Ramp Function Approximations of Michaelis-Menten Functions in Biochemical Dynamical Systems

by

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Abstract

In 2019, Adams, Ehlting, and Edwards developed a four-variable system of ordinary differential equations modelling phenylalanine metabolism in plants according to Michaelis-Menten kinetics. Analysis of the model suggested that when a series of reactions known as the *Shikimate Ester Loop* (SEL) is included, phenylalanine flux into primary metabolic pathways is prioritized over flux into secondary metabolic pathways when the availability of shikimate, a phenylalanine precursor, is low. Adams *et al.* called this mechanism of metabolic regulation the *Precursor Shutoff Valve* (PSV). Here, we attempt to simplify Adams and colleagues' model by reducing the system to three variables and replacing the Michaelis-Menten terms with piecewise-defined approximations we call *ramp functions*. We examine equilibria and stability in this simplified model, and show that PSV-type regulation is still present in the version with the SEL. Then, we define a class of systems structurally similar to the simplified Adams model called *biochemical ramp systems*. We study the properties of the Jacobian matrices of these systems and then explore equilibria and stability in systems of $n \geq 2$ variables. Finally, we make several suggestions regarding future work on biochemical ramp systems.

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Dedicated to my parents and sister

Introduction

Many chemical reactions in biological systems are mediated by macromolecules called *enzymes*. Usually proteins, enzymes function as *catalysts*, substances which increase the rate at which reactions proceed, but are not used up by the reactions [13, ch. 8].

During an enzyme-mediated reaction, the reactant(s) (known as *substrate(s)*) are bound to a region of the enzyme called the *active site* [13, ch. 8]. The binding of the substrate(s) and enzyme forms an *enzyme substrate complex* and facilitates conversion of the substrate(s) into product(s), which are then released from the active site of the enzyme [13, ch. 8].

In the absence of enzymes, many metabolic reactions would proceed at very slow rates, obstructing metabolic pathways [13, ch. 8]. Enzymes are thus critical to keeping metabolic processes in living organisms running smoothly.

Michaelis-Menten kinetics has played an important role in the modelling of enzyme-mediated reactions for more than a century. In the early 1900s, Leonor Michaelis and Maud Menten, refining the efforts of Victor Henri, studied the initial rate at which a substrate is converted into products with the aid of an enzyme catalyst; specifically, they studied the invertase-catalyzed reaction in which sucrose is converted into fructose and glucose [3, 8]. Their results, published in 1913, showed that the initial rate ν of an enzyme-mediated reaction can be represented by a time-independent equation equivalent to

$$\nu = \frac{V_{max}[S]}{K_m + [S]}, \tag{1}$$

where $[S]$ denotes the substrate concentration and V_{max} and K_m are positive parameters that can be determined experimentally [5, 10, 15].

Graphing ν as a function of $[S]$ produces an initial-rate curve with a couple of key features related to the parameters. The value V_{max} represents a saturation point, the maximum value of ν, achieved when an unlimited amount of substrate is available, while K_m (the *Michaelis constant*) represents the substrate concentration at which half of this maximum value is reached [5]. Indeed, it is easy to see that the curve is increasing with

$$\lim_{[S]\to\infty} \frac{V_{max}[S]}{K_m + [S]} = V_{max}$$

and $\nu = V_{max}/2$ at $[S] = K_m$. These features can be seen on the graph of ν in Figure 1 on the next page.

Derivation of equation (1) relies on several assumptions. First, the concentrations of species present during the reaction are subject to conservation conditions. For instance, it is assumed that a state of equilibrium exists as the substrate binds to the enzyme, forming the enzyme-substrate complex; that is, the concentration of the enzyme-substrate complex is assumed to be constant [8, 14]. As mentioned earlier, catalysts increase reaction rates without being consumed by the reactions; thus, the amount of enzyme present, equal to the amount bound to substrate added to the amount left unbound, must also remain constant

[15]. Finally, the unbound substrate, enzyme-substrate complex, and product concentrations must always collectively equal the initial concentration of substrate [15].

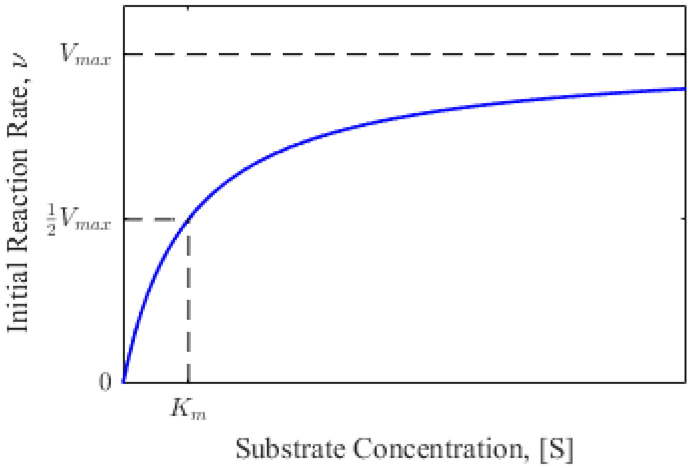


Figure 1: Graph of the Michaelis-Menten initial rate curve $\nu = \dfrac{V_{max}[S]}{K_m + [S]}$. Notice that the point $(K_m, V_{max}/2)$ falls on the curve, and that $\nu \to V_{max}$ as $[S] \to \infty$.

The steps of the derivation also assume that reaction rates and reactant concentrations are proportional to each other; this is the *law of mass action*, which was documented by Guldberg and Waage in the 1860s [15, 17]. Many fields of biology, chemistry, and biochemistry have been influenced by this law. For instance, mathematical models in ecology and epidemiology, such as the famous *Lotka-Volterra* and *SIR* models, use the mass action law to describe population growth and decay rates [17].

These fields have also seen influence, both theoretical and practical, from Michaelis and Menten's work. Equation (1) is vital to the study of topics including enzymology, properties of molecules, and fast chemical reactions, and has use in applications such as enzyme engineering and drug development [3].

A specific application of equation (1) — and the motivating example for this thesis — can be found in [1], a paper in which Adams, Ehlting, and Edwards modelled phenylalanine metabolism in plants. The model (hereafter referred to as the *Adams model*) was structured as a system of four differential equations derived from reactions that follow Michaelis-Menten kinetics. Analysis was performed on two versions of the model: one that included a sequence of enzyme-mediated reactions known as the *Shikimate Ester Loop* (SEL), and one that did not include the SEL.

After studying equilibria in their model, Adams and colleagues' analysis focused on flux into metabolic pathways, with the goal of understanding the function of the SEL. In particular, they examined equilibrium fluxes of the amino acid phenylalanine into *primary* and *secondary metabolic pathways* when the concentration of shikimate, a precursor to phenylalanine, is low. Primary pathways describe metabolic processes required for survival of the plant, whereas metabolic processes that are not essential to life are categorized as secondary pathways [1]. The results of the analysis suggested that in the version of the model with the SEL, phenylalanine is directed toward primary metabolism preferentially over secondary metabolism when shikimate availability is poor, a mechanism of metabolic regulation Adams *et al.* called the *Precursor Shutoff Valve* (PSV). The version of the model without the SEL, which served as an experimental control, only showed evidence of this PSV type regulation when it was much more difficult for phenylalanine to enter the secondary pathway than the primary pathway.

Since the right hand side of equation (1) is nonlinear, analyzing Michaelis-Menten systems such as the Adams model can be difficult. Thus, it is worth considering whether the Adams model can be simplified to a more manageable form. An idea as to how to accomplish this is to replace the nonlinear terms of the model with linear approximations. This approach is not original; piecewise linear approximations in particular have been used for decades to simplify models in mathematical biology. Gene regulation networks, for example, are often modelled as hard switching networks (most notably as *Glass networks*) that use Heaviside step functions [6, 11].

Here, in the first chapter we simplify the Adams model by replacing the Michaelis-Menten functions with piecewise linear *ramp functions*, with a variable reduction as well, and perform analysis similar to that of Adams and colleagues in [1]. Then, we define a class of systems in the second chapter called *biochemical ramp systems*, and explore equilibria and stability in these systems in the following chapters. We end with our conclusions and several suggestions for further study on biochemical ramp systems.

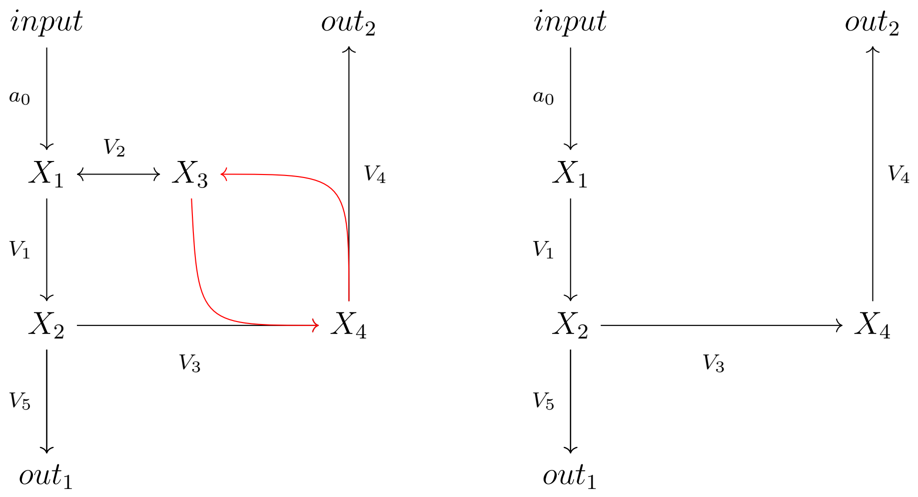
Chapter 1

Analyzing the Adams Model with Ramp Functions

1.1 The Original Model

We begin by describing the model of phenylalanine metabolism in plants developed by Adams *et al*. This description will not be exhaustive; see [1] for a more detailed explanation of the biology underlying the model.

As mentioned in the introduction, Adams and colleagues considered two versions of their model, one with the SEL and one without the SEL. Figure 2 below shows diagram representations of both versions as presented in [1].



(a) Model with the SEL (b) Model without the SEL

Figure 2: Representations of Adams and colleagues' model of phenylalanine metabolism in plants with and without the Shikimate Ester Loop (SEL). The SEL is represented by the red arrows in (a).

As seen in Figure 2, the system receives a constant input a_0; this represents the rate at which shikimate is synthesized by the plant. The V_i are fluxes assumed to follow Michaelis-Menten kinetics, while the X_i represent the concentrations of plastidial shikimate (X_1), phenylalanine (X_2), cytosolic shikimate (X_3), and caffeoyl-shikimate (X_4). Finally, the system outputs out_1 and out_2 represent primary and secondary metabolic pathways respectively; in particular, out_1 represents protein synthesis from phenylalanine, while out_2 represents the monolignol pathway, in which phenylalanine is used in the synthesis of lignin precursors.

The version of the model with the SEL can be described by the system of ordinary differential equations

$$\begin{aligned}\dot{X}_1 &= a_0 - V_1 - V_2\\ \dot{X}_2 &= V_1 - V_3 - V_5\\ \dot{X}_3 &= V_2 - V_3 + V_4\\ \dot{X}_4 &= V_3 - V_4,\end{aligned}$$

while in the no SEL case, we simply have

$$\begin{aligned}\dot{X}_1 &= a_0 - V_1\\ \dot{X}_2 &= V_1 - V_3 - V_5\\ \dot{X}_4 &= V_3 - V_4\end{aligned}$$

as the system shown in Figure 2(b) does not depend on X_3. Here, $\dot{X}_i$ denotes the derivative of X_i with respect to time. From [1], assuming Michaelis-Menten kinetics for the V_i, these equations can be written in full as

$$\begin{aligned}\dot{X}_1 &= a_0 - \frac{a_1X_1}{K_1(1+bX_2)+X_1} - \frac{a_2^+X_1}{K_2^+ + X_1} + \frac{a_2^-X_3}{K_2^- + X_3}\\ \dot{X}_2 &= \frac{a_1X_1}{K_1(1+bX_2)+X_1} - \frac{a_3X_2X_3}{(K_3^2+X_2)(K_3^3+X_3)} - \frac{a_5X_2}{K_5+X_2}\\ \dot{X}_3 &= \frac{a_2^+X_1}{K_2^+ + X_1} - \frac{a_2^-X_3}{K_2^- + X_3} - \frac{a_3X_2X_3}{(K_3^2+X_2)(K_3^3+X_3)} + \frac{a_4X_4}{K_4+X_4}\\ \dot{X}_4 &= \frac{a_3X_2X_3}{(K_3^2+X_2)(K_3^3+X_3)} - \frac{a_4X_4}{K_4+X_4}\end{aligned} \tag{1.1}$$

in the case in which the SEL is present, and as

$$\begin{aligned}
\dot{X}_1 &= a_0 - \frac{a_1 X_1}{K_1(1+bX_2)+X_1} \\
\dot{X}_2 &= \frac{a_1 X_1}{K_1(1+bX_2)+X_1} - \frac{a_3 X_2}{K_3^2+X_2} - \frac{a_5 X_2}{K_5+X_2} \\
\dot{X}_4 &= \frac{a_3 X_2}{K_3^2+X_2} - \frac{a_4 X_4}{K_4+X_4}
\end{aligned} \tag{1.2}$$

in the no SEL case. The input term a_0 is assumed to be non-negative, whereas the remaining a_i and all K_i are strictly positive. In the parameters K_3^2 and K_3^3, the superscripts are **not** exponents; they are simply indices.

Note the parameter b, which models how phenylalanine inhibits it own production, in the $\dot{X}_1$ and $\dot{X}_2$ equations. In [1], most of the Adams model analysis was done assuming $b = 0$; consequently, this will be the only case we consider here. With $b = 0$, the equations contain terms resembling the right hand side of the Michaelis-Menten equation (1), with the a_i for $i > 0$ taking the role of V_{max} and the K_i as the Michaelis constants.

1.2 Variable Reduction and Ramp Functions

Now, we shift our focus to simplifying systems (1.1) and (1.2) with the goal of facilitating analysis. The first thing we will do is reduce the Adams model with the SEL from four variables to three. We accomplish this by combining X_1 and X_3 into one variable, which we will call Y. The reduced version of the model is diagrammed in Figure 3.

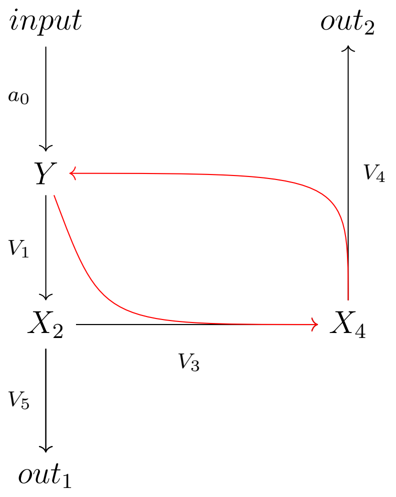


Figure 3: Representation of the model with the SEL from Figure 2(a) with X_1 and X_3 combined into a new variable, Y.

The corresponding differential equations for the three-variable SEL system are

$$\begin{aligned}\dot{Y} &= a_0 - V_1 - V_3 + V_4\\ \dot{X}_2 &= V_1 - V_3 - V_5\\ \dot{X}_4 &= V_3 - V_4,\end{aligned}$$

or in full with $b = 0$,

$$\begin{aligned}\dot{Y} &= a_0 - \frac{a_1 Y}{K_1 + Y} - \frac{a_3 X_2 Y}{(K_3^2 + X_2)(K_3^3 + Y)} + \frac{a_4 X_4}{K_4 + X_4}\\ \dot{X}_2 &= \frac{a_1 Y}{K_1 + Y} - \frac{a_3 X_2 Y}{(K_3^2 + X_2)(K_3^3 + Y)} - \frac{a_5 X_2}{K_5 + X_2}\\ \dot{X}_4 &= \frac{a_3 X_2 Y}{(K_3^2 + X_2)(K_3^3 + Y)} - \frac{a_4 X_4}{K_4 + X_4}.\end{aligned} \tag{1.3}$$

We will not perform a variable reduction on the system without the SEL as it already depends on just three variables. However, we will note that assuming $b = 0$, (1.2) can be written as

$$\begin{aligned}\dot{X}_1 &= a_0 - \frac{a_1 X_1}{K_1 + X_1}\\ \dot{X}_2 &= \frac{a_1 X_1}{K_1 + X_1} - \frac{a_3 X_2}{K_3^2 + X_2} - \frac{a_5 X_2}{K_5 + X_2}\\ \dot{X}_4 &= \frac{a_3 X_2}{K_3^2 + X_2} - \frac{a_4 X_4}{K_4 + X_4}.\end{aligned} \tag{1.4}$$

The second step in our simplification will be to replace Michaelis-Menten terms with piecewise linear approximations. For consistency, every term we replace in (1.3) and (1.4) will have $V_{max} = 1$; this means, for example, that instead of replacing the entire $\frac{a_4 X_4}{K_4 + X_4}$ term in $\dot{X}_4$, only the $\frac{X_4}{K_4 + X_4}$ part will be approximated. As a result, each term being replaced will have the form of a Michaelis-Menten function $M : [0, \infty) \to [0, 1)$ defined by

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

where θ denotes the Michaelis constant.

Below, we define a piecewise linear approximation for M, which we call a *ramp function*. It should be noted that other definitions of ramp functions exist in other contexts; see for example [2] and [4], where ramp functions are defined in three pieces.

Definition 1. [*Ramp Function*] Suppose $\theta > 0$. Then, the ramp function $r : [0, \infty) \to [0, 1]$ with threshold 2θ is defined by

$$r(X) = \begin{cases} \dfrac{X}{2\theta}, & 0 \le X < 2\theta \\ 1, & X \ge 2\theta. \end{cases}$$

As shown by the graph in Figure 4, this approximation maintains the key characteristics of M, namely that θ is mapped to $1/2$ and the limit of the function as X goes to infinity is 1. The point $(\theta, 1/2)$ falls in the linear piece of r, which we will refer to as the *ramp region* of the function. When $r(X) = 1$, meanwhile, we will say that r is in its *saturated region*. The parameter 2θ, as mentioned above, is a *threshold* value; it is the point at which r switches from being in the ramp region to being in the saturated region.

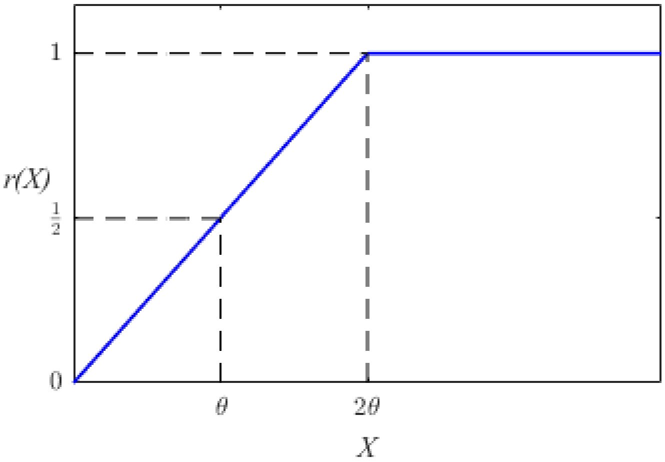


Figure 4: Graph of the ramp function r as defined in Definition 1. Like the Michaelis-Menten function M, $r(\theta) = 1/2$ and $\lim_{X\to\infty} r(X) = 1$.

Using Definition 1, we define the following five ramp functions to approximate the Michaelis-Menten functions seen in (1.3) and (1.4) (note that the function r_1 will be used for both Y and X_1):

$$r_1(Y) = \begin{cases} \dfrac{Y}{2K_1}, & 0 \le Y < 2K_1 \\ 1, & Y \ge 2K_1 \end{cases} \qquad r_3^2(X_2) = \begin{cases} \dfrac{X_2}{2K_3^2}, & 0 \le X_2 < 2K_3^2 \\ 1, & X_2 \ge 2K_3^2 \end{cases}$$

$$r_3^3(Y) = \begin{cases} \dfrac{Y}{2K_3^3}, & 0 \le Y < 2K_3^3 \\ 1, & Y \ge 2K_3^3 \end{cases} \qquad r_5(X_2) = \begin{cases} \dfrac{X_2}{2K_5}, & 0 \le X_2 < 2K_5 \\ 1, & X_2 \ge 2K_5 \end{cases} \tag{1.5}$$

$$r_4(X_4) = \begin{cases} \dfrac{X_4}{2K_4}, & 0 \le X_4 < 2K_4 \\ 1, & X_4 \ge 2K_4 \end{cases}$$

As with K_3^2 and K_3^3, the superscripts in r_3^2 and r_3^3 are indices. With the above ramp functions, the three-variable system with the SEL from (1.3) becomes

$$\begin{aligned}
\dot{Y} &= a_0 - a_1 r_1(Y) - a_3 r_3^2(X_2) r_3^3(Y) + a_4 r_4(X_4) \\
\dot{X}_2 &= a_1 r_1(Y) - a_3 r_3^2(X_2) r_3^3(Y) - a_5 r_5(X_2) \\
\dot{X}_4 &= a_3 r_3^2(X_2) r_3^3(Y) - a_4 r_4(X_4),
\end{aligned} \tag{1.6}$$

while we have

$$\begin{aligned}
\dot{X}_1 &= a_0 - a_1 r_1(X_1) \\
\dot{X}_2 &= a_1 r_1(X_1) - a_3 r_3^2(X_2) - a_5 r_5(X_2) \\
\dot{X}_4 &= a_3 r_3^2(X_2) - a_4 r_4(X_4)
\end{aligned} \tag{1.7}$$

as the approximation for system (1.4) without the SEL.

The rest of this chapter will be spent analyzing (1.6) and (1.7) in a way similar to that of Adams *et al.* in [1]. Our focus in the next two main sections will be on existence and stability of equilibria; under certain parameter conditions, both versions of the Adams model in [1] exhibited a unique, positive equilibrium that was asymptotically stable. Then, we will examine equilibrium flow into primary and secondary metabolic pathways in the system with and without the SEL by producing graphs of the equilibrium fluxes V_4^* and V_5^*.

1.3 Three-Variable Ramp System — With the SEL

Much of this section will be devoted to solving for possible equilibrium points in (1.6) and determining necessary and sufficient conditions on parameters required for existence of these equilibria. There are two main cases we will consider, $K_5 = K_3^2$ and $K_5 < K_3^2$; the case $K_3^2 < K_5$ will be excluded since it was not considered by Adams and colleagues.

These two cases will be relevant when we study flux into metabolic pathways later in this chapter. As described in [1], the parameters K_5 and K_3^2 are the *threshold constants* of the primary and secondary metabolic pathways respectively, representing how "difficult" it is for mass to move into the corresponding pathway.

Each case will contain several subcases regarding whether each ramp function in (1.5) is in its ramp or saturated region. To simplify the labelling of these subcases, we introduce the following terminology:

Definition 2. [α, β, γ *Regions*] Suppose r_i and r_j are distinct ramp functions of X_ℓ with thresholds $2\theta_i$ and $2\theta_j$ respectively. Without loss of generality (WLOG), suppose $2\theta_i < 2\theta_j$. Then, we say that X_ℓ is in its

α *region* if $X_\ell < 2\theta_i < 2\theta_j$,

β *region* if $2\theta_i \leq X_\ell < 2\theta_j$, and

γ *region* if $2\theta_i < 2\theta_j \leq X_\ell$.

If, instead, only one ramp function r_i with threshold $2\theta_i$ is a function of X_ℓ, then X_ℓ will be in its α *region* if $X_\ell < 2\theta_i$ and its γ *region* if $2\theta_i \leq X_\ell$; no β region exists in this case.

In other words, when a variable is associated with two ramp functions (e.g. X_2 with r_5 and r_3^2 when $K_5 < K_3^2$), it will be in its α region when both ramp functions are in the ramp region, β region when the function with the smaller threshold is in the saturated region and the other function is still in the ramp region, and its γ region when both ramp functions are saturated. When a variable is associated with just one ramp function (e.g. X_4 with r_4), being in the α or γ region is equivalent to the ramp function being in its ramp or saturated region respectively.

Throughout all cases and subcases, we will hold several assumptions on parameters. As done in [1], we will assume that $a_3 \leq a_4$. We will also assume an upper bound on a_0 attained from Y^*, the equilibrium value of Y. Setting all three differential equations in (1.6) to zero, we have that

$$\begin{aligned} \dot{Y} + \dot{X}_4 \;=\; 0 \;\Longrightarrow\; a_0 - a_1 r_1(Y^*) \;&=\; 0 \\ \Longrightarrow\; r_1(Y^*) \;&=\; \frac{a_0}{a_1}, \end{aligned}$$

which, since the range of r_1 is $[0,1]$, is valid if and only if $a_0 \leq a_1$.

A tighter bound on a_0, along with an explicit formula for Y^*, is possible depending on which of the thresholds associated with Y ($2K_1$ and $2K_3^3$) is smaller, and which of the Definition 2 regions Y is in. To reduce the number of subcases to consider, here we will assume that Y is in its α region. Hence, we have $Y^* < \min\{2K_1, 2K_3^3\}$ and $r_1(Y^*) = Y^*/(2K_1) < 1$, giving us

$$\frac{Y^*}{2K_1} \;=\; \frac{a_0}{a_1} \;\Longrightarrow\; Y^* \;=\; \frac{2a_0K_1}{a_1}$$

as the explicit equilibrium solution for Y, with $a_0 < a_1$ if $2K_1 \leq 2K_3^3$ or $a_0 < a_1K_3^3/K_1 < a_1$ if $2K_3^3 < 2K_1$. Note that we will briefly consider the case with Y in its γ region in section 1.3.3.

Assumptions on parameters (including non-negativity) and Y^* can be summarized as follows:

$$\begin{aligned} Y^* \;=\; \frac{2a_0K_1}{a_1}, \quad Y^* \;&<\; \min\{2K_1, 2K_3^3\} \\ a_3 \;&\leq\; a_4 \\ a_0 \;&<\; \begin{cases} a_1, & \text{if } 2K_1 \leq 2K_3^3 \\ \dfrac{a_1K_3^3}{K_1}, & \text{if } 2K_3^3 < 2K_1 \end{cases} \\ a_0 \;\geq\; 0, \quad a_i \;>0\;\forall\, i \neq 0, \quad K_i \;&>\; 0\;\forall\, i \end{aligned} \tag{1.8}$$

We are now ready to begin examining equilibria in (1.6).

1.3.1 Equilibria

Subcases regarding which of the Definition 2 regions each variable falls in will be listed in the order (Y, X_2, X_4), e.g (α,γ,α) means Y is in its α region, X_2 is in its γ region, and X_4 is in its α region.

In the $K_5 = K_3^2$ case, the functions r_5 and r_3^2 from (1.5) are identical. As a result, the variable X_2, like X_4, only has an α and a γ region. With the assumption that Y^* is in its α region from (1.8), the $K_5 = K_3^2$ case thus has four subcases: (α,α,α), (α,α,γ), (α,γ,α), and (α,γ,γ). The $K_5 < K_3^2$ case gives X_2 a β region and hence has six subcases, namely the four listed above along with (α,β,α) and (α,β,γ).

Here, we will cover the four subcases common to both cases together. Then, we will consider the two subcases exclusive to the $K_5 < K_3^2$ case.

Equilibria in System (1.6):

Subcase 1 (α,α,α) $\quad [Y < \min\{2K_1, 2K_3^3\},\quad X_2 < 2K_5 \le 2K_3^2,\quad X_4 < 2K_4]$

With every variable in its α region, all ramp functions are in their ramp regions. Thus, the equations in (1.6) take the form

$$\begin{aligned}\dot{Y} &= a_0 - a_1\frac{Y}{2K_1} - a_3\frac{X_2Y}{4K_3^2K_3^3} + a_4\frac{X_4}{2K_4}\\ \dot{X}_2 &= a_1\frac{Y}{2K_1} - a_3\frac{X_2Y}{4K_3^2K_3^3} - a_5\frac{X_2}{2K_5}\\ \dot{X}_4 &= a_3\frac{X_2Y}{4K_3^2K_3^3} - a_4\frac{X_4}{2K_4}.\end{aligned}$$

Using our assumed Y^* value from (1.8), solving $\dot{X}_2 = 0$ and $\dot{X}_4 = 0$ gives

$$X_2^* = \frac{2a_0a_1K_3^2K_3^3K_5}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3} \text{ and } X_4^* = \frac{2a_0^2a_3K_1K_4K_5}{a_4(a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3)}.$$

Since $X_2 < 2K_5$ and $X_4 < 2K_4$, these equilibrium values are possible if and only if $\dfrac{a_0a_1K_3^2K_3^3}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3} < 1$ and $\dfrac{a_0^2a_3K_1K_5}{a_4(a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3)} < 1$. Note that by (1.8), we have

$$\frac{a_0^2a_3K_1K_5}{a_4} \le a_0^2K_1K_5 < \begin{cases} a_0a_1K_1K_3^2 \le a_0a_1K_3^2K_3^3, & \text{if } 2K_1 \le 2K_3^3\\ \dfrac{a_0a_1K_3^3K_1K_3^2}{K_1} = a_0a_1K_3^2K_3^3, & \text{if } 2K_3^3 < 2K_1,\end{cases}$$

and thus $\dfrac{a_0^2 a_3 K_1 K_5}{a_4(a_0 a_3 K_1 K_5 + a_1 a_5 K_3^2 K_3^3)} < \dfrac{a_0 a_1 K_3^2 K_3^3}{a_0 a_3 K_1 K_5 + a_1 a_5 K_3^2 K_3^3}$ always holds. Hence, we only need to worry about the inequality $\dfrac{a_0 a_1 K_3^2 K_3^3}{a_0 a_3 K_1 K_5 + a_1 a_5 K_3^2 K_3^3} < 1$ when it comes to the existence of equilibria.

When $K_5 = K_3^2$, the equilibrium values and parameter condition can be expressed as $X_2^* = \dfrac{2a_0 a_1 K_3^3 K_5}{a_0 a_3 K_1 + a_1 a_5 K_3^3}$, $X_4^* = \dfrac{2a_0^2 a_3 K_1 K_4}{a_4(a_0 a_3 K_1 + a_1 a_5 K_3^3)}$, and $\dfrac{a_0 a_1 K_3^3}{a_0 a_3 K_1 + a_1 a_5 K_3^3} < 1$.

Subcase 2 (α, α, γ) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad X_2 < 2K_5 \le 2K_3^2, \quad 2K_4 \le X_4]$

We have $r_4(X_4) = 1$ in this subcase, and thus $\dot{X}_4 = a_3 \dfrac{X_2 Y}{4K_3^2 K_3^3} - a_4$. Setting this equation equal to zero, we get $X_2^* = \dfrac{2a_1 a_4 K_3^2 K_3^3}{a_0 a_3 K_1}$ if $a_0 \ne 0$. As X_2 is still in its α region, it must be the case that $\dfrac{a_1 a_4 K_3^3}{a_0 a_3 K_1} < K_5/K_3^2 \le 1$. However, by (1.8) we have

$$\frac{a_1 a_4 K_3^3}{a_0 a_3 K_1} \ge \frac{a_1 K_3^3}{a_0 K_1} > \begin{cases} \dfrac{a_0 K_3^3}{a_0 K_1} = \dfrac{K_3^3}{K_1} \ge 1, & \text{if } 2K_1 \le 2K_3^3 \\ \dfrac{a_0}{a_0} = 1, & \text{if } 2K_3^3 < 2K_1. \end{cases}$$

In the special case $a_0 = 0$, we have $Y^* = 0$ and thus $\dot{X}_4 = 0$ if and only if $a_4 = 0$. However, $a_4 > 0$ by assumption. Hence, we must conclude that equilibria are not possible in this subcase.

Subcase 3 (α, γ, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \le 2K_3^2 \le X_2, \quad X_4 < 2K_4]$

Here, the system becomes

$$\begin{aligned} \dot{Y} &= a_0 - a_1 \frac{Y}{2K_1} - a_3 \frac{Y}{2K_3^3} + a_4 \frac{X_4}{2K_4} \\ \dot{X}_2 &= a_1 \frac{Y}{2K_1} - a_3 \frac{Y}{2K_3^3} - a_5 \\ \dot{X}_4 &= a_3 \frac{Y}{2K_3^3} - a_4 \frac{X_4}{2K_4} \end{aligned}$$

as $r_5(X_2) = r_3^2(X_2) = 1$. Solving $\dot{X}_4 = 0$, we get $X_4^* = \dfrac{2a_0 a_3 K_1 K_4}{a_1 a_4 K_3^3}$, which falls in the α region if and only if $\dfrac{a_0 a_3 K_1}{a_1 a_4 K_3^3} < 1$. This inequality is always true assuming (1.8); it obviously holds when $a_0 = 0$, and we showed that $\dfrac{a_1 a_4 K_3^3}{a_0 a_3 K_1} > 1$ when $a_0 \neq 0$ in the previous subcase.

Meanwhile, $\dot{X}_2 = 0$ if and only if $a_0(a_1 K_3^3 - a_3 K_1) = a_1 a_5 K_3^3$, which only makes sense if $a_0 \neq 0$ and $a_1 K_3^3 > a_3 K_1$ since the right hand side is positive. Thus, this condition can also be expressed as $a_0 = \dfrac{a_1 a_5 K_3^3}{a_1 K_3^3 - a_3 K_1}$ with $a_1 K_3^3 > a_3 K_1$.

Finally, with X_2 above both of its thresholds and the differential equations no longer depending on X_2, we can choose any $X_2^* \geq 2K_3^2 \geq 2K_5$ at equilibrium. Hence, an infinite number of equilibria are possible in this subcase.

Subcase 4 (α, γ, γ) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \leq 2K_3^2 \leq X_2, \quad 2K_4 \leq X_4]$

With both r_4 and r_3^2 saturated, the $\dot{X}_4$ equation is simply $\dot{X}_4 = a_3 \dfrac{Y}{2K_3^3} - a_4$. If $a_0 \neq 0$, this equation equals zero if and only if $\dfrac{a_1 a_4 K_3^3}{a_0 a_3 K_1} = 1$; however, we know this expression is greater than 1. When $a_0 = 0$, we again get that $\dot{X}_4 = 0$ if and only if $a_4 = 0$, which is impossible. Thus, equilibria are not possible in this subcase.

Subcases exclusive to the $\mathbf{K_5 < K_3^2}$ Case:

Subcase 5 (α, β, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \leq X_2 < 2K_3^2, \quad X_4 < 2K_4]$

With X_2 in its β region, the function r_5 will be saturated, but r_3^2 will still be in its ramp region. Thus, our equations are

$$\begin{aligned}
\dot{Y} &= a_0 - a_1 \frac{Y}{2K_1} - a_3 \frac{X_2 Y}{4K_3^2 K_3^3} + a_4 \frac{X_4}{2K_4} \\
\dot{X}_2 &= a_1 \frac{Y}{2K_1} - a_3 \frac{X_2 Y}{4K_3^2 K_3^3} - a_5 \\
\dot{X}_4 &= a_3 \frac{X_2 Y}{4K_3^2 K_3^3} - a_4 \frac{X_4}{2K_4}.
\end{aligned}$$

We get the equilibrium values

$$X_2^* = \frac{2(a_0 - a_5) a_1 K_3^2 K_3^3}{a_0 a_3 K_1} \text{ and } X_4^* = \frac{2(a_0 - a_5) K_4}{a_4}$$

from $\dot{X}_2 = 0$ and $\dot{X}_4 = 0$, assuming $a_0 \neq 0$. No equilibria are possible if $a_0 = 0$; the $\dot{X}_2$ equation becomes $-a_5$, which cannot equal zero as we have assumed that a_5 is positive.

The X_2^* and X_4^* values exist in the given regions if and only if $\frac{K_5}{K_3^2} \leq \frac{(a_0 - a_5)a_1K_3^3}{a_0a_3K_1} < 1$ and $\frac{a_0 - a_5}{a_4} < 1$. Note that the first inequality implies the second; by the assumption $a_3 \leq a_4$ from (1.8), the inequality $\frac{a_1K_3^3}{a_0K_1} > 1$ established in the (α, α, γ) subcase, and the fact that the lower bound K_5/K_3^2 implies that $a_0 - a_5$ is positive, we have that $\frac{a_0 - a_5}{a_4} < \frac{(a_0 - a_5)a_1K_3^3}{a_0a_3K_1}$ holds. Thus, $\frac{K_5}{K_3^2} \leq \frac{(a_0 - a_5)a_1K_3^3}{a_0a_3K_1} < 1$ is the relevant inequality here.

Subcase 6 (α, β, γ) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \leq X_2 < 2K_3^2, \quad 2K_4 \leq X_4]$

We have $\dot{X}_4 = a_3\frac{X_2Y}{4K_3^2K_3^3} - a_4$, which is the same as what we had in the (α, α, γ) subcase. Like that subcase, equilibria are not possible here; solving $\dot{X}_4 = 0$ gives $X_2^* = \frac{2a_1a_4K_3^2K_3^3}{a_0a_3K_1}$ with the impossible equilibria conditions $\frac{a_1a_4K_3^3}{a_0a_3K_1} < 1$ $(a_0 \neq 0)$ or $a_4 = 0$ $(a_0 = 0)$.

The equilibria results we have accumulated here are summarized on the next two pages, separated into $K_5 = K_3^2$ and $K_5 < K_3^2$ sections.

1.3.1.1 Summary of Equilibria, $\mathbf{K_5 = K_3^2}$

Here, we summarize our discussion of the existence of equilibria in (1.6) for the $K_5 = K_3^2$ case. Assuming (1.8), equilibria are not possible in the (α, α, γ) and (α, γ, γ) subcases. The results for the other two subcases are described below.

Subcase (α, α, α) $\qquad [Y < \min\{2K_1, 2K_3^3\}, \quad X_2 < 2K_5, \quad X_4 < 2K_4]$

Assume (1.8) holds. Then, there is an equilibrium point

$$Y^* = \frac{2a_0K_1}{a_1}, \quad X_2^* = \frac{2a_0a_1K_3^3K_5}{a_0a_3K_1 + a_1a_5K_3^3}, \quad X_4^* = \frac{2a_0^2a_3K_1K_4}{a_4(a_0a_3K_1 + a_1a_5K_3^3)}$$

if and only if $\dfrac{a_0a_1K_3^3}{a_0a_3K_1 + a_1a_5K_3^3} < 1$.

Subcase (α, γ, α) $\qquad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \leq X_2, \quad X_4 < 2K_4]$

Assume (1.8) holds. Then, there exist equilibria

$$Y^* = \frac{2a_0K_1}{a_1}, \quad X_2^* \geq 2K_5, \quad X_4^* = \frac{2a_0a_3K_1K_4}{a_1a_4K_3^3}$$

if and only if $a_0 = \dfrac{a_1a_5K_3^3}{a_1K_3^3 - a_3K_1}$ and $a_1K_3^3 > a_3K_1$.

1.3.1.2 Summary of Equilibria, $\mathbf{K_5 < K_3^2}$

Next, we summarize our system (1.6) equilibria results for the $K_5 < K_3^2$ case. With the assumptions in (1.8), equilibria are not possible in the (α, α, γ), (α, β, γ), and (α, γ, γ) subcases. The results for the remaining subcases are described below.

Subcase (α, α, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad X_2 < 2K_5 < 2K_3^2, \quad X_4 < 2K_4]$

Assume (1.8) holds. Then, there is an equilibrium point

$$Y^* = \frac{2a_0K_1}{a_1}, \quad X_2^* = \frac{2a_0a_1K_3^2K_3^3K_5}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3}, \quad X_4^* = \frac{2a_0^2a_3K_1K_4K_5}{a_4(a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3)}$$

if and only if $\dfrac{a_0a_1K_3^2K_3^3}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3} < 1.$

Subcase (α, β, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \leq X_2 < 2K_3^2, \quad X_4 < 2K_4]$

Assume (1.8) holds. Then, there is an equilibrium point

$$Y^* = \frac{2a_0K_1}{a_1}, \quad X_2^* = \frac{2(a_0 - a_5)a_1K_3^2K_3^3}{a_0a_3K_1}, \quad X_4^* = \frac{2(a_0 - a_5)K_4}{a_4}$$

if and only if $\dfrac{K_5}{K_3^2} \leq \dfrac{(a_0 - a_5)a_1K_3^3}{a_0a_3K_1} < 1.$

Subcase (α, γ, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 < 2K_3^2 \leq X_2, \quad X_4 < 2K_4]$

Assume (1.8) holds. Then, there exist equilibria

$$Y^* = \frac{2a_0K_1}{a_1}, \quad X_2^* \geq 2K_3^2, \quad X_4^* = \frac{2a_0a_3K_1K_4}{a_1a_4K_3^3}$$

if and only if $a_0 = \dfrac{a_1a_5K_3^3}{a_1K_3^3 - a_3K_1}$ and $a_1K_3^3 > a_3K_1$.

1.3.1.3 Graphs and Uniqueness

We will now visualize the equilibria results summarized above by graphing X_2^* and X_4^* with a_0 as the independent variable. The parameter values we will use are

$$\begin{aligned} a_1 &= 100 & K_1 &= 0.1 \\ a_3 &= 75 & K_3^3 &= 0.1 \\ a_4 &= 75 & K_4 &= 1 \\ a_5 &= 5 & K_5 &= 1, \end{aligned} \tag{1.9}$$

which were the ones used by Adams and colleagues in [1].

Using (1.9) and the equilibria summary in section 1.3.1.1, we have the following graphs for the $K_5 = K_3^2$ case:

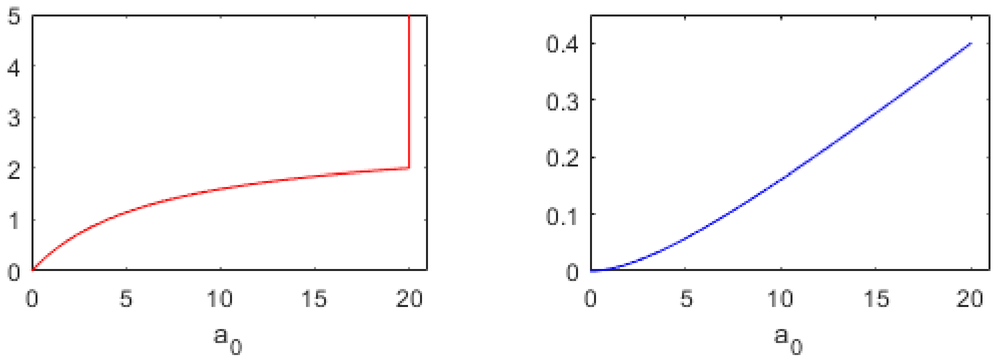
$$X_2^* \begin{cases} = \dfrac{8a_0}{3a_0+20}, & 0 \le a_0 < 20 \\ \ge\ 2, & a_0 = 20 \end{cases} \qquad X_4^* = \begin{cases} \dfrac{2a_0^2}{75a_0+500}, & 0 \le a_0 < 20 \\ \dfrac{a_0}{50}, & a_0 = 20 \end{cases}$$

For the $K_5 < K_3^2$ case, we will take $K_3^2 = 10K_5 = 10$; this will be one of the K_3^2 values we will consider when discussing flux into metabolic pathways near the end of this chapter. With our parameter values and the results from section 1.3.1.2, the graphs for this case are:

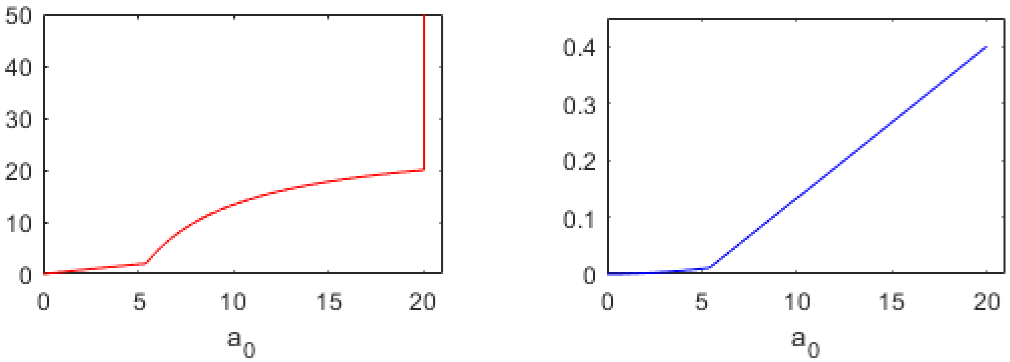
$$X_2^* \begin{cases} = \dfrac{80a_0}{3a_0+200}, & 0 \le a_0 < 200/37 \\ = \dfrac{80}{3} - \dfrac{400}{3a_0}, & 200/37 \le a_0 < 20 \\ \ge\ 20, & a_0 = 20 \end{cases}$$

$$X_4^* = \begin{cases} \dfrac{2a_0^2}{75a_0+5000}, & 0 \le a_0 < 200/37 \\ \dfrac{2a_0}{75} - \dfrac{2}{15}, & 200/37 \le a_0 < 20 \\ \dfrac{a_0}{50}, & a_0 = 20 \end{cases}$$

The graphs are displayed in Figure 5 on the next page.



(a) X_2^*, $K_5 = K_3^2$ (b) X_4^*, $K_5 = K_3^2$



(c) X_2^*, $K_5 < K_3^2$ (d) X_4^*, $K_5 < K_3^2$

Figure 5: Graphs of the equilibrium values X_2^* and X_4^* for the three-variable ramp system (1.6) with the SEL

These graphs emphasize the fact that equilibria in system (1.6) are almost always unique. When a_0 is strictly below the maximum value for which equilibria are possible (which, under our chosen parameters, is $a_0 = \dfrac{a_1 a_5 K_3^3}{a_1 K_3^3 - a_3 K_1} = 20$), X_2^* and X_4^* are both functions of a_0 (as is our Y^* value from (1.8)). It is only when a_0 is exactly equal to this maximum value that we have infinitely many possibilities for X_2^*, as seen in (a) and (c) above. This is a consequence of using ramp functions; our maximum a_0 value here corresponds to the (α, γ, α) subcase with $r_5(X_2) = r_3^2(X_2) = 1$, which has infinitely many solutions.

1.3.2 Stability of Equilibria

The next part of our analysis will focus on the linear stability of equilibria in system (1.6). Our technique will be to look at the eigenvalues of the system's Jacobian evaluated at the equilibrium points summarized in 1.3.1.1 and 1.3.1.2. Remembering that the equations of (1.6) are

$$\begin{aligned}\dot{Y} &= a_0 - a_1 r_1(Y) - a_3 r_3^2(X_2) r_3^3(Y) + a_4 r_4(X_4)\\ \dot{X}_2 &= a_1 r_1(Y) - a_3 r_3^2(X_2) r_3^3(Y) - a_5 r_5(X_2)\\ \dot{X}_4 &= a_3 r_3^2(X_2) r_3^3(Y) - a_4 r_4(X_4),\end{aligned}$$

the general formula for the Jacobian is

$$J(\vec{X}) = \begin{bmatrix} -a_1 \frac{dr_1}{dY} - a_3 r_3^2(X_2)\frac{dr_3^3}{dY} & -a_3 r_3^3(Y)\frac{dr_3^2}{dX_2} & a_4 \frac{dr_4}{dX_4} \\ a_1 \frac{dr_1}{dY} - a_3 r_3^2(X_2)\frac{dr_3^3}{dY} & -a_3 r_3^3(Y)\frac{dr_3^2}{dX_2} - a_5\frac{dr_5}{dX_2} & 0 \\ a_3 r_3^2(X_2)\frac{dr_3^3}{dY} & a_3 r_3^3(Y)\frac{dr_3^2}{dX_2} & -a_4\frac{dr_4}{dX_4} \end{bmatrix}.$$

Note that the ramp functions are not differentiable at threshold, as shown by the corner at $X = 2\theta$ on the general ramp function graph in Figure 4. In subcases with a variable in its β or γ region, we will circumvent this problem by assuming the variable is strictly above the appropriate threshold(s) at equilibrium. For instance, in the (α, γ, α) subcase with $K_5 = K_3^2$, we will assume that $2K_5 < X_2^*$ and disregard the $X_2^* = 2K_5$ possibility.

For asymptotic stability, we want the real part of every eigenvalue λ of J to be negative. The following *Routh–Hurwitz criterion* for three-variable systems (see, for example, [9, ch. 5]) will be useful when looking at the signs of the real parts of eigenvalues:

Theorem 1. ***[Routh-Hurwitz]*** *Let* $\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0$ *be the characteristic equation of a* 3×3 *matrix with solutions* λ_1, λ_2, *and* λ_3. *Then,* $\mathfrak{Re}(\lambda_i) < 0 \ \forall\, i$ *if and only if* $b_1 > 0$, $b_3 > 0$, *and* $b_1 b_2 > b_3$.

We begin our stability discussion with the two subcases common to both section 1.3.1.1 and section 1.3.1.2.

Subcase (α, α, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad X_2 < 2K_5 \le 2K_3^2, \quad X_4 < 2K_4]$

The Jacobian evaluated at the equilibrium point is

$$\begin{bmatrix} -\frac{a_1}{2K_1} - \frac{a_3 X_2^*}{4K_3^2 K_3^3} & -\frac{a_3 Y^*}{4K_3^2 K_3^3} & \frac{a_4}{2K_4} \\ \frac{a_1}{2K_1} - \frac{a_3 X_2^*}{4K_3^2 K_3^3} & -\frac{a_3 Y^*}{4K_3^2 K_3^3} - \frac{a_5}{2K_5} & 0 \\ \frac{a_3 X_2^*}{4K_3^2 K_3^3} & \frac{a_3 Y^*}{4K_3^2 K_3^3} & -\frac{a_4}{2K_4} \end{bmatrix},$$

which has the characteristic equation

$$\lambda^3 + \Big[\frac{a_1}{2K_1} + \frac{a_4}{2K_4} + \frac{a_5}{2K_5} + \frac{a_3}{4K_3^2K_3^3}\big(X_2^* + Y^*\big)\Big]\lambda^2$$

$$+ \Big[\frac{a_1a_4}{4K_1K_4} + \frac{a_1a_5}{4K_1K_5} + \frac{a_4a_5}{4K_4K_5} + \frac{a_1a_3Y^*}{4K_1K_3^2K_3^3} + \frac{a_3a_4Y^*}{8K_3^2K_3^3K_4} + \frac{a_3a_5X_2^*}{8K_3^2K_3^3K_5}\Big]\lambda$$

$$+ \frac{a_1a_4}{4K_1K_4}\Big[\frac{a_5}{2K_5} + \frac{a_3Y^*}{4K_3^2K_3^3}\Big] \;=\; 0.$$

The coefficients of this polynomial are all strictly positive. Notice that the degree 1 coefficient contains an $\frac{a_1a_4}{4K_1K_4}$ term, while the degree 2 coefficient contains a term of the form $\frac{a_5}{2K_5} + \frac{a_3Y^*}{4K_3^2K_3^3}$. The product of these coefficients is then $\frac{a_1a_4}{4K_1K_4}\Big[\frac{a_5}{2K_5} + \frac{a_3Y^*}{4K_3^2K_3^3}\Big]$ added to a positive sum, and is therefore larger than the polynomial's constant term. As a result, the Routh-Hurwitz criterion stated in Theorem 1 is satisfied, allowing us to conclude that the real part of any root of the characteristic polynomial is negative. Thus, the (α, α, α) equilibrium point from 1.3.1.1 and 1.3.1.2 is asymptotically stable.

Subcase (α, γ, α) $\qquad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 \leq 2K_3^2 < X_2, \quad X_4 < 2K_4]$

When a variable is in its γ region and strictly above threshold, all ramp functions associated with that variable are constant and have derivatives equal to zero. As a result, the Jacobian will have a column of zeros and a zero eigenvalue. Thus, in this subcase the Jacobian is

$$\begin{bmatrix} -\frac{a_1}{2K_1} - \frac{a_3}{2K_3^3} & 0 & \frac{a_4}{2K_4} \\ \frac{a_1}{2K_1} - \frac{a_3}{2K_3^3} & 0 & 0 \\ \frac{a_3}{2K_3^3} & 0 & -\frac{a_4}{2K_4} \end{bmatrix},$$

with characteristic equation

$$\lambda\Big[\lambda^2 + \Big(\frac{a_1}{2K_1} + \frac{a_3}{2K_3^3} + \frac{a_4}{2K_4}\Big)\lambda + \frac{a_1a_4}{4K_1K_4}\Big] \;=\; 0.$$

All coefficients of the quadratic term are positive, and hence both roots have negative real parts. In fact, the roots of the quadratic will always be real. Letting

$$P(\lambda) \;=\; \lambda^2 + \Big(\frac{a_1}{2K_1} + \frac{a_3}{2K_3^3} + \frac{a_4}{2K_4}\Big)\lambda + \frac{a_1a_4}{4K_1K_4},$$

we have

$$P\Big(-\Big(\frac{a_1}{2K_1} + \frac{a_3}{2K_3^3} + \frac{a_4}{2K_4}\Big)\Big) \;=\; \frac{a_1a_4}{4K_1K_4} \;> 0,$$

$$
\begin{aligned}
P\Big(-\frac{a_4}{2K_4}\Big) &= -\frac{a_3a_4}{4K_3^3K_4} < 0, \text{ and}\\
P(0) &= \frac{a_1a_4}{4K_1K_4} > 0,
\end{aligned}
$$

meaning that the quadratic must have two roots in the interval

$$
\Big(-\Big(\frac{a_1}{2K_1}+\frac{a_3}{2K_3^3}+\frac{a_4}{2K_4}\Big),\ 0\Big).
$$

Thus, the eigenvalues of the Jacobian in this subcase are all real with $\lambda_1 = 0$ and $\lambda_2, \lambda_3 < 0$. This zero eigenvalue would normally preclude us from being able to determine stability. However, as shown in Figure 5(a) and (c), we have a line of equilibria in this subcase. Hence, we can conclude that we have neutral stability here as the zero eigenvalue corresponds to our line of equilibrium points as a neutrally stable centre manifold.

Finally, we examine the stability of the (α, β, α) equilibrium exclusive to the $K_5 < K_3^2$ case.

Subcase (α, β, α) $\quad [Y < \min\{2K_1, 2K_3^3\}, \quad 2K_5 < X_2 < 2K_3^2, \quad X_4 < 2K_4]$

With X_2 in its β region and greater than $2K_5$, the $a_5/(2K_5)$ term is dropped from the Jacobian and characteristic equation. Hence, we have

$$
\begin{bmatrix}
-\frac{a_1}{2K_1}-\frac{a_3X_2^*}{4K_3^2K_3^3} & -\frac{a_3Y^*}{4K_3^2K_3^3} & \frac{a_4}{2K_4}\\
\frac{a_1}{2K_1}-\frac{a_3X_2^*}{4K_3^2K_3^3} & -\frac{a_3Y^*}{4K_3^2K_3^3} & 0\\
\frac{a_3X_2^*}{4K_3^2K_3^3} & \frac{a_3Y^*}{4K_3^2K_3^3} & -\frac{a_4}{2K_4}
\end{bmatrix}
$$

and

$$
\begin{aligned}
\lambda^3 + \Big[\frac{a_1}{2K_1}+\frac{a_4}{2K_4}+\frac{a_3}{4K_3^2K_3^3}\big(X_2^*+Y^*\big)\Big]\lambda^2&\\
+\Big[\frac{a_1a_4}{4K_1K_4}+\frac{a_1a_3Y^*}{4K_1K_3^2K_3^3}+\frac{a_3a_4Y^*}{8K_3^2K_3^3K_4}\Big]\lambda+\frac{a_1a_3a_4Y^*}{16K_1K_3^2K_3^3K_4} &= 0.
\end{aligned}
$$

The coefficients of this cubic are all positive. Note that the constant term cannot equal zero as the equilibria summary in 1.3.1.2, based on our earlier discussion of equilibria in the (α, β, α) subcase, rules out the existence of equilibria when a_0 (and thus Y^*) equals zero. Multiplying the coefficients of λ^2 and λ, we get $\frac{a_1a_3a_4Y^*}{16K_1K_3^2K_3^3K_4}$ added to several positive terms, thus exceeding the constant term of the polynomial. Hence, Theorem 1 is satisfied, and the equilibrium point is asymptotically stable.

1.3.3 Equilibria with γ Region $\mathbf{Y}^*$

Finally, we will provide equilibria results for system (1.6) covering the case in which Y^* is in its γ region. That is, when $Y^* \geq \max\{2K_1, 2K_3^3\}$ and $r_1(Y^*) = r_3^3(Y^*) = 1$.

Equilibria with γ region Y^* are possible only at one specific a_0 value. In section 1.3, we saw that solving $\dot{Y} + \dot{X}_4 = 0$ gives

$$r_1(Y^*) = \frac{a_0}{a_1},$$

which equals 1 if and only if $a_0 = a_1$. Assuming this and $a_3 \leq a_4$ as we did in (1.8), the assumptions we will make on parameters here are

$$\begin{aligned} Y^* &\geq \max\{2K_1, 2K_3^3\} \\ a_3 &\leq a_4 \\ a_0 &= a_1 \\ a_0 \geq 0, \quad a_i &> 0 \ \forall\, i \neq 0, \quad K_i > 0 \ \forall\, i \end{aligned} \tag{1.10}$$

The equilibria results are summarized below; the details can be handled similarly to section 1.3.1. Four subcases common to both $K_5 = K_3^2$ and $K_5 < K_3^2$ will be listed together, followed by the two $K_5 < K_3^2$ subcases with β regions.

Equilibria in System (1.6):

Subcase 1 (γ, α, α) $[Y^* \geq \max\{2K_1, 2K_3^3\}, \quad X_2 < 2K_5 \leq 2K_3^2, \quad X_4 < 2K_4]$

Assume (1.10) holds. Then, there exist equilibria

$$Y^* \geq \max\{2K_1, 2K_3^3\}, \quad X_2^* = \frac{2a_0K_3^2K_5}{a_3K_5 + a_5K_3^2}, \quad X_4^* = \frac{2a_0a_3K_4K_5}{a_4(a_3K_5 + a_5K_3^2)}$$

if and only if $a_0 < \dfrac{a_3K_5}{K_3^2} + a_5$.

Subcase 2 (γ, α, γ) $[Y^* \geq \max\{2K_1, 2K_3^3\}, \quad X_2 < 2K_5 \leq 2K_3^2, \quad 2K_4 \leq X_4]$

Assuming (1.10), equilibria are not possible in this subcase.

Subcase 3 (γ, γ, α) $[Y^* \geq \max\{2K_1, 2K_3^3\},\ \ 2K_5 \leq 2K_3^2 \leq X_2,\ \ X_4 < 2K_4]$

Assume (1.10) holds. Then, there exist equilibria

$$Y^* \ \geq\ \max\{2K_1, 2K_3^3\},\ \ X_2^* \ \geq\ 2K_3^2 \ \geq\ 2K_5,\ \ X_4^* \ =\ \frac{2a_3K_4}{a_4}$$

if and only if $a_0 = a_3 + a_5$ and $a_3 < a_4$.

Subcase 4 (γ, γ, γ) $[Y^* \geq \max\{2K_1, 2K_3^3\},\ \ 2K_5 \leq 2K_3^2 \leq X_2,\ \ 2K_4 \leq X_4]$

Assume (1.10) holds. Then, there exist equilibria

$$Y^* \ \geq\ \max\{2K_1, 2K_3^3\},\ \ X_2^* \ \geq\ 2K_3^2 \ \geq\ 2K_5,\ \ X_4^* \ \geq\ 2K_4$$

if and only if $a_0 = a_3 + a_5$ and $a_3 = a_4$.

Subcases exclusive to the $\mathbf{K_5 < K_3^2}$ Case:

Subcase 5 (γ, β, α) $[Y^* \geq \max\{2K_1, 2K_3^3\},\ \ 2K_5 \leq X_2 < 2K_3^2,\ \ X_4 < 2K_4]$

Assume (1.10) holds. Then, there exist equilibria

$$Y^* \ \geq\ \max\{2K_1, 2K_3^3\},\ \ X_2^* \ =\ \frac{2(a_0 - a_5)K_3^2}{a_3},\ \ X_4^* \ =\ \frac{2(a_0 - a_5)K_4}{a_4}$$

if and only if $\dfrac{a_3K_5}{K_3^2} + a_5 \leq a_0 < a_3 + a_5$.

Subcase 6 (γ, β, γ) $[Y^* \geq \max\{2K_1, 2K_3^3\},\ \ 2K_5 \leq X_2 < 2K_3^2,\ \ 2K_4 \leq X_4]$

Assuming (1.10), equilibria are not possible in this subcase.

1.4 Three-Variable Ramp System — Without the SEL

Now, we will move on to the existence and stability of equilibria in system (1.7). As with system (1.6), we will focus on the cases $K_5 = K_3^2$ and $K_5 < K_3^2$, with subcases classified using the α, β, and γ regions described in Definition 2.

Once again, we will assume that $a_3 \leq a_4$. A condition on a_0 can be found from X_1^*. Setting $\dot{X}_1 = 0$ in (1.7), we have

$$a_0 - a_1 r_1(X_1^*) \ =\ 0$$

$$\implies r_1(X_1^*) \;=\; \frac{a_0}{a_1}.$$

The value of X_1^* and the exact condition on a_0 depends on whether we want X_1 to be in its α or γ region. If X_1 is below its (only) threshold $2K_1$, then $r_1(X_1^*) = X_1^*/(2K_1) < 1$ and we get the explicit equilibrium solution

$$\frac{X_1^*}{2K_1} \;=\; \frac{a_0}{a_1} \implies X_1^* \;=\; \frac{2a_0K_1}{a_1}$$

if and only if $a_0 < a_1$. Meanwhile, we have $X_1^* \geq 2K_1$ and $r_1(X_1^*) = 1$ if and only if $a_0 = a_1$.

Here, we will not specify whether X_1 is in its α or γ region, and allow for both possibilities. Thus, we can express our upper bound on a_0 as $a_0 \leq a_1$. Our assumptions on parameters can then be summarized as:

$$\begin{aligned} r_1(X_1^*) \;&=\; \frac{a_0}{a_1} \\ a_3 \;&\leq\; a_4 \\ a_0 \;&\leq\; a_1 \\ a_0 \;\geq\; 0, \quad a_i \;&>0 \;\forall\, i \neq 0, \quad K_i \;>\; 0 \;\forall\, i \end{aligned} \tag{1.11}$$

1.4.1 Equilibria

The subcases listed here will use the notation α/γ to denote that X_1 can be in its α **or** γ region. Similar to section 1.3.1, there are four subcases shared by the $K_5 = K_3^2$ and $K_5 < K_3^2$ cases that will be considered together, and two subcases only present in the $K_5 < K_3^2$ case.

When we write the system of equations corresponding to each subcase, we will exclude the $\dot{X}_1$ equation because our assumptions in (1.11) already satisfy $\dot{X}_1 = 0$. Our assumptions also allow us to replace the $a_1 r_1(X_1)$ term in the $\dot{X}_2$ equation with a_0.

Equilibria in System (1.7):

Subcase 1 $(\alpha/\gamma, \alpha, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad X_2 < 2K_5 \leq 2K_3^2, \quad X_4 < 2K_4]$

The system of equations in this subcase is

$$\begin{aligned} \dot{X}_2 \;&=\; a_0 - a_3\frac{X_2}{2K_3^2} - a_5\frac{X_2}{2K_5} \\ \dot{X}_4 \;&=\; a_3\frac{X_2}{2K_3^2} - a_4\frac{X_4}{2K_4}. \end{aligned}$$

Solving $\dot{X}_2 = 0$ and $\dot{X}_4 = 0$, we get

$$X_2^* \;=\; \frac{2a_0K_3^2K_5}{a_3K_5 + a_5K_3^2} \text{ and } X_4^* \;=\; \frac{2a_0a_3K_4K_5}{a_4(a_3K_5 + a_5K_3^2)},$$

which exist in the α region of their respective variables if and only if $\frac{a_0 K_3^2}{a_3 K_5 + a_5 K_3^2} < 1$ and $\frac{a_0 a_3 K_5}{a_4(a_3 K_5 + a_5 K_3^2)} < 1$. Since we have $a_3 \leq a_4$ and $K_5 \leq K_3^2$, the first inequality implies the second. Thus, the parameter restriction we need to consider for existence of equilibria is $\frac{a_0 K_3^2}{a_3 K_5 + a_5 K_3^2} < 1$, which can equivalently be written as $a_0 < \frac{a_3 K_5}{K_3^2} + a_5$.

In the $K_5 = K_3^2$ case, the equilibrium values and condition on a_0 can be stated as $X_2^* = \frac{2a_0 K_5}{a_3 + a_5}$, $X_4^* = \frac{2a_0 a_3 K_4}{a_4(a_3 + a_5)}$, and $a_0 < a_3 + a_5$.

Subcase 2 $(\alpha/\gamma, \alpha, \gamma)$ $\quad [r_1(X_1) = a_0/a_1, \quad X_2 < 2K_5 \leq 2K_3^2, \quad 2K_4 \leq X_4]$

The $\dot{X}_4$ equation is $\dot{X}_4 = a_3 \frac{X_2}{2K_3^2} - a_4$, which equals zero if and only if $X_2^* = \frac{2a_4 K_3^2}{a_3}$. With X_2 in its α region, existence of this value requires $a_4/a_3 < K_5/K_3^2 \leq 1$. However, this inequality cannot be satisfied because of the assumption $a_3 \leq a_4$ from (1.11). Hence, this subcase has no possible equilibria.

Subcase 3 $(\alpha/\gamma, \gamma, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 \leq 2K_3^2 \leq X_2, \quad X_4 < 2K_4]$

Our system of equations is

$$\begin{aligned} \dot{X}_2 &= a_0 - a_3 - a_5 \\ \dot{X}_4 &= a_3 - a_4 \frac{X_4}{2K_4}. \end{aligned}$$

From $\dot{X}_4 = 0$, we get $X_4^* = \frac{2a_3 K_4}{a_4}$ with the parameter condition $a_3 < a_4$. Then, we have that $\dot{X}_2 = 0$ if and only if $a_0 = a_3 + a_5$. With X_2 in its γ region, we can choose any $X_2^* \geq 2K_3^2 \geq 2K_5$ at equilibrium.

Subcase 4 $(\alpha/\gamma, \gamma, \gamma)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 \leq 2K_3^2 \leq X_2, \quad 2K_4 \leq X_4]$

The equations are

$$\begin{aligned} \dot{X}_2 &= a_0 - a_3 - a_5 \\ \dot{X}_4 &= a_3 - a_4. \end{aligned}$$

Again, $\dot{X}_2 = 0$ gives the necessary and sufficient condition $a_0 = a_3 + a_5$. The $\dot{X}_4$ equation, meanwhile, equals zero if and only if $a_3 = a_4$. With both X_2 and X_4 in their γ regions, at equilibrium we can have any $X_2^* \geq 2K_3^2 \geq 2K_5$ and $X_4^* \geq 2K_4$.

Subcases exclusive to the $\mathbf{K_5 < K_3^2}$ Case:

Subcase 5 $(\alpha/\gamma, \beta, \alpha)$ $[r_1(X_1) = a_0/a_1, \quad 2K_5 \leq X_2 < 2K_3^2, \quad X_4 < 2K_4]$

In this subcase, the system becomes

$$\begin{aligned} \dot{X}_2 &= a_0 - a_3\frac{X_2}{2K_3^2} - a_5 \\ \dot{X}_4 &= a_3\frac{X_2}{2K_3^2} - a_4\frac{X_4}{2K_4}. \end{aligned}$$

Solving $\dot{X}_2 = 0$ and $\dot{X}_4 = 0$ gives

$$X_2^* = \frac{2(a_0 - a_5)K_3^2}{a_3} \text{ and } X_4^* = \frac{2(a_0 - a_5)K_4}{a_4},$$

with the parameter conditions $\dfrac{K_5}{K_3^2} \leq \dfrac{a_0 - a_5}{a_3} < 1$ and $\dfrac{a_0 - a_5}{a_4} < 1$. If the first inequality holds, then so does the second one by the $a_3 \leq a_4$ assumption from (1.11). Hence, the given equilibrium exists if and only if $\dfrac{K_5}{K_3^2} \leq \dfrac{a_0 - a_5}{a_3} < 1$, or equivalently, $\dfrac{a_3K_5}{K_3^2} + a_5 \leq a_0 < a_3 + a_5$.

Subcase 6 $(\alpha/\gamma, \beta, \gamma)$ $[r_1(X_1) = a_0/a_1, \quad 2K_5 \leq X_2 < 2K_3^2, \quad 2K_4 \leq X_4]$

This is similar to what we had in the $(\alpha/\gamma, \alpha, \gamma)$ subcase; we have $\dot{X}_4 = a_3\dfrac{X_2}{2K_3^2} - a_4$, and thus $X_2^* = \dfrac{2a_4K_3^2}{a_3}$ with the requirement that $K_5/K_3^2 < a_4/a_3 < 1$. However, $a_4/a_3 \geq 1$ by (1.11) and thus equilibria are not possible.

The following two pages summarize what we have discussed here regarding equilibria in system (1.7).

1.4.1.1 Summary of Equilibria, $\mathbf{K_5 = K_3^2}$

Equilibria are not possible in system (1.7) in the $(\alpha/\gamma, \alpha, \gamma)$ subcase, but are possible in the three other subcases. In each subcase listed below, the α region for X_1 corresponds to $X_1^* = \dfrac{2a_0K_1}{a_1}$ and the condition $a_0 < a_1$ in (1.11), while we have $X_1^* \geq 2K_1$ and $a_0 = a_1$ when X_1 is in its γ region.

Subcase $(\alpha/\gamma, \alpha, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad X_2 < 2K_5, \quad X_4 < 2K_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* = \frac{2a_0K_5}{a_3 + a_5}, \;\; X_4^* = \frac{2a_0a_3K_4}{a_4(a_3 + a_5)}$$

if and only if $a_0 < a_3 + a_5$.

Subcase $(\alpha/\gamma, \gamma, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 \leq X_2, \quad X_4 < 2K_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* \geq 2K_5, \;\; X_4^* = \frac{2a_3K_4}{a_4}$$

if and only if $a_0 = a_3 + a_5$ and $a_3 < a_4$.

Subcase $(\alpha/\gamma, \gamma, \gamma)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 \leq X_2, \quad 2K_4 \leq X_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* \geq 2K_5, \;\; X_4^* \geq 2K_4$$

if and only if $a_0 = a_3 + a_5$ and $a_3 = a_4$.

1.4.1.2 Summary of Equilibria, $\mathbf{K_5 < K_3^2}$

Equilibria are possible in system (1.7) in four of the six subcases, summarized below. Only (α, α, γ) and (α, β, γ) cannot have equilibria under our assumptions in (1.11). We again have $X_1^* = \dfrac{2a_0K_1}{a_1}$ if X_1 is in its α region and $a_0 < a_1$ from (1.11), and $X_1^* \geq 2K_1$ in the case where $a_0 = a_1$ and X_1 is in its γ region.

Subcase $(\alpha/\gamma, \alpha, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad X_2 < 2K_5 < 2K_3^2, \quad X_4 < 2K_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* = \frac{2a_0K_3^2K_5}{a_3K_5 + a_5K_3^2}, \;\; X_4^* = \frac{2a_0a_3K_4K_5}{a_4(a_3K_5 + a_5K_3^2)}$$

if and only if $a_0 < \dfrac{a_3K_5}{K_3^2} + a_5$.

Subcase $(\alpha/\gamma, \beta, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 \leq X_2 < 2K_3^2, \quad X_4 < 2K_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* = \frac{2(a_0 - a_5)K_3^2}{a_3}, \;\; X_4^* = \frac{2(a_0 - a_5)K_4}{a_4}$$

if and only if $\dfrac{a_3K_5}{K_3^2} + a_5 \leq a_0 < a_5 + a_3$.

Subcase $(\alpha/\gamma, \gamma, \alpha)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 < 2K_3^2 \leq X_2, \quad X_4 < 2K_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* \geq 2K_3^2, \;\; X_4^* = \frac{2a_3K_4}{a_4}$$

if and only if $a_0 = a_3 + a_5$ and $a_3 < a_4$.

Subcase $(\alpha/\gamma, \gamma, \gamma)$ $\quad [r_1(X_1) = a_0/a_1, \quad 2K_5 < 2K_3^2 \leq X_2, \quad 2K_4 \leq X_4]$

Assume (1.11) holds. Then, there exist equilibria

$$X_1^* = \frac{2a_0K_1}{a_1} \textbf{ or } X_1^* \geq 2K_1, \;\; X_2^* \geq 2K_3^2, \;\; X_4^* \geq 2K_4$$

if and only if $a_0 = a_3 + a_5$ and $a_3 = a_4$.

1.4.1.3 Graphs and Uniqueness

Again, we will produce graphs of X_2^* and X_4^*, this time using the equilibria results for system (1.7) summarized in sections 1.4.1.1 and 1.4.1.2. We will use the parameter values from (1.9).

For the $K_5 = K_3^2$ case, the graphs for X_2^* and X_4^* will be identical using our parameter values:

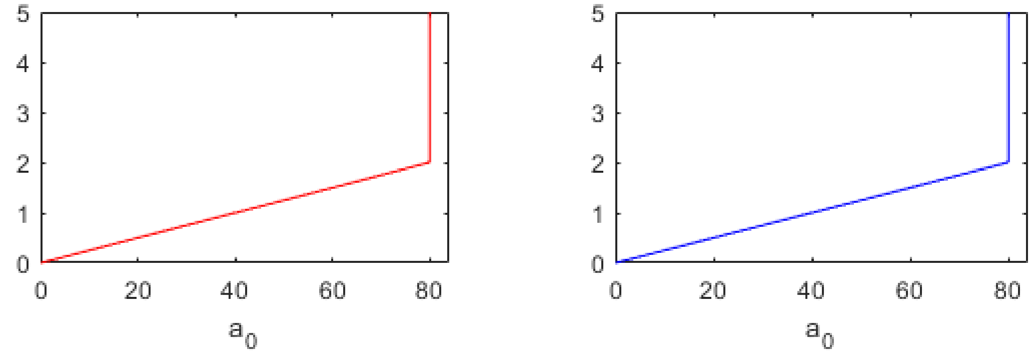
$$\begin{cases} = \dfrac{a_0}{40}, & 0 \leq a_0 < 80 \\ \geq 2, & a_0 = 80 \end{cases}$$

The $K_5 < K_3^2$ case will be handled using $K_3^2 = 10K_5 = 10$ again. The graphs are:

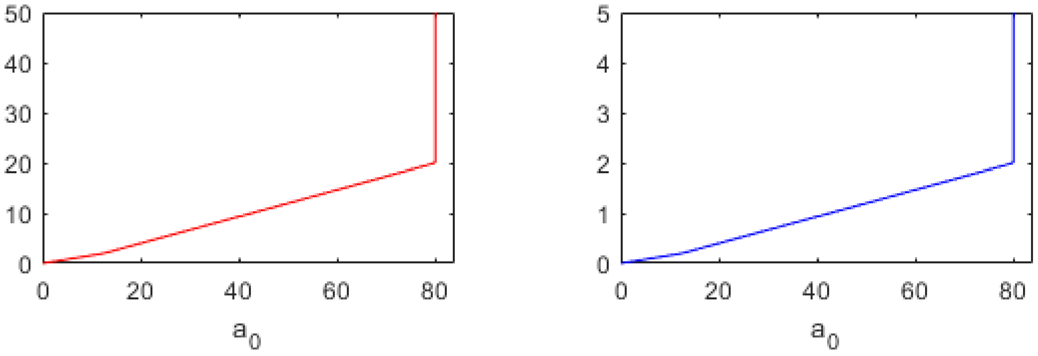
$$X_2^* \begin{cases} = \dfrac{4a_0}{25}, & 0 \leq a_0 < 25/2 \\ = \dfrac{4a_0}{15} - \dfrac{4}{3}, & 25/2 \leq a_0 < 80 \\ \geq 20, & a_0 = 80 \end{cases}$$

$$X_4^* \begin{cases} = \dfrac{2a_0}{125}, & 0 \leq a_0 < 25/2 \\ = \dfrac{2a_0}{75} - \dfrac{2}{15}, & 25/2 \leq a_0 < 80 \\ \geq 2, & a_0 = 80 \end{cases}$$

The graphs are presented on the next page in Figure 6.



(a) X_2^*, $K_5 = K_3^2$ (b) X_4^*, $K_5 = K_3^2$



(c) X_2^*, $K_5 < K_3^2$ (d) X_4^*, $K_5 < K_3^2$

Figure 6: Graphs of the equilibrium values X_2^* and X_4^* for the three-variable ramp system (1.7) without the SEL

As was the case for the system with the SEL, equilibria in system (1.7) are almost always unique. From the above graphs, X_2^* and X_4^* are unique for all a_0 below $a_3 + a_5 = 80$, and only have an infinite number of possible values when a_0 is exactly equal to this upper bound. The same applies to X_1^*; from our assumptions in (1.11), X_1^* is unique for $a_0 < a_1$ and can take on infinitely many possible values only when a_0 equals the upper bound a_1 exactly.

1.4.2 Stability of Equilibria

We will now discuss the linear stability of the equilibria summarized in sections 1.4.1.1 and 1.4.1.2. Again, we will assume that we do not have equilibria at threshold values, and thus all of the derivatives of the ramp functions are defined.

Since the equations in (1.7) are

$$\begin{aligned}\dot{X}_1 &= a_0 - a_1 r_1(X_1) \\ \dot{X}_2 &= a_1 r_1(X_1) - a_3 r_3^2(X_2) - a_5 r_5(X_2)\end{aligned}$$

$$\dot{X}_4 \;=\; a_3 r_3^2(X_2) - a_4 r_4(X_4),$$

the Jacobian is the triangular matrix

$$J(\vec{X}) = \begin{bmatrix} -a_1 \dfrac{dr_1}{dX_1} & 0 & 0 \\ \\ a_1 \dfrac{dr_1}{dX_1} & -a_3 \dfrac{dr_3^2}{dX_2} - a_5 \dfrac{dr_5}{dX_2} & 0 \\ \\ 0 & a_3 \dfrac{dr_3^2}{dX_2} & -a_4 \dfrac{dr_4}{dX_4} \end{bmatrix}.$$

The eigenvalues are thus the diagonal entries $-a_1 \dfrac{dr_1}{dX_1}$, $-a_3 \dfrac{dr_3^2}{dX_2} - a_5 \dfrac{dr_5}{dX_2}$, and $-a_4 \dfrac{dr_4}{dX_4}$, which are always non-positive. A zero eigenvalue is possible if and only if at least one variable is in its γ region.

In both the $K_5 = K_3^2$ and $K_5 < K_3^2$ cases, the (α, α, α) subcase will result in three negative eigenvalues and an asymptotically stable equilibrium point. We will also get asymptotic stability in the (α, β, α) subcase of $K_5 < K_3^2$.

1.5 Flux into Metabolic Pathways

The final piece of our analysis of the ramp systems (1.6) and (1.7) will focus on the primary and secondary metabolic pathways represented in Figure 2 by out_1 and out_2 respectively. In the introduction, we briefly described Adams *et al.*'s analysis of phenylalanine flux into metabolic pathways performed in [1]; their results suggested a prioritization of primary over secondary metabolism in the model with the Shikimate Ester Loop (SEL) when the concentration of the phenylalanine precursor shikimate is low via a mechanism called the Precursor Shutoff Valve (PSV). We begin here with a more detailed explanation of this analysis and the results.

A major focus of Adams and colleagues' work in [1] was to investigate whether the SEL plays a regulatory role in plant metabolism. It had already been established that the SEL is vital to the function of the secondary monolignol pathway, which consists of reactions involving phenylalanine derivatives known as *hydroxycinnamates*. Some of the enzymes catalyzing these reactions cannot bind to their hydroxycinnamate substrates unless shikimate has been ligated to them. This is where the SEL comes in: it consists of three reactions, starting with the one in which shikimate is ligated to a hydroxycinnamate, and ending with one in which the shikimate-hydroxycinnamate bond is broken [1].

What had not been established, however, was whether the SEL can also affect the function of the monolignol pathway via a regulatory mechanism (the PSV) by which primary metabolism is prioritized over secondary metabolism when the rate of shikimate synthesis

(a_0) is low. It had been hypothesized that through this PSV mechanism, the SEL limits flux into the monolignol pathway, leaving most of the phenylalanine for the primary metabolic pathway (protein synthesis). The justification for this mechanism is simple; when shikimate production slows, the concentration of available phenylalanine (X_2) decreases, and thus it is sensible to direct most of the phenylalanine stores to protein synthesis, which is necessary for the plant's survival [1].

Adams *et al.* tested the hypothesis that the SEL carries out PSV regulation in phenylalanine metabolism by graphing the equilibrium fluxes V_4^* (flux into the monolignol pathway) and V_5^* (primary metabolic pathway) as functions of a_0. Graphs were made not only for the system with the SEL ((1.1)), but also for the system without the SEL ((1.2)), which was used as an experimental control. Three graphs for each version of the system were made, with K_3^2 set equal to each of K_5, $10K_5$, and $100K_5$. As mentioned in section 1.3, K_5 and K_3^2 are the threshold constants of the primary and monolignol pathways respectively, denoting the difficultly of entry into these metabolic pathways.

The results presented in [1] supported the idea that the SEL serves a PSV type role in the regulation of phenylalanine metabolism in plants. The graphs for the system with the SEL (for all values of K_3^2) showed that when a_0 is low, the flux V_5^* into the primary pathway reaches near-maximum and is greater than the flux V_4^* into the monolignol pathway. Thus, when the rate at which shikimate is produced is low, phenylalanine is primarily channelled toward protein synthesis.

In the system without the SEL, however, a PSV effect was only seen in the $K_3^2 = 100K_5$ case. When K_3^2 was set closer to K_5 — which, based on kinetic data, seems to be more biologically realistic — the graphs of both V_4^* and V_5^* resembled linear functions of a_0 with a positive slope, with flux into the monolignol pathway exceeding flux into the primary pathway for $a_0 > 0$.

Here, we will create V_4^* and V_5^* graphs for systems (1.6) and (1.7) to determine whether the same results hold after transitioning the model from a four-variable Michaelis-Menten system to a three-variable ramp system.

1.5.1 Parameters and Formulas for Flux Graphs

For consistency, we will make our V_4^* and V_5^* graphs using the same values that Adams and colleagues used in [1] for the a_i and K_i parameters. These are the values from (1.9) that we used to make our X_2^* and X_4^* graphs earlier, along with a set range of a_0 values:

$$\begin{aligned} a_1 &= 100 \\ a_3 &= 75 \\ a_4 &= 75 \\ a_5 &= 5 \\ a_0 &\in [0, 35] \end{aligned} \qquad \begin{aligned} K_1 &= 0.1 \\ K_3^3 &= 0.1 \\ K_4 &= 1 \\ K_5 &= 1 \end{aligned} \tag{1.12}$$

The parameter K_3^2 will take on the values $K_5 = 1$, $10K_5 = 10$, and $100K_5 = 100$ in different graphs. Next, in Adams *et al.*'s work V_4^* and V_5^* were Michaelis-Menten terms of the form

$$\begin{aligned} V_4^* &= \frac{a_4 X_4^*}{K_4 + X_4^*} \\ V_5^* &= \frac{a_5 X_2^*}{K_5 + X_2^*}, \end{aligned}$$

which for us, using the ramp functions defined in (1.5), become

$$\begin{aligned} V_4^* &= a_4 r_4(X_4^*) \\ V_5^* &= a_5 r_5(X_2^*). \end{aligned} \tag{1.13}$$

We will now derive the formulas we will use to graph V_4^* and V_5^*, starting with the system without the SEL.

1.5.1.1 Formulas for the System Without the SEL

Starting with the $K_3^2 = K_5$ graph for system (1.7), we determine the formulas using the equilibria results from section 1.4.1.1. First, we are in the $(\alpha/\gamma, \alpha, \alpha)$ subcase when $a_0 < a_3 + a_5$, which, using the parameter values listed in (1.12), corresponds to $0 \leq a_0 < 75 + 5 = 80$. With both X_2 and X_4 in their α regions, r_4 and r_5 will both be in their ramp regions. Thus, by (1.12), (1.13), and the X_2^* and X_4^* values given in 1.4.1.1, the formulas for V_4^* and V_5^* as functions of a_0 are

$$\begin{aligned} V_4^* &= a_4 \frac{X_4^*}{2K_4} \\ &= \frac{a_4}{2K_4} \cdot \frac{2a_0 a_3 K_4}{a_4(a_3 + a_5)} \\ &= \frac{a_0 a_3}{a_3 + a_5} \\ &= \frac{75 a_0}{80} \\ &= \frac{15}{16} a_0 \end{aligned}$$

and

$$\begin{aligned} V_5^* &= a_5 \frac{X_2^*}{2K_5} \\ &= \frac{a_5}{2K_5} \cdot \frac{2a_0 K_5}{a_3 + a_5} \\ &= \frac{a_0 a_5}{a_3 + a_5} \end{aligned}$$

$$\begin{aligned} &= \frac{5a_0}{80} \\ &= \frac{1}{16}a_0. \end{aligned}$$

We enter a new subcase when a_0 reaches $a_3 + a_5 = 80$; here, it would be the $(\alpha/\gamma, \gamma, \gamma)$ subcase since we have $a_3 = a_4 = 75$. However, we mentioned above that we want to graph over the a_0 interval $[0, 35]$ for consistency with [1]. Hence, the $K_3^2 = K_5$ graph will only include the $(\alpha/\gamma, \alpha, \alpha)$ subcase, with the upper bound on a_0 capped at 35 instead of 80.

For the $K_3^2 = 10K_5$ and $K_3^2 = 100K_5$ graphs, we use the equilibria results from section 1.4.1.2. Starting again with the $(\alpha/\gamma, \alpha, \alpha)$ subcase, the upper bound on a_0 is

$$\frac{a_3K_5}{K_3^2} + a_5 = \frac{75}{K_3^2} + 5,$$

which becomes 25/2 when $K_3^2 = 10$ and 23/4 when $K_3^2 = 100$. For V_4^* and V_5^*, we have

$$\begin{aligned} V_4^* &= a_4\frac{X_4^*}{2K_4} \\ &= \frac{a_4}{2K_4} \cdot \frac{2a_0a_3K_4K_5}{a_4(a_3K_5 + a_5K_3^2)} \\ &= \frac{a_0a_3K_5}{a_3K_5 + a_5K_3^2} \\ &= \frac{75a_0}{75 + 5K_3^2} \\ &= \begin{cases} 3a_0/5, & K_3^2 = 10 \\ 3a_0/23, & K_3^2 = 100 \end{cases} \end{aligned}$$

and

$$\begin{aligned} V_5^* &= a_5\frac{X_2^*}{2K_5} \\ &= \frac{a_5}{2K_5} \cdot \frac{2a_0K_3^2K_5}{a_3K_5 + a_5K_3^2} \\ &= \frac{a_0a_5K_3^2}{a_3K_5 + a_5K_3^2} \\ &= \frac{5K_3^2a_0}{75 + 5K_3^2} \\ &= \begin{cases} 2a_0/5, & K_3^2 = 10 \\ 20a_0/23, & K_3^2 = 100. \end{cases} \end{aligned}$$

Looking at the equilibria in 1.4.1.2, the next range of a_0 values is $\frac{a_3K_5}{K_3^2}+a_5 \leq a_0 < a_3+a_5$ in the $(\alpha/\gamma, \beta, \alpha)$ subcase. The lower bound on a_0 is $25/2$ if $K_3^2 = 10$ and $23/4$ if $K_3^2 = 100$, with the upper bound being 80. Again, we will cut off a_0 at 35. As X_4 is still in its α region, V_4^* is given by

$$\begin{aligned} V_4^* &= a_4\frac{X_4^*}{2K_4} \\ &= \frac{a_4}{2K_4} \cdot \frac{2(a_0 - a_5)K_4}{a_4} \\ &= a_0 - a_5 \\ &= a_0 - 5, \end{aligned}$$

for both $K_3^2 = 10$ and $K_3^2 = 100$. With X_2 in its β region, r_5 is saturated and so $r_5(X_2^*) = 1$. Thus, $V_5^* = a_5 = 5$.

With a_0 reaching 35, we do not have to consider any more subcases for the $K_3^2 = 10K_5$ and $K_3^2 = 100K_5$ graphs. Below, we summarize the formulas we derived in this section.

Graphs with $\mathbf{K_3^2 = K_5}$

Graphed over $0 \leq a_0 \leq 35$,

$$V_4^* = 15a_0/16 \qquad V_5^* = a_0/16$$

Graphs with $\mathbf{K_3^2 = 10K_5}$

$$V_4^* = \begin{cases} 3a_0/5, & 0 \leq a_0 < 25/2 \\ a_0 - 5, & 25/2 \leq a_0 \leq 35 \end{cases} \qquad V_5^* = \begin{cases} 2a_0/5, & 0 \leq a_0 < 25/2 \\ 5, & 25/2 \leq a_0 \leq 35 \end{cases}$$

Graphs with $\mathbf{K_3^2 = 100K_5}$

$$V_4^* = \begin{cases} 3a_0/23, & 0 \leq a_0 < 23/4 \\ a_0 - 5, & 23/4 \leq a_0 \leq 35 \end{cases} \qquad V_5^* = \begin{cases} 20a_0/23, & 0 \leq a_0 < 23/4 \\ 5, & 23/4 \leq a_0 \leq 35 \end{cases}$$

1.5.1.2 Formulas for the System With the SEL

Now, we derive the V_4^* and V_5^* formulas for system (1.6). These formulas will be constructed using the results from sections 1.3.1.1 and 1.3.1.2 with Y^* in its α region; we will not make graphs for the equilibria with Y^* in its γ region described in section 1.3.3.

We begin with $K_3^2 = K_5$ and the equilibria results from 1.3.1.1. Starting with the (α, α, α) subcase, we have the parameter condition $\dfrac{a_0 a_1 K_3^3}{a_0 a_3 K_1 + a_1 a_5 K_3^3} < 1$. Using the parameter values in (1.12), this can be rearranged to give an upper bound on a_0:

$$\begin{aligned}
\frac{a_0 a_1 K_3^3}{a_0 a_3 K_1 + a_1 a_5 K_3^3} &< 1 \\
\iff \frac{10 a_0}{7.5 a_0 + 50} &< 1 \\
\iff 2.5 a_0 &< 50 \\
\iff a_0 &< 20
\end{aligned}$$

For V_4^*, we have

$$\begin{aligned}
V_4^* &= a_4 \frac{X_4^*}{2K_4} \\
&= \frac{a_4}{2K_4} \cdot \frac{2 a_0^2 a_3 K_1 K_4}{a_4 (a_0 a_3 K_1 + a_1 a_5 K_3^3)} \\
&= \frac{a_0^2 a_3 K_1}{a_0 a_3 K_1 + a_1 a_5 K_3^3} \\
&= \frac{7.5 a_0^2}{7.5 a_0 + 50} \\
&= \frac{3 a_0^2}{3 a_0 + 20}
\end{aligned}$$

from (1.13) and the given X_4^*, while V_5^* is

$$\begin{aligned}
V_5^* &= a_5 \frac{X_2^*}{2K_5} \\
&= \frac{a_5}{2K_5} \cdot \frac{2 a_0 a_1 K_3^3 K_5}{a_0 a_3 K_1 + a_1 a_5 K_3^3} \\
&= \frac{a_0 a_1 a_5 K_3^3}{a_0 a_3 K_1 + a_1 a_5 K_3^3} \\
&= \frac{50 a_0}{7.5 a_0 + 50} \\
&= \frac{20 a_0}{3 a_0 + 20}.
\end{aligned}$$

The only other subcase with possible equilibria when $K_3^2 = K_5$ is (α, γ, α). With r_5 in its saturated region, V_5^* is just $a_5 = 5$. Meanwhile, V_4^* is given by

$$\begin{aligned} V_4^* &= a_4 \frac{X_4^*}{2K_4} \\ &= \frac{a_4}{2K_4} \cdot \frac{2a_0 a_3 K_1 K_4}{a_1 a_4 K_3^3} \\ &= \frac{a_0 a_3 K_1}{a_1 K_3^3} \\ &= \frac{7.5 a_0}{10} \\ &= \frac{3}{4} a_0. \end{aligned}$$

The condition on a_0 in this subcase is

$$\begin{aligned} a_0 &= \frac{a_1 a_5 K_3^3}{a_1 K_3^3 - a_3 K_1} \\ &= \frac{50}{2.5} \\ &= 20, \end{aligned}$$

which falls short of the upper bound of 35 we want. To continue the graphs for $a_0 > 20$, we must find a way to extend the definitions of V_4^* and V_5^* beyond values of a_0 for which equilibria are possible. In the (α, γ, α) subcase, the differential equations are

$$\begin{aligned} \dot{Y} &= a_0 - a_1 \frac{Y}{2K_1} - a_3 \frac{Y}{2K_3^3} + a_4 \frac{X_4}{2K_4} \\ \dot{X}_2 &= a_1 \frac{Y}{2K_1} - a_3 \frac{Y}{2K_3^3} - a_5 \\ \dot{X}_4 &= a_3 \frac{Y}{2K_3^3} - a_4 \frac{X_4}{2K_4}, \end{aligned}$$

none of which depend on X_2. From (1.8) and the fact that we have $K_1 = K_3^3 = 0.1$ in (1.12), the given value of Y^* is valid for all $a_0 < a_1 = 100$. Similarly, the X_4^* value in this subcase falls in the α region if and only if

$$\frac{2a_0 a_3 K_1 K_4}{a_1 a_4 K_3^3} < 2K_4 \iff a_0 < \frac{a_1 a_4 K_3^3}{a_3 K_1} = 100.$$

Thus, when a_0 is between 20 and 35, the equilibrium values for Y and X_4 given in the (α, γ, α) subcase in 1.3.1.1 are still possible. We will then assume that as we increase a_0 up to 35, the values of Y and X_4 will continue to follow the given Y^* and X_4^* formulas, with both variables remaining in their α regions. As a result, the $\dot{Y}$ and $\dot{X}_4$ equations will both remain equal to zero.

The $a_0 = \dfrac{a_1 a_5 K_3^3}{a_1 K_3^3 - a_3 K_1}$ condition, as presented in 1.3.1.1, is necessary and sufficient for

$\dot{X}_2 = 0$ to hold. With Y at its equilibrium value and the system parameters set to the values in (1.12), the $\dot{X}_2$ equation becomes

$$\begin{aligned}\dot{X}_2 &= Y^*\left(\frac{a_1}{2K_1} - \frac{a_3}{2K_3^3}\right) - a_5\\ &= \frac{2a_0K_1}{a_1}\left(\frac{a_1}{2K_1} - \frac{a_3}{2K_3^3}\right) - a_5\\ &= \frac{0.2a_0}{100}\left(\frac{25}{0.2}\right) - 5\\ &= \frac{1}{4}a_0 - 5.\end{aligned}$$

When $a_0 > \dfrac{a_1a_5K_3^3}{a_1K_3^3 - a_3K_1} = 20$, this equation is positive. Thus, X_2 will increase when a_0 increases above 20. However, as X_2 was already in its γ region, this increase will not have an effect on V_5^*; X_2 will remain in the γ region, and r_5 will remain saturated.

In summary, when $20 < a_0 \leq 35$, we will graph the fluxes using the same formulas derived above for $a_0 = 20$. That is, the formulas $V_4^* = 3a_0/4$ and $V_5^* = 5$ will be used for all a_0 in the interval $[20, 35]$.

Next, we consider the $K_3^2 = 10K_5$ and $K_3^2 = 100K_5$ cases. As usual, we start with the (α, α, α) subcase in section 1.3.1.2. The upper bound on a_0 in this subcase is

$$\begin{aligned}\frac{a_0a_1K_3^2K_3^3}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3} &< 1\\ \iff \frac{10K_3^2a_0}{7.5a_0 + 50K_3^2} &< 1\\ \iff a_0(10K_3^2 - 7.5) &< 50K_3^2\\ \iff \begin{cases} a_0 < \dfrac{200}{37}, & K_3^2 = 10\\ a_0 < \dfrac{2000}{397}, & K_3^2 = 100.\end{cases}\end{aligned}$$

Our formula for V_4^* is

$$\begin{aligned}V_4^* &= a_4\frac{X_4^*}{2K_4}\\ &= \frac{a_4}{2K_4}\cdot\frac{2a_0^2a_3K_1K_4K_5}{a_4(a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3)}\\ &= \frac{a_0^2a_3K_1K_5}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3}\end{aligned}$$

$$
\begin{aligned}
&= \frac{7.5a_0^2}{7.5a_0 + 50K_3^2} \\
&= \begin{cases} \dfrac{3a_0^2}{3a_0+200}, & K_3^2 \;=\; 10 \\ \dfrac{3a_0^2}{3a_0+2000}, & K_3^2 \;=\; 100, \end{cases}
\end{aligned}
$$

while for V_5^*, we have

$$
\begin{aligned}
V_5^* &= a_5 \frac{X_2^*}{2K_5} \\
&= \frac{a_5}{2K_5} \cdot \frac{2a_0a_1K_3^2K_3^3K_5}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3} \\
&= \frac{a_0a_1a_5K_3^2K_3^3}{a_0a_3K_1K_5 + a_1a_5K_3^2K_3^3} \\
&= \frac{50K_3^2a_0}{7.5a_0 + 50K_3^2} \\
&= \begin{cases} \dfrac{200a_0}{3a_0+200}, & K_3^2 \;=\; 10 \\ \dfrac{2000a_0}{3a_0+2000}, & K_3^2 \;=\; 100. \end{cases}
\end{aligned}
$$

The next subcase in 1.3.1.2 is (α, β, α). We have the parameter condition

$$
\frac{K_5}{K_3^2} \;\le\; \frac{(a_0-a_5)a_1K_3^3}{a_0a_3K_1} \;<\; 1 \iff \frac{1}{K_3^2} \;\le\; \frac{10(a_0-5)}{7.5a_0} \;<\; 1,
$$

which can be rearranged to

$$
\begin{cases} 200/37 \;\le\; a_0 \;<\; 20, & K_3^2 \;=\; 10 \\ 2000/397 \;\le\; a_0 \;<\; 20, & K_3^2 \;=\; 100. \end{cases}
$$

Then, we have

$$
\begin{aligned}
V_4^* &= a_4 \frac{X_4^*}{2K_4} \\
&= \frac{a_4}{2K_4} \cdot \frac{2(a_0-a_5)K_4}{a_4} \\
&= a_0 - a_5 \\
&= a_0 - 5
\end{aligned}
$$

and $V_5^* = a_5 = 5$ since $r_5(X_2^*) = 1$ when X_2^* is in its β region.

The final subcase is (α, γ, α), which is identical to the same subcase when $K_3^2 = K_5$. Thus, V_4^* and V_5^* will be graphed over $20 \leq a_0 \leq 35$, beyond values of a_0 for which equilibria are possible, with $V_4^* = 3a_0/4$ and $V_5^* = 5$.

The graph formulas derived in this section are listed below.

Graphs with $\mathbf{K_3^2 = K_5}$

$$V_4^* = \begin{cases} \dfrac{3a_0^2}{3a_0 + 20}, & 0 \leq a_0 < 20 \\ 3a_0/4, & 20 \leq a_0 \leq 35 \end{cases} \qquad V_5^* = \begin{cases} \dfrac{20a_0}{3a_0 + 20}, & 0 \leq a_0 < 20 \\ 5, & 20 \leq a_0 \leq 35 \end{cases}$$

Graphs with $\mathbf{K_3^2 = 10K_5}$

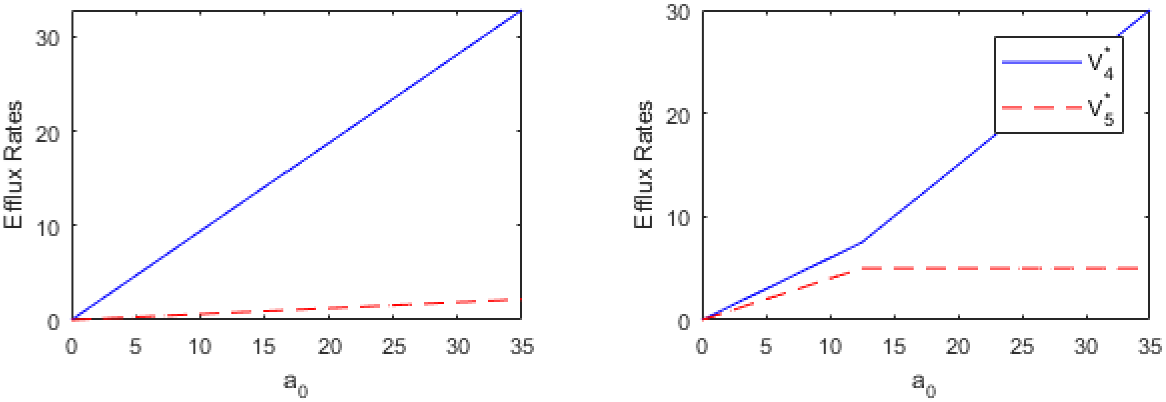
$$V_4^* = \begin{cases} \dfrac{3a_0^2}{3a_0 + 200}, & 0 \leq a_0 < 200/37 \\ a_0 - 5, & 200/37 \leq a_0 < 20 \\ 3a_0/4, & 20 \leq a_0 \leq 35 \end{cases} \qquad V_5^* = \begin{cases} \dfrac{200a_0}{3a_0 + 200}, & 0 \leq a_0 < 200/37 \\ 5, & 200/37 \leq a_0 \leq 35 \end{cases}$$

Graphs with $\mathbf{K_3^2 = 100K_5}$

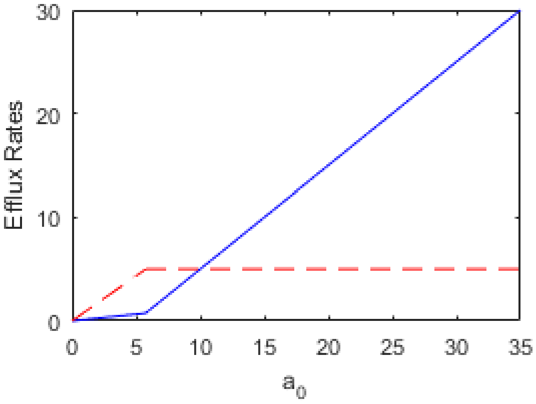
$$V_4^* = \begin{cases} \dfrac{3a_0^2}{3a_0 + 2000}, & 0 \leq a_0 < 2000/397 \\ a_0 - 5, & 2000/397 \leq a_0 < 20 \\ 3a_0/4, & 20 \leq a_0 \leq 35 \end{cases} \qquad V_5^* = \begin{cases} \dfrac{2000a_0}{3a_0 + 2000}, & 0 \leq a_0 < 2000/397 \\ 5, & 2000/397 \leq a_0 \leq 35 \end{cases}$$

1.5.2 Flux Graphs for the Three-Variable Ramp System

With the formulas derived, we now present and discuss the graphs of V_4^* and V_5^* for the three-variable ramp system. The graphs for the system without the SEL are shown in Figure 7, while the graphs displayed in Figure 8 are for the system with the SEL. All graphs were created using MATLAB.



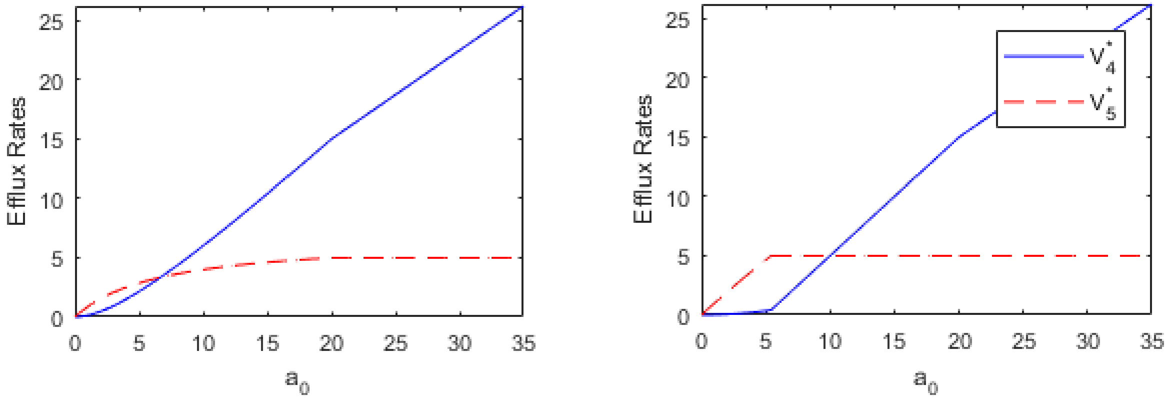
(a) $K_3^2 = K_5$ (b) $K_3^2 = 10K_5$



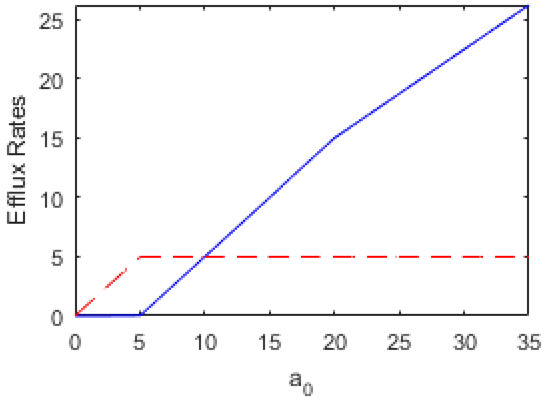
(c) $K_3^2 = 100K_5$

Figure 7: Graphs of the equilibrium fluxes V_4^* (blue, secondary metabolic pathway) and V_5^* (red, primary metabolic pathway) for the three-variable ramp system (1.7) without the SEL.

The graphs in Figure 7 resemble those shown in [1] for the system without the SEL. When K_3^2 is set equal to K_5 or $10K_5$, the fluxes are approximately linear functions of a_0 (except V_5^* when $K_3^2 = 10K_5$, which is more comparable to one of our ramp functions) and flux into the secondary (monolignol) pathway (V_4^*) always exceeds flux into the primary (protein synthesis) pathway (V_5^*) for positive a_0. It is only when K_3^2 is much larger than K_5 that we have evidence of metabolic regulation; when $K_3^2 = 100K_5$, flux into the primary pathway quickly reaches its maximum at $a_0 = 23/4$ and eclipses flux into the monolignol pathway when $a_0 < 10$.



(a) $K_3^2 = K_5$ (b) $K_3^2 = 10K_5$



(c) $K_3^2 = 100K_5$

Figure 8: Graphs of the equilibrium fluxes V_4^* (blue, secondary metabolic pathway) and V_5^* (red, primary metabolic pathway) for the three-variable ramp system (1.6) with the SEL.

Similarly, the graphs for the system with the SEL in Figure 8 resemble their counterparts in [1]. In each of the three, evidence of PSV type regulation is present; there is an interval of small, positive a_0 values for which V_5^* is greater than V_4^* in each graph, with V_5^* reaching its maximum or near-maximum.

1.6 Michaelis-Menten Comparisons and Conclusion

Figures 7 and 8 suggest that equilibrium flux into primary and secondary metabolic pathways in the three-variable ramp system behaves similarly to flux in the original Adams model in [1]. That is, the SEL plays a PSV type role in plant phenylalanine metabolism in which protein synthesis from phenylalanine will be prioritized over the use of phenylalanine in the monolignol pathway when shikimate is being produced at a low rate, regardless of whether the threshold constant of the monolignol pathway (K_3^2) is similar in magnitude to or much larger than that of the primary pathway (K_5). Meanwhile, when the SEL is absent, this metabolic regulation only occurs when it is significantly more difficult for phenylalanine to enter the monolignol pathway than the pathway in which protein is made.

Equilibria results for the three-variable ramp system also show similarities to those in [1]. Ahead of section 1.3, we mentioned that the original Adams model, both with and without the SEL, was determined to have a unique, asymptotically stable equilibrium when certain restrictions on parameters were met. While equilibria in the ramp version of the model are not always asymptotically stable due to the possibility of zero eigenvalues, there are always parameter conditions that allow the three-variable ramp system — regardless of whether we are looking at the system with or without the SEL, or whether $K_5 = K_3^2$ or $K_5 < K_3^2$ — to have a unique, asymptotically stable equilibrium; for instance, each of the equilibria summaries in sections 1.3.1.1, 1.3.1.2, 1.4.1.1, and 1.4.1.2 provides such parameter conditions for an (α, α, α) equilibrium.

Conditions on parameters required for the existence of equilibria also show similarities between the two models. For example, section 1.3 established $a_0 \leq a_1$ as one of the necessary and sufficient conditions for equilibria to exist in system (1.6) with the SEL, while $a_0 < a_1$ was such a condition for the Michaelis-Menten version of the system in [1]. Each version of the SEL system had additional parameter conditions, such as those described in sections 1.3.1 and 1.3.3 for system (1.6), though further comparison is difficult; for instance, another necessary and sufficient bound on a_0 in [1] involved parameters (such a_2^+ and a_2^- from (1.1)) that were excluded from the ramp system due to combining X_1 and X_3 into one variable.

For the version of the model without the SEL, necessary and sufficient conditions for the existence of equilibria were almost identical between the Michaelis-Menten and ramp systems. From (1.11) and the summaries in sections 1.4.1.1 and 1.4.1.2, system (1.7) has equilibria if and only if $a_0 \leq a_1$ and $a_0 \leq a_3 + a_5$, while the Michaelis-Menten system in [1] had an equilibrium if and only if $a_0 < a_1$ and $a_0 < a_3 + a_5$.

Overall, our results in this chapter suggest that the three-variable ramp systems (1.6) and (1.7) behave similarly to the original four-variable, Michaelis-Menten versions of the Adams model analyzed in [1]. This in turn suggests that approximating Michaelis-Menten terms in a system of ordinary differential equations with the ramp functions we defined in Definition 1 back in section 1.2 does not change the general behaviour of the system. If this is true in general, then accurate analysis of any system following Michaelis-Menten kinetics can be made significantly easier through the use of ramp function approximations. In any case, the results presented here warrant further study of systems with Michaelis-Menten terms replaced by ramp functions.

Chapter 2

Biochemical Matrices and Ramp Systems

2.1 Defining Biochemical Matrices

With the analysis of the Adams model with ramp functions complete, we now want to study generalized n-variable systems of differential equations with ramp functions. In this chapter, we will define a class of systems, which we will call *biochemical ramp systems*, similar in structure to systems (1.6) and (1.7).

We characterize the structure of the Adams ramp systems using the (α, α, α) versions of the differential equations. The (α, α, α) subcase is used since no information is lost; in subcases with β or γ regions, variables disappear from equations, leaving behind constant terms that no longer appear in the Jacobian. With every variable in its α region, the equations are

$$\begin{aligned} \dot{Y} &= a_0 - a_1\frac{Y}{2K_1} - a_3\frac{X_2Y}{4K_3^2K_3^3} + a_4\frac{X_4}{2K_4} \\ \dot{X}_2 &= a_1\frac{Y}{2K_1} - a_3\frac{X_2Y}{4K_3^2K_3^3} - a_5\frac{X_2}{2K_5} \\ \dot{X}_4 &= a_3\frac{X_2Y}{4K_3^2K_3^3} - a_4\frac{X_4}{2K_4} \end{aligned} \tag{2.1}$$

and

$$\begin{aligned} \dot{X}_1 &= a_0 - a_1\frac{X_1}{2K_1} \\ \dot{X}_2 &= a_1\frac{X_1}{2K_1} - a_3\frac{X_2}{2K_3^2} - a_5\frac{X_2}{2K_5} \\ \dot{X}_4 &= a_3\frac{X_2}{2K_3^2} - a_4\frac{X_4}{2K_4} \end{aligned} \tag{2.2}$$

for (1.6) and (1.7) respectively. Aside from the constant input term a_0, each term in these equations is proportional to the concentration of one or more chemical species in the system, reminiscent of the law of mass action mentioned in the Introduction.

In fact, the non-constant terms in (2.1) and (2.2) are derived from chemical reactions that follow mass action kinetics. These reactions and their corresponding differential equations are described below. For a detailed explanation of how these equations arise, see [7, ch. 2], for example.

Important Note: For each system of differential equations, we will also list the entries in the system's Jacobian. As we will see, the diagonal entries will always be non-positive; hence, throughout the rest of this thesis, we will use the notation $-a_{ii}$ with $a_{ii} \geq 0$ to denote the entry in the i^{th} row and i^{th} column of the matrices we will be discussing. For $j \neq i$, the entry in row i, column j will be denoted a_{ij}.

As an example, we would list the entries of the matrix

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

as $-a_{11} = -2$, $a_{21} = 1$, $a_{12} = 3$, and $-a_{22} = -4$.

Chemical Reactions Behind (2.1) and (2.2):

1) $W_i \xrightarrow{k} \_\_$

This represents the reaction in which a chemical species W_i is converted into a product not considered as part of our system. The number $k > 0$ is the *rate constant* for this reaction. The differential equation for this reaction, describing the change in the concentration of W_i with respect to time, is

$$[\dot{W_i}] = -k[W_i],$$

which gives us $-a_{ii} = -k$ in the Jacobian.

In Figures 2(b) and 3 in the first chapter, this type of reaction is represented by the arrow going from X_2 (the concentration of phenylalanine) to out_1 (the primary metabolic pathway, which is not modelled by a variable in our equations). The $\dot{X}_2$ equation in both (2.1) and (2.2) contains a $-\frac{a_5}{2K_5}X_2$ term as a result. Figure 2(b) also shows a similar relationship between X_4 and out_2, giving us the $-\frac{a_4}{2K_4}X_4$ term in the $\dot{X}_4$ equation in (2.2).

2) $W_i \xrightarrow{k} W_j$

The reaction in which W_i is converted to a different species in our system, W_j. The corresponding differential equations are

$$
\begin{aligned}
[\dot{W_i}] &= -k[W_i] \\
[\dot{W_j}] &= k[W_i],
\end{aligned}
$$

with Jacobian entries $-a_{ii} = -k$ and $a_{ji} = k$.

The $\pm\frac{a_1}{2K_1}Y$ and $\pm\frac{a_4}{2K_4}X_4$ terms in (2.1) and the $\pm\frac{a_1}{2K_1}X_1$ and $\pm\frac{a_3}{2K_3^2}X_2$ terms in (2.2) come from this reaction type.

3) $W_i + W_j \xrightarrow{k} W_m$

In this reaction, two different species W_i and W_j combine to form a new species, W_m. We have

$$
\begin{aligned}
[\dot{W_i}] &= -k[W_i][W_j] \\
[\dot{W_j}] &= -k[W_i][W_j] \\
[\dot{W_m}] &= k[W_i][W_j]
\end{aligned}
$$

as the system of differential equations in this case. Two columns of the Jacobian will be affected by this reaction; column i will have entries $-a_{ii} = -k[W_j]$, $a_{ji} = -k[W_j]$, and $a_{mi} = k[W_j]$, while in column j, we have $-a_{jj} = -k[W_i]$, $a_{ij} = -k[W_i]$, and $a_{mj} = k[W_i]$.

In Figure 3, the relationship between the species whose concentrations are given by Y, X_2, and X_4 is described by this type of reaction. This relationship is represented by the $\pm\frac{a_3}{4K_3^2K_3^3}X_2Y$ terms in (2.1).

4) $W_i \xrightarrow{k} W_j + W_m$

Finally, we have the reaction in which W_i dissociates into W_j and W_m, giving us the differential equations

$$
\begin{aligned}
[\dot{W_i}] &= -k[W_i] \\
[\dot{W_j}] &= k[W_i] \\
[\dot{W_m}] &= k[W_i].
\end{aligned}
$$

The Jacobian entries corresponding to these equations are $-a_{ii} = -k$, $a_{ji} = k$, and $a_{mi} = k$.

We are considering this type of reaction because it is represented in Figure 3 by the arrows from X_4 to Y and out_2. It should be noted, however, that this reaction type is not explicitly represented in the differential equations of the Adams model, since out_2 is not included as a variable.

With the information on chemical reactions laid out above, we characterize Jacobian matrices that are structurally similar to those of (2.1) and (2.2) ("Adams-like" Jacobians) in the following definition. This characterization will form a major part of our definition of biochemical ramp systems later in this chapter.

Definition 3. [*Adams-like Jacobian*] Let k denote a positive constant. Consider the n-variable system of differential equations $\dot{\vec{X}} = (\dot{X}_1, \dot{X}_2, \ldots, \dot{X}_n)$. The system $\dot{\vec{X}}$ is said to have an *Adams-like Jacobian* if its Jacobian can be written as

$$J(\vec{X}) \;=\; \sum_{\ell=1}^{p} J_\ell(\vec{X}),$$

where $p \in \mathbb{N}$ and each $J_\ell(\vec{X})$ is an $n \times n$ matrix whose entries take one of the following forms:

i) $-a_{ii} = -k$ for some i, and all other entries are zero

ii) $-a_{ii} = -k$ and $a_{ji} = k$ for some i and $j \neq i$, and all other entries are zero

iii) $-a_{ii} = -kX_j$, $a_{ji} = -kX_j$, $a_{mi} = kX_j$, and
$-a_{jj} = -kX_i$, $a_{ij} = -kX_i$, and $a_{mj} = kX_i$
for some i, j, and m all distinct, and all other entries are zero

iv) $-a_{ii} = -k$, $a_{ji} = k$, and $a_{mi} = k$ for some i, j, and m all distinct, and all other entries are zero

Note that k can take a different value in different $J_\ell(\vec{X})$.

Before we define biochemical ramp systems, it would be useful to examine the properties of Jacobian matrices satisfying Definition 3 when evaluated at an equilibrium point. To do this, we define a general class of matrices, called *biochemical matrices*, to describe Adams-like Jacobians evaluated at an equilibrium $\vec{X}^*$ (which, since our variables represent chemical concentrations, will be assumed to be non-negative componentwise):

Definition 4. [*Biochemical Matrix*] Let k, c, and d be constants such that $k > 0$, $c \geq 0$, and $d \geq 0$. An $n \times n$ matrix M is a *biochemical matrix* if it can be written as

$$M \;=\; \sum_{\ell=1}^{p} M_\ell,$$

where $p \in \mathbb{N}$ and each M_ℓ is an $n \times n$ matrix whose entries take one of the following forms:

i) $-a_{ii} = -k$ for some i, and all other entries are zero

ii) $-a_{ii} = -k$ and $a_{ji} = k$ for some i and $j \neq i$, and all other entries are zero

iii) $-a_{ii} = -c$, $a_{ji} = -c$, $a_{mi} = c$, and
$-a_{jj} = -d$, $a_{ij} = -d$, and $a_{mj} = d$
for some i, j, and m all distinct, and all other entries are zero

iv) $-a_{ii} = -k$, $a_{ji} = k$, and $a_{mi} = k$ for some i, j, and m all distinct, and all other entries are zero

Note that k, c, and d can take different values in different M_ℓ.

The properties of a biochemical matrix depend on which of the four M_ℓ types are present, and in what quantity. In the next few sections discussing properties of matrices satisfying Definition 4, we will use the follow terminology to distinguish between matrices with different M_ℓ types:

- A biochemical matrix with at least one M_ℓ of form *i)* or *ii)* in Definition 4 will be said to contain *single reactant and product* (SRP) terms, since the chemical reactions these forms arise from (reactions 1) and 2) described previously) have at most one reactant and one product.
- A biochemical matrix with at least one M_ℓ of form *iii)* contains *combining* terms, referring to reaction type 3) in which two reactants combine to form a product.
- A biochemical matrix with at least one M_ℓ of form *iv)* has *dissociation* terms as this form is derived from reaction 4), in which a species dissociates into two products.

Before we begin discussing matrix properties, we end this section with a few examples of matrices satisfying Definition 4.

2.1.1 Examples of Biochemical Matrices

Example 1. Consider the matrix $M = \sum_{\ell=1}^{3} M_\ell$ given by

$$\begin{bmatrix} -2 & 0 & 5 & 7 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & -5 & -7 \\ 0 & 1 & -5 & -7 \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 5 & 7 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -5 & -7 \\ 0 & 0 & -5 & -7 \end{bmatrix}.$$

This is a biochemical matrix with an M_ℓ of each of the first three types listed in Definition 4. The first component M_1 is of form *i)* with $k = 2$, while M_2 follows form *ii)* with $k = 1$. The third component, M_3, takes the form of *iii)* with $c = 5$ and $d = 7$.

Example 2. The matrix

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

contains a single combining term with $c = d = 2$, along with three SRP terms, one of form $i)$ and two of form $ii)$.

Example 3. In the matrix

$$\begin{bmatrix} -4 & 2 & 0 \\ 4 & -2 & 0 \\ 4 & 2 & -5 \end{bmatrix} = \begin{bmatrix} -4 & 0 & 0 \\ 4 & 0 & 0 \\ 4 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 2 & 0 \\ 0 & -2 & 0 \\ 0 & 2 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -5 \end{bmatrix},$$

we have one M_ℓ of form $i)$ and two dissociation terms, one with $k = 4$ and the other with $k = 2$.

Example 4. The Jacobian of (2.1) evaluated at an equilibrium point (Y^*, X_2^*, X_4^*) is

$$\begin{bmatrix} -\dfrac{a_1}{2K_1} - \dfrac{a_3X_2^*}{4K_3^2K_3^3} & -\dfrac{a_3Y^*}{4K_3^2K_3^3} & \dfrac{a_4}{2K_4} \\ \dfrac{a_1}{2K_1} - \dfrac{a_3X_2^*}{4K_3^2K_3^3} & -\dfrac{a_3Y^*}{4K_3^2K_3^3} - \dfrac{a_5}{2K_5} & 0 \\ \dfrac{a_3X_2^*}{4K_3^2K_3^3} & \dfrac{a_3Y^*}{4K_3^2K_3^3} & -\dfrac{a_4}{2K_4} \end{bmatrix} =$$

$$\begin{bmatrix} -\dfrac{a_1}{2K_1} & 0 & 0 \\ \dfrac{a_1}{2K_1} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} -\dfrac{a_3X_2^*}{4K_3^2K_3^3} & -\dfrac{a_3Y^*}{4K_3^2K_3^3} & 0 \\ -\dfrac{a_3X_2^*}{4K_3^2K_3^3} & -\dfrac{a_3Y^*}{4K_3^2K_3^3} & 0 \\ \dfrac{a_3X_2^*}{4K_3^2K_3^3} & \dfrac{a_3Y^*}{4K_3^2K_3^3} & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & -\dfrac{a_5}{2K_5} & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & \dfrac{a_4}{2K_4} \\ 0 & 0 & 0 \\ 0 & 0 & -\dfrac{a_4}{2K_4} \end{bmatrix}.$$

Example 5. The Jacobian of (2.2) is

$$\begin{bmatrix} -\dfrac{a_1}{2K_1} & 0 & 0 \\ \dfrac{a_1}{2K_1} & -\dfrac{a_3}{2K_3^2}-\dfrac{a_5}{2K_5} & 0 \\ 0 & \dfrac{a_3}{2K_3^2} & -\dfrac{a_4}{2K_4} \end{bmatrix} =$$

$$\begin{bmatrix} -\dfrac{a_1}{2K_1} & 0 & 0 \\ \dfrac{a_1}{2K_1} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & -\dfrac{a_3}{2K_3^2} & 0 \\ 0 & \dfrac{a_3}{2K_3^2} & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & -\dfrac{a_5}{2K_5} & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -\dfrac{a_4}{2K_4} \end{bmatrix}.$$

2.2 Properties of Single Reactant and Product Matrices

Single reactant and product matrices is the name we will give to biochemical matrices that *only* contain SRP terms. Looking at the structure of forms *i*) and *ii*) in Definition 4, it is easy to develop a characterization of SRP matrices, which we present in the theorem below.

Notation note: Since we are using $-a_{ii}$ to denote the i^{th} diagonal entry of a matrix, a_{ii} refers to the *absolute value* of the diagonal entry in the following theorem and beyond. However, we will still be using the notation $\sum_{j=1}^{n} a_{ji}$ to refer to the sum of the elements column i of the matrix, i.e.

$$\sum_{j=1}^{n} a_{ji} \;=\; a_{1i} + a_{2i} + \cdots + a_{i-1,i} - a_{ii} + a_{i+1,1} + \cdots + a_{ni}.$$

Theorem 2. *An $n \times n$ matrix A is an SRP matrix if and only if $\forall\, i$, column i satisfies all of the following:*

- $\sum_{j=1}^{n} a_{ji} \leq 0$
- $0 \leq \sum_{j \neq i} a_{ji} \leq a_{ii}$

- $a_{ji} \leq a_{ii} \quad \forall j \neq i$
- $-a_{ii} \leq 0$ *and* $a_{ji} \geq 0 \quad \forall j \neq i$
- $-a_{ii} = 0 \implies a_{ji} = 0 \quad \forall j \neq i$

Note that the second bullet point above can be equivalently expressed as $\sum_{j \neq i} |a_{ji}| \leq |a_{ii}|$; this means that any SRP matrix is *diagonally dominant* with respect to columns (see [16, ch. 1], for example).

The next theorem we will state here concerns 2×2 matrices. From Definition 4, combining and dissociation terms require a matrix to have at least three rows. Thus, we have the following:

Theorem 3. *All 2×2 matrices satisfying Definition 4 are SRP matrices.*

2.2.1 Eigenvalues of SRP Matrices

The properties listed in Theorem 2 restrict where the eigenvalues of SRP matrices can fall on the complex plane. To determine where on the plane eigenvalues can fall, we will use the *Gershgorin Circle Theorem* (see, for instance, [16, ch. 1]) applied to columns:

Theorem 4. ***[Gershgorin Circle Theorem]*** *Let A be an $n \times n$ matrix. Define the i^{th} Gershgorin disk $\Gamma_i(A)$ by*

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

where

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

Let λ be an eigenvalue of A. Then,

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

In other words, the Gershgorin Circle Theorem says that every eigenvalue of A falls in a disk on the complex plane, centred at a diagonal entry of A with a radius given by the sum of the absolute values of the off-diagonal elements in the same column. Using this, we have the following:

Theorem 5. *Consider an $n \times n$ SRP matrix A. Let λ be an eigenvalue of A. Then,*

i) $\mathfrak{Re}(\lambda) \leq 0$ *and*

ii) $\lambda = bi \implies b = 0$, *where i is the imaginary unit*

Proof. The i^{th} Gershgorin disk is centred at the non-positive real number $-a_{ii}$. From Theorem 2, the radius of this disk satisfies

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

With the radius being smaller than $-a_{ii}$ in magnitude, every point z in the disk satisfies $\mathfrak{Re}(z) \leq 0$. Additionally, the only point on the imaginary axis that the disk can touch is the origin. Thus, $\mathfrak{Re}(\lambda) \leq 0$ as λ must belong to at least one Gershgorin disk, and $0i = 0$ is the only purely imaginary value λ can take. □

In the case of 2×2 matrices, we also have the restriction that eigenvalues must be real:

Theorem 6. *Let A be a 2×2 matrix satisfying Definition 4. If λ is an eigenvalue of A, then $\lambda \in \mathbb{R}$.*

Proof. We have the matrix

$$A \;=\; \begin{bmatrix} -a & b \\ c & -d \end{bmatrix},$$

where a, b, c, and d are non-negative. The characteristic polynomial of A is given by

$$\lambda^2 + (a+d)\lambda + ad - bc,$$

which has discriminant

$$\begin{aligned} (a+d)^2 - 4(ad-bc) \;&=\; a^2 + 2ad + d^2 - 4ad + 4bc \\ &=\; a^2 - 2ad + d^2 + 4bc \\ &=\; (a-d)^2 + 4bc \\ &\geq\; 0. \end{aligned}$$

Thus, the roots of the characteristic polynomial are real. □

Theorem 6 does not apply to SRP matrices of size 3×3 or higher in general. As a counterexample, the SRP matrix

$$\begin{bmatrix} -2 & 1 & 0 \\ 0 & -2 & 1 \\ 1 & 0 & -2 \end{bmatrix}$$

has the complex conjugate pair of eigenvalues $\lambda \approx -2.5 \pm 0.8660i$.

2.2.2 Inverses of SRP Matrices

If an SRP matrix is invertible, the entries of its inverse will be non-positive. To show this, we will use the concept of a *non-singular M-matrix*. The following definition provides a couple of characterizations of such matrices that will be useful to us here. Note that these are far from being the only characterizations; for instance, the survey in [12] provides forty characterizations of non-singular M-matrices.

Definition 5. [*Non-Singular M-Matrix*] Let A be an invertible $n \times n$ matrix such that all off-diagonal entries of A are non-positive, i.e. $a_{ij} \leq 0$ for all $i \neq j$. Then, the following statements are equivalent:

- A is a non-singular M-matrix
- All entries of A^{-1} are non-negative
- If λ is an eigenvalue of A, then $\mathfrak{Re}(\lambda) > 0$

With that, we now have the following theorem:

Theorem 7. *Let A be an invertible SRP matrix. Then, all entries of A^{-1} are non-positive.*

Proof. If A is invertible, then by Theorems 2 and 5 we have the following:

- All off-diagonal entries of A are non-negative
- For any eigenvalue λ of A, $\mathfrak{Re}(\lambda) < 0$

This means that in the matrix $-A$, all off-diagonal entries are non-positive, and the real part of any eigenvalue is positive. Thus, by Definition 5 $-A$ is a non-singular M-matrix, and all entries of $-A^{-1}$ are non-negative. Hence, the entries of A^{-1} are all non-positive. $\square$

Theorem 7 gives us the following corollary regarding the signs of the determinant and cofactors C_{ij} of an invertible SRP matrix:

Corollary 1. Let A be an invertible $n \times n$ SRP matrix. Then,

- If n is even, $\det(A) > 0$ and $C_{ij} \leq 0 \;\; \forall i, j$
- If n is odd, $\det(A) < 0$ and $C_{ij} \geq 0 \;\; \forall i, j$

Proof. We prove the case in which n is even. The proof for odd n is similar.

Since A is invertible, by Theorem 5 all n eigenvalues of A have negative real parts. As n is even and $\det(A)$ is the product of the eigenvalues of A, we have $\det(A) > 0$. Each entry of A^{-1} has the form $\frac{C_{ij}}{\det(A)}$. Since $\det(A) > 0$ and the entries of A^{-1} are non-positive by Theorem 7, it must be the case that $C_{ij} \leq 0 \; \forall i, j$. $\square$

2.3 Properties of Matrices with Combining Terms

Now, we consider biochemical matrices that contain combining terms. That is, matrices satisfying Definition 4 with at least one M_ℓ of form *iii*), and an arbitrary number of M_ℓ of forms *i*) and *ii*). Note that in this thesis, we will not be considering matrices with both combining and dissociation terms. Hence, the matrices discussed in this section can be assumed to not have any M_ℓ of form *iv*).

Like with SRP matrices, several properties of the columns of matrices with combining terms can be derived from the structure of forms *i*), *ii*), and *iii*) in Definition 4. These properties are summarized in the theorem below.

Theorem 8. *Let* $A = \sum_{\ell=1}^{p} A_\ell$ *be a matrix satisfying Definition 4 such that each* A_ℓ *is of form i), ii), or iii). Then,* $\forall i$*, column* i *satisfies all of the following:*

- $\sum_{j=1}^{n} a_{ji} \leq 0$
- $0 \leq \sum_{j \neq i} a_{ji} \leq a_{ii}$
- $|a_{ji}| \leq a_{ii} \quad \forall j \neq i$
- $-a_{ii} \leq 0$
- $-a_{ii} = 0 \implies a_{ji} = 0 \quad \forall j \neq i$

When it comes to eigenvalues of matrices with combining terms, things are less restricted than in the case of SRP matrices. In general, the eigenvalues can be real or complex, with real parts that are negative, positive, or equal to zero. These eigenvalue possibilities are illustrated with the matrices in the next example.

Example 6. Eigenvalues of Matrices with Combining Terms
The single combining term matrix from Example 2 in section 2.1.1,

$$\begin{bmatrix} -5 & -2 & 0 \\ -2 & -2 & 4 \\ 5 & 2 & -5 \end{bmatrix},$$

has a real eigenvalue $\lambda_1 \approx -8.5511$ and two complex eigenvalues $\lambda_{2,3} \approx -1.7244 \pm 0.7312i$. Meanwhile, the eigenvalues of the matrix

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

are the real numbers -4, -3, and 0. Finally,

$$\begin{bmatrix} -5 & 0 & 6 & 10 \\ 0 & -7 & -5 & 14 \\ 0 & -7 & -11 & -10 \\ 0 & 7 & -1 & -28 \end{bmatrix} =$$

$$\begin{bmatrix} -5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -4 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 14 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -14 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -7 & -5 & 0 \\ 0 & -7 & -5 & 0 \\ 0 & 7 & 5 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 6 & 10 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -6 & -10 \\ 0 & 0 & -6 & -10 \end{bmatrix}$$

has three negative and one positive eigenvalues:

$$(\lambda_1, \lambda_2, \lambda_3, \lambda_4) \approx (-31.8205, -15.0562, -5, 0.8767)$$

Eigenvalues with positive real parts are possible in matrices with combining terms because, unlike SRP matrices, the radius of a Gershgorin disk can exceed its centre point in absolute value. This is evident with the 4×4 matrix in Example 6 with a positive eigenvalue; in three columns, the sum of the absolute values of the off-diagonal elements are larger than the absolute value of the diagonal entry. However, it is possible for combining term matrices to be column diagonally dominant (i.e. satisfy $\sum\limits_{j \neq i} |a_{ji}| \leq |a_{ii}| = a_{ii}$ for all i), and in that case we have the following:

Theorem 9. *Let* $A = \sum\limits_{\ell=1}^{p} A_\ell$ *be a matrix satisfying Definition 4 such that each* A_ℓ *is of form i), ii), or iii). Let* λ *be an eigenvalue of* A*. Then, if each column of* A *satisfies* $\sum\limits_{j \neq i} |a_{ji}| \leq a_{ii}$*,* $\mathfrak{Re}(\lambda) \leq 0$*.*

Proof. Follows from Theorems 4 and 8. □

The converse of this theorem does not hold, as shown by the two 3×3 matrices in Example 6.

2.3.1 Eigenvalues of 3×3 Matrices

Another sufficient condition for a matrix with combining terms to have only eigenvalues with non-positive real parts is the matrix being size 3×3. We prove this statement in the Theorem 10 at the end of this section. This proof requires the use of two lemmas, which we will state and prove first.

Lemma 1. *Suppose* $c_1, c_2, \ldots, c_6$ *are constants such that* $|c_i| \leq 1$ *for* $i = 1, 2, \ldots, 6$ *and* $0 \leq c_i + c_{i+1} \leq 1$ *for* $i = 1, 3, 5$. *Then,* $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 \leq 1$.

Proof. To prove this lemma, we will consider several cases regarding the signs of the c_i constants.

Case 1: all $\mathbf{c_i \geq 0}$

Here, we have $0 \leq c_{i+1} \leq 1 - c_i$ for $i = 1, 3, 5$. Thus,

$$\begin{aligned}
c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 &\leq (1-c_1)c_3(1-c_5) + c_1(1-c_3)c_5 + (1-c_1)c_5 \\
&\quad + (1-c_3)(1-c_5) + c_1c_3 \\
&= (c_3 - c_1c_3)(1-c_5) + c_1c_5 - c_1c_3c_5 + c_5 - c_1c_5 \\
&\quad + 1 - c_5 - c_3 + c_3c_5 + c_1c_3 \\
&= c_3 - c_3c_5 - c_1c_3 + c_1c_3c_5 - c_1c_3c_5 + 1 - c_3 + c_3c_5 + c_1c_3 \\
&= 1.
\end{aligned}$$

Cases with negative $\mathbf{c_i}$

Because of our assumption that $0 \leq c_i + c_{i+1}$ for $i = 1, 3, 5$, at most one c_i from each of the three pairs can be negative (e.g. it is not possible to have both $c_1 < 0$ and $c_2 < 0$). Thus, at most three c_i can be less than zero.

Case 2: exactly one $\mathbf{c_i}$ is negative

WLOG, suppose $c_1 < 0$. Then, for $i = 2, 3, \ldots, 6$, we have $0 \leq c_i \leq 1$. Using this and the fact that $0 \leq c_i + c_{i+1} \leq 1$ for $i = 1, 3, 5$,

$$\begin{aligned}
c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 &\leq c_2c_3c_6 + c_2c_5 + c_4c_6 \\
&\leq c_3c_6 + c_5 + c_4c_6 \\
&= c_6(c_3 + c_4) + c_5 \\
&\leq c_6 + c_5 \\
&\leq 1.
\end{aligned}$$

Case 3: exactly two $\mathbf{c_i}$ are negative

We will assume that one of the negative c_i is c_1 WLOG. Then, the other negative c_i must be one of c_3, c_4, c_5, or c_6.

I) *if* $c_1,\ c_3 < 0$

Given that $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 \ = \ c_2(c_3c_6 + c_5) + c_4(c_1c_5 + c_6) + c_1c_3$, we can proceed by considering the signs of $c_3c_6 + c_5$ and $c_1c_5 + c_6$.

i) *if* $c_3c_6 + c_5 \geq 0,\ c_1c_5 + c_6 \geq 0$

We have $c_2(c_3c_6 + c_5) + c_4(c_1c_5 + c_6) + c_1c_3 \ \leq \ c_3c_6 + c_5 + c_1c_5 + c_6 + c_1c_3$ since $0 \leq c_2 \leq 1$ and $0 \leq c_4 \leq 1$.

Now, suppose WLOG, that $c_3 \leq c_1$. Since c_6 is non-negative, this means that $c_3c_6 + c_5 + c_1c_5 + c_6 + c_1c_3 \ \leq \ c_1c_6 + c_5 + c_1c_5 + c_6 + c_1c_3 = (c_1 + 1)(c_5 + c_6) + c_1c_3$. Then, because $0 \leq c_5 + c_6 \leq 1$ and $|c_1| \leq 1 \implies c_1 + 1 \geq 0$, we have $(c_1 + 1)(c_5 + c_6) + c_1c_3 \ \leq \ c_1 + 1 + c_1c_3 = c_1(c_3 + 1) + 1$. Similarly, $c_3 + 1 \geq 0$, so $c_1(c_3 + 1) \leq 0$ and thus $c_1(c_3 + 1) + 1 \leq 1$.

Putting everything together, we therefore have that

$$\begin{aligned} c_2(c_3c_6 + c_5) + c_4(c_1c_5 + c_6) + c_1c_3 \ &\leq \ c_3c_6 + c_5 + c_1c_5 + c_6 + c_1c_3 \\ &\leq \ (c_1 + 1)(c_5 + c_6) + c_1c_3 \\ &\leq \ c_1(c_3 + 1) + 1 \\ &\leq \ 1. \end{aligned}$$

ii) *if* $c_3c_6 + c_5 \leq 0,\ c_1c_5 + c_6 \leq 0$

In this case, $c_2(c_3c_6 + c_5) + c_4(c_1c_5 + c_6) + c_1c_3 \ \leq \ c_1c_3 \ \leq \ 1$ since c_2 and c_4 are non-negative and $|c_1|, |c_3| \leq 1$.

iii) *if* $c_3c_6 + c_5 < 0,\ c_1c_5 + c_6 > 0$

Here, note that $0 \leq c_1 + c_2 \implies -c_1 \leq c_2 \implies c_2(c_3c_6 + c_5) \leq -c_1(c_3c_6 + c_5)$, and that $c_4 \leq 1 \implies c_4(c_1c_5 + c_6) \leq c_1c_5 + c_6$. Additionally, the fact that $c_6 \leq 1$ and $|c_1|, |c_3| \leq 1$ means $1 - c_1c_3 \geq 0$ and $c_6(1 - c_1c_3) \leq 1 - c_1c_3$.

Therefore, we have

$$\begin{aligned} c_2(c_3c_6 + c_5) + c_4(c_1c_5 + c_6) + c_1c_3 \ &\leq \ -c_1(c_3c_6 + c_5) + c_1c_5 + c_6 + c_1c_3 \\ &= \ -c_1c_3c_6 + c_6 + c_1c_3 \\ &= \ c_6(1 - c_1c_3) + c_1c_3 \\ &\leq \ 1 - c_1c_3 + c_1c_3 \\ &= \ 1. \end{aligned}$$

The case with $c_3c_6 + c_5 > 0$ and $c_1c_5 + c_6 < 0$ can be treated similarly.

II) *if* $c_1,\ c_4 < 0$

We have $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 \;=\; c_6(c_2c_3 + c_4) + c_5(c_1c_4 + c_2) + c_1c_3$, where $c_1c_4 + c_2 \geq 0$. The term $c_2c_3 + c_4$ can be positive, negative, or zero; we will consider each of these cases.

i) *if* $c_2c_3 + c_4 \leq 0$

Since $c_6 \geq 0$ and $c_5 \leq 1$, we have $c_6(c_2c_3 + c_4) \leq 0$ and $c_5(c_1c_4 + c_2) \leq c_1c_4 + c_2$. Furthermore, $c_1(c_3 + c_4) \leq 0$ since $0 \leq c_3 + c_4$. Thus,

$$\begin{aligned} c_6(c_2c_3 + c_4) + c_5(c_1c_4 + c_2) + c_1c_3 &\leq c_1c_4 + c_2 + c_1c_3 \\ &= c_1(c_3 + c_4) + c_2 \\ &\leq c_2 \\ &\leq 1. \end{aligned}$$

ii) *if* $c_2c_3 + c_4 > 0$

If $c_1c_4 + c_2 \leq c_2c_3 + c_4$, then, using the fact that $c_1 + c_2$, c_3, and $c_5 + c_6$ are each bounded between 0 and 1 and $c_4 < 0$,

$$\begin{aligned} c_6(c_2c_3 + c_4) + c_5(c_1c_4 + c_2) + c_1c_3 &\leq (c_5 + c_6)(c_2c_3 + c_4) + c_1c_3 \\ &\leq c_2c_3 + c_4 + c_1c_3 \\ &= c_3(c_1 + c_2) + c_4 \\ &\leq c_1 + c_2 + c_4 \\ &\leq 1 + c_4 \\ &< 1. \end{aligned}$$

On the other hand, if $c_2c_3 + c_4 < c_1c_4 + c_2$, then

$$\begin{aligned} c_6(c_2c_3 + c_4) + c_5(c_1c_4 + c_2) + c_1c_3 &\leq (c_5 + c_6)(c_1c_4 + c_2) + c_1c_3 \\ &\leq c_1c_4 + c_2 + c_1c_3 \\ &= c_1(c_3 + c_4) + c_2 \\ &\leq c_2 \\ &\leq 1 \end{aligned}$$

since $0 \leq c_5 + c_6 \leq 1$ and $0 \leq c_3 + c_4 \implies c_1(c_3 + c_4) \leq 0$.

The case in which $c_1 < 0$ and $c_5 < 0$ can be taken care of similarly.

III) *if* $c_1,\ c_6 < 0$

For this case, the only term in $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3$ that can be positive is c_2c_5, which cannot exceed 1. Thus, $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 \;\leq\; c_2c_5 \;\leq\; 1$.

Case 4: exactly three $\mathbf{c_i}$ are negative

We will assume once again, without loss of generality, that one of the negative c_i is c_1. Then, there are four possibilities for what the other two negative c_i are: c_3 and c_5, c_3 and c_6, c_4 and c_5, c_4 and c_6.

I) *if* $c_1,\ c_3,\ c_5 < 0$

Here, the fact that $0 \leq c_1 + c_2$ and $c_3c_6 + c_5 < 0$ implies $c_2(c_3c_6 + c_5) \leq -c_1(c_3c_6 + c_5)$. We also have $c_4(c_1c_5 + c_6) \leq c_1c_5 + c_6$ since $0 \leq c_4 \leq 1$ and $c_1c_5 + c_6 \geq 0$. Similarly, $0 \leq c_6 \leq 1$ and $1 - c_1c_3 \geq 0 \implies c_6(1 - c_1c_3) \leq 1 - c_1c_3$.

Thus, we have

$$\begin{aligned} c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 &= c_2(c_3c_6 + c_5) + c_4(c_1c_5 + c_6) + c_1c_3 \\ &\leq -c_1(c_3c_6 + c_5) + c_1c_5 + c_6 + c_1c_3 \\ &= -c_1c_3c_6 + c_6 + c_1c_3 \\ &= c_6(1 - c_1c_3) + c_1c_3 \\ &\leq 1 - c_1c_3 + c_1c_3 \\ &= 1. \end{aligned}$$

The cases with $c_1, c_3, c_6 < 0$ and $c_1, c_4, c_6 < 0$ can be handled in a similar manner.

II) *if* $c_1,\ c_4,\ c_5 < 0$

For this case, the only term of $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3$ that can be positive is $c_2c_3c_6$, which cannot exceed 1. Thus, $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 \ \leq \ c_2c_3c_6 \leq 1$.

Thus, for any sign combination of the c_i, we have $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 \leq 1$. $\square$

Lemma 2. *Suppose* $c_1, c_2, \ldots, c_6$ *are constants such that* $|c_i| \leq 1$ *for* $i = 1, 2, \ldots, 6$ *and* $0 \leq c_i + c_{i+1} \leq 1$ *for* $i = 1, 3, 5$. *Then, at least one of* $c_1c_3 - 1$, $c_2c_5 - 1$, *and* $c_4c_6 - 1$ *is negative.*

Proof. We have $c_jc_k \leq 1$ for any two of the c_i, and hence each of $c_1c_3 - 1$, $c_2c_5 - 1$, and $c_4c_6 - 1$ is less than or equal to zero. If all three were zero, then it would have to be the case that $|c_i| = 1$ for all $i = 1, 2, \ldots, 6$. Given the restriction $0 \leq c_i + c_{i+1} \leq 1$ for $i = 1, 3, 5$, this is only possible if one member of each c_i, c_{i+1} pair is 1 and the other -1. However, with three positive and three negative c_i, at least one of c_1c_3, c_2c_5, and c_4c_6 must be negative, and thus one of the $c_jc_k - 1$ must be negative as well. Hence, at least one of $c_1c_3 - 1$, $c_2c_5 - 1$, and $c_4c_6 - 1$ will be strictly less than zero. $\square$

With these lemmas proved, we now present and prove Theorem 10.

Theorem 10. *Let* $M = \sum_{\ell=1}^{p} M_\ell$ *be a* 3×3 *matrix satisfying Definition 4 such that each* M_ℓ *has form i), ii), or iii). If* λ *is an eigenvalue of* M*, then* $\mathfrak{Re}(\lambda) \leq 0$.

Proof. We have

$$M = \begin{bmatrix} -A & B & C \\ D & -E & F \\ G & H & -I \end{bmatrix},$$

where, by Theorem 8, the entries satisfy

$$\begin{array}{ccc} A \geq 0 & E \geq 0 & I \geq 0 \\ |D|, |G| \leq A & |B|, |H| \leq E & |C|, |F| \leq I \\ 0 \leq D + G \leq A & 0 \leq B + H \leq E & 0 \leq C + F \leq I. \end{array}$$

We will divide this proof into several cases regarding how many columns of zeros M has (or equivalently, how many of the diagonal entries are zero).

Case 1: M has one column of zeros

WLOG, suppose all entries in the first column are zero. Then, we have

$$M = \begin{bmatrix} 0 & B & C \\ 0 & -E & F \\ 0 & H & -I \end{bmatrix},$$

where E and I are both strictly positive. The characteristic equation is

$$\lambda[\lambda^2 + (I + E)\lambda + IE - FH] = 0,$$

which has a zero eigenvalue from the λ factor in front. In the quadratic term, $I + E$ is positive, while $IE - FH \geq 0$. Thus, the real parts of the roots of the quadratic must be non-positive.

Case 2: M has two columns of zeros

Suppose, WLOG, that the first and second column are full of zeros. Then,

$$M = \begin{bmatrix} 0 & 0 & C \\ 0 & 0 & F \\ 0 & 0 & -I \end{bmatrix},$$

which have eigenvalues 0, 0, and $-I < 0$.

Case 3: M has no columns of zeros

In this case, all three diagonal entries of M are strictly positive in absolute value. Using the properties of the off-diagonal elements listed at the beginning of this proof, we can write the matrix M in the form

$$M = \begin{bmatrix} -A & c_3E & c_5I \\ c_1A & -E & c_6I \\ c_2A & c_4E & -I \end{bmatrix},$$

where $|c_i| \leq 1$ for $i = 1, 2, \ldots, 6$ and $0 \leq c_i + c_{i+1} \leq 1$ for $i = 1, 3, 5$. The matrix has the characteristic equation

$$\lambda^3 - \operatorname{Tr}(M)\lambda^2 - (CG + FH + BD - AI - AE - EI)\lambda - \det(M) = 0.$$

We will proceed by examining the coefficients of this cubic in hopes of determining their signs. First, we have $-\operatorname{Tr}(M) = A + E + I$, which is positive. Determining the signs of the λ coefficient and the constant term will require the use of the two lemmas we proved.

For the degree one term, we have

$$\begin{aligned} -(CG + FH + BD - AI - AE - EI) &= -[c_2c_5AI + c_4c_6EI + c_1c_3AE - AI - AE - EI] \\ &= -[AE(c_1c_3 - 1) + AI(c_2c_5 - 1) + EI(c_4c_6 - 1)]. \end{aligned}$$

By Lemma 2, at least one of the $c_jc_k - 1$ terms is strictly less than zero. Each $c_jc_k - 1$ is multiplied by a positive number, and thus the sum in the square brackets is negative. With the negative sign out front, the λ coefficient is positive.

Finally, the constant term is

$$\begin{aligned} -\det(M) &= AEI - (AFH + BDI + BFG + CDH + CEG) \\ &= AEI - (c_4c_6AEI + c_1c_3AEI + c_2c_3c_6AEI + c_1c_4c_5AEI + c_2c_5AEI) \\ &= -AEI(c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 - 1). \end{aligned}$$

The term $c_2c_3c_6 + c_1c_4c_5 + c_2c_5 + c_4c_6 + c_1c_3 - 1$ is non-positive by Lemma 1. Multiplied by the negative term in front, we have $-\det(M) \geq 0$. We will break this inequality down into $-\det(M) > 0$ and $-\det(M) = 0$ cases.

I) $-\det(M) > 0$

In this case, all coefficients of the characteristic polynomial are positive. We will be able to apply the Routh-Hurwitz criterion stated in Theorem 1 in section 1.3.2 if we can show that $b_1b_2 - b_3 > 0$, where $b_3 = -\det(M)$ and

$$\begin{aligned} b_1b_2 &= -\operatorname{Tr}(M)[-(CG + FH + BD - AI - AE - EI)] \\ &= \operatorname{Tr}(M)[AE(c_1c_3 - 1) + AI(c_2c_5 - 1) + EI(c_4c_6 - 1)] \\ &= -[A + E + I][AE(c_1c_3 - 1) + AI(c_2c_5 - 1) + EI(c_4c_6 - 1)] \\ &= -[AEI(c_1c_3 - 1 + c_2c_5 - 1 + c_4c_6 - 1) + AE(A + E)(c_1c_3 - 1) \end{aligned}$$

$$
\begin{aligned}
&+AI(A+I)(c_2c_5-1)+EI(E+I)(c_4c_6-1)] \\
=\;& -AEI(c_1c_3+c_2c_5+c_4c_6-3)-[AE(A+E)(c_1c_3-1) \\
&+AI(A+I)(c_2c_5-1)+EI(E+I)(c_4c_6-1)].
\end{aligned}
$$

Let $\Sigma = -[AE(A+E)(c_1c_3-1)+AI(A+I)(c_2c_5-1)+EI(E+I)(c_4c_6-1)]$, which is positive by Lemma 2 and the fact that A, E, and I are positive. Then,

$$
\begin{aligned}
b_1b_2-b_3 &= -AEI(c_1c_3+c_2c_5+c_4c_6-3)+\Sigma \\
&\quad +AEI(c_2c_3c_6+c_1c_4c_5+c_2c_5+c_4c_6+c_1c_3-1) \\
&= AEI(c_2c_3c_6+c_1c_4c_5+2)+\Sigma.
\end{aligned}
$$

We have $|c_2c_3c_6+c_1c_4c_5| \leq |c_2c_3c_6|+|c_1c_4c_5| \leq 2$, and so the $AEI(c_2c_3c_6+c_1c_4c_5+2)$ term is non-negative. As $\Sigma > 0$, we conclude that $b_1b_2-b_3 > 0$. Thus, by Theorem 1 the real part of any eigenvalue of M must be negative.

II) $-\det(M) = 0$

When the constant term is zero, the characteristic equation becomes

$$\lambda[\lambda^2 - \mathrm{Tr}(M)\lambda - (CG+FH+BD-AI-AE-EI)] \;=\; 0.$$

The quadratic term has all positive coefficients, and thus its roots have negative real parts. With the λ term out front, all solutions of this equation satisfy $\mathfrak{Re}(\lambda) \leq 0$.

We thus conclude that the real part of any eigenvalue of a 3 × 3 matrix with combining terms is non-positive. □

2.3.2 Matrices with One Combining Term

Biochemical matrices with exactly one combining term (i.e. matrices satisfying Definition 4 such that exactly one M_ℓ is of form *iii*), and any other M_ℓ are of forms *i*) or *ii*)) also have identifiable properties regarding eigenvalues and invertibility. We will state and prove these properties in the next few theorems, making use of the fact that a matrix A' with one combining term and at least one SRP term can be written in the form

$$A' \;=\; A + M_\ell,$$

where A is an SRP matrix and M_ℓ is of form *iii*) from Definition 4. For instance, the matrix with one combining term from Example 2 in section 2.1.1 can be written as

$$
\begin{bmatrix} -5 & -2 & 0 \\ -2 & -2 & 4 \\ 5 & 2 & -5 \end{bmatrix}
=
\begin{bmatrix} -3 & 0 & 0 \\ 0 & 0 & 4 \\ 3 & 0 & -5 \end{bmatrix}
+
\begin{bmatrix} -2 & -2 & 0 \\ -2 & -2 & 0 \\ 2 & 2 & 0 \end{bmatrix}.
$$

The first theorem we present provides a sufficient condition for matrices with one combining term to be invertible.

Theorem 11. *Let A and M_ℓ be $n \times n$ matrices such that A is an SRP matrix and M_ℓ is of form iii) from Definition 4. If A is invertible, then so is $A' = A + M_\ell$.*

Proof. WLOG, we will assume that the indices i, j, and m from *iii)* in Definition 4 for M_ℓ are equal to 1, 2, and 3 respectively. Thus, we have

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

where c and d are non-negative, with A' then having the form

$$\begin{bmatrix} -a_{11} - c & a_{12} - d & a_{13} & \dots & a_{1n} \\ a_{21} - c & -a_{22} - d & a_{23} & \dots & a_{2n} \\ a_{31} + c & a_{32} + d & -a_{33} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{bmatrix}.$$

We will also be assuming, without loss of generality, that n is even (the proof when n is odd is similar). By Corollary 1, this means that $\det(A)$ is positive. Our goal here will be to show that $\det(A') \geq \det(A)$.

To find an expression for $\det(A')$, we use the fact that if J_1, J_2, and J_3 are matrices only differing in the i^{th} column, and the sum of the i^{th} columns of J_2 and J_3 equals the i^{th} column of J_1, then $\det(J_1) = \det(J_2) + \det(J_3)$. This gives us

$$\det(A') = \begin{vmatrix} -a_{11} - c & a_{12} - d & a_{13} & \dots & a_{1n} \\ a_{21} - c & -a_{22} - d & a_{23} & \dots & a_{2n} \\ a_{31} + c & a_{32} + d & -a_{33} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{vmatrix}$$

$$= \begin{vmatrix} -a_{11} & a_{12}-d & a_{13} & \dots & a_{1n} \\ a_{21} & -a_{22}-d & a_{23} & \dots & a_{2n} \\ a_{31} & a_{32}+d & -a_{33} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & \dots & -a_{nn} \end{vmatrix} + \begin{vmatrix} -c & a_{12}-d & a_{13} & \dots & a_{1n} \\ -c & -a_{22}-d & a_{23} & \dots & a_{2n} \\ c & a_{32}+d & -a_{33} & \dots & a_{3n} \\ 0 & a_{42} & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn} \end{vmatrix}.$$

From here, the left determinant can be expressed as

$$\det(A) + \begin{vmatrix} -a_{11} & -d & a_{13} & \dots & a_{1n} \\ a_{21} & -d & a_{23} & \dots & a_{2n} \\ a_{31} & d & -a_{33} & \dots & a_{3n} \\ a_{41} & 0 & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & 0 & a_{n3} & \dots & -a_{nn} \end{vmatrix},$$

while the right determinant is equal to

$$\begin{vmatrix} -c & a_{12} & a_{13} & \dots & a_{1n} \\ -c & -a_{22} & a_{23} & \dots & a_{2n} \\ c & a_{32} & -a_{33} & \dots & a_{3n} \\ 0 & a_{42} & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn} \end{vmatrix} + \begin{vmatrix} -c & -d & a_{13} & \dots & a_{1n} \\ -c & -d & a_{23} & \dots & a_{2n} \\ c & d & -a_{33} & \dots & a_{3n} \\ 0 & 0 & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & a_{n3} & \dots & -a_{nn} \end{vmatrix}.$$

This last determinant is zero due to the proportional columns. As a result, we have

$$\det(A') = \det(A) + \begin{vmatrix} -a_{11} & -d & a_{13} & \dots & a_{1n} \\ a_{21} & -d & a_{23} & \dots & a_{2n} \\ a_{31} & d & -a_{33} & \dots & a_{3n} \\ a_{41} & 0 & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & 0 & a_{n3} & \dots & -a_{nn} \end{vmatrix} + \begin{vmatrix} -c & a_{12} & a_{13} & \dots & a_{1n} \\ -c & -a_{22} & a_{23} & \dots & a_{2n} \\ c & a_{32} & -a_{33} & \dots & a_{3n} \\ 0 & a_{42} & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & a_{n2} & a_{n3} & \dots & -a_{nn} \end{vmatrix}.$$

The middle determinant in the above sum evaluates to $-dC_{12} - dC_{22} + dC_{32}$, where the C_{i2} are cofactors of the SRP matrix A. Since n is even, $C_{12} \leq 0$ by Corollary 1. As $-d$ is also non-positive, the term $-dC_{12}$ must be non-negative. Then, $-dC_{22} + dC_{32}$ is the determinant of the SRP matrix

$$\begin{bmatrix} -a_{11} & 0 & a_{13} & \dots & a_{1n} \\ a_{21} & -d & a_{23} & \dots & a_{2n} \\ a_{31} & d & -a_{33} & \dots & a_{3n} \\ a_{41} & 0 & a_{43} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & 0 & a_{n3} & \dots & -a_{nn} \end{bmatrix},$$

which is A with its second column replaced. If the determinant of this matrix is not zero, then Corollary 1 says it must be positive. As a result, $-dC_{22} + dC_{32} \geq 0$.

Hence, $-dC_{12} - dC_{22} + dC_{32} \geq 0$. Similarly, the third determinant in the above sum is $-cC_{11} - cC_{21} + cC_{31} \geq 0$. We then have $\det(A') \geq \det(A) > 0$, and thus A' is invertible. ☐

Note that the converse of this theorem is not true. To illustrate this, the single combining term matrix

$$\begin{bmatrix} -2 & 5 & 5 \\ 2 & -6 & -5 \\ 0 & -5 & -5 \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 \\ 2 & -1 & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 5 & 5 \\ 0 & -5 & -5 \\ 0 & -5 & -5 \end{bmatrix}$$

is invertible as its eigenvalues are approximately -11.6099 and $-0.6950 \pm 0.6150i$. However, the underlying SRP matrix

$$\begin{bmatrix} -2 & 0 & 0 \\ 2 & -1 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

has a column of zeros and is thus singular.

With Theorem 11, we can prove the following theorem regarding real eigenvalues of matrices with one combining term:

Theorem 12. *Let A and M_ℓ be $n \times n$ matrices such that A is an SRP matrix and M_ℓ is of form iii) from Definition 4. If $\lambda \in \mathbb{R}$ is an eigenvalue of $A' = A + M_\ell$, then $\lambda \leq 0$.*

Proof. We will prove the contrapositive. Suppose $\lambda \in \mathbb{R}$ is positive. Then, $-\lambda I = \sum_{\ell=1}^{n} J_\ell$, where I is the $n \times n$ identity matrix and for $\ell = 1, 2, \dots, n$, J_ℓ has $-a_{\ell\ell} = -\lambda$ and all other entries equal to zero. That is, each J_ℓ has form $i)$ from Definition 4.

Hence, $A - \lambda I$ is an SRP matrix. By Theorem 5 from section 2.2.1, A cannot have any positive eigenvalues. Thus, λ is not an eigenvalue of A, and so $A - \lambda I$ must be invertible. The matrix $A' - \lambda I = (A - \lambda I) + M_\ell$ must also be invertible by Theorem 11. Thus, $\lambda > 0$ is not an eigenvalue of A'. ☐

We conjecture that Theorem 12 can be generalized to cover both real and complex eigenvalues:

Conjecture 1. Let A and M_ℓ be $n \times n$ matrices such that A is an SRP matrix and M_ℓ is of form *iii*) from Definition 4. If λ is an eigenvalue of $A' = A + M_\ell$, then $\mathfrak{Re}(\lambda) \leq 0$.

We end this section by addressing the case in which a matrix has one combining term, but no SRP terms. In other words, when we just have an M_ℓ of form *iii*) from Definition 4.

Theorem 13. *Let M_ℓ be an $n \times n$ matrix of form iii) from Definition 4. Then, if λ is an eigenvalue of M_ℓ, $\lambda \in \mathbb{R}$ and $\lambda \leq 0$.*

Proof. We will assume, without loss of generality, that the indices i, j, and m from *iii*) in Definition 4 for M_ℓ are 1, 2, and 3 respectively. Thus, M_ℓ has the form

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

with characteristic polynomial

$$\begin{aligned} P(\lambda) &= (-\lambda)^{n-2}[(\lambda + d)(\lambda + c) - cd] \\ &= (-\lambda)^{n-2}[\lambda^2 + (c+d)\lambda] \\ &= (-\lambda)^{n-2}\lambda(\lambda + c + d). \end{aligned}$$

The roots of this polynomial are $\lambda = 0$ and $\lambda = -(c+d) \leq 0$. □

2.4 Properties of Matrices with Dissociation Terms

Finally, we examine the properties of biochemical matrices containing dissociation terms. These are matrices that satisfy Definition 4 and have at least one M_ℓ of form *iv*), with any number of M_ℓ taking forms *i*) and *ii*). We will assume that no M_ℓ are of form *iii*).

As usual, we begin with a few properties of the columns of matrices with dissociation terms:

Theorem 14. *Let $A = \sum_{\ell=1}^{p} A_\ell$ be a matrix satisfying Definition 4 such that each A_ℓ is of form i), ii), or iv). Then, $\forall i$, column i satisfies all of the following:*

- $a_{ji} \leq a_{ii} \quad \forall j \neq i$
- $-a_{ii} \leq 0$ *and* $a_{ji} \geq 0 \quad \forall j \neq i$

- $-a_{ii} = 0 \implies a_{ji} = 0 \quad \forall j \neq i$

Unlike terms of forms *i*), *ii*), and *iii*) in Definition 4, dissociation terms allow for positive column sums and for the sum of the off-diagonal elements in a column to exceed the absolute value of the diagonal entry. This is shown by the first two columns of the two dissociation term matrix

$$\begin{bmatrix} -4 & 2 & 0 \\ 4 & -2 & 0 \\ 4 & 2 & -5 \end{bmatrix}$$

from Example 3 in section 2.1.1.

Like matrices with combining terms, dissociation matrices are quite diverse when it comes to eigenvalues. Several examples of matrices with dissociation terms and their eigenvalues are provided in the next example. Most of the example matrices will be written as the sum of an SRP matrix and one or more M_ℓ of form *iv*).

Example 7. Eigenvalues of Matrices with Dissociation Terms
The Example 3 matrix

$$\begin{bmatrix} -4 & 2 & 0 \\ 4 & -2 & 0 \\ 4 & 2 & -5 \end{bmatrix}$$

has eigenvalues -6, -5, and 0. Positive eigenvalues are also possible; examples are the matrices

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

with the eigenvalue $\lambda \approx 0.2751$ (along with two negative eigenvalues approximately equal to -10.8208 and -15.4543), and

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

with $\lambda \approx 4.4372$ (as well as -14 and ≈ -7.4372). Meanwhile, the eigenvalues of

$$\begin{bmatrix} -4 & 7/16 & 0 \\ 4 & -1 & 0 \\ 4 & 1/16 & -1 \end{bmatrix} = \begin{bmatrix} 0 & 7/16 & 0 \\ 0 & -1 & 0 \\ 0 & 1/16 & -1 \end{bmatrix} + \begin{bmatrix} -4 & 0 & 0 \\ 4 & 0 & 0 \\ 4 & 0 & 0 \end{bmatrix}$$

are all negative: -4.5, -1, and -0.5. Finally,

$$\begin{bmatrix} -11 & 3 & 7 & 6 \\ 7 & -15 & 1 & 4 \\ 8 & 10 & -11 & 7 \\ 1 & 0 & 2 & -18 \end{bmatrix} = \begin{bmatrix} -5 & 3 & 7 & 6 \\ 1 & -15 & 1 & 4 \\ 2 & 10 & -11 & 7 \\ 1 & 0 & 2 & -18 \end{bmatrix} + \begin{bmatrix} -6 & 0 & 0 & 0 \\ 6 & 0 & 0 & 0 \\ 6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

has the complex eigenvalues $\lambda \approx -18.3860 \pm 4.0786i$ and two real eigenvalues which are approximately -19.0149 and 0.7868.

Example 7 shows that the equivalents of Theorems 10 and 12 for dissociation matrices do not hold; the real part of an eigenvalue of a 3×3 matrix with dissociation terms can be positive, and matrices can have positive real eigenvalues even with just one dissociation term. We do have, however, the equivalent of Theorem 9 for column diagonally dominant matrices with dissociation terms:

Theorem 15. *Let* $A = \sum_{\ell=1}^{p} A_\ell$ *be a matrix satisfying Definition 4 such that each* A_ℓ *is of form i), ii), or iv). Let* λ *be an eigenvalue of* A*. Then, if each column of* A *satisfies* $\sum_{j \neq i} |a_{ji}| \leq a_{ii}$, $\mathfrak{Re}(\lambda) \leq 0$.

Proof. Follows from Theorems 4 and 14. □

2.4.1 Inverses of Matrices with Dissociation Terms

Back in Theorem 7 in section 2.2.2, we established that the inverse of an SRP matrix has non-positive entries. A similar theorem exists for invertible dissociation matrices:

Theorem 16. *Let* $A = \sum_{\ell=1}^{p} A_\ell$ *be an invertible matrix satisfying Definition 4 such that each* A_ℓ *is of form i), ii), or iv). Then, all entries of* A^{-1} *are non-positive if and only if for every eigenvalue* λ *of* A, $\mathfrak{Re}(\lambda) < 0$.

Proof. Suppose the entries of A^{-1} are all non-positive. By Theorem 14, all off-diagonal entries of A are non-negative. As a result, $-A$ has non-positive off-diagonal entries, and all entries of $-A^{-1}$ are non-negative. Hence, $-A$ is a non-singular M-matrix by Definition 5, and all of its eigenvalues have positive real parts. Thus, every eigenvalue λ of A satisfies $\mathfrak{Re}(\lambda) < 0$.

The proof for the other direction is the same as the proof of Theorem 7. □

Several inverses of dissociation matrices are shown in Example 8 to illustrate how the signs of the entries can vary.

Example 8. Inverses of Matrices with Dissociation Terms
The matrices from Example 7 with positive eigenvalues have inverses given by:

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

$$\begin{bmatrix} -3 & 5 & 6 \\ 3 & -7 & 7 \\ 3 & 7 & -7 \end{bmatrix}^{-1} = \begin{bmatrix} 0 & 1/6 & 1/6 \\ 1/11 & 1/154 & 13/154 \\ 1/11 & 6/77 & 1/77 \end{bmatrix}$$

$$\begin{bmatrix} -11 & 3 & 7 & 6 \\ 7 & -15 & 1 & 4 \\ 8 & 10 & -11 & 7 \\ 1 & 0 & 2 & -18 \end{bmatrix}^{-1} = \begin{bmatrix} 1250/2653 & 138/379 & 1074/2653 & 1049/2653 \\ 221/758 & 115/758 & 91/379 & 85/379 \\ 3565/5306 & 339/758 & 1245/2653 & 1342/2653 \\ 535/5306 & 53/758 & 198/2653 & 60/2653 \end{bmatrix}$$

Notice how all entries of these inverse matrices are non-negative. In contrast, the inverse of the matrix with three negative eigenvalues is

$$\begin{bmatrix} -4 & 7/16 & 0 \\ 4 & -1 & 0 \\ 4 & 1/16 & -1 \end{bmatrix}^{-1} = \begin{bmatrix} -4/9 & -7/36 & 0 \\ -16/9 & -16/9 & 0 \\ -17/9 & -8/9 & -1 \end{bmatrix},$$

which has solely non-positive entries as predicted by Theorem 16.

When an invertible dissociation matrix has at least one eigenvalue with a positive real part, Theorem 16 says that A^{-1} must have at least one positive entry. Based on what we saw in Example 8, however, we hypothesize that there is a stronger restriction on the entries of the inverse matrix:

Conjecture 2. Let $A = \sum_{\ell=1}^{p} A_\ell$ be an invertible matrix satisfying Definition 4 such that each A_ℓ is of form *i*), *ii*), or *iv*). If A has at least one eigenvalue λ such that $\mathfrak{Re}(\lambda) > 0$, then all entries of A^{-1} are non-negative.

2.5 Defining Biochemical Ramp Systems

Finally, we will develop our definition of biochemical ramp systems in this section. We stated at the beginning of this chapter that we want this class of systems to be similar in structure to the Adams model in (1.6) and (1.7), and began to characterize this structure with the Adams-like Jacobian described in Definition 3 in section 2.1. The first thing we will do here is continue with this characterization.

The Jacobian structure defined in Definition 3 was based on the Jacobians of (1.6) and (1.7) with all variables in their α regions. Thus, we want the Jacobian of a general biochemical ramp system with every variable in its α region to satisfy this definition. However, this is a problem as the definition of the α region in Definition 2 back in section 1.3 only covers variables with one or two thresholds, but to keep our definition of biochemical ramp systems as general as possible, we would like to be able to include systems with variables associated with more than two thresholds. We circumvent this issue by introducing the following concept:

Definition 6. [*All Ramp Region*] Let $\dot{\vec{X}} = (\dot{X}_1, \dot{X}_2, \ldots, \dot{X}_n)$ be an n-variable system of differential equations with ramp functions. We say that the system is in the *all ramp region* if every ramp function is in its ramp region, i.e. the output of every ramp function belongs to $[0, 1)$.

Equivalently, a system is in the all ramp region if and only if for every i, the variable X_i is strictly below all of its thresholds. With this concept, we can refine what we wrote above to: the Jacobian of a general biochemical ramp system in the all ramp region satisfies Definition 3. Note that if the system has an equilibrium point in the all ramp region, then the Jacobian evaluated at the equilibrium is a biochemical matrix satisfying Definition 4.

Another aspect of the structure of systems (1.6) and (1.7) is that every time a variable appears in a differential equation, it does so as the input of a ramp function. For instance, the variable X_2 always appears as $r_3^2(X_2)$ or $r_5(X_2)$. We want this to hold for any biochemical ramp system, specifically for the *general formula* of any biochemical ramp system. Here, we are using “general formula” to refer to systems such as (1.6) and (1.7), where each ramp function is written in its general form $r_1(X_1)$, $r_4(X_4)$, etc., in contrast to systems such as (2.1) and (2.2), where each ramp function has been specified to fall in its ramp or saturated region.

It should be noted that it is acceptable if there is a variable that does not appear in any of the differential equations. The above is saying that *if* a variable appears in one or more equations, it must always do so in the context of a ramp function.

The final component of the structure of the three-variable Adams model with ramp functions we need to address is the constant input term a_0. Our definition of biochemical ramp systems will allow each variable to have such a term, which we will assume is non-negative.

Taking everything we have discussed into account, we now present the definition of a biochemical ramp system:

Definition 7. [*Biochemical Ramp System*] Let $\dot{\vec{X}} = (\dot{X}_1, \dot{X}_2, \ldots, \dot{X}_n)$ be an n-variable system of differential equations with ramp functions. The system $\dot{\vec{X}}$ is a *biochemical ramp system* if all of the following hold:

i) When $\dot{\vec{X}}$ is in the all ramp region, its Jacobian $J(\vec{X})$ satisfies Definition 3 *ii*) In the general formula of $\dot{\vec{X}}$, if a variable appears in one or more differential equations, it always does so as the input of a ramp function

iii) For all $i = 1, 2, \ldots, n$, $\dot{X}_i$ has a constant term $x_{i_0} \geq 0$

We conclude this chapter with examples of systems that do and do not qualify as biochemical ramp systems.

2.5.1 Examples and Non-Examples of Biochemical Ramp Systems

In each of the systems that follow, we will assume that the ramp functions r_1, r_2, and r_3 have thresholds $2\theta_1$, $2\theta_2$, and $2\theta_3$ respectively. We begin with several examples of systems that are not biochemical ramp systems, and state which of the three points in Definition 7 is violated.

Example 9. Point i) violated
Consider the system

$$\begin{aligned} \dot{X} &= 2r_1(X) + 1 \\ \dot{Y} &= -r_2(Y). \end{aligned}$$

The Jacobian of the system in the all ramp region is

$$J(\vec{X}) = \begin{bmatrix} 1/\theta_1 & 0 \\ 0 & -1/(2\theta_2) \end{bmatrix},$$

which does not satisfy Definition 3 as one of the diagonal entries is positive. Hence, the system is not a biochemical ramp system.

Example 10. Point ii) violated
The system

$$\begin{aligned} \dot{X} &= -2r_1(X) \\ \dot{Y} &= 2r_1(X) + -r_2(Y) + X + 2X^3 \end{aligned}$$

does not satisfy Definition 7 because in the $\dot{Y}$ equation, the variable X appears three times, but only once as the input of a ramp function.

Example 11. Point iii) violated
In the system

$$\begin{aligned} \dot{X} &= -2r_1(X) - 1 \\ \dot{Y} &= -r_2(Y), \end{aligned}$$

the constant term of $\dot{X}$ is negative, and thus this is not an example of a biochemical ramp system.

Now, we present a couple of examples of systems that do satisfy Definition 7.

Example 12. The system

$$\begin{aligned}\dot{X} &= -r_1(X)\\ \dot{Y} &= r_1(X)\end{aligned}$$

is a biochemical ramp system. The Jacobian when the system is in the all ramp region is

$$J(\vec{X}) = \begin{bmatrix} -1/(2\theta_1) & 0 \\ 1/(2\theta_1) & 0 \end{bmatrix},$$

which is composed of one $J_\ell(\vec{X})$ of form $ii)$ from Definition 3. The only variable that appears in the equations is X, and all of its appearances are as the input of r_1. Finally, the constant term of both equations is zero.

Example 13. Consider the system

$$\begin{aligned}\dot{X} &= -r_1(X)r_2(Y) + 0.5\\ \dot{Y} &= -r_1(X)r_2(Y) + 1\\ \dot{Z} &= r_1(X)r_2(Y) - r_3(Z).\end{aligned}$$

The constant terms in the differential equations are all greater than or equal to zero, all variables appear solely as the inputs of ramp functions, and the Jacobian in the all ramp region is

$$J(\vec{X}) = \begin{bmatrix} -\frac{1}{4\theta_1\theta_2}Y & -\frac{1}{4\theta_1\theta_2}X & 0 \\ -\frac{1}{4\theta_1\theta_2}Y & -\frac{1}{4\theta_1\theta_2}X & 0 \\ \frac{1}{4\theta_1\theta_2}Y & \frac{1}{4\theta_1\theta_2}X & -\frac{1}{2\theta_3} \end{bmatrix},$$

which has $J_\ell(\vec{X})$ of forms $i)$ and $iii)$ from Definition 3. Hence, Definition 7 is satisfied.

Chapter 3

Single Reactant and Product Systems

3.1 General Form of SRP Biochemical Ramp Systems

In this chapter, we will study equilibria and stability in *single reactant and product* biochemical ramp systems. We will consider a system satisfying Definition 7 to be an SRP system if its Jacobian when in the all ramp region is an SRP matix, i.e. each $J_\ell(\vec{X})$ is of form i) or ii) from Definitions 3 and 4 in section 2.1. An example of an SRP biochemical ramp system is the Adams model without the SEL in (1.7); the system's all ramp region Jacobian shown in Example 5 in section 2.1.1 only contains SRP terms.

To facilitate our analysis, the biochemical ramp systems studied in this and the following chapters will be assumed to have a single threshold per variable. In other words, we will be working with the restriction that the only ramp function the variable X_i is associated with is r_i, with threshold $2\theta_i$. System (1.7) with $K_3^2 = K_5$ is an example of an SRP system in which each variable has a single threshold.

With one threshold per variable, the SRP biochemical ramp system $\dot{\vec{X}} = (\dot{X}_1, \dot{X}_2, \ldots, \dot{X}_n)$ has the form

$$\begin{aligned}
\dot{X}_1 &= -a_{11}r_1(X_1) + a_{12}r_2(X_2) + \cdots + a_{1n}r_n(X_n) + x_{1_0} \\
\dot{X}_2 &= a_{21}r_1(X_1) - a_{22}r_2(X_2) + \cdots + a_{2n}r_n(X_n) + x_{2_0} \\
&\vdots \\
\dot{X}_n &= a_{n1}r_1(X_1) + a_{n2}r_2(X_2) + \cdots - a_{nn}r_n(X_n) + x_{n_0},
\end{aligned}$$

or using matrices and vectors,

$$\begin{bmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \vdots \\ \dot{X}_n \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & \ldots & a_{1n} \\ a_{21} & -a_{22} & \ldots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \ldots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(X_1) \\ r_2(X_2) \\ \vdots \\ r_n(X_n) \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ \vdots \\ x_{n_0} \end{bmatrix}.$$

Note that the $n \times n$ matrix A here is an SRP matrix. When the system is in the all ramp region, the Jacobian is the SRP matrix

$$J(\vec{X}) = \begin{bmatrix} -\dfrac{a_{11}}{2\theta_1} & \dfrac{a_{12}}{2\theta_2} & \cdots & \dfrac{a_{1n}}{2\theta_n} \\ \dfrac{a_{21}}{2\theta_1} & -\dfrac{a_{22}}{2\theta_2} & \cdots & \dfrac{a_{2n}}{2\theta_n} \\ \vdots & \vdots & \ddots & \vdots \\ \dfrac{a_{n1}}{2\theta_1} & \dfrac{a_{n2}}{2\theta_2} & \cdots & -\dfrac{a_{nn}}{2\theta_n} \end{bmatrix},$$

which is A with each column scaled by a positive constant. When an SRP term is multiplied by a positive scalar, it is still an SRP term. Thus, A is also an SRP matrix.

The general form of an SRP biochemical ramp system in which every variable has a single threshold is then

$$\dot{\vec{X}} = A\vec{r} + \vec{x_0}, \tag{3.1}$$

where

- A is an $n \times n$ SRP matrix
- $\vec{r} = [r_1(X_1), r_2(X_2), \ldots, r_n(X_n)]^T$ is the vector of ramp functions, where for each i,

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

- $\vec{x_0} = [x_{1_0}, x_{2_0}, \ldots, x_{n_0}]^T$ is the vector of constant input terms, with $x_{i_0} \ge 0$ for each i.

When studying equilibria in systems of form (3.1), we will mainly focus on equilibria in the all ramp region. This is useful as the ramp functions are injective in their ramp regions; every $r_i(X_i^*) \in [0, 1)$ corresponds to a unique X_i^* in $[0, 2\theta_i)$. Also, instead of solving for equilibria directly in terms of the X_i^*, we will solve in terms of the ramp functions, by finding the equilibrium ramp function vector $\vec{r^*}$. This is advantageous because we will just have to ensure that $\vec{r^*} < 1$ componentwise, instead of making sure each variable is below its threshold. Using $\vec{r^*}$ makes the individual thresholds of the X_i^* irrelevant when it comes to finding equilibria in the all ramp region.

If we do ever need to express an equilibrium in the all ramp region in terms of the X_i, converting between $\vec{r^*}$ and $\vec{X}^*$ is straightforward. If we have

$$\vec{r^*} = [s_1^*, s_2^*, \ldots, s_n^*]^T,$$

where each component falls in the interval $[0, 1)$, then for each i,

$$r_i(X_i^*) = s_i^* \iff \frac{X_i^*}{2\theta_i} = s_i^* \iff X_i^* = 2\theta_i s_i^*,$$

and thus

$$\vec{X^*} = [2\theta_1 s_1^*, 2\theta_2 s_2^*, \ldots, 2\theta_n s_n^*]^T.$$

We will now examine the conditions under which systems of form (3.1) have equilibria in the all ramp region, starting with the two-variable case.

3.2 Equilibria in Two-Variable Systems

When the matrix A in (3.1) is 2×2, we are dealing with a system of the form

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & b \\ c & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix}, \tag{3.2}$$

where a, b, c, and d are non-negative and $c \leq a$ and $b \leq d$. As we will see, whether this system has equilibria in the all ramp region depends on the values of the input terms x_0 and y_0. Some weak upper bounds on these constants, which are necessary for the existence of all ramp region equilibria, are provided in the next theorem.

Theorem 17. *Consider a system of form (3.2). If the system has an equilibrium in the all ramp region, then all three of $x_0 \leq a$, $y_0 \leq d$, and $x_0 + y_0 \leq a + d - b - c$ must hold. Additionally, if $ad - bc \neq 0$, these inequalities are strict.*

Proof. We have an equilibrium in which $r_1(X^*) < 1$ and $r_2(Y^*) < 1$. By contradiction, suppose that one of the given inequalities does not hold. If $x_0 > a$, then at equilibrium,

$$\begin{aligned} \dot{X} &= -ar_1(X^*) + br_2(Y^*) + x_0 \\ &> -ar_1(X^*) + br_2(Y^*) + a \\ &= a(1 - r_1(X^*)) + br_2(Y^*) \\ &\geq 0, \end{aligned}$$

contradicting that $\dot{X} = 0$. The $y_0 > d$ case is similar. If $x_0 + y_0 > a + d - b - c$, then

$$\begin{aligned} \dot{X} + \dot{Y} &= (-a + c)r_1(X^*) + (b - d)r_2(Y^*) + x_0 + y_0 \\ &> (-a + c)r_1(X^*) + (b - d)r_2(Y^*) + a + d - b - c \\ &= -(a - c)r_1(X^*) + (a - c) + -(d - b)r_2(Y^*) + (d - b) \\ &= (a - c)[1 - r_1(X^*)] + (d - b)[1 - r_2(Y^*)] \\ &\geq 0 \end{aligned}$$

at equilibrium, contradicting that $\dot{X} + \dot{Y} = 0$.

If the matrix determinant $ad - bc$ is not zero, then a and d must both be greater than zero by Theorem 2 from section 2.2, and at least one of $a - c$ and $d - b$ must be positive.

Then, if we had $x_0 = a$ ($y_0 = d$ is similar) or $x_0 + y_0 = a + d - b - c$, at equilibrium we would have

$$\dot{X} \;=\; a(1 - r_1(X^*)) + br_2(Y^*) \; > 0$$

or

$$\dot{X} + \dot{Y} \;=\; (a - c)[1 - r_1(X^*)] + (d - b)[1 - r_2(Y^*)] \; > 0,$$

both of which produce contradictions. Thus, if the matrix is invertible, the three inequalities must be strict. $\square$

The upper bounds on x_0 and y_0 in Theorem 17 are considered "weak" because the converse of the theorem is not true. As a counterexample, consider the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -20 & 1 \\ 1 & -10 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 19.5 \\ 8 \end{bmatrix}.$$

Here, we have $x_0 = 19.5 < a = 20$, $y_0 = 8 < d = 10$, and $x_0 + y_0 = 27.5 < a + d - b - c = 28$. However, when we set this system equal to zero and solve, we get the unique solution $(r_1(X^*), r_2(Y^*)) = (203/199, 359/398)$. This is not a valid equilibrium point as it falls outside the range of r_1.

Stronger restrictions on x_0 and y_0 depend on whether the 2×2 matrix in (3.2) is invertible or singular. We will consider each of these cases.

3.2.1 Invertible Systems

First, we consider systems of form (3.2) in which

$$A = \begin{bmatrix} -a & b \\ c & -d \end{bmatrix}$$

is invertible. Note that by Corollary 1 from section 2.2.2, $\det(A)$ is positive in this case. Existence of equilibria in the all ramp region are described by the following theorem:

Theorem 18. *Consider a system of form (3.2) in which $ad - bc \neq 0$. Then, there exists an equilibrium point in the all ramp region if and only if both $dx_0 + by_0 < ad - bc$ and $cx_0 + ay_0 < ad - bc$ hold.*

Proof. Setting

$$\begin{bmatrix} -a & b \\ c & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix} = 0,$$

we get the equilibrium solution

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \end{bmatrix} = \frac{1}{ad - bc} \begin{bmatrix} -d & -b \\ -c & -a \end{bmatrix} \begin{bmatrix} -x_0 \\ -y_0 \end{bmatrix} = \frac{1}{ad - bc} \begin{bmatrix} dx_0 + by_0 \\ cx_0 + ay_0 \end{bmatrix}.$$

This solution is non-negative and thus falls in the all ramp region as long as it is less than 1 componentwise; that is, if and only if $dx_0 + by_0 < ad - bc$ and $cx_0 + ay_0 < ad - bc$. ☐

Since A is invertible, if the equilibrium

$$(r_1(X^*), r_2(Y^*)) \;=\; \Big(\frac{dx_0 + by_0}{ad - bc}, \frac{cx_0 + ay_0}{ad - bc}\Big)$$

falls in the all ramp region, then this is the unique equilibrium point for the system. It should be noted that if this equilibrium fell in the saturated region of one or both ramp functions, then we would have infinitely many equilibria; if we had, say, $r_1(X^*) = 1$, then we can pick any $X^* \geq 2\theta_1$ at equilibrium.

We end this section with a theorem describing when we get the origin as the unique equilibrium point of the system:

Theorem 19. *Consider a system of form (3.2) in which $ad - bc \neq 0$. Then, the origin is the system's unique equilibrium if and only if $x_0 = y_0 = 0$.*

Proof. If the origin is an equilibrium point, then we have

$$\begin{bmatrix} -a & b \\ c & -d \end{bmatrix} \vec{0} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix} = 0,$$

which implies $x_0 = y_0 = 0$. Next, if both constant inputs are zero, finding equilibria is equivalent to solving

$$\begin{bmatrix} -a & b \\ c & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} = 0,$$

which, since the 2×2 matrix is invertible, only has the trivial solution $\vec{r^*} = \vec{0}$. ☐

3.2.2 Singular Systems

We now consider the case in which

$$A = \begin{bmatrix} -a & b \\ c & -d \end{bmatrix}$$

is singular, i.e. $ad - bc = 0$. Given that $c \leq a$ and $b \leq d$, there are two main ways in which the determinant of A can be zero: A having a column of zeros (for instance, if $b = d = 0$), or $c = a$ and $b = d$ with both a and d non-zero. We will examine both possibilities.

Case 1: $\mathbf{c = a \neq 0}$ and $\mathbf{b = d \neq 0}$

This case gives us the following theorem:

Theorem 20. *Consider a system of form* (3.2) *in which* $c = a \neq 0$ *and* $b = d \neq 0$. *Then, there exist equilibria in the all ramp region if and only if* $x_0 = y_0 = 0$.

Proof. Here, the system has the form

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & d \\ a & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix}.$$

Adding the differential equations, we get $\dot{X} + \dot{Y} = x_0 + y_0$. If the system has equilibria, then $x_0 + y_0 = 0$ at equilibrium. Since x_0 and y_0 are both non-negative, both must equal zero in order for this hold.

If $x_0 = y_0 = 0$, then setting both equations equal to zero gives

$$r_2(Y^*) \ = \ \frac{a}{d} r_1(X^*),$$

which results in the existence of a line of equilibria in the part of the all ramp region in which $r_1(X^*) < \min\{d/a, 1\}$. □

Case 2: A has a column of zeros

Without loss of generality, we will assume the second column is zero, i.e. $b = d = 0$. Then, $a > 0$ since A cannot be the zero matrix. We then have the following:

Theorem 21. *Consider a system of form* (3.2) *in which* $d = b = 0$ *and* $a > 0$. *If* $c = 0$, *equilibria are possible in the all ramp region if and only if* $x_0 < a$ *and* $y_0 = 0$. *If* $c \neq 0$, *equilibira are possible in the all ramp region if and only if* $x_0 = y_0 = 0$.

Proof. In this case, the system has the form

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & 0 \\ c & 0 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix}.$$

Note that the system does not depend on Y; thus, at an equilibrium point in the all ramp region, $r_2(Y^*)$ can take any value in $[0, 1)$. Setting $\dot{X} = 0$, we get the equilibrium solution $r_1(X^*) = x_0/a$, which falls in the ramp region if and only if $x_0 < a$. From $\dot{Y} = 0$, we have that $cr_1(X^*) + y_0 = 0$, which gives us two possibilities depending on whether c is zero or strictly positive:

- If $c = 0$, then the $\dot{Y} = 0$ equation simply becomes $y_0 = 0$. Hence, we have the line of equilibria

  $$\left(\frac{x_0}{a}, r_2(Y^*) < 1\right)$$

  in the all ramp region if and only if $x_0 < a$ and $y_0 = 0$.

- If $c \neq 0$, then we have

  $$r_1(X^*) \;=\; -\frac{y_0}{c}.$$

  Since $r_1(X^*)$, y_0, and c are all non-negative, this equality is satisfied if and only if both sides are equal to zero. Hence, it must be the case that $r_1(X^*) = y_0 = 0$. Then, in order for the $\dot{X} = 0$ solution $r_1(X^*) = x_0/a$ to still hold, we must also have $x_0 = 0$. Thus, we have the line of equilibria

  $$(0, r_2(Y^*) < 1)$$

  in the all ramp region if and only if $x_0 = y_0 = 0$.

□

Unlike invertible systems, singular systems can have multiple equilibria in the all ramp region. In fact, we have shown in this section that if a system of form (3.2) in which $ad - bc = 0$ has an equilibrium point in the all ramp region, then it actually has infinitely many such points.

3.2.3 Examples

We now provide a few examples of systems of form (3.2) and determine whether or not they have equilibria in the all ramp region.

Example 14. Invertible system with a unique equilibrium point
Consider the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -2 & 1 \\ 1 & -4 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 1/2 \\ 3/2 \end{bmatrix}.$$

Using the fact that

$$\begin{bmatrix} -2 & 1 \\ 1 & -4 \end{bmatrix}^{-1} = \begin{bmatrix} -4/7 & -1/7 \\ -1/7 & -2/7 \end{bmatrix},$$

setting the equations equal to zero gives us

$$\begin{bmatrix} -2 & 1 \\ 1 & -4 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 1/2 \\ 3/2 \end{bmatrix} = 0$$

$$\implies \begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \end{bmatrix} = \begin{bmatrix} -4/7 & -1/7 \\ -1/7 & -2/7 \end{bmatrix} \begin{bmatrix} -1/2 \\ -3/2 \end{bmatrix}$$

$$= \begin{bmatrix} 1/2 \\ 1/2 \end{bmatrix}.$$

Thus, the system has the unique equilibrium point

$$(r_1(X^*), r_2(Y^*)) \;=\; (1/2, 1/2)$$

in the all ramp region.

Example 15. Invertible system with no equilibria
Solving for equilibria in the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-1 & 1\\ 11/20 & -1\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}1/2\\ 1/4\end{bmatrix},$$

we get

$$\begin{bmatrix}r_1(X^*)\\ r_2(Y^*)\end{bmatrix} = \begin{bmatrix}-20/9 & -20/9\\ -11/9 & -20/9\end{bmatrix}\begin{bmatrix}-1/2\\ -1/4\end{bmatrix}$$

$$= \begin{bmatrix}5/3\\ 7/6\end{bmatrix}.$$

Both components of this solution are greater than 1, and thus fall outside the range of the ramp functions. Thus, this system can never be at equilibrium.

Example 16. Singular system with infinitely many equilibrium points
Finally, we consider the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-2 & 1\\ 2 & -1\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix}.$$

Setting either equation to zero gives us the line of equilibria

$$r_2(Y^*) \;=\; 2r_1(X^*).$$

Any point on this line for which $r_1(X^*) < 1/2$ falls in the all ramp region.

3.3 Equilibria in n-Variable Systems

We will now attempt to generalize our results regarding ramp region equilibria in two-variable systems to systems with $n \geq 2$ variables. To begin, we present the general version of Theorem 17:

Theorem 22. *Let* $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ *be a system of form* (3.1) *with* $n \geq 2$ *variables. If the system has an equilibrium in the all ramp region, then both of the following must hold:*

i) $\forall\, i = 1, 2, \ldots, n, \quad x_{i_0} \leq a_{ii}$

ii) $\displaystyle\sum_i x_{i_0} \leq -\sum_{i,j} a_{ij}$

Additionally, these inequalities are strict if A is invertible.

Proof. Similar to Theorem 17, we prove this by contradiction. If we had $x_{i_0} > a_{ii}$ for some i, then at equilibrium

$$\begin{aligned}
\dot{X}_i &= \sum_{j\neq i} a_{ij} r_j(X_j^*) - a_{ii} r_i(X_i^*) + x_{i_0} \\
&> \sum_{j\neq i} a_{ij} r_j(X_j^*) - a_{ii} r_i(X_i^*) + a_{ii} \\
&= \sum_{j\neq i} a_{ij} r_j(X_j^*) + a_{ii}(1 - r_i(X_i^*)) \\
&\geq 0,
\end{aligned}$$

contradicting $\dot{X}_i = 0$. Now, suppose $\displaystyle\sum_i x_{i_0} > -\sum_{i,j} a_{ij}$. Note that $\displaystyle -\sum_{i,j} a_{ij}$ is always non-negative as the column sums of A are non-positive by Theorem 2 from section 2.2, and thus $\displaystyle\sum_{i,j} a_{ij}$ is non-positive. At equilibrium, we have

$$\begin{aligned}
\sum_i \dot{X}_i &= r_1(X_1^*) \sum_j a_{j1} + r_2(X_2^*) \sum_j a_{j2} + \cdots + r_n(X_n^*) \sum_j a_{jn} + \sum_i x_{i_0} \\
&> r_1(X_1^*) \sum_j a_{j1} + r_2(X_2^*) \sum_j a_{j2} + \cdots + r_n(X_n^*) \sum_j a_{jn} - \sum_{i,j} a_{ij} \\
&= [r_1(X_1^*) - 1] \sum_j a_{j1} + [r_2(X_2^*) - 1] \sum_j a_{j2} + \cdots + [r_n(X_n^*) - 1] \sum_j a_{jn} \\
&\geq 0,
\end{aligned}$$

contradicting that $\displaystyle\sum_i \dot{X}_i = 0$.

If A is invertible, then $a_{ii} > 0$ for all i by Theorem 2 and at least one column sum must be strictly negative. At equilibrium, if we had $x_{i_0} = a_{ii}$ for some i or $\displaystyle\sum_i x_{i_0} = -\sum_{i,j} a_{ij}$, then we would have

$$\dot{X}_i = \sum_{j\neq i} a_{ij} r_j(X_j^*) + a_{ii}(1 - r_i(X_i^*)) > 0$$

or

$$\sum_i \dot{X}_i = [r_1(X_1^*) - 1] \sum_j a_{j1} + [r_2(X_2^*) - 1] \sum_j a_{j2} + \cdots + [r_n(X_n^*) - 1] \sum_j a_{jn} > 0,$$

both of which are contradictions. Hence, the inequalities must be strict. □

Again, the converse of Theorem 22 is not true. For instance, the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\\ \dot{Z}\end{bmatrix} = \begin{bmatrix}-1 & 0 & 0\\ 0 & -2 & 0\\ 0 & 1 & -0.5\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\\ r_3(Z)\end{bmatrix} + \begin{bmatrix}0.5\\ 1\\ 0.25\end{bmatrix}$$

satisfies

$$\begin{aligned} x_0 &= 0.5 < a_{11} = 1\\ y_0 &= 1 < a_{22} = 2\\ z_0 &= 0.25 < a_{33} = 0.5\\ x_0 + y_0 + z_0 &= 1.75 < -(1-1-2-0.5) = 2.5, \end{aligned}$$

but the only equilibrium point, $(r_1(X^*), r_2(Y^*), r_3(Z^*)) = (0.5, 0.5, 1.5)$, falls outside the range of r_3.

Like in the two-variable case, additional restrictions on the constant input terms depend on whether or not the matrix A in (3.1) is invertible. Both possibilities are explored in the following sections.

3.3.1 Invertible Systems

When A is invertible, setting

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

gives the equilibrium solution

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

The following theorem guarantees that this solution is always non-negative componentwise:

Theorem 23. *Let* $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ *be a system of form* (3.1) *in which* $\det(A) \neq 0$*. Then,* $-A^{-1}\vec{x_0} \geq 0$ *componentwise.*

Proof. Since A is an SRP matrix, its inverse has all non-positive entries by Theorem 7 from section 2.2.2. Hence, all entries of $-A^{-1}$ are non-negative. As each component of $\vec{x_0}$ is also non-negative, $-A^{-1}\vec{x_0} \geq 0$ componentwise. □

Now that we have established that $\vec{r^*}$ is non-negative, we next need to determine when $\vec{r^*} < 1$ componentwise. Theorem 18 can be adapted to the general $n \times n$ case for this purpose:

Theorem 24. *Let* $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ *be a system of form* (3.1) *in which* $\det(A) \neq 0$*. Then, there exists an equilibrium point in the all ramp region if and only if* $\forall\ i = 1, 2, \ldots, n$*,*

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

where the C_{ji} are cofactors of A.

Proof. The result comes from the fact that

$$A^{-1} = \frac{1}{\det(A)} \begin{bmatrix} C_{11} & C_{21} & \dots & C_{n1} \\ C_{12} & C_{22} & \dots & C_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ C_{1n} & C_{2n} & \dots & C_{nn} \end{bmatrix},$$

which means the equilibrium vector $\vec{r^*} = -A^{-1}\vec{x_0}$ has the form

$$\vec{r^*} = \frac{1}{-\det(A)} \begin{bmatrix} C_{11} & C_{21} & \dots & C_{n1} \\ C_{12} & C_{22} & \dots & C_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ C_{1n} & C_{2n} & \dots & C_{nn} \end{bmatrix} \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ \vdots \\ x_{n_0} \end{bmatrix}.$$

The i^{th} component of this vector is

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

which falls in the all ramp region if and only if it is strictly less than 1. □

Thus, existence of an equilibrium in the all ramp region depends on whether a series of n inequalities involving the x_{i_0} is satisfied. Finding explicit bounds on the x_{i_0}, tighter than the weak upper bounds given in Theorem 22, is difficult in general. However, we will consider a few special cases in the next few theorems.

First, in the case where all of the matrix row sums are non-postive (i.e. $\sum_j a_{ij} \leq 0$, or equivalently, $-\sum_j a_{ij} \geq 0$ for all i), a sufficient condition for the existence of an equilibrium in the all ramp region can be given:

Theorem 25. *Let $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ be a system of form (3.1) such that* $\det(A) \neq 0$ *and $-\sum_j a_{ij} \geq 0\ \forall i$. Let $\vec{1}$ denote the $n \times 1$ vector of all 1s. Then, if $\vec{x_0} < -A\vec{1}$ componentwise, $\dot{\vec{X}}$ has an equilibrium in the all ramp region.*

Proof. For the i^{th} component of $\vec{r^*} = -A^{-1}\vec{x_0}$, we have

$$r_i(X_i^*) = \frac{C_{1i}x_{1_0} + C_{2i}x_{2_0} + \dots + C_{ni}x_{n_0}}{-\det(A)}$$

$$\begin{aligned}
&< \frac{-C_{1i}\sum_{j=1}^{n} a_{1j} - C_{2i}\sum_{j=1}^{n} a_{2j} - \cdots - C_{ni}\sum_{j=1}^{n} a_{nj}}{-\det(A)} \\
&= \frac{a_{1i}C_{1i} + a_{2i}C_{2i} + \cdots + a_{ni}C_{ni} + \sum_{k\neq i}\sum_{j=1}^{n} a_{jk}C_{ji}}{\det(A)} \\
&= \frac{\det(A)+0}{\det(A)} \\
&= 1,
\end{aligned}$$

and thus $\vec{r^*}$ falls in the all ramp region. □

The converse of Theorem 25 does not hold, as shown by the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\\ \dot{Z}\end{bmatrix} = \begin{bmatrix}-15 & 5 & 0\\ 5 & -25 & 0\\ 0 & 0 & -1\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\\ r_3(Z)\end{bmatrix} + \begin{bmatrix}12\\ 7\\ 0\end{bmatrix}.$$

This system has the equilibrium point $(r_1(X^*), r_2(Y^*), r_3(Z^*)) = (67/70, 33/70, 0)$ in the all ramp region. While we have $y_0 = 7 < -\sum_i a_{2i} = 20$ and $z_0 = 0 < -\sum_i a_{3i} = 1$, the inequality $\vec{x_0} < -A\vec{1}$ does not hold as $x_0 = 12 > -\sum_i a_{1i} = 10$.

Next, we consider the case in which exactly one component of $\vec{x_0}$ is non-zero, which is what we have when $a_0 > 0$ in the Adams model:

Theorem 26. *Let $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ be a system of form (3.1) such that* $\det(A) \neq 0$. *Suppose $x_{i_0} > 0$ for some i and $x_{j_0} = 0 \ \ \forall\, j \neq i$. Define $\mathcal{M} > 0$ by*

$$\mathcal{M} \ = \ \min_j \left\{ \frac{-\det(A)}{C_{ij}} \ : \ C_{ij} \neq 0 \right\}.$$

Then, there is an equilibrium point in the all ramp region if and only if $x_{i_0} < \mathcal{M}$.

Proof. First, note that $\mathcal{M}$ is well-defined; at least one C_{ij} must be non-zero or else all entries in column i of A^{-1} are zero, contradicting that A^{-1} is invertible.

The j^{th} component of $\vec{r^*}$ in this case is

$$r_j(X_j^*) \ = \ \frac{x_{i_0}C_{ij}}{-\det(A)}.$$

If there is a j such that $C_{ij} = 0$, then $r_j(X_j^*) = 0$ is guaranteed to be in the ramp region of r_j. For all j such that $C_{ij} \neq 0$, of which there must be at least one, $r_j(X_j^*)$ is in the ramp region if and only if

$$x_{i_0} \ < \ \frac{-\det(A)}{C_{ij}}.$$

Thus, an equilibrium exists in the all ramp region if and only if x_{i_0} is smaller than all such $\dfrac{-\det(A)}{C_{ij}}$, i.e. $x_{i_0} < \mathcal{M}$. □

Finally, we have the n-variable equivalent of Theorem 19 regarding equilibria at the origin:

Theorem 27. *Let* $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ *be a system of form* (3.1) *such that* $\det(A) \neq 0$*. Then, the system has the origin as its unique equilibrium if and only if* $\vec{x_0} = \vec{0}$*.*

Proof. If the origin is an equilibrium point, then at equilibrium, $A\vec{0} + \vec{x_0} = 0 \implies \vec{x_0} = \vec{0}$. If $\vec{x_0} = \vec{0}$, then $A\vec{r} = 0$ only has the solution $\vec{r^*} = \vec{0}$ as A is invertible. □

We end this section by emphasizing the uniqueness of the equilibria found here. Like in the two-variable case, if the equilibrium solution

$$\vec{r^*} \;=\; -A^{-1}\vec{x_0}$$

of an invertible system of form (3.1) falls in the all ramp region, then $\vec{r^*}$ is the system's only equilibrium point.

3.3.2 Singular Systems

Now, we examine equilibria in systems of form (3.1) in which A is singular. The conditions required for equilibria in the all ramp region vary depending on the reason(s) why A is singular (column of zeros, proportional non-zero columns, etc.). We will consider several of these reasons here.

We will begin with the case in which A has a column of zeros; suppose this is column i. Then, if the system has an equilibrium point in the all ramp region, it must have infinitely many such points since we can choose any $r_i(X_i^*) < 1$ at equilibrium.

To aid the search for possible equilibrium solutions, one idea is to reduce the system $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ to the form

$$\dot{\vec{X}} \;=\; A_{i_0}\vec{r}_{i_0},$$

where A_{i_0} is the matrix obtained by replacing column i of A with $\vec{x_0}$, and $\vec{r}_{i_0}$ is obtained by replacing the i^{th} component of $\vec{r}$ with 1. That is, the system

$$\dot{\vec{X}} = \begin{bmatrix} -a_{11} & a_{12} & \dots & a_{1,i-1} & 0 & a_{1,i+1} & \dots & a_{1n} \\ a_{21} & -a_{22} & \dots & a_{2,i-1} & 0 & a_{2,i+1} & \dots & a_{2n} \\ \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\ a_{i1} & a_{i2} & \dots & a_{i,i-1} & 0 & a_{i,i+1} & \dots & a_{in} \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & a_{n,i-1} & 0 & a_{n,i+1} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(X_1) \\ r_2(X_2) \\ \vdots \\ r_i(X_i) \\ \vdots \\ r_n(X_n) \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ \vdots \\ x_{i_0} \\ \vdots \\ x_{n_0} \end{bmatrix}$$

becomes

$$\dot{\vec{X}} = \begin{bmatrix} -a_{11} & a_{12} & \dots & a_{1,i-1} & x_{1_0} & a_{1,i+1} & \dots & a_{1n} \\ a_{21} & -a_{22} & \dots & a_{2,i-1} & x_{2_0} & a_{2,i+1} & \dots & a_{2n} \\ \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\ a_{i1} & a_{i2} & \dots & a_{i,i-1} & x_{i_0} & a_{i,i+1} & \dots & a_{in} \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & a_{n,i-1} & x_{n_0} & a_{n,i+1} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(X_1) \\ r_2(X_2) \\ \vdots \\ 1 \\ \vdots \\ r_n(X_n) \end{bmatrix}.$$

Hence, we can find equilibria of the original system by solving $A_{i_0}\vec{r}_{i_0} = 0$ and then assigning a value to $r_i(X_i^*)$. Some necessary criteria for the existence of equilibria in the all ramp region are given in the next theorem.

Theorem 28. *Let $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ be a system of form (3.1) such that all entries in column i of A are zero for some i. If the reduced system $\dot{\vec{X}} = A_{i_0}\vec{r}_{i_0}$ has an equilibrium with all $r_j(X_j^*) < 1$, then all of the following hold:*

i) $x_{i_0} = 0$

ii) if $a_{ij} \neq 0$ for $j \neq i$, then $r_j(X_j^*) = 0$

iii) A_{i_0} is singular

Proof. At equilibrium, the i^{th} equation of $A_{i_0}\vec{r}_{i_0} = 0$ is

$$a_{i1}r_1(X_1^*) + a_{i2}r_2(X_2^*) + \cdots + x_{i_0} + \cdots + a_{in}r_n(X_n^*) = 0.$$

The a_{ij}, $r_j(X_j^*)$, and x_{i_0} are all non-negative; thus, the only way for the above equation to hold is if each term is zero. Hence, $x_{i_0} = 0$ and $a_{ij}r_j(X_j^*) = 0$ for all $j \neq i$. If $a_{ij} \neq 0$ for some $j \neq i$, then we must have $r_j(X_j^*) = 0$.

Since the i^{th} component of $\vec{r}_{i_0}$ is fixed at 1, any solution to $A_{i_0}\vec{r}_{i_0} = 0$ will be an eigenvector of A_{i_0} corresponding to the eigenvalue $\lambda = 0$. Thus, A_{i_0} must be singular. □

Next, we look at the case where all column sums of A are zero. Necessary and sufficient conditions for the existence of equilibria in the all ramp region in this case are given below.

Theorem 29. *Let $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ be a system of form (3.1) such that for all i, the i^{th} column of A satisfies*

$$\sum_j a_{ji} \;=\; 0.$$

Then, the system has an equilibrium point in the all ramp region if and only if $\vec{x_0} = \vec{0}$.

Proof. If the system has an equilibrium in the all ramp region, then we have

$$\sum_i \dot{X}_i \;=\; \sum_i x_{i_0} = 0$$

at equilibrium. As each component of $\vec{x_0}$ is non-negative, the sum of the components is zero if and only if $x_{i_0} = 0$ for all i.

If $\vec{x_0} = \vec{0}$, then finding equilibria in the system is equivalent to solving $A\vec{r} = 0$, which always has at least the origin as an all ramp region solution. □

Thus, when all columns sum to zero, equilibria in the all ramp region are possible if and only if the system has the form $\dot{\vec{X}} = A\vec{r}$. Whether this system has all ramp region equilibria besides the origin depends on the eigenvectors of A corresponding to the eigenvalue $\lambda = 0$; if there is an eigenvector $\vec{v}$ with all non-negative components, then any positive scalar multiple of $\vec{v}$ such that all components belong to $[0, 1)$ will be an equilibrium point in the all ramp region. However, if it is only possible to have eigenvectors with a mix of positive and negative components, the origin will be the system's only equilibrium in the all ramp region.

Removing the restriction that all column sums are zero, we can examine when any singular system of form $\dot{\vec{X}} = A\vec{r}$ has an infinite number of equilibria in the all ramp region. In the next theorem, we provide three cases that guarantee the existence of a non-negative eigenvector for the eigenvalue $\lambda = 0$, and thus more than the trivial all ramp region equilibrium.

Theorem 30. *Let A be an $n \times n$ singular SRP matrix. If all rows of A sum to zero, or if A has a column of zeros or two proportional non-zero columns, then A has an eigenvector $\vec{v}$ corresponding to the eigenvalue $\lambda = 0$ such that $\vec{v} \geq 0$ componentwise.*

Proof. If all row sums are zero, then we can take $\vec{v} = \vec{1}$ as our eigenvector. Meanwhile, if the i^{th} column of A is zero, then we can choose $\vec{v}$ with components $v_i = 1$ and $v_j = 0$ for all $j \neq i$.

Now, suppose that columns i and j are non-zero with column j equalling column i multiplied by the scalar $-m$. Then, we have

$$\begin{aligned} -a_{jj} &= -m a_{ji} \\ a_{ij} &= (-m)(-a_{ii}). \end{aligned}$$

Since columns i and j are non-zero, it must be the case that $-a_{ii} < 0$ and $-a_{jj} < 0$ by Theorem 2 from section 2.2, while a_{ij} and a_{ji} must both be strictly positive in order for the two equalities above to hold. As a result, the constant $-m$ must be negative, and thus $m > 0$. Hence, we can take $\vec{v}$ to be the vector with $v_i = m$, $v_j = 1$, and $v_k = 0$ for $k \neq i, j$. □

We conjecture that the conclusion of Theorem 30 holds for any singular SRP matrix, thus giving all singular systems $\dot{\vec{X}} = A\vec{r}$ of form (3.1) with $\vec{x_0} = 0$ infinitely many all ramp region equilibria:

Conjecture 3. Let A be an $n \times n$ singular SRP matrix. Then, A has an eigenvector $\vec{v}$ corresponding to the eigenvalue $\lambda = 0$ such that $\vec{v} \geq 0$ componentwise.

3.3.3 Examples

We illustrate what we have discussed with a few examples of systems in $n \geq 3$ variables.

Example 17. Invertible 4×4 system with a unique equilibrium point
We consider the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \\ \dot{W} \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 & 0 \\ 2 & -3 & 0 & 0 \\ 0 & 3 & -1 & 0 \\ 0 & 0 & 1 & -4 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \\ r_4(W) \end{bmatrix} + \begin{bmatrix} 1/4 \\ 1/4 \\ 1/4 \\ 1/4 \end{bmatrix}.$$

The unique equilibrium point of the system is

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \\ r_3(Z^*) \\ r_4(W^*) \end{bmatrix} = \begin{bmatrix} 1/2 & 0 & 0 & 0 \\ 1/3 & 1/3 & 0 & 0 \\ 1 & 1 & 1 & 0 \\ 1/4 & 1/4 & 1/4 & 1/4 \end{bmatrix} \begin{bmatrix} 1/4 \\ 1/4 \\ 1/4 \\ 1/4 \end{bmatrix} = \begin{bmatrix} 1/8 \\ 1/6 \\ 3/4 \\ 1/4 \end{bmatrix},$$

which is in the all ramp region.

Example 18. Singular system with infinitely many equilibria
The system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -3 & 0 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & -2 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}$$

has a column of zeros and a non-zero constant input vector. Thus, we can try putting the system in the $\dot{\vec{X}} = A_{i_0}\vec{r}_{i_0}$ form described in Theorem 28. Doing this, we have to solve

$$\begin{bmatrix} -3 & 0 & 0 \\ 1 & 0 & 0 \\ 1 & 1 & -2 \end{bmatrix} \begin{bmatrix} r_1(X^*) \\ 1 \\ r_3(Z^*) \end{bmatrix} = 0$$

for equilibria. Solving the first two equations gives $r_1(X^*) = 0$, while the third equation yields $r_3(Z^*) = 1/2$. Thus, we have infinitely many equilibria in the all ramp region, given by $(0, r_2(Y^*) < 1, 1/2)$.

3.3.3.1 Adams Model

As mentioned at the beginning of this chapter, the Adams model without the SEL from (1.7) is an SRP biochemical ramp system. Thus, we can solve for equilibria in the model using the linear algebra techniques used throughout this chapter. Assuming $K_3^2 = K_5$ so that the variable X_2 is only associated with the ramp function r_5, we can write system (1.7) in form (3.1) as

$$\begin{bmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_4 \end{bmatrix} = \begin{bmatrix} -a_1 & 0 & 0 \\ a_1 & -(a_3+a_5) & 0 \\ 0 & a_3 & -a_4 \end{bmatrix} \begin{bmatrix} r_1(X_1) \\ r_5(X_2) \\ r_4(X_4) \end{bmatrix} + \begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix}.$$

The 3×3 matrix here has a determinant of $-a_1a_4(a_3+a_5)$, which is non-zero as the a_i for $i > 0$ were assumed to be positive. Thus, the matrix is invertible and equilibria of the system will be given by $\vec{r^*} = -A^{-1}\vec{x_0}$.

It can be verified that

$$\begin{bmatrix} -a_1 & 0 & 0 \\ a_1 & -(a_3+a_5) & 0 \\ 0 & a_3 & -a_4 \end{bmatrix}^{-1} = \begin{bmatrix} \dfrac{-1}{a_1} & 0 & 0 \\ \dfrac{-1}{a_3+a_5} & \dfrac{-1}{a_3+a_5} & 0 \\ \dfrac{-a_3}{a_4(a_3+a_5)} & \dfrac{-a_3}{a_4(a_3+a_5)} & \dfrac{-1}{a_4} \end{bmatrix},$$

and thus

$$\begin{bmatrix} r_1(X_1^*) \\ r_5(X_2^*) \\ r_4(X_4^*) \end{bmatrix} = \begin{bmatrix} \dfrac{1}{a_1} & 0 & 0 \\ \dfrac{1}{a_3+a_5} & \dfrac{1}{a_3+a_5} & 0 \\ \dfrac{a_3}{a_4(a_3+a_5)} & \dfrac{a_3}{a_4(a_3+a_5)} & \dfrac{1}{a_4} \end{bmatrix} \begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} \dfrac{a_0}{a_1} \\ \dfrac{a_0}{a_3+a_5} \\ \dfrac{a_0a_3}{a_4(a_3+a_5)} \end{bmatrix}.$$

If this equilibrium point falls in the all ramp region, we can replace $r_1(X_1^*)$, $r_5(X_2^*)$, and $r_4(X_4^*)$ with $X_1^*/(2K_1)$, $X_2^*/(2K_5)$, and $X_4^*/(2K_4)$ respectively. Then, our equilibrium point is given by

$$X_1^* = \frac{2a_0K_1}{a_1}, \quad X_2^* = \frac{2a_0K_5}{a_3+a_5}, \quad X_4^* = \frac{2a_0a_3K_4}{a_4(a_3+a_5)},$$

which is exactly the solution we got in the (α, α, α) subcase in section 1.4.1.1.

3.4 Stability and Flow in Two-Variable Systems

For this section, we return to two-variable systems of the form

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & b \\ c & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix}$$

seen in (3.2). We will be looking at flow in these systems with the aim of determining whether trajectories move toward equilibria or infinity. Our focus will be on examining how trajectories flow between four regions (or "boxes") of the non-negative quadrant of the XY-plane. These regions are defined based on whether the ramp functions r_1 and r_2 (with thresholds $2\theta_1$ and $2\theta_2$ respectively) are in their ramp or saturated regions. The four boxes are illustrated in the figure below.

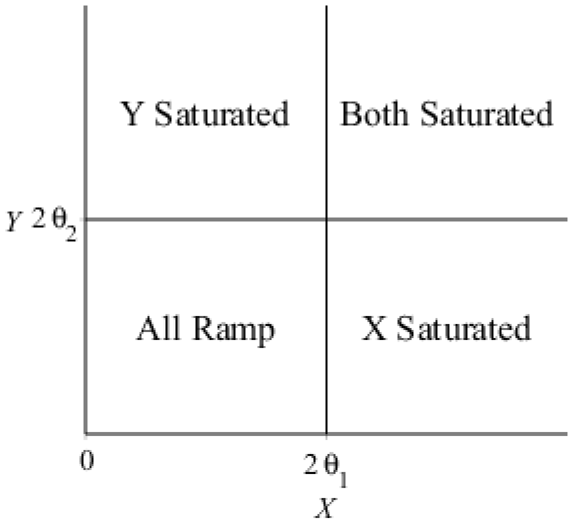


Figure 9: The four regions of phase space for two-variable systems

The boundaries of the regions are outlined in the next definition.

Definition 8. [*Four Regions*] The regions shown in Figure 9 are defined as follows:

- **All Ramp Region**

$$\big\{(X,Y) \;:\; X \in [0, 2\theta_1),\, Y \in [0, 2\theta_2)\big\}$$

$$\iff \big\{(X,Y) \;:\; r_1(X) \in [0,1),\, r_2(Y) \in [0,1)\big\}$$

- **X Saturated Region**

$$\big\{(X,Y) \;:\; X \geq 2\theta_1,\, Y \in [0, 2\theta_2)\big\}$$

$$\iff \big\{(X,Y) \;:\; r_1(X) = 1,\, r_2(Y) \in [0,1)\big\}$$

- **Y Saturated Region**

$$\begin{aligned} &\big\{(X,Y)\ :\ X\in[0,2\theta_1),\, Y\geq 2\theta_2\big\} \\ \iff &\big\{(X,Y)\ :\ r_1(X)\in[0,1),\, r_2(Y)=1\big\} \end{aligned}$$

- **Both Saturated Region**

$$\begin{aligned} &\big\{(X,Y)\ :\ X\geq 2\theta_1,\, Y\geq 2\theta_2\big\} \\ \iff &\big\{(X,Y)\ :\ r_1(X)=r_2(Y)=1\big\} \end{aligned}$$

The first thing we will note regarding flow in systems of the form (3.2) is that it is impossible for trajectories that start in the non-negative quadrant to leave it. Along the X-axis, $\dot{Y}=cr_1(X)+y_0\geq 0$, and along the Y-axis, $\dot{X}=br_2(Y)+x_0\geq 0$, so flow cannot be directed below the X-axis or left of the Y-axis. Aside from this, however, the flow patterns seen in two-variable systems vary, depending on certain properties which will be discussed in the following sections.

3.4.1 Invertible Systems with Equilibria in the All Ramp Region

Here, we are concerned with systems of form (3.2) in which the 2×2 matrix A is invertible (and thus a and d are **positive**), and an equilibrium point exists in the all ramp region (i.e. $r_1(X^*)<1$ and $r_2(Y^*)<1$). The Jacobian J of such a system at its equilibrium point is equal to the SRP matrix A with each column multiplied by a positive scalar; hence, J is also an invertible SRP matrix.

By Theorems 5 and 6 from section 2.2.1, the eigenvalues of J are real and negative. Thus, the equilibrium in the all ramp region is asymptotically stable. Here, we want to show global stability, namely that trajectories starting in one of the saturated boxes ultimately enter the all ramp region.

3.4.1.1 Nullclines: Locations and Flow

An important part of the discussion here will be flow along or toward nullclines. The systems examined in this section have their X nullcline given by

$$\begin{cases} r_1(X) \;=\; \dfrac{x_0}{a}, & b \;=\; 0 \\[2ex] r_2(Y) \;=\; \dfrac{a}{b}r_1(X)-\dfrac{x_0}{b}, & b\;\neq\; 0, \end{cases}$$

with their Y nullcline being

$$r_2(Y) \;=\; \frac{c}{d}r_1(X)+\frac{y_0}{d}.$$

Since we have $x_0 < a$ and $y_0 < d$ by Theorem 17 from section 3.2, these nullclines begin in the all ramp region; the X nullcline (regardless of which formula is used) starts on the X-axis at $r_1(X) = x_0/a$ (or equivalently, $X = (2\theta_1 x_0)/a$), and the Y nullcline starts on the Y-axis at $r_2(Y) = y_0/d$ (i.e. $Y = (2\theta_2 y_0)/d$). Each nullcline eventually enters (or "extends" into) one of the three saturated regions. The saturated region a given nullcline extends into depends on whether the ramp functions reach 1 at the same time, or whether one saturates before the other. These different possibilities will be discussed shortly.

Another thing to note about the nullclines of the systems we will be studying here is that they intersect exactly once. Back in section 3.2.1, we established the uniqueness of an equilibrium point in the all ramp region of an invertible system. Thus, the X and Y nullclines intersect only in the all ramp region, at the system's sole equilibrium.

We now present several examples of invertible systems with an equilibrium in the all ramp region, each illustrating a different possibility for nullcline extensions into saturated regions.

Example 19. X saturated and Y saturated regions each have a nullcline
The system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -2 & 1 \\ 1 & -4 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 1/2 \\ 3/2 \end{bmatrix}$$

from Example 14 in section 3.2.3 has the unique equilibrium $(r_1(X^*), r_2(Y^*)) = (0.5, 0.5)$. The X nullcline of the system is $r_2(Y) = 2r_1(X) - 1/2$, on which falls the point $(r_1(X), r_2(Y)) = (3/4, 1)$; thus, in the Y saturated region, $\dot{X} = 0$ along the line $r_1(X) = 3/4$. Meanwhile, the Y nullcline, given by $r_2(Y) = (1/4)r_1(X) + 3/8$, extends into the X saturated region; the nullcline passes through $(1, 5/8)$, and thus $\dot{Y} = 0$ along $r_2(Y) = 5/8$ when $X \geq 2\theta_1$.

Example 20. Both nullclines in X saturated region
In the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -15 & 5 \\ 5 & -25 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 12 \\ 7 \end{bmatrix},$$

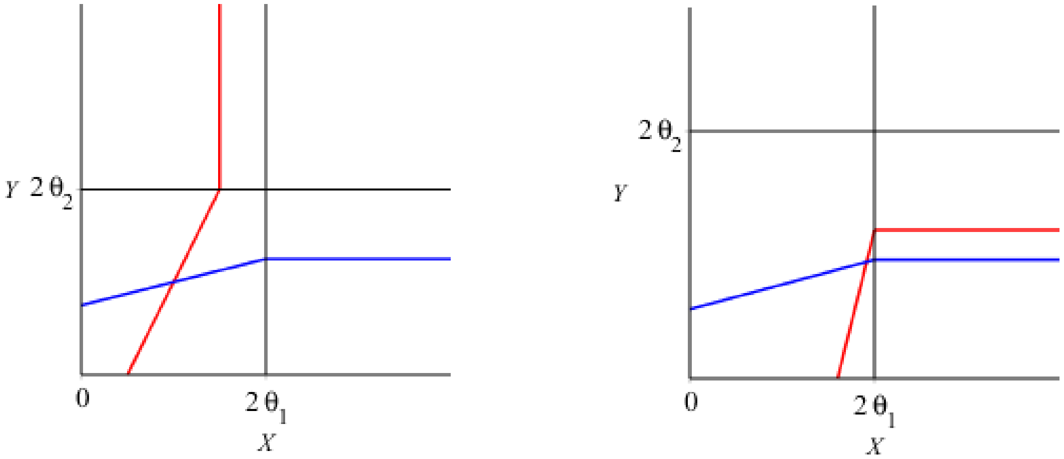
the X nullcline is $r_2(Y) = 3r_1(X) - 12/5$ and the Y nullcline is $r_2(Y) = (1/5)r_1(X) + 7/25$. The nullclines intersect in the all ramp region at $(67/70, 33/70)$. When $r_1(X) = 1$, the X nullcline becomes $r_2(Y) = 3/5$ and the Y nullcline is $r_2(Y) = 12/25$.

Example 21. Both saturated region is a nullcline
The X nullcline of the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -2 & 1 \\ 0 & -2 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 1 \\ 1 \end{bmatrix}$$

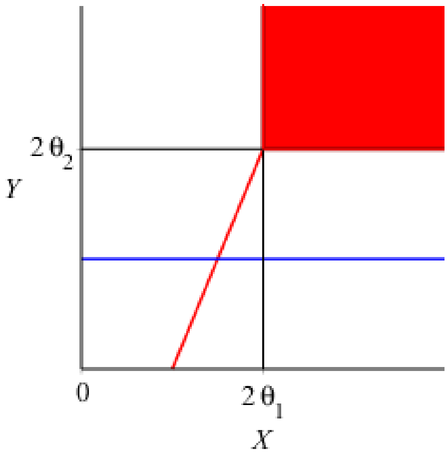
is $r_2(Y) = 2r_1(X) - 1$. The point $(1,1)$ falls on this nullcline, and thus $\dot{X} = 0$ in the entire both saturated box. The Y nullcline is simply the line $r_2(Y) = 1/2$, which intersects the X nullcline at $r_1(X) = 3/4$.

The nullclines of these systems are pictured in the following figure.



(a) Example 19 Nullclines

(b) Example 20 Nullclines



(c) Example 21 Nullclines

Figure 10: Several examples of nullcline extensions into saturated regions. The X nullcline of each system is in red and the Y nullcline is in blue.

When discussing flow along nullclines in saturated regions, the following theorem will be useful:

Theorem 31. *Consider a system of form* (3.2), *in which* $ad - bc \neq 0$ *and an equilibrium exists in the all ramp region. Then, along an* X *nullcline (*Y *nullcline) in a saturated region,* $\dot{Y} < 0$ *(*$\dot{X} < 0$*).*

Proof. Since we have an equilibrium point in the all ramp region, we have the following inequalities from Theorem 18 in section 3.2.1:

1. $dx_0 + by_0 < ad - bc \iff dx_0 - ad < -b(c + y_0)$
2. $cx_0 + ay_0 < ad - bc \iff cb + cx_0 < a(d - y_0)$

First, suppose we have an X nullcline in the X saturated or both saturated region. Then, when $r_1(X) = 1$ we have

$$\dot{X} \;=\; -a + br_2(Y') + x_0 \;=\; 0,$$

where $r_2(Y')$ denotes the fixed value of $r_2(Y)$ along this nullcline extension. Note that $b \neq 0$ in this case. If we had $b = 0$, then

$$\dot{X} \;=\; -a + x_0 \;=\; 0 \;\implies\; x_0 \;=\; a.$$

However, by Theorem 17 we must have $x_0 < a$.

Solving for $r_2(Y')$, we get

$$r_2(Y') \;=\; \frac{a - x_0}{b}.$$

Plugging this and $r_1(X) = 1$ in the $\dot{Y}$ equation, we have

$$\begin{aligned}
\dot{Y} \;&=\; cr_1(X) - dr_2(Y) + y_0 \\
&=\; c - d\Big(\frac{a - x_0}{b}\Big) + y_0 \\
&=\; c + \frac{dx_0 - ad}{b} + y_0 \\
&<\; c + \frac{-b(c + y_0)}{b} + y_0 \\
&=\; 0.
\end{aligned}$$

Now, suppose the X nullcline extends into the Y saturated region. When $r_2(Y) = 1$, we have

$$\begin{aligned}
\dot{X} \;&=\; -ar_1(X') + b + x_0 \;=\; 0 \\
\implies\; r_1(X') \;&=\; \frac{b + x_0}{a}.
\end{aligned}$$

Then, the $\dot{Y}$ equation along this extended nullcline is

$$\begin{aligned}
\dot{Y} \;&=\; c\Big(\frac{b + x_0}{a}\Big) - d + y_0 \\
&=\; \frac{cb + cx_0}{a} - d + y_0
\end{aligned}$$

$$
\begin{aligned}
&< \frac{a(d-y_0)}{a} - d + y_0 \\
&= 0.
\end{aligned}
$$

The case with Y nullclines in saturated regions and $\dot{X} < 0$ can be shown similarly. $\square$

In Examples 19-21, we showed three possible combinations regarding which saturated regions the X and Y nullclines extend into. Theoretically, since each nullcline has three possible saturated regions to extend into, there are nine different arrangements for nullclines in saturated regions. However, in the case of an invertible system with an equilibrium in the all ramp region, not all of these combinations are possible.

For instance, at most one nullcline can extend into the both saturated region. Otherwise, the X and Y nullclines would completely overlap in that box, contradicting the fact that their only intersection is at the equilibrium in the all ramp region. Additionally, if the Y nullcline extends into the Y saturated or both saturated region, then the extended X nullcline must be in the Y saturated region. From Theorem 31, $\dot{X} < 0$ along a Y nullcline in a saturated region, and we earlier established that $\dot{X} \geq 0$ along the Y-axis. Since the vector field is continuous, $\dot{X}$ cannot switch signs without passing through a nullcline first. Hence, the X nullcline must extend into the Y saturated region, either along the Y-axis or as a line in between the Y-axis and extended Y nullcline. Similarly, if the X nullcline extends into the X saturated or both saturated region, then the Y nullcline extends into the X saturated region.

These restrictions leave five possible arrangements for nullclines in saturated regions, which are listed in Table 1.

X Nullcline	Y Nullcline
Y saturated	X saturated
X saturated	X saturated
Y saturated	Y saturated
Both saturated	X saturated
Y saturated	Both saturated

Table 1: The five possible ways in which the nullclines of invertible systems of form (3.2) with equilibria in the all ramp region can extend into saturated regions.

3.4.1.2 Flow in Saturated Regions

Now, we are ready to examine flow patterns in the saturated regions of invertible systems of form (3.2) with equilibria in the all ramp region. For each of the pairings listed in Table

1, our goal will be to show that net flow will always be toward the all ramp region when starting in any of the three saturated regions.

To determine the direction of flow, we will use the signs of the differential equations. Thus, we will first deduce when $\dot{X}$ and $\dot{Y}$ are positive and negative. From (3.2), the $\dot{X}$ equation

$$\dot{X} \ = \ -ar_1(X) + br_2(Y) + x_0$$

is negative when $r_1(X) > x_0/a$ (when $b = 0$) or when $r_2 < (a/b)r_1(X) - x_0/b$ ($b \neq 0$), and positive when these inequalities are reversed. For the equation

$$\dot{Y} \ = \ cr_1(X) - dr_2(Y) + y_0,$$

we have $\dot{Y} < 0$ when $r_2(Y) > (c/d)r_1(X) + y_0/d$, and $\dot{Y} > 0$ when this inequality goes the other way. The signs for $\dot{X}$ and $\dot{Y}$ are summarized in the following two tables.

	$\dot{X} < 0$	$\dot{X} > 0$
$b = 0$	$r_1(X) > \frac{x_0}{a}$	$r_1(X) < \frac{x_0}{a}$
$b \neq 0$	$r_2(Y) < \frac{a}{b}r_1(X) - \frac{x_0}{b}$	$r_2(Y) > \frac{a}{b}r_1(X) - \frac{x_0}{b}$

Table 2: Sign chart for the $\dot{X}$ equation in an invertible system of form (3.2) with all ramp region equilibria.

$\dot{Y} < 0$	$\dot{Y} > 0$
$r_2(Y) > \frac{c}{d}r_1(X) + \frac{y_0}{d}$	$r_2(Y) < \frac{c}{d}r_1(X) + \frac{y_0}{d}$

Table 3: Sign chart for the $\dot{Y}$ equation in an invertible system of form (3.2) with all ramp region equilibria.

We now examine flow in saturated regions by considering each of the nullcline combinations given in Table 1.

Case 1: X Nullcline in Y Saturated Region, Y Nullcline in X Saturated Region

By Table 3, $\dot{Y} < 0$ in the Y saturated and both saturated boxes as they lie above the Y nullcline. Meanwhile, $\dot{X} = 0$ along the X nullcline in the Y saturated region. If the X nullcline is not the Y-axis, then to the left of the nullcline in the Y saturated box (i.e. decreasing $r_1(X)$), $\dot{X} > 0$ by Table 2 (either b case). If we are to the right of the X nullcline in the Y saturated or both saturated region, $\dot{X} < 0$.

Hence, in the Y saturated region, flow is right-downward to the left of the X nullcline (if said nullcline is not the Y-axis), straight downward along the X nullcline, and then left-downward to the right of the X nullcline. In the both saturated region, flow is left-downward. Thus, if a trajectory begins in the Y saturated or both saturated region, it will head towards the all ramp or X saturated region.

In the X saturated region, $\dot{X}$ will always be negative as we are to the right of the X nullcline (large $r_1(X)$). According to Table 3, $\dot{Y}$ will be negative when above the Y nullcline and positive when below it (if said nullcline is not the X-axis). Thus, flow above the Y nullcline will be directed left-downward, then directed strictly to the left along the Y nullcline, and then if there is area below the Y nullcline, flow will be left-upward. As a result, flow in the X saturated region will be toward the Y nullcline, where movement is then straight into the all ramp region.

Thus, any trajectory starting in a saturated region must eventually enter the all ramp region. This flow pattern is visualized in Figure 11. The vector field shown is that of the system in Example 19 and, like all of the vector fields we will present here, was made using Maple.

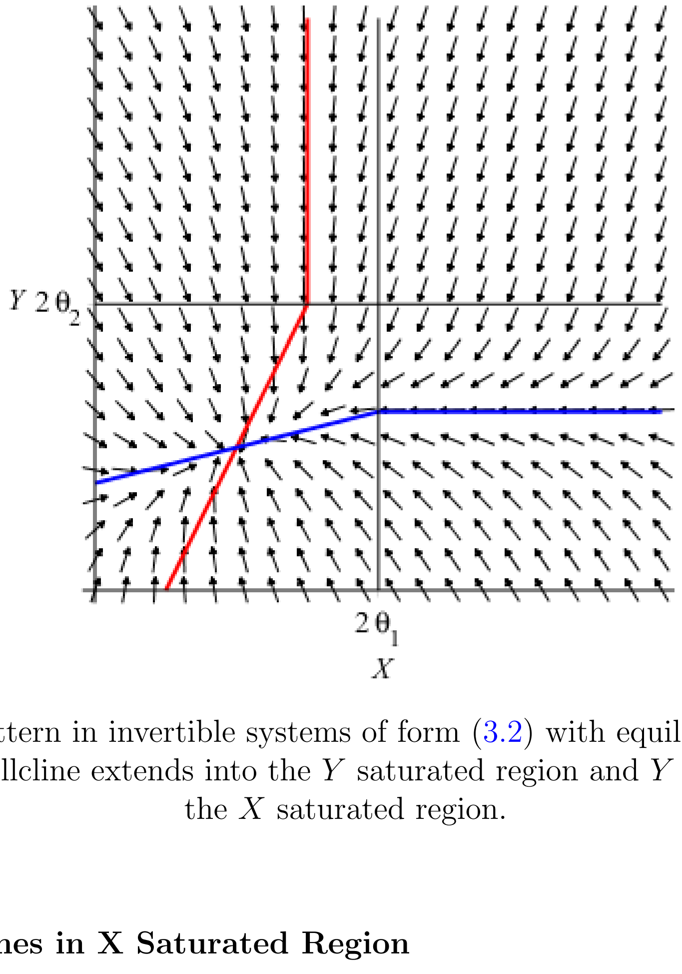


Figure 11: Flow pattern in invertible systems of form (3.2) with equilibria in the all ramp region whose X nullcline extends into the Y saturated region and Y nullcline extends in the X saturated region.

Case 2: Both Nullclines in X Saturated Region

In the Y saturated and both saturated regions, we are above both nullclines. By Tables 2 and 3 (with the $b \neq 0$ case for $\dot{X}$ by the proof of Theorem 31), we have $\dot{X} > 0$ and $\dot{Y} < 0$ in these boxes. Hence, flow will be right-downward, eventually entering either the all ramp or X saturated region.

The X nullcline must be located above the Y nullcline in the X saturated box. We know that $\dot{Y} < 0$ along the X nullcline by Theorem 31, while $\dot{Y} \geq 0$ on the X-axis. By continuity of the vector field, the Y nullcline must therefore lie below the X nullcline.

Thus, in the X saturated region, flow will continue to be right-downward when above the X nullcline, and then straight downward along the nullcline. Between the two nullclines, $\dot{X}$ will become negative like $\dot{Y}$, resulting in left-downward flow toward the Y nullcline, where flow is to the left and into the all ramp region. If the Y nullcline is not the X-axis, then $\dot{Y} > 0$ below the Y nullcline, resulting in left-upward flow toward the Y nullcline and into the all ramp region.

Once again, trajectories starting in saturated regions ultimately move into the all ramp region. The flow pattern for this case, using the vector field of Example 20, is shown in the next figure.

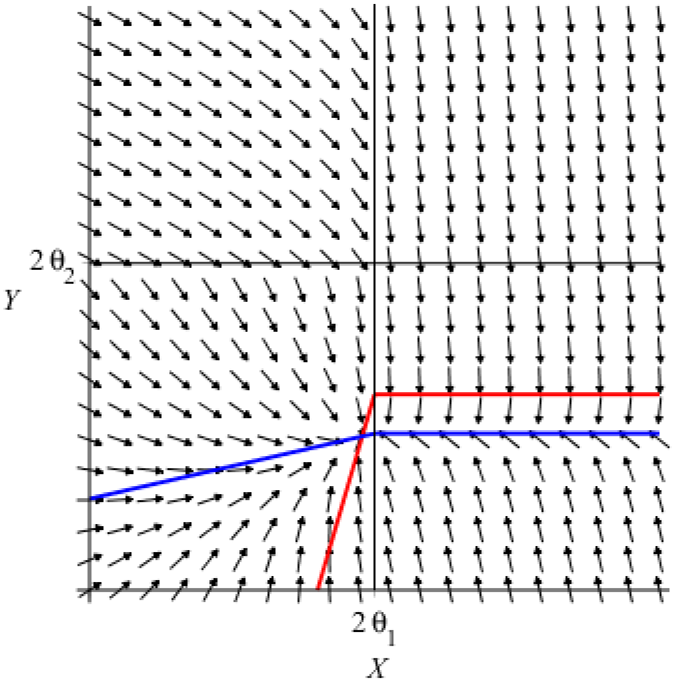


Figure 12: Flow pattern in invertible systems of form (3.2) with equilibria in the all ramp region whose X and Y nullclines both extend into the X saturated region.

The case from Table 1 in which both nullclines extend into the Y saturated region can be handled similarly.

Case 3: X Nullcline in Both Saturated Region, Y Nullcline in X Saturated Region

The Y saturated region is above the Y nullcline and above and to the left of the X nullcline, meaning that $\dot{Y} < 0$ and $\dot{X} > 0$ by Tables 2 and 3 (again, we have $b \neq 0$ in this case). As a result, flow is right-downward toward another box. Then, since the entire both saturated region is an X nullcline, $\dot{Y} < 0$ in the entire box by Theorem 31. Hence, flow in the both saturated region is straight downward into the X saturated region.

We are below the X nullcline in the X saturated region, and thus $\dot{X} < 0$ by Table 2. Above the Y nullcline, $\dot{Y}$ will remain negative. If the Y nullcline is above the X-axis, $\dot{Y}$ will be positive below its nullcline. Thus, flow in the X saturated region will be left-downward above the Y nullcline, straight left along the Y nullcline, and left-upward in the area below the Y nullcline if said area exists. Hence, flow will be toward the Y nullcline, where movement is then into the all ramp region.

As in the previous cases, if a trajectory starts in a saturated region, it will enter the all ramp region in the end. Figure 13 displays the flow pattern discussed here, with the vector field of the system from Example 21.

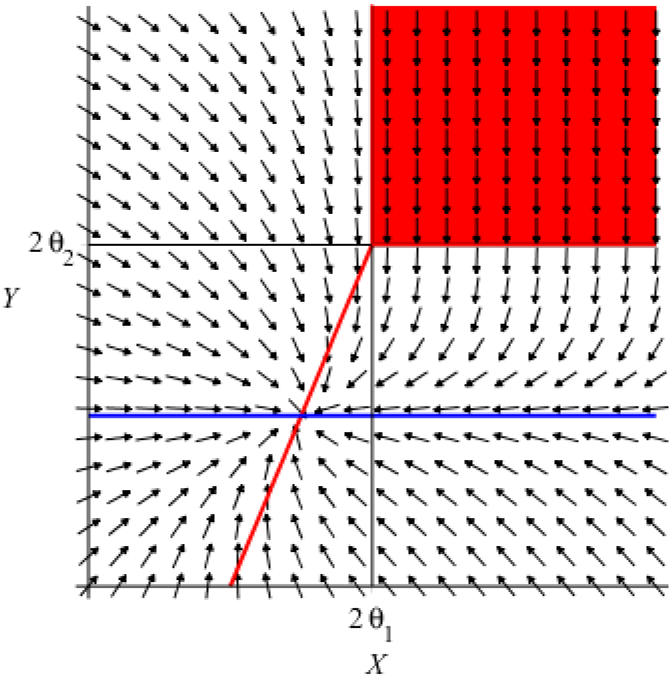


Figure 13: Flow pattern in invertible systems of form (3.2) with equilibria in the all ramp region whose X nullcline extends into the both saturated region and Y nullcline extends into the X saturated region.

The final case listed in Table 1, in which the Y nullcline extends into the both saturated region and the X nullcline into the Y saturated region, is similar.

In every case, we have found that in an invertible system of form (3.2) with an (asymptotically stable) equilibrium point in the all ramp region, trajectories starting outside the all ramp region must eventually enter it. Thus, we have the following:

Theorem 32. *Consider a system of form (3.2), in which $ad - bc \neq 0$ and an equilibrium exists in the all ramp region. Then, this equilibrium is globally stable.*

3.4.2 Singular Systems with Equilibria in the All Ramp Region

We will now consider systems of form (3.2) in which equilibria exist in the all ramp region, but the matrix A is singular. From section 3.2.2, all ramp region equilibria in singular two-variable systems are not unique; if equilibrium points are possible in the all ramp region, a singular system will have infinitely many such points. As we will see in this section, these systems will also have infinitely many equilibrium points in one of the saturated regions.

Since A is a singular SRP matrix, the Jacobian of the system in the all ramp region is also a singular SRP matrix. Hence, the Jacobian has a zero eigenvalue, and so the asymptotic stability of all ramp region equilibria seen in the invertible case is absent here.

Our discussion here will be divided into the same two cases we covered in section 3.2.2.

Case 1: $\mathbf{c = a \neq 0}$ and $\mathbf{b = d \neq 0}$

By Theorem 20, a singular system of this type with equilibria in the all ramp region must have the form

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & d \\ a & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix}.$$

As a result, the X and Y nullclines of the system are identical, given by

$$r_2(Y) = \frac{a}{d} r_1(X).$$

Every point on this nullcline, regardless if in the all ramp or a saturated region, is an equilibrium point. The saturated region the nullcline extends into depends on a and d. If $a < d$, the nullcline extends into the X saturated region as the line $r_2(Y) = a/d$; if $a > d$, we get an extension into the Y saturated region along $r_1(X) = d/a$; and if $a = d$, the nullcline becomes $r_2(Y) = r_1(X)$ and extends into the both saturated region.

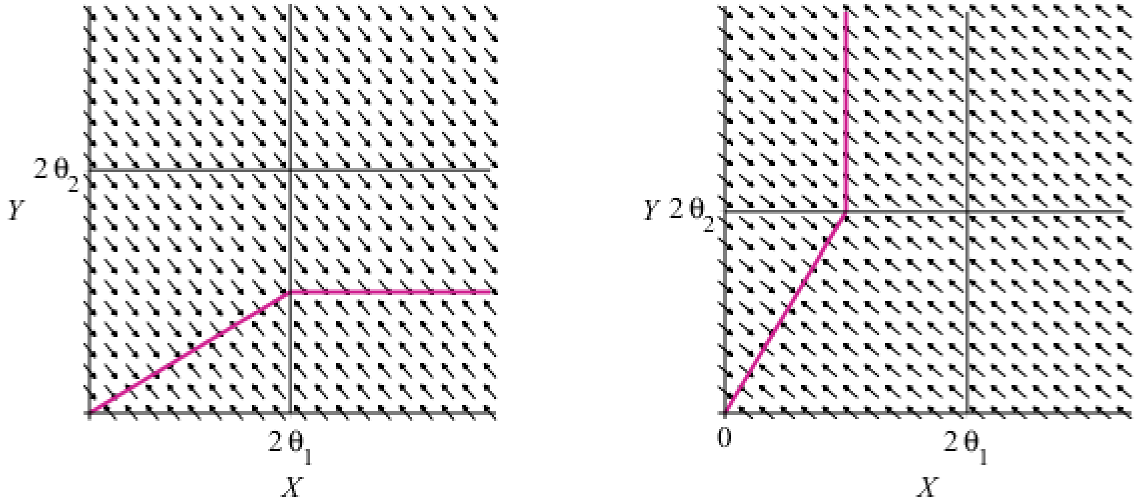
The following table summarizes where $\dot{X}$ and $\dot{Y}$ are positive and negative:

$\dot{X} < 0$	$\dot{X} > 0$	$\dot{Y} < 0$	$\dot{Y} > 0$
$r_2(Y) < \frac{a}{d} r_1(X)$	$r_2(Y) > \frac{a}{d} r_1(X)$	$r_2(Y) > \frac{a}{d} r_1(X)$	$r_2(Y) < \frac{a}{d} r_1(X)$

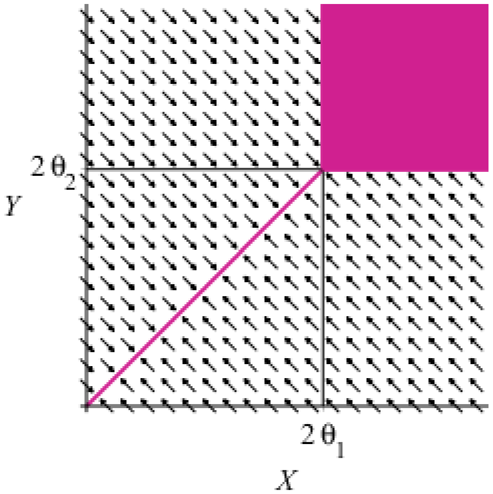
Table 4: Sign chart for the $\dot{X}$ and $\dot{Y}$ equations in a singular system of form (3.2) with all ramp region equilibria and no columns of zeros.

Table 4 tells us that regardless of whether we are in the all ramp or a saturated region, when we are above or to the left of the nullcline, flow is right-downward toward the nullcline, while if we are below or to the right of the nullcline, flow is left-upward toward the nullcline.

Flow patterns for the $a < d$, $a > d$, and $a = d$ cases are visualized in the vector fields provided in the following figure.



(a) $a < d$ (b) $a > d$



(c) $a = d$

Figure 14: Flow patterns in singular systems of form (3.2) with equilibria in the all ramp region and no columns of zeros. Nullclines (equilibria) are shown in purple.

Notice how in all three cases in Figure 14, flow is always to a point on the nullcline (i.e. an equilibrium point). However, trajectories starting at different points on the plane can go to different equilibria, and trajectories can move toward equilibria in saturated regions.

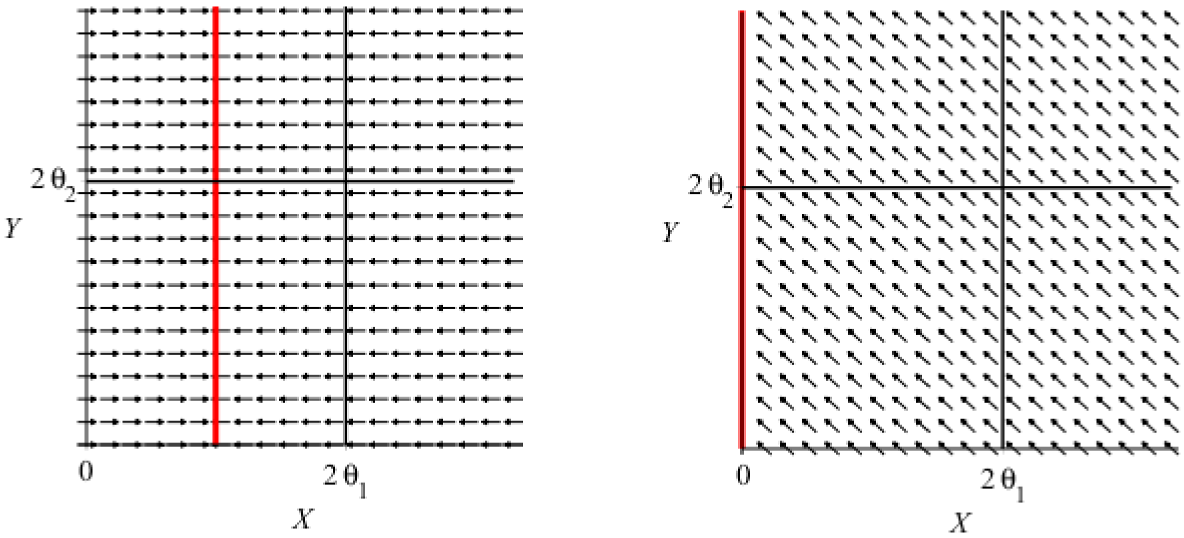
Case 2: A has a column of zeros

Like we did in section 3.2.2, we will assume the second column of A is zero ($b = d = 0$), with $a > 0$. Then, we have the cases $c = 0$ and $c \neq 0$ to consider.

- If $c = 0$ and equilibria exist in the all ramp region, by Theorem 21 the system must have the form
  $$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ 0 \end{bmatrix},$$
  with $x_0 < a$. The X nullcline is given by
  $$r_1(X) \;=\; \frac{x_0}{a},$$
  which extends into the Y saturated region. Meanwhile, $\dot{Y} = 0$ everywhere. As a result, flow in this case is rather simple; if the X nullcline is not the Y-axis, then to the left of the X nullcline ($r_1(X) < x_0/a$), $\dot{X} > 0$ and flow is to the right, while to the right of the X nullcline ($r_1(X) > x_0/a$), $\dot{X} < 0$ and flow is to the left. Thus, flow is directed toward equilibria on the X nullcline, in either the all ramp or Y saturated region.

- If $c \neq 0$, the system has the form
  $$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & 0 \\ c & 0 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix}$$
  by Theorem 21. Both nullclines of the system are given by
  $$r_1(X) \;=\; 0,$$
  which is the Y-axis. As $r_1(X)$ increases, the $\dot{X}$ equation becomes negative while $\dot{Y}$ becomes positive. Hence, whenever $r_1(X) > 0$, the vector field in all four regions will be pointing in the left-upward direction. Trajectories will thus always head toward equilibria on the Y-axis, in either the all ramp or Y saturated region.

Vector fields showing flow in both the $c = 0$ and $c \neq 0$ cases are provided in Figure 15 on the next page.



(a) $c = 0$ (b) $c \neq 0$

Figure 15: Flow patterns in singular systems of form (3.2) with equilibria in the all ramp region and zeros in column two. Lines of equilibria are shown in red.

Overall, trajectories in singular systems of form (3.2) with equilibria in the all ramp region will move toward equilibria. However, with entire lines or regions of equilibria possible in these systems, flow is not toward one equilibrium point in particular. Trajectories with different initial positions can have very different final destinations. Additionally, flow is not guaranteed to be toward the all ramp region; as shown by Figures 14 and 15, trajectories can be directed to equilibria in saturated regions. Thus, the global stability seen in the invertible case is not present here.

3.4.3 Invertible Systems with Equilibria in Saturated Regions

We will briefly touch on invertible systems of form (3.2) in which equilibria exist in saturated regions, i.e. equilibria $(r_1(X^*), r_2(Y^*))$ such that one ramp function is at 1, with the other at or below 1. This occurs when the equilibrium solution

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \end{bmatrix} = \frac{1}{ad - bc} \begin{bmatrix} dx_0 + by_0 \\ cx_0 + ay_0 \end{bmatrix}$$

from the proof of Theorem 18 from section 3.2.1 satisfies $dx_0 + by_0 \leq ad - bc$ and $cx_0 + ay_0 \leq ad - bc$, with equality holding in at least one of these.

We will only be considering the $x_0 < a$ and $y_0 < d$ case here. These inequalities mean that the X and Y nullclines start in the all ramp region, on the X-axis at $r_1(X) = x_0/a$ and the Y-axis at $r_2(Y) = y_0/d$ respectively. The nullclines intersect for the first time at the boundary of a saturated region, where they merge and extend into that saturated region as one nullcline of infinitely many equilibrium points. Note that in the all ramp region, the Y nullcline must always be located above the X nullcline, to ensure an intersection does not occur until the boundary of a saturated region is reached.

The merged nullcline can extend into any of the three saturated regions. Examples of all three possibilities are provided below.

Example 22. Invertible systems with equilibria in saturated regions
In the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-5 & 2\\ 1 & -2\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}4\\ 0\end{bmatrix},$$

equilibria occur along $(r_1(X^*), r_2(Y^*)) = (1, 1/2)$, a line in the X saturated region. Moving the coefficients of this system around, we get

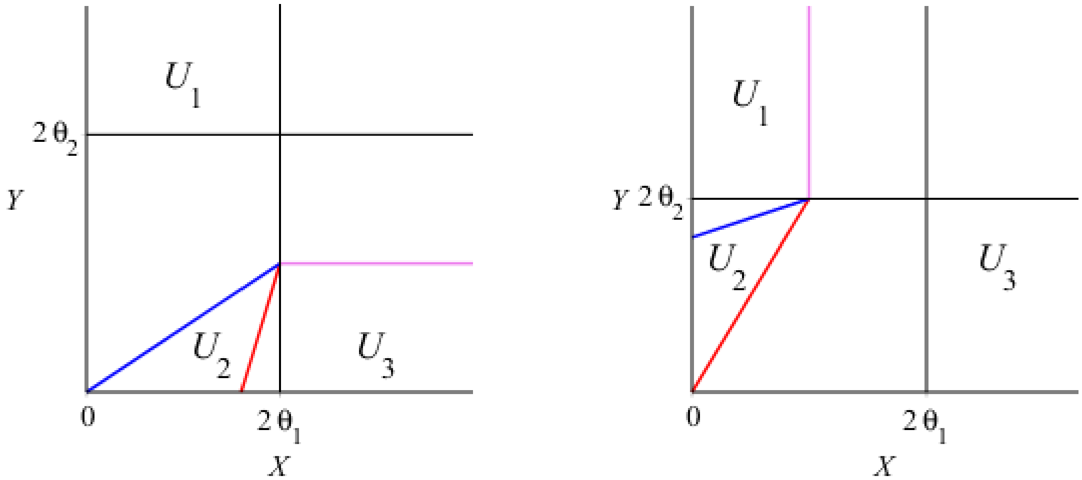
$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-2 & 1\\ 2 & -5\end{bmatrix}\begin{bmatrix}r_1(X^*)\\ r_2(Y^*)\end{bmatrix} + \begin{bmatrix}0\\ 4\end{bmatrix},$$

which has equilibria $(r_1(X^*), r_2(Y^*)) = (1/2, 1)$ in the Y saturated region. Finally, the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-2 & 1\\ 1 & -2\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}1\\ 1\end{bmatrix}$$

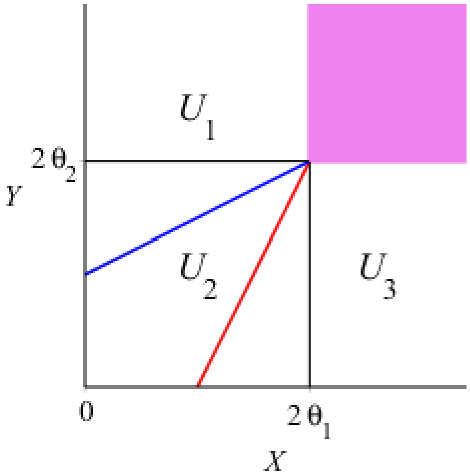
reaches equilibrium at $(r_1(X^*), r_2(Y^*)) = (1, 1)$, the both saturated region.

The sign charts displayed in Tables 2 and 3 in section 3.4.1.2 are accurate for the invertible systems we are interested in here, and thus will be used when discussing flow. To facilitate our discussion of flow, we will also use the fact that the nullclines of the systems of interest divide the non-negative quadrant into three distinct subregions with easily characterizable flow patterns. The nullclines of systems with all three possible equilibria locations, based on the systems in Example 22, are pictured in the figure on the next page. In each image, the subregions the nullclines divide the plane into are labelled U_1, U_2, and U_3.



(a) Equilibria in the X saturated region

(b) Equilibria in the Y saturated region



(c) Equilibria in the both saturated region

Figure 16: Nullclines of invertible systems of form (3.2) in which equilibria are located in saturated regions, $x_0 < a$, and $y_0 < d$ dividing phase space into three subregions, U_1, U_2, and U_3. Red lines are X nullclines, blue lines are Y nullclines, and equilibria are shown in light purple.

The subregions shown in Figure 16 can be described as follows:

- Subregion U_1 encompasses the area above and to the left of all nullclines. Notice how U_1 can include different parts of the four main regions depending on nullcline locations. For instance, U_1 includes part of the all ramp region in both Figures 16(b) and (c), but in (b) only the portion of the Y saturated region to the left of the extended nullcline is included, whereas the entire Y saturated region belongs to U_1 in (c). Meanwhile, U_1 consists of area from all four regions in (a).

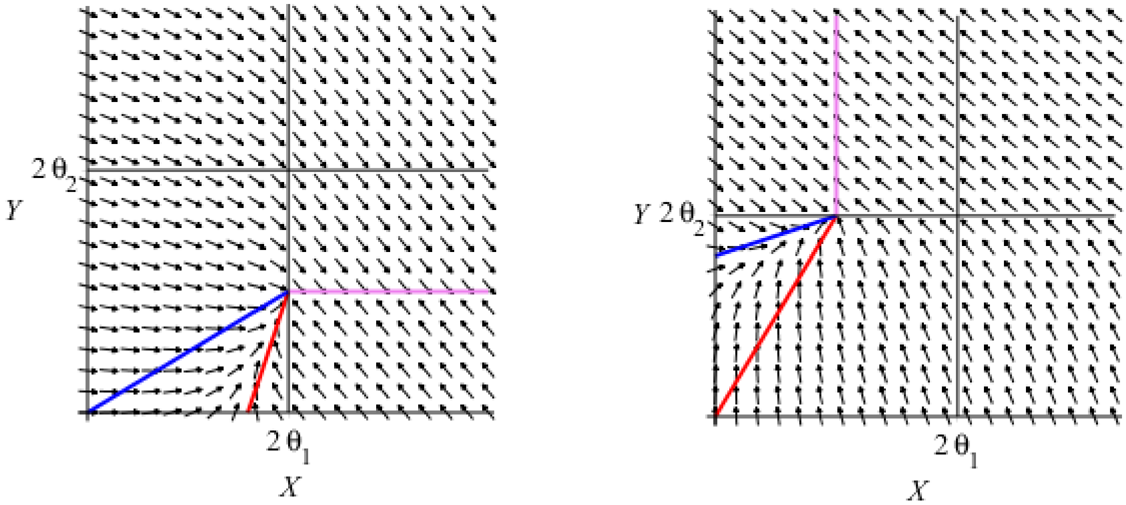
- Subregion U_2 is the part of the all ramp region that lies in between the X and Y nullclines.
- Subregion U_3 is the area below and to the right of all nullclines. Like U_1, which, if any, parts of the four main regions belong to U_3 depend on the arrangement of the nullclines in the plane.

Using Tables 2 and 3, we then have the following flow patterns:

- In subregion U_1, being above and to the left of all nullclines means that $\dot{X} > 0$ and $\dot{Y} < 0$. Hence, flow is right-downward, heading toward either equilibria or the Y nullcline in the all ramp region. Since we have not crossed the X nullcline yet, $\dot{X}$ is still positive on the Y nullcline, resulting in rightward flow into U_2.
- Subregion U_2 is located below the Y nullcline and above the X nullcline. Thus, $\dot{X}$ is again positive, with $\dot{Y}$ also becoming greater than zero. Flow is therefore right-upward, channelled toward the equilibrium point at the saturated region boundary where the nullclines meet.
- With subregion U_3 lying below and to the right of all nullclines, we have $\dot{X} < 0$ and $\dot{Y} > 0$. Thus, flow is left-upward, resulting in movement toward equilibria or the X nullcline in the all ramp region. The $\dot{Y}$ equation is positive along the X nullcline, which means flow is upward into U_2, where movement is then toward an equilibrium point.

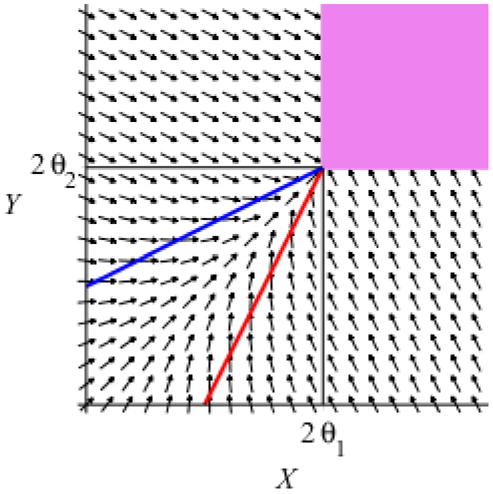
Thus, any trajectory in an invertible system of form (3.2) with equilibria in saturated regions and $x_0 < a$ and $y_0 < d$ will ultimately move toward an equilibrium point. However, similar to what we saw in the previous section with singular systems, trajectories starting at different points on the plane can move toward different equilibria.

The vector fields of the systems from Example 22 are provided in the next figure.



(a) Equilibria in the X saturated region

(b) Equilibria in the Y saturated region



(c) Equilibria in the both saturated region

Figure 17: Flow patterns in invertible systems of form (3.2) with equilibria in saturated regions and $x_0 < a$ and $y_0 < d$. Red lines are X nullclines and blue lines are Y nullclines. Equilibria are shown in light purple.

3.4.4 Systems with no Equilibria

Finally, we will look at systems of form (3.2) that do not have equilibria, with the goal of showing that at least one variable must go to infinity over time. A system fails to have equilibria due to one of two reasons:

1.) the X and Y nullclines never intersect

2.) one or both nullclines does not exist

We will consider both of these reasons, starting with the case where the system is missing one or both nullclines.

3.4.4.1 Non-Existence of Nullclines

The nullcline associated with a variable in a system of form (3.2) fails to exist when the variable's corresponding differential equation can only equal zero when one or both ramp functions take values outside their $[0,1]$ range. For instance, suppose we had a system with the $\dot{Y}$ equation

$$\dot{Y} \;=\; r_1(X) - r_2(Y) + 3.$$

Setting $\dot{Y} = 0$, we get

$$r_2(Y) \;=\; r_1(X) + 3$$

as the Y nullcline. However, for any $r_1(X) \in [0,1]$, we have $r_2(Y) \geq 3$, which is impossible. Thus, $\dot{Y}$ can never be zero.

It is easy to verify that the $\dot{Y}$ equation above is always positive. In fact, this will always be the case when a variable's nullcline does not exist; if $\dot{Y} = cr_1(X) - dr_2(Y) + y_0$ is never zero, then at the origin $\dot{Y} = y_0$ must be strictly positive, and $\dot{Y}$ cannot change signs without first passing through a Y nullcline by continuity of the vector field. The same applies to $\dot{X}$.

Thus, when a variable's nullcline does not exist, the associated differential equation will always be positive. As a result, that variable will go to infinity over time. To determine whether or not nullclines exists in a system of form (3.2), we only need to compare the input terms x_0 and y_0 to a and d, as shown by the theorem below.

Theorem 33. *Consider a system of form* (3.2). *The system lacks an X nullcline (Y nullcline) if and only if $x_0 > a$ ($y_0 > d$).*

Proof. Suppose the system does not have an X nullcline. Then, from our discussion above, we know that

$$\dot{X} \;=\; -ar_1(X) + br_2(Y) + x_0 \;>\; 0$$

for any values that r_1 and r_2 can take. In particular, when $r_1(X) = 1$ and $r_2(Y) = 0$,

$$\begin{aligned} \dot{X} \;&=\; -a + x_0 \;>\; 0 \\ \implies \;\; x_0 \;&>\; a. \end{aligned}$$

Now, suppose that $x_0 > a$. Then for any values of $r_1(X)$ and $r_2(Y)$,

$$\begin{aligned}\dot{X} &= -ar_1(X) + br_2(Y) + x_0\\ &> -ar_1(X) + br_2(Y) + a\\ &= a(1 - r_1(X)) + br_2(Y)\\ &\geq 0.\end{aligned}$$

Since $\dot{X}$ is always positive, the X nullcline does not exist.

The case with the Y nullcline and $y_0 > d$ is similar. □

Any system of form (3.2) satisfying the above theorem will lack at least one nullcline, and thus will have a variable that blows up to infinity. In the next few sections, we will shift focus to systems in which equilibria are not present, but both nullclines are (i.e. $x_0 \leq a$ and $y_0 \leq d$).

3.4.4.2 Invertible Systems with Nullclines and no Equilibria

We consider the case in which the 2×2 matrix from (3.2) is invertible first. An invertible system fails to have equilibria when the "theoretical" equilibrium solution

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \end{bmatrix} = \frac{1}{ad - bc} \begin{bmatrix} dx_0 + by_0 \\ cx_0 + ay_0 \end{bmatrix}$$

from the Theorem 18 proof in section 3.2.1 satisfies at least one of

$$\begin{aligned} dx_0 + by_0 &> ad - bc\\ cx_0 + ay_0 &> ad - bc,\end{aligned}$$

resulting in the impossible equilibrium values $r_1(X^*) > 1$ and/or $r_2(Y^*) > 1$. Note that since $ad - bc > 0$ by Corollary 1 from section 2.2.2, the theoretical equilibrium will never have negative components.

Once again, when determining flow patterns we will need to establish what flow along nullclines is like. For this, we have a theorem analogous to Theorem 31:

Theorem 34. *Consider a system of form* (3.2)*, in which $ad - bc \neq 0$, $x_0 \leq a$, and $y_0 \leq d$. If $dx_0 + by_0 > ad - bc$, then $\dot{X} > 0$ along the Y nullcline and $\dot{Y} > 0$ along the X nullcline. The same conclusion holds if $cx_0 + ay_0 > ad - bc$.*

Proof. If $dx_0 + by_0 > ad - bc$, then we must have $b \neq 0$. Otherwise, given $x_0 \leq a$ we would have

$$dx_0 + by_0 = dx_0 \leq ad = ad - bc,$$

a contradiction. Hence, the nullclines of the system are as follows:

$$X \text{ nullcline: } r_2(Y) = \frac{a}{b} r_1(X) - \frac{x_0}{b}$$

$$Y \text{ nullcline: } r_2(Y) \;=\; \frac{c}{d}r_1(X) + \frac{y_0}{d}$$

Then, along the Y nullcline we have

$$\begin{aligned}\dot{X} \;&=\; -ar_1(X) + b\Big(\frac{c}{d}r_1(X) + \frac{y_0}{d}\Big) + x_0 \\ &=\; \Big(\frac{-ad+bc}{d}\Big)r_1(X) + \frac{dx_0+by_0}{d} \\ &>\; \Big(\frac{-ad+bc}{d}\Big)r_1(X) + \frac{ad-bc}{d} \\ &=\; \Big(\frac{ad-bc}{d}\Big)(1-r_1(X)) \\ &\geq\; 0,\end{aligned}$$

while along the X nullcline,

$$\begin{aligned}\dot{Y} \;&=\; cr_1(X) - d\Big(\frac{a}{b}r_1(X) - \frac{x_0}{b}\Big) + y_0 \\ &=\; \Big(\frac{-ad+bc}{b}\Big)r_1(X) + \frac{dx_0+by_0}{b} \\ &>\; \Big(\frac{-ad+bc}{b}\Big)r_1(X) + \frac{ad-bc}{b} \\ &=\; \Big(\frac{ad-bc}{b}\Big)(1-r_1(X)) \\ &\geq\; 0.\end{aligned}$$

The $cx_0 + ay_0 > ad - bc$ case is similar. Note that this case implies $c \neq 0$. □

Unlike Theorem 31, which only dealt with nullcline flow in saturated regions, the results of Theorem 34 above apply to nullclines in both saturated regions and the all ramp region. That is, in an invertible system with both nullclines and no equilibria, at any given point on the Y nullcline (X nullcline), $\dot{X}$ ($\dot{Y}$) is guaranteed to be positive.

When looking at flow in the systems of interest here, there are slight differences that depend on whether one or both of the theoretical $r_1(X^*)$ and $r_2(Y^*)$ values calculated in the Theorem 18 proof are greater than 1. We will consider the case with both pseudo-equilibrium components greater than 1 first.

Clarifying note: Here, we are **not** saying that it is actually possible to have $r_1(X^*) > 1$ or $r_2(Y^*) > 1$. We are studying systems that do not have equilibria because solving for possible equilibria produces a "solution" satisfying one or both of these impossible inequalities.

Both components greater than 1

When both components of the theoretical equilibrium exceed 1, both of $dx_0+by_0 > ad-bc$

and $cx_0 + ay_0 > ad - bc$ hold. By the proof of Theorem 34, we have $b \neq 0$ and $c \neq 0$, and the nullclines are thus given by:

$$\begin{aligned} X \text{ nullcline: } r_2(Y) &= \frac{a}{b} r_1(X) - \frac{x_0}{b} \\ Y \text{ nullcline: } r_2(Y) &= \frac{c}{d} r_1(X) + \frac{y_0}{d} \end{aligned}$$

In the non-negative quadrant, these nullclines start on the Y-axis (Y nullcline) or the X-axis (X nullcline) and extend into one of the saturated boxes. However, just as was the case for invertible systems with equilibria in the all ramp region, there are restrictions regarding which of the nine nullcline extension combinations are possible. These restrictions ensure that, since we have no equilibria, the nullclines never intersect.

For instance, if the X nullcline extends into the Y or both saturated region, then the Y nullcline must extend into the Y saturated region to the left of the extended X nullcline. This can be seen geometrically; the X nullcline in this case would resemble those shown in Figure 10(a) and (c), and so the only way a Y nullcline can go from the Y-axis to a saturated region without intersecting the X nullcline is if it extends to the left of the X nullcline and into the Y saturated box. Similarly, if the Y nullcline extends into the X or both saturated region, the X nullcline must extend below the Y nullcline and into the X saturated region.

With these restrictions, we have five possibilities regarding nullcline extensions:

X Nullcline	Y Nullcline
X saturated	X saturated
Y saturated	Y saturated
X saturated	Both saturated
Both saturated	Y saturated
X saturated	Y saturated

Table 5: The five possible ways in which the nullclines of invertible systems of form (3.2) with no equilibria can extend into saturated regions.

Our study of flow will focus on three of the pairings listed in Table 5:

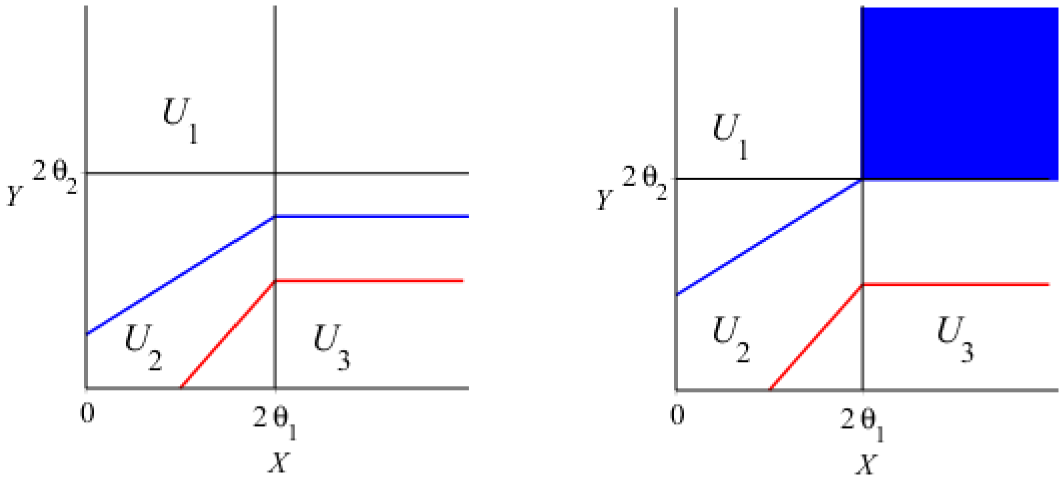
1.) Both nullclines extend into the X saturated region

2.) Y nullcline extends into the both saturated region, X nullcline extends into the X saturated region

3.) X nullcline extends into the X saturated region, Y nullcline extends into the Y saturated region

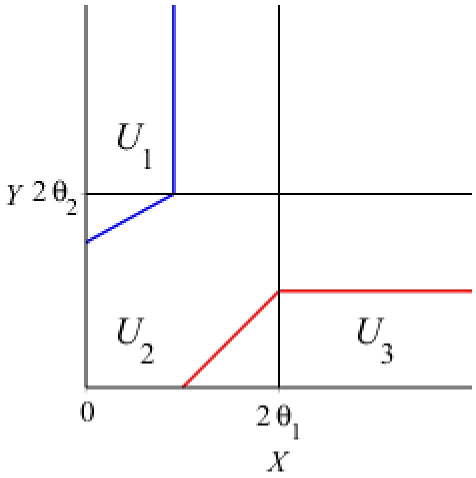
The case in which both nullclines extend into the Y saturated region and the case with the X nullcline extended into the both saturated region are similar to 1.) and 2.) above respectively.

Like in the section on invertible systems with equilibria in saturated regions, the three nullcline pairings listed above divide the non-negative quadrant into U_1, U_2, and U_3 subregions with distinct flow patterns. The nullclines and the labelled subregions are shown in Figure 18.



(a) Both nullclines in X saturated region

(b) Y nullcline in both saturated region



(c) X nullcline in X saturated region, Y nullcline in Y saturated region

Figure 18: Nullclines of invertible systems of form (3.2) with no equilibria and theoretical equilibria $r_1(X^*) > 1$ and $r_2(Y^*) > 1$ dividing phase space into three subregions, U_1, U_2, and U_3. Red lines are X nullclines, blue lines are Y nullclines

The three subregions are similar to their Figure 16 counterparts: U_1 is the area above and to the left of both nullclines, U_2 is the area between the two nullclines, and U_3 is the area below and to the right of the nullclines. Note that since we can have $x_0 = a$ or $y_0 = d$ in these systems, it is possible for U_1 and U_3 to have zero area. For example, if

$$\dot{Y} \;=\; r_1(X) - r_2(Y) + 1,$$

then the Y nullcline is

$$r_2(Y) \;=\; r_1(X) + 1.$$

This nullcline only exists on the portion of the Y-axis that falls in the Y saturated region, and thus no U_1 subregion exists.

Tables 2 and 3 from section 3.4.1.2 are still relevant in this case, and hence flow in each of the subregions will be similar to what was seen in Figure 17:

- If the system has a U_1 subregion, flow will be right-downward toward the Y nullcline. By Theorem 34, $\dot{X} > 0$ at any point on the Y nullcline, resulting in rightward flow.
- Both differential equations are positive in U_2, meanining that flow is right-upward.
- The $\dot{X}$ equation is negative in subregion U_3, if it exists, while $\dot{Y} > 0$. Thus, flow is left-upward toward the X nullcline, where movement is straight upward.

These flow patterns will result in at least one variable going to infinity. In the case where the X nullcline extends into the X saturated region and the Y nullcline into the Y saturated region, as in Figure 18(c), trajectories starting in subregions U_1 or U_3 or on either nullcline will be directed into U_2, where right-upward flow pushes both variables to infinity. In (a) and (b), however, only X will go to infinity; any trajectory is ultimately guided toward the extended Y nullcline, on which movement is strictly to the right.

We now provide examples of systems with the nullcline arrangements shown in Figure 18, along with their vector fields.

Example 23. Both nullclines in the X saturated region
Consider the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-1 & 1\\ 11/20 & -1\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}1/2\\ 1/4\end{bmatrix},$$

which has a theoretical equilibrium point of $(r_1(X^*), r_2(Y^*)) = (5/3, 7/6)$. The nullclines of this system are

$$\begin{aligned} X \text{ nullcline:}\;\; r_2(Y) &= r_1(X) - 1/2 \\ Y \text{ nullcline:}\;\; r_2(Y) &= (11/20)r_1(X) + 1/4, \end{aligned}$$

which extend into the X saturated region as the lines $r_2(Y) = 1/2$ (X nullcline) and $r_2(Y) = 4/5$ (Y nullcline).

The vector field of this system in shown below, with the X nullcline in red and the Y nullcline in blue. Flow is toward the Y nullcline in the X saturated region, where rightward flow causes X to go to infinity.

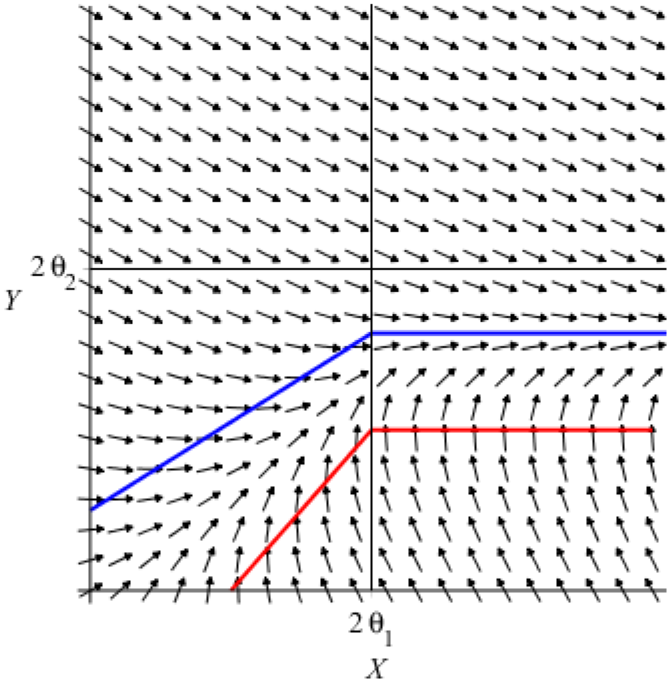


Figure 19: Flow pattern in invertible systems of form (3.2) with no equilibria and both nullclines extended into the X saturated region.

Example 24. X nullcline in the X saturated region, Y nullcline in the both saturated region

Changing the y_0 value of the previous system, we get

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -1 & 1 \\ 11/20 & -1 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 1/2 \\ 9/20 \end{bmatrix},$$

a system with the same X nullcline as the previous example and a Y nullcline given by

$$r_2(Y) = (11/20)r_1(X) + 9/20.$$

The point $(r_1(X), r_2(Y)) = (1, 1)$ falls on the Y nullcline, and thus the Y nullcline extends into the both saturated box. If this system had an equilibrium, it would be $(r_1(X^*), r_2(Y^*)) = (19/9, 29/18)$.

Figure 20 displays the vector field for this system. Movement is toward the both saturated region, where flow is then to the right, causing X to blow up to infinity.

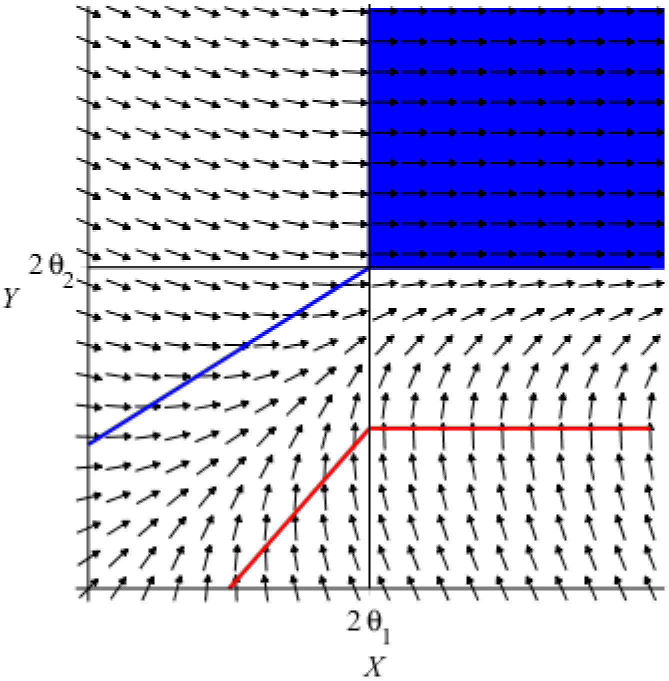


Figure 20: Flow pattern in invertible systems of form (3.2) with no equilibria and the X nullcline extended into the X saturated region and the Y nullcline extended into the both saturated region.

Example 25. X nullcline in the X saturated region, Y nullcline in the Y saturated region

Finally, increasing y_0 to 3/4 results in the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-1 & 1\\ 11/20 & -1\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}1/2\\ 3/4\end{bmatrix}.$$

The Y nullcline is

$$r_2(Y) \ = \ (11/20)r_1(X) + 3/4,$$

which becomes $r_1(X) = 5/11$ in the Y saturated region. The theoretical equilibrium point in this case is $(r_1(X^*), r_2(Y^*)) = (25/9, 41/18)$.

Once again, this system's vector field is shown on the next page. This time, flow is away from both nullclines, resulting in both variables going to infinity.

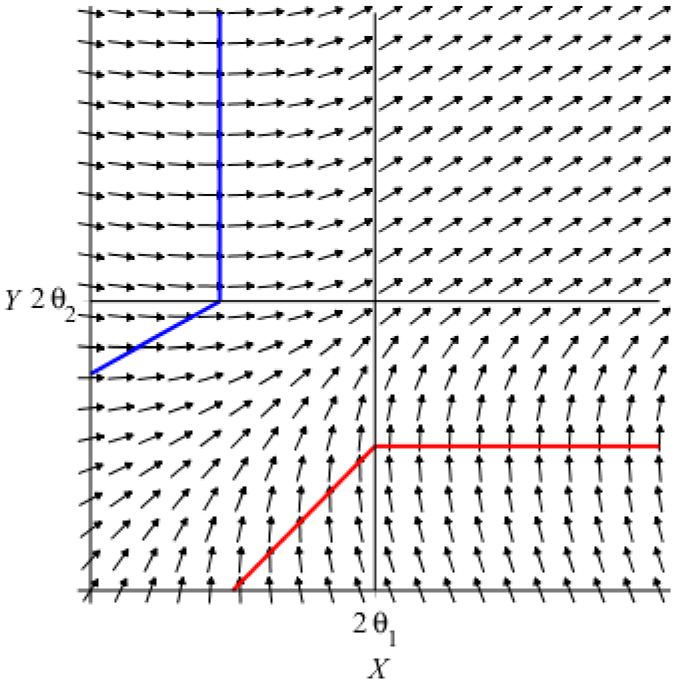


Figure 21: Flow pattern in invertible systems of form (3.2) with no equilibria and the X nullcline extended into the X saturated region and the Y nullcline extended into the Y saturated region.

One component greater than 1

Now, we look at flow in invertible systems in which just one component of the theoretical equilibrium solution from Theorem 18 is greater than 1. WLOG, we will assume the case $r_1(X^*) > 1$ and $r_2(Y^*) \leq 1$, which we have if and only if $dx_0 + by_0 > ad - bc$ and $cx_0 + ay_0 \leq ad - bc$. Remember that these are *theoretical* equilibrium values calculated as done in the proof of Theorem 18, and that we cannot actually have $r_1(X^*) > 1$. Once again, this gives us the nullclines

$$\begin{aligned} X \text{ nullcline: } r_2(Y) &= \frac{a}{b} r_1(X) - \frac{x_0}{b} \\ Y \text{ nullcline: } r_2(Y) &= \frac{c}{d} r_1(X) + \frac{y_0}{d} \end{aligned}$$

When it comes to nullcline extensions, possibilities are very limited. If $r_2(Y^*) < 1$, then both nullclines must extend into the X saturated region. A theoretical equilibrium of $(r_1(X^*) > 1, r_2(Y^*) < 1)$ means that if the ramp functions were allowed to take values greater than 1, the nullclines would eventually intersect at a point in which $r_1(X^*) > 1$, but $r_2(Y^*)$ is still less than 1. Thus, the nullclines must reach the line $r_1(X) = 1$ when $r_2(Y) < 1$.

As discussed in the previous section, the Y nullcline must be situated above the X nullcline to avoid an intersection. Thus, when $r_2(Y^*) < 1$, the system's nullclines resemble those shown in Figure 18(a), and divide phase space into the same three U_1, U_2, and U_3 subregions. By Theorem 34 and the sign charts from Tables 2 and 3, the system has the flow pattern seen in Figure 19, with X going to infinity over time.

If $r_2(Y^*) = 1$, the X nullcline still extends into the X saturated region, as does the Y nullcline in most instances, resulting in the same flow pattern as $r_2(Y^*) < 1$. However, a slightly different pattern is possible in a special case that allows the Y nullcline to extend elsewhere. To have the Y nullcline extend into a saturated region other than the X saturated region, we need

$$r_2(Y) \;=\; \frac{c}{d}r_1(X) + \frac{y_0}{d}$$

to contain a point $(r_1(X) \leq 1, r_2(Y) = 1)$, meaning that $r_2(Y)$ must reach 1 before or at the same time $r_1(X)$ does. If the ramp functions could take values greater than 1, the theoretical equilibrium solution $(r_1(X^*) > 1, r_2(Y^*) = 1)$ would also have to fall on the Y nullcline. The only way both of these are possible is if $c = 0$, and consequently, $y_0 = d$.

Thus, this special case gives us the $\dot{Y}$ equation

$$\dot{Y} \;=\; -dr_2(Y) + d,$$

with Y nullcline $r_2(Y) = 1$. This nullcline consists of the entire Y saturated and both saturated regions. With the X nullcline extended into the X saturated region, we have a nullcline setup similar to those seen in Figure 18, but with no U_1 subregion. Trajectories starting on the X nullcline or subregions U_2 or U_3 will move toward the Y nullcline on the upper half of the non-negative quadrant, where rightward flow pushes X to infinity.

An example illustrating this special case is provided below.

Example 26. Special case $\mathbf{c = 0}$ and $\mathbf{y_0 = d}$

The system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -1 & 1 \\ 0 & -1 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} 1/2 \\ 1 \end{bmatrix}$$

has the theoretical equilibrium point $(r_1(X^*), r_2(Y^*)) = (3/2, 1)$. The X nullcline $r_2(Y) = r_1(X) - 1/2$ extends into the X saturated region. The Y nullcline is $r_2(Y) = 1$, consisting of the Y saturated and both saturated boxes.

The following figure shows this system's vector field. The direction of flow is toward the Y nullcline, where movement is straight rightward, resulting in X going to infinity over time.

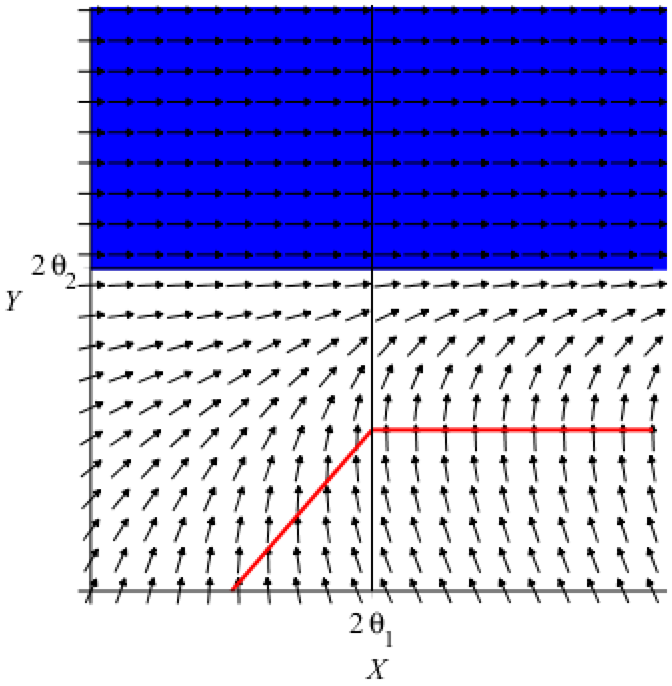


Figure 22: Flow pattern in invertible systems of form (3.2) with no equilibria and the X nullcline extended into the X saturated region and the Y nullcline consisting of the entire Y saturated and both saturated regions.

3.4.4.3 Singular Systems with Nullclines and no Equilibria

Finally, we study flow in singular systems of form (3.2) that have both nullclines, but no equilibria. Again, we will consider the two cases from section 3.2.2 explaining why the 2×2 matrix A is singular.

Case 1: $\mathbf{c = a \neq 0}$ and $\mathbf{b = d \neq 0}$

The system has the form

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \end{bmatrix} = \begin{bmatrix} -a & d \\ a & -d \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \end{bmatrix} + \begin{bmatrix} x_0 \\ y_0 \end{bmatrix},$$

with $x_0 \leq a$ and $y_0 \leq d$ and nullclines

$$\begin{aligned} X \text{ nullcline: } r_2(Y) &= \frac{a}{d} r_1(X) - \frac{x_0}{d} \\ Y \text{ nullcline: } r_2(Y) &= \frac{a}{d} r_1(X) + \frac{y_0}{d} \end{aligned}$$

These nullclines intersect if and only if $x_0 = y_0 = 0$. Since we are interested in the case in which equilibria do not exist, at least one of x_0 and y_0 must be positive, i.e. $x_0 + y_0 > 0$.

With no equilibria, flow patterns here will be similar to those in invertible systems with nullclines and no equilibria. The signs of $\dot{X}$ and $\dot{Y}$ still follow Tables 2 and 3 from section 3.4.1.2, and with nullclines that cannot intersect, only the five extension combinations listed in Table 5 are possible. Flow along nullclines is the same as in systems that satisfy Theorem 34; along the Y nullcline, we have

$$\begin{aligned}\dot{X} &= -ar_1(X) + d\Big(\frac{a}{d}r_1(X) + \frac{y_0}{d}\Big) + x_0 \\ &= x_0 + y_0 \\ &> 0,\end{aligned}$$

and along the X nullcline,

$$\begin{aligned}\dot{Y} &= ar_1(X) - d\Big(\frac{a}{d}r_1(X) - \frac{x_0}{d}\Big) + y_0 \\ &= x_0 + y_0 \\ &> 0.\end{aligned}$$

Thus, a singular system of this form will have a flow pattern resembling that of an invertible system with no equilibria and one of the nullcline arrangements from Table 5 in section 3.4.4.2, with the result that at least one variable goes to infinity over time.

Case 2: A has a column of zeros

As usual, we assume that the second column is zero, giving us the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-a & 0\\ c & 0\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}x_0\\ y_0\end{bmatrix}.$$

The X nullcline is $r_1(X) = x_0/a$, with $\dot{X} > 0$ when $r_1(X) < x_0/a$ and (if $x_0 < a$) $\dot{X} < 0$ when $r_1(X) > x_0/a$.

- If $c = 0$, then $\dot{Y} = y_0$. We do not want $y_0 = 0$ here, since then every point on the X nullcline would be an equilibrium for the system. However, if $y_0 > 0$, there is no Y nullcline and Y grows without bound. Hence, the $c = 0$ case is notable in that existence of both nullclines always results in the existence of equilibria, and absence of equilibria requires the absence of at least one of the nullclines.

- If $c \neq 0$, then the Y nullcline is given by $r_1(X) = -y_0/c$. This only makes sense if $y_0 = 0$, resulting in the Y nullcline being the Y-axis. For any $r_1(X) > 0$, $\dot{Y}$ will be positive. To avoid a nullcline intersection, we must have $x_0 > 0$, placing the X nullcline to the right of the Y-axis.

  Thus, flow along the Y-axis will be rightward, then right-upward in the region between the Y-axis and the X nullcline. If $x_0 < a$, there is a region to the right of the X

nullcline, where flow is left-upward. Hence, flow is toward the X nullcline, along which flow is straight upward, resulting in Y going to infinity.

An example of a system with this flow pattern is shown below.

Example 27. Column of zeros with $\mathbf{c \neq 0}$ and $\mathbf{y_0 = 0}$
Consider the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\end{bmatrix} = \begin{bmatrix}-5 & 0\\ 1 & 0\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\end{bmatrix} + \begin{bmatrix}4\\ 0\end{bmatrix}$$

Both nullclines are vertical lines, given by $r_1(X) = 4/5$ for the X nullcline and $r_1(X) = 0$ for the Y nullcline. Equilibria are not possible in this system. The system's vector field is shown in Figure 23.

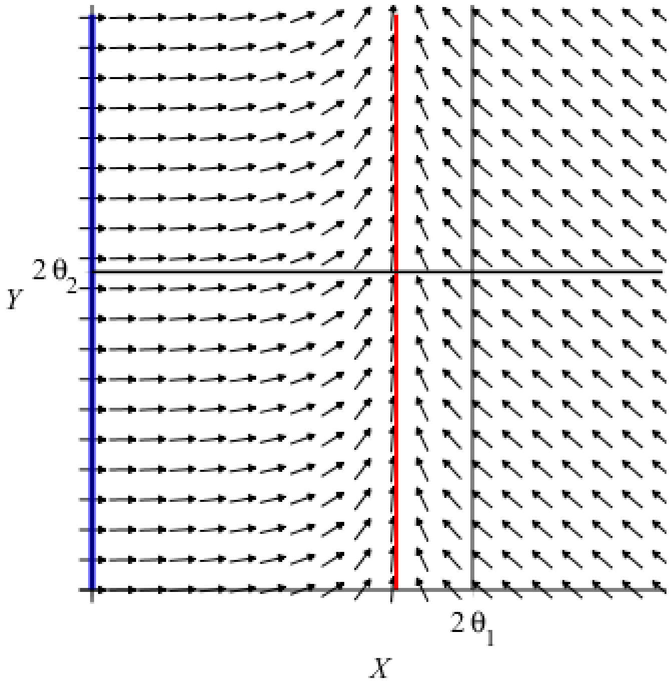


Figure 23: Flow pattern in singular systems of form (3.2) with no equilibria, zeros in column two, $c \neq 0$, and $y_0 = 0$. The X nullcline is in red and the Y nullcline is in blue.

3.4.4.4 Conclusion

Our study of flow in two-variable systems with no equilibria has shown that at least one variable must go to infinity, regardless of whether the system's 2×2 matrix is invertible or singular. Thus, we have the following:

Theorem 35. *Consider a system of form (3.2) that does not have any equilibria. Then, at least one variable will go to infinity over time.*

3.5 Flow in n-Variable Systems

Here, we discuss flow in systems of form

$$\dot{\vec{X}} = A\vec{r} + \vec{x_0}$$

from (3.1) with $n \geq 2$ variables in general. Since flow is much more complex in higher dimensional systems, the discussion will be brief in comparison to the two-variable case.

We begin by defining the regions (or boxes) trajectories can flow between in the non-negative orthant, the equivalent of the four regions of two-variable systems seen in Figure 9 and defined in Definition 8 back in section 3.4. Since each of the n ramp functions has two possible states, namely being in its ramp region or being in its saturated region, phase space is divided into 2^n regions. One of these is the all ramp region, while the remaining $2^n - 1$ are saturated regions. The boundaries of these regions are given below in Definition 9.

Definition 9. [2^n *Regions*] Let $\dot{\vec{X}} = A\vec{r} + \vec{x_0}$ be a system of form (3.1) with n variables $X_1, X_2, \ldots, X_n$, and corresponding ramp functions $r_1, r_2, \ldots, r_n$ with thesholds $2\theta_1, 2\theta_2, \ldots, 2\theta_n$ respectively. Then, the 2^n regions of phase space are defined as follows:

- **All Ramp Region**

$$\begin{aligned} &\big\{(X_1, X_2, \ldots, X_n) \;:\; X_i \in [0, 2\theta_i) \;\forall i = 1, 2, \ldots, n\big\} \\ \iff &\big\{(X_1, X_2, \ldots, X_n) \;:\; r_i(X_i) \in [0, 1) \;\forall i = 1, 2, \ldots, n\big\} \end{aligned}$$

- **All Saturated Region**

$$\begin{aligned} &\big\{(X_1, X_2, \ldots, X_n) \;:\; X_i \geq 2\theta_i \;\forall i = 1, 2, \ldots, n\big\} \\ \iff &\big\{(X_1, X_2, \ldots, X_n) \;:\; r_i(X_i) = 1 \;\forall i = 1, 2, \ldots, n\big\} \end{aligned}$$

For the other saturated regions, where some but not all of the ramp functions are in their saturated regions, consider a non-empty subset $\{X_{b_1}, X_{b_2}, \ldots, X_{b_m}\}$ of $\{X_1, X_2, \ldots, X_n\}$ where $m < n$. Letting $B = \{b_1, b_2, \ldots, b_m\}$, we have the

- $\mathbf{X_{b_1} X_{b_2} \ldots X_{b_m}}$ **Saturated Region**

$$\begin{aligned} &\big\{(X_1, X_2, \ldots, X_n) \;:\; X_i \geq 2\theta_i \;\forall i \in B,\;\; X_j \in [0, 2\theta_j) \;\forall j \notin B\big\} \\ \iff &\big\{(X_1, X_2, \ldots, X_n) \;:\; r_i(X_i) = 1 \;\forall i \in B,\;\; r_j(X_j) \in [0, 1) \;\forall j \notin B\big\} \end{aligned}$$

We now present a few theorems describing flow in n-variable systems, starting with the n-dimensional equivalent of Theorem 33 from section 3.4.4.1. For this, we use the fact that if the X_i nullcline does not exist, then $\dot{X}_i$ is always positive; similar to the two-variable case, at the origin $\dot{X}_i = x_{i_0}$ must be positive, and $\dot{X}_i$ can only change signs after passing through an X_i nullcline because the vector field is continuous.

Theorem 36. *Consider a system of form* (3.1)*. The system lacks an* X_i *nullcline if and only if* $x_{i_0} > a_{ii}$*.*

Proof. If the system lacks an X_i nullcline, then when $r_i(X_i) = 1$ and $r_j(X_j) = 0\,\forall j \neq i$,

$$\begin{aligned} \dot{X}_i &= -a_{ii} + x_{i_0} > 0 \\ \implies x_{i_0} &> a_{ii}. \end{aligned}$$

If $x_{i_0} > a_{ii}$, then

$$\begin{aligned} \dot{X}_i &= \sum_{j \neq i} a_{ij} r_j(X_j) - a_{ii} r_i(X_i) + x_{i_0} \\ &> \sum_{j \neq i} a_{ij} r_j(X_j) - a_{ii} r_i(X_i) + a_{ii} \\ &= a_{ii}(1 - r_i(X_i)) + \sum_{j \neq i} a_{ij} r_j(X_j) \\ &\geq 0, \end{aligned}$$

and hence $\dot{X}_i$ is always positive. □

Thus, like in two-variable systems, if for some i the input term x_{i_0} in an n-variable system is larger than the absolute value of the diagonal entry a_{ii}, then X_i grows without bound.

Next, the following two theorems provide some insight into flow in invertible systems with an equilibrium in the all ramp region. In the first theorem below, we show that when all ramp functions are saturated, at least one of the differential equations must be negative.

Theorem 37. *Consider an invertible system of form* (3.1) *that has an equilibrium point in the all ramp region. Then, in the all saturated region,* $\exists i : \dot{X}_i < 0$

Proof. By Theorem 22 from section 3.3, we have $\sum_i x_{i_0} < -\sum_{i,j} a_{ij}$. With all ramp functions at 1, we then see that

$$\begin{aligned} \sum_i \dot{X}_i &= \sum_{i,j} a_{ij} + \sum_i x_{i_0} \\ &< \sum_{i,j} a_{ij} - \sum_{i,k} a_{ij} \\ &= 0. \end{aligned}$$

Since the sum of all the differential equations is negative, we must have $\dot{X}_i < 0$ for at least one i. $\square$

Finally, we show that for every i, $\dot{X}_i$ must be negative at some point in the X_i saturated region (i.e the region of phase space in which r_i is the only ramp function at 1). We use the fact that when the $n \times n$ matrix is invertible, $a_{ii} > 0$ for all i.

Theorem 38. *Consider an invertible system of form (3.1) that has an equilibrium point in the all ramp region. Then, $\forall i \;\; \dot{X}_i < 0$ at some point in the X_i saturated region.*

Proof. We have $x_{i_0} < a_{ii}$ for every i by Theorem 22. Thus, if we choose $r_j(X_j) = 0 \,\forall j \neq i$ along with $r_i(X_i) = 1$, we have

$$\begin{aligned} \dot{X}_i &= -a_{ii} + x_{i_0} \\ &< -a_{ii} + a_{ii} \\ &= 0 \end{aligned}$$

as desired. For another option, since

$$\dot{X}_i = \sum_{j \neq i} a_{ij} r_j(X_j^*) - a_{ii} r_i(X_i^*) + x_{i_0} = 0$$

at the equilibrium point in the all ramp region, we will have $\dot{X}_i < 0$ if we increase $r_i(X_i)$ to 1 and leave all other ramp functions at their equilibrium values. $\square$

3.5.1 Nullclines in Invertible Systems with Equilibria in the All Ramp Region

This section will make some observations about nullclines in invertible n-variable systems with equilibria in the all ramp region. As we will see, the properties we saw with nullclines in the two-variable equivalent do not carry over as-is to systems with more than two variables.

Our observations will be guided by the following example:

Example 28. Nullclines in an invertible 3-Variable system
We will consider the invertible system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -5 & 2 & 1 \\ 0 & -4 & 1 \\ 0 & 0 & -3 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} 4 \\ 1 \\ 0 \end{bmatrix},$$

which has an equilibrium point in the all ramp region at $(r_1(X^*), r_2(Y^*), r_3(Z^*)) = (9/10, 1/4, 0)$.

The nullclines of this system are given by the equations

$$\begin{aligned} X \text{ nullcline:} \quad & -5r_1(X) + 2r_2(Y) + r_3(Z) + 4 = 0 \\ Y \text{ nullcline:} \quad & -4r_2(Y) + r_3(Z) + 1 = 0 \end{aligned}$$

$$Z \text{ nullcline: } r_3(Z) = 0$$

The first thing we will examine is nullcline extensions into saturated regions. With $n = 3$ variables, phase space has $2^3 = 8$ regions, seven of which are saturated regions. All eight regions are listed in Table 6 below.

All Ramp Region	XY Saturated Region
X Saturated Region	XZ Saturated Region
Y Saturated Region	YZ Saturated Region
Z Saturated Region	All Saturated Region

Table 6: The eight regions, as defined in Definition 9, of the non-negative quadrant in a three-variable system of form (3.1).

Starting with the X nullcline, it can be verified that $(1, 1/2, 0)$ and $(1, 0, 1)$ satisfy the equation given above. Thus, the X nullcline extends into the X saturated and XZ saturated regions. We do not get an extension into the region in which just Z is saturated; setting $r_3(Z) = 1$, we have

$$\begin{aligned} \dot{X} &= -5r_1(X) + 2r_2(Y) + 5 \\ &= 5(1 - r_1(X)) + 2r_2(Y), \end{aligned}$$

which requires $r_1(X) = 1$ to equal zero. Then, when Y is saturated,

$$\begin{aligned} \dot{X} &= -5r_1(X) + r_3(Z) + 6 \\ &\geq -5 + 0 + 6 \\ &= 1, \end{aligned}$$

and thus $\dot{X} \neq 0$ in the three regions in which Y is saturated.

Next, the Y nullcline extends into three saturated regions — X saturated, Z saturated, and XZ saturated regions — confirmed by the fact that $(1, 1/4, 0)$, $(0, 1/2, 1)$, and $(1, 1/2, 1)$ satisfy $\dot{Y} = 0$. The nullcline does not extend into any of the remaining saturated regions because when $r_1(Y) = 1$,

$$\begin{aligned} \dot{Y} &= r_3(Z) - 3 \\ &< 0. \end{aligned}$$

Finally, the Z nullcline is simply the plane $Z = 0$, which exists in the X saturated, Y saturated, and XY saturated regions.

Back in section 3.4.1, we saw that in invertible systems with equilibria in the all ramp region, the nullclines started in the all ramp region and then each extended into exactly one saturated region. As shown above, however, this conclusion does not hold in higher dimensions; each of the Example 28 nullclines extends into multiple saturated regions. The exact number of saturated regions the nullclines extend into varies; the Y and Z nullclines each extend into three saturated regions, but the X nullcline only extends into two.

The next topic we will examine is flow along nullclines in saturated regions. In Theorem 31, we established that in invertible two-variable systems with equilibria in the all ramp region, $\dot{X} < 0$ along a Y nullcline in saturated regions, and vice versa. However, when moving to higher dimensions, it is possible for a differential equation to be positive on another variable's nullcline in a saturated region, and a differential equation can even change signs along such a nullcline.

For instance, in Example 28 we have

$$\dot{X} \;=\; -5r_1(X) + 2r_2(Y) + 4$$

along the Z nullcline $r_3(Z) = 0$. In the Y and XY saturated regions, this becomes

$$\dot{X} \;=\; -5r_1(X) + 6,$$

which is always positive. Meanwhile, in the X saturated region we have

$$\dot{X} \;=\; 2r_2(Y) - 1.$$

This gives us $\dot{X} < 0$ when $r_2(Y) < 1/2$, $\dot{X} = 0$ at $r_2(Y) = 1/2$, and $\dot{X} > 0$ when $r_2(Y) > 1/2$.

Note that when $\dot{X} \geq 0$ along the Z nullcline, $\dot{Y}$ will be negative. The $\dot{Y}$ equation along the Z nullcline is

$$\dot{Y} \;=\; -4r_2(Y) + 1.$$

In the Y and XY saturated regions, this becomes

$$\begin{aligned}\dot{Y} &= -4 + 1\\ &= -3,\end{aligned}$$

while in the X saturated region with $r_2(Y) \geq 1/2$,

$$\begin{aligned}\dot{Y} &= -4r_2(Y) + 1\\ &\leq -4(1/2) + 1\\ &= -1.\end{aligned}$$

With this, we end the chapter with a conjecture that at any point along a nullcline in a saturated region, at least one differential equation will be negative:

Conjecture 4. Consider an invertible system of form (3.1) with $n > 2$ variables that has an equilibrium point in the all ramp region. Pick a point P^* on the X_i nullcline in a saturated region. Then, $\exists\, j \neq i : \dot{X}_j < 0$ at P^*.

Chapter 4

Invertible Systems with One Combining Term

4.1 General Form of Invertible Biochemical Ramp Systems with One Combining Term

With our analysis of SRP systems complete, we now consider biochemical ramp systems with exactly one combining term. A system satisfying Definition 7 from section 2.5 with $n \geq 3$ variables contains a single combining term if the Jacobian

$$J(\vec{X}) = \sum_{\ell=1}^{p} J_\ell(\vec{X})$$

in the all ramp region contains one $J_\ell(\vec{X})$ of form *iii*) from Definition 3 in section 2.1, and the remaining $p-1$ $J_\ell(\vec{X})$ are of forms *i*) and *ii*).

Without loss of generality, we will assume that in the $J_\ell(\vec{X})$ of form *iii*), the indices i, j, and m from Definition 3 are 1, 2, and 3 respectively. In other words, we assume that the system's combining term is derived from a chemical reaction of the form

$$W_1 + W_2 \xrightarrow{k} W_3$$

for some $k > 0$. As a result, the $\dot{X}_1$ and $\dot{X}_2$ equations will each contain a $-kr_1(X_1)r_2(X_2)$ term, while $\dot{X}_3$ will have a $kr_1(X_1)r_2(X_2)$ term.

We will also be assuming that the Jacobian evaluated at a point $\vec{X}'$ in the all ramp region (not necessarily an equilibrium point - we want to include systems with no equilibria here) has the form

$$J(\vec{X}') = A + M_\ell$$

previously seen in Theorems 11 and 12 from section 2.3.2, where A is an SRP matrix and M_ℓ is of form *iii*) from Definition 4. Here, we will be interested in the case where the SRP matrix is invertible.

Thus, the invertible biochemical ramp systems we will be considering here have the form

$$\begin{bmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \\ \dot{X}_4 \\ \vdots \\ \dot{X}_n \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{12} & a_{13} & a_{14} & \dots & a_{1n} \\ a_{21} & -a_{22} & a_{23} & a_{24} & \dots & a_{2n} \\ a_{31} & a_{32} & -a_{33} & a_{34} & \dots & a_{3n} \\ a_{41} & a_{42} & a_{43} & -a_{44} & \dots & a_{4n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{n4} & \dots & -a_{nn} \end{bmatrix} \begin{bmatrix} r_1(X_1) \\ r_2(X_2) \\ r_3(X_3) \\ r_4(X_4) \\ \vdots \\ r_n(X_n) \end{bmatrix} + \begin{bmatrix} -kr_1(X_1)r_2(X_2) \\ -kr_1(X_1)r_2(X_2) \\ kr_1(X_1)r_2(X_2) \\ 0 \\ \vdots \\ 0 \end{bmatrix} + \begin{bmatrix} x_{1_0} \\ x_{2_0} \\ x_{3_0} \\ x_{4_0} \\ \vdots \\ x_{n_0} \end{bmatrix},$$

which can be expressed more compactly as

$$\dot{\vec{X}} = A\vec{r} + \vec{k} + \vec{x_0}, \tag{4.1}$$

where

- A is an invertible $n \times n$ SRP matrix with $n \geq 3$
- $\vec{r} = [r_1(X_1), r_2(X_2), \dots, r_n(X_n)]^T$ is the vector of ramp functions, where for each i,

$$r_i(X_i) = \begin{cases} \dfrac{X_i}{2\theta_i}, & 0 \leq X_i < 2\theta_i \\ 1, & X_i \geq 2\theta_i \end{cases}$$

- $\vec{k} = [-kr_1(X_1)r_2(X_2),\ -kr_1(X_1)r_2(X_2),\ kr_1(X_1)r_2(X_2),\ 0,\ \dots,\ 0]^T$ is the combining term vector, with $k > 0$.
- $\vec{x_0} = [x_{1_0}, x_{2_0}, \dots, x_{n_0}]^T$ is the vector of constant input terms, with $x_{i_0} \geq 0$ for each i.

As we will see later in this chapter in section 4.7.1, the Adams model with the SEL from (1.6) is a system of form (4.1) when we have $K_3^2 = K_5$ and $K_3^3 = K_1$.

4.2 Necessary Conditions for Equilibria in the All Ramp Region

Like the previous chapter, the main focus here will be on determining when systems of form (4.1) have equilibria in the all ramp region. In this section, we present upper bounds on the x_{i_0} necessary for the existence of all ramp region equilibria, similar to what we did for SRP systems in Theorems 17 and 22 back in sections 3.2 and 3.3.

Theorem 39. *Let $\dot{\vec{X}} = A\vec{r} + \vec{k} + \vec{x_0}$ be a system of form (4.1). If the system has an equilibrium in the all ramp region, then all of the following must hold:*

i) $x_{1_0} < a_{11} + k, \quad x_{2_0} < a_{22} + k$

ii) $x_{i_0} < a_{ii} \quad \forall i \geq 3$

iii) $\displaystyle\sum_i x_{i_0} < -\sum_{i,j} a_{ij} + k$

Proof. Like with Theorems 17 and 22, we use proof by contradiction. We will make use of the following: $k[1 - r_1(X_1^*)r_2(X_2^*)]$ is strictly positive, $a_{ii} > 0$ for all i since A is invertible, and all column sums of A are non-positive.

To prove that *i)* holds, suppose that $x_{1_0} \geq a_{11} + k$. Then at equilibrium, we have

$$\begin{aligned}
\dot{X}_1 &= -a_{11}r_1(X_1^*) + \sum_{i \neq 1} a_{1i}r_i(X_i^*) - kr_1(X_1^*)r_2(X_2^*) + x_{1_0} \\
&\geq -a_{11}r_1(X_1^*) + \sum_{i \neq 1} a_{1i}r_i(X_i^*) - kr_1(X_1^*)r_2(X_2^*) + a_{11} + k \\
&= a_{11}[1 - r_1(X_1^*)] + k[1 - r_1(X_1^*)r_2(X_2^*)] + \sum_{i \neq 1} a_{1i}r_i(X_i^*) \\
&> 0,
\end{aligned}$$

contradicting $\dot{X}_1 = 0$. The proof for $x_{2_0} < a_{22} + k$ is similar.

For $i \geq 4$, the proof from Theorem 22 can be used to show *ii)* holds. The $i = 3$ case is similar; assuming $x_{3_0} \geq a_{33}$, we have

$$\begin{aligned}
\dot{X}_3 &= -a_{33}r_3(X_3^*) + \sum_{i \neq 3} a_{3i}r_i(X_i^*) + kr_1(X_1^*)r_2(X_2^*) + x_{3_0} \\
&\geq a_{33}[1 - r_3(X_3^*)] + \sum_{i \neq 3} a_{3i}r_i(X_i^*) + kr_1(X_1^*)r_2(X_2^*) \\
&> 0,
\end{aligned}$$

at equilibrium, a contradiction.

Finally, suppose $\displaystyle\sum_i x_{i_0} \geq -\sum_{i,j} a_{ij} + k$. Then at equilibrium,

$$\begin{aligned}
\sum_i \dot{X}_i &= \sum_i \left(r_i(X_i^*) \sum_j a_{ji} \right) - kr_1(X_1^*)r_2(X_2^*) + \sum_i x_{i_0} \\
&\geq \sum_i \left(r_i(X_i^*) \sum_j a_{ji} \right) - kr_1(X_1^*)r_2(X_2^*) - \sum_{i,j} a_{ij} + k \\
&= \sum_i \left([r_i(X_i^*) - 1] \sum_j a_{ji} \right) + k[1 - r_1(X_1^*)r_2(X_2^*)] \\
&> 0,
\end{aligned}$$

contradicting $\displaystyle\sum_i \dot{X}_i = 0$. □

As was the case with Theorems 17 and 22, the converse of Theorem 39 is not true. A counterexample is the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \\ \dot{W} \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 & 0 \\ 0 & -3 & 0 & 0 \\ 0 & 0 & -4 & 1 \\ 0 & 0 & 0 & -5 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \\ r_4(W) \end{bmatrix} + \begin{bmatrix} -r_1(X)r_2(Y) \\ -r_1(X)r_2(Y) \\ r_1(X)r_2(Y) \\ 0 \end{bmatrix} + \begin{bmatrix} 1 \\ 1 \\ 3.5 \\ 4.5 \end{bmatrix}.$$

Here, $k = 1$ and the input terms satisfy

$$\begin{aligned} x_0 &= 1 < a_{11} + k = 3 \\ y_0 &= 1 < a_{22} + k = 4 \\ z_0 &= 3.5 < a_{33} = 4 \\ w_0 &= 4.5 < a_{44} = 5 \\ x_0 + y_0 + z_0 + w_0 &= 10 < -\sum_{i,j} a_{i,j} + k = 14. \end{aligned}$$

However, if each of the four equations are set equal to zero, one can show that the only possible equilibrium points $(r_1(X^*), r_2(Y^*), r_3(Z^*), r_4(W^*))$ are

$$\left(\frac{-3+\sqrt{15}}{2}, \frac{-3+\sqrt{15}}{3}, \frac{42-5\sqrt{15}}{20}, \frac{4.5}{5}\right) \approx \big(0.4365,\ 0.2910,\ 1.1318,\ 0.9\big)$$

$$\left(\frac{-(3+\sqrt{15})}{2}, \frac{-(3+\sqrt{15})}{3}, \frac{42+5\sqrt{15}}{20}, \frac{4.5}{5}\right) \approx \big(-3.4365,\ -2.2910,\ 3.0683,\ 0.9\big),$$

both of which have at least one component falling outside the range of the ramp functions.

4.3 Solving for Equilibria

Our strategy for finding equilibria in systems of form (4.1) will make use of the fact that since A is invertible, solving

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

for $\vec{r^*}$ is equivalent to doing the same in

$$\vec{r^*} + A^{-1}\vec{k} = -A^{-1}\vec{x_0}. \tag{4.2}$$

The right hand side of (4.2) is the equilibrium solution to the corresponding SRP system

$$\dot{\vec{X}} = A\vec{r} + \vec{x_0}.$$

To make our proceeding analysis easier to follow, we will denote the i^{th} component of the right hand side by S_i, i.e.

$$-A^{-1}\vec{x_0} \;=\; [S_1,\; S_2,\; \ldots,\; S_n]^T. \tag{4.3}$$

By Theorem 23 from section 3.3.1, we know that $\forall i,\; S_i \geq 0$.

On the left hand side, the i^{th} component of $A^{-1}\vec{k}$ is given by

$$\frac{1}{\det(A)}\begin{bmatrix} C_{1i} & C_{2i} & C_{3i} & \ldots & C_{ni}\end{bmatrix}\begin{bmatrix} -kr_1(X_1^*)r_2(X_2^*) \\ -kr_1(X_1^*)r_2(X_2^*) \\ kr_1(X_1^*)r_2(X_2^*) \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

$$= \frac{-kr_1(X_1^*)r_2(X_2^*)C_{1i} - kr_1(X_1^*)r_2(X_2^*)C_{2i} + kr_1(X_1^*)r_2(X_2^*)C_{3i}}{\det(A)}$$

$$= \frac{kr_1(X_1^*)r_2(X_2^*)(C_{3i} - C_{1i} - C_{2i})}{\det(A)}.$$

If we let

$$D_i \;=\; \frac{C_{3i} - C_{1i} - C_{2i}}{\det(A)} \quad \forall i, \tag{4.4}$$

then the i^{th} component of $A^{-1}\vec{k}$ is $kr_1(X_1^*)r_2(X_2^*)D_i$.

Thus, putting everything together, the i^{th} equation we need to solve is

$$r_i(X_i^*) + kr_1(X_1^*)r_2(X_2^*)D_i \;=\; S_i. \tag{4.5}$$

Much of the rest of this chapter will be spent solving the equations in (4.5), and determining the conditions under which solutions fall in the all ramp region. We begin with a theorem regarding D_1 and D_2 that will be useful.

Theorem 40. *Let A be an $n \times n$ invertible SRP matrix. For all i, define D_i as in (4.4). Then, $D_1 \geq 0$ and $D_2 \geq 0$.*

Proof. We prove the result for D_1 (D_2 is similar), which is given by

$$D_1 \;=\; \frac{C_{31} - C_{11} - C_{21}}{\det(A)}.$$

Suppose n is even. Then by Corollary 1 from section 2.2.2, $\det(A) > 0$ and $C_{ij} \leq 0$ for all cofactors of A. Hence, we have $-C_{21} \geq 0$. Now, we employ a technique previously done in the proof of Theorem 11: replace the first column of A with $-a_{11} = -1$, $a_{31} = 1$, and all other entries zero. This new matrix is an SRP matrix of even size with determinant $-C_{11} + C_{31}$, which is either zero or positive by Corollary 1.

Thus, $C_{31} - C_{11} - C_{21} \geq 0$. Combined with the fact that $\det(A) > 0$, this means $D_1 \geq 0$. The odd n case can be handled in a similar fashion. □

It should be noted that there is not an equivalent theorem for the other D_i. When $i \geq 3$, D_i can be positive, negative, or zero.

We now begin solving the equations in (4.5). Setting $i = 2$, we have

$$r_2(X_2^*) + kr_1(X_1^*)r_2(X_2^*)D_2 \;=\; S_2,$$

and thus

$$r_2(X_2^*) \;=\; \frac{S_2}{1 + kr_1(X_1^*)D_2} \tag{4.6}$$

is the equilibrium value of $r_2(X_2)$ in terms of $r_1(X_1^*)$. Substituting this into the $i = 1$ equation in (4.5), we have

$$\begin{aligned} & r_1(X_1^*) + kr_1(X_1^*)r_2(X_2^*)D_1 \;=\; S_1 \\ \Longrightarrow\quad & r_1(X_1^*) + kr_1(X_1^*)\left(\frac{S_2}{1 + kr_1(X_1^*)D_2}\right)D_1 \;=\; S_1 \\ \Longrightarrow\quad & r_1(X_1^*)(1 + kr_1(X_1^*)D_2) + kr_1(X_1^*)S_2D_1 \;=\; S_1(1 + kr_1(X_1^*)D_2) \\ \Longrightarrow\quad & r_1(X_1^*)(1 + kr_1(X_1^*)D_2) + kr_1(X_1^*)S_2D_1 - S_1(1 + kr_1(X_1^*)D_2) \;=\; 0, \end{aligned}$$

which simplifies to

$$kD_2r_1(X_1^*)^2 + (1 + kD_1S_2 - kD_2S_1)r_1(X_1^*) - S_1 \;=\; 0. \tag{4.7}$$

4.4 Solving for $\mathbf{r_1(X_1^*)}$

The approach we take to solving (4.7) for $r_1(X_1^*)$ depends on the coefficient of the $r_1(X_1^*)^2$ term, kD_2. Since $D_2 \geq 0$, we have two cases:

1.) $D_2 = 0$, and (4.7) is a linear equation in $r_1(X_1^*)$

2.) $D_2 > 0$, and (4.7) is a quadratic equation in $r_1(X_1^*)$

We will consider each of these cases separately.

4.4.1 $\mathbf{D_2 = 0}$ Case

If $D_2 = 0$, then (4.7) becomes

$$(1 + kD_1S_2)r_1(X_1^*) - S_1 \;=\; 0.$$

With the kD_1S_2 term being non-negative, we can divide by the $r_1(X_1^*)$ coefficient and get

$$r_1(X_1^*) \;=\; \frac{S_1}{1 + kD_1S_2}.$$

This equilibrium value is always non-negative, and thus falls in the all ramp region if and only if

$$\frac{S_1}{1 + kD_1S_2} \;<\; 1$$
$$\iff S_1 \;<\; 1 + kD_1S_2.$$

4.4.2 $\mathbf{D_2 > 0}$ Case

If $D_2 > 0$, we find $r_1(X_1^*)$ by solving for the roots of the quadratic

$$kD_2r_1(X_1^*)^2 + (1 + kD_1S_2 - kD_2S_1)r_1(X_1^*) - S_1.$$

Note that this quadratic must have real roots as the discriminant,

$$(1 + kD_1S_2 - kD_2S_1)^2 + 4kD_2S_1,$$

is always non-negative. Thus, letting

$$b \;=\; 1 + kD_1S_2 - kD_2S_1, \tag{4.8}$$

the roots of the quadratic are given by

$$r_1(X_1^*) \;=\; \frac{-b \pm \sqrt{b^2 + 4kD_2S_1}}{2kD_2}.$$

Since we need $r_1(X_1^*) \geq 0$, we must determine the signs of the two roots. The denominator $2kD_2$ is positive, so we only need to consider the sign of the numerator. As both terms under the square root are non-negative, we have

$$\sqrt{b^2 + 4kD_2S_1} \;\geq\; |b|,$$

which gives us two cases to consider.

Case 1: $\mathbf{\sqrt{b^2 + 4kD_2S_1} > |b|}$

In this case, we have $-b + \sqrt{b^2 + 4kD_2S_1} > 0$ and $-b - \sqrt{b^2 + 4kD_2S_1} < 0$.

Case 2: $\sqrt{\mathbf{b^2 + 4kD_2S_1}} = |\mathbf{b}|$

This equality is true if and only if $4kD_2S_1 = 0$. Since k and D_2 are assumed to be strictly positive, this means $S_1 = 0$. With $S_1 = 0$, $b = 1 + kD_1S_2$, which is positive. Hence, $|b| = b$ and so $-b + \sqrt{b^2 + 4kD_2S_1} = -b + b = 0$ and $-b - \sqrt{b^2 + 4kD_2S_1} = -b - b = -2b < 0$.

In either case, taking $-\sqrt{b^2 + 4kD_2S_1}$ in the numerator always yields a negative value for $r_1(X_1^*)$, whereas $+\sqrt{b^2 + 4kD_2S_1}$ gives $r_1(X_1^*) \geq 0$. Thus, we only take the positive square root in the above expression, giving

$$r_1(X_1^*) \; = \; \frac{-b + \sqrt{b^2 + 4kD_2S_1}}{2kD_2}.$$

Next, we determine under what conditions this $r_1(X_1^*)$ value will fall in the all ramp region. Assuming $r_1(X_1^*) < 1$, we have

$$\begin{aligned} -b + \sqrt{b^2 + 4kD_2S_1} \; &< \; 2kD_2 \\ \implies \sqrt{b^2 + 4kD_2S_1} \; &< \; 2kD_2 + b. \end{aligned}$$

Squaring both sides, we then find that

$$\begin{aligned} b^2 + 4kD_2S_1 \; &< \; (2kD_2 + b)^2 \; = \; 4k^2D_2^2 + 4kD_2b + b^2 \\ \implies \; 4kD_2S_1 \; &< \; 4kD_2(kD_2 + b) \\ \implies \; S_1 \; &< \; kD_2 + b \; = \; kD_2 + 1 + kD_1S_2 - kD_2S_1 \\ \implies \; S_1(1 + kD_2) \; &< \; 1 + kD_2 + kD_1S_2 \\ \implies \; S_1 \; &< \; 1 + \frac{kD_1S_2}{1 + kD_2}. \end{aligned}$$

We can show that

$$S_1 \; < \; 1 + \frac{kD_1S_2}{1 + kD_2} \; \implies \; r_1(X_1^*) \; < \; 1$$

by reversing the above steps. Note that we will have no issues taking a square root and maintaining the direction of the inequality when getting to $b^2 + 4kD_2S_1 < (2kD_2 + b)^2$ because $2kD_2 + b$ is positive assuming the given upper bound on S_1:

$$\begin{aligned} 2kD_2 + b \; &= \; 2kD_2 + 1 + kD_1S_2 - kD_2S_1 \\ &> \; 2kD_2 + 1 + kD_1S_2 - kD_2\left(1 + \frac{kD_1S_2}{1 + kD_2}\right) \\ &= \; kD_2 + 1 + kD_1S_2 - \frac{k^2D_1D_2S_2}{1 + kD_2} \end{aligned}$$

$$
\begin{aligned}
&= \frac{(1+kD_2)^2 + (kD_1S_2)(1+kD_2) - k^2D_1D_2S_2}{1+kD_2} \\
&= \frac{(1+kD_2)^2 + kD_1S_2 + k^2D_1D_2S_2 - k^2D_1D_2S_2}{1+kD_2} \\
&= \frac{(1+kD_2)^2 + kD_1S_2}{1+kD_2} \\
&> 0.
\end{aligned}
$$

Thus, we conclude that $r_1(X_1^*)$ falls in the all ramp region if and only if

$$S_1 < 1 + \frac{kD_1S_2}{1+kD_2}.$$

4.4.3 Summary

We summarize our findings regarding $r_1(X^*)$ here. First, note that if we set $D_2 = 0$ in the upper bound on S_1 above, we get

$$
\begin{aligned}
S_1 &< 1 + \frac{kD_1S_2}{1+kD_2} \\
&= 1 + \frac{kD_1S_2}{1+0} \\
&= 1 + kD_1S_2,
\end{aligned}
$$

which is what we had in section 4.4.1. Hence, the upper bound found in section 4.4.2 applies to both the $D_2 = 0$ and $D_2 > 0$ cases.

With that, we can now state that the equilibrium value of $r_1(X)$ is

$$r_1(X_1^*) = \begin{cases} \dfrac{S_1}{1+kD_1S_2}, & D_2 = 0 \\ \dfrac{-b+\sqrt{b^2+4kD_2S_1}}{2kD_2}, & D_2 > 0, \end{cases} \tag{4.9}$$

which falls in the all ramp region if and only if

$$S_1 < 1 + \frac{kD_1S_2}{1+kD_2}.$$

4.5 Simplifying $\mathbf{r_2(X_2^*)}$

From (4.6), we know that the equilibrium value of $r_2(X_2)$ is

$$r_2(X_2^*) \;=\; \frac{S_2}{1 + kr_1(X_1^*)D_2}.$$

With (4.9), we can substitute in a value for $r_1(X_1^*)$ and then simplify to get an expression for $r_2(X_2^*)$ independent of $r_1(X_1^*)$. The $r_1(X_1^*)$ value we use depends on whether D_2 is zero or positive. Both cases will be considered, starting with $D_2 > 0$.

4.5.1 $\mathbf{D_2 > 0}$ Case

When $D_2 > 0$, we use the $r_1(X_1^*)$ value from (4.9) with the square root. Substituting this value into the solution for $r_2(X_2^*)$, we have

$$\begin{aligned}
r_2(X_2^*) &= \frac{S_2}{1 + kr_1(X_1^*)D_2} \\
&= \frac{S_2}{1 + \frac{-b+\sqrt{b^2+4kD_2S_1}}{2}} \\
&= \frac{S_2}{\frac{2-b+\sqrt{b^2+4kD_2S_1}}{2}} \\
&= \frac{2S_2}{2 - b + \sqrt{b^2 + 4kD_2S_1}}.
\end{aligned}$$

Our next step is to eliminate the square root in the denominator. We could accomplish this using the conjugate

$$2 - b - \sqrt{b^2 + 4kD_2S_1},$$

but we first must ensure that it is non-zero. Note that if $kD_1S_2 = 0$, which happens if $D_1 = 0$ or $S_2 = 0$, then

$$\begin{aligned}
2 - b &= 2 - (1 - kD_2S_1) \\
&= 1 + kD_2S_1
\end{aligned}$$

and

$$\begin{aligned}
\sqrt{b^2 + 4kD_2S_1} &= \sqrt{(1 - kD_2S_1)^2 + 4kD_2S_1} \\
&= \sqrt{1 + 2kD_2S_1 + (kD_2S_1)^2} \\
&= \sqrt{(1 + kD_2S_1)^2} \\
&= 1 + kD_2S_1,
\end{aligned}$$

making the conjugate expression equal to zero.

Hence, we will consider $D_1 = 0$ and $D_1 > 0$ subcases here. The $S_2 = 0$ possibility will be addressed within each subcase.

4.5.1.1 $\mathbf{D_1 = 0}$ Subcase

The denominator of the expression for $r_2(X_2^*)$ becomes

$$\begin{aligned} 2 - b + \sqrt{b^2 + 4kD_2S_1} &= 1 + kD_2S_1 + 1 + kD_2S_1 \\ &= 2(1 + kD_2S_1) \end{aligned}$$

when $D_1 = 0$. Thus, we have

$$\begin{aligned} r_2(X_2^*) &= \frac{2S_2}{2 - b + \sqrt{b^2 + 4kD_2S_1}} \\ &= \frac{2S_2}{2(1 + kD_2S_1)} \\ &= \frac{S_2}{1 + kD_2S_1}. \end{aligned}$$

If we had $S_2 = 0$, then the denominator of the above expression would be the same, and we would simply get $r_2(X_2^*) = 0$ as our equilibrium solution for $r_2(X_2)$.

In this subcase, the equilibrium solution falls in the all ramp region if and only if

$$S_2 < 1 + kD_2S_1.$$

4.5.1.2 $\mathbf{D_1 > 0}$ Subcase

We will start by assuming $S_2 > 0$. Then, we can multiply $r_2(X_2^*)$ by the conjugate of the denominator as follows:

$$\begin{aligned} r_2(X_2^*) &= \frac{2S_2}{2 - b + \sqrt{b^2 + 4kD_2S_1}} \cdot \frac{2 - b - \sqrt{b^2 + 4kD_2S_1}}{2 - b - \sqrt{b^2 + 4kD_2S_1}} \\ &= \frac{2S_2(2 - b - \sqrt{b^2 + 4kD_2S_1})}{(2 - b)^2 - (b^2 + 4kD_2S_1)} \\ &= \frac{2S_2(2 - b - \sqrt{b^2 + 4kD_2S_1})}{4 - 4b + b^2 - b^2 - 4kD_2S_1} \end{aligned}$$

$$\begin{aligned}
&= \frac{2S_2(2-b-\sqrt{b^2+4kD_2S_1})}{4(1-b-kD_2S_1)} \\
&= \frac{2S_2(2-b-\sqrt{b^2+4kD_2S_1})}{4(1-(1+kD_1S_2-kD_2S_1)-kD_2S_1)} \\
&= \frac{2S_2(2-b-\sqrt{b^2+4kD_2S_1})}{-4kD_1S_2} \\
&= \frac{b-2+\sqrt{b^2+4kD_2S_1}}{2kD_1}.
\end{aligned}$$

If $S_2 = 0$, then the numerator of this final expression is

$$\begin{aligned}
b-2+\sqrt{b^2+4kD_2S_1} &= -(2-b-\sqrt{b^2+4kD_2S_1}) \\
&= 0,
\end{aligned}$$

giving us $r_2(X_2^*) = 0$ as expected from (4.6). Hence, the expression for $r_2(X_2^*)$ we just found can be used for any $S_2 \geq 0$.

We now need to determine when this $r_2(X_2^*)$ value falls in the all ramp region. Assuming $r_2(X_2^*) < 1$, we have

$$\sqrt{b^2+4kD_2S_1} < 2kD_1+2-b,$$

and then

$$\begin{aligned}
b^2+4kD_2S_1 &< (2(kD_1+1)-b)^2 \\
&= 4(kD_1+1)^2-4b(kD_1+1)+b^2 \\
\Longrightarrow\quad 4kD_2S_1 &< 4(kD_1+1)[kD_1+1-b] \\
\Longrightarrow\quad \frac{kD_2S_1}{1+kD_1} &< kD_1+1-b \\
&= kD_1+1-(1+kD_1S_2-kD_2S_1) \\
&= kD_1-kD_1S_2+kD_2S_1 \\
\Longrightarrow\quad kD_1S_2 &< kD_1+kD_2S_1-\frac{kD_2S_1}{1+kD_1} \\
\Longrightarrow\quad S_2 &< 1+\frac{D_2S_1}{D_1}-\frac{D_2S_1}{D_1(1+kD_1)} \\
&= 1+\frac{D_2S_1(1+kD_1)-D_2S_1}{D_1(1+kD_1)}
\end{aligned}$$

$$= \ 1 + \frac{kD_1D_2S_1}{D_1(1+kD_1)}$$

$$\implies \ S_2 \ < \ 1 + \frac{kD_2S_1}{1+kD_1}.$$

Reversing the above steps, we can show that

$$S_2 \ < \ 1 + \frac{kD_2S_1}{1+kD_1} \quad \implies \quad r_2(X_2^*) \ < \ 1.$$

Again, taking the square root at the last step will not be an issue since $2(kD_1+1) - b$ is positive under the assumed upper bound for S_2; this can be shown by noting that

$$2(kD_1+1) - b \ = \ 2kD_1 + 1 + kD_2S_1 - kD_1S_2,$$

and the upper bound on S_2 have the same form as $2kD_2 + b$ and the upper bound on S_1 respectively from section 4.4.2, and thus the proof used there works here.

Hence, the value of $r_2(X_2^*)$ found in this section falls in the all ramp region if and only if

$$S_2 \ < \ 1 + \frac{kD_2S_1}{1+kD_1}.$$

4.5.2 $\mathbf{D_2 = 0}$ Case

Setting $D_2 = 0$ in the expression for $r_2(X_2^*)$ in (4.6), we get

$$\begin{aligned} r_2(X_2^*) \ &= \ \frac{S_2}{1 + kr_1(X_1^*)(0)} \\ &= \ S_2. \end{aligned}$$

As we will see below, this solution is just a special case of the solutions found in sections 4.5.1.1 and 4.5.1.2.

From (4.8), we have

$$b \ = \ 1 + kD_1S_2$$

when $D_2 = 0$. Then, the $r_2(X_2^*)$ value from section 4.5.1.1 becomes

$$\begin{aligned} r_2(X_2^*) \ &= \ \frac{S_2}{1 + k(0)S_1} \\ &= \ S_2, \end{aligned}$$

and from section 4.5.1.2, we have

$$r_2(X_2^*) \ = \ \frac{b - 2 + \sqrt{b^2 + 4kD_2S_1}}{2kD_1}$$

$$\begin{aligned}
&= \frac{1 + kD_1S_2 - 2 + \sqrt{(1 + kD_1S_2)^2}}{2kD_1} \\
&= \frac{kD_1S_2 - 1 + 1 + kD_1S_2}{2kD_1} \\
&= \frac{2kD_1S_2}{2kD_1} \\
&= S_2.
\end{aligned}$$

Thus, $r_2(X_2^*) = S_2$ is already covered by the equilibrium values found in the $D_2 > 0$ section. We then only need to consider $D_1 = 0$ and $D_1 > 0$ when it comes to the equilibrium value of $r_2(X_2)$.

4.5.3 Summary

Similar to what we had with $r_1(X_1^*)$, the upper bound on S_2 found in the $D_1 > 0$ subcase also applies to the $D_1 = 0$ subcase. When we have $D_1 = 0$, the S_2 upper bound from section 4.5.1.2 becomes

$$\begin{aligned}
S_2 &< 1 + \frac{kD_2S_1}{1 + k(0)} \\
&= 1 + kD_2S_1,
\end{aligned}$$

which is what we had in section 4.5.1.1.

Thus, the equilibrium value of $r_2(X_2^*)$ is

$$r_2(X_2^*) = \begin{cases} \dfrac{S_2}{1 + kD_2S_1}, & D_1 = 0 \\ \dfrac{b - 2 + \sqrt{b^2 + 4kD_2S_1}}{2kD_1}, & D_1 > 0, \end{cases} \tag{4.10}$$

which falls in the all ramp region if and only if

$$S_2 < 1 + \frac{kD_2S_1}{1 + kD_1}.$$

4.6 $\mathbf{r_i(X_i^*)}$ for $\mathbf{i \geq 3}$, Equilibria Summary, and Stability

From (4.5), for $i \geq 3$ we have

$$r_i(X_i^*) = S_i - kr_1(X_1^*)r_2(X_2^*)D_i, \tag{4.11}$$

the exact value of which depends on which $r_1(X_1^*)$ and $r_2(X_2^*)$ values from (4.9) and (4.10) are used.

To determine when $r_i(X_i^*)$ falls in the all ramp region, we not only need to ensure that $r_i(X_i^*) < 1$, but also $r_i(X_i^*) \geq 0$. Since there is no sign restriction for D_i when $i \geq 3$, we cannot guarantee that (4.11) is non-negative. Thus, the above equilibrium value falls in the all ramp region if and only if

$$\max\{0, kr_1(X_1^*)r_2(X_2^*)D_i\} \leq S_i < 1 + kr_1(X_1^*)r_2(X_2^*)D_i.$$

We now consolidate our results regarding equilibria in systems of form (4.1) into the following theorem:

Theorem 41. *Let* $\dot{\vec{X}} = A\vec{r} + \vec{k} + \vec{x_0}$ *be a system of form* (4.1)*. Define* S_i *and* D_i *for all* i *as in* (4.3) *and* (4.4) *respectively, and let* $b = 1 + kD_1S_2 - kD_2S_1$*. Then, the 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:

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

$$\max\{0, kr_1(X_1^*)r_2(X_2^*)D_i\} \leq S_i < 1 + kr_1(X_1^*)r_2(X_2^*)D_i \quad \forall i \geq 3$$

Based on our work in this chapter and Theorem 41, systems of form (4.1) can have at most one equilibrium point in the all ramp region. While the quadratic in (4.7) theoretically allows for multiple equilibria, we saw in section 4.4.2 that one of the roots always yields a negative $r_1(X_1^*)$ value, thus preventing the existence of multiple all ramp region equilibria.

The Jacobian of a system of form (4.1) evaluated at an equilibrium point is a biochemical matrix in which exactly one M_ℓ is of form *iii*) from Definition 4. Back in section 2.3.2, we hypothesized that all eigenvalues of such matrices have non-negative real parts in conjecture 1; however, this is still unresolved, although we do know that all real eigenvalues are non-negative by Theorem 12. In Theorems 9 and 10 from sections 2.3 and 2.3.1, we saw a couple of cases that guarantee all eigenvalues have non-positive real parts, namely if the radius of each Gershgorin disk is small or if the Jacobian at the equilibrium point is of size 3×3.

A special case regarding stability is when S_1 or S_2 are zero. If we have $S_1 = 0$, then we must have $r_1(X_1^*) = 0$; this can be seen from the equilibrium values given in Theorem 41 or from the fact that (4.5) with $i = 1$ becomes

$$r_1(X_1^*) + kr_1(X_1^*)r_2(X_2^*)D_1 \;=\; 0,$$

which holds if and only if $r_1(X_1^*) = 0$ since each term on the left hand side is non-negative. Similarly, $r_2(X_2^*) = 0$ if and only if $S_2 = 0$.

Thus, when we have $S_1 = S_2 = 0$, both $r_1(X_1^*)$ and $r_2(X_2^*)$, and consequently X_1^* and X_2^*, will be zero. If the system has an equilibrium point in the all ramp region, the single M_ℓ of form $iii)$ from Definition 4 will have $c = d = 0$ when the Jacobian is evaluated at the equilibrium. As a result, the combining term is wiped out, leaving the Jacobian as an invertible SRP matrix. By Theorem 5 from section 2.2.1, the eigenvalues of the Jacobian at the equilibrium point must all have strictly negative real parts, resulting in the equilibrium being asymptotically stable.

4.7 Examples

Here, we work on finding equilibria in several example systems of form (4.1).

Example 29. System with $\mathbf{D_2 = 0}$
We consider the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 \\ 0 & -3 & 4 \\ 0 & 0 & -4 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} -r_1(X)r_2(Y) \\ -r_1(X)r_2(Y) \\ r_1(X)r_2(Y) \end{bmatrix} + \begin{bmatrix} 2 \\ 1 \\ 1 \end{bmatrix},$$

with $k = 1$. Putting the system into form (4.2) after multiplying by

$$A^{-1} = \begin{bmatrix} -1/2 & 0 & 0 \\ 0 & -1/3 & -1/3 \\ 0 & 0 & -1/4 \end{bmatrix},$$

we get

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \\ r_3(Z^*) \end{bmatrix} + \begin{bmatrix} (1/2)r_1(X^*)r_2(Y^*) \\ 0 \\ -(1/4)r_1(X^*)r_2(Y^*) \end{bmatrix} = \begin{bmatrix} 1 \\ 2/3 \\ 1/4 \end{bmatrix}.$$

Immediately, with $D_2 = 0$ we get $r_2(Y^*) = 2/3$. Solving for $r_1(X^*)$ next, we have

$$r_1(X^*)\Big(1 + \frac{1}{2}r_2(Y^*)\Big) \;=\; 1,$$

and thus

$$\begin{aligned} r_1(X^*) &= \frac{1}{1+\frac{1}{2}r_2(Y^*)} \\ &= \frac{1}{1+\frac{1}{2}\cdot\frac{2}{3}} \\ &= \frac{1}{1+\frac{1}{3}} \\ &= \frac{3}{4}. \end{aligned}$$

Finally, for $r_3(Z^*)$ we get

$$\begin{aligned} r_3(Z^*) &= \frac{1}{4}+\frac{1}{4}r_1(X^*)r_2(Y^*) \\ &= \frac{1}{4}\Big(1+\frac{3}{4}\cdot\frac{2}{3}\Big) \\ &= \frac{1}{4}\Big(1+\frac{1}{2}\Big) \\ &= \frac{3}{8}. \end{aligned}$$

Thus, our system has the unique equilibrium point

$$(r_1(X^*),\ r_2(Y^*),\ r_3(Z^*)) = (3/4,\ 2/3,\ 3/8),$$

which falls in the all ramp region.

Example 30. System with $\mathbf{D_2 > 0}$
Taking $k = 1$ again, we now find equilibria in the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 \\ 0 & -3 & 0 \\ 2 & 3 & -4 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} -r_1(X)r_2(Y) \\ -r_1(X)r_2(Y) \\ r_1(X)r_2(Y) \end{bmatrix} + \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}.$$

Here, the inverse matrix is

$$A^{-1} = \begin{bmatrix} -1/2 & 0 & 0 \\ 0 & -1/3 & 0 \\ -1/4 & -1/4 & -1/4, \end{bmatrix}$$

and so the system is

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \\ r_3(Z^*) \end{bmatrix} + \begin{bmatrix} (1/2)r_1(X^*)r_2(Y^*) \\ (1/3)r_1(X^*)r_2(Y^*) \\ (1/4)r_1(X^*)r_2(Y^*) \end{bmatrix} = \begin{bmatrix} 1/2 \\ 1/3 \\ 3/4 \end{bmatrix}$$

in form (4.2).

This time, we will find the equilibrium values of the ramp functions using the formulas listed in Theorem 41. The D_i and S_i are

$$\begin{aligned} D_1 &= 1/2 & S_1 &= 1/2 \\ D_2 &= 1/3 & S_2 &= 1/3 \\ D_3 &= 1/4 & S_3 &= 3/4, \end{aligned}$$

with b from (4.8) being

$$\begin{aligned} b &= 1 + kD_1S_2 - kD_2S_1 \\ &= 1 + \left(\frac{1}{2}\cdot\frac{1}{3}\right) - \left(\frac{1}{2}\cdot\frac{1}{3}\right) \\ &= 1. \end{aligned}$$

Notice that D_3 is positive here. In the previous example, we had $D_3 = -1/4$, thus illustrating the lack of sign restrictions on the D_i for $i \geq 3$.

The $r_1(X_1^*)$ value from Theorem 41 we will use is the $D_2 > 0$ one. Thus, we have

$$\begin{aligned} r_1(X^*) &= \frac{-b + \sqrt{b^2 + 4kD_2S_1}}{2kD_2} \\ &= \frac{-1 + \sqrt{1 + 4(1/3)(1/2)}}{2/3} \\ &= \frac{-1 + \sqrt{1 + \frac{2}{3}}}{2/3} \\ &= \frac{-1 + \sqrt{\frac{5}{3}}}{2/3} \\ &= \frac{-3 + 3\sqrt{\frac{5}{3}}}{2} \\ &\approx 0.4365. \end{aligned}$$

For $r_2(Y^*)$, we use the $D_1 > 0$ solution and get

$$\begin{aligned} r_2(Y^*) &= \frac{b - 2 + \sqrt{b^2 + 4kD_2S_1}}{2kD_1} \\ &= \frac{-1 + \sqrt{5/3}}{1} \end{aligned}$$

$$
\begin{aligned}
&= \sqrt{5/3} - 1 \\
&\approx 0.2910.
\end{aligned}
$$

Then, $r_3(Z^*)$ is

$$
\begin{aligned}
r_3(Z^*) &= S_3 - kr_1(X_1^*)r_2(X_2^*)D_3 \\
&= \frac{3}{4} - \frac{1}{4}\left(\frac{-3+3\sqrt{\frac{5}{3}}}{2}\right)\left(\sqrt{\frac{5}{3}}-1\right) \\
&= \frac{3}{4} - \frac{3}{4}\left(\frac{-1+\sqrt{\frac{5}{3}}}{2}\right)\left(\sqrt{\frac{5}{3}}-1\right) \\
&= \frac{3}{4}\left(1 - \frac{\frac{8}{3}-2\sqrt{\frac{5}{3}}}{2}\right) \\
&= \frac{3}{4}\left(\frac{2\sqrt{\frac{5}{3}}-\frac{2}{3}}{2}\right) \\
&= \frac{-1+3\sqrt{\frac{5}{3}}}{4} \\
&= \approx 0.7183.
\end{aligned}
$$

Thus, the system has the equilibrium point

$$
\left(\frac{-3+3\sqrt{\frac{5}{3}}}{2},\ \sqrt{\frac{5}{3}}-1,\ \frac{-1+3\sqrt{\frac{5}{3}}}{4}\right) \approx (0.4365,\ 0.2910,\ 0.7183)
$$

in the all ramp region.

4.7.1 Adams Model

When each variable has a single threshold, the system with the SEL from (1.6) is of form (4.1). To have a single threshold per variable, we assume the $K_3^2 = K_5$ and $K_3^3 = K_1$ case. We will use r_1 and r_5 as the ramp functions associated with Y and X_2 respectively.

Then, system (1.6) can be written in form (4.1) as

$$\begin{bmatrix} \dot{Y} \\ \dot{X}_2 \\ \dot{X}_4 \end{bmatrix} = \begin{bmatrix} -a_1 & 0 & a_4 \\ a_1 & -a_5 & 0 \\ 0 & 0 & -a_4 \end{bmatrix} \begin{bmatrix} r_1(Y) \\ r_5(X_2) \\ r_4(X_4) \end{bmatrix} + \begin{bmatrix} -a_3 r_1(Y) r_5(X_2) \\ -a_3 r_1(Y) r_5(X_2) \\ a_3 r_1(Y) r_5(X_2) \end{bmatrix} + \begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix},$$

with $k = a_3$. The 3×3 matrix has determinant $-a_1 a_4 a_5$, which is negative. Using the fact that

$$\begin{bmatrix} -a_1 & 0 & a_4 \\ a_1 & -a_5 & 0 \\ 0 & 0 & -a_4 \end{bmatrix}^{-1} = \begin{bmatrix} -1/a_1 & 0 & -1/a_1 \\ -1/a_5 & -1/a_5 & -1/a_5 \\ 0 & 0 & -1/a_4 \end{bmatrix},$$

the system can be put into form (4.2) as

$$\begin{bmatrix} r_1(Y^*) \\ r_5(X_2^*) \\ r_4(X_4^*) \end{bmatrix} + \begin{bmatrix} -1/a_1 & 0 & -1/a_1 \\ -1/a_5 & -1/a_5 & -1/a_5 \\ 0 & 0 & -1/a_4 \end{bmatrix} \begin{bmatrix} -a_3 r_1(Y^*) r_5(X_2^*) \\ -a_3 r_1(Y^*) r_5(X_2^*) \\ a_3 r_1(Y^*) r_5(X_2^*) \end{bmatrix} = \begin{bmatrix} 1/a_1 & 0 & 1/a_1 \\ 1/a_5 & 1/a_5 & 1/a_5 \\ 0 & 0 & 1/a_4 \end{bmatrix} \begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix}$$

$$\Longrightarrow \begin{bmatrix} r_1(Y^*) \\ r_5(X_2^*) \\ r_4(X_4^*) \end{bmatrix} + \begin{bmatrix} 0 \\ a_3 r_1(Y^*) r_5(X_2^*)(1/a_5) \\ a_3 r_1(Y^*) r_5(X_2^*)(-1/a_4) \end{bmatrix} = \begin{bmatrix} a_0/a_1 \\ a_0/a_5 \\ 0 \end{bmatrix}.$$

The S_i and D_i are

$$\begin{aligned} D_1 &= 0 & S_1 &= a_0/a_1 \\ D_2 &= 1/a_5 & S_2 &= a_0/a_5 \\ D_3 &= -1/a_4 & S_3 &= 0. \end{aligned}$$

With $D_1 = 0$, we have

$$b = 1 - kD_2 S_1$$

and

$$\sqrt{b^2 + 4kD_2 S_1} = 1 + kD_2 S_1.$$

By Theorem 41, the equilibrium values of the ramp functions are:

$$\begin{aligned} r_1(Y^*) &= \frac{-b + \sqrt{b^2 + 4kD_2 S_1}}{2kD_2} \\ &= \frac{-(1 - kD_2 S_1) + 1 + kD_2 S_1}{2kD_2} \\ &= \frac{2kD_2 S_1}{2kD_2} \\ &= S_1 \end{aligned}$$

$$= \frac{a_0}{a_1},$$

$$\begin{aligned}
r_5(X_2^*) &= \frac{S_2}{1 + kD_2S_1} \\
&= \frac{a_0/a_5}{1 + \frac{a_0a_3}{a_1a_5}} \\
&= \frac{a_0}{a_5 + \frac{a_0a_3}{a_1}} \\
&= \frac{a_0}{\frac{a_1a_5 + a_0a_3}{a_1}} \\
&= \frac{a_0a_1}{a_0a_3 + a_1a_5},
\end{aligned}$$

$$\begin{aligned}
r_4(X_4^*) &= S_3 - kr_1(Y^*)r_5(X_2^*)D_3 \\
&= 0 - a_3\Big(\frac{a_0}{a_1}\Big)\Big(\frac{a_0a_1}{a_0a_3 + a_1a_5}\Big)\Big(\frac{-1}{a_4}\Big) \\
&= \frac{a_0^2a_3}{a_4(a_0a_3 + a_1a_5)}
\end{aligned}$$

When these values fall in the all ramp region, we have

$$Y^* = \frac{2a_0K_1}{a_1},\ X_2^* = \frac{2a_0a_1K_5}{a_0a_3 + a_1a_5},\ X_4^* = \frac{2a_0^2a_3K_4}{a_4(a_0a_3 + a_1a_5)},$$

which is the equilibrium point given in the (α, α, α) subcase in section 1.3.1.1 when K_3^3 is set equal to K_1.

Chapter 5

Systems with Dissociation Terms

5.1 General Form of Biochemical Ramp Systems with Dissociation Terms

Finally, we examine systems with dissociation terms in this section. A biochemical ramp system contains dissociation terms if its Jacobian

$$J(\vec{X}) \;=\; \sum_{\ell=1}^{p} J_\ell(\vec{X})$$

in the all ramp region contains *at least* one $J_\ell(\vec{X})$ of form iv) from Definition 3 in section 2.1, and all $J_\ell(\vec{X})$ are of forms i), ii), and iv). Any number of SRP terms are allowed, but we will assume no combining terms are present.

Systems with dissociation terms thus have a form very similar to that of SRP systems seen in (3.1):

$$\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}, \tag{5.1}$$

where

- $A_d = \displaystyle\sum_{\ell=1}^{p} A_{d_\ell}$ is an $n \times n$ biochemical matrix , $n \geq 3$, such that at least one A_{d_ℓ} is of form iv) from Definition 4, and all A_{d_ℓ} are of forms i), ii), and iv).
- $\vec{r} = [r_1(X_1), r_2(X_2), \ldots, r_n(X_n)]^T$ is the vector of ramp functions, where for each i,
$$r_i(X_i) \;=\; \begin{cases} \dfrac{X_i}{2\theta_i}, & 0 \leq X_i < 2\theta_i \\ 1, & X_i \geq 2\theta_i \end{cases}$$
- $\vec{x_0} = [x_{1_0}, x_{2_0}, \ldots, x_{n_0}]^T$ is the vector of constant input terms, with $x_{i_0} \geq 0$ for each i.

As usual, we will focus on finding equilibria in the all ramp region in systems of form (5.1). To begin, we present some upper bounds on the x_{i_0} necessary for the existence of equilibria in the all ramp region, similar to what we did in the previous two chapters with Theorems 17, 22, and 39. In the following theorem, we make use of the fact that if the i^{th} column contains dissociation term(s), then the diagonal entry is $-(a_{ii}+k)$ for $a_{ii} \geq 0$ and some $k > 0$, and if said column has no dissociation terms, then the diagonal entry is just $-a_{ii}$.

Theorem 42. *Let $\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}$ be a system of form (5.1). If the system has an equilibrium in the all ramp region, then $\forall\, i$:*

- *if column i has dissociation term(s), $x_{i_0} < a_{ii} + k$.*
- *if column i does not have any dissociation terms, $x_{i_0} \leq a_{ii}$. If A_d is invertible, this inequality is strict.*

Proof. For the first bullet point, if we had $x_{i_0} \geq a_{ii} + k$, then at equilibrium

$$\begin{aligned}
\dot{X}_i &= -(a_{ii}+k)r_i(X_i^*) + \sum_{j\neq i} a_{ij}r_j(X_j^*) + x_{i_0} \\
&\geq -(a_{ii}+k)r_i(X_i^*) + \sum_{j\neq i} a_{ij}r_j(X_j^*) + a_{ii} + k \\
&= (a_{ii}+k)[1 - r_i(X_i^*)] + \sum_{j\neq i} a_{ij}r_j(X_j^*) \\
&> 0,
\end{aligned}$$

a contradiction. For the second bullet, the proof is similar to the proof of Theorem 22. □

Note that unlike previous theorems, this one does not include the inequality

$$\sum_i x_{i_0} \leq -\sum_{i,j} a_{ij}.$$

In SRP and one combining term systems, the matrices always had non-positive column sums, which allowed us to bound the sum of the constant input terms above by the negative of the sum of all the matrix entries. However, as we saw in Example 7 from section 2.4, dissociation matrices can have positive column sums. This makes it difficult to bound the sum of the inputs as the negative sum of the entries can be negative.

In the special case where all column sums are non-negative, however, we have the following:

Theorem 43. *Let $\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}$ be a system of form (5.1) such that all column sums of A_d are non-negative. If the system has an equilibrium point in the all ramp region, then both of the following hold:*

i) $\vec{x_{i_0}} = \vec{0}$

ii) if $\sum_j a_{ji} > 0$ *for some* i*, then* $r_i(X_i^*) = 0$

Proof. At equilibrium, we have

$$\sum_i \dot{X}_i \;=\; r_1(X_1^*)\sum_j a_{j1} + r_2(X_2^*)\sum_j a_{j2} + \cdots + r_n(X_n^*)\sum_j a_{jn} + \sum_i x_{i_0} \;=\; 0.$$

Each term in this sum is non-negative, and thus the sum equals zero if and only if each term is zero. As a result, we have

$$\sum_i x_{i_0} \;=\; 0,$$

which implies $\vec{x_{i_0}} = \vec{0}$ as each x_{i_0} is non-negative. Then, for all i,

$$r_i(X_i^*)\sum_j a_{ji} \;=\; 0,$$

which, if the i^{th} column sum is strictly positive, implies $r_i(X_i^*) = 0$. □

Once again, we have that the converse of Theorem 42 is not true. In the system

$$\begin{bmatrix}\dot{X}\\ \dot{Y}\\ \dot{Z}\end{bmatrix} = \begin{bmatrix}-9 & 7 & 4\\ 6 & -8 & 3\\ 5 & 1 & -9\end{bmatrix}\begin{bmatrix}r_1(X)\\ r_2(Y)\\ r_3(Z)\end{bmatrix} + \begin{bmatrix}0\\0\\1\end{bmatrix},$$

for instance, we have the invertible single dissociation term matrix

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

from Example 7, with

$$\begin{aligned} x_0 &\;=\; 0 \;<\; a_{11} + k \;=\; 9\\ y_0 &\;=\; 0 \;<\; a_{22} \;=\; 8\\ z_0 &\;=\; 1 \;<\; a_{33} \;=\; 9. \end{aligned}$$

However, all components of the sole equilibrium solution are negative and thus fall outside the range of the ramp functions: $(-53/46, -51/46, -15/23)$

Further discussion on equilibria in systems of form (5.1) will be divided into cases regarding whether A_d is invertible or singular. Many of the results in the following two sections will be similar to what we had with SRP systems; forms (3.1) and (5.1) are structurally similar with both having the form

$$M\vec{r} + \vec{x_0},$$

where M is an $n \times n$ matrix with non-positive diagonal entries and non-negative off-diagonals.

5.2 Invertible Systems

In a system of form (5.1) in which A_d is invertible, we have the equilibrium solution

$$\vec{r^*} \;=\; -A_d^{-1}\vec{x_0}. \tag{5.2}$$

To see when this solution falls in the all ramp region, we can slightly tweak Theorem 24:

Theorem 44. *Let* $\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}$ *be a system of form* (5.1) *in which* $\det(A_d) \neq 0$. *Then, there exists an equilibrium in the all ramp region if and only if* $\forall\ i = 1, 2, \ldots, n$,

$$0 \;\leq\; \frac{\sum_{j=1}^{n} C_{ji}x_{j_0}}{-\det(A)} \;<\; 1,$$

where the C_{ji} *are cofactors of* A.

Proof. Similar to the proof of Theorem 24 in section 3.3.1. $\square$

Note the inclusion of the zero lower bound in the statement of Theorem 44, which was not present in Theorem 24. This is because the equilibrium solution in (5.2) is not guaranteed to be non-negative componentwise. As we saw in section 2.4.1 with Example 8 and Theorem 16, it is possible for A_d^{-1} to have positive entries. Consequently, $-A_d^{-1}$ can have negative entries, which could result in one or more components of $-A_d^{-1}\vec{x_0}$ being negative.

The equilibrium solution $-A_d^{-1}\vec{x_0}$ is guaranteed to be non-negative componentwise if all entries of $-A_d^{-1}$ are non-negative. By Theorem 16, this happens if and only if the real part of every eigenvalue of A_d is negative. Thus, if A_d has an eigenvalue with a positive real part, $-A_d^{-1}$ has at least one negative entry and hence it is possible that at least one component of $-A_d^{-1}\vec{x_0}$ is negative.

In Conjecture 2, we hypothesized that if the real part of at least one of the eigenvalues of A_d is positive, then all entries of A_d^{-1} are non-negative (i.e. all entries of $-A_d^{-1}$ are non-positive); this was suggested based on what we saw in Example 8. While this conjecture has been neither proved nor disproved, we have the following when $-A_d^{-1}$ has all non-positive entries:

Theorem 45. *Let* $\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}$ *be a system of form* (5.1) *in which* $\det(A_d) \neq 0$ *such that all entries of* $-A_d^{-1}$ *are non-positive (i.e.* A_d^{-1} *is non-negative entrywise). Then, there is an equilibrium point in the all ramp region if and only if* $\vec{x_0} = \vec{0}$.

Proof. If $\vec{x_0} = \vec{0}$, then from (5.2) we have

$$\vec{r^*} \;=\; -A_d^{-1}\vec{0} \;=\; \vec{0}.$$

Now, suppose we have an equilibrium point in the all ramp region. Then, the i^{th} component of the equilibrium solution is

$$r_i(X_i^*) \;=\; \frac{C_{1i}}{-\det(A)}x_{1_0} + \frac{C_{2i}}{-\det(A)}x_{2_0} + \cdots + \frac{C_{ni}}{-\det(A)}x_{n_0},$$

with

$$\frac{C_{ji}}{-\det(A)} \;\le\; 0$$

for all j. Hence, the above sum consists solely of non-positive terms, and gives us a value in $[0, 1)$ if and only if every term is zero.

Thus, every time we have a j such that

$$\frac{C_{ji}}{-\det(A)} \;<\; 0,$$

we must have $x_{j_0} = 0$. In the case that $C_{ji} = 0$ for some j, there must be an m such that

$$\frac{C_{jm}}{-\det(A)} \;<\; 0,$$

or else $-A_d^{-1}$ would have a column of zeros. Thus, the expression for $r_m(X_m^*)$ will force us to have $x_{j_0} = 0$. □

5.3 Singular Systems

The theorems presented for singular SRP systems back in section 3.3.2 also apply to system of form (5.1) when A_d is singular. For instance, if the i^{th} column of A_d is zero, we can put the system in the form

$$\dot{\vec{X}} \;=\; A_{d_{i_0}} \vec{r}_{i_0}$$

by replacing the i^{th} column of A_d with $\vec{x_{i_0}}$ and the i^{th} component of $\vec{r}$ with 1, and then we have the equivalent of Theorem 28:

Theorem 46. *Let $\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}$ be a system of form (5.1) such that all entries in column i of A are zero for some i. If the reduced system $\dot{\vec{X}} = A_{d_{i_0}}\vec{r}_{i_0}$ has an equilibrium with all $r_j(X_j^*) < 1$, then all of the following hold:*

i) $x_{i_0} = 0$

ii) *if $a_{ij} \neq 0$ for $j \neq i$, then $r_j(X_j^*) = 0$*

iii) *$A_{d_{i_0}}$ is singular*

Proof. Same as the proof of Theorem 28. □

If all columns of A_d sum to zero, we have the following result with the same proof as that of Theorem 29:

Theorem 47. *Let $\dot{\vec{X}} = A_d\vec{r} + \vec{x_0}$ be a system of form (5.1) such that for all i, the i^{th} column of A satisfies*

$$\sum_j a_{ji} \;=\; 0.$$

Then, the system has an equilibrium point in the all ramp region if and only if $\vec{x_0} = \vec{0}$.

When $\vec{x_0} = \vec{0}$, any singular dissociation system will have infinitely many equilibria in the all ramp region if and only if A_d has an eigenvector corresponding to $\lambda = 0$ with all non-negative components. The conditions listed in Theorem 30 that guarantee the existence of such an eigenvector also apply here:

Theorem 48. *Let $A_d = \sum_{\ell=1}^{p} A_{d_\ell}$ be a singular $n \times n$ biochemical matrix such that at least one A_{d_ℓ} is of form iv) from Definition 4, and all A_{d_ℓ} are of forms i), ii), and iv). If all rows of A_d sum to zero, or if A_d has a column of zeros or two proportional non-zero columns, then A_d has an eigenvector $\vec{v}$ corresponding to the eigenvalue $\lambda = 0$ such that $\vec{v} \geq 0$ componentwise.*

5.4 Stability and Examples

In general, equilibria in systems of form (5.1) can be stable or unstable. The Jacobian of the system in the all ramp region contains dissociation terms, and we know from Example 7 in section 2.4 that the real parts of the eigenvalues of such matrices can be positive, negative, or zero. Theorem 15 provides a sufficient condition for all eigenvalues to have non-negative real parts. In the case where A_d is invertible, we will have an asymptotically stable equilibrium point in the all ramp region if and only if A_d^{-1} is non-positive entrywise by Theorem 16.

We end with a few examples of finding equilibria in dissociation systems.

Example 31. Invertible system with an all ramp equilibrium
Consider the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -2 & 0 & 0 \\ 2 & -1 & 0 \\ 2 & 0 & -1 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} 0.25 \\ 0.25 \\ 0.25 \end{bmatrix}$$

where

$$\begin{bmatrix} -2 & 0 & 0 \\ 2 & -1 & 0 \\ 2 & 0 & -1 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} + \begin{bmatrix} -2 & 0 & 0 \\ 2 & 0 & 0 \\ 2 & 0 & 0 \end{bmatrix}$$

contains one dissociation term, and

$$\begin{bmatrix} -2 & 0 & 0 \\ 2 & -1 & 0 \\ 2 & 0 & -1 \end{bmatrix}^{-1} = \begin{bmatrix} -0.5 & 0 & 0 \\ -1 & -1 & 0 \\ -1 & 0 & -1 \end{bmatrix}.$$

Then, the system has the unique equilibrium point

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \\ r_3(Z^*) \end{bmatrix} = \begin{bmatrix} 0.5 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{bmatrix} \begin{bmatrix} 0.25 \\ 0.25 \\ 0.25 \end{bmatrix} = \begin{bmatrix} 0.125 \\ 0.5 \\ 0.5 \end{bmatrix}$$

in the all ramp region.

Example 32. Invertible system with no equilibria
Changing the previous system slightly, consider

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -2 & 1 & 0 \\ 2 & -1 & 1 \\ 2 & 0 & -1 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} 0.25 \\ 0 \\ 0 \end{bmatrix}.$$

Here,

$$\begin{bmatrix} -2 & 1 & 0 \\ 2 & -1 & 1 \\ 2 & 0 & -1 \end{bmatrix} = \begin{bmatrix} 0 & 1 & 0 \\ 0 & -1 & 1 \\ 0 & 0 & -1 \end{bmatrix} + \begin{bmatrix} -2 & 0 & 0 \\ 2 & 0 & 0 \\ 2 & 0 & 0 \end{bmatrix}$$

is still a matrix with one dissociation term, but its inverse now has non-negative entries:

$$\begin{bmatrix} -2 & 1 & 0 \\ 2 & -1 & 1 \\ 2 & 0 & -1 \end{bmatrix}^{-1} = \begin{bmatrix} 0.5 & 0.5 & 0.5 \\ 2 & 1 & 1 \\ 1 & 1 & 0 \end{bmatrix}$$

Then, we have

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \\ r_3(Z^*) \end{bmatrix} = \begin{bmatrix} -0.5 & -0.5 & -0.5 \\ -2 & -1 & -1 \\ -1 & -1 & 0 \end{bmatrix} \begin{bmatrix} 0.25 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} -0.125 \\ -0.5 \\ -0.25 \end{bmatrix}.$$

This falls outside the range of all three ramp functions, and thus this system does not have any equilibria.

Example 33. Singular system with infinitely many equilibria
Finally, we consider the system

$$\begin{bmatrix} \dot{X} \\ \dot{Y} \\ \dot{Z} \end{bmatrix} = \begin{bmatrix} -2 & 1 & 1 \\ 1 & -2 & 1 \\ 1 & 1 & -2 \end{bmatrix} \begin{bmatrix} r_1(X) \\ r_2(Y) \\ r_3(Z) \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

The matrix

$$\begin{bmatrix} -2 & 1 & 1 \\ 1 & -2 & 1 \\ 1 & 1 & -2 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} + \begin{bmatrix} -1 & 0 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 1 & 0 \\ 0 & -1 & 0 \\ 0 & 1 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 1 \\ 0 & 0 & 1 \\ 0 & 0 & -1 \end{bmatrix}$$

contains three dissociation terms and is singular since all column sums are zero, as are all row sums. From Theorem 47, we have an equilibrium solution if and only if $\vec{x_0} = 0$; since this is indeed the case here, we know the origin is an equilibrium point. By Theorem 48, the matrix has an eigenvector will all non-negative components; from the proof of Theorem 30 in section 3.3.2, $\vec{v} = \vec{1}$ is such an eigenvector.

Thus, we have that

$$\begin{bmatrix} r_1(X^*) \\ r_2(Y^*) \\ r_3(Z^*) \end{bmatrix} = \begin{bmatrix} t \\ t \\ t \end{bmatrix}$$

is an equilibrium in the all ramp region for any $t \in [0, 1)$.

Conclusions and Future Work

In Chapter 1, we introduced *ramp functions* in Definition 1 as piecewise linear approximations of Michaelis-Menten functions, with the goal of facilitating analysis of Adams and colleagues' model of phenylalanine metabolism in plants. As summarized in section 1.6, the results of our analysis of the Adams model with ramp functions were very similar to those of the analysis of the original model in [1].

Our results provided evidence that replacing Michaelis-Menten terms in dynamical systems with ramp functions does not fundamentally alter the behaviour of such systems. Thus, it may be possible to model biochemical systems that would normally be expected to follow Michaelis-Menten kinetics with ramp functions instead. Since ramp functions are linear, unlike Michaelis-Menten functions, they should make analysis of systems noticeably easier.

We broadened the application of ramp functions in Chapter 2 by establishing a class of biochemical systems called *biochemical ramp systems* in Definition 7. In the chapters that followed, we accumulated results regarding equilibria and stability in certain subclasses of these systems, namely SRP systems (Chapter 3), single combining term systems (Chapter 4), and systems with dissociation terms (Chapter 5).

The theory developed in Chapters 2-5 can be used to study the properties of certain systems with Michaelis-Menten terms replaced with ramp functions. However, there is still much theory left to develop. For instance, Chapter 4 only covered invertible systems with one combining term, leaving theory regarding singular systems with one combining term and systems with multiple combining terms still in need of development. Equilibria and stability in systems containing both combining and dissociation terms is another topic that should be explored in the future.

Additionally, some of the theory developed here is incomplete. As an example, flow in SRP systems with three or more variables is an unresolved area in general; while section 3.5 briefly delved into this topic, it is not yet known whether certain properties seen in two-variable systems, such as the global stability of equilibria in the all ramp region in invertible systems and blowup in systems with no equilibria, carry over. Conjecture 4 from section 3.5.1, concerning flow along nullclines in these systems, is also an open problem.

Another issue is that our analysis of general biochemical ramp systems here focused on the case in which each variable was associated with exactly one ramp function. As seen in the Adams ramp system in (1.6) and (1.7) when $K_3^2 \neq K_5$ or $K_3^3 \neq K_1$, however, it is possible for a variable to be the input of multiple ramp functions. Thus, further work on biochemical ramp systems should cover the case of more than one ramp function per variable.

More avenues for future work can opened up by expanding the definition of biochemical ramp systems to include systems with terms derived from chemical reactions not covered back in section 2.1. A couple of reaction types that could be added are

$$2W_i \xrightarrow{k} W_j$$

and

$$W_i \ + W_j \xrightarrow{k} W_g \ + W_h \, .$$

Each of the above suggestions for future work is a step toward building a broad, general theory for biochemical ramp systems, one that applies to a wide range of dynamical systems after their Michaelis-Menten terms have been replaced by ramp functions.

In addition to our biochemical ramp system theory, we also had some interesting linear algebra results here. We introduced the concept of a *biochemical matrix* in Definition 4, and devoted much of Chapter 2 to studying the properties of this class of matrices. Many properties, such as those regarding eigenvalues and the signs of the entries of the inverse of a biochemical matrix, were useful when studying equilibria and stability in biochemical ramp systems in the later chapters.

There are many opportunities for further study when it comes to biochemical matrices. For instance, we have three unresolved conjectures regarding these matrices: Conjecture 1 from section 2.3.2 concerning eigenvalues of matrices with one combining term, Conjecture 2 from section 2.4.1 concerning the entries of the inverse of a matrix with dissociation terms, and Conjecture 3 from section 3.3.2 concerning eigenvectors of singular SRP matrices. Additionally, expanding the definition of a biochemical ramp system to include more reaction types will also allow us to expand the class of biochemical matrices; this will give us new subclasses of matrices to study.

Overall, here we have begun developing the theory behind a class of biochemical dynamical systems that seem to behave similarly to their Michaelis-Menten counterparts, but are much simpler to analyze. Continued evolution of this theory depends on further study of the properties of these systems, as well as the biochemical matrices underlying them.

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