. As a result, any trajectory beginning outside the all ramp region must eventually enter it.

We begin by considering $\dot{x}_1$. First, suppose that $\theta_1 \leq \theta_{11}$ and $a_{11} > \sum_{j\neq 1} a_{1j} + x_{1_0}$. Then for $x_1 \geq 2\theta_1$, we have that

$$\begin{aligned}
\dot{x}_1 \;&=\; -a_{11} + \sum_{j\neq 1} a_{1j} r_j(x_j) - k r_{11}(x_1) r_{22}(x_2) + x_{1_0} \\
&<\; -\Big(\sum_{j\neq 1} a_{1j} + x_{1_0}\Big) + \sum_{j\neq 1} a_{1j} r_j(x_j) - k r_{11}(x_1) r_{22}(x_2) + x_{1_0} \\
&=\; \sum_{j\neq 1} a_{1j}[r_j(x_j) - 1] - k r_{11}(x_1) r_{22}(x_2) \\
&\leq\; 0.
\end{aligned}$$

Next, suppose $\theta_{11} < \theta_1$ and $a_{11} > \dfrac{\theta_1}{\theta_{11}}\Big(\sum_{j\neq 1} a_{1j} + x_{1_0}\Big)$. Note that when $x_1 \geq 2\theta_{11}$, the minimum value of $r_1(x_1)$ is

$$r_1(2\theta_{11}) \;=\; \frac{2\theta_{11}}{2\theta_1} \;=\; \frac{\theta_{11}}{\theta_1},$$

and hence $a_{11} r_1(x_1) \geq a_{11}\dfrac{\theta_{11}}{\theta_1}$. Thus, when $x_1 \geq 2\theta_{11}$ we have

$$\begin{aligned}
\dot{x}_1 \;&=\; -a_{11} r_1(x_1) + \sum_{j\neq 1} a_{1j} r_j(x_j) - k r_{22}(x_2) + x_{1_0} \\
&\leq\; -a_{11}\frac{\theta_{11}}{\theta_1} + \sum_{j\neq 1} a_{1j} r_j(x_j) - k r_{22}(x_2) + x_{1_0} \\
&<\; -\frac{\theta_{11}}{\theta_1}\cdot\frac{\theta_1}{\theta_{11}}\Big(\sum_{j\neq 1} a_{1j} + x_{1_0}\Big) + \sum_{j\neq 1} a_{1j} r_j(x_j) - k r_{22}(x_2) + x_{1_0}
\end{aligned}$$

$$= \sum_{j\neq 1} a_{1j}[r_j(x_j) - 1] - kr_{22}(x_2)$$

$$\leq 0.$$

Hence, if

$$a_{11} > \max\left\{ \sum_{j\neq 1} a_{1j} + x_{1_0}, \frac{\theta_1}{\theta_{11}}\Big(\sum_{j\neq 1} a_{1j} + x_{1_0}\Big)\right\},$$

then the $\dot{x}_1$ equation will be negative whenever x_1 is above its smallest threshold. The case with a_{22} and $\dot{x}_2$ is similar.

We finish with the $\ell = 3$ and $m = 5$ cases; the remaining cases are similar. If

$$a_{33} > \sum_{j\neq 3} a_{3j} + k + x_{3_0},$$

then when $x_3 \geq 2\theta_3$,

$$\dot{x}_3 = -a_{33} + \sum_{j\neq 3} a_{3j} r_j(x_j) + kr_{11}(x_1)r_{22}(x_2) + x_{3_0}$$

$$< -\Big(\sum_{j\neq 3} a_{3j} + k + x_{3_0}\Big) + \sum_{j\neq 3} a_{3j} r_j(x_j) + kr_{11}(x_1)r_{22}(x_2) + x_{3_0}$$

$$\leq 0.$$

Finally, if $a_{55} > \sum_{j\neq 5} a_{5j} + x_{5_0}$, we have that

$$\dot{x}_5 = -a_{55} + \sum_{j\neq 5} a_{5j} r_j(x_j) + x_{5_0}$$

$$< -\Big(\sum_{j\neq 5} a_{5j} + x_{5_0}\Big) + \sum_{j\neq 5} a_{5j} r_j(x_j) + x_{5_0}$$

$$\leq 0$$

when $x_5 \geq 2\theta_5$. □

3.1.2 A Simple Class of Systems

We continue our study of systems with one double combining term with the class of 4-variable systems defined by the equations

$$\begin{aligned}
\dot{x} &= -kr_{11}(x)r_{22}(y) - ar_1(x) + x_0 \\
\dot{y} &= -kr_{11}(x)r_{22}(y) - br_2(y) + y_0 \\
\dot{z} &= kr_{11}(x)r_{22}(y) - cr_3(z) \\
\dot{w} &= kr_{11}(x)r_{22}(y) - dr_4(w).
\end{aligned} \tag{3.2}$$

where x_0 and y_0 are non-negative and all other parameters are positive. The ramp function r_i has threshold $2\theta_i$ while r_{ii} for $i = 1, 2$ has threshold $2\theta_{ii}$. This class of systems can be written in form (3.1) as

$$\begin{bmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \\ \dot{w} \end{bmatrix} = \begin{bmatrix} -a & 0 & 0 & 0 \\ 0 & -b & 0 & 0 \\ 0 & 0 & -c & 0 \\ 0 & 0 & 0 & -d \end{bmatrix} \begin{bmatrix} r_1(x) \\ r_2(y) \\ r_3(z) \\ r_4(w) \end{bmatrix} + \begin{bmatrix} -kr_{11}(x)r_{22}(y) \\ -kr_{11}(x)r_{22}(y) \\ kr_{11}(x)r_{22}(y) \\ kr_{11}(x)r_{22}(y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \\ 0 \\ 0 \end{bmatrix}.$$

Here, our analysis of system (3.2) will consist of solving for an equilibrium point in the all ramp region, followed by determining parameter conditions sufficient for the existence of this equilibrium. In the all ramp region, system (3.2) becomes

$$\begin{aligned}
\dot{x} &= -\frac{kxy}{4\theta_{11}\theta_{22}} - \frac{ax}{2\theta_1} + x_0 \\
\dot{y} &= -\frac{kxy}{4\theta_{11}\theta_{22}} - \frac{by}{2\theta_2} + y_0 \\
\dot{z} &= \frac{kxy}{4\theta_{11}\theta_{22}} - \frac{cz}{2\theta_3} \\
\dot{w} &= \frac{kxy}{4\theta_{11}\theta_{22}} - \frac{dw}{2\theta_4}.
\end{aligned}$$

Equilibrium values for y, z, and w can be expressed in terms of x^* and y^* as

$$\begin{aligned}
y^* &= \frac{y_0}{\frac{b}{2\theta_2} + \frac{kx^*}{4\theta_{11}\theta_{22}}} = \frac{4y_0\theta_{11}\theta_{22}\theta_2}{2b\theta_{11}\theta_{22} + k\theta_2 x^*} \\
z^* &= \frac{k\theta_3 x^* y^*}{2c\theta_{11}\theta_{22}} \\
w^* &= \frac{k\theta_4 x^* y^*}{2d\theta_{11}\theta_{22}}
\end{aligned} \tag{3.3}$$

Setting $\dot{x} = 0$ using the above value for y^*, we get that x^* must be a solution to

$$ka\theta_2 x^2 + 2Bx - 4C = 0,$$

where

$$B = ky_0\theta_1\theta_2 + ab\theta_{11}\theta_{22} - kx_0\theta_1\theta_2$$
$$C = bx_0\theta_1\theta_{11}\theta_{22}.$$

As with system (2.3), the above quadratic will only have a single non-negative root, obtained from taking the positive root in the quadratic formula. Hence, we have

$$x^* = \frac{-2B + \sqrt{4B^2 + 16ka\theta_2 C}}{2ka\theta_2} = \frac{-B + \sqrt{B^2 + 4ka\theta_2 C}}{ka\theta_2}. \tag{3.4}$$

Now, we will determine parameter conditions sufficient for the equilibrium values given in (3.3) and (3.4) to actually fall in the all ramp region. For y^*, we want parameters such that $y^* < \min\{2\theta_2, 2\theta_{22}\}$. One way we can do this is to choose parameters such that the ratio $\frac{4y_0\theta_{11}\theta_{22}\theta_2}{2b\theta_{11}\theta_{22}}$ is always less than the smaller of $2\theta_2$ and $2\theta_{22}$. A little algebra reveals that

$$y_0 < \min\left\{b, \frac{b\theta_{22}}{\theta_2}\right\}$$

is the parameter condition we want.

Next, we will find a condition on x_0 such that $x^* < \min\{2\theta_1, 2\theta_{11}\}$ always holds in a couple of steps. First, it would be useful to have a parameter condition such that B is non-negative; this will allow us to invoke the inequality

$$-B + \sqrt{B^2 + 4ka\theta_2 C} \leq -B + B + 2\sqrt{ka\theta_2 C} = 2\sqrt{ka\theta_2 C}$$

involving the denominator of x^*. Using the expression for B above, we find that $B \geq 0$ if and only if

$$x_0 \leq y_0 + \frac{ab\theta_{11}\theta_{22}}{k\theta_1\theta_2}.$$

Assuming this inequality on x_0, we then want

$$\frac{2\sqrt{ka\theta_2 C}}{ka\theta_2} < \min\{2\theta_1, 2\theta_{11}\}$$

to hold; this happens if $x_0 < \frac{ka\theta_1\theta_2}{b\theta_{11}\theta_{22}}$ for the case in which $2\theta_1$ is the smaller threshold, and if $x_0 < \frac{ka\theta_{11}\theta_2}{b\theta_1\theta_{22}}$ if $2\theta_{11}$ is smaller.

Thus, taking

$$x_0 < \min\left\{y_0 + \frac{ab\theta_{11}\theta_{22}}{k\theta_1\theta_2}, \frac{ka\theta_1\theta_2}{b\theta_{11}\theta_{22}}, \frac{ka\theta_{11}\theta_2}{b\theta_1\theta_{22}}\right\}$$

gives us that

$$x^* = \frac{-B + \sqrt{B^2 + 4ka\theta_2 C}}{ka\theta_2}$$

$$
\begin{aligned}
&< \frac{2\sqrt{ka\theta_2 C}}{ka\theta_2} \\
&< \min\{2\theta_1, 2\theta_{11}\}.
\end{aligned}
$$

Finally, we have $z^* < 2\theta_3$ and $w^* < 2\theta_4$ if and only if $\dfrac{kx^*y^*}{4\theta_{11}\theta_{22}} < \min\{c, d\}$. Hence, if all three of

$$
\begin{aligned}
x_0 &< \min\left\{y_0 + \frac{ab\theta_{11}\theta_{22}}{k\theta_1\theta_2}, \frac{ka\theta_1\theta_2}{b\theta_{11}\theta_{22}}, \frac{ka\theta_{11}\theta_2}{b\theta_1\theta_{22}}\right\} \\
y_0 &< \min\left\{b, \frac{b\theta_{22}}{\theta_2}\right\} \qquad (3.5) \\
\frac{kx^*y^*}{4\theta_{11}\theta_{22}} &< \min\{c, d\}
\end{aligned}
$$

hold, then the equilibrium given in (3.3) and (3.4) falls in the all ramp region.

Regarding stability, the Jacobian of (3.1) evaluated at the equilibrium in the all ramp region is

$$
\begin{bmatrix}
-\dfrac{ky^*}{4\theta_{11}\theta_{22}} - \dfrac{a}{2\theta_1} & -\dfrac{kx^*}{4\theta_{11}\theta_{22}} & 0 & 0 \\
-\dfrac{ky^*}{4\theta_{11}\theta_{22}} & -\dfrac{kx^*}{4\theta_{11}\theta_{22}} - \dfrac{b}{2\theta_2} & 0 & 0 \\
\dfrac{ky^*}{4\theta_{11}\theta_{22}} & \dfrac{kx^*}{4\theta_{11}\theta_{22}} & -\dfrac{c}{2\theta_3} & 0 \\
\dfrac{ky^*}{4\theta_{11}\theta_{22}} & \dfrac{kx^*}{4\theta_{11}\theta_{22}} & 0 & -\dfrac{d}{2\theta_4}
\end{bmatrix}.
$$

The eigenvalues are $-\dfrac{c}{2\theta_3}$, $-\dfrac{d}{2\theta_4}$, and the eigenvalues of

$$
\begin{bmatrix}
-\dfrac{ky^*}{4\theta_{11}\theta_{22}} - \dfrac{a}{2\theta_1} & -\dfrac{kx^*}{4\theta_{11}\theta_{22}} \\
-\dfrac{ky^*}{4\theta_{11}\theta_{22}} & -\dfrac{kx^*}{4\theta_{11}\theta_{22}} - \dfrac{b}{2\theta_2}
\end{bmatrix}.
$$

The 2×2 matrix has characteristic polynomial

$$
\lambda^2 + \left[\frac{k(x^* + y^*)}{4\theta_{11}\theta_{22}} + \frac{a}{2\theta_1} + \frac{b}{2\theta_2}\right]\lambda + \frac{kax^*}{8\theta_1\theta_{11}\theta_{22}} + \frac{kby^*}{8\theta_{11}\theta_{22}\theta_2} + \frac{ab}{4\theta_1\theta_2},
$$

which will always have strictly positive coefficients, even if one or both of x^* and y^* are zero. Hence, both eigenvalues of the 2×2 matrix will have negative real part. Thus, the equilibrium in the all ramp region is asymptotically stable.

3.1.2.1 Comparisons to Michaelis-Menten

We will now examine how ramp system (3.2) compares to its Michaelis-Menten counterpart. For this, we will assume each variable has only one associated threshold, i.e. $\theta_1 = \theta_{11}$ and $\theta_2 = \theta_{22}$. We will use θ_1 and θ_2 to denote the thresholds associated with x and y respectively. The Michaelis-Menten system is then defined by the equations

$$\begin{aligned}
\dot{x} &= -k\Big(\frac{x}{\theta_1 + x} \cdot \frac{y}{\theta_2 + y}\Big) - \frac{ax}{\theta_1 + x} + x_0 \\
\dot{y} &= -k\Big(\frac{x}{\theta_1 + x} \cdot \frac{y}{\theta_2 + y}\Big) - \frac{by}{\theta_2 + y} + y_0 \\
\dot{z} &= k\Big(\frac{x}{\theta_1 + x} \cdot \frac{y}{\theta_2 + y}\Big) - \frac{cz}{\theta_3 + z} \\
\dot{w} &= k\Big(\frac{x}{\theta_1 + x} \cdot \frac{y}{\theta_2 + y}\Big) - \frac{dw}{\theta_4 + w}.
\end{aligned} \tag{3.6}$$

We want to know when system (3.6) has an equilibrium at which every variable is non-negative. It turns out that the existence of such an equilibrium is equivalent to ramp system (3.2) having an equilibrium in the all ramp region; in fact, this is true for any ramp system and corresponding Michaelis-Menten system in which every variable has exactly one threshold. We prove this in the following theorem:

Theorem 3.1.3. *Consider an n-variable biochemical ramp system in which, for all i, variable x_i is the input of exactly one ramp function r_i. Then, the system has an equilibrium in the all ramp region if and only if the corresponding Michaelis-Menten system has a non-negative equilibrium.*

Proof. Suppose the ramp system has an equilibrium point $(x_1^*, x_2^*, \ldots, x_n^*)$ in the all ramp region. At this equilibrium, the ith ramp function takes the value $r_i(x_i^*) = c_i$, where we have $c_i < 1$. In the corresponding Michaelis-Menten system, $r_i(x_i)$ is replaced with $\dfrac{x_i}{\theta_i + x_i}$, and there is a unique $x_i' \geq 0$ at which $\dfrac{x_i'}{\theta_i + x_i'} = c_i$, specifically $x_i' = \dfrac{c_i\theta_i}{1 - c_i}$.

Thus, in the Michaelis-Menten system at $(x_1', x_2', \ldots, x_n')$, each Michaelis-Menten function takes the same value as the corresponding ramp function in the ramp system at $(x_1^*, x_2^*, \ldots, x_n^*)$. Hence, all of the equations in the Michaelis-Menten system will equal zero at the x_i'.
The proof in the other direction is similar. □

To illustrate the idea behind Theorem 3.1.3, consider the system

$$\begin{aligned}
\dot{u} &= -2r_1(u)^2 - r_1(u) + 1 \\
\dot{v} &= r_1(u) - 3r_2(v) + 0.25
\end{aligned}$$

where r_1 has threshold $2\theta_1 = 2$ and r_2 has threshold $2\theta_2 = 3$. This system has an equilibrium in the all ramp region at $(u^*, v^*) = (1, 0.75)$, at which we have $r_1(u^*) = 0.5$ and $r_2(v^*) = 0.25$. The corresponding Michaelis-Menten system with $\theta_1 = 1$ and $\theta_2 = 1.5$ is then

$$\begin{aligned} \dot{u} &= -2\Big(\frac{u}{1+u}\Big)^2 - \frac{u}{1+u} + 1 \\ \dot{v} &= \frac{u}{1+u} - \frac{3v}{1.5+v} + 0.25. \end{aligned}$$

By the proof of Theorem 3.1.3, this system has an equilibrium satisfying $\dfrac{u^*}{1+u^*} = 0.5$ and $\dfrac{v^*}{1.5+v^*} = 0.25$, i.e. at $(u^*, v^*) = (1, 0.5)$.

Thus, Michaelis-Menten system (3.6) has a non-negative equilibrium if and only if ramp system (3.2) has an equilibrium in the all ramp region, assuming the $\theta_1 = \theta_{11}$ and $\theta_2 = \theta_{22}$ case. Note that with these equalities, the parameter conditions given in (3.5) simplify to

$$\begin{aligned} x_0 &< \min\Big\{y_0 + \frac{ab}{k}, \frac{ka}{b}\Big\} \\ y_0 &< b \\ \frac{kx^*y^*}{4\theta_1\theta_2} &< \min\{c, d\} \end{aligned} \tag{3.7}$$

Hence, when each variable has a single threshold, conditions (3.7) are sufficient for ramp system (3.2) to have an equilibrium in the all ramp region, which then implies Michaelis-Menten system (3.6) has a non-negative equilibrium.

At the equilibrium in the all ramp region, the ramp functions in (3.2) take the values

$$\begin{aligned} r_1(x^*) &= \frac{x^*}{2\theta_1} \qquad r_3(z^*) = \frac{z^*}{2\theta_3} \\ r_2(y^*) &= \frac{y^*}{2\theta_2} \qquad r_4(w^*) = \frac{w^*}{2\theta_4}. \end{aligned}$$

Then, using the values (x^*, y^*, z^*, w^*) given in (3.3) and (3.4) when $\theta_1 = \theta_{11}$ and $\theta_2 = \theta_{22}$, Michaelis-Menten system (3.6) has the non-negative equilibrium (x', y', z', w') given by

$$\begin{aligned}
\frac{x'}{\theta_1 + x'} &= \frac{x^*}{2\theta_1} \iff x' = \frac{x^*\theta_1}{2\theta_1 - x^*} \\
\frac{y'}{\theta_2 + y'} &= \frac{y^*}{2\theta_2} \iff y' = \frac{y^*\theta_2}{2\theta_2 - y^*} \\
\frac{z'}{\theta_3 + z'} &= \frac{z^*}{2\theta_3} \iff z' = \frac{z^*\theta_3}{2\theta_3 - z^*} \\
\frac{w'}{\theta_4 + w'} &= \frac{w^*}{2\theta_4} \iff w' = \frac{w^*\theta_4}{2\theta_4 - w^*}.
\end{aligned} \tag{3.8}$$

Next, it would be interesting to see how equilibrium values for systems (3.2) and (3.6) compare quantitatively. We will do this by graphing the equilibrium value of x for both systems as a function of x_0, similar to what we did in Figure 2.1.1 for systems (2.1) and (2.3). With $\theta_1 = \theta_{11}$ and $\theta_2 = \theta_{22}$, the equilibrium value $x = x^*$ given in (3.4) for system (3.2) becomes

$$\begin{aligned}
x^* &= \frac{-\theta_1\theta_2(ky_0 + ab - kx_0) + \sqrt{[\theta_1\theta_2(ky_0 + ab - kx_0)]^2 + 4ka(\theta_1\theta_2)^2 bx_0}}{ka\theta_2} \\
&= \frac{-\theta_1\left[ky_0 + ab - kx_0 - \sqrt{(ky_0 + ab - kx_0)^2 + 4kabx_0}\right]}{ka},
\end{aligned} \tag{3.9}$$

which will also be used in the expression for x' in (3.8).

We will graph the equilibrium value of x as long as the value of x^* given in (3.9) is below $2\theta_1$; that is, as long as the value of $r_1(x^*)$ in ramp system (3.2) remains in its ramp region. Setting $x^* = 2\theta_1$, we get that

$$x_0 = \frac{ky_0 + ab + ka}{b + k}.$$

Thus, we will graph the equilibrium value of x for x_0 values ranging from 0 to $\dfrac{ky_0 + ab + ka}{b + k}$.

Figure 3.1.1 displays the graph showing the equilibrium value of x for ramp system (3.2) and Michaelis-Menten system (3.6). The diagram is reminiscent of what was seen in Figure 2.1.1 for systems (2.1) and (2.3). While the curves are qualitatively similar, showing that the equilibrium value increases as x_0 increases, there are notable quantitative differences; the curves are close to each other for smaller values of x_0, but after a certain point, the Michaelis-Menten curve quickly pulls away and grows arbitrarily large as x_0 approaches $\dfrac{ky_0 + ab + ka}{b + k}$, while the ramp function curve always stays bounded for $x_0 < \dfrac{ky_0 + ab + ka}{b + k}$.

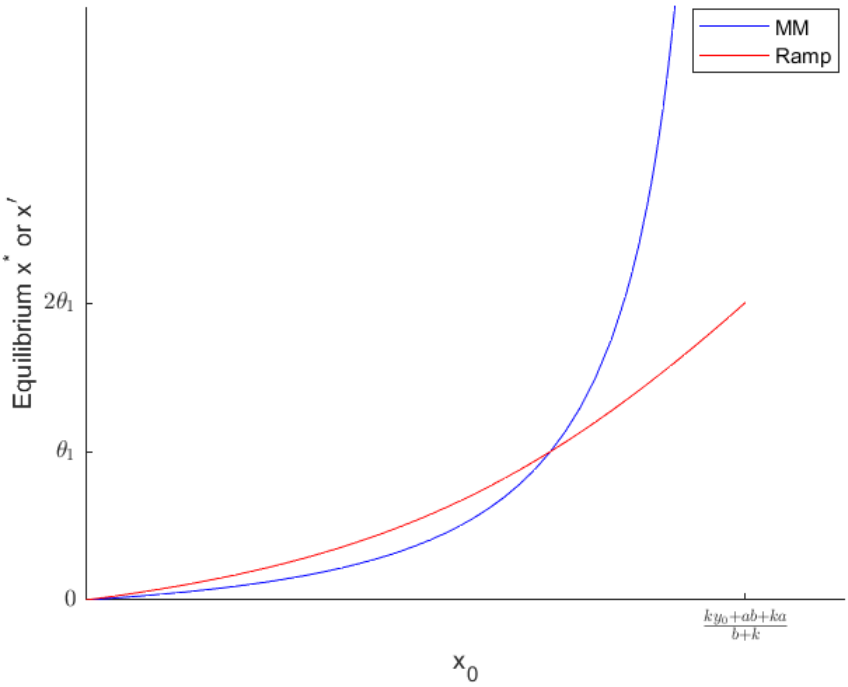


Figure 3.1.1: Equilibrium value of x for the ramp system (3.2) (x^*, red line) and the Michaelis-Menten system (3.6) (x', blue line) as a function of x_0. Note that the red curve only represents x^* values that fall in the all ramp region for system (3.2). Parameters are $\theta_1 = b = y_0 = 1$, $a = 0.5$, and $k = 4$.

It is not surprising that x', the equilibrium value of x in the Michaelis-Menten case, grows to infinity as x_0 approaches $\dfrac{ky_0 + ab + ka}{b + k}$. As x_0 increases, the equilibrium value of x for the ramp system, x^*, increases toward $2\theta_1$. As a result, the denominator of x' as given in (3.8) approaches zero from the right as x^* approaches $2\theta_1$ from below, thus resulting x' growing without bound. We would see something similar with the equilibrium values of all four variables for the Michaelis-Menten system; with the expressions given in (3.8), as the equilibrium value of a variable in the ramp system approaches its threshold, the corresponding equilibrium value in the Michaelis-Menten system approaches positive infinity.

In fact, we would see the same unbounded equilibrium values for any pair of corresponding ramp and Michaelis-Menten systems described by Theorem 3.1.3. In the proof of that theorem, we saw that the equilibrium value x_i^* of the variable x_i in the ramp system satisfies $r_i(x_i^*) = c_i$. The equilibrium value of x_i in the corresponding Michaelis-Menten system was then given by $x_i' = \dfrac{c_i\theta_i}{1 - c_i}$, which grows to infinity as c_i approaches 1, or in other words, as the ramp function r_i approaches saturation.

Note that ramp system (3.2) does have an analog to the unbounded equilibrium values

seen in Michaelis-Menten system (3.6), in that at $x_0 = \dfrac{ky_0 + ab + ka}{b + k}$ there is a whole line of equilibria satisfying $x^* \geq 2\theta_1$, similar to the vertical line at $a_0 = b + c$ in Figure 2.1.1. This line corresponds to the special case in which $r_1(x^*) = 1$, and we did not include this line in Figure 3.1.1 because our analysis of system (3.2) solely focused on equilibria in the all ramp region.

We end this section with a discussion of the difficulties that can arise when analyzing the Michaelis-Menten system corresponding to ramp system (3.2) in the case in which x and y each have two associated thresholds. The idea behind the proof of Theorem 3.1.3 — which relies on finding equilibria by ensuring the corresponding ramp and Michaelis-Menten functions are equal to the same value at equilibrium — does not work in general for system in which a variable has multiple thresholds.

As an example, consider the single-variable ramp system

$$\dot{s} \;=\; -2r_1(s) - r_2(s) + 1,$$

where r_1 has threshold $2\theta_1 = 4$ and r_2 has threshold $2\theta_2 = 5$. This system has an equilibrium in the all ramp region at $s^* = 10/7 \approx 1.429$, at which we have

$$\begin{aligned} r_1(s^*) \;&=\; 5/14 \;\approx\; 0.357 \\ r_2(s^*) \;&=\; 2/7 \;\approx\; 0.286. \end{aligned}$$

In the corresponding Michaelis-Menten system

$$\dot{s} \;=\; -\frac{2s}{2+s} - \frac{s}{2.5+s} + 1,$$

the equilibrium is at $s' = \dfrac{-5 + \sqrt{185}}{8} \approx 1.075$, at which

$$\begin{aligned} M_1(s') \;&=\; \frac{s'}{2+s'} \;\approx\; 0.35 \\ M_2(s') \;&=\; \frac{s'}{2.5+s'} \;\approx\; 0.301. \end{aligned}$$

Hence, trying to solve for the equilibrium point in the Michaelis-Menten system by setting $M_1(s') = r_1(s^*)$ and $M_2(s') = r_2(s^*)$ will not work.

When the thresholds θ_1 and θ_{11} are not necessarily equal, nor are θ_2 and θ_{22}, the $\dot{x}$ and $\dot{y}$ equations of the Michaelis-Menten system corresponding to ramp system (3.2) are

$$\begin{aligned} \dot{x} \;&=\; -k\Big(\frac{x}{\theta_{11}+x} \cdot \frac{y}{\theta_{22}+y}\Big) - \frac{ax}{\theta_1 + x} + x_0 \\ \dot{y} \;&=\; -k\Big(\frac{x}{\theta_{11}+x} \cdot \frac{y}{\theta_{22}+y}\Big) - \frac{by}{\theta_2 + y} + y_0. \end{aligned} \tag{3.10}$$

Trying to solve $\dot{y} = 0$ for y^* in terms on x, we soon get that

$$(\theta_{22}+y^*)(\theta_2+y^*)y_0 \;=\; kM_{11}(x)y^*(\theta_2+y^*)+by^*(\theta_{22}+y^*),$$

where $M_{11}(x)=\dfrac{x}{\theta_{11}+x}$. Thus, we have to solve a quadratic in y^*. Once we do this, we still have the difficult task of solving for x^*. Substituting y^* into $\dot{x}=0$ will give us at least a quadratic in x^*, and likely something even more complicated as y^* depends on a Michaelis-Menten function in x.

This is to show that despite the equations given in (3.10) appearing relatively simple, solving for equilibria is a rather tedious and messy process. When multiple thresholds per variable are involved, solving for equilibria in Michaelis-Menten systems quickly becomes difficult; we do not have a version of Theorem 3.1.3 relating equilibria in ramp and Michaelis-Menten systems for the multi-threshold case, and, unless working with systems such as (2.3) and (2.11), we often have to deal with products or powers of Michaeli-Menten functions.

This provides an argument for the use of ramp functions to facilitate the analysis of Michaelis-Menten systems with multiple thresholds per variable — while solving for x^* and y^* in (3.10) is difficult, we were able to solve for these values in ramp system (3.2) relatively easily.

3.1.3 Eigenvalues of General Matrices

Earlier, we looked at the Jacobian of system (3.2) when in the all ramp region and determined that, when evaluated at equilibrium, it always has eigenvalues with negative real parts. Here, we will consider the eigenvalues of a wider array of matrices with double combining terms.

In general, we will define a *matrix with double combining terms* as being the Jacobian of a mass action systems containing at least one double combining term and an arbitrary number of SRP terms evaluated at a positive equilibrium point. A double combining reaction of the form $X_i+X_j \xrightarrow{k} X_k+X_\ell$ will affect columns i and j of the Jacobian. Column i will contain terms of the form $\pm kx_j^*$ when evaluated at a positive equilibrium, with the negative terms appearing in the ith and jth entries of that column, and the positive terms appearing in the kth and ℓth entries. Similarly, column j will contain $-kx_i^*$ terms in the ith and jth entries, and $+kx_i^*$ terms in the kth and ℓth entries.

We will begin with several examples of matrices with double combining terms to illustrate the possible eigenvalues — positive vs negative, real vs complex — they can have. Each matrix will be written as the sum of an SRP matrix and matrices containing the double combining terms. First, the matrix

$$\begin{bmatrix} -3 & -4 & -3 & 0 \\ -1 & -5 & 3 & 4 \\ 1 & 4 & -4 & 2 \\ 3 & 4 & 3 & -7 \end{bmatrix} =$$

$$\begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 4 \\ 0 & 0 & -1 & 2 \\ 0 & 0 & 0 & -7 \end{bmatrix} + \begin{bmatrix} -2 & -4 & 0 & 0 \\ -2 & -4 & 0 & 0 \\ 2 & 4 & 0 & 0 \\ 2 & 4 & 0 & 0 \end{bmatrix} + \begin{bmatrix} -1 & 0 & -3 & 0 \\ 1 & 0 & 3 & 0 \\ -1 & 0 & -3 & 0 \\ 1 & 0 & 3 & 0 \end{bmatrix}$$

is the Jacobian of a system with two double combining terms, one derived from the reaction $X_1 + X_2 \to X_3 + X_4$ and the other from $X_1 + X_3 \to X_2 + X_4$. This matrix has two real eigenvalues approximately equal to -10.79238 and -7.48238, as well as a complex conjugate pair approximately equal to $-0.36262 \pm 1.36464i$. Meanwhile, the eigenvalues of the matrix

$$\begin{bmatrix} -3 & -1 & 3 & 0 \\ -2 & -2 & 3 & 4 \\ 3 & 1 & -13 & 2 \\ 2 & 2 & 3 & -7 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 3 & 0 \\ 0 & -1 & 3 & 4 \\ 1 & 0 & -13 & 2 \\ 0 & 1 & 3 & -7 \end{bmatrix} + \begin{bmatrix} -2 & -1 & 0 & 0 \\ -2 & -1 & 0 & 0 \\ 2 & 1 & 0 & 0 \\ 2 & 1 & 0 & 0 \end{bmatrix}$$

with a single double combining term are all real and negative, being approximately -14.56818, -8.49616, -1.56363, and -0.37202.

It is also possible for a matrix with double combining terms to have eigenvalues with positive real parts. For instance, the matrix

$$\begin{bmatrix} -102 & -30 & 3 & 4 \\ -100 & -42 & 4 & 7 \\ 100 & 33 & -17 & 3 \\ 101 & 39 & 10 & -14 \end{bmatrix} = \begin{bmatrix} -2 & 0 & 3 & 4 \\ 0 & -12 & 4 & 7 \\ 0 & 3 & -17 & 3 \\ 1 & 9 & 10 & -14 \end{bmatrix} + \begin{bmatrix} -100 & -30 & 0 & 0 \\ -100 & -30 & 0 & 0 \\ 100 & 30 & 0 & 0 \\ 100 & 30 & 0 & 0 \end{bmatrix}$$

has a positive eigenvalue of approximately 0.01638, along with three negative eigenvalues approximately equal to -142.60074, -22.151, and -10.26464. This example is notable as it shows that the conjecture we discussed back in Section 1.2.2, which hypothesizes that matrices with one combining term cannot have eigenvalues with positive real parts, does not hold for matrices with one double combining term.

We end this section with a few sufficient conditions for a matrix with double combining terms to have only eigenvalues with non-positive real parts.

Proposition 3.1.4. Let A be an $n \times n$ matrix with at least one double combining term. Let λ be an eigenvalue of A. If either of the following hold

- A satisfies points $a.$) and $b.$) from Proposition 1.1.9
- A is a matrix with exactly one double combining term and has the form

$$A = \begin{bmatrix} -a_{11}-c & a_{12}-d & 0 & 0 & 0 & \dots & 0 \\ a_{21}-c & -a_{22}-d & 0 & 0 & 0 & \dots & 0 \\ a_{31}+c & a_{32}+d & -a_{33} & a_{34} & a_{35} & \dots & a_{3n} \\ a_{41}+c & a_{42}+d & a_{43} & -a_{44} & a_{45} & \dots & a_{4n} \\ a_{51} & a_{52} & a_{53} & a_{54} & -a_{55} & \dots & a_{5n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{n4} & a_{n5} & \dots & -a_{nn} \end{bmatrix}$$

with c and d positive,

then $\mathfrak{Re}(\lambda) \leq 0$.

Proof. The result follows from Proposition 1.1.9 and the proof of Proposition 1.2.2. □

Proposition 3.1.5. Suppose A is an $n \times n$ matrix with exactly one double combining term and has the form

$$A = \begin{bmatrix} -a_{11}-c & a_{12}-d & 0 & 0 & a_{15} & \dots & a_{1n} \\ a_{21}-c & -a_{22}-d & 0 & 0 & a_{25} & \dots & a_{2n} \\ a_{31}+c & a_{32}+d & -a_{33} & a_{34} & a_{35} & \dots & a_{3n} \\ a_{41}+c & a_{42}+d & a_{43} & -a_{44} & a_{45} & \dots & a_{4n} \\ a_{51} & a_{52} & 0 & 0 & -a_{55} & \dots & a_{5n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & 0 & 0 & a_{n5} & \dots & -a_{nn} \end{bmatrix},$$

where

$$a_{11} > \sum_{i \neq 1} a_{i1}, \quad a_{22} > \sum_{i \neq 2} a_{i2},$$

all entries in columns three and four are zero, except possibly a_{33}, a_{43}, a_{34}, and a_{44}, and c and d are positive. Then if λ is an eigenvalue of A, $\mathfrak{Re}(\lambda) \leq 0$.

Proof. The proof will be very similarly to that of Proposition 1.2.5. We will once again use the concept of similar matrices, using the diagonal matrix

$$S = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & \dots & 0 \\ 0 & 1 & 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 1/m & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & 1/m & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \dots & 1 \end{bmatrix}, \text{ with } S^{-1} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & \dots & 0 \\ 0 & 1 & 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & m & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & m & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \dots & 1 \end{bmatrix},$$

where $m > 0$. Then, A is similar to the matrix $B = SAS^{-1}$, which is

$$B = \begin{bmatrix} -a_{11} - c & a_{12} - d & 0 & 0 & a_{15} & \dots & a_{1n} \\ a_{21} - c & -a_{22} - d & 0 & 0 & a_{25} & \dots & a_{2n} \\ (a_{31} + c)/m & (a_{32} + d)/m & -a_{33} & a_{34} & a_{35}/m & \dots & a_{3n}/m \\ (a_{41} + c)/m & (a_{42} + d)/m & a_{43} & -a_{44} & a_{45}/m & \dots & a_{4n}/m \\ a_{51} & a_{52} & 0 & 0 & -a_{55} & \dots & a_{5n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & 0 & 0 & a_{n5} & \dots & -a_{nn} \end{bmatrix}.$$

As with the proof of Proposition 1.2.5, our goal here is to show there exists an $m > 1$ such that Proposition 1.1.9 applies to the first and second columns of B. That is, we want $m > 1$ such that

$$|a_{21} - c| + \frac{a_{31} + c}{m} + \frac{a_{41} + c}{m} + \sum_{i=5}^{n} a_{i1} \;\leq\; a_{11} + c$$

$$|a_{12} - d| + \frac{a_{32} + d}{m} + \frac{a_{42} + d}{m} + \sum_{i=5}^{n} a_{i2} \;\leq\; a_{22} + d$$

both hold.

Focusing on column 1 first, suppose $|a_{21} - c| = a_{21} - c$. Then, for $m > 1$ we have that

$$\begin{aligned} a_{21} - c + \frac{a_{31} + c}{m} + \frac{a_{41} + c}{m} + \sum_{i=5}^{n} a_{i1} \;&\leq \sum_{i \neq 1} a_{i1} + c\Big(\frac{2}{m} - 1\Big) \\ &< \; a_{11} + c\Big(\frac{2}{m} - 1\Big) \\ &< \; a_{11} + c. \end{aligned}$$

Next, suppose $|a_{21} - c| = c - a_{21}$. As with the proof of Proposition 1.2.5, we will break this case into two subcases:

1.) *If $a_{21} > 0$:* We have that

$$\begin{aligned} c - a_{21} + \frac{a_{31} + c}{m} + \frac{a_{41} + c}{m} + \sum_{i=5}^{n} a_{i1} \;&\leq -a_{21} + a_{31} + \cdots + a_{n1} + c\Big(\frac{2}{m} + 1\Big) \\ &< \; a_{11} - 2a_{21} + c\Big(\frac{2}{m} + 1\Big) \end{aligned}$$

if $m > 1$. When $m = \dfrac{c}{a_{21}}$, we have

$$a_{11} - 2a_{21} + c\Big(\frac{2}{m} + 1\Big) \;=\; a_{11} + c,$$

and this becomes a strict inequality as m increases further. Hence, choosing

$$m \;>\; \max\Big\{1, \frac{c}{a_{21}}\Big\}$$

establishes the desired inequality.

2.) *If $a_{21} = 0$:* Since $\sum_{i\neq 1} a_{i1} < a_{11}$, there is an $\epsilon \in (0, a_{11}]$ such that $\sum_{i\neq 1} a_{i1} = a_{11} - \epsilon$. Then for $m > 1$,

$$\begin{aligned} c + \frac{a_{31}+c}{m} + \frac{a_{41}+c}{m} + \sum_{i=5}^{n} a_{i1} \;&\leq \sum_{i\neq 1} a_{i1} + c\Big(\frac{2}{m}+1\Big) \\ &=\; a_{11} - \epsilon + c\Big(\frac{2}{m}+1\Big). \end{aligned}$$

We then want the inequality $a_{11} - \epsilon + c\Big(\frac{2}{m}+1\Big) \leq a_{11} + c$ to hold:

$$\begin{aligned} a_{11} - \epsilon + c\Big(\frac{2}{m}+1\Big) \;&\leq\; a_{11} + c \\ \iff 2c/m \;&\leq\; \epsilon \\ \iff 2c/\epsilon \;&\leq\; m \end{aligned}$$

Hence, choosing $m > \max\{1, 2c/\epsilon\}$ will produce the desired inequality.

Hence, we can always find an $m = m' > 1$ such that the desired bound on the entries of column 1 holds. Similarly, we can find an $m = m'' > 1$ such that the desired bound on the entries in the second column holds. Thus, taking $m = \max\{m', m''\}$ ensures that we can apply Proposition 1.1.9 and obtain the result regarding the eigenvalues of A. □

3.2 Reactions of the form $X + Y \to 2X$

The next type of reaction we will introduce is of the form $X + Y \xrightarrow{k} 2X$ (or $X + Y \xrightarrow{k} 2Y$) , in which species X and Y react to form two molecules of X (or Y) at rate $k > 0$. An example of a system containing a term derived from such a reaction is the following version of the Lotka-Volterra predator-prey model from [9]:

$$\begin{aligned} \dot{x} \;&=\; \alpha x - \beta xy \\ \dot{y} \;&=\; \beta xy - \gamma y, \end{aligned} \tag{3.11}$$

Here, the $\pm\beta xy$ terms are obtained from the reaction $X + Y \xrightarrow{\beta} 2Y$; the βxy term in the $\dot{y}$ equation is positive as this reaction results in a net gain of one molecule of Y. We will analyze the Lotka-Volterra model in more depth in Section 5.3.

In this section, our focus will be on the reaction $X + Y \xrightarrow{k} 2X$, in which we lose one molecule of Y but have a net gain of one molecule of X; hence, the mass action system corresponding to this reaction is

$$\begin{aligned} \dot{x} &= kxy \\ \dot{y} &= -kxy. \end{aligned}$$

The Jacobian of this system is then

$$\begin{bmatrix} ky & kx \\ -ky & -kx \end{bmatrix}.$$

Notice that if the value of y is positive, so is the upper diagonal entry of this matrix. Thus, in a mass action system derived from at least one $X + Y \to 2X$ reaction, it is possible that the Jacobian, when evaluated at a non-negative equilibrium, has a positive diagonal entry.

The presence of a positive diagonal entry may result in the Jacobian having eigenvalues with positive real parts, as the Gershgorin disk associated with the affected column will be centered at a positive real number on the complex plane. In the following section, we will provide several results describing when positive eigenvalues are, or are not, possible.

3.2.1 Eigenvalues of the Jacobian

Here, we will focus on the Jacobian matrices of n-variable mass action systems derived from exactly one $X + Y \to 2X$ reaction and an arbitrary number of SRP reactions. WLOG, we will assume the $X + Y \to 2X$ reaction is of the form $X_1 + X_2 \to 2X_1$ involving the first two chemical species. We will also assume the Jacobian is evaluated at a non-negative equilibrium in which both x_1^* and x_2^* are strictly positive. Thus, the Jacobian matrices of interest will have the form

$$\begin{bmatrix} -a_{11} + b & a_{12} + c & a_{13} & \dots & a_{1n} \\ a_{21} - b & -a_{22} - c & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}, \tag{3.12}$$

where b and c are positive and the a_{ij} form an SRP matrix.

We begin by providing conditions for a 2×2 matrix to have eigenvalues with strictly negative real parts:

Proposition 3.2.1. Let

$$A \;=\; \begin{bmatrix} -a_{11}+b & a_{12}+c \\ a_{21}-b & -a_{22}-c \end{bmatrix}$$

be a 2×2 matrix of form (3.12) with eigenvalues λ_1 and λ_2. Then, $\mathfrak{Re}(\lambda_1) < 0$ and $\mathfrak{Re}(\lambda_2) < 0$ if and only if one of the following holds:

1.) $a_{12} = a_{22}, \quad a_{11} > a_{21}, \quad \text{and} \quad b < c + a_{11} + a_{22}$

2.) $a_{12} < a_{22} \quad \text{and} \quad b < \min\left\{ c + a_{11} + a_{22},\; \dfrac{a_{11}a_{22} - a_{12}a_{21} + c(a_{11} - a_{21})}{a_{22} - a_{12}} \right\}$

Proof. Note that as the a_{ij} form an SRP matrix, we have that $a_{11} \geq a_{21}$ and $a_{22} \geq a_{12}$.

The characteristic polynomial of A is

$$\lambda^2 - \mathrm{tr}(A)\lambda + \det(A),$$

where

$$\begin{aligned} -\mathrm{tr}(A) &= a_{11} + a_{22} + c - b \\ \det(A) &= a_{11}a_{22} - a_{12}a_{21} + c(a_{11} - a_{21}) + b(a_{12} - a_{22}). \end{aligned}$$

Both roots of the characteristic polynomial will have negative real part if and only if $-\mathrm{tr}(A)$ and $\det(A)$ are both positive. It is easy to see that we will have $-\mathrm{tr}(A) > 0$ if and only if $b < c + a_{11} + a_{22}$.

Then, $\det(A) > 0$ holds if and only if

$$a_{11}a_{22} - a_{12}a_{21} + c(a_{11} - a_{21}) \;>\; b(a_{22} - a_{12}).$$

Note that as $a_{11} \geq a_{21}$ and $a_{22} \geq a_{12}$, the terms $a_{11}a_{22} - a_{12}a_{21}$, $c(a_{11} - a_{21})$, and $b(a_{22} - a_{12})$ are all non-negative. If $a_{22} = a_{12}$, then the above inequality becomes

$$(a_{22} + c)(a_{11} - a_{21}) \;>\; 0,$$

which holds if and only if $a_{11} > a_{21}$. This thus establishes the conditions given in 1.).

If $a_{22} > a_{12}$, then the above inequality simply becomes

$$\frac{a_{11}a_{22} - a_{12}a_{21} + c(a_{11} - a_{21})}{a_{22} - a_{12}} \;>\; b,$$

giving us the conditions in 2.) after taking

$$b < \min\left\{ c + a_{11} + a_{22},\; \frac{a_{11}a_{22} - a_{12}a_{21} + c(a_{11} - a_{21})}{a_{22} - a_{12}} \right\}$$

to ensure the positivity of both the trace and the determinant of A. □

The remaining propositions here will provide conditions for matrices of form (3.12) to exhibit eigenvalues with positive real parts.

Proposition 3.2.2. Suppose A is an $n \times n$ matrix of form (3.12). If $b > c + \sum_i a_{ii}$, then the matrix has an eigenvalue with positive real part.

Proof. The condition on b means that the trace of the matrix, $b - c - \sum_i a_{ii}$, is positive. Since the sum of the eigenvalues must equal the trace, this means at least one eigenvalue must have positive real part. □

Proposition 3.2.3. Suppose A is an $n \times n$ matrix of form (3.12) in which the a_{i1} are all equal to zero:

$$A = \begin{bmatrix} b & a_{12}+c & a_{13} & \dots & a_{1n} \\ -b & -a_{22}-c & a_{23} & \dots & a_{2n} \\ 0 & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}$$

Then, if A is invertible, A has an eigenvalue with positive real part.

Proof. WLOG, suppose the dimension n of A is even; the case in which n is odd is similar.

Consider the matrix

$$A' = \begin{bmatrix} -b & a_{12}+c & a_{13} & \dots & a_{1n} \\ b & -a_{22}-c & a_{23} & \dots & a_{2n} \\ 0 & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix},$$

which is A with the first column multiplied by -1, and hence $\det(A) = -\det(A')$. Note that A' is an SRP matrix, and is invertible because A is invertible. Hence, $\det(A')$ is positive by Theorem 1.1.7.

Thus, $\det(A) < 0$. Since the determinant of A is equal to the product of the eigenvalues of A, of which there are an even number, at least one must have positive real part in order for $\det(A)$ to be negative. □

Proposition 3.2.4. Consider an $n \times n$ matrix A of form (3.12). Let

$$A' = \begin{bmatrix} -a_{11} & a_{12}+c & a_{13} & \dots & a_{1n} \\ a_{21} & -a_{22}-c & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}$$

be the SRP matrix obtained from A by removing the b terms in column 1. Then, $\lambda > 0$ is an eigenvalue of A if and only if

$$b = \frac{\det(A' - \lambda I)}{C_{12} - C_{11}},$$

where C_{11} and C_{12} are cofactors of the matrix $A' - \lambda I$.

Proof. WLOG, suppose that n is even; the case in which n is odd is similar.

We know that λ is an eigenvalue of A if and only if $\det(A - \lambda I) = 0$. Note that

$$\det(A - \lambda I) = \begin{vmatrix} -a_{11}+b-\lambda & a_{12}+c & a_{13} & \dots & a_{1n} \\ a_{21}-b & -a_{22}-c-\lambda & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{vmatrix}$$

$$= \begin{vmatrix} -a_{11}-\lambda & a_{12}+c & a_{13} & \dots & a_{1n} \\ a_{21} & -a_{22}-c-\lambda & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{vmatrix}$$

$$+ \begin{vmatrix} b & a_{12}+c & a_{13} & \dots & a_{1n} \\ -b & -a_{22}-c-\lambda & a_{23} & \dots & a_{2n} \\ 0 & a_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{vmatrix}$$

$$= \det(A' - \lambda I) + \begin{vmatrix} b & a_{12}+c & a_{13} & \dots & a_{1n} \\ -b & -a_{22}-c-\lambda & a_{23} & \dots & a_{2n} \\ 0 & a_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{vmatrix}.$$

From here, the determinant on the right is

$$\begin{vmatrix} b & a_{12}+c & a_{13} & \dots & a_{1n} \\ -b & -a_{22}-c-\lambda & a_{23} & \dots & a_{2n} \\ 0 & a_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{vmatrix} = b(C_{11} - C_{12}),$$

where C_{11} and C_{12} are cofactors of $A' - \lambda I$. Thus, $\det(A - \lambda I) = 0$ is equivalent to

$$\det(A' - \lambda I) + b(C_{11} - C_{12}) = 0. \tag{3.13}$$

Note that $\det(A' - \lambda I) > 0$ by Theorem 1.1.7; $A' - \lambda I$ is an SRP matrix of even dimension, and must be invertible as $\lambda > 0$ cannot be an eigenvalue of the SRP matrix A'.

Hence, if we can show that $C_{11} - C_{12}$ is non-zero, we can solve for b in (3.13) and obtain the target equality. First, note that the SRP matrix

$$B = \begin{bmatrix} -b & a_{12}+c & a_{13} & \dots & a_{1n} \\ b & -a_{22}-c-\lambda & a_{23} & \dots & a_{2n} \\ 0 & a_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{bmatrix}$$

has determinant $b(C_{12} - C_{11})$, which must be non-negative due to the dimension being even. Hence, if $C_{11} - C_{12}$ is non-zero, then $C_{12} - C_{11}$ is also non-zero and positive. This means that if we can show $C_{11} - C_{12}$ is non-zero, the expression $b = \dfrac{\det(A' - \lambda I)}{C_{12} - C_{11}}$ will be positive as desired.

So, we will now show that the matrix B is non-singular. We will accomplish this by considering the similar matrix SBS^{-1}, where S and S^{-1} are the diagonal matrices

$$S = \begin{bmatrix} 1 & 0 & 0 & \dots & 0 \\ 0 & 1/m & 0 & \dots & 0 \\ 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 1 \end{bmatrix} \text{ and } S^{-1} = \begin{bmatrix} 1 & 0 & 0 & \dots & 0 \\ 0 & m & 0 & \dots & 0 \\ 0 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 1 \end{bmatrix}.$$

Then, SBS^{-1} multiplies by the second row of B by $1/m$ and the second column by m:

$$SBS^{-1} = \begin{bmatrix} b & m(a_{12}+c) & a_{13} & \dots & a_{1n} \\ -b/m & -a_{22}-c-\lambda & a_{23}/m & \dots & a_{2n}/m \\ 0 & ma_{32} & -a_{33}-\lambda & \dots & a_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & ma_{n2} & a_{n3} & \dots & -a_{nn}-\lambda \end{bmatrix}.$$

We want to show that there is a value of m such that none of the Gershgorin disks associated with the columns of SBS^{-1} include the origin, implying that SBS^{-1}, and thus B, is non-singular. Choosing $m > 1$, the third through nth columns will satisfy this; since each column already satisfies $\sum_{i \neq j} a_{ij} \leq a_{jj}$ and λ is positive, we have $\sum_{i \neq j} a_{ij} < a_{jj} + \lambda$, with the multiplication by $1/m$ in row 2 making the sum on the left even smaller. Hence, the radii of the disks corresponding to columns 3 through n are too small to allow the disks to include the origin.

Furthermore, choosing $m > 1$ results in the radius of the disk corresponding to the first column being $b/m < b$, and thus this disk falls entirely on the right hand side of the complex plane. So, the only thing we need to look at is column 2. The radius r of its Gershgorin disk satisfies

$$\begin{aligned} r &= mc + m\sum_{i \neq 2} a_{i2} \\ &\leq m(c + a_{22}). \end{aligned}$$

Thus, if we can find an m such that $m(c+a_{22}) < a_{22}+c+\lambda$, then r will be strictly less than $a_{22}+c+\lambda$ and we will be done. Assuming $m > 1$, we have that

$$\begin{aligned} & m(c+a_{22}) < a_{22}+c+\lambda \\ \iff & (m-1)(a_{22}+c) < \lambda \\ \iff & m < \frac{\lambda}{a_{22}+c} + 1. \end{aligned}$$

Hence, choosing $1 < m < \dfrac{\lambda}{a_{22}+c} + 1$ gives us the desired result. We can thus solve for b in

(3.13) and conclude that $\det(A - \lambda I) = 0$ if and only if $b = \dfrac{\det(A' - \lambda I)}{C_{12} - C_{11}}$. □

Proposition 3.2.4 provides a way to generate a matrix of form (3.12) with an eigenvalue $\lambda > 0$ of our choice: after choosing appropriate values for c and the a_{ij}, we set $b = \dfrac{\det(A' - \lambda I)}{C_{12} - C_{11}}$ as given in the proposition. This gives rise to the following corollary:

Corollary 3.2.5. For any $n \geq 2$ and $\lambda > 0$, there exists an $n \times n$ matrix of form (3.12) with λ as an eigenvalue.

3.2.2 A Class of Two-Variable Systems

Now, we will analyze a class of two-variable biochemical ramp systems containing exactly one term deriving from an $X + Y \to 2X$ reaction when in the all ramp region. To make things as complex as possible, this class of systems in the all ramp region will also contain terms derived from every possible SRP reaction involving at most two chemical species X and Y. Thus, these systems will derive from the following seven reactions when in the all ramp region:

$$\begin{array}{ll} 0 \xrightarrow{a} X & X \xrightarrow{k_3} Y \\ 0 \xrightarrow{b} Y & Y \xrightarrow{k_4} X \\ X \xrightarrow{k_1} 0 & X + Y \xrightarrow{k_5} 2X \\ Y \xrightarrow{k_2} 0 & \end{array} \tag{3.14}$$

The mass action system corresponding to the reactions given in (3.14) is

$$\begin{aligned} \dot{x} &= -(k_1 + k_3)x + k_4 y + k_5 xy + a \\ \dot{y} &= -(k_2 + k_4)y + k_3 x - k_5 xy + b, \end{aligned}$$

which can be written in the slightly more simplified form

$$\begin{aligned} \dot{x} &= -d_1 x + d_2 xy + d_3 y + a \\ \dot{y} &= -d_4 y - d_2 xy + d_5 x + b \end{aligned} \tag{3.15}$$

with $d_1 > d_5$ and $d_4 > d_3$.

We will analyze ramp systems that resemble system (3.15) when in the all ramp region. To facilitate our analysis, we will assume we only have one ramp function associated with each variable. Thus, here we will be studying ramp systems of the form

$$\begin{aligned} \dot{x} &= -c_1 r_1(x) + c_2 r_1(x) r_2(y) + c_3 r_2(y) + a \\ \dot{y} &= -c_4 r_2(y) - c_2 r_1(x) r_2(y) + c_5 r_1(x) + b, \end{aligned} \tag{3.16}$$

where r_1 has threshold $2\theta_1$ and r_2 has threshold $2\theta_2$. Similar to (3.15), we have $c_1 > c_5$ and $c_4 > c_3$. Since we want all of the reactions from (3.14) to be represented in this system in the all ramp region, all parameters, including a and b, are strictly positive. Note that in the all ramp region, system (3.16) becomes

$$\begin{aligned} \dot{x} &= -\frac{c_1 x}{2\theta_1} + \frac{c_2 xy}{4\theta_1\theta_2} + \frac{c_3 y}{2\theta_2} + a \\ \dot{y} &= -\frac{c_4 y}{2\theta_2} - \frac{c_2 xy}{4\theta_1\theta_2} + \frac{c_5 x}{2\theta_1} + b, \end{aligned} \tag{3.17}$$

which has the same form as (3.15) with

$$\begin{aligned} d_1 &= \frac{c_1}{2\theta_1} & d_4 &= \frac{c_4}{2\theta_2} \\ d_2 &= \frac{c_2}{4\theta_1\theta_2} & d_5 &= \frac{c_5}{2\theta_1}. \\ d_3 &= \frac{c_3}{2\theta_2} \end{aligned}$$

We will now determine when system (3.16) has an equilibrium in the all ramp region. Setting the $\dot{y}$ equation from (3.17) equal to zero, we get that

$$y^* = \frac{2\theta_2(c_5 x^* + 2\theta_1 b)}{2\theta_1 c_4 + c_2 x^*} \tag{3.18}$$

at equilibrium. Substituting this expression for y^* into the $\dot{x}$ equation from (3.17), we find that $x = x^*$ must be a solution to

$$c_2(c_1 - c_5)x^2 + 2\theta_1 C x - 4\theta_1^2(c_3 b + c_4 a) = 0,$$

where

$$C = c_1 c_4 - c_2 b - c_3 c_5 - c_2 a.$$

Note that as $c_1 > c_5$, the coefficient of the x^2 term in the above quadratic is positive. This, along with the fact that all parameters are positive, also implies that the discriminant is strictly positive and larger than $(2\theta_1 C)^2$ in magnitude. Hence, only the positive root from the quadratic formula yields a non-negative value for x^*:

$$\begin{aligned} x^* &= \frac{-2\theta_1 C + \sqrt{4\theta_1^2 C^2 + 16\theta_1^2 c_2(c_1 - c_5)(c_3 b + c_4 a)}}{2c_2(c_1 - c_5)} \\ &= \frac{-\theta_1 C + \theta_1\sqrt{C^2 + 4c_2(c_1 - c_5)(c_3 b + c_4 a)}}{c_2(c_1 - c_5)} \end{aligned} \tag{3.19}$$

As we did with system (3.2) with a double combining term, we will now derive parameter conditions sufficient for the equilibrium values given in (3.18) and (3.19) to fall in the all ramp region (i.e. $x^* < 2\theta_1$ and $y^* < 2\theta_2$). Starting with x^*, it would be useful to choose parameters such that $C > 0$ so that we can use the inequality

$$\begin{aligned} -C + \sqrt{C^2 + 4c_2(c_1 - c_5)(c_3 b + c_4 a)} &< -C + C + 2\sqrt{c_2(c_1 - c_5)(c_3 b + c_4 a)} \\ &= 2\sqrt{c_2(c_1 - c_5)(c_3 b + c_4 a)}. \end{aligned}$$

We have $C > 0$ if and only if $c_1 > \dfrac{c_2 a + c_2 b + c_3 c_5}{c_4}$. Then, we will want the inequality

$$\frac{\sqrt{c_2(c_1 - c_5)(c_3 b + c_4 a)}}{c_2(c_1 - c_5)} < 1$$

to hold, which happens if and only if $c_1 > \dfrac{c_3 b + c_4 a + c_2 c_5}{c_2}$.

Hence, choosing

$$c_1 > \max\left\{\frac{c_2 a + c_2 b + c_3 c_5}{c_4}, \frac{c_3 b + c_4 a + c_2 c_5}{c_2}\right\}$$

gives us

$$\begin{aligned} x^* &= \frac{-\theta_1 C + \theta_1\sqrt{C^2 + 4c_2(c_1 - c_5)(c_3 b + c_4 a)}}{c_2(c_1 - c_5)} \\ &< \frac{2\theta_1\sqrt{c_2(c_1 - c_5)(c_3 b + c_4 a)}}{c_2(c_1 - c_5)} \\ &< 2\theta_1 \end{aligned}$$

as desired. Assuming $x^* < 2\theta_1$ holds, then the condition $c_4 > c_5 + b$ is sufficient for the y^* value given in (3.18) to be strictly less than $2\theta_2$:

$$\begin{aligned} y^* &= \frac{2\theta_2(c_5 x^* + 2\theta_1 b)}{2\theta_1 c_4 + c_2 x^*} \\ &< \frac{2\theta_2(2\theta_1 c_5 + 2\theta_1 b)}{2\theta_1 c_4} \end{aligned}$$

$$= \frac{2\theta_2(c_5+b)}{c_4}$$

$$< 2\theta_2.$$

Thus, if

$$c_1 > \max\left\{\frac{c_2a+c_2b+c_3c_5}{c_4}, \frac{c_3b+c_4a+c_2c_5}{c_2}\right\}$$

$$c_4 > c_5+b$$

both hold, then system (3.16) has the unique equilibrium point $(x^*, y^*) = ((3.19), (3.18))$ in the all ramp region.

With regards to stability, the Jacobian of the all ramp region system (3.17) is

$$J = \begin{bmatrix} -\frac{c_1}{2\theta_1} + \frac{c_2}{4\theta_1\theta_2}y^* & \frac{c_2}{4\theta_1\theta_2}x^* + \frac{c_3}{2\theta_2} \\ -\frac{c_2}{4\theta_1\theta_2}y^* + \frac{c_5}{2\theta_1} & -\frac{c_4}{2\theta_2} - \frac{c_2}{4\theta_1\theta_2}x^* \end{bmatrix}$$

when evaluated at the equilibrium point. The trace of this matrix is

$$-\frac{c_1}{2\theta_1} + \frac{c_2}{4\theta_1\theta_2}y^* - \frac{c_4}{2\theta_2} - \frac{c_2}{4\theta_1\theta_2}x^*.$$

To determine the sign of the trace, note that the x nullcline of system (3.16) is given by

$$r_2(y) = \frac{c_1r_1(x)-a}{c_2r_1(x)+c_3}.$$

The equilibrium point (x^*, y^*) must fall on this nullcline; hence, we have that

$$r_2(y^*) = \frac{c_1r_1(x^*)-a}{c_2r_1(x^*)+c_3}$$

$$< \frac{c_1r_1(x^*)}{c_2r_1(x^*)}$$

$$= \frac{c_1}{c_2},$$

or equivalently, $y^* < \frac{2c_1\theta_2}{c_2}$. The trace of J thus satisfies

$$-\frac{c_1}{2\theta_1} + \frac{c_2}{4\theta_1\theta_2}y^* - \frac{c_4}{2\theta_2} - \frac{c_2}{4\theta_1\theta_2}x^*$$

$$< \left(\frac{c_2}{4\theta_1\theta_2}\cdot\frac{2c_1\theta_2}{c_2}\right) - \frac{c_1}{2\theta_1} - \frac{c_4}{2\theta_2} - \frac{c_2}{4\theta_1\theta_2}x^*$$

$$= -\frac{c_4}{2\theta_2} - \frac{c_2}{4\theta_1\theta_2}x^*$$

$$< \ 0.$$

Next, the Jacobian has determinant

$$\det(J) \ = \ \frac{c_1c_4 - c_3c_5}{4\theta_1\theta_2} + \frac{(c_1 - c_5)c_2x^*}{8\theta_1^2\theta_2} + \frac{(c_3 - c_4)c_2y^*}{8\theta_1\theta_2^2}.$$

Using the fact that $c_1 > c_5$, $c_4 > c_3$, and $y^* < \dfrac{2c_1\theta_2}{c_2}$, we then have that

$$\begin{aligned}
\det(J) \ &> \ \frac{c_1c_4 - c_3c_5}{4\theta_1\theta_2} + \frac{(c_1 - c_5)c_2x^*}{8\theta_1^2\theta_2} + \left(\frac{(c_3 - c_4)c_2}{8\theta_1\theta_2^2} \cdot \frac{2c_1\theta_2}{c_2}\right) \\
&= \ \frac{c_1c_4 - c_3c_5}{4\theta_1\theta_2} + \frac{(c_1 - c_5)c_2x^*}{8\theta_1^2\theta_2} + \frac{(c_3 - c_4)c_1}{4\theta_1\theta_2} \\
&= \ \frac{c_3(c_1 - c_5)}{4\theta_1\theta_2} + \frac{(c_1 - c_5)c_2x^*}{8\theta_1^2\theta_2} \\
&> \ 0.
\end{aligned}$$

Thus, as J has a negative trace and a positive determinant, both of its eigenvalues must have strictly negative real parts. As a result, when system (3.16) has an equilibrium in the all ramp region, it is asymptotically stable.

Finally, we consider global flow in system (3.16) when there is an equilibrium in the all ramp region. The x and y nullclines are given by

$$r_2(y) \ = \ \frac{c_1r_1(x) - a}{c_2r_1(x) + c_3} \ \text{ and } \ r_2(y) \ = \ \frac{c_5r_1(x) + b}{c_2r_1(x) + c_4}$$

respectively. We have that

$$\frac{c_1r_1(x) - a}{c_2r_1(x) + c_3} \ > \ \frac{c_5r_1(x) + b}{c_2r_1(x) + c_4}$$

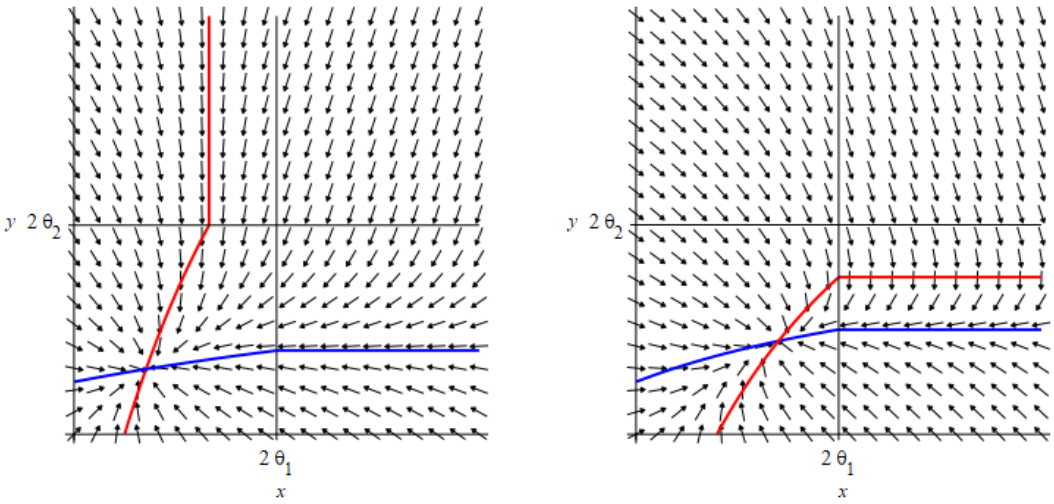
if and only if

$$c_2(c_1 - c_5)(r_1(x))^2 + Cr_1(x) - (c_3b + c_4a) \ > \ 0,$$

where C is defined as in the x^* expression from (3.19). Note that setting $r_1(x) = \dfrac{x}{2\theta_1}$ yield us the same quadratic from which we derived (3.19); hence, the above inequality tells us that for $x > x^*$, the x nullcline of system (3.16) will be positioned above the y nullcline on the Cartesian plane.

Similar calculations show that for $x < x^*$, the y nullcline of (3.16) will lie above the x nullcline. The $\dot{x}$ equation from (3.16) is positive for y values that fall above or to the left of the x nullcline, and negative for y values below or to the right, while we have $\dot{y} > 0$ for y values below or to the right of the y nullcline and $\dot{y} < 0$ for y values above or to the left of said nullcline.

The positioning of the nullclines and the signs of $\dot{x}$ and $\dot{y}$ result in global flow in system (3.16) being toward the equilibrium point in the all ramp region. Figure 3.2.1 shows a couple of example vector fields, demonstrating two possibilities for the box of phase space in which the x nullcline enters after the all ramp region.



(a) (b)

Figure 3.2.1: Flow in system (3.16) when an equilibrium exists in the all ramp region. For each example, the x nullcline is shown in red while the y nullcline is shown in blue.

3.2.2.1 Comparisons to Michaelis-Menten

As a Michaelis-Menten system, (3.16) becomes

$$\begin{aligned} \dot{x} &= -c_1 M_1(x) + c_2 M_1(x) M_2(y) + c_3 M_2(y) + a \\ \dot{y} &= -c_4 M_2(y) - c_2 M_1(x) M_2(y) + c_5 M_1(x) + b, \end{aligned} \tag{3.20}$$

where $M_1(x) = \dfrac{x}{\theta_1 + x}$ and $M_2(y) = \dfrac{y}{\theta_2 + y}$. By Theorem 3.1.3, system (3.20) has a non-negative equilibrium if and only if system (3.16) has an equilibrium in the all ramp region; this non-negative equilibrium (x', y') is given by

$$\begin{aligned} \frac{x'}{\theta_1 + x'} &= \frac{x^*}{2\theta_1} \iff x' = \frac{x^* \theta_1}{2\theta_1 - x^*} \\ \frac{y'}{\theta_2 + y'} &= \frac{y^*}{2\theta_2} \iff y' = \frac{y^* \theta_2}{2\theta_2 - y^*}, \end{aligned} \tag{3.21}$$

where x^* and y^* are from (3.19) and (3.18) respectively.

The Jacobian of (3.20) is

$$\begin{bmatrix} -c_1 M_1'(x) + c_2 M_1'(x) M_2(y) & c_2 M_1(x) M_2'(y) + c_3 M_2'(y) \\ c_5 M_1'(x) - c_2 M_1'(x) M_2(y) & -c_2 M_1(x) M_2'(y) - c_4 M_2'(y) \end{bmatrix}$$

in general, and when evaluated at the equilibrium (3.21), an argument similar to that used for ramp system (3.16) shows that both eigenvalues have negative real parts. Hence, equilibrium (3.21) is asymptotically stable.

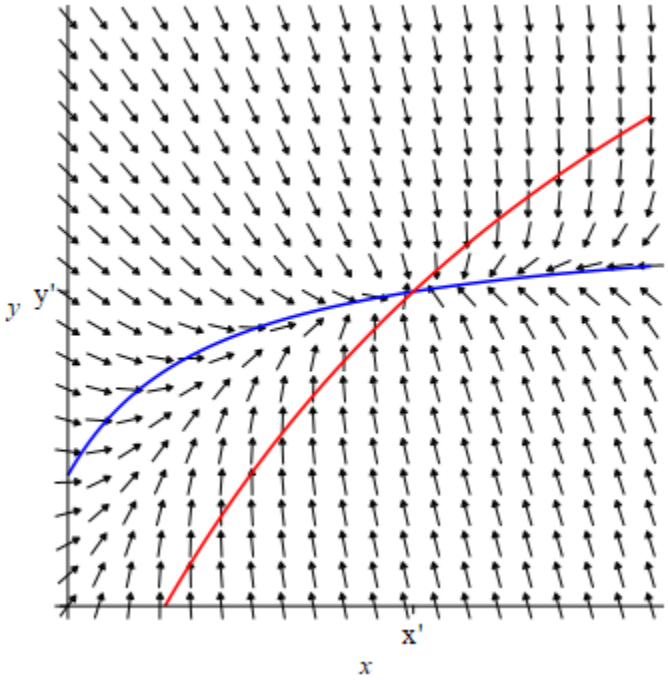


Figure 3.2.2: Flow in system (3.20) in the first quadrant when the equilibrium point (x', y') given in (3.21) exists. The x nullcline is shown in red while the y nullcline is shown in blue.

Additionally, when the equilibrium (3.21) exists, flow in the first quadrant in system (3.20) is similar to that of the ramp system, with the same placement of nullclines and signs of the $\dot{x}$ and $\dot{y}$ equations. As a result, flow in this region is toward the equilibrium point; this is demonstrated in the vector field shown in Figure 3.2.2.

3.2.2.2 No Equilibria and Unbounded Flow

The final piece of our analysis of ramp system (3.16) will focus on the absence of equilibria. In particular, here we will show that when (3.16) has no equilibria, not even in a saturated region, flow will be unbounded.

Note that the equilibrium values for x^* and y^* given in (3.19) and (3.18) respectively can equivalently be written as

$$r_1(x^*) = \frac{-C + \sqrt{C^2 + 4c_2(c_1 - c_5)(c_3 b + c_4 a)}}{2c_2(c_1 - c_5)}$$

$$r_2(y^*) = \frac{c_5 r_1(x^*) + b}{c_4 + c_2 r_1(x^*)},$$

where C is as defined for the x^* value (3.19). System (3.16) will have no equilibria if at least one of $r_1(x^*) > 1$ or $r_2(y^*) > 1$ holds, or equivalently, if we have $x^* > 2\theta_1$ and/or $y^* > 2\theta_2$ using the expressions given in (3.19) and (3.18).

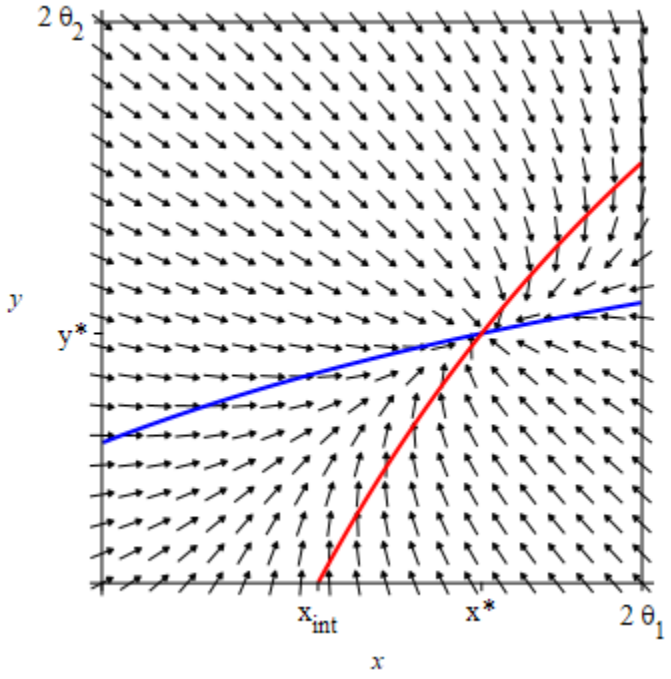
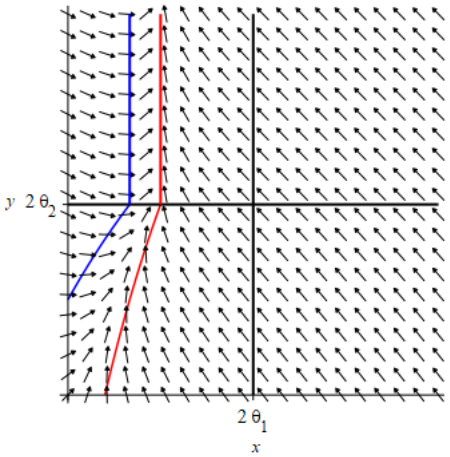


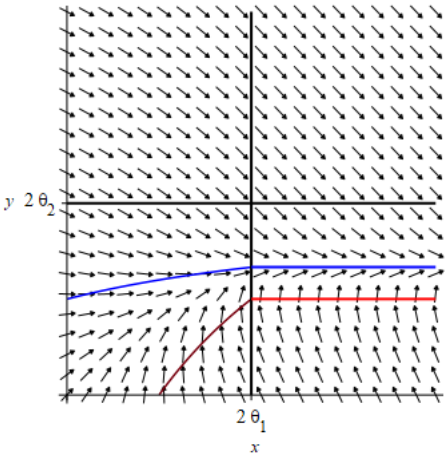
Figure 3.2.3: Flow in the all ramp region of system (3.16) when there is an equilibrium (x^*, y^*). The x nullcline is shown in red while the y nullcline is shown in blue. The x intercept of the x nullcline is $x_{\text{int}} = \dfrac{2a\theta_1}{c}$.

Figure 3.2.3 above shows the flow pattern in the all ramp region of system (3.16) when an equilibrium exists in this box; this particular vector field is the all ramp region of Figure 3.2.1(b). The all ramp region is a rectangle whose top and right borders are defined by the lines $y = 2\theta_2$ and $x = 2\theta_1$ respectively, and the flow on these lines define flow in the saturated regions.

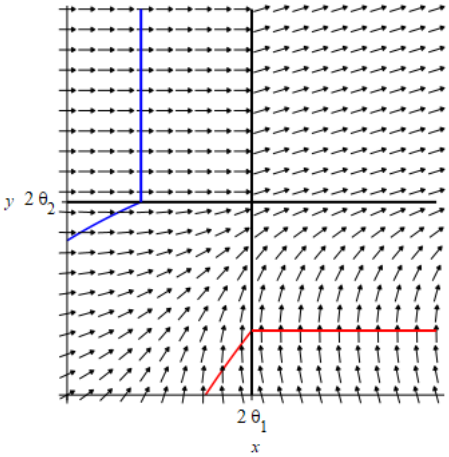
We would like to examine flow in saturated regions when the lines $y = 2\theta_2$ and/or $x = 2\theta_1$ are moved down or to the left such that the equilibrium (x^*, y^*) shown in Figure 3.2.3 no longer falls in the all ramp region rectangle, whether on the boundary or in the interior; that is, we want to move the line $y = 2\theta_2$ down such that it lies strictly below y^*, or move the line



(a) $2\theta_1 > x^*$



(b) $2a\theta_1/c_1 < 2\theta_1 < x^*$



(c) $2a\theta_1/c_1 < 2\theta_1 < x^*$

Figure 3.2.4: Flow patterns in ramp system (3.16) with no equilibria, sorted by where the line $x = 2\theta_1$ was moved relative to x^* and $x_{\text{int}} = 2a\theta_1/c_1$. In each example, the x nullcline is given in red while the y nullcline is given in blue.

$x = 2\theta_1$ to the left such that it falls strictly to the left of x^*, or do both of these maneuvers. Note that we do not want the point (x^*, y^*) to fall, say, on the line $y = 2\theta_2$, because that corresponds to $r_2(y^*) = 1$ above, and hence we can still have an equilibrium in a saturated region.

We now discuss the various ways in which the equilibrium (x^*, y^*) can be excised from the all ramp region, categorized based on the placement of the line $x = 2\theta_1$, and the effect on global flow in ramp system (3.16):

- First, suppose we leave the line $x = 2\theta_1$ where it is in Figure 3.2.3, located to the right

of x^*. Then, to exclude the equilibrium from the all ramp rectangle, we must move the line $y = 2\theta_2$ downward so that it falls strictly below (x^*, y^*). When we do this, the line $y = 2\theta_2$ will then intersect the x nullcline (given in red in Figure 3.2.3) at a point in which $\dot{y}$ is positive; as a result, the x nullcline will extend into the region in which y is saturated, and flow will be straight upward, resulting in y growing without bound. An example of this type of flow pattern is shown in Figure 3.2.4(a).

- The x nullcline $r_2(y) = \dfrac{c_1 r_1(x) - a}{c_2 r_1(x) + c_3}$ has an x-intercept in the all ramp region at $x = \dfrac{2a\theta_1}{c_1}$; this is given in Figure 3.2.3 as x_{int}. If we move the line $x = 2\theta_1$ such that it falls between the x-intercept of the x nullcline and x^* (i.e. $2a\theta_1/c_1 < 2\theta_1 < x^*$), then the equilibrium is excluded from the all ramp region, and we have the following regarding the placement of $y = 2\theta_2$:

  - If the line $y = 2\theta_2$ remains strictly above the y nullcline (given in blue in Figure 3.2.3) for $x < 2\theta_1$, then — since we moved $x = 2\theta_1$ to be in between $2a\theta_1/c_1$ and x^* — the y nullcline will hit $x = 2\theta_1$ before $y = 2\theta_2$, and thus will extend into the region in which x is saturated. But since $2\theta_1$ is now to the left of x^*, the y nullcline enters the region in which x is saturated when $\dot{x}$ is still positive, resulting in rightward flow. Hence, x will grow without bound. This case is illustrated in Figure 3.2.4(b).
  - If we place the line $y = 2\theta_2$ such that it intersects the x nullcline before intersecting $x = 2\theta_1$, then we will get a flow pattern reminiscent of Figure 3.2.4(a) — the x nullcline will extend into the y saturated region at a point at which $\dot{y}$ is positive.
  - Lastly, suppose the line $y = 2\theta_2$ is placed such that the point $(x, y) = (2\theta_1, 2\theta_2)$ falls between both nullclines. From Figure 3.2.3, both differential equations are positive in the region between both nullclines for $x < x^*$; hence, $\dot{x}$ and $\dot{y}$ will both be positive at the newly moved point $(2\theta_1, 2\theta_2)$, meaning that both will be positive in the region in which both x and y are saturated. Thus, we will get the unbounded flow pattern shown in Figure 3.2.4(c).

  Note that in the special case $2a\theta_1/c_1 = 2\theta_1$, one of the above three points will apply, still giving us unbounded flow.

- Finally, suppose we move the line $x = 2\theta_1$ such that it is to the left of the x intercept of the x nullcline ($2\theta_1 < 2a\theta_1/c_1$). In this case, the x nullcline fails to exist in the ramp system, and the $\dot{x}$ equation from (3.16) will always be positive.

Thus, we find that whenever system (3.16) does not have an equilibrium, flow is unbounded.

3.3 Reactions of the Form $mX \to Y$

The final reaction type we will consider in this chapter is $mX \xrightarrow{k} Y$, in which m molecules of X are converted into a single molecule of Y at rate k. Here, we assume m is a positive integer, and also larger than 1; if $m = 1$, then we would just have an SRP reaction. An example of a reaction of this form with $m = 2$ is $2\mathrm{H} \to \mathrm{H}_2$, in which two atoms of hydrogen (H) combine to form molecular hydrogen (H_2) [19].

With mass action kinetics, the reaction $mX \xrightarrow{k} Y$ corresponds to the differential equations

$$\begin{aligned} \dot{x} &= -mkx^m \\ \dot{y} &= kx^m. \end{aligned}$$

Note here that the $\dot{x}$ equation has an extra factor of m not present in the $\dot{y}$ equation; this is because the reaction consumes m molecules of species X while only producing one molecule of Y. The Jacobian corresponding to this system is

$$\begin{bmatrix} -m^2kx^{m-1} & 0 \\ mkx^{m-1} & 0. \end{bmatrix}$$

As $m > 1$, when x is positive we will have $m^2kx^{m-1} > mkx^{m-1}$, and also $-m^2kx^{m-1} < 0$. Thus, a reaction of the form $mX \to Y$ behaves similarly to an SRP term in the Jacobian, producing a non-positive diagonal entry along with a corresponding non-negative entry in the same column of at most equal magnitude. As a result, addition of a term of the form $mX \to Y$ to a system of SRP terms cannot result in eigenvalues with positive real parts arising.

3.3.1 A Class of Systems with SRP Terms

We will first study two-variable ramp systems derived from a single reaction of the form $mX \to Y$ when in the all ramp region, along with SRP terms. In general, these are systems of the form

$$\begin{aligned} \dot{x} &= -mkr_{11}(x)^m - ar_1(x) + br_2(y) + x_0 \\ \dot{y} &= kr_{11}(x)^m + cr_1(x) - dr_2(y) + y_0, \end{aligned} \tag{3.22}$$

where x_0 and y_0 are non-negative and all other parameters are positive. The constants a, b, c, and d are chosen such that

$$\begin{bmatrix} -a & b \\ c & -d \end{bmatrix}$$

is an SRP matrix, and thus we have that $a \geq c$ and $d \geq b$. We allow the variable x to have two associated ramp functions, r_{11} with threshold $2\theta_{11}$ and r_1 with threshold $2\theta_1$, while y is only associated with r_2 with threshold $2\theta_2$.

Our focus with system (3.22) will be on equilibria in the all ramp region. In particular, we would like to see if the presence of the x^m terms can result in multiple equilibrium points. In the all ramp region, the equations of (3.22) become

$$\begin{aligned} \dot{x} &= -\frac{mkx^m}{(2\theta_{11})^m} - \frac{ax}{2\theta_1} + \frac{by}{2\theta_2} + x_0 \\ \dot{y} &= \frac{kx^m}{(2\theta_{11})^m} + \frac{cx}{2\theta_1} - \frac{dy}{2\theta_2} + y_0. \end{aligned} \tag{3.23}$$

Setting the $\dot{y}$ equation here equal to zero, we find that the equilibrium value of y in the all ramp region must satisfy

$$y^* = \frac{2\theta_2}{d}\left(\frac{k(x^*)^m}{(2\theta_{11})^m} + \frac{cx^*}{2\theta_1} + y_0\right). \tag{3.24}$$

Substituting this value for y into $\dot{x}$ from (3.23), we find that x^* must be a root of the polynomial

$$\frac{k}{(2\theta_{11})^m}\left(m - \frac{b}{d}\right)x^m + \frac{1}{2\theta_1}\left(a - \frac{bc}{d}\right)x - \left(\frac{by_0}{d} + x_0\right). \tag{3.25}$$

The constant term of this polynomial is non-negative, while the conditions $m > 1$, $a \geq c$, and $d \geq b$ imply that the coefficient of x is non-negative while the coefficient of x^m is strictly positive. If the constant term is zero — which happens if and only if $x_0 = y_0 = 0$ — then the polynomial equals zero at $x = 0$ and is positive for $x > 0$; hence, the polynomial has a single non-negative root, and thus (3.22) has a unique equilibrium in the all ramp region at $(x^*, y^*) = (0, 0)$.

If the constant term is negative, then (3.25) is negative at $x = 0$. Then, the derivative of the polynomial with respect to x is

$$\frac{km}{(2\theta_{11})^m}\left(m - \frac{b}{d}\right)x^{m-1} + \frac{1}{2\theta_1}\left(a - \frac{bc}{d}\right),$$

which is positive for $x > 0$. Hence, polynomial (3.25) is strictly increasing on $(0, \infty)$, and will cross the x-axis at exactly one $x = x^* > 0$. Thus, the polynomial will again have a unique non-negative root, meaning that system (3.22) will again have a single equilibrium in the all ramp region, provided that $x^* < \min\{2\theta_1, 2\theta_{11}\}$ and $y^* < 2\theta_2$ hold.

Thus, system (3.25) cannot have more than one equilibrium point in the all ramp region. Now, we will derive sufficient parameter conditions for the unique all ramp region equilibrium to actually fall in this region. Above, we saw that in the special case $x_0 = y_0 = 0$, system (3.25) has an equilibrium at the origin, which will exist regardless of the values taken by the other parameters.

So, suppose at least one of x_0 and y_0 is positive (so the constant term of polynomial (3.25) is negative). One way we can ensure polynomial (3.25) has a root satisfying $x < \min\{2\theta_1, 2\theta_{11}\}$ is to choose parameters such that the polynomial is positive when x reaches its lower threshold, meaning that the polynomial had to have switched from negative to positive at some $x^* < \min\{2\theta_1, 2\theta_{11}\}$. If $2\theta_1 \leq 2\theta_{11}$, the polynomial will be positive at $x = 2\theta_1$ if and only if

$$a \;>\; x_0 + \frac{b(c+y_0)}{d} + \frac{k\theta_1^m}{\theta_{11}^m}\left(\frac{b}{d} - m\right) \;=\; \tau_1.$$

If $2\theta_{11}$ is the smaller threshold, then the condition on a becomes

$$a \;>\; \frac{\theta_1}{\theta_{11}}\left(x_0 + \frac{b(k+y_0)}{d} - mk\right) + \frac{bc}{d} \;=\; \tau_{11},$$

and thus choosing $a > \max\{\tau_1, \tau_{11}\}$ will ensure (3.25) is positive at $x = \min\{2\theta_1, 2\theta_{11}\}$.

The value for y^* given in (3.24) satisfies $y^* < 2\theta_2$ if and only if

$$\frac{k(x^*)^m}{(2\theta_{11})^m} + \frac{cx^*}{2\theta_1} + y_0 \;<\; d.$$

Assuming we choose a as above to ensure $x^* < \min\{2\theta_1, 2\theta_{11}\}$, this condition on y^* can be met by choosing $d > k + c + y_0$.

Thus, if the parameter conditions

$$\begin{aligned} a \;&>\; \max\{\tau_1,\, \tau_{11}\} \\ d \;&>\; k + c + y_0 \end{aligned}$$

hold, then system (3.22) has an equilibrium point (x^*, y^*) in the all ramp region, where x^* is the unique non-negative root of the polynomial (3.25) and y^* is given in (3.24).

3.3.1.1 Multiple Terms

Our next step will be to expand on system (3.22) to cover systems derived from multiple $mX \to Y$ reactions. Additionally, we will also allow reactions of the form $pY \to X$, in which p molecules of Y react to produce a single molecule of X. In general, we will be looking at systems of the form

$$\begin{aligned} \dot{x} \;&=\; -\sum_{i=1}^{\alpha} m_i k_i r_{1_i}(x)^{m_i} + \sum_{i=1}^{\beta} s_i r_{2_i}(y)^{p_i} - a r_1(x) + b r_2(y) + x_0 \\ \dot{y} \;&=\; \sum_{i=1}^{\alpha} k_i r_{1_i}(x)^{m_i} - \sum_{i=1}^{\beta} p_i s_i r_{2_i}(y)^{p_i} + c r_1(x) - d r_2(y) + y_0, \end{aligned} \tag{3.26}$$

where the parameters a, b, c, d, x_0, and y_0 are as in (3.22), as are the ramp functions r_1 and r_2. In the all ramp region, system (3.26) becomes

$$\begin{aligned} \dot{x} &= -\sum_{i=1}^{\alpha} \frac{m_i k_i x^{m_i}}{2\theta_{1_i}} + \sum_{i=1}^{\beta} \frac{s_i y^{p_i}}{2\theta_{2_i}} - \frac{ax}{2\theta_1} + \frac{by}{2\theta_2} + x_0 \\ \dot{y} &= \sum_{i=1}^{\alpha} \frac{k_i x^{m_i}}{2\theta_{1_i}} - \sum_{i=1}^{\beta} \frac{p_i s_i y^{p_i}}{2\theta_{2_i}} + \frac{cx}{2\theta_1} - \frac{dy}{2\theta_2} + y_0, \end{aligned} \tag{3.27}$$

which allows us to see the reactions from which the higher degree terms are derived:

- We have α reactions of the form $m_i X \xrightarrow{K_i} Y$, where $K_i = \dfrac{k_i}{2\theta_{1_i}}$ and the m_i are distinct integers all greater than 1. Note that we have allowed each of these α reactions to be associated with its own ramp function; the ith reaction is associated with the function r_{1_i} with threshold $2\theta_{1_i}$. Thus, along with r_1, the variable x has $\alpha + 1$ associated ramp functions.
- Similarly, we have β reactions of the form $p_i Y \xrightarrow{S_i} X$, where $S_i = \dfrac{s_i}{2\theta_{2_i}}$ and the p_i are distinct integers greater than 1 (note, however, that it is possible for some p_j to equal some m_ℓ). The variable y has $\beta + 1$ associated ramp functions.

Now, we will determine whether it is possible for system (3.26) to have more than one equilibrium point in the all ramp region. First, note that if one variable is zero at equilibrium, then so is the other. To see this, if $x^* = 0$ at equilibrium then from $\dot{x} = 0$ we have

$$\sum_{i=1}^{\beta} s_i r_2(y^*)^{p_i} + b r_2(y^*) + x_0 = 0,$$

which holds if and only if y^* and x_0 are both zero. Similarly, if $y^* = 0$ then we get $x^* = y_0 = 0$ from the $\dot{y} = 0$ equation. Thus, an equilibrium of (3.26) will either be the origin or strictly positive.

Now, imagine the curves $\dot{x} = 0$ and $\dot{y} = 0$, with $\dot{x}$ and $\dot{y}$ from (3.27), drawn in $\mathbb{R}^2$. Suppose these curves intersect at some non-negative (x^*, y^*), which, as mentioned above, will either be the origin or a point with strictly positive components. We will now determine if a second such intersection is possible. At $x' > x^*$, the x terms in both $\dot{x}$ and $\dot{y}$ are larger in magnitude than they were at x^*. As a result, a positive y value that makes each differential equation zero must then be larger than y^* to compensate.

Thus, if the curves $\dot{x} = 0$ and $\dot{y} = 0$ are still in the first quadrant at x', they must pass through y values greater than y^*. Suppose (x', y_1) lies on the curve $\dot{x} = 0$ and (x', y_2) lies on $\dot{y} = 0$. Then, y_1 must be greater than y_2:

- At x', the x terms in $\dot{x}$ are larger in magnitude than the x terms in $\dot{y}$ due to the multiplication by $m_i > 1$. Thus, y_1 needs to be larger in order to balance out the larger x terms.

- Additionally, the y terms in $\dot{y}$ grow more quickly than those in $\dot{x}$ due to the multiplication by $p_i > 1$. Hence, y_2 does not need to be as large in order to cancel out the x terms.

What this means is if the curves $\dot{x} = 0$ and $\dot{y} = 0$ pass through positive y values at any $x' > x^*$, then the $\dot{x} = 0$ curve will always be drawn above the $\dot{y} = 0$. As a result, the two curves will never intersect in the positive quadrant again. Hence, in the all ramp region, system (3.26) can have at most one equilibrium.

We end this section with necessary conditions on x_0 and y_0 for the existence of an all ramp region equilibrium for system (3.26):

Proposition 3.3.1. Suppose system (3.26) has an equilibrium (x^*, y^*) in the all ramp region. Then, both of the following hold:

$$x_0 < a + \sum_{i=1}^{\alpha} m_i k_i$$

$$y_0 < d + \sum_{i=1}^{\beta} p_i s_i$$

Proof. We will use the fact that at an equilibrium in the all ramp region, each ramp function takes a value strictly less than 1.

By contradiction, suppose $x_0 \geq a + \sum_{i=1}^{\alpha} m_i k_i$. Then at the equilibrium (x^*, y^*) we have

$$\begin{aligned}
\dot{x} &= -\sum_{i=1}^{\alpha} m_i k_i r_{1_i}(x^*)^{m_i} + \sum_{i=1}^{\beta} s_i r_{2_i}(y^*)^{p_i} - a r_1(x^*) + b r_2(y^*) + x_0 \\
&\geq \sum_{i=1}^{\alpha} m_i k_i [1 - r_{1_i}(x^*)^{m_i}] + a[1 - r_1(x^*)] + \sum_{i=1}^{\beta} s_i r_{2_i}(y^*)^{p_i} + b r_2(y^*) \\
&> 0,
\end{aligned}$$

a contradiction. The condition on y_0 is similar. □

3.3.2 A Class of Systems with Two Equilibria

Above, we saw that neither system (3.22) nor system (3.26) had the potential to exhibit multiple equilibria in the all ramp region. Here, we will analyze a system with a term derived from an $mX \to Y$ reaction in which two equilibria can exist in the all ramp region simultaneously under the correct parameter conditions. This system has a term derived from

an $X + Y \to 2X$ reaction and, to facilitate our analysis, assumes $m = 2$ and one threshold per variable:

$$\begin{aligned} \dot{x} &= -2kr_1(x)^2 + ar_1(x)r_2(y) - br_1(x) \\ \dot{y} &= kr_1(x)^2 - ar_1(x)r_2(y) - cr_2(y) + y_0. \end{aligned} \tag{3.28}$$

Here, $y_0 \geq 0$ while all other parameters are positive. We will assume that $a > \max\{b, k\}$; the justification for this will be explored as we look at parameter conditions for the existence of equilibria. Ramp functions r_1 and r_2 have thresholds $2\theta_1$ and $2\theta_2$ respectively.

We will now begin solving for equilibria in system (3.28). The equations in the all ramp region are

$$\begin{aligned} \dot{x} &= -\frac{2kx^2}{4\theta_1^2} + \frac{axy}{4\theta_1\theta_2} - \frac{bx}{2\theta_1} \\ \dot{y} &= \frac{kx^2}{4\theta_1^2} - \frac{axy}{4\theta_1\theta_2} - \frac{cy}{2\theta_2} + y_0. \end{aligned} \tag{3.29}$$

From $\dot{y} = 0$, we get that

$$y^* = \frac{\theta_2(k(x^*)^2 + 4y_0\theta_1^2)}{\theta_1(ax^* + 2c\theta_1)}. \tag{3.30}$$

Substituting this into the $\dot{x}$ equation, we see that $x = x^*$ must be a root of the polynomial

$$x\Big[kax^2 + 2\theta_1(2kc + ab)x + 4\theta_1^2(bc - ay_0)\Big]. \tag{3.31}$$

We immediately see that polynomial (3.31) has a root at $x = 0$. Plugging this into (3.30), we get that

$$y^* = \frac{2y_0\theta_2}{c},$$

which falls in the ramp region for r_2 if and only if $y^* < 2\theta_2$, i.e. $y_0 < c$. Hence, system (3.28) has an equilibrium in the all ramp region at $(x^*, y^*) = (0, 2y_0\theta_2/c)$ if and only if $y_0 < c$.

A second equilibrium is obtained from the quadratic term in (3.31). The coefficient of x in this quadratic is positive, while the discriminant evaluates to

$$4\theta_1^2\Big[4k^2c^2 + a^2b^2 + 4ka^2y_0\Big],$$

which is also strictly positive. Hence, the quadratic has at most one positive root, given by

$$\begin{aligned} x^* &= \frac{-2\theta_1(2kc + ab) + \sqrt{4\theta_1^2\Big[4k^2c^2 + a^2b^2 + 4ka^2y_0\Big]}}{2ka} \\ &= \frac{-\theta_1(2kc + ab) + \theta_1\sqrt{4k^2c^2 + a^2b^2 + 4ka^2y_0}}{ka}. \end{aligned} \tag{3.32}$$

The x^* value given in (3.32) is negative for certain assignments of parameters; we find that $x^* > 0$ if and only if the condition

$$y_0 \; > \; \frac{bc}{a}$$

holds. This inequality illustrates why we assumed $a > b$ above — it allows for the condition $\frac{bc}{a} < y_0 < c$ to hold, which makes it possible for the $x^* = 0$ equilibrium to coexist with an equilibrium at which x is positive. Next, we want the positive x^* from (3.32) to actually fall in the all ramp region; this requires $x^* < 2\theta_1$, which holds if and only if

$$y_0 \; < \; k + b + \frac{c(2k+b)}{a}.$$

Finally, subbing the positive x^* from (3.32) into the expression for y^* given in (3.30), we have that $y^* < 2\theta_2$ if and only if

$$y_0 \; < \; c + \frac{ax^*}{2\theta_1} - \frac{k(x^*)^2}{4\theta_1^2}.$$

Note that this condition automatically holds if we choose y_0 such that

$$\frac{bc}{a} \; < \; y_0 \; < \; \min\left\{c, \;\; k + b + \frac{c(2k+b)}{a}\right\},$$

which is necessary and sufficient for the equilibrium $(0, 2y_0\theta_2/c)$ to fall in the all ramp region and for x^* from (3.32) to satisfy $x^* < 2\theta_1$ simultaneously. With y_0 in this range, the term

$$\frac{ax^*}{2\theta_1} - \frac{k(x^*)^2}{4\theta_1^2}$$

is positive as $x^* < 2\theta_1$ along with the assumption that $a > k$. Hence, $y_0 < c$ implies $y_0 < c + \frac{ax^*}{2\theta_1} - \frac{k(x^*)^2}{4\theta_1^2}$ also holds.

Thus, in summary we have the following regarding equilibria in the all ramp region for system (3.28):

- The equilibrium $(x_1^*, y_1^*) = \left(0, \frac{2y_0\theta_2}{c}\right)$ falls in the all ramp region if and only if $y_0 < c$.

- The positive equilibrium $(x_2^*, y_2^*) = ((3.32), (3.30))$ falls in the all ramp region if and only if

$$\frac{bc}{a} \; < \; y_0 \; < \; \min\left\{k + b + \frac{c(2k+b)}{a}, \;\; c + \frac{ax^*}{2\theta_1} - \frac{k(x^*)^2}{4\theta_1^2}\right\}.$$

- The equilibria (x_1^*, y_1^*) and (x_2^*, y_2^*) coexist in the all ramp region if and only if

$$\frac{bc}{a} \;<\; y_0 \;<\; \min\left\{c,\;\; k+b+\frac{c(2k+b)}{a}\right\}.$$

3.3.2.1 Stability and Flow

We now consider the stability of the two equilibria system (3.28) can have in the all ramp region. The Jacobian of the all ramp region system (3.29) is

$$\begin{bmatrix} -\dfrac{kx}{\theta_1^2}+\dfrac{ay}{4\theta_1\theta_2}-\dfrac{b}{2\theta_1} & \dfrac{ax}{4\theta_1\theta_2} \\ \dfrac{kx}{2\theta_1^2}-\dfrac{ay}{4\theta_1\theta_2} & -\dfrac{ax}{4\theta_1\theta_2}-\dfrac{c}{2\theta_2}. \end{bmatrix} \tag{3.33}$$

At the equilibrium $(x_1^*, y_1^*) = \left(0, \dfrac{2y_0\theta_2}{c}\right)$, the Jacobian simply becomes

$$\begin{bmatrix} \dfrac{ay_0}{2\theta_1 c}-\dfrac{b}{2\theta_1} & 0 \\ -\dfrac{ay_0}{2\theta_1 c} & -\dfrac{c}{2\theta_2} \end{bmatrix}.$$

One eigenvalue, $-c/2\theta_2$, is always negative. The other eigenvalue, $\dfrac{ay_0}{2\theta_1 c}-\dfrac{b}{2\theta_1}$, is negative if $y_0 < bc/a$ and positive if $y_0 > bc/a$. Thus, when (x_1^*, y_1^*) is the only equilibrium in the all ramp region, both eigenvalues are negative and (x_1^*, y_1^*) is asymptotically stable. However, once y_0 passes the value bc/a and the second, positive equilibrium emerges, (x_1^*, y_1^*) loses stability and becomes a saddle point.

For the positive equilibrium $(x_2^*, y_2^*) = ((3.32), (3.30))$, note that from $\dot{x} = 0$ in (3.28), the value y_2^* must satisfy

$$r_2(y_2^*) \;=\; \frac{2kr_1(x_2^*)+b}{a},$$

or equivalently, since we are assuming (x_2^*, y_2^*) exists in the all ramp region,

$$y_2^* \;=\; \frac{2\theta_2(kx_2^*+b\theta_1)}{a\theta_1}.$$

Using this value for y_2^*, the upper left diagonal entry of (3.33) evaluated at (x_2^*, y_2^*) becomes

$$-\frac{kx_2^*}{\theta_1^2}+\frac{ay_2^*}{4\theta_1\theta_2}-\frac{b}{2\theta_1} \;=\; -\frac{kx_2^*}{\theta_1^2}+\frac{kx_2^*+b\theta_1}{2\theta_1^2}-\frac{b}{2\theta_1}$$

$$= -\frac{kx_2^*}{2\theta_1^2},$$

which is negative. Hence, as the lower diagonal entry of (3.33) is also negative, the trace of the Jacobian is negative. The determinant is then

$$\frac{ak(x_2^*)^2}{8\theta_1^3\theta_2} + \frac{bax_2^*}{8\theta_1^2\theta_2} + \frac{kcx_2^*}{2\theta_1^2\theta_2} + \frac{bc}{4\theta_1\theta_2} - \frac{acy_2^*}{8\theta_1\theta_1^2} = \frac{ak(x_2^*)^2}{8\theta_1^3\theta_2} + \frac{bax_2^*}{8\theta_1^2\theta_2} + \frac{kcx_2^*}{4\theta_1^2\theta_2},$$

which is positive. Thus, with a negative trace and a positive determinant, both eigenvalues of (3.33) evaluated at (x_2^*, y_2^*) have negative real parts, and (x_2^*, y_2^*) is asymptotically stable when it exists in the all ramp region.

For flow, note that system (3.28) has two x nullclines, the line $x = 0$ and

$$r_2(y) = \frac{2kr_1(x) + b}{a} \tag{3.34}$$

When $x > 0$, the $\dot{x}$ equation is positive when $r_2(y) > \dfrac{2kr_1(x) + b}{a}$ and negative when $r_2(y) < \dfrac{2kr_1(x) + b}{a}$; thus, we will have rightward flow at points in the first quadrant in $\mathbb{R}^2$ located above or to the left of the second x nullcline, and leftward flow when below or to the right of this nullcline. Then, the y nullcline of (3.28) is given by

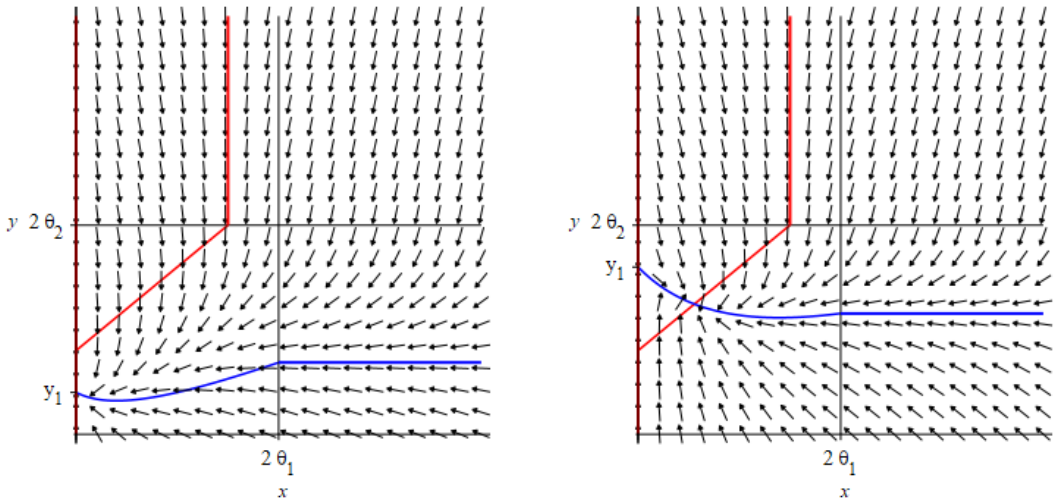
$$r_2(y) = \frac{kr_1(x)^2 + y_0}{ar_1(x) + c}. \tag{3.35}$$

The $\dot{y}$ equation is positive when $r_2(y) < \dfrac{kr_1(x)^2 + y_0}{ar_1(x) + c}$ and negative when $r_2(y) > \dfrac{kr_1(x)^2 + y_0}{ar_1(x) + c}$. Thus, we will have downward flow when above or to the left of the y nullcline, and upward flow when below or to the right of the y nullcline.

When system (3.28) only has the equilibrium $(x_1^*, y_1^*) = (0, 2y_0\theta_2/c)$ in the all ramp region (i.e. when $y_0 < bc/a$), the x nullcline given in (3.34) intersects the line $x = 0$ at $r_2(y) = b/a$, or equivalently, $y = 2b\theta_2/a$. This intersection point lies above (x_1^*, y_1^*), and since the nullclines cannot intersect a second time in the single equilibrium case, the x nullcline (3.34) will always be located above or to the left of the y nullcline (3.35) in $\mathbb{R}^2_+$. This nullcline placement, along with the sign patterns of the $\dot{x}$ and $\dot{y}$ equations described above, results in global flow being directed toward (x_1^*, y_1^*). A vector field illustrating this case is shown in Figure 3.3.1(a).

Next, we consider the case in which (x_1^*, y_1^*) coexists with the positive equilibrium $(x_2^*, y_2^*) = ((3.32), (3.30))$. On the line $x = 0$, the $\dot{y}$ equation will be positive for $y < y_1^*$ and negative for $y > y_1^*$; hence, flow along the y axis is toward (x_1^*, y_1^*).

As $y_0 > bc/a$ when the two equilibria coexist, the x nullcline (3.34) intersects $x = 0$ below (x_1^*, y_1^*), thus initially placing the y nullcline (3.35) above the nullcline (3.34) in the first quadrant. After the two nullclines meet at (x_2^*, y_2^*), however, the positions of the nullclines



(a) $y_0 < \dfrac{bc}{a}$ (b) $\dfrac{bc}{a} < y_0 < C$

Figure 3.3.1: Flow in system (3.28) when (a) one equilibrium exists in the all ramp region and (b) when two equilibria exist in the all ramp region. In (b), $C = \min\left\{c, k+b+\dfrac{c(2k+b)}{a}\right\}$. In each case, the y coordinate of the equilibrium point $(0, 2y_0\theta_2/c)$ is indicated by y_1. For each example, the x nullclines are shown in red while the y nullcline is shown in blue.

will switch and the x nullcline (3.34) will be above or to the left of the y nullcline for $x > x_2^*$. This can be seen from the fact that

$$\frac{2kr_1(x)+b}{a} > \frac{kr_1(x)^2+y_0}{ar_1(x)+c}$$

holds if and only if

$$kar_1(x)^2 + (2kc+ab)r_1(x) + bc - ay_0 > 0.$$

The above quadratic, after setting $r_1(x) = \dfrac{x}{2\theta_1}$ and clearing denominators, is the quadratic term from (3.31) from which x_2^* was derived; hence, the above inequality holds for all $x > x_2^*$.

Thus, in the two equilibria case the placement of nullclines and signs of the differential equations produces a vector field resembling the one shown in Figure 3.3.1(b), in which flow along the y axis is toward (x_1^*, y_1^*), while global flow for trajectories with $x > 0$ is toward the positive equilibrium (x_2^*, y_2^*).

We summarize our analysis of system (3.28) in the following theorem:

Theorem 3.3.2. *Consider a system of form* (3.28)*. Then:*

1.) System (3.28) has the equilibrium $(x_1^*, y_1^*) = \left(0, \dfrac{2y_0\theta_2}{c}\right)$ *in the all ramp region if and only if* $y_0 < c$*; the positive equilibrium* $(x_2^*, y_2^*) = ((3.32), (3.30))$ *exists in the all ramp region if and only if*

$$\frac{bc}{a} \;<\; y_0 \;<\; \min\left\{k + b + \frac{c(2k+b)}{a},\;\; c + \frac{ax^*}{2\theta_1} - \frac{k(x^*)^2}{4\theta_1^2}\right\}.$$

2.) The equilibria (x_1^*, y_1^*) *and* (x_2^*, y_2^*) *exist in the all ramp region simultaneously if and only if*

$$\frac{bc}{a} \;<\; y_0 \;<\; \min\left\{c,\;\; k + b + \frac{c(2k+b)}{a}\right\}.$$

3.) If $y_0 < bc/a$*, then* (x_1^*, y_1^*) *is asymptotically stable; if* $y_0 > b/c$*, then* (x_1^*, y_1^*) *is a saddle point. If* (x_2^*, y_2^*) *exists in the all ramp region, it is always asymptotically stable.*

4.) Global flow is toward (x_1^*, y_1^*) *if it is the only equilibrium in the all ramp region. If both equilibria exist in the all ramp region, flow along the line* $x = 0$ *is toward* (x_1^*, y_1^*)*, but global flow for* $x > 0$ *is toward* (x_2^*, y_2^*)*.*

3.3.2.2 Comparisons to Michaelis-Menten

With Michaelis-Menten terms instead of ramp functions, system (3.28) becomes

$$\begin{aligned} \dot{x} &= -2kM_1(x)^2 + aM_1(x)M_2(y) - bM_1(x) \\ \dot{y} &= kM_1(x)^2 - aM_1(x)M_2(y) - cM_2(y) + y_0, \end{aligned} \tag{3.36}$$

where $M_1(x) = \dfrac{x}{\theta_1 + x}$ and $M_2(y) = \dfrac{y}{\theta_2 + y}$.

Parameter conditions for the existence of non-negative equilibria in Michaelis-Menten system (3.36) are very similar to the ones for system (3.28) to have equilibria in the all ramp region. Like with the ramp system, (3.36) can exhibit two distinct equilibria:

- The equilibrium $(x_1', y_1') = \left(0, \dfrac{y_0\theta_2}{c - y_0}\right)$ has a non-negative y component if and only if $y_0 < c$.
- A positive equilibrium satisfying

$$M_1(x_2') \;=\; \frac{-(2kc + ab) + \sqrt{4k^2c^2 + a^2b^2 + 4ka^2y_0}}{2ka} \;=\; A'$$

$$M_2(y_2') \;=\; \frac{kM_1(x_2')^2 + y_0}{aM_1(x_2') + c} \;=\; B',$$

or equivalently,

$$x_2' \;=\; \frac{\theta_1 A'}{1 - A'}$$

$$y_2' \;=\; \frac{\theta_2 B'}{1 - B'},$$

exists if and only if

$$\frac{bc}{a} \;<\; y_0 \;<\; \min\left\{k + b + \frac{c(2k+b)}{a},\;\; c + aM_1(x_2') - kM_1(x_2')^2\right\}.$$

- The equilibria (x_1', y_1') and (x_2', y_2') coexist in the first quadrant if and only if

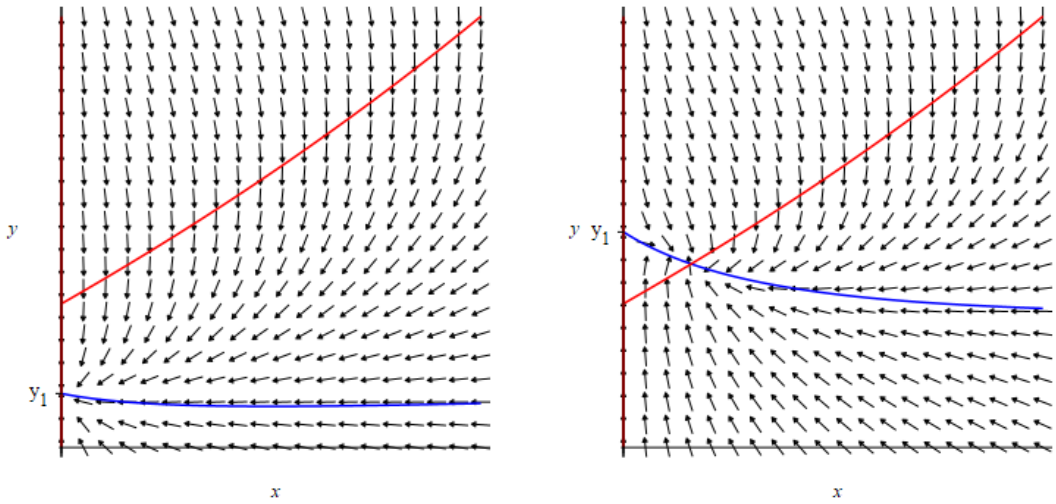
$$\frac{bc}{a} \;<\; y_0 \;<\; \min\left\{c,\;\; k + b + \frac{c(2k+b)}{a}\right\}.$$

Regarding stability of equilibria, the Jacobian of system (3.36) is

$$\begin{bmatrix} -4kM_1(x)M_1'(x) + aM_1'(x)M_2(y) - bM_1'(x) & aM_1(x)M_2'(y) \\ \\ 2kM_1(x)M_1'(x) - aM_1'(x)M_2(y) & -aM_1(x)M_2'(y) - cM_2'(y) \end{bmatrix}.$$

Analysis of this matrix evaluated at the equilibrium points (x_1', y_1') and (x_2', y_2') can be handled similarly to that of the Jacobian (3.33) of the ramp system (3.28) and will produce the same results. That is, the equilibrium (x_1', y_1') is asymptotically stable when $y_0 < bc/a$ and is a saddle point when $y_0 > bc/a$, losing stability upon the emergence of the positive equilibrium (x_2', y_2'), which is always asymptotically stable when it exists.

Flow in system (3.36) is also similar to its ramp counterpart. Our analysis for system (3.28) regarding the placement of nullclines and signs of the differential equations also applies to system (3.36) in the first quadrant with the same results. Flow in the first quadrant is toward (x_1', y_1') when it is the only non-negative equilibrium of the system. When (x_1', y_1') and (x_2', y_2') coexist in the first quadrant, flow along the line $x = 0$ is toward (x_1', y_1') but trajectories starting in the interior of the first quadrant approach (x_2', y_2') over time. Example vector fields of system (3.36) are shown in Figure 3.3.2 below.



(a) $y_0 < \dfrac{bc}{a}$ (b) $\dfrac{bc}{a} < y_0 < C$

Figure 3.3.2: Flow in the first quadrant for system (3.36) when (a) one non-negative equilibrium exists and (b) when two non-negative equilibria exist. In (b), $C = \min\left\{c, k+b+\dfrac{c(2k+b)}{a}\right\}$. In each case, the y coordinate of the equilibrium point $(0, y_0\theta_2/(c-y_0))$ is indicated by y_1. For each example, the x nullclines are shown in red while the y nullcline is shown in blue.

Chapter 4

Deficiency Theory

4.1 Introduction and Definitions

In this chapter, we will discuss an advantage of using ramp functions over Michaelis-Menten functions, namely the ability to apply deficiency results from chemical reaction network theory. As mentioned in the Introduction, the most famous of these results, the Deficiency Zero Theorem, was developed in the early 1970s with the work of Feinberg, Horn, and Jackson [8, 11, 12].

Before presenting deficiency results, we first have to introduce several definitions and concepts that will be used throughout this chapter. Our definitions and notation will be adapted from Feinberg's book [9].

First, the entities that appear on either side of a reaction arrow are called *complexes*. For example, the reaction $X + Y \to 2Z$ involves the complexes $X + Y$ and $2Z$. Note that this is distinct from the concept of a chemical *species* that we have been referring to in the previous chapters; the reaction $X + Y \to 2Z$ involves three species, X, Y, and Z.

It will now be useful to formally define the concept of a chemical reaction network:

Definition 4.1.1. [*Chemical Reaction Network*]
A chemical reaction network consists of three finite sets $\mathscr{S}$, $\mathscr{C}$, and $\mathscr{R}$ in which

a.) $\mathscr{S}$ is the set of chemical species

b.) $\mathscr{C}$ is the set of complexes

c.) $\mathscr{R}$ is the set of reactions, such that $\forall C \in \mathscr{C}$,

  i.) $C \to C \notin \mathscr{R}$

  ii.) $\exists C' \in \mathscr{C}$ such that $C \to C' \in \mathscr{R}$ or $C' \to C \in \mathscr{R}$

Each complex in a chemical reaction network can be associated with a non-negative vector in $\mathbb{R}^{|\mathscr{S}|}_{\geq 0}$. The entries of the vector corresponding to complex C are obtained from the

stoichiometric coefficients of the species in C, i.e. the coefficients in front of each species in C. For instance, if our network consists of just the reaction $X + Y \to 2Z$, the vector in $\mathbb{R}^3_{\geq 0}$ associated with the complex $X + Y$, assuming the species are ordered (X, Y, Z), is $(1, 1, 0)$ as the coefficients of X and Y are both 1 in $X + Y$ and Z has a stoichiometric coefficient of zero in this complex. The complex $2Z$ then corresponds to the vector $(0, 0, 2)$.

We can also associate a vector in $\mathbb{R}^{|\mathscr{S}|}$ to every reaction in our network. If the vectors corresponding to complexes C and C' are v_C and $v_{C'}$ respectively, then the reaction $C \to C'$ has corresponding *reaction vector* $v_{C'} - v_C$. Thus, the reaction vector corresponding to $X + Y \to 2Z$ is

$$\begin{bmatrix} 0 \\ 0 \\ 2 \end{bmatrix} - \begin{bmatrix} 1 \\ 1 \\ 0 \end{bmatrix} = \begin{bmatrix} -1 \\ -1 \\ 2 \end{bmatrix}.$$

The span of the reaction vectors of a chemical reaction network defines the *stoichiometric subspace*, denoted by S, of the network. If the dimension of S is s, we say that the *rank* of the network is s.

Next, the stoichiometric subspace of a reaction network gives rise to the concept of *stoichiometric compatibility* and corresponding *stoichiometric compatibility classes*:

Definition 4.1.2. [*Stoichiometric Compatibility*]
Consider a chemical reaction network with stoichiometric subspace S. Let v_1 and v_2 be vectors in $\mathbb{R}^{|\mathscr{S}|}_{\geq 0}$. Then,

a.) The stoichiometric compatibility class containing v_1 is the set $(v_1 + S) \cap \mathbb{R}^{|\mathscr{S}|}_{\geq 0}$.

b.) The positive stoichiometric compatibility class containing v_1 is the set $(v_1 + S) \cap \mathbb{R}^{|\mathscr{S}|}_{+}$.

c.) v_1 and v_2 are stoichiometrically compatible (i.e. are in the same stoichiometric compatibility class) if $v_2 - v_1 \in S$.

The definitions and concepts we have discussed so far are illustrated in the following example.

Example 4.1.3. Consider the chemical reaction network shown below.

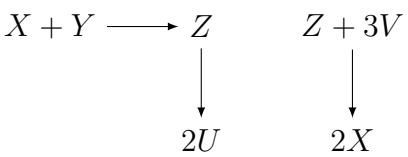


Figure 4.1.1: An example chemical reaction network.

The sets $\mathscr{S}$, $\mathscr{C}$, and $\mathscr{R}$ from Definition 4.1.1 for this network are

$$\begin{aligned}\mathscr{S} &= \{X, Y, Z, U, V\}\\ \mathscr{C} &= \{X+Y, Z, 2U, Z+3V, 2X\}\\ \mathscr{R} &= \{X+Y \to Z, Z \to 2U, Z+3V \to 2X\}\end{aligned}$$

The three reaction vectors for the network, assuming we order the species as (X, Y, Z, U, V), are

$$\begin{bmatrix}-1\\-1\\1\\0\\0\end{bmatrix}, \begin{bmatrix}0\\0\\-1\\2\\0\end{bmatrix}, \begin{bmatrix}2\\0\\-1\\0\\-3\end{bmatrix}.$$

The stoichiometric subspace S of the network is the span of these vectors; hence, S is the linear subspace of $\mathbb{R}^5$ consisting of vectors of the form

$$c_1\begin{bmatrix}-1\\-1\\1\\0\\0\end{bmatrix} + c_2\begin{bmatrix}0\\0\\-1\\2\\0\end{bmatrix} + c_3\begin{bmatrix}2\\0\\-1\\0\\-3\end{bmatrix} = \begin{bmatrix}-c_1+2c_3\\-c_1\\c_1-c_2-c_3\\2c_2\\-3c_3\end{bmatrix},$$

where c_1, c_2, and c_3 are real scalars. Since the reaction vectors are linearly independent, the dimension of S is 3, and thus the network has rank $s = 3$.

The network shown in Figure 4.1.1 is presented as a *standard reaction diagram*, in which each complex is represented exactly once. Such a diagram can be thought of as a directed graph (digraph) in which the complexes are the vertices. The connected components of a standard reaction diagram are called *linkage classes*. Thus, the network in Figure 4.1.1 has two linkage classes, one composed of the set of complexes $\{X+Y, Z, 2U\}$ and the other the complexes $\{Z+3V, 2X\}$.

A standard reaction diagram provides information on a chemical reaction network's *reversibility*. A network is said to be *weakly reversible* if the existence of a directed path from complex C to complex C' implies the existence of a directed path from C' back to C. The network shown in Figure 4.1.1 is not weakly reversible; for instance, while there is a directed path from the complex $X+Y$ to the complex $2U$, there is no such path from $2U$ back to $X+Y$.

The network shown in Figure 4.1.2, however, is weakly reversible. The linkage class shown on the left simply represents the reversible reaction $2X+Y \rightleftharpoons Z+U$, and thus we can freely "move" from one complex to the other. In the right linkage class, there is a directed path between any pair of complexes; we can move from W to X, for instance, via

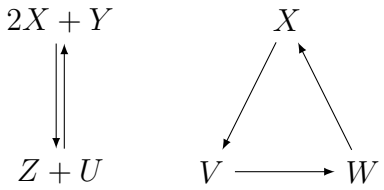


Figure 4.1.2: A weakly reversible chemical reaction network with two linkage classes.

the path $W \to X$, and then from X to W via $X \to V \to W$.

A network is *reversible* if $C \to C' \in \mathscr{R}$ implies $C' \to C \in \mathscr{R}$, i.e. all reactions are reversible. Neither the network in Figure 4.1.1 nor the one in Figure 4.1.2 are reversible as most of the reactions are one-way.

Complexes C and C' are said to be *strongly linked* if either $C = C'$ or there is both a directed path from C to C' and such a path from C' to C. Strongly linked complexes are part of the same *strong-linkage class*. If there is no directed path from a complex in a strong-linkage class to a complex outside the strong-linkage class, the strong-linkage class is said to be *terminal*.

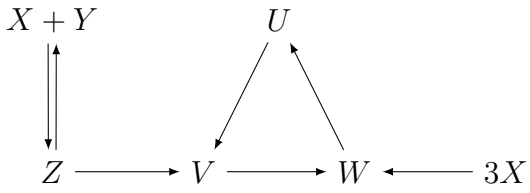


Figure 4.1.3: A chemical reaction network with three strong-linkage classes, one of which is a terminal strong-linkage class.

We can illustrate the concept of strong-linkage classes and terminal strong-linkage classes with the network shown in Figure 4.1.3. This network is composed of three strong-linkage classes: one containing the complexes $X + Y$ and Z, another containing U, V, and W, and the last containing just the complex $3X$. The strong-linkage class containing U, V, and W is terminal; there are no reaction arrows *leaving* this strong-linkage class. The other two strong-linkage classes, however, are not terminal due to presence of the reactions $Z \to V$ and $3X \to W$.

The final concept we will need before discussing deficiency is that of a *kinetics* for a reaction network. Note that in the following definition, we use the support of a vector v, denoted supp v, to mean the set of chemical species whose corresponding entries in v are non-zero. For instance, earlier we mentioned that if our network consists of just the reaction $X + Y \to Z$, the vector corresponding to the complex $X + Y$, assuming the order (X, Y, Z), is $(1, 1, 0)$; hence, supp$(1, 1, 0)$ is simply the set $\{X, Y\}$.

Definition 4.1.4. [*Kinetics*]

Consider a chemical reaction network with species set $\mathscr{S} = \{X_1, X_2, \ldots, X_n\}$. For each complex $C \in \mathscr{C}$, denote the corresponding vector in $\mathbb{R}^{|\mathscr{S}|}_{\geq 0}$ by v_C. Let $x = (x_1, x_2, \ldots, x_n) \in \mathbb{R}^{|\mathscr{S}|}_{\geq 0}$ denote the concentrations of $X_1, X_2, \ldots, X_n$ at some instant in time.

Then, a kinetics $\mathscr{K}$ for the reaction network is, for every reaction $C \to C' \in \mathscr{R}$, the assignment of a continuously differentiable rate function $\mathscr{K}_{C\to C'} : \mathbb{R}^{|\mathscr{S}|}_{\geq 0} \to \mathbb{R}_{\geq 0}$ such that $\mathscr{K}_{C\to C'}(x) > 0$ if and only if supp $v_C \subseteq$ supp x. In other words, $\mathscr{K}_{C\to C'}(x)$ is positive if and only if each species in the reacting complex C has a strictly positive concentration.

The following example makes use of Definition 4.1.4 to show that it does, indeed, apply to Michaelis-Menten kinetics:

Example 4.1.5. We can model the reactions $X_1 + X_2 \xrightarrow{k_1} 2X_2$ and $X_1 \xrightarrow{k_2} 0$ using Michaelis-Menten terms with the system of differential equations

$$\begin{aligned}
\dot{x}_1 &= -k_1\left(\frac{x_1}{\theta_1 + x_1} \cdot \frac{x_2}{\theta_2 + x_2}\right) - k_2\frac{x_1}{\theta_3 + x_1} \\
\dot{x}_2 &= k_1\left(\frac{x_1}{\theta_1 + x_1} \cdot \frac{x_2}{\theta_2 + x_2}\right),
\end{aligned}$$

where the parameters are all positive. The kinetics this system arises from consists of the functions

$$\begin{aligned}
\mathscr{K}_{X_1+X_2\to 2X_2}(x_1, x_2) &= \frac{k_1 x_1 x_2}{(\theta_1 + x_1)(\theta_2 + x_2)} \\
\mathscr{K}_{X_1\to 0}(x_1, x_2) &= \frac{k_2 x_1}{\theta_3 + x_1}.
\end{aligned}$$

Note that the vector $x = (x_1, x_2)$ is in $\mathbb{R}^2_{\geq 0}$ because while 0 counts as a complex, it does *not* count as a chemical species. We see that these two functions satisfy the conditions given in Definition 4.1.4; both are continuously differentiable for all $(x_1, x_2) \in \mathbb{R}^2_{\geq 0}$, $\mathscr{K}_{X_1+X_2\to 2X_2}$ is positive if and only if x_1 and x_2 are both positive, and $\mathscr{K}_{X_1\to 0}$ is positive if and only if x_1 is positive.

We derived the differential equations by multiplying $\mathscr{K}_{X_1+X_2\to 2X_2}$ and $\mathscr{K}_{X_1\to 0}$ by the appropriate constants representing the net gain or loss of species in the reactions. In general, the $\dot{x}_i$ equation for a network with kinetics $\mathscr{K}$ is the ith component of

$$\sum_{C\to C'\in\mathscr{R}} \mathscr{K}_{C\to C'}(v_{C'} - v_C),$$

where $v_{C'} - v_C$ is the reaction vector corresponding to $C \to C'$. Thus, the above system can also be written in the form

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \mathscr{K}_{X_1+X_2\to 2X_2}\begin{bmatrix} -1 \\ 1 \end{bmatrix} + \mathscr{K}_{X_1\to 0}\begin{bmatrix} -1 \\ 0 \end{bmatrix}.$$

Now that we have defined a kinetics in general, we can formally define mass action kinetics:

Definition 4.1.6. [*Mass Action Kinetics*]
Consider a chemical reaction network with species set $\mathscr{S} = \{X_1, X_2, \ldots, X_n\}$. For each complex $C \in \mathscr{C}$, let C_i be the ith component of the corresponding vector $v_C \in \mathbb{R}^{|\mathscr{S}|}_{\geq 0}$. Let $x = (x_1, x_2, \ldots, x_n) \in \mathbb{R}^{|\mathscr{S}|}_{\geq 0}$ denote the concentrations of $X_1, X_2, \ldots, X_n$ at some instant in time.

Then, a kinetics $\mathscr{K}$ for the reaction network is mass action if for every reaction $C \to C' \in \mathscr{R}$,

$$\mathscr{K}_{C\to C'}(x) \;=\; k_{C\to C'} \prod_{i=1}^{n} x_i^{C_i},$$

where $k_{C\to C'} > 0$.

As an example, if we want to model the system defined by the reactions $3X_1 + 2X_2 \xrightarrow{k_1} 5X_2 + 4X_3$ and $0 \xrightarrow{k_2} X_1$ with mass action kinetics, we would have that

$$\begin{aligned} \mathscr{K}_{3X_1+2X_2\to 5X_2+4X_3}(x_1, x_2, x_3) \;&=\; k_1 x_1^3 x_2^2 x_3^0 \;=\; k_1 x_1^3 x_2^2 \\ \mathscr{K}_{0\to X_1}(x_1, x_2, x_3) \;&=\; k_2 x_1^0 x_2^0 x_3^0 \;=\; k_2. \end{aligned}$$

Then, using the fact that the corresponding reaction vectors are $(-3, 3, 4)$ and $(1, 0, 0)$, the system of differential equations describing these two reactions is

$$\begin{aligned} \dot{x}_1 \;&=\; -3k_1 x_1^3 x_2^2 + k_2 \\ \dot{x}_2 \;&=\; 3k_1 x_1^3 x_2^2 \\ \dot{x}_3 \;&=\; 4k_1 x_1^3 x_2^2. \end{aligned}$$

Notice that this system satisfies the Hungarian Lemma 1.1.1 characterizing when a polynomial system is mass action. The lemma and Definition 4.1.6 are equivalent in that a system of polynomials satisfies Lemma 1.1.1 if and only if it can be derived from a chemical reaction network endowed with mass actions kinetics as defined in Definition 4.1.6.

4.1.1 Deficiency

We are now ready to define the *deficiency* of a network:

Definition 4.1.7. [*Deficiency*]
The deficiency $\delta \geq 0$ of a chemical reaction network is

$$\delta \;=\; m - \ell - s,$$

where m is the number of complexes in the network, ℓ is the number of linkage classes, and s is the rank of the network.

As an example, the network shown in Figure 4.1.1 has five complexes, two linkage classes, and we determined that its rank is three. Therefore, the deficiency of the network is $\delta = 5 - 2 - 3 = 0$. Another example is provided below.

Example 4.1.8. Consider the following network:

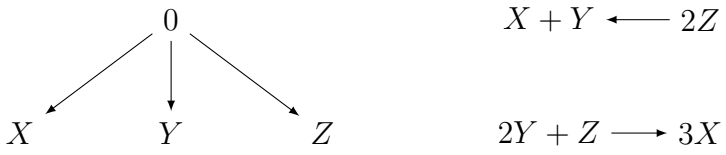


Figure 4.1.4: A chemical reaction network with a deficiency of two.

This network has complex set

$$\mathscr{C} \;=\; \{0, X, Y, Z, X+Y, 2Z, 2Y+Z, 3X\},$$

which contains eight elements, so $m = 8$. There are three connected components in Figure 4.1.4, so the network has $\ell = 3$ linkage classes. Finally, the rank of the network is $s = 3$; the reaction vectors corresponding to the reactions in the leftmost linkage class are simply the standard basis vectors of $\mathbb{R}^3$ (as mentioned earlier, 0 does not count as a species). Thus, the network has deficiency $\delta = 8 - 3 - 3 = 2$.

We can also talk about the *deficiency of a linkage class*; this is calculated as if the linkage class in question was an entire reaction network on its own. That is, the deficiency of the ith linkage class of a network is

$$\delta_i \;=\; m_i - 1 - s_i,$$

where m_i is the number of complexes in the ith linkage class and s_i is the rank of the linkage class. For instance, the leftmost (first) linkage class of the network in Figure 4.1.4 has $m_1 = 4$ complexes $(0, X, Y, Z)$ and rank $s_1 = 3$, thus its deficiency is $\delta_1 = 4 - 1 - 3 = 0$. The other two linkage classes also have deficiency zero, as they each contain two complexes and have a rank of one due to having only one associated reaction vector each.

We end this section with the statement of two results relating to the deficiency of a chemical reaction network, the Deficiency Zero Theorem and the Deficiency One Theorem. We will discuss applications of these theorems to biochemical ramp systems in the following section. Note that in the statement of the theorems, by an "assignment of rate constants" we mean an assignment of the positive $k_{C\to C'}$ constants given in Definition 4.1.6.

Theorem 4.1.9. ***(Deficiency Zero).*** *Consider a weakly reversible chemical reaction network with deficiency $\delta = 0$. If the network is endowed with mass action kinetics, then for any assignment of rate constants, the corresponding system of differential equations satisfies the following:*

a.) Each positive stoichiometric compatibility class contains exactly one equilibrium.

b.) The unique equilibrium in each positive stoichiometric compatibility class is asymptotically stable.

Theorem 4.1.10. ***(Deficiency One).*** *Consider a chemical reaction network with deficiency δ such that each of its ℓ linkage classes contains exactly one terminal strong-linkage class. Let δ_i be the deficiency of the i-th linkage class, and suppose that*

i.) $\delta_i \leq 1$, $i = 1, 2, \ldots, \ell$

ii.) $\sum_{i=1}^{\ell} \delta_i = \delta$

both hold. If, when endowed with mass action kinetics, there is an assignment of rate constants such that the corresponding system of differential equations has a positive equilibrium, then:

a.) Each positive stoichiometric compatibility class contains exactly one equilibrium.

b.) The Jacobian evaluated at any positive equilibrium point is invertible.

Additionally, if the network is weakly reversible, then the corresponding mass action system of differential equations always has a positive equilibrium for any assignment of rate constants.

4.2 Applications to Biochemical Ramp Systems

Theorems 4.1.9 and 4.1.10 provide results useful for the analysis of mass action systems. This provides a motivation for using ramp functions in the place of Michaelis-Menten functions: since ramp systems are mass action in the all ramp region, the theorems can be applied, whereas they cannot be applied to a system with Michaelis-Menten kinetics.

Thus, ramp functions can facilitate the analysis of complicated Michaelis-Menten systems through the application of Theorems 4.1.9 and 4.1.10 to the all ramp region system. For instance, if we model a weakly reversible network with deficiency zero using ramp functions, Theorem 4.1.9 tells us that the all ramp region system has a unique asymptotically stable equilibrium in each positive stoichimetric compatiblity class. We would still have to determine under what parameter conditions these equilibria actually fall in the all ramp region, but these calculations would be much easier than trying to solve for equilibria in the corresponding Michaelis-Menten system.

We will now show how the Deficiency Zero and One Theorems can be applied to the Adams model of plant metabolism with ramp functions, something we previously discussed in [6].

4.2.1 Adams Model without the SEL

In Section 2.3.1.1, we saw that system (3), the Adams model without the SEL modeled with ramp functions, becomes

$$\begin{aligned}
\dot{x_1} &= a_0 - \frac{a_1 x_1}{2K_1} \\
\dot{x_2} &= \frac{a_1 x_1}{2K_1} - \frac{a_3 x_2}{2K_3^2} - \frac{a_5 x_2}{2K_5} \\
\dot{x_3} &= \frac{a_3 x_2}{2K_3^2} - \frac{a_4 x_3}{2K_4}
\end{aligned}$$

in the all ramp region. This is a mass action system derived from five SRP reactions: $0 \to X_1$, $X_1 \to X_2$, $X_2 \to X_3$, $X_2 \to 0$, and $X_3 \to 0$. Note that we have assumed $a_0 > 0$ here; if $a_0 = 0$, then the reaction $0 \to X_1$ would not be present. The corresponding standard reaction diagram for this system is shown in Figure 4.2.1.

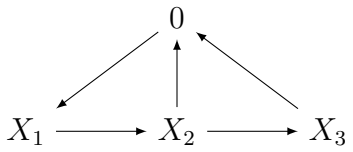


Figure 4.2.1: Standard reaction diagram of the Adams model without the SEL.

From Figure 4.2.1, the system without the SEL has $m = 4$ complexes and $\ell = 1$ linkage class. Assuming the species are ordered (X_1, X_2, X_3), the stoichiometric subspace, the span of the reaction vectors, is

$$\begin{aligned}
S &= \text{span}\left\{ \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix} \right\} \\
&= \text{span}\left\{ \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix} \right\} \\
&= \mathbb{R}^3.
\end{aligned}$$

Hence, the reaction vectors span all of $\mathbb{R}^3$. This means the system has rank $s = 3$, and the only positive stoichiometric compatibility class is $\mathbb{R}^3_+$.

The Adams model without the SEL thus has deficiency $\delta = 4 - 1 - 3 = 0$. Additionally, from Figure 4.2.1 the system is weakly reversible. Hence, the Deficiency Zero Theorem 4.1.9 applies, and says that the above mass action system of differential equations admits a unique, asymptotically stable, equilibrium in its sole positive stoichiometric compatibility class for any assignment of parameters.

This is consistent with what we saw in Section 2.3.1.1; there, we found a unique equilibrium point (x_1^*, x_2^*, x_3^*), which is positive if $a_0 > 0$. The only thing we had to do in addition was determine conditions on parameters such that the equilibrium falls in the all ramp region.

Note that in the special case $a_0 = 0$, the removal of the reaction $0 \to X_1$ results in the network no longer being weakly reversible, and thus the Deficiency Zero Theorem no longer applies.

4.2.2 Adams Model with the SEL

The equation for system (4), the Adams model with the SEL, when in the all ramp region were previously given in (5) as

$$\begin{aligned}
\dot{y} &= a_0 - \frac{a_1}{2K_1}y - \frac{a_3}{4K_3^2K_3^3}x_2y + \frac{a_4}{2K_4}x_3 \\
\dot{x}_2 &= \frac{a_1}{2K_1}y - \frac{a_3}{4K_3^2K_3^3}x_2y - \frac{a_5}{2K_5}x_2 \\
\dot{x}_3 &= \frac{a_3}{4K_3^2K_3^3}x_2y - \frac{a_4}{2K_4}x_3.
\end{aligned}$$

Assuming $a_0 > 0$, this is a mass action system derived from the reactions $0 \to Y$, $Y \to X_2$, $Y + X_2 \to X_3$, $X_3 \to Y$, and $X_2 \to 0$. The standard reaction diagram for this system is shown in Figure 4.2.2.

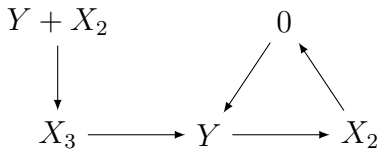


Figure 4.2.2: Standard reaction diagram of the Adams model with the SEL.

The Adams model with the SEL has $m = 5$ complexes and $\ell = 1$ linkage class. The stoichiometric subspace, assuming species are ordered (Y, X_2, X_3), is

$$\begin{aligned}
S &= \text{span}\left\{ \begin{bmatrix}1\\0\\0\end{bmatrix}, \begin{bmatrix}-1\\1\\0\end{bmatrix}, \begin{bmatrix}-1\\-1\\1\end{bmatrix}, \begin{bmatrix}1\\0\\-1\end{bmatrix}, \begin{bmatrix}0\\-1\\0\end{bmatrix} \right\} \\
&= \text{span}\left\{ \begin{bmatrix}1\\0\\0\end{bmatrix}, \begin{bmatrix}0\\-1\\0\end{bmatrix}, \begin{bmatrix}1\\0\\-1\end{bmatrix} \right\} \\
&= \mathbb{R}^3,
\end{aligned}$$

and hence we again have a system with rank $s = 3$ and a single positive stoichiometric compatibility class, $\mathbb{R}^3_+$. The network shown in Figure 4.2.2 thus has a deficiency of $\delta = 5 - 1 - 3 = 1$.

The Adams model with the SEL is not a weakly reversible network, but it does contain a single terminal strong-linkage class; this is the triangle formed by the complexes 0, Y, and X_2, none of which have any reaction arrows pointing away from them. Hence, the conditions of the Deficiency One Theorem 4.1.10 are met, and thus the theorem tells us that *if* there is an assignment of parameters such that the mass action system admits a positive equilibrium, then each positive stoichiometric compatibility class contains exactly one equilibrium and the Jacobian evaluated at a positive equilibrium does not have any zero eigenvalues.

In Section 2.4.2.1, we determined an expression for a positive equilibrium (y^*, x_2^*, x_3^*) of the Adams model with the SEL in the all ramp region. Since this system only has one positive stoichiometric compatibility class, Theorem 4.1.10 allows us to confirm that this equilibrium is indeed unique. The result that the Jacobian is non-singular when evaluated at the equilibrium point is consistent with [5, 6], which showed the Jacobian will always have eigenvalues with strictly negative real parts.

While analysis of the Adams model with and without the SEL is simple enough that Theorems 4.1.9 and 4.1.10 do not add additional information that we couldn't determine through algebraic means, these theorems are useful tools to have for larger, more complex systems that are not as easy to algebraically manipulate. The theorems can give us an indication, for instance, of whether multiple positive equilibria are possible in the all ramp region.

4.3 Results for General Networks

In this section, we will provide deficiency results for chemical reaction networks built from the reaction types we have considered previously, such as SRP and combining reactions. Our focus will primarily be on determining which systems have deficiency zero, and under what circumstances the addition of new reactions can result in a change in the deficiency.

Our first couple of results will make reference to the undirected graph underlying a standard reaction diagram; what we mean by this is the graph obtained by replacing the reaction arrow(s) connecting two complexes with a single, undirected edge. Figure 4.3.1 shows an example standard reaction diagram and the corresponding underlying undirected graph.

We begin with the following lemma stating that the deficiency of a reaction network will not change if we add reaction arrows between two complexes already in the same linkage class:

Lemma 4.3.1. Consider a chemical reaction network in which complexes C and C' are in the same linkage class. Then, adding the reaction(s) $C \to C'$, $C' \to C$, or $C \rightleftharpoons C'$ will not change the deficiency of the network.

(a) Standard reaction diagram

(b) Underlying undirected graph

Figure 4.3.1: The standard reaction diagram for a chemical reaction network and the corresponding underlying undirected graph.

Proof. WLOG, suppose we added the reaction $C \to C'$. Since the addition of this reaction did not change the number of complexes or linkage classes in the system, in order to show that the deficiency did not change we need to prove adding this reaction did not change the rank of the network. Thus, we have to show that the reaction vector corresponding to $C \to C'$, $v_{C'} - v_C$, was already in the span of the pre-existing reaction vectors.

As C and C' are in the same linkage class, they are in the same connected component in the underlying undirected graph for the network. Thus, there is a path $C, C_1, C_2, \dots C_k, C'$ from C to C' in the undirected graph. Suppose that in the standard reaction diagram for the network, this path is oriented $C \to C_1 \to C_2 \to \cdots \to C_k \to C'$; it won't matter if we have $C_{j+1} \to C_j$ for some j instead, since the reaction vectors for $C_{j+1} \to C_j$ and $C_j \to C_{j+1}$ only differ by a factor of -1.

Suppose the linkage class containing C and C' contains α chemical species $X_1, X_2, \dots, X_\alpha$. Then, complex C_j can be written in the form $a_{1j}X_1 + a_{2j}X_2 + \cdots + a_{\alpha j}X_\alpha$, where the a_{ij} are non-negative integers in which some may be zero; for instance, the complex $X_1 + 2X_3$ in a linkage class containing species X_1, X_2, and X_3 can be written as $X_1 + 0X_2 + 2X_3$. The complexes C and C' will be written the same way, using $j = 0$ for C and $j = k + 1$ for C'.

Now, we consider the $k+1$ reaction vectors corresponding to $C \to C_1$, $C_1 \to C_2$, $\dots$, $C_k \to C'$. The ith component of each of these vectors is $a_{i1} - a_{i0}$ for $C \to C_1$, $a_{i2} - a_{i1}$ for $C_1 \to C_2$, $\dots$, and $a_{ik+1} - a_{ik}$ for $C_k \to C'$.

Summing up these vectors, the ith component is thus $a_{ik+1} - a_{i0}$, the ith component of $v_{C'} - v_C$. Thus, the reaction vector corresponding to $C \to C'$ is in the span of the reaction vectors corresponding to the reactions $C \to C_1 \to C_2 \to \cdots \to C_k \to C'$. Hence, adding this additional reaction did not change the rank of the system, and the deficiency remained unchanged. □

As an example of Lemma 4.3.1, considering the chemical reaction network shown in Figure 4.3.2. Adding the reaction arrow between the compelxes $X + Y$ and U does not change the rank of the system; ordering the species as (X, Y, Z, U), the reaction vector for $X + Y \to U$ is the sum of the reaction vectors for $X + Y \to Z$, $Z \to X$, and $X \to U$ (where the reaction vector for $X \to U$ is just the reaction vector for $U \to X$ multiplied by -1):

(a) Original network (b) With $X + Y \to U$ added

Figure 4.3.2: Adding the reaction $X + Y \to U$ did not change the network's rank or deficiency.

$$\begin{bmatrix} -1 \\ -1 \\ 0 \\ 1 \end{bmatrix} = \begin{bmatrix} -1 \\ -1 \\ 1 \\ 0 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ -1 \\ 0 \end{bmatrix} - \begin{bmatrix} 1 \\ 0 \\ 0 \\ -1 \end{bmatrix}.$$

Thus, the reaction vector for $X + Y \to U$ was already in the span of the pre-existing reaction vectors, so adding the reaction did not change the network's rank.

4.3.1 A Class of Networks with Deficiency Zero

Here, we will prove that chemical reaction networks in which each species appears in exactly one complex are deficiency zero. The network shown in Figure 4.3.1 is an example of such a network, but the Adams model with the SEL as shown in Figure 4.2.2 is not, as Y and X_2 each appear in two complexes.

Theorem 4.3.2. *Consider a chemical reaction network in which each chemical species appears in exactly one complex. Then, the deficiency of the network is $\delta = 0$.*

Proof. We will first show that the statement holds for a network with just one linkage class; in this case, we want to show that the deficiency satisfies $m - 1 - s = 0$, and hence we need to prove that the rank of the system is $m - 1$.

We start by considering networks whose underlying undirected graph is a tree (i.e. is acyclic). We will show that such a network has deficiency zero via induction on the number of complexes m. The base case is $m = 2$ — Definition 4.1.1 implies a chemical reaction network must contain at least two complexes — which refers to a network consisting of two complexes C and C' connected by a reaction arrow(s). The rank of such a system is $m - 1 = 1$ since there is only one associated reaction vector.

Now, suppose any network with $m = k \geq 2$ complexes whose underlying graph is a tree has rank $k - 1$. We now consider a network with $k + 1$ complexes $C_1, C_2, \ldots, C_{k+1}$ and a tree structure. As a tree with more than one vertex, the graph underlying the network with $k + 1$ complexes must have at least two leaves (i.e. complexes connected to only one other complex). Hence, there is a complex C_i that is connected to exactly one other complex by

a reaction arrow in the network, and we can assume C_i is not the zero complex. WLOG, suppose C_i was connected to the complex C_a by the reaction $C_i \to C_a$.

If C_i is removed, the remaining k complexes form a network whose underlying graph is still a tree (since C_i was a leaf), and by the induction hypothesis this network has rank $k-1$. By our assumption that each species appears in exactly one complex, C_i must contain a species not present in any other complex in the network; suppose this is the jth species. Hence, if we add C_i back to the network, the reaction vector corresponding to $C_i \to C_a$ has a non-zero jth component, while every other reaction vector has zero in the jth component. Thus, the reaction vector for $C_i \to C_a$ is linearly independent of the other reaction vectors, so adding C_i back increases the rank of the network from $k-1$ to k.

Hence, we have that a network whose underlying graph is a tree will always have rank $m-1$, and thus deficiency zero. For an arbitrary network with one linkage class, the underlying graph has a spanning tree (i.e. a tree subgraph containing all complexes). The network represented by this spanning tree has rank $m-1$. The original network is obtained from this spanning network by adding in the remaining reaction arrows between complexes. From the proof of Lemma 4.3.1, adding reaction arrows between complexes in the same linkage class does not change the deficiency of the system. Thus, the original arbitrary network must have a deficiency of zero.

Finally, we show the result holds for a network with $\ell > 1$ linkage classes. From above, the deficiency of each linkage class on its own is zero, with the ith linkage class having rank $m_i - 1$, where m_i is the number of complexes in the ith linkage class. Since each species appears in only one complex, each species also appears in just one linkage class. Hence, the linkage classes are independent of each other, in the sense that two reaction vectors derived from distinct linkage classes are linearly independent. As a result, the rank of the entire network is just the sum of the ranks of the individual linkage classes, which is $s = \sum_{i=1}^{\ell}(m_i - 1) = m - \ell$, and hence the deficiency is $\delta = m - \ell - s = 0$. □

In particular, Theorem 4.3.2 describes networks built solely from SRP reactions (*SRP networks*). Hence, we have the following corollary:

Corollary 4.3.3. A chemical reaction network containing only SRP reactions has a deficiency of zero.

4.3.2 Networks with One Combining Reaction

We know from Corollary 4.3.3 above that SRP networks are deficiency zero. Here, our goal will be to determine whether the deficiency changes when a single combining reaction $X + Y \to Z$ (or equivalently, the dissociation reaction $Z \to X + Y$ or the reversible reaction $X + Y \leftrightharpoons Z$) is then added to such a network.

When adding a combining reaction, one of the following will happen:

1.) The reaction $X + Y \to Z$ forms its own linkage class. In this case, both complexes are new, and in particular Z was not present in the original SRP network, so the reaction vector for $X+Y \to Z$ is the only one with a non-zero Zth component. Hence, the rank of the network increases by 1 with the addition of the new reaction, and the system's deficiency remains zero: $\delta = (m+2) - (\ell+1) - (s+1) = 0$.

2.) The reaction $X + Y \to Z$ joins a pre-existing linkage class. Then, only the complex $X + Y$ is new. The reaction vector for $X + Y \to Z$ may or may not be in the span of the other reaction vectors, so the rank may either stay the same or increase by 1; the deficiency will thus either remain 0 or increase to 1.

Hence, a network with one combining term will have a deficiency of either zero or one. We will characterize the system structures required for an increase in the deficiency. First, however, we will state and prove a couple of useful propositions.

Proposition 4.3.4. Consider a linkage class consisting solely of SRP reactions that does not contain the 0 complex. Suppose this linkage class contains m species $X_1, X_2, \ldots, X_m$. Let $v_1, v_2, \ldots, v_k \in \mathbb{R}^m$ be the reaction vectors corresponding to this linkage class. Then, if u is a standard basis vector of $\mathbb{R}^m$ or a non-zero multiple of such a vector, $u \notin \text{span}\{v_1, v_2, \ldots, v_k\}$.

Proof. The linkage class satisfies $\delta = m - 1 - s = 0$, and hence the rank of the linkage class is $m - 1$; the reaction vectors cannot span all of $\mathbb{R}^m$ as a result, and at least one standard basis vector must be missing from the span. Here, we will show that *all* of the standard basis vectors are missing; the fact that a non-zero multiple of such a vector cannot be in the span will then follow.

By contradiction, suppose that there is a standard basis vector belonging to $\text{span}\{v_1, v_2, \ldots, v_k\}$; WLOG, suppose this is $e_1 = (1, 0, \ldots, 0)$. Then, there exist constants a_i not all zero such that

$$\begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k.$$

We then have that

$$\begin{bmatrix} 1 \\ -1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k + \begin{bmatrix} 0 \\ -1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

$$\implies \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k + \begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

and so the standard basis vector e_2 belongs to the span of the v_i and the reaction vector for $X_1 \to X_2$. Similarly, we can see that e_i for $i = 3, 4, \ldots, m$ belongs to the span of the v_i and the reaction vector for $X_1 \to X_i$.

Thus, if we take our SRP linkage class and add each reaction $X_1 \to X_i$ for $i \neq 1$ (if not already present), then we get a network in which each standard basis vector belongs to the span of the reaction vectors; this network with added reactions is thus rank m. However, adding these additional reactions does not change the fact that this is an SRP linkage class, and thus the deficiency remains zero, meaning that the rank must remain $m - 1$, a contradiction. So the initial assumption that e_1 was in $\text{span}\{v_1, v_2, \ldots, v_m\}$ must be false. □

Proposition 4.3.5. Consider a linkage class consisting solely of SRP reactions that does not contain the 0 complex. Suppose this linkage class contains m species $X_1, X_2, \ldots, X_m$. Let $v_1, v_2, \ldots, v_k \in \mathbb{R}^m$ be the reaction vectors corresponding to this linkage class.

Suppose that $u \in \mathbb{R}^m$ is a vector such that the ith and jth entries, for some i and j distinct, equal $a \neq 0$, and all other entries are zero. Then, $u \notin \text{span}\{v_1, v_2, \ldots, v_k\}$.

Proof. WLOG, suppose $u = (a, a, 0, \ldots, 0)$. By contradiction, suppose that u is in the span of the reaction vectors. Then, we have constants $a_1, a_2, \ldots, a_k$ such that

$$\begin{bmatrix} a \\ a \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k.$$

Adding the vector $(a, -a, 0, \ldots, 0)$ to both sides, we get that

$$\begin{bmatrix} 2a \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k + a \begin{bmatrix} 1 \\ -1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

and thus a non-zero multiple of a standard basis vector is in the span of $v_1, v_2, \ldots, v_k$ and the reaction vector $X_2 \to X_1$. However, by Proposition 4.3.4 this is impossible. Hence, it must be the case that $u \notin \text{span}\{v_1, v_2, \ldots, v_k\}$. □

We now have the following theorem:

Theorem 4.3.6. *Suppose we have a network consisting solely of SRP reactions. Then, addition of a reaction of the form $X + Y \to Z$, $Z \to X + Y$, or $X + Y \rightleftharpoons Z$ will result in the system's deficiency increasing to 1 if and only if at least one of the following is true:*

a.) 0 and X are in the same linkage class, and Z and Y are in the same linkage class

b.) 0 and Y are in the same linkage class, and Z and X are in the same linkage class

Proof. WLOG, assume we added the reaction $X + Y \to Z$. Suppose that X, Y, and Z are ordered as the first, second, and third species in the network respectively, so the reaction vector for $X + Y \to Z$ is $(-1, -1, 1, 0, \ldots, 0)$.

We start by proving the reverse implication. Suppose case $a.$) holds (the proof for $b.$) is similar), so 0 and X are in the same linkage class, as are Z and Y. This assumption means that only the $X + Y$ is new, with Z already having been present in the SRP system. Thus, the number of complexes has increased by 1, while the number of linkage classes remains the same. To show the system is deficiency one, we must show that the rank hasn't changed, which we will show by proving that the reaction vector for $X + Y \to Z$ can already be written as a linear combination of the other reaction vectors in the system.

Since X and 0 are in the same linkage class, by the proof of Lemma 4.3.1 the reaction vector for $X \to 0$, which is $(-1, 0, \ldots, 0)$, is in the span of the other reaction vectors for this linkage class. Similarly, as Y and Z are in the same linkage class, the vector $(0, -1, 1, 0, \ldots, 0)$, corresponding to the reaction $Y \to Z$, is in the span of the other reaction vectors.

Hence, the vector $(-1, -1, 1, 0, \ldots, 0)$ is also in the span of the other reaction vectors of the network, and so addition of the reaction $X + Y \to Z$ did not change the network's rank.

Now, we will focus on the forward implication. Suppose that the addition of the $X + Y \to Z$ reaction increased the deficiency of the network to 1. Then, the vector $(-1, -1, 1, 0 \ldots, 0)$ must be a linear combination of the pre-existing SRP reaction vectors.

To prove that the forward conclusion holds, we will first show that Z must be in the same linkage class as at least one of X and Y. We will prove this by contradiction: suppose that Z shares a linkage class with neither X nor Y. Then, there are two cases we will consider:

1.) Z and 0 are not in the same linkage class: Since $(-1, -1, 1, 0 \ldots, 0)$ is in the span of the SRP reaction vectors, and each species in an SRP network appears in exactly one linkage class, the vector $(0, 0, 1, 0, \ldots, 0)$ must be a linear combination of the reaction vectors in Z's linkage class; since Z does not appear in any other linkage class, Z's linkage class is the only one whose reaction vectors can have a vector with a non-zero third component in their span. And we specifically need the vector $(0, 0, 1, 0, \ldots, 0)$,

with zeros in all other entries, from Z's linkage class because a) X and Y are not in the same linkage class as Z, so the first and second components cannot be non-zero and b) if we had a non-zero ith entry for $i \geq 4$, we wouldn't be able to cancel it out in the linear combination with reaction vectors from other linkage classes, since if the ith species appears in Z's linkage class, it cannot appear in another one as well.

However, if Z and 0 are not in the same linkage class, by Proposition 4.3.4 it is impossible for $(0, 0, 1, 0, \ldots, 0)$ to be in the span of the reaction vectors from Z's linkage class.

2.) Z and 0 are in the same linkage class: With 0 in the same linkage class as Z, then by the proof of Lemma 4.3.1, the reaction vector for $0 \to Z$, which is $(0, 0, 1, 0, \ldots, 0)$, must be in the span of the reaction vectors in 0 and Z's linkage class.

So, the vector $(-1, -1, 0, \ldots, 0)$ must be a linear combination of the remaining reaction vectors from outside Z's linkage class. Again, there are a couple of cases to consider:

a.) X and Y are not in the same linkage class: Then, similar to what we saw in case 1.) above, we must be able to write $(-1, 0, \ldots, 0)$ as a linear combination of reaction vectors from X's linkage class, and similarly $(0, -1, 0, \ldots, 0)$ as a linear combination of reaction vectors from Y's. However, by our assumption that Z lies in a separate linkage class from both X and Y, neither X nor Y can share a linkage class with 0 in this case, and thus this is impossible by Proposition 4.3.4.

b.) X and Y are in the same linkage class: In this case, we must be able to write $(-1, -1, 0, \ldots, 0)$ as a linear combination of reaction vectors from X and Y's shared linkage class. But since X and Y's linkage class does not contain 0, by Proposition 4.3.5 this is impossible.

Based on the above, we get a problem when assuming that Z is in the same linkage class as neither X nor Y. Hence, if the system is deficiency one when $X + Y \to Z$ is added, then Z must be in the same linkage class as X or Y or both.

WLOG, suppose Z shares a linkage class with Y. To complete the proof, we must show that X and 0 share a linkage class. There are a couple of cases to consider here:

1.) X is not in the same linkage class as Y and Z: Then, there must be a linear combination of reaction vectors in X's linkage class that produces the vector $(-1, 0, \ldots, 0)$. However, as we've seen previously, this is only possible if 0 belongs to the same linkage class as X.

2.) X is in the same linkage class as Y and Z: By assumption, the vector $(-1, -1, 1, 0, \ldots, 0)$ is a linear combination of the reaction vectors in this class. That is,

$$\begin{bmatrix} -1 \\ -1 \\ 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k.$$

where the a_i are constants and the v_i are the reaction vectors in the linkage class containing X, Y, and Z. Rearranging, we get that

$$\begin{bmatrix} -1 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k + \begin{bmatrix} 0 \\ 1 \\ -1 \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

which means that $(-1, 0, \ldots, 0)$ is a linear combination of the reaction vectors $v_1, \ldots v_k$ and $(0, 1, -1, \ldots, 0)$, which is the reaction vector corresponding to the reaction $Z \to Y$. But as we've seen before, this is only possible if the 0 complex is present in this linkage class.

□

We have the following corollary from Theorem 4.3.6:

Corollary 4.3.7. Suppose we add a single reaction of the form $X + Y \to Z$, $X + Y \leftarrow Z$, or $X + Y \leftrightharpoons Z$ to an SRP network. If the 0 complex is not present in the network, then the system's deficiency remains zero after the new reaction is added.

4.3.3 Networks with an $mX \to Y$ Reaction

Similar to what we did in Theorem 4.3.6, here we want to determine under what conditions the addition of the reaction $mX \to Y$ — or the similar reactions $Y \to mX$ or $mX \leftrightharpoons Y$ — to an SRP system results in an increase in deficiency. Adding a single reaction of this type may result in the deficiency staying zero, or it may increase to one. The following theorem characterizes when the deficiency becomes one:

Theorem 4.3.8. *Consider a network with just SRP reactions. Suppose we add a single reaction of the form $mX \to Y$, $Y \to mX$, or $mX \leftrightharpoons Y$ with $m > 1$. Then, the network with the added reaction has deficiency one if and only if the complexes X, Y, and 0 are in the same linkage class.*

Proof. WLOG, suppose we add the reaction $mX \to Y$, and suppose the corresponding reaction vector is $(-m, 1, 0, \ldots, 0)$ (i.e. X and Y are numbered as the first and second species respectively).

We begin with the reverse implication. First, suppose that X, Y, and 0 are in the same linkage class. When the reaction $mX \to Y$ is added, the number of complexes the increases by 1 (since $m > 1$, mX is a distinct complex from X), but the number of linkage classes remains the same as our assumption means Y was already present in the SRP system. To show that the system now has deficiency one, then, we must show that addition of the reaction did not change the system's rank; that is, we must show the vector $(-m, 1, 0, \ldots, 0)$ is in the span of the pre-existing SRP reaction vectors.

Since X and 0 are in the same linkage class, by the proof of Lemma 4.3.1 the reaction vector for $X \to 0$, $(-1, 0, \ldots, 0)$ is in the span of the reaction vectors in X and 0's linkage class. Thus, the vector $(-m, 0, \ldots, 0)$ is also a linear combination of such vectors via multiplication by m.Similarly, as Y and 0 are in the same linkage class, the vector $(0, 1, 0, \ldots, 0)$ is a linear combination of reaction vectors in this linkage class. Hence, the vector $(-m, 1, 0, \ldots, 0)$ is also a linear combination of such vectors, and we are done.

For the forward implication, we will prove the contrapositive: if X, Y, and 0 are not all in the same linkage class, then the system's deficiency must remain zero after $mX \to Y$ is added. First, note that if $mX \to Y$ forms its own linkage class, then both mX and Y are new complexes (and hence Y cannot share a linkage class with X and 0), and the reaction vector for $mX \to Y$ is the only one with a non-zero second component. As a result, the deficiency is still zero: $\delta = (m' + 2) - (\ell + 1) - (s + 1) = 0$ (here, we've denoted the number of complexes in the original SRP network by m').

So, we just need to consider the case in which $mX \to Y$ does not form its own linkage class, i.e. Y was already present in the SRP system. In this case, the number of complexes increased by 1 with addition of the new reaction, while the number of linkage classes stayed the same. Hence, to show the system's deficiency is still zero, we need to show that the rank has increased, i.e. that $(-m, 1, 0, \ldots, 0)$ is *not* in the span of the SRP vectors. There are a few cases to consider.

1.) X and Y are in different linkage classes: if $(-m, 1, 0, \ldots, 0)$ was in the span of the SRP reaction vectors, then the $(-m, 0, \ldots, 0)$ vector must be a linear combination of vectors in X's linkage class and similarly, the vector $(0, 1, 0, \ldots, 0)$ must be obtainable from the reaction vectors in Y's linkage class.

   Thus, if $(-m, 1, 0, \ldots, 0)$ was in the span of the SRP vectors, then we must be able to get multiples of two standard basis vectors from two different linkage classes. However, this is impossible by Proposition 4.3.4 because since X and Y are in separate linkage classes, at least one of them does not share a linkage class with 0.

2.) X and Y are in the same linkage class, 0 is in a different class or not present: First, consider the case in which X and Y are the only two species in their linkage class in the SRP system. Then, their linkage class is of the form $X \to Y$, $Y \to X$, or $X \rightleftharpoons Y$,

and thus any linear combination of reactions vectors produces a vector of the form $(-a, a, 0, \ldots, 0)$, and $(-m, 1, 0, \ldots, 0)$ does not have this form.

Next, suppose X and Y's linkage class contains at least one other species Z, and let Z correspond to the third entry in the reaction vectors. Let $v_1, v_2, \ldots, v_k$ be the reaction vectors for this linkage class. If $(-m, 1, 0, \ldots, 0)$ was in the span of the SRP vectors, then it would be in the span of the v_i (due to, as mentioned above, each species in an SRP system being in exactly one linkage class). Thus, there would exist a_i not all zero such that

$$\begin{bmatrix} -m \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_k v_k$$

Then, adding the vector $(1, -1, 0, \ldots, 0)$ to both sides, we get

$$\begin{bmatrix} -m+1 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = a_1 v_1 + a_2 v_2 + \cdots + a_m v_m + \begin{bmatrix} 1 \\ -1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}.$$

Since $m > 1$, $-m + 1$ is not zero, and thus the vector $(-m + 1, 0, \ldots, 0)$ is a non-zero multiple of a standard basis vector. The expression above says that this vector is in the span of $v_1, v_2, \ldots, v_k, (1, -1, 0, \ldots, 0)$, i.e. in the span of the reaction vectors of X and Y's linkage class along with the reaction vector for $Y \to X$ added. But this means that a non-zero multiple of a standard basis vector is in the span of reaction vectors from a linkage class that does not contain 0, which is impossible.

3.) X was not present in the SRP system: then, clearly $(-m, 1, 0, \ldots, 0)$ is not in the span of the SRP reaction vectors, since it's impossible to get a non-zero first entry with no X complex present in the system.

In any case, we find that $(-m, 1, 0, \ldots, 0)$ is not in the span of the SRP reaction vectors, and thus the system's deficiency remains zero after adding $mX \to Y$. □

We get the following corollary similar to the previous section:

Corollary 4.3.9. Suppose we add a single reaction of the form $mX \to Y$, $Y \to mX$, or $mX \leftrightharpoons Y$ to an SRP network. If the 0 complex is not present in the network, then the system's deficiency remains zero after the new reaction is added.

4.3.4 Weakly Reversible SRP Networks

We know from Corollary 4.3.3 that SRP networks are deficiency zero. If an SRP network is also weakly reversible, then the Deficiency Zero Theorem applies to the corresponding system of mass action differential equations, which can give us useful information regarding the existence of equilibria and their stability.

Here, we will consider weakly reversible SRP networks with two species X and Y and aim to establish the structure of their corresponding systems of differential equations using mass action kinetics. In doing so, we will make it possible to determine from the differential equations whether a two-variable SRP system can be represented by a weakly reversible standard reaction diagram.

An SRP network with two species can have at most three complexes (X, Y, 0). First, we consider the case in which our network only contains the two complexes X and Y. In this case, the only way we have a weakly reversible network is if we have the reversible reaction $X \leftrightharpoons Y$. This gives us the system of differential equations shown in (4.1), where k_1 and k_2 are positive.

$$\begin{aligned} \dot{x} &= -k_1 x + k_2 y \\ \dot{y} &= k_1 x - k_2 y \end{aligned} \tag{4.1}$$

Now, we consider the case in which our network has all three of the complexes X, Y, and 0. With three complexes, there are multiple ways to get a weakly reversible network. First, we consider the case in which the network has a directed triangle between these three complexes; there are two possible orientations for this, shown in Figure 4.3.3.

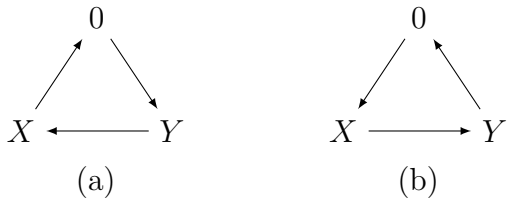


Figure 4.3.3: Weakly reversible networks with an underlying directed triangle.

Before writing out the equations for a network with a directed triangle, note that such a network may have additional reactions in addition to the three in the triangle; for instance, a network could have the three reactions shown in Figure 4.3.3(a) along with the reverse reaction $0 \to X$. We want to include the possibility of these additional reactions in

our differential equations. To do this, we will represent possible additional reactions using constants $c_i \geq 0$.

For example, the general form for a system with the triangle in the 4.3.3(a) orientation is

$$\begin{aligned} \dot{x} &= -k_1 x + k_2 y - c_4 x + c_5 \\ \dot{y} &= -k_2 y + k_3 + c_4 x - c_6 y. \end{aligned} \tag{4.2}$$

Here, the k_i are positive, and represent the three reactions we must have in order to have the triangle oriented as in Figure 4.3.3(a). Meanwhile, the c_i are non-negative, and represent the possible reverse reactions $0 \to X$, $X \to Y$, and $Y \to 0$ that may be present.

Similarly, for Figure 4.3.3(b), we have the general system of equations

$$\begin{aligned} \dot{x} &= -k_1 x + k_2 - c_4 x + c_5 y \\ \dot{y} &= k_1 x - k_3 y - c_5 y + c_6. \end{aligned} \tag{4.3}$$

Finally, a weakly reversible network can have the underlying reactions shown in Figure 4.3.4. Note that in this figure, reversible reactions are indicated by the double-sided arrows; thus, the network shown in Figure 4.3.4(a) consists of the reactions $X \leftrightharpoons 0$ and $Y \leftrightharpoons 0$.

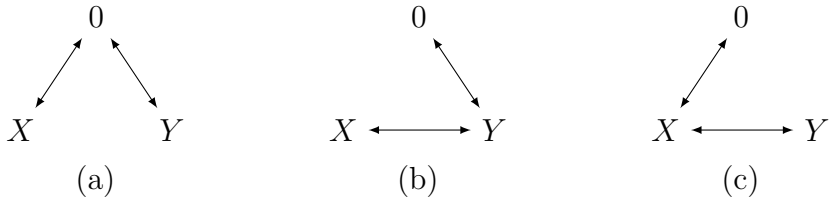


Figure 4.3.4: The final form of weakly reversible two-variable networks.

When it comes to equations for the three network structures shown above, we again want to consider the possibility of additional reactions being present (e.g. we want to include the possibility of a system with the form of Figure 4.3.4(a) with the reaction $X \to Y$ added). So, as we did above, we will include terms with non-negative constants c_i to denote possible additional reactions. Then, Figure 4.3.4 gives us the following general differential equations, in the order (a), (b), and (c):

$$\begin{aligned} \dot{x} &= -k_1 x + k_2 - c_4 x + c_5 y \\ \dot{y} &= -k_3 y + k_4 + c_4 x - c_5 y, \end{aligned} \tag{4.4}$$

$$\begin{aligned} \dot{x} &= -k_1 x + k_2 y - c_5 x + c_6 \\ \dot{y} &= k_1 x - k_2 y - k_3 y + k_4, \end{aligned} \tag{4.5}$$

and

$$\begin{aligned} \dot{x} &= -k_1 x + k_2 y - k_3 x + k_4 \\ \dot{y} &= k_1 x - k_2 y - c_5 y + c_6. \end{aligned} \tag{4.6}$$

Based on our work here, we can say the following about when a two-variable SRP system in weakly reversible:

Theorem 4.3.10. *An SRP network with two species is weakly reversible if and only if, when endowed with mass action kinetics, the corresponding system of differential equations has at least one of the forms* (4.1)-(4.6).

Additionally, we have the following sufficient condition for a general n-species SRP network to *not* be weakly reversible:

Proposition 4.3.11. Consider an SRP network with n species $X_1, X_2, \ldots, X_n$. With mass action kinetics, the corresponding system of differential equations is

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \vdots \\ \dot{x}_n \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & \ldots & a_{1n} \\ a_{21} & -a_{22} & \ldots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \ldots & -a_{nn} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ \vdots \\ x_{n_0} \end{bmatrix},$$

where the $n \times n$ matrix is an SRP matrix and the x_{i_0} are non-negative.

Suppose $\exists i$ such that $x_{i_0} > 0$. Then if all column sums of the SRP matrix are zero, the network is not weakly reversible.

Proof. If $x_{i_0} > 0$, then the network contains the reaction $0 \to X_i$. If the network was weakly reversible, then there would have to be a directed path back to 0; hence, there would have to be a j (which may or may not equal i) such that $X_j \to 0$ is a reaction in the network. Such a reaction, if it exists, would contribute a $-kx_j$ term in the $\dot{x}_j$ equation, but there would be no corresponding $+kx_j$ term in any other equation. Hence, the SRP matrix will contain a $-k$ term in the jth diagonal entry that is not matched by a $+k$ term in the same column. As a result, the jth diagonal entry will be larger in magnitude than the sum of the off-diagonal entries in the same column, and thus the jth column sum is non-zero. Hence, if all column sums are zero, there is no $X_j \to 0$ reaction to accompany the $0 \to X_i$ reaction, and the network is not weakly reversible. □

Chapter 5

Other Results

5.1 Compositions of Ramp Functions

In this section, we will consider systems in which ramp functions are composed inside other functions. We aim to compare the qualitative behaviour of such systems to their Michaelis-Menten counterparts. Note that the systems considered in this section will not necessarily be biochemical ramp systems as defined in Definition 1.1.2; we will keep the systems as general as possible.

5.1.1 Single-Variable Systems

We first consider systems in a single variable, x, involving a continuous, differentiable function f. The ramp systems composed with f will have the form

$$\dot{x} \;=\; f(r(x)), \tag{5.1}$$

where the ramp function r has threshold 2θ. The corresponding Michaelis-Menten system is then

$$\dot{x} \;=\; f\Big(\frac{x}{\theta + x}\Big) \;=\; f(M(x)) \tag{5.2}$$

We have the following:

Theorem 5.1.1. *The number of equilibria system (5.1) has in the all ramp region is equal to the number of non-negative equilibria system (5.2) has. Furthermore, stability of equilibria is the same between the two systems.*

Proof. Suppose $0 \leq y^*$ is such that $f(y^*) = 0$. Then, system (5.1) has the corresponding equilibrium $x_1 = 2\theta y^*$ in the all ramp region and system (5.2) has the non-negative equilibrium $x_2 = \dfrac{\theta y^*}{1 - y^*}$ if and only if $y^* < 1$. Hence, every $y^* \in [0, 1)$ such that $f(y^*) = 0$ corresponds to a unique equilibrium in both systems.

The sole eigenvalue of system (5.1) at an equilibrium in the all ramp region is given by

$$\frac{1}{2\theta} \cdot f'(y^*),$$

while the eigenvalue associated with the corresponding non-negative equilibrium in system (5.2) is

$$\frac{\theta}{(\theta + x_2)^2} \cdot f'(y^*).$$

These eigenvalues are positive multiples of $f'(y^*)$, and thus have the same sign.

We can also see that the flow pattern in the all ramp region of system (5.1) will be qualitatively the same as flow in the first quadrant of system (5.2). This can be seen from the fact that for $y \in [0, 1)$,

$$f(r(2\theta y)) \;=\; f\Big(M\Big(\frac{\theta y}{1-y}\Big)\Big) \;=\; f(y),$$

and thus $f(r(x'))$ for $x' = 2\theta y$ is positive (or negative or zero) if and only if $f(M(x''))$ for $x'' = \dfrac{\theta y}{1-y}$ is also positive (or negative or zero).

Since these expressions for x' and x'' are continuous and strictly increasing functions of y, this means that every region in which $f(r(x))$ is positive, negative, or zero has a corresponding equivalent region in which $f(M(x))$ is also positive, negative, or zero, and hence flow and stability of equilibria in the all ramp region of system (5.1) is the same as that in the first quadrant in system system (5.2). □

The conclusion of Theorem 5.1.1 is illustrated by the example below.

Example 5.1.2. Consider the ramp system

$$\dot{x} \;=\; \sin(7r(x))$$

and corresponding Michaelis-Menten system

$$\dot{x} \;=\; \sin(7M(x)).$$

These are systems (5.1) and (5.2) with $f(x) = \sin(7x)$. For this example, we will assume that the ramp function has threshold $2\theta = 1$.

In the all ramp region, $r(x) = x$ and thus equilibria in the ramp system must satisfy $7x^* = n\pi$ where $n \in \mathbb{Z}_{\geq 0}$. We get that $x^* = \dfrac{n\pi}{7}$, which falls in the all ramp region if and only if $n < 7/\pi$. This gives three equilibrium solutions, corresponding to $n = 0, 1, 2$:

$$(x_1^*, x_2^*, x_3^*) \;=\; \Big(0, \frac{\pi}{7}, \frac{2\pi}{7}\Big) \;\approx\; (0, 0.4488, 0.8976)$$

The eigenvalue of the ramp system is given by $7\cos(7x)$; we get an eigenvalue of 7 at x_1^* and x_3^* and -7 at x_2^*. In the all ramp region, the function $\sin(7r(x))$ is positive for $x \in (0, x_2^*)$

and $x \in (x_3^*, 1)$ and negative for $x \in (x_2^*, x_3^*)$. Thus, the equilibrium x_2^* is stable while the other two equilibria are unstable.

Equilibria in the Michaelis-Menten system are given by $x' = \dfrac{0.5n\pi}{7 - n\pi}$ if and only if $n < 7/\pi$, again giving us three possibilities:

$$(x_1', x_2', x_3') \;=\; \left(0, \frac{0.5\pi}{7-\pi}, \frac{\pi}{7-2\pi}\right) \;\approx\; (0, 0.4071, 4.3827)$$

The Michaelis-Menten system has eigenvalue $\dfrac{3.5}{(0.5+x)^2}\cos\left(\dfrac{7x}{0.5+x}\right)$, which is positive when evaluated at x_1' and x_3' and negative at x_2'. The function $\sin(7M(x))$ is positive for $x \in (0, x_2')$ and $x \in (x_3', \infty)$ and negative for $x \in (x_2', x_3')$. Similar to what we saw in the ramp system, the equilibrium x_2' is stable while the other two equilibria are unstable.

5.1.2 Multi-Variable Systems

Now, we will expand on our work above by considering compositions in more than one variable. In general, we will be studying ramp systems of the form

$$\vec{\dot{x}} \;=\; \vec{F}(\vec{r}(\vec{x})), \tag{5.3}$$

along with the corresponding Michaelis-Menten system

$$\vec{\dot{x}} \;=\; \vec{F}(\vec{M}(\vec{x})), \tag{5.4}$$

where

- $\vec{x} = (x_1, x_2, \ldots, x_n)$ is the vector of n variables
- $\vec{F}(\vec{x}) = (F_1(\vec{x}), F_2(\vec{x}), \ldots, F_n(\vec{x}))$ is a continuous, differentiable vector function
- $\vec{r}(\vec{x}) = (r_1(x_1), r_2(x_2), \ldots, r_n(x_n))$ is the vector of ramp functions, where r_i has threshold $2\theta_i$
- $\vec{M}(\vec{x}) = (M_1(x_1), M_2(x_2), \ldots, M_n(x_n))$ is the vector of Michaelis-Menten functions, where $M_i(x_i) = \dfrac{x_i}{\theta_i + x_i}$

We will first focus on determining when equilibria for systems (5.3) and (5.4) share the same stability. Later, we will provide an example showing that in general, stability of equilibria is *not* necessarily the same between the two systems.

Suppose $x^* = (x_1^*, x_2^*, \ldots, x_n^*)$ is such that $\vec{F}(x^*) = 0$. Then, system (5.3) has the equilibrium

$$y^* \;=\; (y_1^*, y_2^*, \ldots, y_n^*)$$

$$= (2\theta_1 x_1^*, 2\theta_2 x_2^*, \ldots, 2\theta_n x_n^*)$$

in the all ramp region and system (5.4) has the non-negative equilibrium

$$\begin{aligned} z^* &= (z_1^*, z_2^*, \ldots, z_n^*) \\ &= \left(\frac{\theta_1 x_1^*}{1 - x_1^*}, \frac{\theta_2 x_2^*}{1 - x_2^*}, \ldots, \frac{\theta_n x_n^*}{1 - x_n^*}\right) \end{aligned}$$

if and only if $x_1^* < 1$ for all i.

The entry in row i column j of J_r, the Jacobian of system (5.3) in the all ramp region, evaluated at y^* is $\frac{1}{2\theta_j} \cdot \frac{\partial F_i}{\partial x_j}(x^*)$. The same entry in J_M, the Jacobian of system (5.4), evaluated at z^*, is $\frac{\theta_j}{(\theta_j + z_j^*)^2} \cdot \frac{\partial F_i}{\partial x_j}(x^*)$. Thus, the jth column of J_r is equal to the jth column of J_M multiplied by $\frac{(\theta_j + z_j^*)^2}{2\theta_j^2}$.

If there is a $c > 0$ such that $\frac{(\theta_j + z_j^*)^2}{2\theta_j^2} = c$ for all j, then $J_r = cJ_M$ and the eigenvalues of each Jacobian are just positive multiples of each other; hence, the signs of the real parts will be the same between the two. Such a c exists if and only if

$$\begin{aligned} \frac{(\theta_j + z_j^*)^2}{2\theta_j^2} &= c \\ \implies (z_j^*)^2 + 2\theta_j z_j^* + \theta_j^2(1 - 2c) &= 0 \\ \implies z_j^* &= \theta_j(-1 \pm \sqrt{2c}) \end{aligned}$$

for all j. Note that the only way to get a non-negative z_j^* here is if $c \geq 1/2$ and thus $z_j^* = (\sqrt{2c} - 1)\theta_j$, taking the positive square root above.

Thus, if there is a $c \geq 1/2$ such that $z_j^* = (\sqrt{2c} - 1)\theta_j$ for all j, the Jacobians J_r and J_M evaluated at y^* and z^* respectively will be positive multiples of each other, and thus the real parts of their eigenvalues will have the same signs. We summarize this in the following theorem, letting $k = \sqrt{2c} - 1$:

Theorem 5.1.3. *Consider systems of form (5.3) and (5.4). Suppose $x^* \in \mathbb{R}^n_{\geq 0}$ is such that each component satisfies $x_i^* < 1$ and $\vec{F}(x^*) = 0$. Let $y^*, z^* \in \mathbb{R}^n_{\geq 0}$ be such that $\vec{F}(\vec{r}(y^*)) = \vec{F}(\vec{M}(z^*)) = \vec{F}(x^*) = 0$. Denote the Jacobians of (5.3) and (5.4) evaluated at y^* and z^* respectively by J_r and J_M*

If there is a $k \geq 0$ such that $z_j^* = k\theta_j$ for all j, then J_r and J_M are positive multiples of each other, and thus the real parts of their eigenvalues have the same signs.

Provided we have no eigenvalues with real part 0, Theorem 5.1.3 provides a sufficient

condition for equilibria in systems (5.3) and (5.4) to have the same stability. However, it will not be the case that equilibria in the two systems always have the same stability, as we show in the example below.

Example 5.1.4. Consider the vector function

$$\vec{F}(x,y) = \begin{bmatrix} -x+y+\dfrac{1}{6} \\ -3x+2y+\dfrac{1}{2} \end{bmatrix}.$$

Note that $F(x,y)=0$ has the unique solution $(x,y)=(1/6,0)$.

We will compose $\vec{F}$ with ramp functions $r_1(x)$ and $r_2(y)$ with thresholds $2\theta_1 = 0.8$ and $2\theta_2 = 2$ respectively. Thus, the corresponding system of form (5.3) in the all ramp region is given by

$$\begin{aligned} \dot{x} &= -\frac{x}{0.8}+\frac{y}{2}+\frac{1}{6} \\ \dot{y} &= -\frac{3x}{0.8}+y+\frac{1}{2}, \end{aligned}$$

while the Michaelis-Menten system of form (5.4) is

$$\begin{aligned} \dot{x} &= -\frac{x}{0.4+x}+\frac{y}{1+y}+\frac{1}{6} \\ \dot{y} &= -\frac{3x}{0.4+x}+\frac{2y}{1+y}+\frac{1}{2}. \end{aligned}$$

Notice that the ramp system is *not* mass action; Lemma 1.1.1 is not satisfied as the $\dot{y}$ equation contains a negative term that does not contain the variable y.

For the ramp system, the equilibrium is $(r_1(x^*), r_2(y^*)) = (1/6, 0)$ or $(x^*, y^*) = (2/15, 0)$. The Jacobian evaluated at this equilibrium is

$$\begin{bmatrix} -5/4 & 1/2 \\ -15/4 & 1 \end{bmatrix},$$

which has characteristic polynomial $\lambda^2 + 0.25\lambda + 5/8$. The eigenvalues are $\lambda \approx -0.125 \pm 0.7806i$, and hence the equilibrium is asymptotically stable.

Meanwhile, in the Michaelis-Menten system the equilibrium occurs at $(x', y') = (0.08, 0)$. The Jacobian at this point is

$$J_M(X^*, Y^*) = \begin{bmatrix} -125/72 & 1 \\ -125/24 & 2 \end{bmatrix},$$

with characteristic polynomial $\lambda^2 - \dfrac{19}{72}\lambda + \dfrac{125}{72}$. The eigenvalues are $\lambda \approx 0.1319 \pm 1.31099i$,

and thus the equilibrium point is unstable.

The equilibrium point differs in stability between the two systems; it is stable in the ramp system but unstable in the Michaelis-Menten system. The reason for this is that in multi-variable systems, it is not just the sign of the entries of the Jacobian that matters, but their magnitude as well. In the ramp system, the magnitude of the diagonal Jacobian entries was such that overall, the trace was negative (-0.25), but in the Michaelis-Menten Jacobian, the differing size of the diagonal entries resulted in a positive trace ($19/72$). This is enough to flip the signs of the eigenvalues between the two matrices.

5.2 Mixed Systems

This section examines what we will call *mixed* systems, referring to systems of differential equations in which variables appear both as the input of ramp functions and outside ramp functions; these systems are thus not biochemical ramp systems as defined in Definition 1.1.2. As usual, we aim to compare the behaviour of these systems with their counterparts in which the ramp functions are replaced by Michaelis-Menten terms.

5.2.1 An Example Class of Systems

The first mixed system we will consider is the simple single-variable system

$$\dot{x} \;=\; ar(x) - bx, \tag{5.5}$$

where a and b are positive parameters and r has threshold 2θ. This system always has an equilibrium point at $x^* = 0$. Whether additional equilibria exist depends on the parameters.

When r is in its ramp region, system (5.5) becomes

$$\dot{x} \;=\; \Big(\frac{a}{2\theta} - b\Big)x.$$

A non-zero equilibrium exists in this region if and only if we are dealing with the special case $a = 2\theta b$; if this equality holds, then every $x \in [0, 2\theta]$ is an equilibrium point of system (5.5). Note that the threshold value $x = 2\theta$ is included because at this value, the right hand side of the $\dot{x}$ becomes $a - 2\theta b$, which is zero when $a = 2\theta b$.

In general, however, it will not be the case that $a = 2\theta b$, and thus we will not have additional equilibria when r is in its ramp region. When $x > 2\theta$, r is saturated, and system (5.5) becomes

$$\dot{x} \;=\; a - bx,$$

which has the positive equilibrium point $x^* = a/b$ if and only if $x^* > 2\theta$, i.e. $a > 2\theta b$.

When it comes to stability of $x^* = 0$, the derivative of the right hand side of (5.5) when r is in its ramp region is

$$\frac{a}{2\theta} - b.$$

This value is negative for $a < 2\theta b$ and positive for $a > 2\theta b$. Thus, the equilibrium at the origin is asymptotically stable if a is less than $2\theta b$ in value, but becomes unstable when a exceeds $2\theta b$ and the positive equilibrium in r's saturated region emerges.

The positive equilibrium $x^* = a/b$ is always stable when it exists; when r is saturated, the derivative of the right hand side of (5.5) is $-b$, which is always negative.

A summary of equilibria in system (5.5) is provided in Table 1 below, covering the $a < 2\theta b$ and $a > 2\theta b$ cases; the special case $a = 2\theta b$ is excluded.

	$a < 2\theta b$	$a > 2\theta b$
Non-Neg Equilibria	$x^* = 0$ only	$x^* = 0$ and $x^* = a/b$
Stability of $x^* = 0$	Stable	Unstable
Stability of $x^* > 0$	—	Stable

Table 1: Summary of equilibria results for mixed ramp system (5.5).

Now, we will analyze the Michaelis-Menten counterpart to system (5.5),

$$\dot{x} = \frac{ax}{\theta + x} - bx. \tag{5.6}$$

Equilibria of system (5.6) are the solutions to

$$bx^2 + (b\theta - a)x = 0,$$

of which there are two: $x^* = 0, \dfrac{a - \theta b}{b}$. The second equilibrium point is positive if and only if $a > \theta b$.

The derivative of the right hand side of (5.6) is

$$\frac{a\theta}{(\theta + x)^2} - b.$$

At $x^* = 0$, the derivative becomes $(a/\theta) - b$, which is negative for $a < \theta b$ and positive for $a > \theta b$. Thus, as with system (5.5), the origin is stable when it is the only non-negative point, but becomes unstable when the positive equilibrium emerges.

At $x^* = (a - \theta b)/b$, the derivative evaluates to

$$\frac{b(\theta b - a)}{a},$$

which is always negative when this equilibrium exists ($a > \theta b$). Thus, the positive equilibrium will be stable when it exists.

Once again, we summarize the equilibria results for system (5.6) in the following table:

	$a < \theta b$	$a > \theta b$
Non-Neg Equilibria	$x^* = 0$ only	$x^* = 0$ and $x^* = (a - \theta b)/b$
Stability of $x^* = 0$	Stable	Unstable
Stability of $x^* > 0$	—	Stable

Table 2: Summary of equilibria results for mixed Michaelis-Menten system (5.6).

From Tables 1 and 2, we see that the behaviour of systems (5.5) and (5.6) is qualitatively similar: both always have an equilibrium at the origin, and a positive equilibrium exists if a is above a certain value. The equilibrium at the origin is stable when the positive equilibrium does not exist, but becomes unstable when the positive equilibrium emerges. Meanwhile, the positive equilibrium is always stable when it exists.

However, there is a slight quantitative difference between the two systems that should be noted: the value above which a must be in order for the positive equilibrium to exist. In system (5.5), this value is $2\theta b$, but in system (5.6) it is θb. This is notable as in our previous comparisons of ramp and Michaelis-Menten systems with one threshold per variable, parameter conditions for the existence of equilibria were identical between the two systems; for instance, the conditions for coexistence of the two equilibria in systems (3.28) and (3.36) are exactly the same, and Theorem 3.1.3 provided an equivalence between the existence of equilibria in the all ramp region and the existence of non-negative equilibria in Michaelis-Menten systems.

Thus, while systems (5.5) and (5.6) are qualitatively similar, we need to be mindful of quantitative differences that can result in different behaviour between the two. For instance, if we were working with a value of $a \in (\theta b, 2\theta b)$, then the Michaelis-Menten system (5.6) would have a positive equilibrium, but the ramp system (5.5) would only have the equilibrium at $x^* = 0$.

5.2.2 A Ramp and Michaelis-Menten System with Different Behaviour

The slight difference in parameter conditions for systems (5.5) and (5.6) to exhibit positive equilibria raises the question: is it possible for a mixed system with, say, ramp functions to always have equilibria, while the corresponding Michaelis-Menten system only admits equilibria for specific parameter values? To answer this, consider the system

$$\dot{x} \;=\; ar(x) - x^2 + 3\theta x - \Big(\frac{3a + 9\theta^2}{4}\Big), \tag{5.7}$$

where $a > 0$ and 2θ is the threshold for the ramp function r. In the ramp region, solving $\dot{x} = 0$ gives the equilibrium solutions

$$x^* \;=\; \frac{3\theta}{2},\; \frac{3\theta}{2} + \frac{a}{2\theta}.$$

The equilibrium $x^* = 3\theta/2$ always falls in the ramp region for r, while the second equilibria satisfies $x^* < 2\theta$ if and only if $a < \theta^2$. When r is saturated, solving for equilibria gives

$$x^* \;=\; \frac{3\theta \pm \sqrt{a}}{2}.$$

The negative root will never satisfy $x^* \geq 2\theta$, but the positive root will if and only if $a \geq \theta^2$.

Thus, system (5.7) will always have two positive equilibrium points: one at $x^* = 3\theta/2$, and a second, larger equilibrium whose location (ramp vs saturated region) depends on the value of a relative to θ^2.

In the ramp region, the derivative of the right hand side of (5.7) is

$$\frac{a}{2\theta} - 2x + 3\theta.$$

At $x^* = 3\theta/2$, the derivative becomes $a/(2\theta)$, and thus this equilibrium is unstable. If the second equilibrium $x^* = \dfrac{3\theta}{2} + \dfrac{a}{2\theta}$ exists in this region, then the derivative at this value is $-a/(2\theta)$, and hence the second equilibrium is stable.

When r is saturated, the derivative of the right hand side is

$$-2x + 3\theta.$$

At the second equilibrium $x^* = \dfrac{3\theta + \sqrt{a}}{2}$, if it falls in this region instead of the ramp region, the derivative becomes $-\sqrt{a}$, and thus the equilibrium is stable.

Thus, the equilibrium $x^* = 3\theta/2$ of system (5.7) is unstable, but the second positive equilibrium will always be stable, regardless of whether it is located in the ramp region or the saturated region.

Now, we want to compare our equilibria results for system (5.7) to those of the corresponding Michaelis-Menten system

$$\dot{x} \;=\; \frac{ax}{\theta + x} - x^2 + 3\theta x - \Big(\frac{3a + 9\theta^2}{4}\Big). \tag{5.8}$$

Equilibria of system (5.8) are roots of the cubic

$$x^3 - 2\theta x^2 - \Big(\frac{a + 3\theta^2}{4}\Big)x + \frac{3a\theta + 9\theta^3}{4}. \tag{5.9}$$

Does this cubic always have positive roots? The answer is no — Figure 5.2.1 graphs the cubic with $a = 7$ and θ set to the values $0.1, 0.5, 1$, and 2. We can see that while two real, positive roots exist for the $\theta = 0.1$ case graphed in blue, none of the other three curves intersect the y-axis for $x \geq 0$.

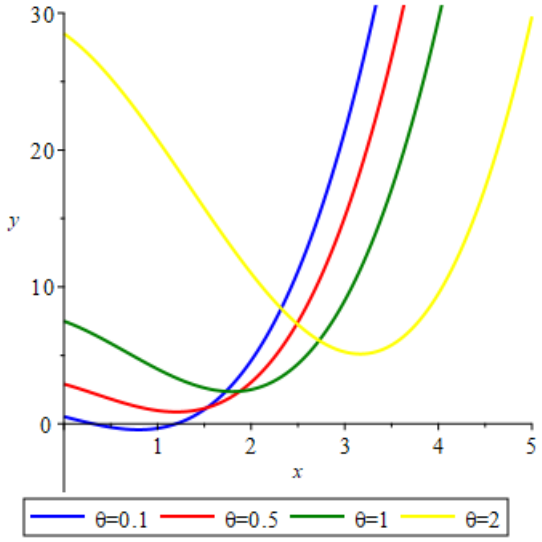


Figure 5.2.1: Graph of cubic (5.9) for $x \geq 0$ with $a = 7$ and $\theta = 0.1$ (blue), 0.5 (red), 1 (green), and 2 (yellow).

Thus, we have a notable difference between systems (5.7) and (5.8): while the ramp system (5.7) will always have two positive equilibrium points, Michaelis-Menten system (5.8) is not guaranteed to have a single non-negative equilibrium.

5.2.3 A Class of Two-Variable Systems

We will now consider the two-variable mixed system

$$\begin{aligned} \dot{x} &= b_1 r_1(x) - a_{11}x + a_{12}y + c \\ \dot{y} &= b_2 r_2(y) - a_{22}y + d, \end{aligned} \tag{5.10}$$

where all parameters are positive, r_1 and r_2 have thresholds $2\theta_1$ and $2\theta_2$ respectively, and the a_{ij} form an SRP matrix (that is, $a_{12} \leq a_{22}$). Starting with $\dot{y} = 0$, the value of y at equilibrium is

$$y^* = \frac{2d\theta_2}{2a_{22}\theta_2 - b_2}$$

in the ramp region for r_2 if and only if $b_2 + d < 2a_{22}\theta_2$, or

$$y^* = \frac{b_2 + d}{a_{22}}$$

when r_2 is saturated if and only if $b_2 + d \geq 2a_{22}\theta_2$. One of these conditions on parameters will always hold, and thus we will always be able to find a positive y^*.

Once we have found y^*, the equilibrium value of x is given by

$$x^* = \frac{2\theta_1(a_{12}y^* + c)}{2a_{11}\theta_1 - b_1}$$

when r_1 is in its ramp region if and only if $a_{12}y^* + b_1 + c < 2a_{11}\theta_1$, or

$$x^* = \frac{b_1 + a_{12}y^* + c}{a_{11}}$$

when r_1 is saturated if and only if $a_{12}y^* + b_1 + c \geq 2a_{11}\theta_1$. Again, one of these conditions of parameters will always hold, so we will always be able to find an x^*. Hence, system (5.10) will always have a positive equilibrium (x^*, y^*).

The Jacobian of system (5.10) will be a triangular matrix. The diagonal entry in the first column is given by $-b_1/(2\theta_1) - a_{11}$ if x^* falls in the ramp region for r_1, or simply $-a_{11}$ if x^* falls in the region where r_1 is saturated. In the latter case, the corresponding eigenvalue is obviously negative. When x^* lies in the ramp region for r_1, the parameter condition $a_{12}y^* + b_1 + c < 2a_{11}\theta_1$ implies that $b_1 < 2a_{11}\theta_1$, and thus $-b_1/(2\theta_1) - a_{11}$ is negative as well. Hence, in either case the eigenvalue given by the first diagonal entry will be negative.

Similarly, the diagonal entry in the second column of the Jacobian will also always be negative. Hence, the equilibrium point (x^*, y^*) is always asymptotically stable.

Now, consider the corresponding Michaelis-Menten system

$$\begin{aligned} \dot{x} &= \frac{b_1 x}{\theta_1 + x} - a_{11}x + a_{12}y + c \\ \dot{y} &= \frac{b_2 y}{\theta_2 + y} - a_{22}y + d. \end{aligned} \tag{5.11}$$

From the $\dot{y}$ equation, an equilibrium value of y must satisfy

$$a_{22}y^2 + (a_{22}\theta_2 - d - b_2)y - d\theta_2 = 0.$$

The quadratic term has a sole non-negative root given by

$$y^* = \frac{d + b_2 - a_{22}\theta_2 + \sqrt{(a_{22}\theta_2 - d - b_2)^2 + 4a_{22}d\theta_2}}{2a_{22}}. \tag{5.12}$$

Substituting this y^* value into the $\dot{x}$ equation, we find that x^* must be a root of the quadratic

$$a_{11}x^2 + (a_{11}\theta_1 - a_{12}y^* - c - b_1)x - a_{12}\theta_1 y^* - c\theta_1.$$

Again, this quadratic has one non-negative root given by

$$x^* = \frac{-\beta + \sqrt{\beta^2 + 4a_{11}(a_{12}\theta_1 + c\theta_1)}}{2a_{11}}, \tag{5.13}$$

where $\beta = a_{11}\theta_1 - a_{12}y^* - c - b_1$. Hence, system (5.11) always admits a unique positive equilibrium, with the x^* and y^* values given by (5.13) and (5.12) respectively.

The Jacobian of system (5.11) at the positive equilibrium is the triangular matrix

$$\begin{bmatrix} \dfrac{b_1\theta_1}{(\theta_1 + x^*)^2} - a_{11} & a_{12} \\ 0 & \dfrac{b_2\theta_2}{(\theta_2 + y^*)^2} - a_{22}, \end{bmatrix}$$

and thus the eigenvalues are equal to the diagonal entries. We will determine the sign of the eigenvalues by first considering the diagonal entry in the second column. With the y^* value given in (5.12), this eigenvalue becomes

$$\frac{4b_2\theta_2(a_{22})^2}{(d + b_2 + a_{22}\theta_2 + \sqrt{(a_{22}\theta_2 - d - b_2)^2 + 4a_{22}d\theta_2})^2} - a_{22}.$$

The denominator of this fraction expands out to be

$$(d + b_2 + a_{22}\theta_2)^2 + 2(d + b_2 + a_{22}\theta_2)\gamma + (a_{22}\theta_2 - d - b_2)^2 + 4a_{22}d\theta_2$$

where $\gamma = \sqrt{(a_{22}\theta_2 - d - b_2)^2 + 4a_{22}d\theta_2}$. Now, the term $(d + b_2 + a_{22}\theta_2)^2 + (a_{22}\theta_2 - d - b_2)^2$ evaluates to

$$2d^2 + 2b_2^2 + 2(a_{22}\theta_2)^2 + 4b_2d.$$

Note that we have

$$\begin{aligned} 2b_2^2 + 2(a_{22}\theta_2)^2 - 4b_2\theta_2a_{22} &= 2(b_2 - a_{22}\theta_2)^2 \\ &\geq 0, \end{aligned}$$

and thus $2b_2^2 + 2(a_{22}\theta_2)^2 \geq 4b_2\theta_2a_{22}$. Hence, since the denominator contains $2b_2^2 + 2(a_{22}\theta_2)^2$ added to several other positive terms, the denominator must be strictly greater than $4b_2\theta_2a_{22}$. Hence, the eigenvalue satisfies

$$\begin{aligned} \frac{4b_2\theta_2(a_{22})^2}{(d + b_2 + a_{22}\theta_2 + \gamma)^2} - a_{22} &< \frac{4b_2\theta_2(a_{22})^2}{4b_2\theta_2a_{22}} - a_{22} \\ &= 0, \end{aligned}$$

and is thus negative. Similarly, the eigenvalue $\dfrac{b_1\theta_1}{(\theta_1 + x^*)^2} - a_{11}$ will also always be negative. Thus, the positive equilibrium of system (5.11) is stable.

Thus, systems (5.11) and (5.10) display similar qualitative behaviour: both have a unique positive equilibrium regardless of parameter assignments, and this equilibrium is stable.

5.3 Lotka-Volterra Systems

This final section will consider the possibility of oscillations and periodic orbits in ramp systems. Such behaviour is know to be possible in general mass action systems; for instance, [3] provides several examples of planar mass action systems with periodic solutions. A concrete example can be found in Selkov's model of glycolysis [18]. A version of his model, found in sources such as [20], is given by the mass action system

$$\begin{aligned} \dot{x} &= -x + ay + x^2 y \\ \dot{y} &= -ay - x^2 y + b, \end{aligned}$$

where x and y represent the concentrations of adenosine diphosphate and fructose-6-phosphate respectively, which is known to produce oscillations under certain assignments of parameters.

The oscillatory system we will be focusing on here, however, is the Lotka-Volterra predator-prey model developed by Alfred Lotka [13, 14] and Vito Volterra [22] in the early twentieth century. This model is described by the system of differential equations

$$\begin{aligned} \dot{x} &= \alpha x - \beta xy \\ \dot{y} &= \delta xy - \gamma y, \end{aligned} \tag{5.14}$$

where x and y represent the populations of a prey and predator species respectively, and α, β, δ, and γ are positive constants. Note that this version of the model differs slightly from the one shown in (3.11), which assumed $\delta = \beta$; here, we will not be assuming such a restriction on δ and β.

The Lotka-Volterra model (5.14) is a mass action system and thus can be derived from a set of reactions representing ecological processes and the relationship between the two species. For instance, the αx term in the $\dot{x}$ equation can be obtained from the reaction $X \xrightarrow{\alpha} 2X$, which can be interpreted as the natural growth rate of the prey; the prey population increases at a rate proportional to its current population. The $-\gamma y$ term in the $\dot{y}$ equation comes from the reaction $Y \xrightarrow{\gamma} 0$, which tells us that the predator species dies off at a rate proportional to its current population.

The xy terms in each equation describe the effects of predation on the two populations, with the prey population decreasing and the predator population increasing as a result of this interaction. A corresponding reaction is $X + Y \xrightarrow{\beta} bY$, where b is an integer greater than 1; note that this reaction contributes a $\beta(b-1)xy$ term to the $\dot{y}$ in (5.14), and thus we have $\delta = \beta(b-1)$.

5.3.1 Mass Action Results

Before we look at a version of the Lotka-Volterra model containing ramp functions, we will first cover equilibria results for system (5.14), which have been known since the original work of Lotka and Volterra [13, 14, 22] . This system admits two equilibria: one at $(x^*, y^*) = (0, 0)$,

describing the extinction of both species, and a positive one given by $(x^*, y^*) = (\gamma/\delta, \alpha/\beta)$, representing coexistence of the predator and prey.

The Jacobian of (5.14) is

$$\begin{bmatrix} \alpha - \beta y & -\beta x \\ \delta y & \delta x - \gamma \end{bmatrix}.$$

When evaluated at $(0, 0)$, this becomes a diagonal matrix with eigenvalues α and $-\gamma$; the origin is thus a saddle point. At the positive equilibrium, the Jacobian becomes

$$\begin{bmatrix} 0 & -\dfrac{\beta\gamma}{\delta} \\ \dfrac{\alpha\delta}{\beta} & 0 \end{bmatrix},$$

with characteristic polynomial $\lambda^2 + \alpha\gamma$. Thus, the eigenvalues $\lambda_{1,2} = \pm\sqrt{\alpha\gamma}i$ are purely imaginary.

The positive equilibrium $(x^*, y^*) = (\gamma/\delta, \alpha/\beta)$ is, in fact, a centre enclosed by periodic closed orbits. This can be seen from the fact that in the first quadrant, a first integral for system (5.14) is given by

$$\begin{aligned} \frac{dx}{dy} &= \frac{x(\alpha - \beta y)}{y(\delta x - \gamma)} \\ \implies \int \frac{\delta x - \gamma}{x} dx &= \int \frac{a - \beta y}{y} dy \\ \implies \delta x - \gamma \ln(x) + \beta y - \alpha \ln(y) &= C, \end{aligned} \tag{5.15}$$

which defines a class of closed curves for a constant C. Several closed trajectories for system (5.14) are shown in Figure 5.3.1.

5.3.2 Ramp System Results

We will now consider the behaviour of system (5.14) when the variables are instead the input of ramp functions. The Lotka-Volterra model then becomes

$$\begin{aligned} \dot{x} &= \alpha r_1(x) - \beta r_1(x) r_2(y) \\ \dot{y} &= \delta r_1(x) r_2(y) - \gamma r_2(y), \end{aligned} \tag{5.16}$$

where r_1 and r_2 have thresholds $2\theta_1$ and $2\theta_2$ respectively.

Ramp system (5.16) always has an equilibrium at the origin. In the all ramp region, the equations have the form

$$\dot{x} = \frac{\alpha x}{2\theta_1} - \frac{\beta x y}{4\theta_1\theta_2}$$

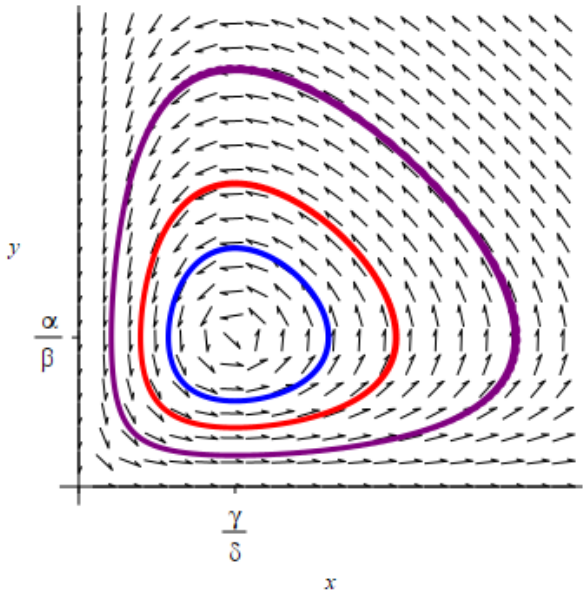


Figure 5.3.1: Vector field and closed trajectories enclosing the positive equilibrium $(x^*, y^*) = (\gamma/\delta, \alpha/\beta)$ in Lotka-Volterra system (5.14). Three trajectories in the first quadrant are shown, each displayed in a different colour.

$$\dot{y} \;=\; \frac{\delta x y}{4\theta_1\theta_2} - \frac{\gamma y}{2\theta_2},$$

and thus the positive equilibrium

$$(x^*, y^*) \;=\; \left(\frac{2\theta_1\gamma}{\delta}, \frac{2\theta_2\alpha}{\beta}\right) \tag{5.17}$$

exists in the all ramp region if and only if $\gamma < \delta$ and $\alpha < \beta$. The Jacobian of system (5.16) in the all ramp region is given by

$$\begin{bmatrix} \dfrac{\alpha}{2\theta_1} - \dfrac{\beta y}{4\theta_1\theta_2} & -\dfrac{\beta x}{4\theta_1\theta_2} \\ \dfrac{\delta y}{4\theta_1\theta_2} & \dfrac{\delta x}{4\theta_1\theta_2} - \dfrac{\gamma}{2\theta_2} \end{bmatrix}.$$

At the origin, the Jacobian evaluates to

$$\begin{bmatrix} \dfrac{\alpha}{2\theta_1} & 0 \\ 0 & -\dfrac{\gamma}{2\theta_2} \end{bmatrix},$$

with real eigenvalues of opposite signs; thus, the origin of the ramp model is still a saddle point.

Meanwhile, the Jacobian is

$$\begin{bmatrix} 0 & -\dfrac{\beta x^*}{4\theta_1\theta_2} \\ \dfrac{\delta y^*}{4\theta_1\theta_2} & 0 \end{bmatrix}$$

at the positive equilibrium (x^*, y^*) given in (5.17) above. With a trace of zero and a positive determinant, the eigenvalues of this matrix are purely imaginary. The goal of our analysis here will be to determine whether this positive equilibrium, when it exists in the all ramp region, will still be embedded within closed curves as in the mass action system. In particular, we want to determine whether trajectories starting outside the all ramp region are closed, thus spanning multiple boxes of phase space.

5.3.2.1 Closed Trajectories

We begin our quest to show that system (5.16) has closed trajectories when the positive equilibrium falls in the all ramp region by first computing first integrals for each region of phase space. In the all ramp region, using the equations given above we have that

$$\begin{aligned} \frac{dx}{dy} &= \frac{x\left[\frac{\alpha}{2\theta_1} - \frac{\beta y}{4\theta_1\theta_2}\right]}{y\left[\frac{\delta x}{4\theta_1\theta_2} - \frac{\gamma}{2\theta_2}\right]} \\ \Longrightarrow \int \Big(\frac{\delta}{4\theta_1\theta_2} - \frac{\gamma}{2\theta_2 x}\Big)dx &= \int \Big(\frac{\alpha}{2\theta_1 y} - \frac{\beta}{4\theta_1\theta_2}\Big)dy \\ \Longrightarrow \frac{\delta x}{4\theta_1\theta_2} - \frac{\gamma}{2\theta_2}\ln x + \frac{\beta y}{4\theta_1\theta_2} - \frac{\alpha}{2\theta_1}\ln y &= C \end{aligned} \tag{5.18}$$

for an arbitrary constant C.

Next, in the x saturated region — the box of phase space defined by $x \geq 2\theta_1$ and $y < 2\theta_2$ — the equations of system (5.16) become

$$\begin{aligned} \dot{x} &= \alpha - \frac{\beta y}{2\theta_2} \\ \dot{y} &= \Big(\frac{\delta - \gamma}{2\theta_2}\Big)y. \end{aligned}$$

A first integral is then given by

$$\begin{aligned} \frac{dx}{dy} &= \frac{\alpha - \frac{\beta y}{2\theta_2}}{\left(\frac{\delta-\gamma}{2\theta_2}\right)y} \\ \implies \int(\delta-\gamma)dx &= \int\left(\frac{2\theta_2\alpha}{y} - \beta\right)dy \\ \implies (\delta-\gamma)x - 2\theta_2\alpha\ln y + \beta y &= C \end{aligned} \tag{5.19}$$

Meanwhile, in the y saturated region, the box defined by $x < 2\theta_1$ and $y \geq 2\theta_2$, the equations become

$$\begin{aligned} \dot{x} &= \left(\frac{\alpha-\beta}{2\theta_1}\right)x \\ \dot{y} &= \frac{\delta x}{2\theta_1} - \gamma, \end{aligned}$$

with first integral

$$\begin{aligned} \frac{dx}{dy} &= \frac{\left(\frac{\alpha-\beta}{2\theta_1}\right)x}{\frac{\delta x}{2\theta_1} - \gamma} \\ \implies \int\left(\delta - \frac{2\theta_1\gamma}{x}\right)dx &= \int(\alpha-\beta)dy \\ \implies \delta x - 2\theta_1\gamma\ln x - (\alpha-\beta)y &= C \end{aligned} \tag{5.20}$$

Finally, in the both saturated region, where $x \geq 2\theta_1$ and $y \geq 2\theta_2$, we have the equations

$$\begin{aligned} \dot{x} &= \alpha - \beta \\ \dot{y} &= \delta - \gamma \end{aligned}$$

and first integral

$$\begin{aligned} \frac{dx}{dy} &= \frac{\alpha-\beta}{\delta-\gamma} \\ \implies \int(\delta-\gamma)dx &= \int(\alpha-\beta)dy \\ \implies (\delta-\gamma)x - (\alpha-\beta)y &= C \end{aligned} \tag{5.21}$$

Now, we will follow a trajectory of system (5.16) starting in the interior of the first quadrant and show that it must be a closed curve. We will follow the trajectory with help from the vector field for the system shown in Figure 5.3.2 below; note that this image displays

the x nullclines $x = 0$ and $y = \dfrac{2\theta_2\alpha}{\beta}$ in red with the y nullclines $y = 0$ and $x = \dfrac{2\theta_1\gamma}{\delta}$ in blue. From Figure 5.3.2, trajectories starting close to the positive equilibrium stay in the all ramp region and form closed curves as in the mass action Lotka-Volterra system. So, we will consider the behaviour of a trajectory that passes through at least one saturated region.

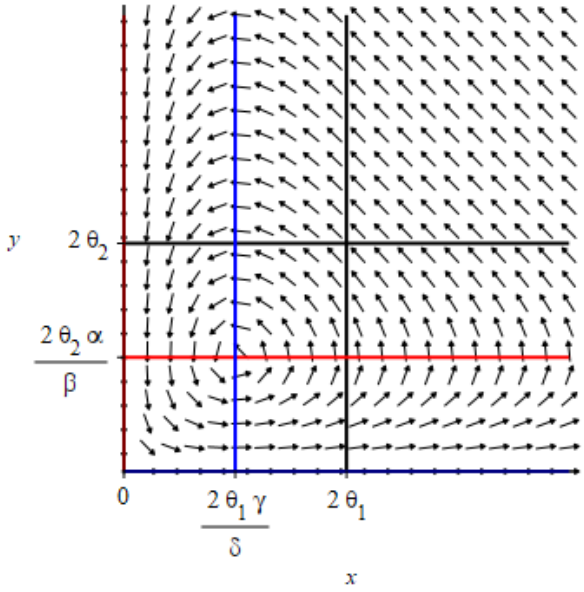


Figure 5.3.2: Vector field of ramp system (5.16) when the positive equilibrium $(x^*, y^*) = (2\theta_1\gamma/\delta, 2\theta_2\alpha/\beta)$ exists in the all ramp region. The x nullclines are shown in red while the y nullclines are shown in blue.

Suppose we have a trajectory starting on the boundary of the all ramp region and the x saturated region, at a point $(x, y) = (2\theta_1, y_1)$ with $0 < y_1 < 2\theta_2$. This point corresponds to the trajectory in the all ramp region defined by

$$\frac{\delta}{2\theta_2} - \frac{\gamma}{2\theta_2}\ln(2\theta_1) + \frac{\beta y_1}{4\theta_1\theta_2} - \frac{\alpha}{2\theta_1}\ln y_1 \;=\; C_1$$

using the first integral given in (5.18) for some constant C_1. On the x saturated side, the corresponding curve using the first integral (5.19) is

$$2\theta_1(\delta - \gamma) - 2\theta_2\alpha\ln y_1 + \beta y_1 \;=\; C_2.$$

The first equation here can be rearranged to the form

$$2\theta_1(\delta - \gamma) - 2\theta_2\alpha\ln y_1 + \beta y_1 \;=\; 4\theta_1\theta_2 C_1 + 2\theta_1\gamma\ln(2\theta_1) - 2\theta_1\gamma,$$

the left side of which is the first integral on the x saturated side. Thus, we have that

$$4\theta_1\theta_2 C_1 + 2\theta_1\gamma\ln(2\theta_1) - 2\theta_1\gamma \;=\; C_2. \tag{5.22}$$

The trajectory will then move into the x saturated region following the curve

$$(\delta - \gamma)x - 2\theta_2\alpha \ln y + \beta y \;=\; C_2.$$

From the vector field in Figure 5.3.2, the trajectory may cross into the all ramp region again or may cross into the both saturated region; we will consider both of these cases.

Case 1: The trajectory hits the boundary of the all ramp region, at a point $(x, y) = (2\theta_1, y_2)$ with $y_1 < y_2 < 2\theta_2$. The first integral on the x saturated side at this point is

$$2\theta_1(\delta - \gamma) - 2\theta_2\alpha \ln y_2 + \beta y_2 \;=\; C_2.$$

On the all ramp region side, the first integral at this point is

$$\frac{\delta}{2\theta_2} - \frac{\gamma}{2\theta_2}\ln(2\theta_1) + \frac{\beta y_2}{4\theta_1\theta_2} - \frac{\alpha}{2\theta_1}\ln y_2 \;=\; C_3.$$

A rearrangement of this equation gives us that

$$2\theta_1(\delta - \gamma) - 2\theta_2\alpha \ln y_2 + \beta y_2 \;=\; 4\theta_1\theta_2 C_3 + 2\theta_1\gamma \ln(2\theta_1) - 2\theta_1\gamma,$$

and thus

$$4\theta_1\theta_2 C_3 + 2\theta_1\gamma \ln(2\theta_1) - 2\theta_1\gamma \;=\; C_2.$$

From (5.22), this then means that $C_1 = C_3$. Hence, the trajectory ends up rejoining the initial curve in the all ramp region, moving along the curve

$$\frac{\delta x}{4\theta_1\theta_2} - \frac{\gamma}{2\theta_2}\ln x + \frac{\beta y}{4\theta_1\theta_2} - \frac{\alpha}{2\theta_1}\ln y \;=\; C_1.$$

From here, the trajectory may remain in the all ramp region until it reaches the point $(2\theta_1, y_1)$ on the boundary of the x saturated region again, thus forming a closed curve. However, from Figure 5.3.2 we can see that a trajectory in the all ramp region can also enter the y saturated region; we will now consider this sub-case.

Suppose the trajectory hits the boundary between the all ramp and y saturated regions at $(x, y) = (x_1, 2\theta_2)$ where $0 < x_1 < 2\theta_1$. The trajectory is described by the curve

$$\frac{\delta x_1}{4\theta_1\theta_2} - \frac{\gamma}{2\theta_2}\ln x_1 + \frac{\beta}{2\theta_1} - \frac{\alpha}{2\theta_1}\ln(2\theta_2) \;=\; C_1$$

on the all ramp region side, and, using the first integral from (5.20),

$$\delta x_1 - 2\theta_1\gamma \ln(x_1) - 2\theta_2(\alpha - \beta) \;=\; C_4$$

for some constant C_4 on the y saturated side. From the all ramp region first integral, we get that

$$\delta x_1 - 2\theta_1\gamma \ln(x_1) - 2\theta_2(\alpha - \beta) \;=\; 4\theta_1\theta_2 C_1 + 2\theta_2\alpha \ln(2\theta_2) - 2\theta_2\alpha,$$

and thus

$$4\theta_1\theta_2 C_1 + 2\theta_2\alpha \ln(2\theta_2) - 2\theta_2\alpha \;=\; C_4. \tag{5.23}$$

The trajectory then follows the curve

$$\delta x - 2\theta_1\gamma \ln x - (\alpha - \beta)y \;=\; C_4$$

in the y saturated region until it reaches the boundary of the all ramp region again at a point $(x, y) = (x_2, 2\theta_2)$ with $x_2 < x_1$. The first integral on the y saturated side at this point is then

$$\delta x_2 - 2\theta_1\gamma \ln(x_2) - 2\theta_2(\alpha - \beta) \;=\; C_4.$$

On the all ramp region side, the first integral at this point is

$$\frac{\delta x_2}{4\theta_1\theta_2} - \frac{\gamma}{2\theta_2}\ln x_2 + \frac{\beta}{2\theta_1} - \frac{\alpha}{2\theta_1}\ln(2\theta_2) \;=\; C_5,$$

or equivalently,

$$\delta x_2 - 2\theta_1\gamma \ln(x_2) - 2\theta_2(\alpha - \beta) \;=\; 4\theta_1\theta_2 C_5 + 2\theta_2\alpha \ln(2\theta_2) - 2\theta_2\alpha.$$

Hence, we have that

$$4\theta_1\theta_2 C_5 + 2\theta_2\alpha \ln(2\theta_2) - 2\theta_2\alpha \;=\; C_4,$$

and thus $C_1 = C_5$ using (5.23). Therefore, the trajectory rejoins the original curve in the all ramp region, creating a closed orbit.

Case 2: The trajectory hits the boundary of the both saturated region at the point $(x, y) = (x_3, 2\theta_2)$, where $x_3 > 2\theta_1$. The first integral on the x saturated side at this point is given by

$$(\delta - \gamma)x_3 - 2\theta_2\alpha \ln(2\theta_2) + 2\theta_2\beta \;=\; C_2,$$

or equivalently,

$$(\delta - \gamma)x_3 - 2\theta_2(\alpha - \beta) \;=\; C_2 + 2\theta_2\alpha \ln(2\theta_2) - 2\theta_2\alpha.$$

On the both saturated side, the first integral from (5.21) at $(x_3, 2\theta_2)$ is

$$(\delta - \gamma)x_3 - 2\theta_2(\alpha - \beta) \;=\; C_6.$$

Hence, we have that

$$C_2 + 2\theta_2\alpha \ln(2\theta_2) - 2\theta_2\alpha \;=\; C_6. \tag{5.24}$$

The trajectory then follows the curve

$$(\delta - \gamma)x - (\alpha - \beta)y \;=\; C_6$$

while in the both saturated region. As seen in Figure 5.3.2, the trajectory will eventually reach the boundary of the y saturated region at a point $(x, y) = (2\theta_1, y_3)$ with $y_3 > 2\theta_2$. The first integral at this point in the both saturated region is

$$2\theta_1(\delta-\gamma)-(\alpha-\beta)y_3 \;=\; C_6,$$

from which we can derive that

$$y_3 \;=\; \frac{2\theta_1(\delta-\gamma)-C_6}{\alpha-\beta}.$$

Note that we know that $\alpha-\beta$ is non-zero because if the positive equilibrium exists in the all ramp region, then $\alpha<\beta$. At $(2\theta_1, y_3)$, the first integral in the y saturated region is then

$$\begin{aligned} 2\theta_1\delta-2\theta_1\gamma\ln(2\theta_1)-(\alpha-\beta)y_3 \;&=\; C_7 \\ \implies y_3 \;&=\frac{2\theta_1\delta-2\theta_1\gamma\ln(2\theta_1)-C_7}{\alpha-\beta}. \end{aligned}$$

Equating both expressions for y_3, we find that

$$C_6 \;=\; C_7+2\theta_1\gamma\ln(2\theta_1)-2\theta_1\gamma.$$

This expression for C_6, combined with (5.22) and (5.24), gives us that

$$4\theta_1\theta_2C_1+2\theta_2\alpha\ln(2\theta_2)-2\theta_2\alpha \;=\; C_7. \tag{5.25}$$

Finally, the trajectory moves along

$$\delta x-2\theta_1\gamma\ln x-(\alpha-\beta)y \;=\; C_7$$

in the y saturated region until reaching the boundary of the all ramp region at $(x,y)=(x_4,2\theta_2)$ with $x_4<2\theta_1$. The first integral in the y saturated region at this point is

$$\delta x_4-2\theta_1\gamma\ln x_4-2\theta_2(\alpha-\beta) \;=\; C_7,$$

while on the all ramp region side, we have

$$\frac{\delta x_4}{4\theta_1\theta_2}-\frac{\gamma}{2\theta_2}\ln x_4+\frac{\beta}{2\theta_1}-\frac{\alpha}{2\theta_1}\ln(2\theta_2) \;=\; C_8.$$

A rearrangement of the latter equation gives

$$\delta x_4-2\theta_1\gamma\ln x_4-2\theta_2(\alpha-\beta) \;=\; 4\theta_1\theta_2C_8+2\theta_2\alpha\ln(2\theta_2)-2\theta_2\alpha,$$

and thus we have

$$4\theta_1\theta_2C_8+2\theta_2\alpha\ln(2\theta_2)-2\theta_2\alpha \;=\; C_7.$$

This expression for C_7, along with the one given in (5.25), tells us that $C_1=C_8$. Hence, the trajectory rejoins the initial curve in the all ramp region, and is closed.

Thus, we have shown that when ramp system (5.16) has a positive equilibrium in the all ramp region, the closed trajectories seen in the original Lotka-Volterra model are still present, and they can span multiple boxes of phase space. Several trajectories for system (5.16) are shown in Figure 5.3.3.

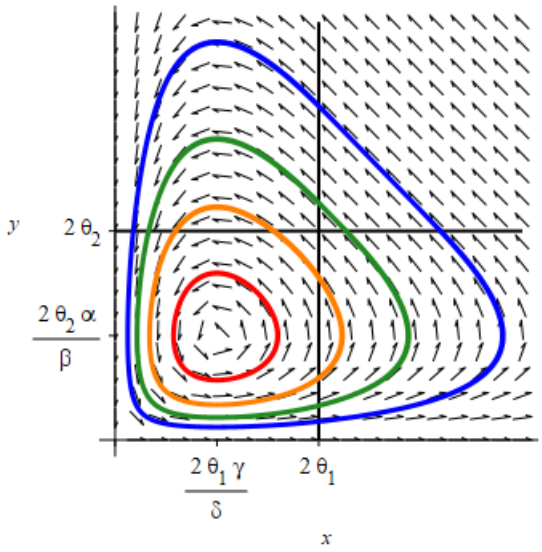


Figure 5.3.3: Trajectories of ramp system (5.16) when the positive equilibrium $(x^*, y^*) = (2\theta_1\gamma/\delta, 2\theta_2\alpha/\beta)$ falls in the all ramp region. Four closed trajectories are shown, each represented in a different colour.

5.3.2.2 Unbounded Behaviour

We will now consider the behaviour of ramp system (5.16) when it does not have a positive equilibrium in the all ramp region, with the goal of showing that unbounded flow will always result in this case. Note that from Figures 5.3.1, 5.3.2, and 5.3.3, flow on the x-axis for $x > 0$, for both the ramp and original mass action model, is unbounded; this represents the idea that when there are no predators, the prey population is free to grow without bound.

However, we have seen that when system (5.16) has a positive equilibrium in the all ramp region and both populations are initially positive, we get bounded, closed curves and not unbounded behaviour; our goal with this section is to show that when such an equilibrium does not exist in the all ramp region, unbounded flow is possible even if both variables are initially positive.

The positive equilibrium $(r_1(x^*), r_2(y^*)) = (\gamma/\delta, \alpha/\beta)$ of system (5.16) falls outside the all ramp region if and only if at least one of $\gamma \geq \delta$ or $\alpha \geq \beta$ holds. We will first consider the case in which we have $\gamma = \delta$ and $\alpha < \beta$; under these assumptions, we have $r(x^*) = 1$ and $y^* = 2\theta_2\alpha/\beta$, and thus every point (x, y^*) with $x \geq 2\theta_1$ is an equilibrium.

From (5.16), for $x > 0$ the $\dot{x}$ equation is positive when $r_2(y) < \alpha/\beta$ and negative when $r_2(y) > \alpha/\beta$. With $\gamma = \delta$, the $\dot{y}$ equation is zero when $r_1(x) = 1$ and, for positive y, is negative when $r_1(x) < 1$; thus, when $y > 0$ the $\dot{y}$ equation is zero for every $x \geq 2\theta_1$ and is negative everywhere to the left of the line $x = 2\theta_1$. The resulting flow pattern is shown in Figure 5.3.4, where we can see that trajectories starting in the interior of the first quadrant can become unbounded in the x direction.

The cases in which $\alpha = \beta$ and $\gamma < \delta$ or $\alpha = \beta$ and $\gamma = \delta$ are similar, and will produce

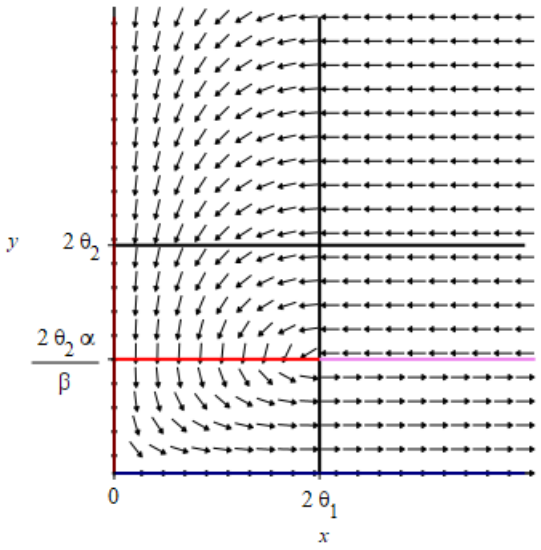


Figure 5.3.4: Vector field of ramp system (5.16) when every point $(x, 2\theta_2\alpha/\beta)$ for $x \geq 2\theta_1$ is an equilibrium; this line of equilibria is shown in light purple. The x nullclines are displayed in red while the y nullcline $y = 0$ is shown in blue. Note that while the region defined by $x \geq 2\theta_1$ is also a y nullcline, it is not coloured in here.

flow patterns similar to the one in Figure 5.3.4 displaying unbounded flow in either the x or y direction. Note that in the double equality case, every point in the both saturated region ($x \geq 2\theta_1$ and $y \geq 2\theta_2$) is an equilibrium.

Finally, we have the case in which $\gamma > \delta$ or $\alpha > \beta$. If the latter holds, then the $\dot{x}$ equation from (5.16) satisfies

$$\begin{aligned} \dot{x} &= \alpha r_1(x) - \beta r_1(x) r_2(y) \\ &> \beta r_1(x)[1 - r_2(y)] \\ &\geq 0 \end{aligned}$$

for all $x > 0$, and thus an initially positive prey population will grow without bound. If $\gamma > \delta$, then for $y > 0$ the $\dot{y}$ satisfies

$$\begin{aligned} \dot{y} &= \delta r_1(x) r_2(y) - \gamma r_2(y) \\ &< \gamma r_2(y)[r_1(x) - 1] \\ &\leq 0, \end{aligned}$$

and thus if both populations are initially positive, the predator population will decline to zero over time, after which point the prey population will grow without bound.

5.3.3 Michaelis-Menten Results

We end with an analysis of the Lotka-Volterra model containing Michaelis-Menten terms:

$$\begin{aligned} \dot{x} &= M_x(\alpha - \beta M_y) \\ \dot{y} &= M_y(\delta M_x - \gamma) \end{aligned} \tag{5.26}$$

Here, $M_x = \dfrac{x}{\theta_1 + x}$ and $M_y = \dfrac{y}{\theta_2 + y}$ for arbitrary positive constants θ_1 and θ_2. As with the mass action and ramp models, system (5.26) admits two non-negative equilibria: one at the origin, and one at $(x^*, y^*) = \left(\dfrac{\gamma\theta_1}{\delta - \gamma}, \dfrac{\alpha\theta_2}{\beta - \alpha}\right)$, which is positive if and only if $\gamma < \delta$ and $\alpha < \beta$.

System (5.26) has Jacobian

$$\begin{bmatrix} (\alpha - \beta M_y)\dfrac{dM_x}{dx} & -\beta M_x \dfrac{dM_y}{dy} \\ \delta M_y \dfrac{dM_x}{dx} & (\delta M_x - \gamma)\dfrac{dM_y}{dy} \end{bmatrix},$$

where $\dfrac{dM_x}{dx} = \dfrac{\theta_1}{(\theta_1 + x)^2}$ and $\dfrac{dM_y}{dy} = \dfrac{\theta_2}{(\theta_2 + y)^2}$. At the origin, the Jacobian becomes

$$\begin{bmatrix} \alpha/\theta_1 & 0 \\ 0 & -\gamma/\theta_2 \end{bmatrix},$$

and thus is again a saddle point. At the positive equilibrium (x^*, y^*) given above, the Jacobian is

$$J(X^*, Y^*) = \begin{bmatrix} 0 & -\dfrac{\beta\theta_2 M_{x^*}}{(\theta_2 + y)^2} \\ \dfrac{\delta\theta_1 M_{y^*}}{(\theta_1 + x)^2} & 0 \end{bmatrix}.$$

This matrix has trace 0 and determinant $\dfrac{\beta\delta\theta_1\theta_2 M_{x^*} M_{y^*}}{(\theta_1 + x)^2(\theta_2 + y)^2}$; when x^* and y^* are positive, the determinant is positive. Hence, when the second equilibrium is positive, the eigenvalues of the Jacobian are purely imaginary.

Now, we consider trajectories of system (5.26). A first integral is given by

$$\begin{aligned} \frac{dx}{dy} &= \frac{M_x(\alpha - \beta M_y)}{M_y(\delta M_x - \gamma)} \\ \implies \int \frac{\delta M_x - \gamma}{M_x} dx &= \int \frac{\alpha - \beta M_y}{M_y} dy \end{aligned}$$

$$\implies (\delta-\gamma)x-\gamma\theta_1\ln x-\alpha\theta_2\ln y+(\beta-\alpha)y \;=\; C$$

If the system has a positive equilibrium, then the coefficients $\delta-\gamma$ and $\beta-\alpha$ are positive. Letting

$$\begin{aligned}\delta-\gamma &= \delta'\\ \gamma\theta_1 &= \gamma'\\ \alpha\theta_2 &= \alpha'\\ \beta-\alpha &= \beta',\end{aligned}$$

this first integral becomes

$$\delta' x-\gamma'\ln x-\alpha'\ln y+\beta' y \;=\; C,$$

which has the same form as the first integral (5.15) of the mass action Lotka-Volterra model. Hence, when system (5.26) has a positive equilibrium, we expect to see closed curves in the first quadrant; several such trajectories are shown in Figure 5.3.5.

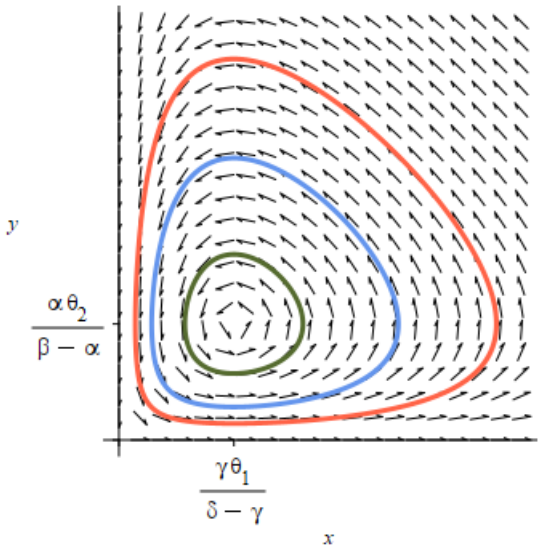


Figure 5.3.5: Trajectories of Michaelis-Menten system (5.26) when the positive equilibrium $(x^*,y^*)=\left(\dfrac{\gamma\theta_1}{\delta-\gamma},\dfrac{\alpha\theta_2}{\beta-\alpha}\right)$ exists. Three closed trajectories are shown, each represented in a different colour.

Next, we will show that when system (5.26) does not have a positive equilibrium, then, similar to what we saw with the ramp system (5.16), unbounded flow is possible even when both variables are initially positive. The Michaelis-Menten system fails to have a positive equilibrium if and only if $\gamma\geq\delta$ and/or $\alpha\geq\beta$. If $\alpha\geq\beta$, then for $x>0$ the $\dot{x}$ equation in (5.26) satisfies

$$\begin{aligned}\dot{x} &= M_x(\alpha - \beta M_y) \\ &\geq \beta M_x(1 - M_y) \\ &> 0,\end{aligned}$$

while if $\gamma \geq \delta$, the $\dot{y}$ equation satisfies

$$\begin{aligned}\dot{y} &= M_y(\delta M_x - \gamma) \\ &\leq \delta M_y(M_x - 1) \\ &< 0\end{aligned}$$

for $y > 0$. Thus, when system (5.26) does not have a positive equilibrium, initially positive trajectories will ultimately become unbounded in the x direction: $\dot{x}$ will either always be positive for $x > 0$, or y will decline toward the $x > 0$ part of the x-axis, along which flow is to the right.

Conclusions and Future Work

With this dissertation, we have built upon the foundation laid by [5, 6] regarding ramp functions and their application as approximations of Michaelis-Menten functions. The concept of a biochemical ramp system introduced in [5] was limited in scope, only covering systems derived from three main reaction types, but we expanded this class of systems in Definition 1.1.2 to include all ramp systems that are mass action in the all ramp region.

Chapters 2 and 3 analyzed classes of biochemical ramp systems not studied in [5], namely those with multiple thresholds associated with each variable and those derived from reactions not of the SRP, combining, or dissociation types. The qualitative behaviour, namely the existence and number of equilibria and global flow, was identical between these ramp systems and their Michaelis-Menten counterparts in the instances that we made a comparison, strengthening the argument presented in [5, 6] that ramp functions are good approximations to Michaelis-Menten terms.

However, there is still much work than can be done in the analysis of the classes of ramp systems studied in the second and third chapters. A couple of avenues for future study are as follows:

- There was a large focus on systems containing SRP terms; Sections 2.1-2.3 exclusively covered SRP systems with multiple thresholds, while every system covered in Chapter 3 included SRP terms in addition to their new reaction types. Thus, one might consider analyzing systems derived from a more diverse set of reaction types, with SRP terms limited or excluded altogether, such as systems with both combining and double combining terms or systems derived solely from, say, dissociation reactions and reactions of the form $mX \to Y$.

  Several questions can be investigated through the analysis of these systems: do the corresponding ramp and Michaelis-Menten systems still display qualitatively similar behaviour? If not, can we determine under what circumstances the systems diverge in their behaviour?

- In systems with a single threshold per variable, Theorem 3.1.3 established a relationship between the existence of equilibria in the all ramp region and the existence of non-negative equilibria in the corresponding Michaelis-Menten system. Is there an analogous result for systems with multiple thresholds per variable?

Other notable results from Chapter 2 were found in Sections 2.3.1.1 and 2.4.2.1, where we were able to apply our techniques for solving for equilibria in ramp systems with multiple thresholds per variable to the Adams model (3) without the SEL and the model (4) with the SEL respectively. Previous techniques developed in [5] could only apply to the case in which each variable had one associated threshold, and thus here we were able to solve for equilibria in the completely general case.

In Chapter 4, we introduced the concept of the deficiency of a chemical reaction network along with the Deficiency Zero Theorem 4.1.9 and Deficiency One Theorem 4.1.10. We

explained that since these theorems provide results on mass action systems, they can be applied to biochemical ramp systems in the all ramp region. While the application of these theorems to the Adams model didn't provide any new insight, we argued that these theorems could be invaluable to the analysis of more complex systems. In particular, the analysis of Michaelis-Menten systems with a large number of variables can be facilitated by replacing the Michaelis-Menten terms with ramp functions and then using one of the deficiency theorems, if applicable.

We also produced deficiency results for certain classes of networks, such as characterizing when the deficiency of an SRP system increases after the addition of a combining of $mX \to Y$ reaction. We also focused on weakly reversible SRP networks, with Theorem 4.3.10 characterizing the system of differential equations corresponding to a two-species weakly reversible SRP network and Proposition 4.3.11 providing a sufficient condition for such a network with n species to not be weakly reversible. There is potential for more work to be done in this area: can we characterize the mass action differential equations corresponding to a weakly reversible SRP network in n variables in general? Knowing whether a given system of differential equations can be derived from a weakly reversible SRP network is useful for analysis — we have shown that an SRP network always has a deficiency of zero, and if said network is also weakly reversible, the Deficiency Zero Theorem applies and can tell us about the number of possible equilibria and their stability.

The first two sections of Chapter 5 considered ramp functions in contexts outside biochemical ramp systems, namely as compositions with other functions and in mixed systems in which variables could also appear outside the input of a ramp function. The results presented in these sections are interesting in that they were the first time notable differences in the qualitative behaviour of ramp systems and their Michaelis-Menten counterparts were observed. While single-variable compositions and the two-variable class of mixed systems (5.10) and (5.11) still displayed qualitatively similar behaviour between the ramp and Michaelis-Menten models, the composition system from Example 5.1.4 and the mixed systems (5.7) and (5.8) had notable differences; in Example 5.1.4, the unique equilibrium point did not have the same stability in the ramp and Michaelis-Menten model, and while system (5.7) always has two positive equilibria, its Michaelis-Menten counterpart (5.8) only exhibits equilibria under certain parameter assignments.

The differences seen between these corresponding ramp and Michaelis-Menten systems raise several questions that can be pursued in future research:

- When do systems of form (5.3) and (5.4) — systems with compositions of ramp and Michaelis-Menten functions respectively — display qualitatively similar behaviour? In Example 5.1.4, the difference in stability between the ramp and Michaelis-Menten systems resulted from a difference in the magnitude of certain Jacobian entries, which was enough to flip the sign of the trace. Can we determine conditions on, say, system parameters that ensure the eigenvalues cannot switch signs between the two? Can we expand or generalize Theorem 5.1.3 to describe when the real parts of the eigenvalues of the Jacobians of the ramp and Michaelis-Menten systems have the same signs?

- Similarly, can we determine when the qualitative behaviour of a mixed system with Michaelis-Menten terms is maintained after replacing the Michaelis-Menten terms with ramp functions?

- We noted that the ramp system in Example 5.1.4 is not mass action when in the all ramp region. Similarly, system (5.7) is also not mass action when $r(x)$ is in its ramp region; this is because of the negative constant term. In contrast, the systems we studied in Chapters 2 and 3 that displayed identical behaviour between the ramp and Michaelis-Menten versions *are* mass action when in the all ramp region.

  This makes one wonder: is it important whether or not a ramp system is mass action when in the all ramp region? Is there something "special" about mass action systems that makes it more likely for a ramp system that is mass action in the all ramp region to behave qualitatively similar to its Michaelis-Menten counterpart?

We began looking at oscillations in ramp systems with the Lotka-Volterra model in Section 5.3. Notably, we were able to show that system (5.16) still exhibits closed orbits when it has a positive equilibrium in the all ramp region, and it is possible for these closed orbits to cross multiple boxes of phase space. Similar results were found for the Michaelis-Menter counterpart, system (5.26).

Our work on the Lotka-Volterra model only scratches the surface of what we could learn about closed orbits in ramp systems. Future work could follow multiple paths:

- Is it possible for a ramp system to have closed orbits, but the corresponding Michaelis-Menten system does not? Or vice versa?

- We saw that when the positive equilibrium for system (5.16) fell in a saturated region or didn't exist, initially positive trajectories could become unbounded over time. Will this always be the case? That is, if a ramp system has an equilibrium in the all ramp region that is enclosed within a closed orbit, will moving the equilibrium (via a reassignment of parameter values) to a saturated region or outside the range of the ramp functions completely always result in unbounded behaviour?

- System (5.16) only contains two variables, and one threshold per variable. Are closed orbits possible in three-variable biochemical ramp systems? If so, can they span multiple regions of phase space like the Lotka-Volterra ramp system?

  How would introducing multiple thresholds per variable affect the ability of a system to produce closed orbits? Would it be possible to have a closed orbit that does not pass through the all ramp region?

Finally, throughout this work we tackled several linear algebra problems, some of which are not fully resolved:

- In Section 1.2.2, we proved several special cases of a conjecture proposed in [5] claiming that matrices with one combining term cannot have eigenvalues with positive real

parts. A proof of the general case has still not been found, and appears to be quite the undertaking. Further work on this conjecture could prove to be an interesting problem, and a full proof would aid stability analysis in systems with one combining term.

- Similarly, Section 3.1.3 provided several conditions for a matrix with one double combining term to have eigenvalues with non-positive real parts. Can we develop a theorem generalizing when such a matrix has only eigenvalues with non-positive real parts? Or can we determine the conditions under which such a matrix will have an eigenvalue with positive real part?

- Section 1.2.3 presented a conjecture from [5] stating that if an invertible dissociation matrix has an eigenvalue with positive real part, then its inverse cannot have negative entries. We showed that while the conjecture is true for 3×3 matrices, it is not true for larger matrices in general. When does the conjecture hold for matrices of size 4×4 or higher, though? What structure does the matrix need to have in order for the conclusion of the conjecture to hold?

In summary, here we have expanded on the ideas from [5, 6] regarding the use of piecewise linear ramp approximations to Michaelis-Menten terms. We broadened the definition of a biochemical ramp system to cover a wider variety of systems, and developed new theory by considering topics such as ramp systems with multiple thresholds per variable, systems with additional reaction types, compositions of ramp functions, mixed systems, and oscillations that were not covered previously. Our work has further suggested that biochemical ramp systems behave qualitatively identical to their Michaelis-Menten counterparts, and they also have the advantage of satisfying the Deficiency Zero and Deficiency One Theorems when in the all ramp region. The results in the final chapter, however, suggest that differences in behaviour can manifest in systems that do not satisfy the definition of a biochemical ramp system.

Overall, there is still much theory to develop regarding ramp systems. Future work on ramp systems can focus on areas such as the existence of closed orbits in systems not of the Lotka-Volterra form and determining when the eigenvalues of the Jacobian have non-positive real parts, all while continuing to compare the qualitative behaviour of the system to the corresponding system with Michaelis-Menten terms.

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