Existence and uniqueness of attracting slow manifolds: An application of the Ważewski principle

by

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A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Master of Mathematics
in
Applied Mathematics

Waterloo, Ontario, Canada, 2017

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

In this work we present some of the geometric constructs that aid the application of the Ważewski Theorem. To illustrate the procedure the Michaelis-Menten mechanism will be considered. We show that $\mathcal{M}$, a slow manifold, exists and is fully contained in a given set V. The set V must satisfy that its set of ingress points I with respect to de differential system of equations are strict. The Ważewski Theorem asserts that if the subset of strict ingress points of V is not a retract of the whole set then there exist a trajectory ϕ contained in V for all positive/negative values of time. More specifically, the theorem establishes that if we can find a set $Z \subset V \cup I$ such that $Z \cap I$ is a retract of I but not a retract of Z then ϕ exists.

For the construction of the set V the existence of continuously differentiable functions which behave similarly to Liapunov functions on some parts of their zero-levels is required. The starting point to define such functions was to use the expressions obtained from the quasi steady state and rapid equilibrium assumptions (QSSA and REA).

One surprising property of $\mathcal{M}$ is that it is the only trajectory that stays in the set V. To discuss uniqueness of the slow manifold we show the following two conditions are satisfied:

- One of the coordinates, let us say x_i is monotone and $0 < x_i < \infty$. The cross-section given by x_i constant has either a non-decreasing or fixed diameter as x_i increases.
- The distance between two different solutions in V is non-decreasing as x_i increases.

with respect to a chosen variable, any two solutions in the polyfacial set V are always moving apart and the diameter of the cross sections of V is either decreasing or constant.

Acknowledgments

I would like to thank my supervisor Dr. David Siegel and committee members, Dr. Sue Ann Campbell and Dr. Brian Ingalls, for taking the time to read this work and provide constructive feedback.

I would like to thank the Applied Mathematics Department of the University of Waterloo for all the resources provided. I especially would like to thank administrative Laura Frazee who has a great talent to keep things on track, the help provided is much appreciated.

Finally, I would like to thank my mother and my husband for all the unconditional love and support.

Dedication

To Hortensia and Fidel.

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Chapter 1

Introduction

Modeling problems that involve different time scales give rise to systems of differential equations of the following form

$$\begin{aligned} \mathbf{x}' &= f(\mathbf{x}, \mathbf{z}, \varepsilon) \\ \mathbf{z}' &= \varepsilon g(\mathbf{x}, \mathbf{z}, \varepsilon). \end{aligned} \tag{1.1}$$

Where $\mathbf{x} \in \mathbb{R}^n$, $\mathbf{z} \in \mathbb{R}^m$, $\varepsilon \in \mathbb{R}$ and the functions $f, g \in C^r$, where $r > 1$. It is assumed that ε is a small positive parameter. Here, the prime symbol denotes the derivative with respect to the independent variable t. When the system involves two different time scales, the parameter ε is significant since it establishes the difference between time scales.

Systems of differential equations such as (1.1) arise naturally when modeling biological processes. The following authors present some applications where such type of systems are obtained [2–4, 7, 14, 18].

From a geometric point of view, the analysis of systems of equations like (1.1) requires the system to posses a normally hyperbolic invariant manifold (NHIM), which can be thought of as a generalization of a hyperbolic fixed point. The concept of NHIM was introduced by Neil Fenichel in 1972. An introduction to geometric methods for singular perturbation problems can be found in work by Tasso J. Kaper [14] and by Christopher K.R.T Jones [12]. These two references also contain an outline of Fenichel's theory for singular perturbation problems.

System (1.1) can be reformulated via a change of time scale as

$$\begin{aligned} \varepsilon\dot{\mathbf{x}} &= f(\mathbf{x}, \mathbf{z}, \varepsilon) \\ \dot{\mathbf{z}} &= g(\mathbf{x}, \mathbf{z}, \varepsilon). \end{aligned} \tag{1.2}$$

Derivatives in system (1.2) are with respect to the variable $\tau = \varepsilon t$. Note that as long as $\varepsilon > 0$, both systems are equivalent. The case $\varepsilon = 0$ gives reduced expressions of (1.1) and (1.2). Both formulations are used to gain insight about the case where $\varepsilon > 0$. If $\varepsilon = 0$ in system (1.1) yields

$$\begin{aligned} \mathbf{x}' &= f(\mathbf{x}, \mathbf{z}, 0) \\ \mathbf{z}' &= 0. \end{aligned} \tag{1.3}$$

Here the variable $\mathbf{x}$ is changing while $\mathbf{z}$ remains constant. The set of critical points for (1.3), given by the condition $f(\mathbf{x}, \mathbf{z}, 0) = 0$, is an l-dimensional manifold $\mathcal{M}_0$. Under some conditions which are related to the linearization of (1.1) at each point of $\mathcal{M}_0$, see 3.3.3 for an example, the manifold $\mathcal{M}_0$ is said to be *normally hyperbolic invariant manifold.*

Fenichel's theory, which applies to case where $\mathcal{M}_0$ is a compact manifold without boundary, gives conditions under which the NHIM persists when the perturbation is turned on. That is, it establishes that if in the limit as ε approaches zero, the system has a normally hyperbolic invariant manifold $\mathcal{M}_0$, then there exist manifolds $\mathcal{M}_\varepsilon$ for ε sufficiently small and positive. The persistent manifolds, $\mathcal{M}_\varepsilon$, are called *slow manifolds.*

For planar systems, other arguments have been used to give a description of the slow dynamics of a system. See for example the work presented by Fraser [7], Fraser & Roussel [18] and Calder & Siegel [2, 3]. For the Michaelis-Menten and Lindemann mechanisms of enzyme kinetics they have shown that in the substrate/complex plane, the slow and asymptotic motion of the system is bounded above by the Rapid Equilibrium (RE) and below by the quasi steady-state approximation (QSSA). In reference [18], Fraser and Roussel follow an iterative approach where the separation of fast and slow time scales is exploited to find low-dimensional manifolds in the space of species concentrations. Calder and Siegel used fences and antifunnel theory [10, Ch 1,4] to show that inside the region described by the RE and QSSA there is an exceptional solution that stays inside and attracts all other solutions. This exceptional solution is called *the slow manifold* and is usually denoted $\mathcal{M}_\varepsilon$.

The work presented here follows the same spirit as the work done in [2, 3, 7, 18]. We look for conditions on existence and uniqueness of an exceptional solution $\mathcal{M}$ that stays inside a particular region and attracts all other solutions. Our aim is to present some geometric constructs and use the Ważewski method to determine the existence and uniqueness of the slow manifold $\mathcal{M}$. The name and notation for $\mathcal{M}$ is taken from the framework of geometric singular perturbation theory. The relevance of the tools presented here is that they are applicable to higher dimensional systems.

Existence of the slow manifold is justified by the so called Ważewski method, an outline of the method and its relation to Conley index theory is presented by Roman Srzednicki in [20]. The method follows a topological approach to differential equations and is due to Tadeusz Ważewski (1896-1972) who introduced it in [22]. It gives a way to prove existence of solutions that remain in a *polyfacial set* V for all positive/negative values of time. The polyfacial set V must satisfy that its set of ingress points I are strict.

This thesis is organized as follows. In Chapter 2, concepts and theorems from analysis and topology are introduced. A simplified version of the Ważewski Theorem is presented also in Chapter 2. Applications of the theorem are introduced in Chapters 4 and 5.

An important piece for the application of the Ważewski Theorem is the construction of the polyfacial set V for the differential equation. Such construction is based on the existence of continuously differentiable functions that behave similarly to Liapunov functions on some parts of their zero-level sets. For the examples presented here, a starting point for those functions are the expressions obtained by the RE and QSSA assumptions. In Chapter 3 we briefly mention how those expressions are obtained for the Michaelis-Menten system. Also, in Chapter 3 some of the concepts related to geometric singular perturbation theory are illustrated.

In Chapters 4 and 5 we present an argument based on the Ważewski Principle to show there exist a unique trajectory $\mathcal{M}$ fully contained in a polyfacial set V. We illustrate the concepts used by applying them to some simple models like the Michaelis-Menten system.

Finally, Ważeski's method, although an existence result, helps us determine conditions applicable to higher dimensions for the existence of a trajectory fully contained in a polyfacial set V. Uniqueness of such trajectory is justified showing that the following two conditions are satisfied:

- One of the coordinates, let us say x_i is monotone and $0 < x_i < \infty$. The cross-section given by x_i constant has either a non-decreasing or fixed diameter as x_i increases.

- The distance between two different solutions in V is non-decreasing as x_i increases.

These concepts and conditions are justified in Appendices A and B.

Final remarks are presented in Chapter 6.

Chapter 2

Background Material

In this chapter we review some of the key concepts that will arise hereafter in the exposition of this work. The main goal of this chapter is to present the *Ważewski method*, also known as the retract method. It was first introduced in the middle of the twentieth century by the polish mathematician Tadeusz Ważewski in [22]. The method follows a topological approach to differential equations and gives a way to prove existence of solutions that remain in a given set V for all negative values of time. The construction of V presented here is based on the existence of functions which behave similarly to Liapunov functions on some parts of their zero-level set, a neat procedure is presented in [20]. The retract method asserts that there is a solution contained in V for all negative values of time if the subset of strict ingress points of V is not a retract of the whole set V.

2.1 Basic results from topology

The Ważewski method is based on concepts and theorems from analysis and topology. The definitions and theorems of this section can be found for example in [9, 16].

Definition. A topological space is an ordered pair (X, τ), where X is a set and τ is a collection of subsets of X satisfying the following three axioms:

1) X and $\emptyset$ belongs to τ

2) any union of elements of τ still belong to τ

3) the intersection of any finite number of elements of τ still belongs to τ

The elements of τ are called open sets and τ is called a topology on X.

Example 2.1.1. *Every metric space can be given a topology in which the basic open sets are the open balls defined by a metric. For example let us take $X = R^n$, with the Euclidean metric. Let τ be the set of open subsets that can be realized as the union of open balls, that is, $A \in \tau$ if for all $x_0 \in A$ there exists $r > 0$, which depends on x_0, such that $B(x_0, r) \subset A$, then $A = \bigcup\limits_{x_0 \in A} B(x_0, r)$.*

Definition. Let X and Y be two topological spaces. We say the map $f : X \to Y$ is continuous if for every open set $A \subset Y$ the inverse image of A,

$$f^{-1}(A) = \{x \in X \mid f(x) \in A\},$$

is an open subset of X.

Definition. Let X be a topological space and $A \subset X$. A continuous map $r : X \to A$ such that $r(a) = a$ for all $a \in A$ is called a **retraction** from X to A.

The set A is called a **retract** of X if there is a retraction $r : X \to A$.

Definition. A space is connected if it cannot be represented as the union of two or more disjoint nonempty open subsets.

If X is a connected set, the following theorem will be very useful to determine whether a set $A \subset X$, is a retract of X.

Theorem 2.1.2. *Let X be a connected set and $r : X \to A$ a continuous function. The image of X under r, $r(X)$, is a connected set as well.*

Proof. The idea of the proof is as follows. Let us assume that $r(X)$ is not connected. Then, there exist A_1 and A_2, open sets (relative to $r(X)$), such that $A_1 \cap A_2 = \emptyset$, and $r(X) \subseteq A_1 \cup A_2$. Also, $r(X) \cap A_1 \neq \emptyset$ and $r(X) \cap A_2 \neq \emptyset$. Let us now take a look at the set $r^{-1}(A_1)$ and $r^{-1}(A_2)$. Since $r(X) \cap A_1 \neq \emptyset$ we have that $r^{-1}(A_1) \neq \emptyset$ and an open set, since r is continuous, similar for $r^{-1}(A_2)$. Note that $r^{-1}(A_1) \cap r^{-1}(A_2) = \emptyset$, otherwise if there exists $x \in r^{-1}(A_1) \cap r^{-1}(A_2)$ it will imply that $r(x) \in A_1$ and $r(x) \in A_2$ but $A_1 \cap A_2 = \emptyset$ so this can not happen. Finally, we will show that $X = r^{-1}(A_1) \cup r^{-1}(A_2)$. If $x \in X$, then $r(x) \in r(X)$ which implies $r(x) \in A_1$ or $r(x) \in A_2$ hence $x \in r^{-1}(A_1)$ or $x \in r^{-1}(A_2)$. We have shown that X is disconnected, which is a contraction. Therefore $r(X)$ has to be connected when X is connected. □

Example 2.1.3. *Let us consider the set $S = [a, b]$, and $A = \{a\}$. Then we have that A is a retract of S. We could just take $r(x) = a$ which is a continuous function and the identity when the domain is restricted to the set A.*

On the other hand, if we consider the set $A = \{a, b\}$ instead, by the previous theorem A cannot be a retract of S. Since S is connected, the image of S under a continuous function has to be a connected as well.

Note. This type of argument is used in one of the applications of the Ważewski theorem presented in Chapter 4.

Another useful result is the No Retraction Theorem (NRT) which is equivalent to Brouwer's Fixed Point Theorem. We present a popular version of the NRT, which states that there is no retraction from the unit ball to the unit circle. A general version, together with its proof can be found for example in [9].

Theorem 2.1.4 (No Retraction Theorem)**.** *Let*

$$D^2 = \{(x, y) \in \mathbb{R}^2 \mid x^2 + y^2 \leq 1\}$$

and

$$S^1 = \{(x, y) \in \mathbb{R}^2 \mid x^2 + y^2 = 1\}.$$

There is no retraction $r : D^2 \to S^1$.

There are several proofs of the NRT, for a self-contained proof see for example [13]. The NRT holds in higher dimensions, for example, it can be shown that there is no retraction from the n-dimensional ball to its boundary. Furthermore, the NRT is also valid for a general bounded open subset B of $\mathbb{R}^n$ with a smooth boundary S, or a set homeomorphic to an n-dimensional ball, see [9, 13].

Note. The NRT argument is used in one of the applications of the Ważewski theorem which is presented in Chapter 5.

2.2 Flows, trajectories and semi trajectories on a topological space

Let us consider the following initial value problem

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$$
$$\mathbf{x}(0) = \mathbf{x_0}, \tag{2.1}$$

where $\mathbf{x} : \mathbb{R} \to \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a continuous vector field. We assume that for each point $\mathbf{x_0}$ in the phase space there exists a unique solution $t \mapsto \phi(\mathbf{x_0}, t)$ of the initial value problem (2.1) that passes through $\mathbf{x_0}$. Such a solution might not be defined for all $t \in \mathbb{R}$.

The definitions presented in the remaining sections of this chapter can be consulted in [20, pp.594-620].

Definition. Let X be a topological space and let D be an open subset of $X \times \mathbb{R}$. A **local flow** is a continuous map $\phi : D \to X$ such that for every $\mathbf{x} \in X$ the set $\{t : (\mathbf{x}, t) \in D\}$ is equal to an open interval (α_x, ω_x), where $-\infty < \alpha_x \leq 0 \leq \omega_x < \infty$.

If $t \in (\alpha_x, \omega_x)$ then $\alpha_{\phi(x,t)} = \alpha_x - t$ and $\omega_{\phi(x,t)} = \omega_x - t$. Also, the local flow ϕ satisfies the following:

$$\phi(\mathbf{x}, 0) = \mathbf{x},$$

$$\phi(\mathbf{x}, s + t) = \phi(\phi(s, \mathbf{x}), t).$$

If $D = X \times \mathbb{R}$, then a local flow is called a **flow**.

Note. In this work if $A \subset X$ and $J \subset \mathbb{R}$ we will write $\phi(A, J)$ instead of $\phi(A \times J)$.

Definition. Let $\mathbf{x} \in X$ and ϕ be a local semiflow on X.

The **positive semitrajectory** of $\mathbf{x}$ is given by the set

$$\phi^+(x) := \phi(x, [0, \omega_x)).$$

Similarly, the **negative semitrajectory** of $\mathbf{x}$ is

$$\phi^-(x) := \phi(x, (\alpha_x, 0]).$$

If ϕ is a local flow then we call the **trajectory** of $\mathbf{x}$ the following set

$$\phi(x) := \phi(x, (\alpha_x \omega_x)).$$

2.3 Ingress, egress and outward tangency points

In what follows, let us consider V to be an open subset of the phase space $\mathbb{R}^n$. The next definition gives a classification of points on V and the boundary of V when we consider the trajectories passing through those points.

Note. We use ∂V to denote set of points in the boundary of V. The set $\overline{V} = V \cup \partial V$ and $\mathbb{R}^n \setminus \overline{V}$ denotes the complement of $\overline{V}$ in $\mathbb{R}^n$.

Definition. Let V be an open set in $\mathbb{R}^n$, take $\mathbf{x} \in \partial V$.

- We say that $\mathbf{x}$ is an **ingress point** of V with respect to (2.1) if there exist an $\varepsilon > 0$ such that $\phi(\mathbf{x}, t) \in V$ for $0 < t < \varepsilon$. Moreover, if $\phi(\mathbf{x}, t) \in \mathbb{R}^n \setminus \overline{V}$ for $-\varepsilon < t < 0$ then $\mathbf{x}$ is called strict ingress point.
- Similarly, we say that $\mathbf{x}$ is an **egress point** of V if there exist an $\varepsilon > 0$ such that $\phi(\mathbf{x}, t) \in V$ for $-\varepsilon < t < 0$. Moreover, if $\phi(\mathbf{x}, t) \in \mathbb{R}^n \setminus \overline{V}$ for $0 < t < \varepsilon$ then $\mathbf{x}$ is called strict egress point.
- Finally, $\mathbf{x}$ is an **outward tangency** point of V if there exist $\varepsilon > 0$ such that $\phi(\mathbf{x}, t) \in \mathbb{R}^n \setminus \overline{V}$ for all $t \in (-\varepsilon, 0) \cup (0, \varepsilon)$.

Example 2.3.1. *For one example the set of points described above is visualized in the Figure 2.1. In this case, let us assume the open set that we are referring to is given by*

$$V = \{(x_1, x_2) \mid |x_1| < 1, |x_2| < 1\}$$

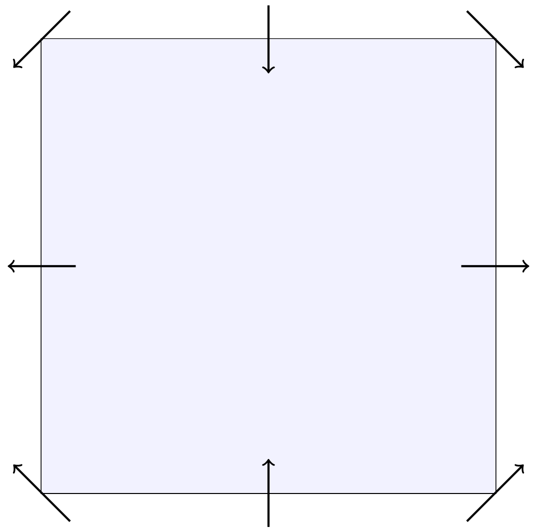


Figure 2.1: Illustration of ingress, egress and outward tangency points.

and the vector field is $\mathbf{f} = (f_1, f_2)$ *which satisfies*

$$x_1 f_1(x_1, x_2) > 0 \quad \text{if} \quad |x_1| = 1,\ |x_2| \leq 1,$$

and

$$x_2 f_2(x_1, x_2) < 0 \quad \text{if} \quad |x_1| \leq 1,\ |x_2| = 1.$$

This is, the open vertical sides of the square consist of strict egress points. Similarly, the open horizontal sides consist of strict ingress points, and the four vertices of the square form the set of outward tangency points.

The retract method asserts that there is a solution contained in V for all negative values of time if the subset of strict ingress points of V is not a retract of the whole set V. In the following section, we present a way to construct a polyfacial sets V for a vector field described by $\mathbf{f}$. The construction of such set gives us a neat way to determine whether a point $\mathbf{x} \in \partial V$ is either strict egress, strict ingress or an outward tangency point.

2.4 Polyfacial sets

Here we present a way to construct *polyfacial sets* in differential equations. Such construction is based on the existence of continuously differentiable functions which behave similarly to Liapunov functions on some parts of their zero-level set. The main purpose of such construction is to have a neat way to determine whether a point $\mathbf{x} \in \partial V$ is either strict egress, strict ingress or outward tangency point.

Let p and q be nonnegative integers such that $p + q \geq 1$. Consider the continuously differentiable functions $l_i, m_j : \mathbb{R}^n \to \mathbb{R}$ where $i = 1, 2, \ldots, p$ and $j = 1, 2, \ldots, q$. Let the set V be described in the following way

$$V := \{\mathbf{x} \in \mathbb{R}^n \mid l_i < 0 \quad \forall i = 1, 2, \ldots, p, \quad m_j < 0 \quad \forall j = 1, 2, \ldots, q\}.$$

Furthermore, let us consider the following sets

$$L_i := \{\mathbf{x} \in \partial V \mid l_i(\mathbf{x}) = 0\}$$

$$M_i := \{\mathbf{x} \in \partial V \mid m_i(\mathbf{x}) = 0\}.$$

Definition. The set V describe above is called a *polyfacial set determined* by the set of functions $\{l_i, m_i\}$ for $i = 1, 2, \ldots, p$, and $j = 1, 2, \ldots, q$.

Note. The possibility to have either $L_i = \emptyset$ or $M_i = \emptyset$ is not excluded. This is actually the case in the example presented in Chapter 4 where the set $L_i = \emptyset$. The set of functions determining the set V are given by the QSSA and RE approximations which are described in more detail in the following chapter.

Definition. If for every $i = 1, 2, \ldots, p$ and $j = 1, 2, \ldots, q$ the following conditions are satisfied

$$\mathbf{f}(\mathbf{x}) \cdot \nabla l_i(\mathbf{x}) > 0, \quad \text{if} \quad \mathbf{x} \in L_i \tag{2.2}$$

$$\tag{2.3}$$

$$\mathbf{f}(\mathbf{x}) \cdot \nabla m_i(\mathbf{x}) < 0, \quad \text{if} \quad \mathbf{x} \in M_i. \tag{2.4}$$

Then we say that the set V is a *polyfacial set for the differential equation* $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ determined by $\{l_i, m_i\}$.

For the case where $\mathbf{x} \in \partial V$, we have defined above in section 2.3 the concepts of strict ingress, strict egress and outward tangency point of V. When V is a *polyfacial set for the differential equation* $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ the following Proposition presented in [20] provides a way to determine which points of ∂V are in each set.

Proposition 2.4.1. *Let V be a* polyfacial set for the differential equation $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$.

a) The point $\mathbf{x} \in \partial V$ is a strict ingress point if and only if satisfies $\mathbf{x} \in M_j$ for some $j = 1, 2, \ldots, q$ and $\mathbf{x} \notin L_i$ for every $i = 1, 2, \ldots p$.

b) Similarly, the point $\mathbf{x} \in \partial V$ is a strict egress point if and only if $\mathbf{x} \in L_i$ for some $i = 1, 2, \ldots, p$ and $\mathbf{x} \notin M_j$ for every $j = 1, 2, \ldots q$.

c) The point $\mathbf{x} \in \partial V$ is a outward tangency point if and only if $\mathbf{x} \in L_i \cap M_i$ for some $i = 1, 2, \ldots, p$ and $j = 1, 2, \ldots q$.

Proof. a) Let $\mathbf{x} \in \partial V$, note that

$$\partial V \subset \bigcup_{i=1}^{p} L_i \cup \bigcup_{j=1}^{q} M_i. \tag{2.5}$$

($\Rightarrow$ If $\mathbf{x}$ is a strict ingress point, then $\mathbf{x} \notin L_i$ every $i = 1, 2, \ldots, p$. For the relation established in equation (2.5), it follows that $\mathbf{x} \in M_j$ for some $j = 1, 2, \ldots, q$.

($\Leftarrow$ Assume $\mathbf{x}$ is in some M_j, for $j = 1, 2, \ldots, q$ and $\mathbf{x} \notin L_i$ every $i = 1, 2, \ldots, p$. Note that for any point $\mathbf{x} \in \overline{V}$ we have that $m_j(\mathbf{x}) \leq 0$ for $j = 1, 2, \ldots, q$. Since each m_j is a continuous function, when $m_j(\mathbf{x}) < 0$ then

$$m_j(\phi(\mathbf{x}, t)) < 0$$

for $t > 0$ sufficiently small.

On the other hand, if $m_j(\mathbf{x}) = 0$, this is $\mathbf{x} \in M_j$ for some $j = 1, 2, \ldots, q$, then

$$\phi(x, (-\varepsilon_j, 0)) \subset \mathbb{R}^n \setminus \overline{V}$$

and

$$m_j(\phi(x, t)) < 0 \quad \text{if} \quad 0 < t < \varepsilon_j \quad \text{for some} \quad \varepsilon_j > 0.$$

Therefore, in each case there exist an $\varepsilon > 0$ such that $\phi(\mathbf{x}, t) \in V$ for $0 < t < \varepsilon$ and $\phi(\mathbf{x}, t) \in \mathbb{R}^n \setminus \overline{V}$ for $-\varepsilon < t < 0$ thus $\mathbf{x}$ is in the set of strict ingress points of V.

b) It follows from a) after reversing the time direction.

c) ($\Rightarrow$ For the relation established in equation (2.5), and parts a) and b) it follows that $\mathbf{x} \in L_i \cap M_j$ for some $i = 1, 2, \ldots, p$ and some $j = 1, 2, \ldots, q$.

($\Leftarrow$ $\mathbf{x} \in L_i \cap M_j$ for some $i = 1, 2, \ldots, p$ and $j = 1, 2, \ldots, q$. Since each m_j and l_i are continuous functions, when $m_j(\mathbf{x}) < 0$ then $m_j(\phi(\mathbf{x}, t)) < 0$ for $t > 0$ sufficiently small. Similarly $l_i(\mathbf{x}) < 0$ then $l_i(\phi(\mathbf{x}, t)) < 0$ for $t < 0$ sufficiently small.

On the other hand, if $m_j(\mathbf{x}) = 0$, this is $\mathbf{x} \in M_j$ for some j, then

$$\phi(x, (-\varepsilon_j, 0)) \subset \mathbb{R}^n \setminus \overline{V}$$

and

$$m_j(\phi(\mathbf{x}, t)) < 0 \text{ if } \quad 0 < t < \varepsilon_j \quad \text{for some} \quad \varepsilon_j > 0$$

Similarly, $l_i(x) = 0$, this is $\mathbf{x} \in L_i$ for some i, then

$$\phi(x, (0, \varepsilon_i)) \subset \mathbb{R}^n \setminus \overline{V}$$

and

$$l_i(\phi(x, t)) < 0 \quad \text{if} \quad -\varepsilon_i < t < 0 \quad \text{for some} \quad \varepsilon_i > 0.$$

Let $\varepsilon = min\{\varepsilon_i, \varepsilon_j\}$. Therefore, $\phi(x, t) \in \mathbb{R}^n \setminus \overline{V}$ for $(-\varepsilon, 0) \cup (0, \varepsilon)$, hence $\mathbf{x}$ is an outward tangency point.

□

Note. When considering a polyfacial set V for the differential equation

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}),$$

based on the previous Proposition 2.4.1 we can determine when a point $\mathbf{x} \in \partial V$ is either strict egress point, strict ingress point or outward tangency point. Other possibilities hold when the inequalities 2.2 are not strict. See example presented in Chapter 4 where the origin is an equilibrium point, it is in the boundary of the set V and is not either egress, ingress or outward tangency point.

In this work we will use part a) of the Proposition's proof to show that a given point of $\mathbf{x}$ in the boundary of V is a strict ingress points.

An extended version of the Ważewski method for equations without the uniqueness of IVP and with weak inequalities 2.2 is presented in [20, pp.614-617].

2.5 Ważewski theorem

Next, we will consider a particular case of the theorem presented by Ważewski in [22]. The Ważewski method and several extensions are discussed in [20, Chapter 7].

Assume that the equation $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ generates a local flow. Let I^* denote the set of ingress points, and I the set of strict ingress points with respect to $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$. Although the theorem is usually presented in terms of the egress points to better suit our purposes we present the theorem in terms of the ingress points.

Theorem 2.5.1 (Ważewski principle)**.** *Let V be an open set in $\mathbb{R}^n$, with I^* and I the set of ingress and strict ingress points with respect to $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ respectively. If $I^* = I$ and there is a set $Z \subset V \cup I$ such that*

- *$Z \cap I$ is a retract of I, and*
- *$Z \cap I$ is not a retract of Z.*

Then, there exist at least a point $\mathbf{x}_0 \in Z \setminus I$ such that $\phi(\mathbf{x}_0, (\alpha_{\mathbf{x}_0}, 0])$, the negative semitrajectory of $\mathbf{x}_0$, is contained in V.

Proof. Let us consider a point $\mathbf{x}_0 \in V$ such that $\phi(\mathbf{x}_0, (\alpha_{x_0}, 0]) \cap (\mathbb{R}^n \setminus V) \neq \emptyset$, that is, part of the local trajectory through $\mathbf{x}_0$ lies outside of V. The previous property of the trajectory passing through $\mathbf{x}_0$ implies that there is a first time t_{x_0} for which $\phi(\mathbf{x}_0, t_{x_0}) \in I$ and $\phi(\mathbf{x}_0, t) \in V$ for $t \in [0, t_{x_0})$. Let us refer to the point $\phi(\mathbf{x}_0, t_{x_0})$ as the consequent of $\mathbf{x}_0$ and denote it as $C(\mathbf{x}_0)$, see Figure 2.2. Let us now collect all the points in V such that its consequent exist in the set $G = \{\mathbf{x}_0 \in V : C(\mathbf{x}_0) \text{ exist}\}$.

In the next step we will establish a relationship between points that are in G with points lying in I. Let us define the map $K : G \cup I \to I$ such that

$$K(\mathbf{x}) = C(\mathbf{x}) \quad \text{if} \quad \mathbf{x} \in G$$

and

$$K(\mathbf{x}) = \mathbf{x} \quad if \quad \mathbf{x} \in I.$$

We first prove that K is continuous and therefore a retraction from $G \cup I$ to I.

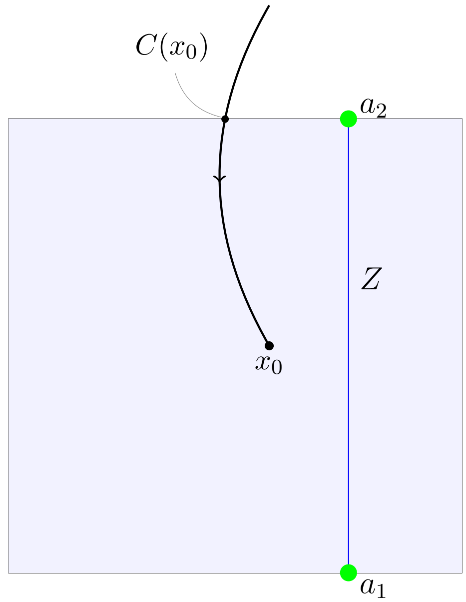


Figure 2.2: Same as in example 2.3.1, the set of strict ingress points I, are the open horizontal sides of the square. The set $Z = \{(\mathbf{x}_0, x_2) \mid |\mathbf{x}_0| < 1, |\mathbf{x}_2| \leq 1\}$ and $Z \cap I = \{a_1, a_2\}$ is a retract of I but is not a retract of Z since Z is a connected set.

- If $\mathbf{x} \in G$ and $C(\mathbf{x}) = \phi(\mathbf{x}, t_x)$, since $I = I^*$ there is a $\varepsilon_0 > 0$ such that

$$\phi(C(\mathbf{x}), (0, \varepsilon_0)) \subset V$$

  and

$$\phi(C(\mathbf{x}), (-\varepsilon_0, 0)) \in \mathbb{R}^n \setminus V.$$

  Since $\phi(\mathbf{x}, s)$ is continuous in $(\mathbf{x}, s)$, for any $\varepsilon > 0$, there is an $\delta > 0$ such that $\|\phi(\mathbf{y}, s) - \phi(\mathbf{x}, s)\| < \varepsilon$ for $s \in (-\varepsilon_0, \varepsilon_0)$ whenever $\|\mathbf{y} - \mathbf{x}\| < \delta$. This implies that $C(\mathbf{y}) \to C(\mathbf{x})$ if $\mathbf{y} \to \mathbf{x}$.

- The case where $\mathbf{x} \in I$ follows the same argument about the continuity of $\phi(\mathbf{x}, t)$.

Therefore, since K is a continuous function, we have shown that I is a retract of $G \cup I$.

Finally, let us assume that the conclusion of the theorem is not true.

Let us suppose that for all $\mathbf{x}_0 \in Z \setminus I$ there exist its consequent $C(\mathbf{x}_0)$. The fact that

$$(Z \setminus I) \subset G \quad \text{implies that} \quad Z \subset G \cup I.$$

Since we assume that $Z \cap I$ is a retract of I, there exist a continuous map

$$H : I \to Z \cap I$$

such that

$$H(\mathbf{x}) = \mathbf{x} \quad \text{for} \quad \mathbf{x} \in Z \cap I.$$

The composition map

$$(H \circ K) : G \cup I \to Z \cap I \quad \text{is continuous}$$

and

$$(H \circ K)(\mathbf{x}) = \mathbf{x} \quad \text{for} \quad \mathbf{x} \in Z \cap I.$$

Therefore $Z \cap I$ is a retract of $G \cup I$. However, since $Z \subset G \cup I$, the map

$$(H \circ K) : Z \to Z \cap I$$

is a retraction of Z into $Z \cap I$ which is a contradiction.

$\square$

Chapter 3

Michaelis-Menten Model

In this chapter we explore some of the properties of the **Michaelis-Menten model** which is the one of the simplest approaches to study reactions that are catalyzed by enzymes.

3.1 One Substrate Reaction

The **Michaelis-Menten model** is one of the simplest approaches to study reactions that are catalyzed by enzymes. **Enzymes** which are mostly proteins, have great catalytic power and specificity. They can accelerate the rate of a chemical reaction by a factor of a million or more. This allows an enzyme-catalyzed reaction to occur in milliseconds compared to the years it could take without the catalyzing enzyme. A table comparing the estimated non-enzymatic reaction rate constants and the catalytic proficiency of some enzymes can be found in [1, Ch 8]. Enzymes are highly specific, they usually catalyze only one reaction, or a set of related reactions, and act with only one reactant which is called **substrate**. These two main properties of enzymes, great catalytic power and high specificity, are considered when modeling enzyme-catalyzed reactions.

The **Michaelis-Menten model** models a single substrate binding to the active site on the enzyme leading to the formation of the reaction's product. The reduced form of the model presented below assumes an intermediate step in the catalysis of substrate to product, the formation of an enzyme-substrate complex from which product and enzyme are released. Schematically this is represented as

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \overset{k_2}{\rightarrow} P + E \tag{3.1}$$

The enzyme E combines with the substrate S to form the enzyme-substrate complex ES at a constant rate k_1. The ES complex can either dissociate to E and S with a rate constant k_{-1} or it can lead to the formation of product P with a rate constant k_2. In this scheme, another assumption made is that the product never binds the free enzyme, this can be the case in the initial stage of the reaction when concentration of product is very low or motivated by the fact that in the laboratory, measurements of reactions rates are typically carried out in the absence of product. The reversible case is consider for example in [11, 15].

3.1.1 Associated System of Differential Equations

We will use $[\cdot]$ to denote concentration of the reactants, then let

$$s(t) = [S], e(t) = [E], c(t) = [ES] \quad \text{and} \quad p(t) = [P]$$

to represent the concentration at a given time t of substrate, enzyme, enzyme-substrate complex and reaction's product respectively. Hereafter, we assume the variables satisfy $s > 0$, $e, c, p \geq 0$. The non-negativity of solutions of chemical kinetics systems when the initial values are non-negative is known to hold, see for example [21, Ch.12]. We also assume the parameters $k_1, k_{-1}, k_2 > 0$.

Applying the law of mass action, the reaction network (3.1) can be modeled by the following system of differential equations

$$\begin{aligned} \dot{s} &= -k_1 se + k_{-1} c, \\ \dot{e} &= -k_1 se + k_2 c + k_{-1} c, \\ \dot{c} &= k_1 se - (k_2 + k_{-1}) c, \\ \dot{p} &= k_2 c. \end{aligned} \tag{3.2}$$

The system (3.2) has two linear conservation relations. Note that $\dot{e} + \dot{c} = 0$, if we assume $c(0) = p(0) = 0$, this implies $e(t) + c(t) = e_0$, where e_0 is the initial concentration of the enzyme. Also, note that $\dot{s} + \dot{c} + \dot{p} = 0$, thus $s(t) + c(t) + p(t) = s_0$, where $s_0 > 0$ is the initial concentration of the substrate. Hence, an insight of system (3.2) can be gained by analyzing

$$\begin{aligned} \dot{s} &= -k_1 s(e_0 - c) + k_{-1} c, \\ \dot{c} &= k_1 s(e_0 - c) - (k_2 + k_{-1}) c, \\ \dot{p} &= k_2 c. \end{aligned} \tag{3.3}$$

In Figure 3.1 we present a simulation of system (3.3) where a separation of timescales can be observed. On the fast timescale, formation of enzyme-substrate complex c occurs very fast, it remains fairly steady until much of the substrate has been consumed and then falls again to zero. The falling of c takes longer when $e(0) = e_0$ is small compared to $s(0) = s_0$. The formation of product proceeds on the slower timescale.

3.2 Rapid Equilibrium and Quasi-Steady-State Assumptions

The **rapid equilibrium and quasi-steady-state assumptions** (hereafter abbreviated REA and QSSA respectively), are two common approaches for model reduction by separation of timescales. More information about these approach can be found for example in [11, 15, 17].

We present below two approximations for the concentration of complex C which later are used to describe a polyfacial set for the differential system of equations (3.3). These approximations are obtained following the assumptions made in the REA and QSSA.

In the network (3.1) that we are considering, there are two processes involved, the reversible association/dissociation $S+E \leftrightarrow C$ and the product formation where $C \to P+E$. The time constants for those reactions events are respectively

$$t_1 = \frac{1}{k_1 + k_{-1}}$$

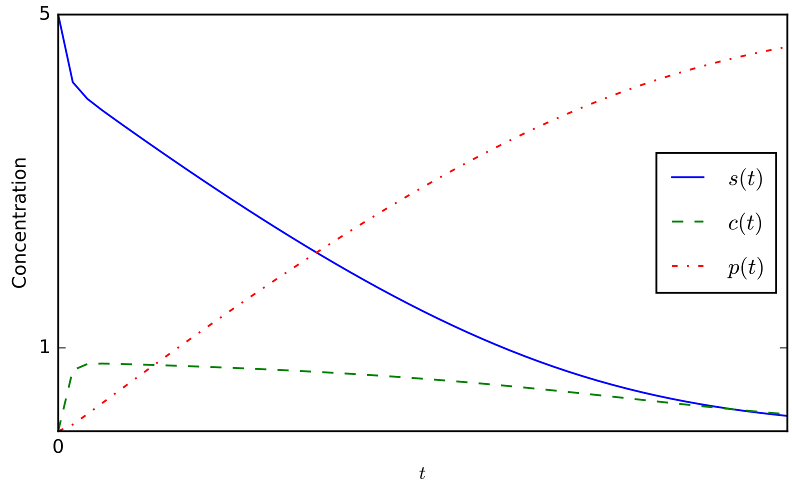


Figure 3.1: Simulation of the Michaelis-Menten system (3.3). Two timescales can be observed, one is the transient timescale, near $t = 0$. The complex C reaches its quasi-steady state. The product formation proceeds on the slower timescale, the substrate concentration changes significantly while the concentration of C remains along its quasi-steady state for some time. The parameter values used are $k_1 = 40$, $k_{-1} = 20$, $k_2 = 16$, $c(0) = p(0) = 0$, $s_0 = 5$ and $e_0 = 1$.

and

$$t_2 = \frac{1}{k_2}.$$

If $t_1 \ll t_2$ this can be thought as if the association/dissociation process reaches equilibrium faster compared to the product formation process.

The differentiable equations associated with the reversible association/dissociation reaction are

$$\begin{aligned}\dot{s} &= -k_1 se + k_{-1}c,\\ \dot{c} &= k_1 se - k_{-1}c,\\ \dot{e} &= -k_1 se + k_{-1}c.\end{aligned} \tag{3.4}$$

In the **REA** we assume that the association/dissociation reaction (3.4) is in equilibrium at all times. This is translated to have $\dot{s} = \dot{c} = 0$ from where we obtain the following expression

$$c = \frac{k_1}{k_{-1}} se.$$

Using that $e(t) = e_0 - c(t)$, the REA the approximation for c is

$$c_{re} = \frac{k_1 e_0 s}{k_{-1} + k_1 s}. \tag{3.5}$$

A second approximation for c is given by the **QSSA** which is justified assuming two things. First, a difference in the time constants, $t_1 \ll t_2$. This can be interpreted as if the reactions involving complex C occurs on the fast timescale. Second, there is an assumption about the concentration of s, it is assumed that $s \gg e_0$. With the two previous assumptions in mind we have that the enzyme-substrate complex reaches quickly its steady-state concentration compared to the substrate.

If c is in its quasi-steady state, from system (3.3) it satisfies

$$0 = k_1 s(e_0 - c) - (k_2 + k_{-1})c.$$

Solving for c we get

$$c_{ss} = \frac{k_1 s e_0}{k_2 + k_{-1} + k_1 s}. \tag{3.6}$$

3.3 Nondimensionalization of the system.

Multiscale phenomena it is often approached using singular perturbation methods. A first step in such case is to identify a small parameter from the system. For the QSSA, we required that $s_0 \gg e_0$, thus a possible small parameter for the system is given by $\varepsilon = e_0/s_0$.

Next, we rewrite system (3.3) as a singular perturbation problem. This can be done in several ways see for example [3, 8, 15, 17, 18]. We follow the one presented in [8, 15, 17]. Let $s_0 = s(0)$, $e_0 = e(0)$ and

$$K_m = \frac{k_{-1} + k_2}{k_1},$$

where K_m is called the Michaelis constant. Consider the following dimensionless quantities:

$$\begin{aligned}\varepsilon &= \frac{e_0}{s_0}, \quad K = \frac{k_{-1}+k_2}{k_1 s_0} = \frac{K_m}{s_0},\\ \lambda &= \frac{k_2}{k_1 s_0}, \quad \tau = k_1 e_0 t,\\ u(\tau) &= \frac{s(t)}{s_0}, \quad v(\tau) = \frac{c(t)}{e_0}.\end{aligned} \tag{3.7}$$

The non-dimensional form of system (3.3) is

$$\begin{aligned}u' &= -u + (u + K - \lambda)v,\\ \varepsilon v' &= u - (u+K)v.\end{aligned} \tag{3.8}$$

Where the initial conditions are now $u(0) = 1$ and $v(0) = 0$. With solutions for v and u we can find the other two variables. Recall that $e(t) = e_0 - c(t)$ thus $e(\tau) = e_0 - e_0 v(\tau)$. To determine $p(t)$ we should solve $P' = \lambda v$ where $P(\tau) = p(t)/s_0$.

In the system (3.8) the derivatives are with respect to the variable τ. The variables u and v, represent the scaled substrate and complex concentrations respectively. Note that the parameters are now $0 \le \varepsilon < 1$, K and λ with $K - \lambda = k_{-1}/k_1 s_0 > 0$. In the framework of singular perturbation theory, ε is a singular perturbation parameter and K, λ are ordinary parameters.

The equivalent non-dimensional form of equations (3.5) and (3.6) are given as follows

$$v_{re}(\tau) = \frac{u(\tau)}{K - \lambda + u(\tau)}, \tag{3.9}$$

and

$$v_{ss}(\tau) = \frac{u(\tau)}{K + u(\tau)}. \tag{3.10}$$

3.3.1 Equilibrium points

It is easy to check that when $\varepsilon > 0$ the only equilibrium point of the system (3.8) is $(u, v) = (0, 0)$. Next we show it is asymptotically stable.

Proposition 3.3.1. *If $\varepsilon > 0$, the system (3.8) has an asymptotically stable equilibrium point at the origin.*

Proof. The Jacobian matrix at the origin is

$$J(0,0) = \begin{bmatrix} -1 & K-\lambda \\ \frac{1}{\varepsilon} & \frac{-K}{\varepsilon} \end{bmatrix}.$$

It has distinct eigenvalues ν_1 and ν_2 such that

$$\nu_1 = \frac{-(\frac{K}{\varepsilon}+1) + \sqrt{(\frac{K}{\varepsilon}+1)^2 - \frac{4\lambda}{\varepsilon}}}{2} = \frac{-(K+\varepsilon) + \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda}}{2\varepsilon},$$

and

$$\nu_2 = \frac{-(\frac{K}{\varepsilon}+1) - \sqrt{(\frac{K}{\varepsilon}+1)^2 - \frac{4\lambda}{\varepsilon}}}{2} = \frac{-(K+\varepsilon) - \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda}}{2\varepsilon}.$$

We show next that both eigenvalues are real. Note that $\lambda = K - \frac{k_{-1}}{k_1 s_0}$, therefore the discriminant is

$$\begin{aligned} K^2 + 2\varepsilon K + \varepsilon^2 - 4\varepsilon\lambda &= K^2 + 2\varepsilon K + \varepsilon^2 - 4\varepsilon K + \frac{4k_{-1}}{k_1 s_0} \\ &= K^2 - 2\varepsilon K + \varepsilon^2 + \frac{4k_{-1}}{k_1 s_0} \\ &= (K-\varepsilon)^2 + \frac{4k_{-1}}{k_1 s_0} > 0. \end{aligned}$$

Since the discriminant is positive, ν_1 and ν_2 are real-valued eigenvalues.

Finally, note that $n_2 < n_1$. After few steps we can justify that $\nu_1 < 0$ having both eigenvalues being real and negative. Simply note that

$$\begin{aligned} 2\varepsilon\nu_1 &= -(K+\varepsilon) + \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda} \\ &= \left(-(K+\varepsilon) + \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda}\right)\left(\frac{-(K+\varepsilon) - \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda}}{-(K+\varepsilon) - \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda}}\right) \\ &= \frac{4\varepsilon\lambda}{-(K+\varepsilon) - \sqrt{(K+\varepsilon)^2 - 4\varepsilon\lambda}} < 0. \end{aligned}$$

Therefore, since the eigenvalues of the Jacobian matrix ν_1, ν_2 are real and satisfy

$$\nu_1 < \nu_2 < 0,$$

the origin is an asymptotically stable equilibrium point. □

3.3.2 Phase portrait

In this section we will explore the qualitative behaviour of solutions to the system (3.8). First, let us reconsider equations (3.5) and (3.6) but now as functions of the variable u. This is, let

$$V_{re}(u) = \frac{u}{K - \lambda + u}, \tag{3.11}$$

and

$$V_{ss}(u) = \frac{u}{K + u}. \tag{3.12}$$

In the $uv-plane$, when $\varepsilon \neq 0$, equations (3.11) and (3.12) coincide with the zero isoclines of the system. This is, they are solutions to $u' = 0$ and $v' = (1/\varepsilon)(u - (u + K)v) = 0$.

The qualitative behaviour of solutions can be observed in the sketch of the phase portrait presented in Figure 3.2. The origin is the only equilibrium and is asymptotically stable. We can observe that the two zero isoclines (3.11) and (3.12) describe similar curves and form a narrowing region in which trajectories eventually enter and never leave. After solutions enter this trapping region, they follow along the isoclines. Note that trajectories get very close to the horizontal isocline for small ε as u gets large. This will be consistent with the fact that QSSA agrees with the real solutions as they approach to its steady state.

Inside the region described by the zero isoclines, there appears to be an exceptional solution that stays inside and attracts all other solutions. This exceptional solution is often called *the slow manifold* and will be denoted $\mathcal{M}$. The name and notation of $\mathcal{M}$ comes from the framework of geometric singular perturbation theory. We will give a brief description below.

Several authors have observed and give detail descriptions of slow manifolds that attract other solutions. See for example the work of Calder and Siegel [2, 3], Fraser and Roussel [18], Fraser [7] where different arguments are used to prove the existence and uniqueness

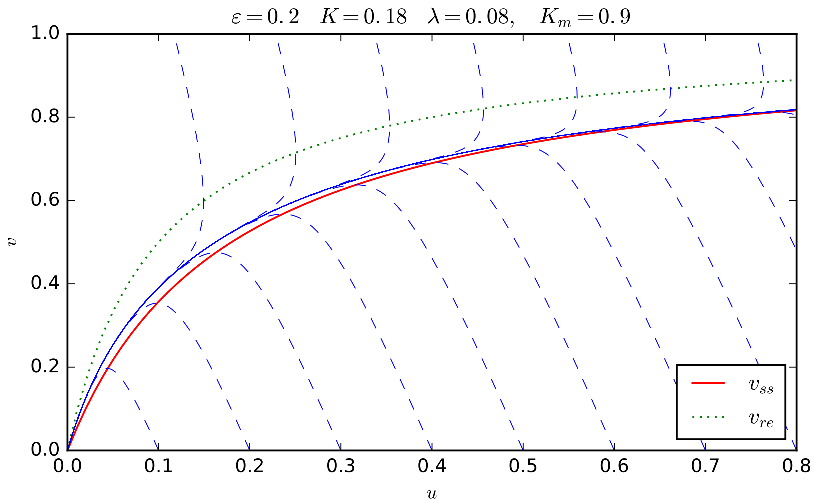


Figure 3.2: Simulation of the non-dimensional system (3.8). The trajectories have been obtained by numerical integration of the system. Parameters were chosen such that assumptions for REA and QSSA were satisfied, see section 3.2. The parameter values used are $k_1 = 40$, $k_{-1} = 20$, $k_2 = 16$, $c(0) = p(0) = 0$, $s_0 = 5$ and $e_0 = 1$.

of $\mathcal{M}$ in planar systems. In chapter 4, using the Ważewski theorem, we will give a description of such region as a polyfacial set V and prove the existence and uniqueness of a slow manifold $\mathcal{M}$ that stays inside V and attracts all the other trajectories.

3.3.3 Fast-slow systems and the slow manifold

A natural framework for the analysis of systems like (3.13) is provided by geometric singular perturbation theory (GSPT). In this work we are following the same notation used when treating slow-fast systems with GSPT. In this section we introduce some of the geometric constructs and concepts relevant for this work.

A first necessary step is the introduction of a small parameter ε. If we assume the initial amount of substrate is more abundant than the total enzyme, the chosen small parameter is $\varepsilon = e_0/s_0$. The system of interest is given as follows

$$\begin{aligned} u' &= -u + (u + K - \lambda)v, \\ \varepsilon v' &= u - (u + K)v. \end{aligned} \tag{3.13}$$

The variables u and v are functions of variable τ and the prime denotes differentiation with respect to τ. Initial conditions are $u(0) = 1$ and $v(0) = 0$. The variable τ is called the *slow time* because it defines the time-scale on which the slow variables evolve.

In the context of geometric singular perturbation theory, system (3.13) is usually studied along with its reformulation in terms of another scale of time. If $\varepsilon > 0$, let us define the fast time scale given by $\hat{t} = \tau/\varepsilon$. The system obtained where the dot denotes differentiation taken with respect to the variable $\hat{t}$ is

$$\begin{aligned} \dot{u} &= \varepsilon(-u + (u + K - \lambda)v), \\ \dot{v} &= u - (u + K)v. \end{aligned} \tag{3.14}$$

Note that whenever $\varepsilon \neq 0$, the so called *fast system* (3.14) and *slow system* (3.13) are equivalent. There are two limiting behaviours associated with the case $\varepsilon \to 0$. If $\varepsilon = 0$, we have the following two reduced cases:

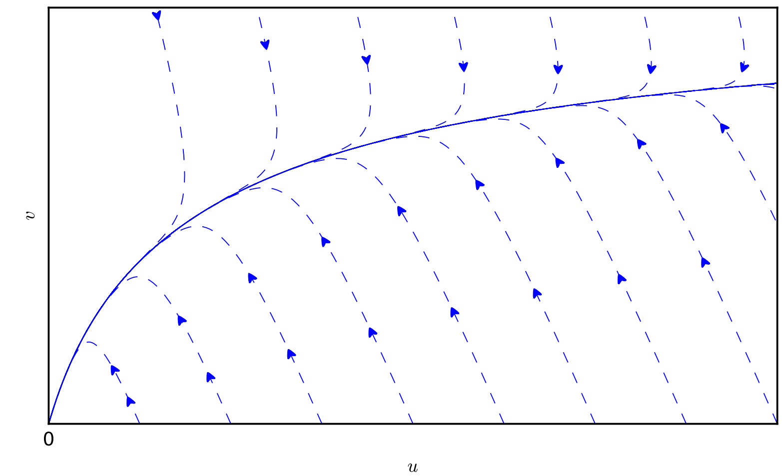
$$\begin{aligned} u' &= -u + (u + K - \lambda)v, \\ 0 &= u - (u + K)v, \end{aligned} \tag{3.15}$$

and

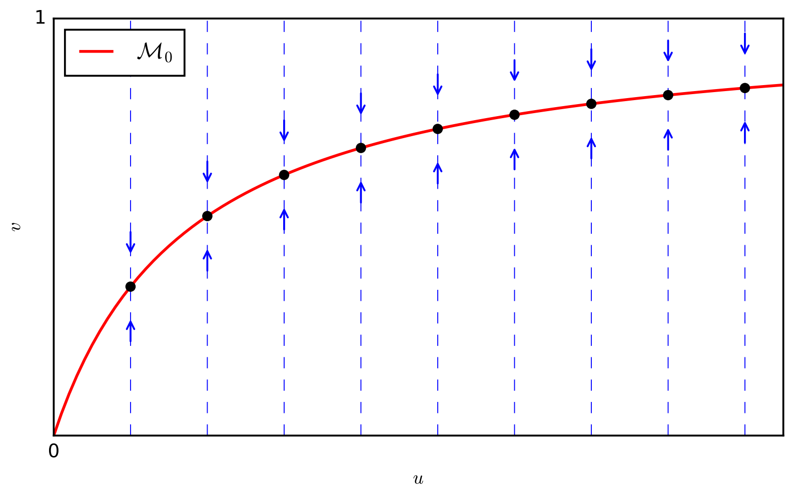
$$\begin{aligned} \dot{u} &= 0, \\ \dot{v} &= u - (u + K)v. \end{aligned} \tag{3.16}$$

The first equation of the reduced slow system (3.15), describes the rate of change of the slow variable u. The second equation, corresponds to the zero level set of the function $g(u, v) = u - (u + K)v$, it gives an algebraic constraint delimiting the dynamics of u to occur in there. Furthermore, in the phase space, the zero level set of g is a one-dimensional manifold $\mathcal{M}_0$ given by $\mathcal{M}_0 = \{(u, v) \mid v = \frac{u}{K+u}\}$, it describes the graph of (3.12). On the other hand, from the perspective of the reduced fast system (3.16), $\mathcal{M}_0$ is a manifold of fixed points thus trivially invariant. See Figure 3.3 for phase portraits of systems (3.14) and (3.16).

Proposition 3.3.2. *Each point $(u, \frac{u}{K+u})$ on $\mathcal{M}_0$ is an asymptotically stable fixed point of $\dot{v} = u - (u + K)v$ (second equation in the reduced fast system (3.16)).*



(a) Phase portrait of system (3.14), $0 < \varepsilon \ll 1$.



(b) Phase portrait of system (3.16), $\varepsilon = 0$.

Figure 3.3: Sketch of the phase portraits of the fast and reduced fast system.

Proof. Note that considering the whole system (3.16) we have that u is constant. If $v < \frac{u}{K+u}$ then $\dot{v} > 0$ and if $v > \frac{u}{K+u}$ we have $\dot{v} < 0$.

Keeping in mind that u is constant, if we look at the Jacobian (a 1-dimensional matrix), it has a negative eigenvalue which is given by $-(u+K)$. Therefore $v = \frac{u}{K+u}$ is asymptotically stable. $\square$

Since each point $(u, \frac{u}{K+u})$ on $\mathcal{M}_0$ is a hyperbolic fixed point of the reduced fast system (3.16), $\mathcal{M}_0$ is a *normally hyperbolic invariant manifold.*

Fenichel's theory, which applies to case where $\mathcal{M}_0$ is a compact manifold without boundary, gives conditions under which NHIM persist when the perturbation is turned on. This establishes that if in the limit $\varepsilon \to 0$, the system has a normally hyperbolic invariant manifold $\mathcal{M}_0$, then there exist manifolds $\mathcal{M}_\varepsilon$ for ε sufficiently small positive. The persistent manifolds, $\mathcal{M}_\varepsilon$, are labeled *slow manifolds.* Using tools from GSPT, it is possible to give a complete geometric and analytical description of all solutions in the vicinity of $\mathcal{M}_\varepsilon$, also, to say something about how trajectories approach the manifold. For results in compact NHIM see for example Fenichel's work [6], Jones [12] or Sakamoto [19]. The noncompact case is presented for example by Eldering in [5].

In section 3.3.2, we presented the phase portrait of the system 3.13 for the case where $0 < \varepsilon < 1$. We mentioned that it appears to be an exceptional solution, $\mathcal{M}$, that stays inside the region delimited by the zero isoclines and attracts all other solutions. According to the concepts that we have just presented, this solution is a slow manifold. Note that in the uv-plane, the graph of the horizontal isocline of system (3.13), agrees with the set described by $\mathcal{M}_0$. In this work we will not use GSPT to further analyze system (3.13). Instead, in chapter 4 we will give a description of the region delimited by the zero isoclines in terms of polyfacial sets. Later we prove the existence and uniqueness of a slow manifold $\mathcal{M}_\varepsilon$ that is fully contained in the set. We will use the Ważewski theorem to prove its existence.

Chapter 4

Application of Ważewski Theorem in the Michaelis-Menten system

In this chapter we present an argument based on the Ważewski Principle to show there exist a unique trajectory $\mathcal{M}$ fully contained in a given region. To illustrate the concepts and results we are considering the Michaelis-Menten model whose dimensionless form is given as follows

$$\begin{aligned} u' &= -u + (u + K - \lambda)v, \\ \varepsilon v' &= u - (u + K)v, \end{aligned} \tag{4.1}$$

where $0 < \varepsilon \ll 1$ and the parameters K, λ are defined in section 3.3. First we will go over the description of the region in question, whose construction comes from what is called a *polyfacial set*. Such construction is based on the existence of continuous functions which behave similarly to Liapunov functions on some parts of their zero-levels sets. For the construction of the polyfacial set we are using the functions given by the QSSA and REA which where discussed in great detail in Chapter 3.

4.1 Existence and uniqueness of the slow manifold

In what follows it will be useful to rewrite system (4.1) in the following form. If $0 < \varepsilon \ll 1$ let

$$\mathbf{x}' = \mathbf{F}(\mathbf{x}), \tag{4.2}$$

where

$$\mathbf{x} = \begin{bmatrix} u \\ v \end{bmatrix}$$

and

$$\mathbf{F}(\mathbf{x}) = \begin{bmatrix} -u + (u + K - \lambda)v \\ (1/\varepsilon)(u - (u + K)v). \end{bmatrix}$$

4.1.1 Polyfacial set

Consider the following continuously differentiable functions $m_1, m_2 : \mathbb{R}^2_{\geq 0} \to \mathbb{R}$ given as follows:

$$m_1(u, v) = u - (u + K)v$$

and

$$m_2(u, v) = -u + (u + K - \lambda)v.$$

The polyfacial set determined by the set of functions $\{m_1, m_2\}$ is defined as

$$\begin{aligned} V &= \{(u, v) \in \mathbb{R}^2_{>0} \mid \ m_1(u, v) < 0,\ m_2(u, v) < 0\} \\ &= \{(u, v) \in \mathbb{R}^2_{>0} \mid \ \frac{u}{u + K} < v < \frac{u}{u + K - \lambda}\}. \end{aligned} \tag{4.3}$$

Consider also the following sets

$$M_1 = \{(u, v) \in \partial V \mid \ m_1(u, v) = 0\} = \{(u, v) \in \partial V \mid \ v = \frac{u}{u + K}\},$$

and

$$M_2 = \{(u, v) \in \partial V \mid \ m_2(u, v) = 0\} = \{(u, v) \in \partial V \mid \ v = \frac{u}{u + K - \lambda}\}.$$

Note. With respect to section 2.4, since the origin is an asymptotically stable equilibrium point, the "L_i" sets are empty. This also implies that the set of egress and outward tangency points of V with respect to (4.2) are empty too.

4.1.2 Set of strict ingress points

Let $\mathbf{x} = (u, v) \in \overline{V}$ and ϕ be the local flow generated by (4.2). Recall that the set of egress points of V is empty, thus when $\mathbf{x} \in \partial V$, $\mathbf{x}$ is either an ingress point or an equilibrium point. We have shown in previous Chapter 3 the origin is the only equilibrium point and is locally asymptotically stable. Below we prove that if $\mathbf{x} \in \partial V$ and $\mathbf{x} \neq (0,0)$, then it is a strict ingress point.

Proposition 4.1.1. *The set of strict ingress points of V with respect to (4.2) is given by*

$$I = (M_1 \cup M_2) \setminus (0,0).$$

Furthermore, V is positively invariant.

Proof. 1. If $(u, v) \in M_1$ and $(u, v) \neq (0,0)$ then $v = \frac{u}{u+K}$.

$$\begin{aligned}
\mathbf{F}(u,v) \cdot (1-v, -(u+K)) &= (1-v)\left(-u + (u+K-\lambda)\right) - \left(\frac{u+K}{\varepsilon}\right)(u - (u+K)v) \\
&= \left(1 - \frac{u}{u+K}\right)\left(-u + (u+K-\lambda)\left(\frac{u}{u+K}\right)\right) \\
&= \frac{-\lambda K u}{(u+K)^2} < 0.
\end{aligned} \tag{4.4}$$

2. If $(u, v) \in M_2$ and $(u, v) \neq (0,0)$ then $v = \frac{u}{u+K-\lambda}$.

$$\begin{aligned}
\mathbf{F}(u,v) \cdot (-1+v, u+K-\lambda) &= (v-1)\left(-u + (u+K-\lambda)\right) + \left(\frac{u+K-\lambda}{\varepsilon}\right)(u - (u+K)v) \\
&= \left(\frac{u+K-\lambda}{\varepsilon}\right)\left(u - (u+K)\left(\frac{u}{u+K-\lambda}\right)\right) \\
&= \frac{-\lambda u}{\varepsilon} < 0.
\end{aligned} \tag{4.5}$$

Hence, when $(u, v) \neq (0,0)$ the normal vectors to the surfaces described by $m_i = 0$, $i = 1, 2$, and the vector field are pointing to opposite directions. The set of strict ingress points of V with respect to (4.2) is given by

$$I = (M_1 \cup M_2) \setminus (0,0).$$

Furthermore, once solutions enter V they stay there since

$$F(u,v) \cdot \nabla m_1(u,v) < 0$$

and

$$F(u,v) \cdot \nabla m_2(u,v) < 0.$$

Therefore V is a invariant set.

□

4.1.3 An application of the Ważewski theorem

To use the Ważewski theorem we should find a set $Z \subset V \cup I$ satisfying the following two conditions:

1. $Z \cap I$ is a retract of I
2. $Z \cap I$ is not a retract of Z.

A simple choice of the set Z is given as follows. For a given value of $u = u_0 > 0$, take

$$Z = \left\{ (u,v) \mid u = u_0 > 0, \ \frac{u}{u+K} \leq v \leq \frac{u}{u+K-\lambda} \right\}. \tag{4.6}$$

A description of Z and $Z \cap I$ is sketched in Figure 4.1.

Proposition 4.1.2. *Let $u = u_0 > 0$, $a_1 = \frac{u_0}{u_0+K}$ and $a_2 = \frac{u_0}{u+K-\lambda}$. The set $Z \cap I = \{a_1, a_2\}$ is a retract of I but is not a retract of Z.*

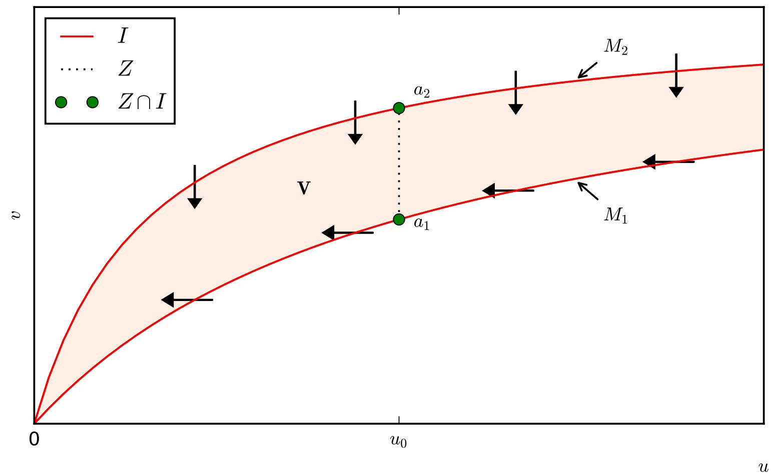


Figure 4.1: The set V is represented in the shaded area. The set of strict ingress points of set V with respect to the system (4.2) is $I = (M_1 \cup M_2) \setminus (0,0)$. The set $Z \cap I = \{a_1, a_2\}$ is a retract of I but is not a retract of Z.

Proof. For the first part of the statement, consider the function $r : I \to Z \cap I$ define as follows

$$r(u,v) = \begin{cases} (u_0, a_1) \ if \ (u,v) \in M_1 \\ (u_0, a_2) \ if \ (u,v) \in M_2. \end{cases}$$

The function r, is continuous and the identity when the domain is restricted to $Z \cap I$. Therefore, r is a retraction from I to $Z \cap I$.

On the other hand, $Z \cap I = \{a_1, a_2\}$ is not a connected set on the uv-plane. Using Theorem 2.1.2 we can justify that $Z \cap I$ is not a retract of Z. $\square$

In section 3.3.2, we presented the phase portrait of the system 4.1 for the case where $0 < \varepsilon < 1$. We mentioned that it appears to be an exceptional solution, $\mathcal{M}$, that stays inside the region described here as the polyfacial set. In the following proposition we prove this statement.

Proposition 4.1.3. *Consider the sets V, I and Z as described above. There exist a slow manifold $\mathcal{M}$ for system (4.2) that is fully contained in the set V. Furthermore, the slow manifold $\mathcal{M}$ is the only trajectory that lies entirely inside V.*

Proof. Existence of $\mathcal{M}$ is given by the Ważewski Theorem 2.5.1. If the set Z is given by (4.6), we have shown in Proposition 4.1.2 that $Z \cap I$ is a retract of I but not a retract of Z therefore we can conclude there is at least an $\mathbf{x}_0 \in Z$ such that the negative semitrajectory of $\mathbf{x}_0$ is contained in V. Furthermore, since the set of egress points of V is empty we have that $\phi(\mathbf{x}_0, t)$ exists for $-\infty < t < \infty$ and $\phi(\mathbf{x}_0, t) \in V$ for all t. In such case,the slow manifold is given by

$$\mathcal{M}(\mathbf{x}_0) = \phi(x_0, t) \quad \text{where} \quad -\infty < t < \infty.$$

Uniqueness of $\mathcal{M}$ is justified by Proposition A.0.1 presented in Appendix A.

For the set described by V, let us consider the vertical cross sections given as follows

$$D_{u_0} = \left\{ (u_0, v) \in \mathbb{R}^2 \mid u_0 > 0, \quad \frac{u_0}{u_0 + K} \leq v \leq \frac{u_0}{u_0 + K - \lambda} \right\}.$$

For a given $u_0 > 0$, the diameter of the cross sections is given by

$$Diam(D_{u_0}) = sup\{\|p_1 - p_2\| \mid p_1, p_2 \in D_{u_0}\} = \frac{u_0 \lambda}{(u_0 + K - \lambda)(u_0 + K)}.$$

We can observe that $Diam(D_{u_0}) \to 0$ as $u_0 \to \infty$.

As in Proposition A.0.1, if $\varepsilon > 0$ and $(-u + (u + K - \lambda)v) \neq 0$ let

$$\frac{dv}{du} = \frac{u - (u + K)v}{\varepsilon(-u + (u + K - \lambda)v)} = g(u, v) \tag{4.7}$$

Next we will show that the distance between two solutions is nondecreasing if $\frac{\partial g}{\partial v} \geq 0$ in the region V.

Let us consider $v_1(u)$ and $v_2(u)$ two different solutions of system (4.7) in V. To simplify the argument, let us assume that $v_1(u) > v_2(u)$ and consider the difference of those two solutions. First note that

$$\begin{aligned}\frac{\partial g}{\partial v} &= \frac{\partial}{\partial v}\left(\frac{u-(u+K)v}{\varepsilon(-u+(u+K-\lambda)v)}\right)\\ &= \frac{1}{\varepsilon}\frac{\lambda u}{(-u+(u+K-\lambda)v)^2}\\ &\geq 0 \quad \text{when} \quad (u,v)\in V.\end{aligned}$$

Then, taking the derivative of $v_1(u) - v_2(u)$ we observe that

$$\begin{aligned}\frac{d}{du}(v_1(u)-v_2(u)) = g(u,v_1(u)) - g(u,v_2(u))\\ = \int_{v_2(u)}^{v_1(u)} \frac{\partial}{\partial v} g(u,s)ds \geq 0,\end{aligned}$$

which implies that the distance between v_1 and v_2 is nondecreasing.

Finally, since $Diam(D_{u_0}) \to 0$ as $u_0 \to \infty$ and the distance between v_1 and v_2 is nondecreasing there cannot be more that one solution that stays in V. Hence the slow manifold $\mathcal{M}$ is the only trajectory that lies entirely inside the polyfacial set V.

□

Chapter 5

Applications of the Ważewski Theorem for systems in $\mathbb{R}^3$

The main goal of this chapter is to present some of the ideas involved when trying to use the *Ważewski theorem* for systems whose dimension is greater than two.

5.1 A Toy Model

Let us consider the following system in $\mathbb{R}^3$

$$\begin{aligned}\dot{x} &= \lambda_1 x,\\ \dot{y} &= \lambda_2 y,\\ \dot{z} &= \lambda_3 z.\end{aligned} \tag{5.1}$$

where $\lambda_1 < \lambda_2 < \lambda_3 < 0$. In terms of slow/fast variables, the slow direction in this case is the z axis.

5.1.1 Polyfacial set

Similar to section 4.1.1 of Chapter 4, let us consider the continuously differentiable function $m_1 : R^3_{\geq 0} \to \mathbb{R}$ given as follows

$$m_1(x, y, z) = x^2 + y^2 - 1.$$

The polyfacial set determined by $\{m_1\}$ is

$$
\begin{aligned}
V &= \{(x,y,z) \in \mathbb{R}^3_{>0} \mid \ m_1(x,y,z) < 0\} \\
&= \{(x,y,z) \in \mathbb{R}^3_{>0} \mid \ x^2 + y^2 < 1\}.
\end{aligned} \tag{5.2}
$$

Note that V is a open set whose boundary includes the shell and bottom part of the vertical cylinder. The boundary of V it is described as follows

$$
\partial V = \{(x,y,z) \in \mathbb{R}^3_{\geq 0} \mid \ z > 0, \ x^2 + y^2 = 1\} \cup \{(x,y,z) \in \mathbb{R}^3_{\geq 0} \mid \ z = 0, \ x^2 + y^2 \leq 1\}.
$$

5.1.2 Set of strict ingress points

To determine the set of strict ingress points of V we should split the analysis into to cases.

- If $z > 0$, and $(x,y,z) \in \partial V$. This implies $m_1(x,y,z) = 0$ and the normal vector of the surface described is $(2x, 2y, 0)$. Therefore, the following inequality is satisfied

$$
\begin{aligned}
\mathbf{f}(x,y,x) \cdot \nabla m_1(x,y,z) &= (\lambda_1 x, \lambda_2 y, \lambda_3 z) \cdot (2x, 2y, 0) \\
&= 2\lambda_1 x^2 + 2\lambda_2 y^2 \\
&< 2\lambda_2 (x^2 + y^2) \\
&= 2\lambda_2 < 0.
\end{aligned} \tag{5.3}
$$

- If $z = 0$, and $(x,y,z) \in \partial V$. The normal vector of the surface described is $(0,0,1)$ and we have that

$$
\begin{aligned}
\mathbf{f}(x,y,x) \cdot (0,0,1) &= (\lambda_1 x, \lambda_2 y, \lambda_3 z) \cdot (0,0,1) \\
&= \lambda_3 z \\
&= 0 \quad \text{since} \quad z = 0
\end{aligned} \tag{5.4}
$$

Proposition 5.1.1. *The set of strict ingress points of V with respect to the system (5.1) is*

$$
I = \{(x,y,z) \in \partial V \mid \ z > 0, \ m_1 = 0\} = \{(x,y,z) \in \mathbb{R}^3_{>0} \mid \ x^2 + y^2 = 1\}.
$$

Proof. This is a consequence of inequality (5.3). The normal vectors to the surfaces described by $m_1 = 0$ and the vector field are pointing to opposite directions. □

In the following proposition we verify that the only equilibrium point of the system (5.1) is $(x, y, z) = (0, 0, 0)$ and it is asymptotically stable.

Proposition 5.1.2. *The system (5.1) has an asymptotically stable equilibrium point at the origin.*

Proof. The Jacobian matrix at the origin is

$$J(0,0,0) = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}.$$

It has distinct, real-valued eigenvalues

$$\lambda_1 < \lambda_2 < \lambda_3 < 0,$$

hence the origin is an asymptotically stable equilibrium point. $\square$

By the previous proposition, we have that the set of egress points of V with respect to the system (5.1) is empty.

Note. We haven not said what happens with the points at the bottom boundary of V. Since the xy plane is invariant, by inequality (5.4) the set of points

$$T = \{(x, y, z) \in \mathbb{R}^3_{\geq 0} \mid \ z = 0,\ x^2 + y^2 \leq 1\},$$

can not be classified according to definition 2.3 given in Chapter 2. However, the Ważewski theorem still applies in this case.

An extended version of the Ważewski method, which is not considered in this work, is presented in [20, pp.614-617]. It considers the case where IVP do not have unique solution and there are weak inequalities like 5.4.

5.1.3 Existence of the slow manifold

The Ważewski theorem provides conditions for the existence of a solution $\mathcal{M}$ that lies entirely in the polyfacial set V. Compared to the polyfacial set of the example presented in Chapter 4, here the set V is not "narrowing" as the slow variable increases. This condition was used before to show uniqueness. However, when $z = z_0$ for z_0 a positive constant, the cross sections of V are equal. This property of V will be useful when looking for conditions to justify uniqueness of $\mathcal{M}$.

Although we know that the z-axis is the trajectory that we are looking for, let us see how the Ważewski principle could be used in this case. For $z = z_0$ with z_0 a positive constant, let us consider the set

$$Z = \{(x, y, z_0) \in \mathbb{R}^3 \mid z_0 > 0,\ x^2 + y^2 \leq 1\},$$

which satisfies $Z \subset V \cup I$, see Figure 5.1.

Based on the conditions of Theorem 2.5.1 we should show that $Z \cap I$ is a retract of I but not a retract of Z. We prove this in the next steps

a) The set
$$Z \cap I = \{(x, y, z_0) \in \mathbb{R}^3 \mid z_0 > 0,\ x^2 + y^2 = 1\}$$
is a retract of I.
Let $r : I \to Z \cap I$ be the projection function given by $r(x, y, z) = (x, y, z_0)$. The function r is continuous and the identity when its domain is restricted to $Z \cap I$. Therefore r satisfies the conditions for being a retraction from I to $Z \cap I$.

b) the set $Z \cap I$ is not a retract of Z.
This is a direct application of the No Retraction Theorem 2.1.4.

Therefore by the Ważewski theorem, there is at least one point $p \in Z \setminus I$ such that the negative semitrajectory of p is contained in V. Since the set of egress points is empty, once solutions enter in V they do not leave, therefore we can conclude that the trajectory passing through p satisfies

$$\phi(p, t) \in V \quad \text{for all} \quad -\infty < t < \infty$$

In such case, the slow manifold is given by

$$\mathcal{M}(p) = \phi(p, t) \quad \text{where} \quad -\infty < t < \infty.$$

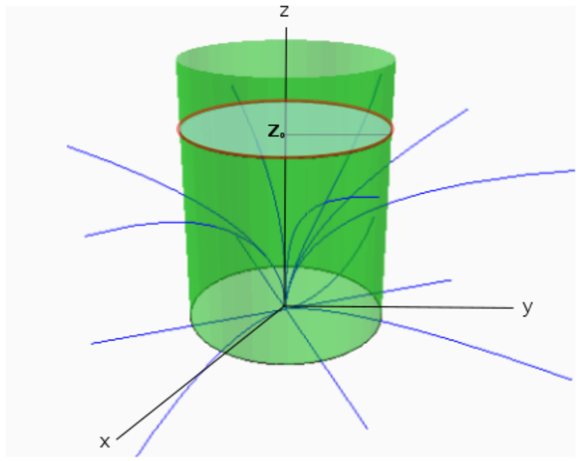


Figure 5.1: Solutions enter the cylinder and approach the origin, tangent to z-axis. The set $Z \cap I = \{(x, y, z_0) \in \mathbb{R}^3 \mid z_0 > 0,\ x^2 + y^2 = 1\}$ is the circle in red.

5.1.4 Uniqueness of the slow manifold

Uniqueness of $\mathcal{M}$ is justified by Propositions A.0.1 and B.0.1 presented in Appendixes A and B.

For the polyfacial set V, let us consider the horizontal cross sections given as follows

$$D_{z_0} = \left\{(x, y, z_0) \in \mathbb{R}^3 \mid z_0 > 0, \quad x^2 + y^2 = 1\right\}.$$

In this case the cross sections D_{z_0} are unit circles whose diameter defined is bounded.

Following the procedure outlined in Appendixes A and B, as $\dot{z} < 0$ in V we can consider x and y as functions of z. The system in terms of the slower variable z is given as follows

$$\begin{aligned} \frac{dx}{dz} &= \frac{\lambda_1}{\lambda_3}\frac{x}{z}, \\ \frac{dy}{dz} &= \frac{\lambda_2}{\lambda_3}\frac{y}{z}. \end{aligned} \tag{5.5}$$

Note that the Jacobian matrix of system (5.5), is given by

$$J = \frac{1}{z}\begin{pmatrix} \frac{\lambda_1}{\lambda_3} & 0 \\ 0 & \frac{\lambda_2}{\lambda_3} \end{pmatrix},$$

which is a positive definite matrix when $z > 0$. Let $\mu_1 = \frac{\lambda_1}{\lambda_3}$ and $\mu_2 = \frac{\lambda_2}{\lambda_3}$, $\mu_1 > \mu_2 > 1$. Note that the smallest eigenvalue of J is $\frac{\mu_2}{z}$.

Let $\mathbf{v_1}(z)$ and $\mathbf{v_2}(z)$ be two different solutions to system (5.5). Consider the squared difference of v_1 and v_2, this is $v(z) = |\mathbf{v_1}(z) - \mathbf{v_2}(z)|^2$, then we have

$$\begin{aligned} \frac{dv}{dz} &\geq 2\mu_2 \frac{v}{z} \\ \frac{dv}{v} &\geq 2\mu_2 \frac{dz}{z} \\ \ln|v| &\geq 2\mu_2 \ln z + C \\ v &\geq K_1 z^{2\mu_2}, \end{aligned} \tag{5.6}$$

that is, $|v_1(z) - v_2(z)| \geq K z^{\mu_2} > 0$ for all $z > 0$. More details of the previous inequalities are developed in Appendix B.

Relation (5.6) implies that in the phase space, with respect to the variable z, any two different solutions move apart from each other. Thus at most one of the two trajectories can remain in Z.

Using the Ważewski principle, we have shown that there is a trajectory of $p \in Z$, that is fully contained in V. Based on the calculations done above, $\mathcal{M}(p)$ is the unique trajectory fully contained in V since any other trajectory will have to eventually leave V.

5.2 A single-substrate enzyme-catalyzed reaction

Let us consider the following version of a system describing an enzyme catalyzed reaction where a single substrate is involved.

$$S + E \xrightarrow{k_1} C_1 \xrightarrow{k_2} C_2 \xrightarrow{k_3} P + E \tag{5.7}$$

As we have done it before, we will use $[\cdot]$ to denote concentration of the reactants. Let $s(t) = [S], e(t) = [E], c_1(t) = [C_1]$, $c_2(t) = [C_2]$ and $p(t) = [P]$ represent the concentration at a given time t of the reactants. Here s is substrate, e stands for enzyme, c_1 is the enzyme-substrate complex, c_2 is the enzyme-product complex and p is product. We assume that all variables are greater or equal than zero. The non-negativity of solutions of chemical kinetics systems when the initial values are non-negative is known to hold, see [21, Ch.12].

By the law of mass action, the full system of ODEs has four equations:

$$\begin{aligned}
\dot{s} &= -k_1 s e,\\
\dot{e} &= -k_1 s e + k_3 c_2,\\
\dot{c_1} &= k_1 s e - k_2 c_1,\\
\dot{c_2} &= k_2 c_1 - k_3 c_2,\\
\dot{p} &= k_3 c_2.
\end{aligned}$$

Note that the enzyme is not consumed in the reaction hence the total enzyme concentration, denoted e_0, remains constant. Also, $\dot{e} + \dot{c_1} + \dot{c_2} = 0$ and $c_1(0) = c_2(0) = 0$, so we can replace the variable e by

$$e = e_0 - c_1 - c_2 \tag{5.8}$$

and eliminate the differential equation for e. Also, only to make calculations easier, let us take all the parameters k_i, $i = 1, 2, 3$ equal to one. The resulting system is

$$\begin{aligned}
\dot{c_1} &= s(e_0 - c_1 - c_2) - c_1,\\
\dot{c_2} &= c_1 - c_2,\\
\dot{s} &= -s(e_0 - c_1 - c_2).
\end{aligned} \tag{5.9}$$

5.2.1 Polyfacial set

Consider the following continuously differentiable functions $m_i : \mathbb{R}^3_{\geq 0} \to \mathbb{R}$, for $i = 1, 2, 3$ given as follows:

$$\begin{aligned}
m_1(c_1, c_2, s) &= c_1 + c_2 - e_0,\\
m_2(c_1, c_2, s) &= 2c_2 - c_1 - e_0,\\
m_3(c_1, c_2, s) &= s(e_0 - c_1 - c_2) - 2c_1
\end{aligned}$$

The polyfacial set determined by the set of functions $\{m_i\}$ for $i = 1, 2, 3$ is defined by

$$V = \{(c_1, c_2, s) \in \mathbb{R}^3_{>0} \mid \; m_i(c_1, c_2, s) < 0, i = 1, 2, 3\}. \tag{5.10}$$

Furthermore, let us consider the following sets:

$$\begin{aligned}
M_1 &= \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; m_1(c_1, c_2, s) = 0\} = \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; c_1 + c_2 - e_0 = 0\}, \\
M_2 &= \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; m_2(c_1, c_2, s) = 0\} = \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; 2c_2 - c_1 - e_0 = 0\}, \\
M_3 &= \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; m_5(c_1, c_2, s) = 0\} = \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; s(e_0 - c_1 - c_2) - 2c_1 = 0\}. \\
M_4 &= \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; c_1 > 0, c_2 = 0, 0 < s < \frac{2c_1}{e_0 - c_1 - c_2}\}, \\
M_5 &= \{(c_1, c_2, s) \in \mathbb{R}^3_{\geq 0} \mid \; s = 0, c_2 < e_0 - c_1, c_2 < (c_1 + e_0)/2\},
\end{aligned}$$

The sets M_i, for $i = 1, 2, \ldots, 5$ describe simple surfaces in R^3. The boundary of V is determined by the union of such sets. A cross section of V given when $s = s_0 > 0$, is illustrated in Figure 5.2.

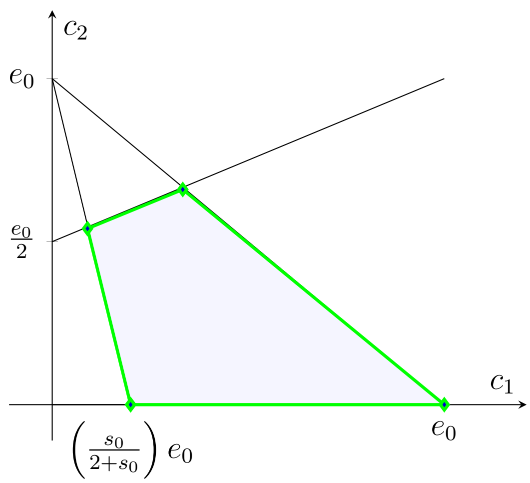


Figure 5.2: A cross section of V for a given $s = s_0$.

5.2.2 Set of strict ingress points

In this section we will classify the points in the boundary of V as equilibrium or egress points. We will show that the origin, which belongs to ∂V, is the only equilibrium point of the system.

Proposition 5.2.1. *The system (5.9) has a locally asymptotically stable node at the origin.*

Proof. The Jacobian matrix evaluated at the origin is

$$A = \begin{bmatrix} -1 & 0 & e_0 \\ 1 & -1 & 0 \\ 0 & 0 & -e_0 \end{bmatrix}.$$

We assume that $e_0 > 0$ and $e_0 \neq 1$, the matrix A has real negative eigenvalues $\nu_1 = \nu_2 = -1$ and $\nu_3 = -e_0$. Therefore, the origin is a locally asymptotically stable node.

Furthermore, if $e_0 \neq 1$, the stable subspace E^s of the linearized system at the origin is

$$E^s = Span \left\{ \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1-e_0 \\ 1 \\ \frac{(e_0-1)^2}{e_0} \end{bmatrix} \right\}.$$

$\square$

Proposition 5.2.2. *Let*

$$I_1 = \{(c_1, c_2, s) \in \partial V \mid s > 0, m_i = 0, \ i = 1, 2, 3\}$$

and

$$I_2 = \{(c_1, c_2, s) \in \partial V \mid \ c_1 > 0, c_2 = 0, 0 < s < \frac{2c_1}{e_0 - c_1 - c_2}\}.$$

The set of strict ingress points of V with respect to (5.9) is given by

$$I = (I_1 \cup I_2) \setminus (0, 0, 0).$$

Proof. The vector field is described by

$$\mathbf{f}(c_1, c_2, s) = (\dot{c_1}, \dot{c_2}, \dot{s}).$$

a) If $(c_1, c_2, s) \in M_1$ and $(c_1, c_2, s) \neq (0,0,0)$, then $c_1 + c_2 - e_0 = 0$ with

$$\begin{aligned} \nabla m_1 \cdot \mathbf{f}(c_1, c_2, s) &= (1,1,0) \cdot (\dot{c_1}, \dot{c_2}, \dot{s}) \\ &= \dot{c_1} + \dot{c_2} \\ &= -c_2 < 0. \end{aligned}$$

b) If $(c_1, c_2, s) \in M_2$ and $(c_1, c_2, s) \neq (0,0,0)$, then $2c_2 = c_1 + e_0$ with

$$\begin{aligned} \nabla m_2(c_1, c_2, s) \cdot \mathbf{f}(c_1, c_2, s) &= (-1,2,0) \cdot (\dot{c_1}, \dot{c_2}, \dot{s}) \\ &= -\dot{c_1} + 2\dot{c_2} \\ &= -s(e_0 - c_1 - c_2) + c_1 + 2c_1 - 2c_2 \\ &= -s(e_0 - c_1 - c_2) + 2c_1 - e_0 < 0 \quad \text{when} \quad 2c_1 - e_0 < 0. \end{aligned}$$

Note that if $(c_1, c_2, s) \in V$, then we can assume $2c_1 - e_0 < 0$. In the c_1c_2-plane, the intersection of the lines $2c_2 = c_1 + e_0$ and $c_2 = e_0 - c_1$ occurs at the point $c_1 = e_0/3$. Therefore we are interested in the sign of $\nabla m_2(c_1, c_2, s) \cdot \mathbf{f}(c_1, c_2, s)$ only for the case where $c_1 \leq e_0/3$ which implies $2c_1 - e_0 < 0$.

c) If $(c_1, c_2, s) \in M_3$ and $(c_1, c_2, s) \neq (0,0,0)$ then $s(e_0 - c_1 - c_2) - 2c_1 = 0$ with

$$\begin{aligned} \nabla m_3(c_1, c_2, s) \cdot \mathbf{f}(c_1, c_2, s) &= (-s-2, -s, e_0 - c_1 - c_2) \cdot (\dot{c_1}, \dot{c_2}, \dot{s}) \\ &= -(s+2)c_1 - s(c_1 - c_2) - s(e_0 - c_1 - c_2)^2 \\ &= -s\left(c_1 + \frac{2c_1}{s} + c_1 - c_2 + (e_0 - c_1 - c_2)^2\right) \\ &= \frac{-2c_1}{e_0 - c_1 - c_2}\left(c_1 + \frac{s(e_0 - c_1 - c_2)}{s} + c_1 - c_2 + (e_0 - c_1 - c_2)^2\right) \\ &= \frac{-2c_1}{e_0 - c_1 - c_2}\left(2c_1 + e_0 - c_1 - c_2 - c_2 + (e_0 - c_1 - c_2)^2\right) \\ &= \frac{-2c_1}{e_0 - c_1 - c_2}\left(c_1 - 2c_2 + e_0 + (e_0 - c_1 - c_2)^2\right) < 0. \end{aligned}$$

Note that if $(c_1, c_2, s) \in V$, then $2c_2 - c_1 - e_0 < 0$.

d) Similarly, if $(c_1, c_2, s) \in M_4$ and $(c_1, c_2, s) \neq (0,0,0)$ then $c_1 > 0$, $c_2 = 0$, and $0 < s < \frac{2c_1}{e_0 - c_1 - c_2}$. In this case, an outward normal vector to portion of plane described by M_4 is for example $(0,-1,0)$ then

$$\begin{aligned}(0,-1,0)\cdot\mathbf{f}(c_1,c_2,s) &= (0,-1,0)\cdot(\dot{c_1},\dot{c_2},\dot{s})\\ &= -\dot{c_2}\\ &= -c_1 < 0.\end{aligned}$$

e) Finally, if $(c_1,c_2,s)\in M_5$ and $(c_1,c_2,s)\neq(0,0,0)$ then $s=0$, $c_2<e_0-c_1$ and $c_2<\frac{c_1+e_0}{2}$. In this case, an outward normal vector to portion of plane described by M_4 is for example $(0,0,-1)$ then

$$\begin{aligned}(0,0,-1)\cdot\mathbf{f}(c_1,c_2,s) &= (0,0,-1)\cdot(\dot{c_1},\dot{c_2},\dot{s})\\ &= -\dot{s} = 0.\end{aligned}$$

Note that the c_1c_2-plane is an invariant set. By the previous equation the set of points described by the set M_5, which is part of ∂V, can not be classified according to definition 2.3 given in Chapter 2. However, the Ważewski theorem still applies in this case. An extended version of the Ważewski method, which is not considered in this work, is presented in [20, pp.614-617]. It considers the case where IVP do not have unique solution and there are weak inequalities as this case.

□

We have shown that the vector field and the respective outward normal vectors of the surfaces describing ∂V have opposite directions. Therefore, the set I as defined above is the set of strict ingress points of V with respect to the system (5.9). Furthermore, parts a) to e) imply the set V is positively invariant, trajectories enter V and they do not leave. Hence the set of egress points of V with respect to the system (5.9) is empty.

5.2.3 Existence of the slow manifold

The Ważewski theorem provides conditions for the existence of a solution $\mathcal{M}$ that lies entirely in the polyfacial set V. To use the theorem, we need to find a set Z such that $Z\cap I$ is a retract of I but not a retract of Z.

For $s=s_0$, where s_0 is a positive constant, let

$$Z=\{(c_1,c_2,s)\in\mathbb{R}^3_{\geq 0}\mid s=s_0>0,\ m_i(c_1,c_2,s_0)\leq 0,\ i=1,2,3\}.$$

a) $Z \cap I$ is a retract of I;

The set $Z \cap I$ is the convex irregular quadrilateral in Figure 5.2. Such quadrilateral, drew in green, it is delimited by the c_1-axis and the lines

$$c_2 = e_0 - c_1, \; c_2 = \frac{c_1 + e_0}{2} \quad \text{and} \quad c_2 = e_0 - c_1 - \frac{2c_1}{s_0}.$$

Now, we need to find a continuous map $T : I \to Z \cap I$ such that $T(x) = x$ for all $x \in Z \cap I$. The construction of the proposed continuous map T involves some transformations. First we "straighten" the surface described by the set of ingress points. With reference to Figure 5.2, the line trough the point $(0, e_0)$ and any point (c_1, c_2) in the quadrilateral or the region that is bounded by, intersects the c_1-axis at $(\sigma, 0)$, where $\sigma = \frac{e_0 c_1}{e_0 - c_2}$. Similarly, the line through $(-e_0, 0)$ and (c_1, c_2) intersects the c_2-axis at $(0, \tau)$, where $\tau = \frac{e_0 c_2}{e_0 + c_1}$. Solving for c_1 and c_2 in terms of (σ, τ) gives

$$\begin{aligned} c_1 &= \tfrac{e_0}{\sigma\tau + e_0^2}(-\sigma\tau + e_0\sigma), \\ c_2 &= \tfrac{e_0}{\sigma\tau + e_0^2}(\sigma\tau + e_0\tau). \end{aligned}$$

The points in V for a given $s > 0$ are those with $\frac{e_0 s}{2+s} < \sigma < e_0$ and $0 < \tau < \frac{e_0}{2}$, which in Figure 5.3 is represented by the green rectangle $ABCD$ in the $\sigma\tau$-plane. For a given $s = s_0$, this rectangle can be continuously mapped by a function ϕ onto the rectangle $a'b'c'd'$ in the $\sigma'\tau'$-plane. In this case, let $\phi(\sigma, \tau) = (\sigma', \tau')$ where

$$\sigma' = \tfrac{(2+s)\sigma}{2+s_0} + \tfrac{(s_0 - s)}{2+s_0} \text{ and } \tau' = \tau.$$

This leads to the continuous map T where $T(c_1, c_2, s) = (c_1', c_2', s_0)$ with

$$\begin{aligned} c_1' &= \tfrac{e_0}{\sigma'\tau + e_0^2}(-\sigma'\tau + e_0\sigma'), \\ c_2' &= \tfrac{e_0}{\sigma'\tau + e_0^2}(\sigma'\tau + e_0\tau). \end{aligned}$$

Therefore $Z \cap I$ is a retract of I.

b) It can be justify that $Z \cap I$ is not a retract of Z using the No Retraction Theorem 2.1.4. There are a couple of results that we need:

- First, $Z \cap I$ is a convex polygonal region, see Figure 5.2. It can be shown that $Z \cap I$ is homeomorphic to the unit square $S = \{(x, y) \mid |x| \leq 1, |y| \leq 1\}$.

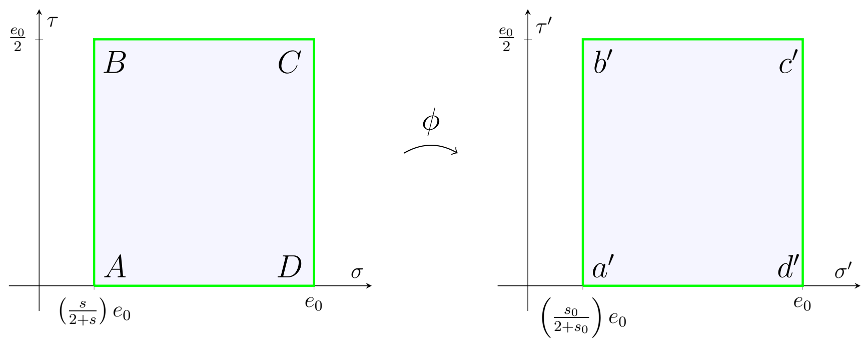


Figure 5.3: Rectangle $ABCD$ can be mapped onto the rectangle with $s = s_0$ $a'b'c'd'$.

- Second, the unit disk $D^2 = \{(x, y) \mid x^2 + y^2 \leq 1\}$ is homeomorphic to the unit square, see [16, p.19].

By Ważewski theorem, there is at least one point $p \in Z \setminus I$ such that the negative semitrajectory of p is contained in V. Since the set of egress points is empty, once solutions enter in V they do not leave. Hence, the trajectory passing through p, let us denote it $\mathcal{M}(p)$, is fully contained in V.

Furthermore, let us look at the linearization of the system (5.9) around the origin. We have shown in Proposition 5.2.1 that the system (5.9) has a locally asymptotically stable node at the origin. Also, the stable subspace E^s of the linearized system at the origin is

$$E^s = Span\left\{\begin{bmatrix}0\\1\\0\end{bmatrix}, \begin{bmatrix}1\\0\\0\end{bmatrix}, \begin{bmatrix}1-e_0\\1\\\frac{(e_0-1)^2}{e_0}\end{bmatrix}\right\}.$$

The generalized eigenvectors

$$\begin{bmatrix}0\\1\\0\end{bmatrix} \text{ and } \begin{bmatrix}1\\0\\0\end{bmatrix}$$

correspond to the repeated eigenvalue $\nu_1 = \nu_2 = -1$. If we assume e_0 is a small quantity such that $0 < e_0 < 1$, similarly to the assumption made in the Michaelis-Menten system in Chapter 3, then the slow direction followed for the trajectories approaching the origin is determined by the eigenvector

$$\mathbf{v_s} = \begin{bmatrix} 1-e_0 \\ 1 \\ \frac{(e_0-1)^2}{e_0} \end{bmatrix}.$$

This eigenvector corresponds to the eigenvalue $\nu_3 = -e_0$. Observe that v_s is pointing into the first octant of the phase space when $0 < e_0 < 1$.

Note that at the origin, the tangent vector to $\mathcal{M}(p)$ is $\mathbf{v_s}$. We want to show that solutions approach the origin tangent to the slow direction vector $\mathbf{v_s}$. Let us calculate the dot product of $\mathbf{v_s}$ with the outward normal vector of the surface M_3 to verify they have opposite directions. We only need to consider M_3 since the rest of the surfaces describing ∂V do not pass through the origin.

If $(c_1, c_2, s) \in M_3$ then

$$\nabla m_3(c_1, c_2, s) \cdot \mathbf{v_s} = (-s-2, -s, e_0 - c_1 - c_2) \cdot \left(1-e_0, 1, \frac{(e_0-1)^2}{e_0}\right).$$

At the origin,

$$\begin{aligned} \nabla m_3(0,0,0) \cdot \mathbf{v_s} &= (-2, 0, e_0) \cdot \left(1-e_0, 1, \frac{(e_0-1)^2}{e_0}\right) \\ &= 2(e_0-1) + (e_0-1)^2 \\ &= (e_0-1)(1+e_0) < 0 \quad \text{since} \quad 0 < e_0 < 1. \end{aligned}$$

In summary, using the Ważewski theorem we have shown that $\mathcal{M}(p)$ exist and stays inside the set V. Solutions approach the origin tangent to $\mathcal{M}$(p) along the slow direction. In that sense we say that $\mathcal{M}(p)$ is a slow attracting manifold.

Chapter 6

Final Remarks

In this work we presented an application of the Ważewski theorem to justify existence and uniqueness of an exceptional solution $\mathcal{M}$ that stays inside a particular region and attracts all other solutions. Our principal goal was to present the geometric constructs and results involved in the so called Ważewski method. The relevance of the tools presented here is that they are applicable to higher dimensional systems.

The method presented follows a topological approach to differential equations and is due to Tadeusz Ważewski (1896-1972) who introduced it in [22]. It gives a way to prove existence of solutions that remain in a *polyfacial set* V for all positive/negative values of time. The polyfacial set V must satisfy that its set of ingress points I are strict. The Ważewski Theorem asserts that there is a solution contained in V for all positive/negative values of time if the subset of strict ingress points of V is not a retract of the whole set V. The relevant concepts and a simplified version of the Theorem was presented in Chapter 2.

In this work an important piece for the application of the Ważewski Theorem was the construction of the polyfacial set V for the differential equation. Such construction is based on the existence of continuously differentiable functions that behave similarly to Liapunov functions on some parts of their zero-level sets. To illustrate the concepts and results related to the Ważewski Theorem we have presented the Michaelis-Menten model which is one of the simplest is approaches to study reactions that are catalyzed by enzymes. A starting point for those functions that define the polyfacial set are the expressions obtained from RE and QSSA type assumptions.

The Ważewski theorem is an existence result. It has the great advantage that it can be used in higher dimensional autonomous systems. As we showed in the models considered, when there are two different time scales and some enzyme-catalyzed reactions we get a neat tool to show existence of slow attracting manifolds in a polyfacial set. In the author's experience writing this work, the construction of the polyfacial sets and determining whether the points in its boundary are strict ingress points could become an difficult task.

For the models considered, a surprising property of $\mathcal{M}$ was to be the only trajectory that stays in the set V and attracts the other trajectories entering V. To discuss uniqueness of the slow manifold, we look at two things: first, we determine if the solutions were "moving apart" from each other in the phase space. Second, we look at the cross sections of the region described by V. By observing that the cross sections of the region described by V were in a sense "narrowing" or have a fixed diameter we were able to justify uniqueness when the difference between two different solutions is nondecreasing in V.

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Appendices

Appendix A

One criteria to justify uniqueness of the slow manifold

Let us assume that we have a system of differential equations of the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \tag{A.1}$$

where $\mathbf{x}(\mathbf{t}) = (x_1(t), x_2(t), \ldots, x_n(t)) \in \mathbb{R}^n$, and $\mathbf{f}(\mathbf{x}) = (f_1(\mathbf{x}), \ldots, f_n(\mathbf{x}))$. If D is an open subset of $\mathbb{R}^n$, we assume $\mathbf{f} \in C(D, \mathbb{R}^n)$ and is Lipschitz continuous such that there exist an unique solution to the initial value problem.

If $f_n(\mathbf{x}) \neq 0$ then system (A.1) is equivalent to the following one

$$\begin{aligned} \frac{dx_1}{dx_n} &= \frac{f_1(\mathbf{x})}{f_n(\mathbf{x})}, \\ &\vdots \\ \frac{dx_{n-1}}{dx_n} &= \frac{f_{n-1}(\mathbf{x})}{f_n(\mathbf{x})}. \end{aligned} \tag{A.2}$$

It might result useful to rewrite (A.2) in its shorter form

$$\mathbf{y}' = \mathbf{g}(x_n, \mathbf{y}), \tag{A.3}$$

where

$$\mathbf{y} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_{n-1} \end{bmatrix}$$

and

$$\mathbf{g}(x_n, \mathbf{y}) = \begin{bmatrix} \frac{f_1(\mathbf{x})}{f_n(\mathbf{x})} \\ \vdots \\ \frac{f_{n-1}(\mathbf{x})}{f_n(\mathbf{x})}. \end{bmatrix}.$$

Note. System (A.3) is no longer autonomous. We will assume that $\mathbf{g}$ satisfies necessary conditions such that the initial value problem has an unique solution. Also, note that any solution $\mathbf{y}$ is now given in terms of x_n, this is

$$\mathbf{y}(x_n) = \begin{bmatrix} x_1(x_n) \\ \vdots \\ x_{n-1}(x_n) \end{bmatrix}.$$

Let us assume that we have a positively invariant unbounded region $\mathcal{T}$ in $\mathbb{R}^n$ such that there exist at least one trajectory fully contained in there. An example of such region could be the polyfacial sets V described in Chapters 4 and 5. In the following proposition we establish a criteria to determine uniqueness of solutions that are fully contained in $\mathcal{T}$.

We show that if the distance between two different trajectories in $\mathcal{T}$ with respect to system (A.3) never decreases and the diameter of the cross-sections is bounded or tends to zero then at least on of the solutions will eventually have to leave the region $\mathcal{T}$.

Proposition A.0.1. *With respect to system (A.3) let us consider the unbounded region $\mathcal{T}$ which is described as follows*

$$\mathcal{T} = \{(x_1, \ldots, x_{n-1}, x_n) \in \mathbb{R}^n \mid (x_1, \ldots, x_{n-1}) \in D_{x_n}, x_n > 0\},$$

where $D_{x_n} \neq 0$, the cross-section, is a bounded region in $\mathbb{R}^{n-1}$. Let us consider the diameter of the cross-section, $diam(D_{x_n})$, given as

$$diam(D_{x_n}) = sup\{|p_1 - p_2| \mid p_1, p_2 \in D_{x_n}\}.$$

Two possibilities are considered:

- *if $diam(D_{x_n}) \to 0$ as $x_n \to \infty$ and the distance between different solutions to system (A.3) in $\mathcal{T}$ does not decrease as $x_n \to \infty$, or*

- *if for all values of x_n $diam(D_{x_n})$ is bounded and the distance between different solutions to system (A.3) in $\mathcal{T}$ is unbounded as $x_n \to \infty$.*

Then, there can only be one trajectory fully contained in $\mathcal{T}$.

Proof. Let $\mathbf{z}(x_n)$ and $\mathbf{y}(x_n)$ be two different solutions to system (A.3) in $\mathcal{T}$ and $d(z, y)$ the distance between them. In the phase space, let us consider cross-sections at fixed values of x_n with diameter $diam(D_{x_n})$.

- If $diam(D_{x_n}) \to 0$ as $x_n \to \infty$, and the distance between different solutions never decreases. This is, if for all $\alpha_1 < \alpha_2$

  $$d(z(\alpha_1), y(\alpha_1)) \leq d(z(\alpha_2), y(\alpha_2)).$$

  Then, there is a $x_n = \alpha > 0$ such that $d(z(\alpha), y(\alpha)) > diam(D_\alpha)$ thus the two trajectories cannot stay inside the trapping region.

- Similarly, if for all values of x_n, the diameter of the cross-section satisfies

  $$diam(D_{x_n}) \leq k,$$

  where $k > 0$ and $d(z, y) \to \infty$ as $x_n \to \infty$. Then, there is a $x_n = \alpha > 0$ such that

  $$d(z(\alpha), y(\alpha)) > diam(D_\alpha)$$

  which means that at least one trajectory has to leave the trapping region.

In either case we have that if there is a trajectory fully contained in $\mathcal{T}$ this has to be unique.

□

Appendix B

Dispersion of solutions in the phase space

Let us assume that we have a system of differential equations of the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \tag{B.1}$$

where $\mathbf{x}(\mathbf{t}) = (x_1(t), x_2(t), \ldots, x_n(t)) \in \mathbb{R}^n$, and $\mathbf{f}(\mathbf{x}) = (f_1(\mathbf{x}), \ldots, f_n(\mathbf{x}))$. If $f_n(\mathbf{x}) \neq 0$ then system (B.1) is equivalent to have

$$\begin{aligned} \frac{dx_1}{dx_n} &= \frac{f_1(\mathbf{x})}{f_n(\mathbf{x})}, \\ &\vdots \\ \frac{dx_{n-1}}{dx_n} &= \frac{f_{n-1}(\mathbf{x})}{f_n(\mathbf{x})}. \end{aligned}$$

Or in a shorter notation

$$\mathbf{y}' = \mathbf{g}(x_n, \mathbf{y}). \tag{B.2}$$

Let $J \subset \mathbb{R}$ and $V \subset \mathbb{R}^{n-1}$ be open and convex such that $g \in C(J \times V, \mathbb{R}^{n-1})$. Note that any solution $\mathbf{y}$ of system (B.2) is given now in terms of x_n, this is,

$$\mathbf{y}(x_n) = \begin{bmatrix} x_1(x_n) \\ \vdots \\ x_{n-1}(x_n) \end{bmatrix}.$$

Below, we present sufficient conditions to determine if distance between two different solutions in the phase space is nondecreasing. We consider the particular case where the symmetric part of the Jacobian matrix is a positive-semidefinite matrix.

Proposition B.0.1. *Let $\mathbf{z}, \mathbf{y} \in V$ two different solutions of system (B.2) and*

$$\mathbf{Dg} = \mathbf{D_y g}(x_n, \mathbf{y})$$

the Jacobian matrix of $\mathbf{g}$. If $\mathbf{Dg}$ is a positive-semidefinite matrix, it follows that as $x_n \in J$ increases the distance between different solutions is nondecreasing.

Proof. Let us consider the following derivative

$$\begin{aligned} \frac{d}{dx_n}|\mathbf{z}-\mathbf{y}|^2 &= \frac{d}{dx_n}(\mathbf{z}-\mathbf{y})\cdot(\mathbf{z}-\mathbf{y}) \\ &= 2(\mathbf{z}-\mathbf{y})\cdot(\mathbf{z}'-\mathbf{y}') \\ &= 2(\mathbf{z}-\mathbf{y})\cdot(\mathbf{g}(x_n,\mathbf{z})-\mathbf{g}(x_n,\mathbf{y})) \\ &= 2(\mathbf{z}-\mathbf{y})^T\left(\int_0^1 \mathbf{Dg}(x_n, \mathbf{y}+s(\mathbf{z}-\mathbf{y}))ds\right)(\mathbf{z}-\mathbf{y}) \\ &\geq 2\lambda_0|\mathbf{z}-\mathbf{y}|^2. \end{aligned} \tag{B.3}$$

Observe that convexity of V ensures that $F(s) = \mathbf{Dg}(x_n, \mathbf{y}+s(\mathbf{z}-\mathbf{y}))$ for $s \in [0,1]$ is defined.

Note. To obtain the last inequality in B.3 we are using the following three facts:

1.

$$\begin{aligned} \mathbf{g}(x_n,\mathbf{z})-\mathbf{g}(x_n,\mathbf{y}) &= \int_0^1 \frac{d}{ds}\mathbf{g}(x_n,\mathbf{y}+s(\mathbf{z}-\mathbf{y}))ds \\ &= \left(\int_0^1 \mathbf{Dg}(x_n,\mathbf{y}+s(\mathbf{z}-\mathbf{y}))ds\right)(\mathbf{z}-\mathbf{y}). \end{aligned} \tag{B.4}$$

2. In a quadratic form $v^T Av$, we can assume that $A = A^T$ since

$$v^T Av = v^T((A + A^T)/2)v.$$

The matrix obtained by taking the "average" of A and A^T, this is $(A + A^T)/2$, is called the symmetric part of A.

3. Finally, if the eigenvalues of A are $\lambda_{max} \geq \ldots \lambda_{min}$ we have

$$\lambda_{min} v^T v \leq v^T Av \leq \lambda_{max} v^T v.$$

Therefore, the last inequality in (B.3) follows by assuming that

$$\frac{1}{2}(\mathbf{Dg}(w) + \mathbf{Dg}^T(w))$$

is a positive-semidefinite matrix with λ_0 the smallest eigenvalue.

The calculations done in (B.3) imply that as x_n increases, the distance between different solutions never decreases. This is, in the phase space any two different solutions "move apart" as x_n increases.

Furthermore, solving the differential inequality (B.3) we get

$$|\mathbf{z}(x_n) - \mathbf{y}(x_n)| \geq e^{\lambda_0 x_n} |\mathbf{x}(0) - \mathbf{y}(0)|.$$

□

In an applied context, a possible difficulty might arise when determining if the symmetric part of $\mathbf{Dg}(w)$ is a positive-semidefinite matrix, specially if the parameters involved are unknown.

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