Properties of the Michaelis-Menten Mechanism in Phase Space

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Abstract: We study the two-dimensional reduction of the Michaelis-Menten reaction of enzyme kinetics. First, we prove the existence and uniqueness of a slow manifold between the horizontal and vertical isoclines. Second, we determine the concavity of all solutions in the first quadrant. Third, we establish the asymptotic behaviour of all solutions near the origin, which generally is not given by a Taylor series. Finally, we determine the asymptotic behaviour of the slow manifold at infinity. To this end, we show that the slow manifold can be constructed as a centre manifold for a fixed point at infinity.

Keywords: Michaelis-Menten, enzyme, slow manifold, centre manifold, asymptotics

1 Introduction

The Michaelis-Menten (more accurately the Michaelis-Menten-Henri) mechanism is the simplest chemical network which models the formation of a product through an enzymatic catalysis of a substrate. See, for example, [9, 11, 17, 25], Chapter 1 of [14], and Chapter 10 of [16]. In particular, an enzyme reacts with the substrate and reversibly forms an intermediate complex, which then decays into the product and original enzyme. Symbolically,

\[
S + E \xrightleftharpoons[k_{-1}]{k_1} C \xrightarrow{k_2} P + E,
\]

where \( S \) stands for substrate, \( E \) stands for enzyme, \( C \) stands for complex, and \( P \) stands for product. By the Law of Mass Action we have a set of four differential equations for the
concentrations $s, e, c, \text{ and } p$:

\[
\begin{align*}
\dot{s} &= k_{-1}c - k_1se, \\
\dot{e} &= (k_{-1} + k_2)c - k_1se, \\
\dot{c} &= k_1se - (k_{-1} + k_2)c, \\
\dot{p} &= k_2c.
\end{align*}
\]

Taking initial conditions $s(0) = s_0, e(0) = e_0, c(0) = 0,$ and $p(0) = 0$, we have $e = e_0 - c$ and two independent differential equations:

\[
\begin{align*}
\dot{s} &= k_{-1}c - k_1(e_0 - c), \\
\dot{c} &= k_1(e_0 - c) - (k_{-1} + k_2)c.
\end{align*}
\]

To simplify even further, the Quasi-Steady-State Approximation (QSSA) was introduced by Briggs and Haldane\cite{3}. This takes $\dot{c} = 0$ to hold after a short time, giving

\[
\begin{align*}
\dot{c} &= e_0s K_m + s \\
\dot{p} &= k_2e_0s K_m + s,
\end{align*}
\]

where $K_m := \frac{k_{-1} + k_2}{k_{-1}}$ is called the Michaelis constant. This is generally thought to be valid when $e_0 \ll s_0$. The expression for $\dot{p}$ gives a measure of the velocity of the reaction. Experiments have been fitted to the quasi-steady-state approximation. This type of approximation is often used to simplify other chemical kinetics systems including those of different and more complicated enzyme reactions which may involve inhibition or cooperativity effects\cite{5, 14, 15}.

Another approximation, though less common than QSSA, is the (rapid) Equilibrium Approximation (EA), which originated with Henri and was popularized by Michaelis and Menten. This takes $\dot{s} = 0$ to hold after a short time, giving

\[
\begin{align*}
\dot{c} &= e_0s K_s + s \\
\dot{p} &= k_2e_0s K_s + s,
\end{align*}
\]

where $K_s := \frac{k_{-1}}{k_1}$.

The validity of QSSA can be examined from several points of view. First the equations are written in a non-dimensional form, introducing a small positive parameter $\varepsilon$. This can be done in several different ways\cite{7, 25}. In the traditional scaling\cite{16, 18, 20}, $\varepsilon = \frac{e_0}{s_0}$. Following\cite{22, 23, 24}, we have

\[
\begin{align*}
\dot{x} &= -x + (1 - \eta)y + xy, \\
\dot{y} &= \varepsilon^{-1}(x - y - xy),
\end{align*}
\]

where $x := \frac{k_1s}{k_{-1} + k_2}$ is a scaled substrate concentration, $y := \frac{e}{e_0}$ is a scaled complex concentration, $t := k_1e_0\tau$ is a scaled time, $\tau$ is the original time, $\tau = \frac{d}{dt}$, and $e_0 := e(0) + e(0)$. The parameters are given by $\varepsilon := \frac{k_1e_0}{k_{-1} + k_2}$ and $\eta := \frac{k_2}{k_{-1} + k_2}$. Note that $\varepsilon > 0$ and $0 < \eta < 1$.

When $\varepsilon$ is small, the system (1) is a singular perturbation problem. A matched asymptotic analysis yields the QSSA as the zeroth-order term in the outer expansion\cite{16}. The
correctness of this analysis is proved using Tikhonov-Levinson theory \cite{20}. Explicit bounds on the approximations have been obtained for small $\varepsilon$ \cite{25}. Centre manifold theory \cite{4} and geometric singular perturbation theory \cite{13} have been applied to give an invariant manifold $M_\varepsilon$, called a slow manifold, within distance $O(\varepsilon)$ of $M_0$, the quasi-steady-state manifold $y = \frac{x}{1+x}$. Trajectories approach the slow manifold exponentially fast and then evolve along it at a slower rate.

Several chemists have observed and theoretically investigated slow manifolds which attract other solutions. In general slow manifolds are not uniquely defined. In two-dimensional cases, Fraser and Roussel \cite{8, 22, 23, 24} take as a slow manifold the solution between the horizontal and vertical isoclines, which are the quasi-steady-state and the equilibrium approximations, respectively. Roussel, for example, provided a heuristic argument based on antifunnel theory that there is indeed such a solution \cite{23}. Davis and Skodje \cite{6} take as a slow manifold the trajectory joining a saddle at infinity and a stable node, approaching in a slow direction. This paper was motivated by the work of Fraser and Roussel.

Occasionally, we may refer to the system (1) in the compact form

$$\dot{x} = g(x). \tag{2}$$

We will also work with the one-dimensional version of (1), given by

$$y' = f(x, y), \tag{3}$$

where $'=\frac{d}{dx}$. Explicitly,

$$g(x) := \left(\begin{array}{c}
-x + (1-\eta)y + xy \\
\varepsilon^{-1}(x - y - xy)
\end{array}\right) \quad \text{and} \quad f(x, y) := \frac{x - y - xy}{\varepsilon[-x + (1-\eta)y + xy]}.$$

In this paper, we do not need to assume that $\varepsilon$ is small. The focus is on the behaviour of solutions in the phase plane, that is, considering $y$ as a function of $x$. In §2 we give the basic phase portrait of (1) in the first quadrant and the linearization at the origin. In §3 we describe the isocline structure which is exploited in subsequent sections. In §4 we prove the existence and uniqueness of the slow manifold, which we denote by $M$, between the horizontal and vertical isoclines. These were discussed in a more informal way by Fraser (see, for example, \cite{8}). In §5 we determine the concavity of all solutions except the slow manifold by analyzing an auxiliary function. In §6 we determine the behaviour of solutions near the origin by using Poincaré’s Theorem (see, for example, \cite{2} p.190); one-dimensional solutions $y(x)$ are generally not given by a Taylor series, which has sometimes been assumed. This analysis applies to any two-dimensional system with a Hurwitz-stable equilibrium point. In §7 we determine when solutions enter $\Gamma_1$, which is a region bounded below by the horizontal isocline and above by the isocline for the slope of the slow manifold at the origin. In §8 we establish properties of the slow manifold: concavity, monotonicity, and asymptotic behaviour at the origin and infinity. Finally, in §9 we state some open questions.
2 Phase Portrait

The qualitative behaviour of solutions is revealed by the phase portrait. See, for example, Figure 1, which is a phase portrait for certain values of the parameters. To find the horizontal and vertical isoclines, set, respectively, $\dot{y} = 0$ and $\dot{x} = 0$ in \((1)\) to obtain the graphs

$$y = H(x) := \frac{x}{1 + x} \quad \text{and} \quad y = V(x) := \frac{x}{1 - \eta + x}.$$ 

Note that the EA corresponds to the vertical isocline and the QSSA corresponds to the horizontal isocline. (One may refer to $y = H(x)$ as the quasi-steady-state manifold and $y = V(x)$ as the rapid equilibrium manifold.) Observe that

$$\lim_{x \to \infty} H(x) = 1 = \lim_{x \to \infty} V(x) \quad \text{and} \quad H(0) = 0 = V(0).$$

Since both $H$ and $V$ are strictly increasing and $V(x) > H(x)$ for all $x > 0$, there is a narrow region between the isoclines:

$$\Gamma_0 := \{(x, y) : x > 0, \ H(x) \leq y \leq V(x)\}.$$ 

**Theorem 1.** Let $\mathbf{x}(t)$ be a solution to \((1)\). Then, there exists a $t^* > 0$ such that

$$(x(t), y(t)) \in \Gamma_0 \ \forall \ t \geq t^*.$$
Proof: First, we show that solutions can enter $\Gamma_0$ but not leave it, that is, show that $\Gamma_0$ is positively invariant. It follows from the differential equation that $g \cdot \hat{n} < 0$ along both the vertical and horizontal isoclines, where $\hat{n}$ is the outward unit normal vector. Hence, $\Gamma_0$ is positively invariant.

Second, we establish that solutions outside $\Gamma_0$ eventually enter $\Gamma_0$. Call $y(x)$ the corresponding one-dimensional solution. If $y(x)$ is below the horizontal isocline $H(x)$, then $-\varepsilon^{-1} \leq y'(x) < 0$, and so $y$ must intersect $H$ for a lower value of $x$. Similarly, if $y(x)$ is above the vertical isocline $V(x)$, then $-\infty < y'(x) < -\varepsilon^{-1}$, and so $y$ must intersect $V$ for a higher value of $x$. \hfill \square

Behaviour of solutions near the origin, the only equilibrium point, is governed by the linearization matrix

$$A := \frac{\partial g}{\partial x}\bigg|_{x=0} = \begin{pmatrix} -1 & 1 - \eta \\ \varepsilon^{-1} & -\varepsilon^{-1} \end{pmatrix}. \tag{4}$$

The eigenvalues of $A$ are given by

$$\lambda_{\pm} := \frac{-(\varepsilon + 1) \pm \sqrt{(\varepsilon + 1)^2 - 4\varepsilon \eta}}{2\varepsilon}, \tag{5}$$

which are real-valued and distinct. One can prove that

$$\lambda_- < -1 < \lambda_+ < 0,$$

thus implying that the origin is asymptotically stable. Corresponding eigenvectors are

$$v_{\pm} := \begin{pmatrix} 1 - \eta \\ \lambda_{\pm} + 1 \end{pmatrix}.$$ 

Observe that $v_+$ points into the positive quadrant while $v_-$ does not. The slope of the eigenvector $v_+$ at the origin is very important, and will be denoted by

$$\sigma := \frac{\lambda_+ + 1}{1 - \eta}.$$

Asymptotically, we have that

$$\sigma = 1 + \varepsilon \eta + O(\varepsilon^2) \quad \text{as} \quad \varepsilon \to 0.$$

Observe also that the slope of the slow manifold at the origin lies between the slope of the horizontal isocline and the slope of the vertical isocline. That is,

$$1 < \sigma < (1 - \eta)^{-1}.$$

The original, time-dependent differential equation (1) has linearization

$$\dot{x} = Ax, \tag{6}$$
where the matrix $A$ is as in (4). Since the eigenvalues are real-valued and distinct, the initial value problem

$$
\dot{x} = Ax, \quad x(0) = x_0
$$

has solution of the form

$$
x(t) = c_- e^{\lambda_- t} v_- + c_+ e^{\lambda_+ t} v_+.
$$

We will assume, to avoid triviality, that $x_0 \neq 0$. The coefficients $c_\pm$ can be determined in terms of left eigenvalues and eigenvectors. The left eigenvectors can be taken to be

$$
\hat{v}_\pm := \left( \frac{\varepsilon^{-1}}{\lambda_\pm + 1} \right).
$$

Using the orthogonality condition $\hat{v}_\pm^T v_\pm = 0$ we see that

$$
c_\pm = \frac{\hat{v}_\pm^T x_0}{\hat{v}_\pm^T v_\pm}.
$$

**Proposition 2.** Let $y$ be a solution to (3) which lies inside $\Gamma_0$ for $x \in (0,a)$, where $a > 0$. Then,

$$
\lim_{x \to 0^+} y(x) = 0 \quad \text{and} \quad \lim_{x \to 0^+} y'(x) = \sigma.
$$

**Proof:** We should begin by emphasizing that solutions $x(t)$ to (1) enter and forever remain in the interior of $\Gamma_0$. By hypothesis, $H(x) < y(x) < V(x)$ for all $x \in (0,a)$. The Squeeze Theorem establishes the first limit since $H(0) = 0$ and $V(0) = 0$.

To establish the second result, observe that the function $g$, as in (2), is of class $C^2$ with $g(0) = 0$ and the matrix $A$ has strictly negative eigenvalues. It follows from Hartman’s Theorem (see, for example, [21] p.127), which is a stronger version of the Hartman-Grobman Theorem and applies even in cases of resonance, that the phase portrait of (1) behaves like the phase portrait of (6) diffeomorphically in a neighbourhood of the origin. Therefore, solutions to the nonlinear system have slope $\sigma$ as they approach the origin too. \[\square\]

**Remark 3.** Since any solution $x(t)$, except the trivial solution, eventually enters $\Gamma_0$ and then approaches the origin asymptotically, we can now say definitively that the origin is globally asymptotically stable.

### 3 The Isocline Structure

The nature of the level curves, or isoclines, $c = f(x, y(x))$ reveals to us a surprising amount of insight into the behaviour of solutions to (3). Consider

$$
c = f(x, y(x)), \quad \text{(7)}
$$

where $f$ is as in the differential equation (3) and $c \in \mathbb{R}$. For a given $x > 0$ and $c \in \mathbb{R}$, (7) is invertible and we can solve for $y(x)$, yielding

$$
y(x) = F(x, c) := \frac{x}{K(c) + x}, \quad \text{(8)}
$$

6
for $c \neq -\varepsilon^{-1}$, where

$$K(c) := \frac{1 + \varepsilon(1 - \eta)c}{1 + \varepsilon c}.$$ 

Observe that $y'(x) = f(x, y(x))$ and $y(x) = F(x, y'(x))$ for solutions $y$ of (3) for values of $x$ for which the solution is defined. Throughout this paper, level curves of $f$ will be denoted by $w$. If the slope associated with $w$ is required, we specify this and write $w(x) = F(x, c)$. For completeness, we will agree that $F(x, -\varepsilon^{-1}) = 0$.

The function $K$, which is sketched in Figure 2 and the isoclines, which are sketched in Figure 3 have the following, easy-to-prove properties.

**Proposition 4.** The isoclines and the function $K$ satisfy the following.

(a) The function $K$ is strictly decreasing everywhere except at $c = -\varepsilon^{-1}$, where it has a vertical asymptote.

(b) The function $K$ satisfies $1 - \eta < K(c) < 1$ for $0 < c < \infty$, which corresponds to the interior of $\Gamma_0$. Furthermore, we have that $K(0) = 1$ corresponds to the horizontal isocline and $\lim_{c \to \infty} K(c) = 1 - \eta$ corresponds to the vertical isocline.

(c) The function $K$ satisfies the important relation $K(\sigma) = \sigma^{-1}$.

(d) Define the function $u(c) := cK(c)$ for $c > 0$. The function $u$ is strictly increasing, satis-
7.3 Global Asymptotic Stability

c switches from $+\infty$ to $-\infty$

$y = V(x)$

increasing $c$

$y = \frac{\sigma}{1 + \varepsilon}$

$y = \frac{1}{1 + \varepsilon}$

increasing $c$

$y = \frac{1}{1 + \varepsilon}$

$y = \frac{\sigma}{1 + \varepsilon}$

increasing $c$

From $-\infty$ to $-\varepsilon^{-1}$

From $-\varepsilon^{-1}$ to $+\infty$

Figure 7.3: Sketch of the isocline structure of (7.1). The horizontal or vertical isoclines. Furthermore, solutions cannot escape from $\Gamma$ since solutions do not intersect. Hence, $\Gamma$ is positively invariant.

(b) We will break the proof into cases.

Case 1: Since $\Gamma$ is positively invariant, for all $c > 0$.

Case 2: Suppose, on the contrary, that $c$ does not enter $\Gamma$. It follows that $c > V$ for all $c > 0$. Using the differential equation (7.1), we know $0$ and $\dot{c} < 0$ for all $c > 0$. Now, we see from the definition (7.3) of the function $\mathbf{u}(c)$ that $c > V$ for all $c > 0$.

Thus, $c$ is $\in (0, \infty)$ for all $c \in (0, \sigma)$ and $c \in (\sigma, \infty)$.

See Figure 4.

(e) Any of the isoclines $w$ satisfy the differential equation

$$w(w - 1) + xw' = 0.$$ (9)

Note that the isoclines are hyperbolas. There are two exceptional isoclines, namely $w(x) = F(x, -\varepsilon^{-1}) = 0$ and $w(x) = F(x, -\varepsilon^{-1}(1 - \eta)^{-1}) = 1$. The vertical isocline, $V$, also is somewhat of an exceptional case. Approaching it from below, one encounters increasing $c$ up to $+\infty$. After passing through $V$, the slopes increase from $-\infty$.

4 Existence and Uniqueness of the Slow Manifold

We provide a brief review of fences and antifunnels, which form the backbone of the existence-uniqueness proof that follows.

Phase spaces of differential equations often exhibit curious curves and regions known as fences, funnels, and antifunnels. The best source of information on funnels and antifunnels is [12], Chapters 1 and 4.
Figure 4: Graph of the function $u(c)$ given in Proposition 4(d) for arbitrary $\varepsilon > 0$ and $\eta \in (0, 1)$. The function is strictly increasing for $c > 0$ for every admissible $\varepsilon$ and $\eta$. Furthermore, $u'(0) = 1$ and asymptotically $u$ has slope $1 - \eta$ as $c \to \infty$. Incidentally, $u(c) - (1 - \eta)c = \varepsilon - 1\eta + O(c^{-1})$ as $c \to \infty$.

Definition 5. Let $I = [a, b)$ be an interval (where $a < b \leq \infty$) and consider the first-order differential equation $y' = f(x, y)$ over $I$. Let $\alpha$ and $\beta$ be continuously-differentiable functions satisfying

$$
\alpha'(x) \leq f(x, \alpha(x)) \quad \text{and} \quad f(x, \beta(x)) \leq \beta'(x)
$$

(10)

for all $x \in I$.

(a) The curves $\alpha$ and $\beta$ satisfying (10) are, respectively, a lower fence and an upper fence. If there is always a strict inequality in (10), the fences are strong. Otherwise, the fences are weak.

(b) If $\beta(x) < \alpha(x)$ on $I$, then the set

$$
\Gamma := \{(x, y) : x \in I, \beta(x) \leq y \leq \alpha(x)\}
$$

is called an antifunnel. The antifunnel is narrowing if

$$
\lim_{x \to b^-} |\alpha(x) - \beta(x)| = 0.
$$

Theorem 6 (Antifunnel Theorem, [12] p.31-33). Let $\Gamma$ be an antifunnel with strong lower and upper fences $\alpha$ and $\beta$, respectively, for the differential equation $y' = f(x, y)$ over the interval $I := [a, b)$ (where $a < b \leq \infty$). Then, there exists a solution $y(x)$ to the differential equation such that

$$
\beta(x) < y(x) < \alpha(x) \quad \text{for all} \quad x \in I.
$$

If, in addition, $\Gamma$ is narrowing and $\frac{\partial f}{\partial y}(x, y) \geq 0$ in $\Gamma$, then the solution $y(x)$ is unique.

We cannot use $\Gamma_0$ as an antifunnel (in the sense of Definition 4). The key to our proof is considering the isocline for slope $\sigma$, the slope of the slow manifold at the origin. We will call this isocline $\alpha$. Proposition 4(c) and (8) tell us that $\alpha$ is given by the simple expression

$$
\alpha(x) = \frac{x}{\sigma^{-1} + x}.
$$

(11)
The defining feature of $\alpha$ is $\sigma \equiv f(x, \alpha(x))$. Moreover, this function $\alpha$ has the remarkable property that $\alpha'(0) = \sigma$. That is, the isocline for slope $\sigma$ has slope $\sigma$ at the origin. Define the region
\[ \Gamma_1 := \{(x, y) : x > 0, H(x) \leq y \leq \alpha(x)\}, \]
which is a subset of $\Gamma_0$ because $H(x) < \alpha(x) < V(x)$ for all $x > 0$.

**Theorem 7.**

(a) There exists a unique slow manifold $y = M(x)$ in $\Gamma_1$ for the differential equation (3).

(b) The slow manifold $y = M(x)$ is also the only solution that lies entirely inside $\Gamma_0$.

**Proof:**

(a) We will show that the Antifunnel Theorem can be applied to the interval $[a, \infty)$, where $a > 0$ is arbitrary. First, we show that the curve $y = \alpha(x)$ is a strong lower fence and the curve $y = H(x)$ is a strong upper fence for the differential equation (3) for $x > 0$. Now, the derivative of solutions along the concave-down curve $y = \alpha(x)$ is identically $\sigma$.

Thus, 
\[ \alpha'(x) < \alpha'(0) = \sigma = f(x, \alpha(x)) \quad \forall \ x > 0. \]

Hence, by definition, $y = \alpha(x)$ is a strong lower fence for $x > 0$. To show that $y = H(x)$ is a strong upper fence for $x > 0$, consider that
\[ f(x, H(x)) = 0 < H'(x) \quad \forall \ x > 0. \]

Second, observe that the strong fences satisfy $\alpha(x) > H(x)$ for $x > 0$ and
\[ \lim_{x \to \infty} |\alpha(x) - H(x)| = 0. \]

By definition, $\Gamma_1$ is a narrowing antifunnel.

Finally, a quick calculation shows that $\frac{\partial f}{\partial y} \geq 0$ in $\Gamma_1$. So, all the conditions for the Antifunnel Theorem (Theorem 6) have been established. Therefore, there exists a unique solution $y = M(x)$ to (3) that lies entirely in $\Gamma_1$.

(b) Obviously, any solution other than the slow manifold eventually leaves $\Gamma_1$. If the solution leaves $\Gamma_1$ through the horizontal isocline it also leaves $\Gamma_0$, since both regions share the same lower boundary. If the solution leaves $\Gamma_1$ through the $\alpha$ isocline, while in $\Gamma_0$ the solution will have slopes in the range $\sigma < y' < \infty$ and hence will eventually leave $\Gamma_0$ since the upper boundary of $\Gamma_0$ is bounded above by the line $y = 1$.

$\square$
Remarks 8.

(i) Theorem 7 shows that
\[ \frac{x}{1 + x} < \mathcal{M}(x) < \frac{x}{\sigma^{-1} + x} \quad \forall \ x > 0. \]

Thus, the necessity of the EA is diminished in the sense that \( \alpha \) serves as a smaller upper bound on \( \mathcal{M} \). Furthermore, it follows from the isocline structure that \( \mathcal{M}(x) \) is strictly increasing, since solutions of the differential equation inside the antifunnel but not on the boundary have strictly positive slope. Note that this bound is especially tight when \( \varepsilon \) is small, since
\[ \sigma^{-1} = 1 - \varepsilon \eta + \mathcal{O}(\varepsilon^2) \quad \text{as} \quad \varepsilon \to 0. \]

(ii) Slow manifolds, like centre manifolds, are generally not unique and are defined locally. In our case, all solutions that have slope \( \sigma \) at the origin are slow manifolds. However, we look at the global phase portrait and refer to the unique solution within \( \Gamma_1 \) as the slow manifold.

5 Concavity

Let \( y \) be a solution to (3), which we assume is not the slow manifold because we will deal with that case later. Then, of course, \( y'(x) = f(x, y(x)) \) and so by the Chain Rule,
\[ y''(x) = p(x, y(x))h(x, y(x)), \]
where
\[ p(x, y) := \varepsilon^{-1}\eta \left[ -x + (1 - \eta + x)y \right]^{-2} \]
and
\[ h(x, y) := y(y - 1) + xf(x, y). \]

The function \( p(x, y) \) is positive everywhere except along the vertical isocline, where it is undefined. The function \( h(x) := h(x, y(x)) \), the sign of which determines that of \( y''(x) \), has derivative
\[ h'(x) = 2y(x)y'(x) + xp(x)h(x), \]
where \( p(x) := p(x, y(x)) \). The concavity of all solutions in all regions of the non-negative quadrant can be deduced using this auxiliary function \( h \). Table I summarizes what we will develop in this section. They are all suggested by the phase portrait in Figure I.
### Region | Concavity of Solutions
--- | ---
$0 \leq y < M$ | concave down
$M < y < \alpha$ | concave down, then inflection point, then concave up
$\alpha \leq y < V$ | concave up
$V < y < 1$ | concave down
$y \geq 1$ | concave up, then inflection point, then concave down

Table 1: A summary of the concavity of solutions of (3) in the non-negative quadrant.

**Remarks 9.**

(i) Let $y$ be a solution to (3) and fix $x_0 > 0$. Define $w(x) := F(x, y'(x_0))$ to be the isocline through $(x_0, y(x_0))$. By virtue of the isocline structure, $y''(x_0) > 0$ if and only if $y'(x_0) > w'(x_0)$ and $y''(x_0) < 0$ if and only if $y'(x_0) < w'(x_0)$. Indeed, from (9) and (13),

$$h(x_0) = x_0[y'(x_0) - w'(x_0)],$$

which confirms this fact. The similarity of the form of $h(x)$ and the differential equation (9) that the isoclines satisfy is not a coincidence.

(ii) The function $h$ cannot tell us anything about the concavity of solutions at $x = 0$, not even by taking a limit.

Many of the following proofs will involve the following elementary lemma, so we single it out here. We omit the proof in the interest of space.

**Lemma 10.** Let $I$ be one of the intervals $[a, b], (a, b), [a, b)$, and $(a, b)$. Suppose that $\phi \in C(I)$ is a function having at least one zero in $I$.

(a) If $I = (a, b]$ or $I = [a, b]$, then the function $\phi$ has a right-most zero in $I$. Likewise, if $I = [a, b)$ or $I = (a, b]$, then the function $\phi$ has a left-most zero in $I$.

(b) If $\phi \in C^1(I)$ and $\phi'(x) > 0$ for every zero of $\phi$ in $I$, then $\phi$ has exactly one zero in $I$.

**Proposition 11.** Let $y(x)$ be any solution to (3) lying below the slow manifold, say with domain $(0, a]$ and $y(a) = 0$. Then, $y$ is concave down for all $x \in (0, a]$.

**Proof:** Let $h$ be defined as in (13) with respect to the solution $y$. There are two regions to consider, namely where $y(x) > H(x)$ and where $y(x) \leq H(x)$. It is clear from (12) and (13) that $y''(x) < 0$ for $y(x) \leq H(x)$, noting that $0 \leq y(x) < 1$ and $y'(x) < 0$. The solution $y(x)$ crosses the horizontal isocline, say at $x = x_2 \in (0, a)$. Here, $h(x_2) < 0$ using (13). Suppose that the proposition is false and that there are one or more inflection points. Applying Lemma 11 let $x_1 \in (0, x_2)$ be the right-most zero of $h$. Now, from (14),

$$h'(x_1) = 2y(x_1)y'(x_1) > 0.$$
Then, \( h \) is positive in a neighbourhood to the right of \( x_1 \). Since \( h(x_2) < 0 \), by the Intermediate Value Theorem, \( h \) has a zero in \((x_1, x_2)\) which contradicts the fact that \( x_1 \) is the right-most zero. Therefore, there is no inflection point.

Proposition 12. Let \( y \) be a solution to (3) between \( \alpha \) and \( V \) over \((a, b)\). Then, \( y \) is concave up on \((a, b)\).

Proof: Fix \( x_0 \in (a, b) \) and let \( c := y'(x_0) \) and \( r := K(c) \). Let \( w(x) := F(x, c) \) be the isocline through \((x_0, y(x_0))\). With \( h \) defined as in (13) with respect to \( y \), we have

\[
h(x_0) = x_0[y'(x_0) - w'(x_0)] = x_0 \left[ \frac{c(r + x_0)^2 - r}{(r + x_0)^2} \right],
\]

where we used the expression for \( h \) in (15). Since \( c > \sigma \), applying Proposition 4 we know \( rc > 1 \) which implies \( r > \sqrt{rc^{-1}} \). Suppose, on the contrary, that \( y''(x_0) \leq 0 \). Then,

\[
c(r + x_0)^2 - r \leq 0 \implies x_0 \leq \sqrt{rc^{-1}} - r < 0.
\]

This is a contradiction.

Proposition 13. Let \( y \) be a solution to (3) lying between \( M \) and \( \alpha \), with domain \((0, a)\) and \( y(a) = \alpha(a) \). Then, \( y \) has exactly one inflection point \( x_1 \in (0, a) \). Moreover, \( y \) is concave down on \((0, x_1)\) and concave up on \((x_1, a)\).

Proof: We know \( y'(0) = \sigma \) and \( y'(a) = \sigma \). Hence, by Rolle’s Theorem, \( y \) has an inflection point \( x_1 \in (0, a) \). To prove uniqueness of the inflection point, let \( h \) be as in (13) with respect to the solution \( y \). Now, if \( x \) is a zero of \( h \), then

\[
h'(x) = 2y(x)y'(x) > 0.
\]

By Lemma 10 there is at most one zero of \( h \). Moreover, since \( h'(x_1) > 0 \), \( y \) is concave down on \((0, x_1)\) and concave up on \((x_1, a)\).

Proposition 14. Let \( y \) be a solution to (3) which lies above \( V \) and below 1, with domain \([a, b)\) and \( \lim_{x \to b^-} y(x) = V(b) \). Then, \( y \) is concave down for all \( x \in [a, b) \).

Proof: It is clear from the expression for \( h \), (13), where \( h \) is defined with respect to the solution \( y \), and the fact that \( y' < 0 \) in that region.

Proposition 15. Let \( y \) be a solution to (3) which lies above 1, with domain \([0, a]\), where \( y(a) = 1 \). Then, there exists a unique inflection point \( x_1 \in (0, a) \). Moreover, \( y \) is concave up over \([0, x_1)\) and concave down over \((x_1, a]\).
Proof: Let $h$ be defined as in (13) with respect to the solution $y$. Now,

$$y'(0) = -\varepsilon^{-1}(1 - \eta)^{-1} = y'(a).$$

By Rolle’s Theorem, there exists $x_1 \in (0, a)$ such that $y''(x_1) = 0$. The uniqueness of the inflection point follows from the fact that any zero $x$ of $h$ satisfies $h'(x) < 0$ and an application of Lemma 10. Moreover, since $h'(x_1) < 0$, $y$ is concave up on $[0, x_1)$ and concave down on $(x_1, a)$. □

Remark 16. We now know that solutions can only have inflection points between $\mathcal{M}$ and $\alpha$ and above $y = 1$. There are, in fact, curves along which solutions have zero second derivative. To find them, one could, for example, use Maple to solve $\frac{d}{dx}(f(x, y(x))) = 0$ for $y(x)$, the solutions unfortunately being rather long and messy. There are three solutions. One curve lies below the $x$-axis and is discarded. The other two curves are in the positive quadrant, one lying between $\mathcal{M}$ and $\alpha$ (and which is a lower fence actually), the other starting at $(0, 1)$ and increasing with $x$. See Figure 5.

6 Behaviour of Solutions Near the Origin

It was argued in [19] and [22], for example, that the slow manifold can be written as a Taylor series of the form $\mathcal{M}(x) = \sum_{n=0}^{\infty} \sigma_n x^n$ at the origin. This is a traditional approach but we will show that this approach is not always valid. However, in the realm that is usually...
considered for the Michaelis-Menten Mechanism, namely $0 < \varepsilon \ll 1$, a very high number of terms of this Taylor series is correct.

Intuitively, we know that $\mathcal{M}$ lies between the horizontal and vertical isoclines which both have limit zero as $x \to 0^+$, and $\mathcal{M}$ shares the same direction as the slow eigenvector $\mathbf{v}_+$ at the origin. Hence, it must be that

$$\sigma_0 = 0 \quad \text{and} \quad \sigma_1 = \sigma.$$  \hfill (16a)

By substituting the series into the differential equation, one can obtain all the coefficients recursively:

$$\sigma_n = -\frac{\sum_{k=2}^{n-1} [(n-k)\sigma_{n-k} + (1-\eta)(n-k+1)\sigma_{n-k+1}]\sigma_k}{\varepsilon^{-1} + (1-\eta)(n+1)\sigma_1 - n}$$

$$- \frac{[(n-1)\sigma_1 + \varepsilon^{-1}]\sigma_{n-1}}{\varepsilon^{-1} + (1-\eta)(n+1)\sigma_1 - n}. \hfill (16b)$$

Let $y$ be any solution to (3) that lies inside $\Gamma_0$. Since no property of the slow manifold was used in constructing the above series which all other solutions do not possess, we can equally well write

$$y(x) = \sum_{i=0}^{\infty} \sigma_i x^i. \hfill (17)$$

Define

$$\kappa := \frac{\lambda_-}{\lambda_+} = \frac{\varepsilon + 1 + \sqrt{(\varepsilon + 1)^2 - 4\varepsilon \eta}}{\varepsilon + 1 - \sqrt{(\varepsilon + 1)^2 - 4\varepsilon \eta}}. \hfill (18)$$

where we made use of the expression for $\lambda_-$ and $\lambda_+$. \hfill (5)

Re-arranging (18), we see that $\eta$ can be written in terms of $\varepsilon$ and $\kappa$ as

$$\eta = \frac{\kappa(\varepsilon + 1)^2}{\varepsilon(\kappa + 1)^2}. \hfill (19)$$

This can tell us when the parameter $\kappa$ takes on certain values. However, for a given $\varepsilon > 0$ and $n \in \mathbb{N} \setminus \{1\}$, there may not be a corresponding $\eta \in (0, 1)$ that gives $\kappa = n$. It can be shown that

$$\kappa = \frac{1}{\varepsilon \eta} + \frac{2(1-\eta)}{\eta} + \mathcal{O}(\varepsilon) \quad \text{as} \quad \varepsilon \to 0$$

and thus $\kappa \to \infty$ as $\varepsilon \to 0$. That is, if $\varepsilon$ is very small, which is the case traditionally considered, $\kappa$ is very large. Many results that follow will involve $\kappa$ and so it is a good idea to keep this in mind.

Observe that $\kappa > 1$ and that we can choose values of the parameters $\varepsilon$ and $\eta$ to achieve any desired value of $\kappa$ we wish. The following is easy to prove.

**Proposition 17.** Consider the constant $\kappa > 1$ and the coefficient $\sigma_2$.

(a) There is resonance with the eigenvalues $\{\lambda_-, \lambda_+\}$ if and only if $\kappa \in \mathbb{N} \setminus \{1\}$. (See, for example, [2] for a discussion of resonance.)
Figure 6: The graph of $\eta(\varepsilon, \kappa)$ for an arbitrary, fixed $\varepsilon > 0$. The physically relevant values of $\kappa$ are $\kappa > 1$. Observe that $\frac{\partial \eta}{\partial \kappa} > 0$ for $0 < \kappa < 1$ and $\frac{\partial \eta}{\partial \kappa} < 0$ for $\kappa > 1$ with a global maximum at $\kappa = 1$. Furthermore, there is an inflection point at $\kappa = 2$ and $\eta \to 0$ as $\kappa \to \infty$. Observe that the maximum value satisfies $(\varepsilon+1)^2/4\varepsilon \geq 1$ for all $\varepsilon > 0$ and hence for any permissible value of $\varepsilon$ there are values of $\kappa$ (in a neighbourhood of $\kappa = 1$) which give inadmissible values of $\eta$.

(b) For the numbers $\kappa$ and $\sigma_2$, $\kappa \in (1, 2)$ if and only if $\sigma_2 > 0$. Furthermore, $\kappa > 2$ if and only if $\sigma_2 < 0$.

Proposition 18. Consider the constant $\kappa > 1$ and the coefficients $\{\sigma_i\}_{i=0}^{\infty}$.

(a) If $\kappa \not\in \mathbb{N}$, then all of $\{\sigma_i\}_{i=0}^{\infty}$ are defined.

(b) If $\kappa \in \mathbb{N} \setminus \{1\}$, then $\{\sigma_i\}_{i=0}^{\kappa-1}$ are all defined but $\sigma_\kappa$ is not defined (and hence all subsequent $\sigma_n$ are not defined).

Proof: We know from (16a) that the coefficients $\sigma_0$ and $\sigma_1$ are always defined. Consider the expression (16b), which gives the recursive descriptions of the coefficients. Solving

$$
\varepsilon^{-1} + (1 - \eta)(j+1)\sigma_1 - j = 0, \quad j \in \{2, 3, \ldots\}
$$

gives

$$
\eta = \frac{j(\varepsilon+1)^2}{\varepsilon(j+1)^2}.
$$

From (19), this is true if and only if $\kappa = j$. Hence, if $\kappa \in \mathbb{N} \setminus \{1\}$, then $\{\sigma_i\}_{i=0}^{\kappa-1}$ are all defined but $\sigma_\kappa$ is not defined. If $\kappa \not\in \mathbb{N} \setminus \{1\}$, then all the coefficients are defined. \qed

A classic method of finding an asymptotic expression for a solution to a one-dimensional differential equation $y' = f(x, y)$ is the power series method. Here, one *assumes* a solution of
the form $y(x) = \sum_{n=0}^{\infty} a_n x^n$, substitutes into the differential equation, and arrives at recursive relationships for the coefficients which are then solved. However, this is not always reliable.

**Theorem 19.** Consider the system of ordinary differential equations

$$
\dot{x} = Ax + b(x), \quad x(0) = x_0, \quad x = \left( \begin{array}{c} x \\ \frac{y}{y} \end{array} \right) \in \mathbb{R}^2,
$$

(20)

where the matrix $A$ is Hurwitz (asymptotically stable), the vector field $b$ is analytic with $\|b(x)\| = O(\|x\|^2)$ as $\|x\| \to 0$, and $\|x_0\|$ is sufficiently small. Let the eigenvalues be $\lambda_+$ and $\lambda_-$, where $\lambda_- < \lambda_+ < 0$, and define the ratio $\kappa := \frac{\lambda_-}{\lambda_+} > 1$. Suppose that $\kappa \notin \mathbb{N}$ (i.e. no resonance) and the eigenvector $v_+$ satisfies $(v_+)_1 \neq 0$. If $x(t)$ is a solution to (20) which approaches the origin in the slow direction and (for simplicity) is strictly positive for sufficiently large $t$, then

$$
y(t) = \sum_{n=1}^{[\kappa]} \sigma_n x(t)^n + C x(t)^\kappa + o(x(t)^\kappa) \quad \text{as} \quad t \to \infty
$$

for some constants $\{\sigma_n\}_{n=1}^{[\kappa]}$ (which are independent of initial condition) and $C$ (which depends on the initial condition).

**Proof:** In order to derive the necessary asymptotic expansion for $y(t)$ in terms of $x(t)$, we make use of the linearized problem

$$
\dot{z} = Az, \quad z(0) = z_0.
$$

(21)

To avoid the trivial solutions, which have nothing to offer us, we will assume that $x_0, z_0 \neq 0$. Let $x(t)$ and $z(t)$ be, respectively, the unique solutions to (20) and (21), both of which tend to the origin as time tends to infinity. We will not consider the initial conditions $x_0$ and $z_0$ to be independent so that the solutions $x(t)$ and $z(t)$ can be related. Furthermore, we need both $\|x_0\|$ and $\|z_0\|$ to be small.

The solution to the linear problem $z(t)$ can be written in the explicit form

$$
z(t) = c_+ e^{\lambda_+ t} v_+ + c_- e^{\lambda_- t} v_-,
$$

where $c_+ > 0$ (since we assumed that solutions approach the origin from the right in the slow direction).

We know that there is no resonance with the eigenvalues. Moreover, the eigenvalues are in the Poincaré domain. Applying Poincaré’s Theorem (see, for example, [2] p.190), there is a quadratic vector field $q$ such that $x = z + q(z)$. Hence, we can write (not uniquely if $\kappa \in \mathbb{Q}$)

$$
x(t) \sim \sum_{(m,n) \in S} a_{mn} e^{(m\lambda_- + n\lambda_+) t} = \sum_{(m,n) \in S} a_{mn} e^{(m\kappa n + n) \lambda_+ t} \quad \text{as} \quad t \to \infty \quad (22a)
$$

$$
y(t) \sim \sum_{(m,n) \in S} b_{mn} e^{(m\lambda_- + n\lambda_+) t} = \sum_{(m,n) \in S} b_{mn} e^{(m\kappa n + n) \lambda_+ t} \quad \text{as} \quad t \to \infty, \quad (22b)
$$

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where
\[ S := \{(m, n) : m, n \in \mathbb{Z}, m, n \geq 0, m + n \geq 1\}. \]

Let \( \ell := \lceil \kappa \rceil \). Then, the first \( \ell + 1 \) most dominant terms in (22) are, in order of decreasing dominance,
\[ e^{\lambda_+ t}, e^{2\lambda_+ t}, \ldots, e^{\ell \lambda_+ t}, e^\lambda t. \]
To see why this is the case, we make two observations. First, the fact that the listed exponentials are in decreasing order of dominance is obvious except maybe for the last two. Since \( \kappa = \frac{\lambda_+}{\lambda_-} > \ell \), we have \( \lambda_- < \ell \lambda_+ < 0 \). Second, there cannot be any other exponentials of the form \( e^{(m \lambda_+ + n \lambda_-) t} \) in between those listed.

For our purposes, we need only the first \( \ell + 1 \) terms of (22) and hence we write
\[ x(t) = \sum_{m=1}^{\ell} a_m e^{m \lambda_+ t} + a_{\ell+1} e^\lambda t + o(e^\lambda t) \quad \text{as} \quad t \to \infty \]  
(23a)
\[ y(t) = \sum_{m=1}^{\ell} b_m e^{m \lambda_+ t} + b_{\ell+1} e^\lambda t + o(e^\lambda t) \quad \text{as} \quad t \to \infty, \]  
(23b)
where \( a_1 \neq 0 \). The coefficients can be related using the differential equation. To write \( y(t) \) in terms of \( x(t) \), we will successively eliminate the exponentials. Manipulating (23a) and (23b),
\[ y(t) - \sigma_1 x(t) = \sum_{m=2}^{\ell} b_m^{(2)} e^{m \lambda_+ t} + b_{\ell+1}^{(2)} e^\lambda t + o(e^\lambda t), \]  
(24)
where \( \sigma_1 := \frac{b_1}{a_1} \) and \( b_m^{(2)} := b_m - \sigma_1 a_m \). To go further, observe that we can write powers of \( x(t) \) as
\[ x(t)^n = a_1^n e^{n \lambda_+ t} + \sum_{m=n+1}^{\ell} c_{mn} e^{m \lambda_+ t} + o(e^\lambda t) \quad \text{as} \quad t \to \infty, \]
where \( n \in \{2, \ldots, \ell\} \). Solving for the most dominant exponential,
\[ e^{n \lambda_+ t} = \frac{1}{a_1^n} x(t)^n - \sum_{m=n+1}^{\ell} \left( \frac{c_{mn}}{a_1^n} \right) e^{m \lambda_+ t} + o(e^\lambda t) \quad \text{as} \quad t \to \infty. \]  
(25)

With (25), we can successively eliminate the exponentials of (24)—each time introducing other exponential terms but none of order already eliminated—until we are left with an expression of the form
\[ y(t) - \sum_{m=1}^{\ell} \sigma_m x(t)^m = b_{\ell+1}^{(\ell+1)} e^\lambda t + o(e^\lambda t) \quad \text{as} \quad t \to \infty. \]  
(26)
Since \( x(t)^\kappa = a_1^\kappa e^\lambda t + o(e^\lambda t) \) and hence
\[ e^\lambda t = \frac{1}{a_1^\kappa} x(t)^\kappa + o(e^\lambda t) \quad \text{as} \quad t \to \infty, \]
we can write (26) as
\[ y(t) - \sum_{m=1}^{\ell} \sigma_m x(t)^m = C x(t)^\kappa + o \left( e^{-\ell t} \right) \quad \text{as} \quad t \to \infty, \]
where
\[ C := \frac{b_{\ell+1} - \sigma_1 a_{\ell+1}}{a_1^\kappa}. \]

The desired conclusion follows. \( \square \)

**Remark 20.** The coefficients \( \{\sigma_n\}_{n=1}^{\ell} \) are calculated using the power series method. That is, one assumes that the solution to the one-dimensional version of (20) is \( y(x) = \sum_{n=0}^{\infty} \sigma_n x^n \) (where \( \sigma_0 = 0 \) by necessity). The purpose of the theorem is to tell us how many of the resulting terms apply to all solutions.

**Corollary 21.** There exists a solution to (20) such that
\[ y(t) \sim \sum_{n=1}^{\infty} \sigma_n x(t)^n \quad \text{as} \quad t \to \infty \]
for some constants \( \{\sigma_n\}_{n=1}^{\infty} \).

**Proof:** Choose the initial condition \( z_0 \) so that it is parallel to the slow eigenvector \( v_+ \). Then,
\[ z(t) = c_+ e^{\lambda_+ t} v_+ \]
and hence we can write
\[ x(t) \sim \sum_{m=1}^{\infty} a_m e^{m \lambda_+ t} \quad \text{and} \quad y(t) \sim \sum_{m=1}^{\infty} b_m e^{m \lambda_+ t} \quad \text{as} \quad t \to \infty. \]

Any positive integer power of \( x(t) \) will be a series of the same form as \( x(t) \) and \( y(t) \). Successively eliminating exponents, just like in the proof of the theorem, gives us our desired conclusion. \( \square \)

Now, we apply this general result to the Michaelis-Menten Mechanism.

**Lemma 22.** Let \( y \) be a solution to (3) lying inside \( \Gamma_0 \) and let the ratio of the eigenvalues be \( \kappa > 1 \). Suppose that \( \kappa \notin \mathbb{N} \) (i.e. there is no resonance). Then,
\[ y(x) = \sum_{n=1}^{\lfloor \kappa \rfloor} \sigma_n x^n + C x^\kappa + o(x^\kappa) \quad \text{as} \quad x \to 0^+, \]
where \( \{\sigma_n\}_{n=1}^{\lfloor \kappa \rfloor} \) are as in (17) and \( C \) is some constant that distinguishes the solution \( y(x) \) from other such solutions.
Proof: This proof is a simple application of Theorem [19]. The original, time-dependent differential equation (1) can be written
\[ \dot{x} = Ax + b(x), \quad x(0) = x_0 \] (27)
where the analytic vector field \( b \) is given by
\[ b(x) := xy \left( \frac{1}{\varepsilon-1} \right). \]
Observe that
\[ \|b(x)\| = O\left(\|x\|^2\right) \quad \text{as} \quad \|x\| \to 0. \]
This is fairly obvious but can be shown directly:
\[ 0 \leq (x - y)^2 = x^2 + y^2 - 2xy = \|x\|^2 - \frac{2}{\sqrt{1+\varepsilon}} \|b(x)\| \]
and hence
\[ \|b(x)\| \leq \frac{\sqrt{1+\varepsilon} - 2}{2} \|x\|^2. \]
The linearized problem is
\[ \dot{z} = Az, \quad z(0) = z_0, \] (28)
where the matrix \( A = \left( \begin{matrix} \frac{1}{\varepsilon-1} & -1 \\ -\eta & \frac{1}{\varepsilon-1} \end{matrix} \right) \) was given in (1). Again, we will assume that \( x_0, z_0 \neq 0 \) and, in particular, lie in the positive quadrant. Let \( x(t) \) and \( z(t) \) be, respectively, the unique solutions to (27) and (28). The initial conditions \( x_0 \) and \( z_0 \) are not independent so that the solutions \( x(t) \) and \( z(t) \) can be related. Furthermore, we need both \( \|x_0\| \) and \( \|z_0\| \) to be small. The solution to the linear problem \( z(t) \), as we have seen earlier, can be written explicitly as
\[ z(t) = c_+ e^{\lambda_+ t} v_+ + c_- e^{\lambda_- t} v_-, \quad c_\pm := \frac{\hat{v}_T z_0}{\hat{v}_T v_\pm} \]
with \( c_+ > 0 \) and the sign of \( c_- \) depending on which side of \( v_+ \) the initial point \( z_0 \) lies.

Finally applying Theorem [19] after dropping the time dependence we can say that
\[ y(x) = \sum_{n=1}^{\ell} \hat{\sigma}_n x^n + C x^\kappa + o(x^\kappa) \quad \text{as} \quad x \to 0^+ \]
for some constants \( \{\hat{\sigma}_n\}_{n=1}^{\ell} \) and \( C \), where \( \ell := [\kappa] \). By uniqueness, we have \( \hat{\sigma}_n = \sigma_n \) for all \( n \in \{1, \ldots, \ell\} \).

\[ \square \]

Remark 23. For \( \kappa \in (1, 2) \), we can manipulate the given constants to get
\[ C = \frac{c_- (\lambda_- - \lambda_+)}{c_+^\kappa (1-\eta)^\kappa}. \]
All or Most Solutions Must Enter the Antifunnel

We now investigate conditions under which solutions enter $\Gamma_1$.

**Theorem 24.** Let $x(t)$ be a solution to (1) and suppose there is no resonance, i.e. $\kappa \not\in \mathbb{N}$.

(a) If $\kappa > 2$, then there exists a $t^* > 0$ such that 

$$(x(t), y(t)) \in \Gamma_1 \forall t \geq t^*.$$ 

(b) If $\kappa < 2$, then there exist solutions $x(t)$ which do not enter $\Gamma_1$. Moreover, solutions that do not enter $\Gamma_1$ must enter $\Gamma_0$ through the vertical isocline $V$ to the left of the line $y = \sigma x$.

**Proof:** We begin by noting that if a solution $x(t)$ enters $\Gamma_1$, it forever remains in $\Gamma_1$. This is because $g \cdot \hat{n} < 0$ along $\alpha$ and $H$, where $\hat{n}$ is the unit normal vector. Let $y$ be the corresponding one-dimensional solution.

(a) Applying Lemma 22, we can write 

$$y(x) = \sigma x + \sigma_2 x^2 + o(x^2) \quad \text{as} \quad x \to 0^+.$$ 

Furthermore, since $\kappa > 2$ we have $\sigma_2 < 0$. Thus, 

$$\lim_{x \to 0^+} y'(x) = 2\sigma_2 < 0.$$ 

Since solutions are concave down only when they lie below the isocline $\alpha$, $x(t)$ eventually enters the $\Gamma_1$ antifunnel.

(b) From Lemma 22 we have 

$$y(x) = \sigma x + Cx^\kappa + o(x^\kappa) \quad \text{as} \quad x \to 0^+$$ 

for some constant $C$. It follows that there are some solutions to (3) that are concave up at the origin—the ones for which $C > 0$—and curve away from $\alpha$ and exit $\Gamma_0$ through the vertical isocline. Moreover, since $\sigma_2 > 0$, by virtue of Corollary 21 it follows that there is a solution with a Taylor series at the origin that does not enter $\Gamma_1$ from above. See Figure 7.

We know already that $x(t)$ eventually enters $\Gamma_0$. If $x(t)$ enters $\Gamma_0$ through the horizontal isocline, it also enters $\Gamma_1$. Denote by $(x^*, y^*)$ the point of intersection of the line $y = \sigma x$ and the vertical isocline $y = V(x)$ (that is, $y^* = \sigma x^* = V(x^*)$). Assume that $x(t)$ enters $\Gamma_0$ through the vertical isocline to the right of $(x^*, y^*)$. We claim that $x(t)$ also enters $\Gamma_1$. Suppose that $y$ intersects the vertical isocline at $x = x_1$. Observe that $x_1 \geq x^*$, by assumption, and $y(x_1) \leq \sigma x_1$. By the Mean Value Theorem, there is a $x_0 \in (0, x_1)$ such that 

$$0 \leq y'(x_0) = \frac{y(x_1) - 0}{x_1 - 0} = \frac{y(x_1)}{x_1} \leq \frac{\sigma x_1}{x_1} = \sigma.$$ 

By Virtue of the isocline structure, $H(x_0) \leq y(x_0) \leq \alpha(x_0)$ and therefore $x(t)$ eventually enters $\Gamma_1$. 

$\square$
8 Properties of the Slow Manifold

Finally, we present some important properties of the slow manifold.

**Proposition 25.** The slow manifold \( y = M(x) \) is concave down for all \( x > 0 \).

**Proof:** Construct a sequence of functions \( \{y_n\}_{n=N}^{\infty} \) as follows. Fix \( x_0 > 0 \) and let \( y_n \) be the solution to (3) such that

\[
y_n(x_0) = M(x_0) - \frac{1}{n}.
\]

The number \( N \) is taken large enough so that \( y_N(x_0) \geq 0 \). Thus, by Proposition 11, \( y''_n(x_0) < 0 \) for all \( n \). Now,

\[
y''_n(x_0) = p(x_0, y_n(x_0)) h(x_0, y_n(x_0))
\]

and

\[
M''(x_0) = p(x_0, M(x_0)) h(x_0, M(x_0)).
\]

By construction,

\[
\lim_{n \to \infty} y_n(x_0) = M(x_0).
\]

Letting \( n \to \infty \) in (29) and applying (30), continuity tells us

\[
\lim_{n \to \infty} y''_n(x_0) = M''(x_0).
\]

Since \( y''_n(x_0) < 0 \) for all \( n \), \( M''(x_0) \leq 0 \). Since \( x_0 \) was arbitrary, \( M''(x) \leq 0 \) for all \( x > 0 \).
We now establish a strict inequality. Suppose that $M''(x^*) = 0$ for $x^*>0$. If $h$ is as in (13) with respect to the solution $M$, we have $h'(x^*) > 0$. This contradicts the fact that $h(x) \leq 0$ for all $x > 0$. □

**Proposition 26.** The slow manifold $y = M(x)$ satisfies, for all $x > 0$,

\[ 0 < H(x) < M(x) < \alpha(x) < 1. \]

Furthermore,

\[ \lim_{x \to 0^+} M(x) = 0 \quad \text{and} \quad \lim_{x \to \infty} M(x) = 1. \]

**Proof:** The first result follows from Theorem 7 and the definition of $\alpha$, (11). To establish the other two results, note that the functions $H$, $\alpha$, and $M$ are all continuous for $x > 0$. Since

\[ \lim_{x \to 0^+} H(x) = \lim_{x \to 0^+} \alpha(x) = 0 \quad \text{and} \quad \lim_{x \to \infty} H(x) = \lim_{x \to \infty} \alpha(x) = 1, \]

the results follow from the Squeeze Theorem. □

**Proposition 27.** The slope of the slow manifold $y = M(x)$ satisfies, for $x > 0$,

\[ 0 < M'(x) < \sigma. \]

Furthermore,

\[ \lim_{x \to 0^+} M'(x) = \sigma \quad \text{and} \quad \lim_{x \to \infty} M'(x) = 0. \]

**Proof:** The first result follows from the fact that the slow manifold lies within $\Gamma_1$, which consists of nested isoclines of slopes varying from 0 to $\sigma$.

To prove the second result, observe that the direction of the slow manifold at the origin must correspond to the slow eigenvector at the origin, which has slope $\sigma$.

To prove the third result, we note that, since $M$ is strictly increasing and concave down, there is a $c \in [0, \sigma)$ such that

\[ \lim_{x \to \infty} M'(x) = c. \]

Suppose, on the contrary, that $c > 0$. By the Fundamental Theorem of Calculus,

\[ M(x) = \int_0^x M'(u) \, du > \int_0^x c \, du = cx. \]

However, for sufficiently large $x$, $cx > \alpha(x)$, a contradiction. □

The slow manifold has also been approximated, for large $x$, in the asymptotic series

\[ M(x) \sim \rho_0 + \rho_1 x^{-1} + \rho_2 x^{-2} + \cdots \quad \text{as} \quad x \to \infty. \] (31)
The coefficients can be obtained by substituting the series into the differential equation and are given recursively by

\[
\rho_0 = 1, \quad \rho_1 = -1, \quad \rho_2 = 1,
\]

\[
\rho_n = -\rho_{n-1} + \varepsilon \sum_{i=1}^{n-2} i \rho_{i} [\rho_{n-i-1} + (1 - \eta) \rho_{n-i-2}] \quad \text{for } n > 2. \tag{32}
\]

Observe that all the coefficients are polynomials in \(\varepsilon\) and \(\eta\). As we will establish now, the series (31) is fully correct.

**Proposition 28.** For large \(x\), the slow manifold satisfies

\[
\mathcal{M}(x) \sim \sum_{n=0}^{\infty} \rho_n x^{-n} \quad \text{as } x \to \infty
\]

where \(\{\rho_i\}_{i=0}^{\infty}\) are as in (32). For small \(x\), in the case of no resonance (i.e. \(\kappa \not\in \mathbb{N}\)), the slow manifold satisfies

\[
\mathcal{M}(x) = \sum_{i=1}^{[\kappa]} \sigma_i x^i + C x^\kappa + o(x^\kappa) \quad \text{as } x \to 0^+
\]

for some constant \(C\).

**Proof:** The second conclusion follows from Lemma 22. To prove the first conclusion, observe that for any \(c > 0\) there exists a \(x^* > 0\) such that

\[
H(x) < \mathcal{M}(x) < F(x, c)
\]

for all \(x > x^*\). This is because \(\mathcal{M}\) is concave down and \(\lim_{x \to \infty} \mathcal{M}'(x) = 0\). Hence,

\[
1 - x^{-1} + O(x^{-2}) < \mathcal{M}(x) < 1 - K(c) x^{-1} + O(x^{-2}) \quad \text{as } x \to \infty.
\]

Since \(c > 0\) was arbitrary and \(K(c) \to 1\) as \(c \to 0\), it follows that

\[
\lim_{x \to \infty} \frac{\mathcal{M}(x) - 1}{-x^{-1}} = 1.
\]

Hence,

\[
\mathcal{M}(x) = 1 - x^{-1} + o(x^{-1}) \quad \text{as } x \to \infty.
\]

Unfortunately, this is as much information that we can extract using the isoclines. To obtain the remaining terms of the asymptotic series, we will use the Centre Manifold Theorem (see, for example, [4]).

Under the change of variables

\[
X := x^{-1}, \quad Y := y - (1 - x^{-1}), \quad (33)
\]
we arrive at the system
\[
\begin{align*}
\dot{X} &= -X^2 g_1 \left( X^{-1}, 1 - X + Y \right) \\
\dot{Y} &= -X^2 g_1 \left( X^{-1}, 1 - X + Y \right) + g_2 \left( X^{-1}, 1 - X + Y \right),
\end{align*}
\] (34)

where \( g_1 \) and \( g_2 \) are as in (2). The system (34) is not polynomial but there is no harm, because the resulting one-dimensional differential equation will be the same, in considering the system
\[
\begin{align*}
\dot{X} &= -X^3 g_1 \left( X^{-1}, 1 - X + Y \right) \\
\dot{Y} &= -X^3 g_1 \left( X^{-1}, 1 - X + Y \right) + X g_2 \left( X^{-1}, 1 - X + Y \right),
\end{align*}
\] (35)

which is polynomial. Expanding, we get the expressions
\[
\begin{align*}
X^3 g_1 \left( X^{-1}, 1 - X + Y \right) &= -X^2 \left[ \eta X - Y + (1 - \eta) X (X - Y) \right] \\
X g_2 \left( X^{-1}, 1 - X + Y \right) &= \varepsilon^{-1} \left( X^2 - XY - Y \right).
\end{align*}
\]

The system (35), as we see, is a bit more messy than the original system (3). The eigenvalues of the matrix for the linear part of the new system (35), which is diagonal by construction, are 0 and \(-\varepsilon^{-1}\). We know from centre manifold theory that there is a centre manifold which, we claim, must be the slow manifold.

Observe that the \( Y \)-axis is invariant. Moreover, the fixed point \((X, Y) = (0, 0)\) is a saddle node (or a degenerate saddle). The physically relevant portion of the phase portrait, namely \( X \geq 0 \) and \( Y \geq -1 \), consists of two hyperbolic sectors, one with the positive \( Y \)-axis and the centre manifold as boundaries and the other with the negative \( Y \)-axis and the centre manifold as boundaries. See Figure 8. This can be shown using techniques in §9.21 of [1] (in particular Theorem 65). This also is a consequence of the phase portrait of the original system (1). It follows that the centre manifold is indeed the slow manifold.

By the Centre Manifold Theorem, the slow manifold (in the new coordinates) can be written
\[
\mathcal{M}(X) \sim \sum_{i=2}^{\infty} \hat{\rho}_i X^i \quad \text{as} \quad X \to 0^+,
\]
for some coefficients \( \{\hat{\rho}_i\}_{i=2}^{\infty} \). The first two terms are given by \( \hat{\rho}_2 = 1 \) and \( \hat{\rho}_3 = \varepsilon \eta - 1 \). Reverting back to the original coordinates,
\[
\mathcal{M}(x) \sim 1 - x^{-1} + \sum_{i=2}^{\infty} \hat{\rho}_i x^{-i} \quad \text{as} \quad x \to \infty.
\]

Observing that the coefficients in (32) are generated uniquely from the differential equation, the conclusion follows. \(\square\)
Figure 8: A phase portrait for (35) for $\varepsilon = 5.0$ and $\eta = 0.8$.

Remarks 29.

(i) We use the ad hoc transformation (33) because it is inspired by the series for $\mathcal{M}$ which we wish to obtain and it also results in a system which is in the canonical form of the Centre Manifold Theorem. Others, for example, [6, 10], have used Poincaré compactification to study the behaviour of $\mathcal{M}$ at infinity and found that the fixed point is a degenerate saddle.

(ii) The Centre Manifold Theorem can be applied at the origin as well. See, for example, [4] pages 8–10. However, this result gives a smooth solution for small $\varepsilon$ only. This is because in order to apply the Centre Manifold Theorem, the differential equation $\dot{\varepsilon} = 0$ is appended to the system (2) which gives the zero eigenvalue. A centre manifold exists in a neighbourhood of $(x, y, \varepsilon) = (0, 0, 0)$.

Proposition 30. In the case of no resonance, i.e. $\kappa \not\in \mathbb{N}$, the second derivative of the slow manifold satisfies

$$\lim_{x \to 0^+} \mathcal{M}''(x) = \begin{cases} 2\sigma_2, & \text{if } \kappa > 2 \\ -\infty, & \text{if } \kappa < 2 \end{cases}.$$  

Proof: The proof involves an easy application of Lemma 22 and the fact that the slow manifold is concave down at the origin. $\square$
Remark 31. The quasi-steady-state approximation has traditionally been used to approximate the long-term behaviour (in time) of solutions to (1). Is this justified? Recall that

\[ H(x) = \frac{x}{1 + x} \quad \text{and} \quad \alpha(x) = \frac{x}{\sigma^{-1} + x}. \]

It follows that the QSSA is good when \( \sigma \approx 1 \). Recall also that \( \sigma = 1 + \mathcal{O}(\varepsilon) \) as \( \varepsilon \to 0 \). Hence, the QSSA is a good approximation when \( \varepsilon \) is small. However, the function \( \alpha(x) \) has slope \( \alpha'(0) = \sigma \) at the origin and so is a good approximation for solutions near the origin for any \( \varepsilon \). Furthermore, since \( \kappa = (\varepsilon \eta)^{-1} + \mathcal{O}(1) \) as \( \varepsilon \to 0 \), a large number of Taylor coefficients are correct in the asymptotic expansion at the origin for the slow manifold if \( \varepsilon \) is small.

9 Open Questions

In the analysis of the behaviour at the origin, we assume non-resonance of the eigenvalues of the linearization at the origin. The resonance cases still need to be investigated.

S. Fraser and M. Roussel\[8, 19, 22, 23, 24\] have introduced and investigated an iteration scheme to approximate the slow manifold. Specifically, the iterates are defined by \( y_{n+1} := F(x, y'_n) \), where \( F \) is as in [8]. A definitive proof of convergence of the scheme which is valid for all values of the parameters \( \varepsilon \) and \( \eta \) has not yet been given. The scheme can diverge for certain values of the parameters and certain choices of initial iterate and converge for others. Convergence has been examined, for example, in [13]. In this particular paper, the Fraser iterates and perturbation series for \( \mathcal{M} \) in \( \varepsilon \) were compared. Specifically, if \( \{y_n\}_{n=0}^\infty \) are the Fraser iterates with initial iterate \( y_0 := H \) and

\[ \mathcal{M}(x) = \sum_{m=0}^{\infty} \mathcal{M}_m(x) \varepsilon^m \]

is the perturbation series for \( \mathcal{M} \), then for each \( n \)

\[ y_n(x) = \sum_{m=0}^{n} \mathcal{M}_m(x) \varepsilon^m + \mathcal{O}(\varepsilon^{n+1}) \quad \text{as} \quad \varepsilon \to 0. \]

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