

MA599
Non-Linear Systems and Mathematical Biology

Chun Kit Tsoi, Nevin Leal, Luigi Giulio Grandi

March 20, 2017

University of
Kent

Contents

1	Introduction	2
2	The First Order Ordinary Differential Equation(ODE) system	3
2.1	Introduction of the First Order DE System	3
2.2	The First Order Differential Equation System	4
2.3	General Solutions for First Order ODEs of Two Components . .	5
3	Nonlinear Systems	7
3.1	Population Models	7
4	Lyapunov Functions	11
4.1	Constructing a Lyapunov Function	12
4.2	Lyapunov First Stability Theorem	16
4.3	Lyapunov Second Stability Theorem	17
5	Scalar Equations and Stability	20
5.1	Phase Plane Analysis of First Order Differential Equations . . .	21
5.2	Bifurcation Diagram for First Order Differential Equations . . .	22
5.2.1	First Order Linear Case	22
5.2.2	First Order Nonlinear Case	23
5.3	Meaning of Stability	26
5.4	Strong Linear Stability	28
6	Reaction Kinetics	30
6.1	Basic Enzyme Kinetics	30
6.2	Non-Reversible Kinetic Reaction	30
6.3	Reversible Kinetic Reaction	32
6.4	Michaelis–Menten Model	33
6.5	Transient Time Estimates and Non-dimensionalisation	36
6.6	Michaelis-Menten Quasi-Steady State Analysis	38
6.7	Suicide Substrate Kinetics	43
6.8	Cooperative Phenomena	51
6.9	Multiple Steady States, Mushrooms and Isolats	53
7	Conclusion	55
8	Appendix	57

Abstract

In this project, we will study the relationship between mathematical biology and differential equation systems. We will see how complex biological and biochemical processes can develop a mathematical model that helps simplify these processes which will, in turn, make them easier to understand.

Chapter 1

Introduction

We will explore more advanced topics such as the Michaelis-Menten model, and how there is a correlation between substrate velocity and the maximum velocity. In this project, we will also explore the unique cases in Reaction Kinetics, such as how multiple steady states are formed in a system and what impact this has on the behaviour of phase portraits. Another fact to be considered is that we will explore more basic mathematical concepts applied to the real world . An example which we have included is population models and what factors cause the population to increase and decrease over certain amounts of time. This is a form of a nonlinear system and is a mathematical way to describe the vast majority of the phenomena in the world. In order for us to study Reaction Kinetics in Mathematical Biology , we must further our understanding of basic mathematical topics in great detail. We will explore linear systems, nonlinear systems and scalar equations in further detail to provide us with the foundations to learn Reaction Kinetics.

Chapter 2

The First Order Ordinary Differential Equation(ODE) system

2.1 Introduction of the First Order DE System

An Ordinary Differential Equation (ODE) is a differential equation containing one or more functions of one dependent variable and its derivatives. The ODE is particularly important in biology. It can be used to find the change of body temperature, bacterial populations and the enzyme reaction. Throughout this chapter, we will use information from [4] to assist us with the basic knowledge of the topic.

Definition 1. let y be a dependent variable and t an independent variable, and $y = f(x)$ is an unknown function of t . The notation for differentiation varies depending upon the author and upon which notation is most useful for the task at hand.

The form of the ODE is shown as following,

$$\begin{aligned}\frac{dy_1}{dt} &= f_1(t, y_1, y_2, \dots, y_n), & y_1(t_0) &= y_{1,0}, \\ \frac{dy_2}{dt} &= f_2(t, y_1, y_2, \dots, y_n), & y_2(t_0) &= y_{2,0}, \\ &\dots & \\ \frac{dy_n}{dt} &= f_n(t, y_1, y_2, \dots, y_n), & y_n(t_0) &= y_{n,0}.\end{aligned}\tag{2.1}$$

This is known as canonical form. The component of system is determined by the number of dependent variables. When the initial conditions are given at a

common point, t_0 , then the set of (2.1) has a solution of the following form:

$$\begin{aligned} y_1 &= F_1(t), \\ y_2 &= F_2(t), \\ &\dots \\ y_n &= F_n(t). \end{aligned} \tag{2.2}$$

The system equations are represented by

$$\begin{aligned} \frac{dy}{dt} &= f(t, y), \\ y(t_0) &= y_0, \\ y &= F(t), \end{aligned} \tag{2.3}$$

where $y(t_0) = y_0$ is the vector of initial conditions and $y = F(t)$ is the solution.

2.2 The First Order Differential Equation System

We will use information from [13] in this section. We will be discussing the basic idea of ODEs and its solving techniques so that we can apply this to mathematical biology. Consider the first-order ODE model

$$\frac{dy}{dt} = f(t, y), \tag{2.4}$$

where y is a function of t and the initial condition at $t_0 = 0$ is

$$y(0) = y_0. \tag{2.5}$$

First of all, we can check if (2.4) and (2.5) has a solution by the Existence and Uniqueness Theorem. A steady state of a differential equation is the solution which does not vary with t .

Definition 2. Suppose that $f(t, y)$ are continuous on a closed rectangle R of $t - y$ plane. If $(t_0, y_0) \in \mathbb{R}$ then the Initial Value Problem is

$$\frac{dy}{dt} = f(t, y), \quad y(t_0) = y_0.$$

This has a unique solution on some t -interval containing t_0 .

If (2.4) and (2.5) satisfies Definition 2, then we can solve the ODE analytically and can find its general solution. The general solution of a given first order ODE (2.4), can locally be written in the form $\phi(t, y) = c$, where $\phi(t, y)$ is the first integral and c is an arbitrary constant. However, there are a lot of ways to solve first order ODEs. An example of this would be separating variables using the integrating factor by substitution. We have come across this previously in Stage 1. We will now briefly be discussing these techniques.

(a) Separating the Variables: If an ODE is in the form

$$\frac{dy}{dt} = \frac{g(t)}{h(y)}, \quad (2.6)$$

and it is in any neighbourhood where $g(t) \neq 0$ then the general solution is

$$\int h(y)dy = \int g(t)dt + c. \quad (2.7)$$

(b) Integrating Factor: If an ODE is in the form

$$\frac{dy}{dt} + p(t)y = g(t), \quad (2.8)$$

then we use the integrating factor $I(x) = \exp(\int p(t)dt)$, and introduce a new dependent variable $z = I(x)y$. Thus, the original ODE is equivalent to

$$\frac{dz'}{dy} = I(x)b(x), \quad (2.9)$$

where the equation becomes separable like (2.7).

2.3 General Solutions for First Order ODEs of Two Components

In this section, we will be using information from [3]. If a first order ODE is in the form $\dot{x} = Ax$ with $x \in \mathbb{R}^n$, and the square matrix A , is diagonisable¹, then we say A has a general solution in the matrix form

$$X(t) = \sum_{i=1}^n V_i x_i(0) e^{\lambda_i t} = \sum_{i=1}^n C_i e^{\lambda_i t}, \quad (2.10)$$

where λ_i are the eigenvalues of A , $V_i \in \mathbb{R}^n$ and the corresponding eigenvectors of A and n is the number of components. Since we have come across this in stage 1, we will explain it briefly by giving an example.

Consider the ODE system

$$\begin{aligned} \frac{ds}{dt} &= -ks + kp, \\ \frac{dp}{dt} &= ks - kp. \end{aligned} \quad (2.11)$$

This is a two components system since there are two dependent variables, s and p . To solve (2.11), we can write the equation in the form $\dot{x} = Ax$, where

$$A = \begin{pmatrix} s & p \end{pmatrix} = \begin{pmatrix} -k & k \\ k & -k \end{pmatrix}. \quad (2.12)$$

¹If $A = (a_{ij})$ is a square matrix $n \times n$, then the entries a_{ii} are the diagonal entries. A square matrix is known to be diagonal if all non-diagonal entries are zero.

We use the change of variables method to diagonalise the matrix A . To solve two components of first order differential equation, we need to find its eigenvalues and eigenvectors. We rewrite (2.11) in the form

$$\begin{pmatrix} \frac{ds}{dt} \\ \frac{dp}{dt} \end{pmatrix} = \begin{pmatrix} -1 & 1 \\ 1 & -1 \end{pmatrix} \begin{pmatrix} s \\ p \end{pmatrix}. \quad (2.13)$$

To get the eigenvalues, we have to solve $\det(A - \lambda I) = 0$. This can be applied in the following matrix:

$$\det \begin{pmatrix} -1 - \lambda & 1 \\ 1 & -1 - \lambda \end{pmatrix} = 0, \quad (2.14)$$

where the solution is

$$\lambda_1 = 0, \quad \lambda_2 = -2. \quad (2.15)$$

We now have the solutions in the form $Av = \lambda v$ for each eigenvalue λ ,

$$v_1 = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 \\ 1 \end{pmatrix}, \quad v_2 = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 \\ -1 \end{pmatrix}, \quad (2.16)$$

where v_1 is corresponding to λ_1 and v_2 is corresponding to λ_2 . From both v_1 and v_2 of A , we create a new matrix V where v_1 is the first column of the matrix and v_2 is the second column. As shown below

$$V = (v_1 \ v_2) = \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 1 \\ 1 & -1 \end{pmatrix}. \quad (2.17)$$

We then diagonalize A , which gives us the diagonal matrix D equal to

$$V^{-1}AV = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 0 & -2 \end{pmatrix}. \quad (2.18)$$

A first order DE of a two component system is in the form $\frac{dx}{dt} = Ax$, where A is a diagonalisable matrix. By definition, we know the general solution is a linear combination in the exponential form, $e^{\lambda_i t}$, where λ_i denotes the eigenvalues of the matrix A . This can be represented in the following equation

$$X(t) = v_1 s(0)e^{\lambda_1 t} + v_2 p(0)e^{\lambda_2 t} = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t}, \quad (2.19)$$

where C_i s denote the constants.

Therefore, the general solution in this case is

$$X(t) = \frac{1}{\sqrt{2}} \left(\begin{pmatrix} 1 \\ 1 \end{pmatrix} + \begin{pmatrix} 1 \\ -1 \end{pmatrix} \right) e^{-2t}. \quad (2.20)$$

We will use this result as example in the future (see section (6.3)).

Chapter 3

Nonlinear Systems

A system is a set of related elements working together to give a joint outcome. There are essentially two types of systems: linear and nonlinear systems. We used [9] and [10] from the bibliography, to provide us with information for this section.

It is often said that nonlinear systems describe the vast majority of the phenomena in our world. In a nonlinear system, the output is not directly proportional to the input. It is not considered linear when there is at least one variable with the exponent greater than one and/or there is a product of variables in one of the elements. The world of nonlinearity is considered to be highly illogical.

P.G. Drazin defines nonlinear systems as a set of nonlinear equations. These can be algebraic, functional, ordinary differential, partial differential, integral or a combination of these. Due to the lack of understanding in them, nonlinear systems are often defined by what they are not, meaning that a nonlinear system is a system that fails to be linear, and unlike linear systems, they are very unpredictable and chaotic.

3.1 Population Models

Nonlinear systems can be applied to many different fields. One of these is population growth/decay. There are different models to explain this phenomena, from classical to more complex models. The easiest model is the single specie model, where $N(t)$ denotes the population at time t which can be shown in the following:

$$\frac{dN}{dt} = \text{births} - \text{deaths} + \text{migration}. \quad (3.1)$$

If births and migration are higher than the number of deaths then the system is set to grow exponentially. Otherwise, it will eventually decay to zero. From simpler systems, more precise models have been presented like the self limiting model. As $\frac{\text{birth}}{\text{death}} = r$ model can grow exponentially to infinity it is considered

obsolete, so the carrying capacity(or limit), K , is added to the ratio r , giving the following equation

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K} \right), \quad (3.2)$$

where both r and K are constants greater than zero, where r is considered to be the linear birth rate. As $t \rightarrow \infty$, the population will tend to K no matter what initial value is. When $t = 0$, we have the initial value N_0 , giving the equation

$$N(t) = \frac{N_0 K e^{rt}}{K + N_0(e^{rt} - 1)} = \frac{N_0 K}{K e^{-rt} + N_0(1 - e^{-rt})} \rightarrow \frac{N_0 K}{N_0} \quad \text{as } t \rightarrow \infty. \quad (3.3)$$

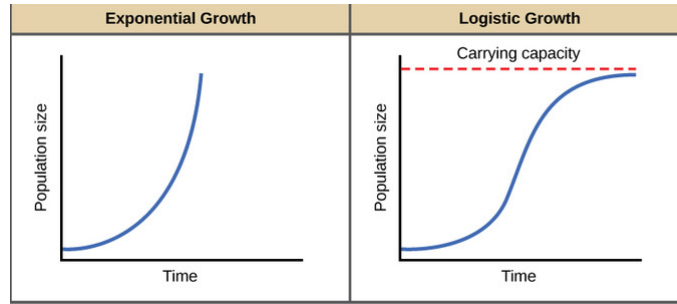


Figure 3.1: The graphs show how, without a carrying capacity, the population will grow infinitely (left). Shows the impact of a carrying capacity on the population, which shows the growth slowly reducing until it gets to the maximum population (right).[16]

Another important parameter to be considered is the harvesting ratio, which is the number of individuals removed from the population. This will be the subtraction of a constant, say E , multiplied by the total population from the equation (3.3), giving

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K} \right) - EN. \quad (3.4)$$

As the previous model states, K is the carrying capacity, which is the maximum population that sustained, whilst r denotes the growth rate. If $E > r$, then the harvesting constant is bigger than the growth rate resulting in the extinction of the population N .

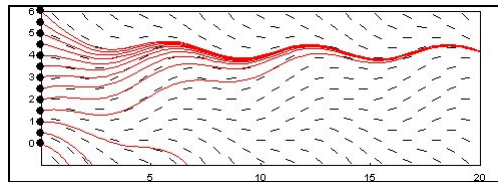


Figure 3.2: This graph shows how the population will die out if the harvesting constant is bigger than the growth rate. Once reached the maximum capacity it will fluctuate.[15]

An autonomous system in the form of a differential equation can be seen in the form

$$\frac{du}{dt} = f(u, v), \quad \frac{dv}{dt} = g(u, v). \quad (3.5)$$

Different types of species can interact and affect positively or negatively on a different specie. There are mainly three different types of relation:

- (a) When the presence of a species reduce the growth rate of another species, then the system is known as the predator-prey system.
- (b) If the growth rate of both species are decreased by the presence of each other then the system is called the competition system.
- (c) If both species' growth rate is enhanced to increase by the presence of the other then the system is called mutualism.

Considering case (a), in absence of a predator in the predator-prey system, the prey population will increase. The presence of a predator will reduce the number of prey, and also increase their population. However, in the absence of prey, the number of predators will decrease. These factors contribute to the following equation:

$$\frac{dN}{dt} = N(a - bP), \quad \frac{dP}{dt} = P(cN - d), \quad (3.6)$$

where a, b, c and d are positive constants.

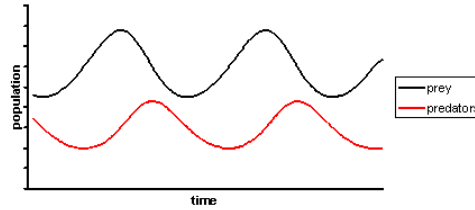


Figure 3.3: From the graph, we can deduce, that as the population of the prey increases, so does the population of the predators. However, when the number of the predators is higher it will have an impact on the population of the prey. This means the prey population decreases, which will then result in a cut of the predator's population.[14]

In a Competition system (b), the equations will differ as both species are endangered by the other. Therefore,

$$\frac{dN_1}{dt} = r_1 N_1 (1 - a_{12} N_2), \quad \frac{dN_2}{dt} = r_2 N_2 (1 - a_{21} N_1), \quad (3.7)$$

where r_1, r_2, a_{12} and a_{21} are constants greater than zero and the r_i are the two birth/death rates and a_{ij} is the competitive effect of population j on i .

Lastly, when a mutualism is experienced, both populations have a positive effect on the others population growth. This will give an equation with only positive

terms,

$$\frac{dN_1}{dt} = r_1 N_1 + a_1 N_1 N_2, \quad \frac{dN_2}{dt} = r_2 N_2 a_2 N_2 N_1, \quad (3.8)$$

where r_i and a_i are positive constants. In the real world, at least one of the species has a benefit, therefore a realistic model can be

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{K_1} + b_{12} \frac{N_2}{K_1} \right), \quad \frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_2}{K_2} + b_{21} \frac{N_1}{K_2} \right), \quad (3.9)$$

where both species have limited carrying capacities K_1 , K_2 and r_1, r_2, b_{12}, b_{21} are positive constants.

Chapter 4

Lyapunov Functions

Aleksandr Mikhailovich Lyapunov was a Russian mathematician that throughout the 19th and 20th century. He contributed to many mathematical concepts such as: **Lyapunov function**, Lyapunov's theorem, **Lyapunov stability** and many others. This chapter uses informations from [10] and [11].

Definition 3. A Lyapunov function is a scalar equation $V(x, y)$, and is defined in a region \mathfrak{D} that is continuous, positive definite where $V(x, y) > 0$ for all $(x, y) \in \mathfrak{D}$. It also has continuous first-order partial derivatives at every point of \mathfrak{D} . The derivative of V with respect to the system $(x, y)' = f(x, y)$, can be written as $V^*(x, y)$ is defined as the dot product:

$$V^*(x, y) = \nabla V(x, y) \cdot f(x, y) \quad (4.1)$$

We can also define the derivatives of the trajectories by also differentiating with respect to time.

Lyapunov functions are used in order to prove that a stationary point is Lyapunov stable. However, unlike the definition of Lyapunov stability, Lyapunov functions can be considered as energy functions. By working out the Lyapunov function, we can determine the energy of trajectory as it approaches the origin. The Lyapunov function can be denoted as $V(x, y)$, which is the zero solution of the system. This can be represented in the example below.

Example: Considering the system

$$\dot{x} = f(x, y), \quad (4.2)$$

$$\dot{y} = g(x, y), \quad (4.3)$$

where the point $(0, 0)$ is a stable steady state. A steady state is a solution of a differential equation that does not vary with t . This is explored in more detail in the next chapter. If the point $(0, 0)$ is a stable steady, then we say there exists some domain \mathfrak{D} , restricted around the neighbourhood of the origin as $t \rightarrow \infty$. Using the fact that $V(x, y)$ is the energy function and is greater

than 0 for $(x, y) \in \mathfrak{D}$ with $V = 0$ at the origin. We say that each trajectory in \mathfrak{D} approaches the origin with less energy as t tends to infinity meaning that $V(x, y)$ does decrease. $V(x, y)$ can be defined in some domain \mathfrak{D} containing the origin. Then:

1. $V(x, y)$ is positive definite if $V(0, 0) = 0$ and $V(x, y) > 0$ for all points in \mathfrak{D} .
2. $V(x, y)$ is negative definite if $V(0, 0) = 0$ and $V(x, y) < 0$ for all points in \mathfrak{D} .
3. $V(x, y)$ is positive semi definite if $V(0, 0) = 0$ and $V(x, y) \geq 0$ for all points in \mathfrak{D} .
4. $V(x, y)$ is negative semi definite if $V(0, 0) = 0$ and $V(x, y) \leq 0$ for all points in \mathfrak{D} .

Furthermore,

$$\frac{dV}{dt} = \frac{dx}{dt} \frac{\partial V}{\partial x} + \frac{dy}{dt} \frac{\partial V}{\partial y} \quad (4.4)$$

$$= \frac{\partial V}{\partial x} f(x, y) + \frac{\partial V}{\partial y} g(x, y). \quad (4.5)$$

The definition above only takes into consideration the positive definite case of $V(x, y)$. If $V(x, y)$ is a Lyapunov function, then $V(x, y)$ decreases along the trajectories, which therefore means $V(x, y)$ is strictly positive. However, these functions can be complicated, but the first step when finding the stability of the stationary point is to show that some trajectories stay in the neighbourhood of G .

Theorem 4. Suppose that G is a bounded domain in \mathbb{R}^n with boundary ∂G , and that $V : cl(G) \rightarrow \mathbb{R}$ is a Lyapunov function. If there exists $x_0 \in G$ such that $V(x) > V(x_0)$ for all $x \in \partial G$ then

$$S(x_0) = \{x \in cl(G) | V(x) \leq V(x_0)\}$$

is bounded set in G and $\varphi(x_0, t) \in S(x_0)$ for all $t \geq 0$.

4.1 Constructing a Lyapunov Function

Lyapunov functions can be constructed in four different ways: **The variable gradient** method, **Krasovskii's** method, **Zubov's** method and the **Energy-Casimir** method.

In the variable gradient method, it is assumed that the gradient is an unknown Lyapunov function and by integrating the assumed gradient, we can find the Lyapunov function.

Proposition 1: The function $g : \mathbb{R}^n \rightarrow \mathbb{R}^n$ is the gradient vector of a scalar-valued function $v : \mathbb{R}^n \rightarrow \mathbb{R}$ if and only if:

$$\frac{\partial g_i}{\partial x_j} = \frac{\partial g_j}{\partial x_i}, \quad i, j = 1, \dots, n. \quad (4.6)$$

Where $g_i(x) = \frac{\partial V}{\partial x_i}$.

Example: Consider the nonlinear system

$$\begin{aligned} \dot{x}(t) &= x_2(t), \quad \dot{x}_1(0) = x_{10}, \quad t \geq 0, \\ \dot{x}_2 &= -[x_1(t) + x_2(t)] - \sin(x_1(t) + x_2(t)). \end{aligned} \quad (4.7)$$

To construct a Lyapunov function for (4.7).

Let $g(x) = [a_{11}x_1 + a_{12}x_2, a_{21}x_1 + a_{22}x_2]^T$ and let $a_{12} = a_{21} = \beta$ such that the symmetry requirement (4.6) holds.

Now,

$$\dot{V}(x) = g^T(x)f(x) = (a_{11}x_1 + \beta x_2)x_2 - (\beta x_1 + a_{22}x_2)[(x_1 + x_2) + \sin(x_1 + x_2)]. \quad (4.8)$$

Taking $a_{11} = 2\beta$, $a_{22} = \beta$ and $\beta > 0$ it follows that

$$\dot{V}(x) = \beta x_1^2 - \beta(x_1 + x_2)\sin(x_1 + x_2) < 0, \quad (x_1, x_2) \in \mathfrak{D}. \quad (4.9)$$

Where $\mathfrak{D} \triangleq \{(x_1, x_2) : |x_1 + x_2| < \pi\}$.

Hence,

$$\begin{aligned} V(x) &= \int_0^1 [g_1(\sigma x_1, \sigma x_2)x_1 + g_2(\sigma x_1, \sigma x_2)x_2]d\sigma \\ &= \int_0^1 \beta[2x_1^2 + 2x_1x_2 + x_2^2]\sigma d\sigma \\ &= \beta x_1^2 + \beta x_1x_2 + \frac{1}{2}\beta x_2^2. \end{aligned} \quad (4.10)$$

Note that $V(0, 0) = 0$ and $V(x_1, x_2) = \frac{1}{2}\beta x_1^2 + \frac{1}{2}\beta(x_1 + x_2)^2$, $(x_1, x_2) \in \mathbb{R} \times \mathbb{R} \neq (0, 0)$ and hence $V(x)$, $x \in \mathfrak{D}$, is a Lyapunov function for (4.7).

Krasovskii's method imply that the following proposition is needed.

Proposition 2: Let $f, g : \mathbb{R}^n \rightarrow \mathbb{R}^n$ be continuously differentiable functions such that $f(0) = 0$ then for every $x \in \mathbb{R}^n$ there exists $\alpha \in [0, 1]$ such that,

$$g^T(x)f(x) = g^T(x)\frac{\partial f}{\partial x}(\alpha x)x. \quad (4.11)$$

Theorem 5. Let $x(t) \equiv 0$ be an equilibrium point for the system

$$\dot{x}(t)f(x(t)), \quad x(0) = x_0, \quad t \geq 0, \quad (4.12)$$

where $f : \mathfrak{D} \rightarrow \mathbb{R}^n$ is continuously differentiable and \mathfrak{D} is an open set with

$0 \in \mathfrak{D}$. Assume there exist positive matrices $P \in \mathbb{R}^{n \times n}$ and $R \in \mathbb{R}^{n \times n}$ such that

$$\left[\frac{\partial f}{\partial x}(x) \right]^T P + P \left[\frac{\partial f}{\partial x}(x) \right] - R, \quad x \in \mathfrak{D}, \quad x \neq 0, \quad (4.13)$$

then the zero solution $x(t) \equiv 0$ to (4.12) is a unique asymptotically stable equilibrium with Lyapunov function $V(x) = f^T(x)Pf(x)$. In addition, if $\mathfrak{D} = \mathbb{R}^n$, then the zero solution $x(t) \equiv 0$ to (4.12) is a unique globally asymptotically stable equilibrium.

This is known as Krasovskii's theorem.

Example: Consider the nonlinear system

$$\begin{aligned} \dot{x}_1(t) &= -3x_1(t) + x_2(t), & x_1(0) &= x_{10}, & t &\geq 0, \\ \dot{x}_2 &= x_1(t) - x_2(t) - x_2^3(t), & x_2(0) &= x_{20}. \end{aligned} \quad (4.14)$$

Note that $(0, 0)$ is the equilibrium point of (4.14).

Next, evaluating

$$\frac{\partial f}{\partial x} = \begin{bmatrix} \frac{\partial f_1(x)}{\partial x_1} & \frac{\partial f_1(x)}{\partial x_2} \\ \frac{\partial f_2(x)}{\partial x_1} & \frac{\partial f_2(x)}{\partial x_2} \end{bmatrix} = \begin{bmatrix} -3 & 1 \\ 1 & -1 - 3x_2^2 \end{bmatrix}, \quad (4.15)$$

it can be easily be shown that (4.12) holds with $P = I_2$ and $R = I_2$ so that all the conditions of Krasovskii's theorem are satisfied.

Hence, the zero solution $(x_1(t), x_2(t)) \equiv (0, 0)$ to (4.14) is globally asymptotically stable with Lyapunov function $V(x) = f^T(x)Pf(x) = f^T(x)f(x) = (-3x_1 + 3x_2)^2 + (x_1 - x_2 - x_2^2)^2$.

Unlike the previous two methods, **Zubov's method** characterizes a domain of attraction for a given nonlinear system. This is known as Zubov's theorem, which is the following:

Theorem 6. Consider the nonlinear system with $f(0) = 0$. Let $\mathfrak{D} \subset \mathbb{R}^n$ be bounded and assume there exists a continuously differentiable function $V : \mathfrak{D} \rightarrow \mathbb{R}$ and a continuous function $h : \mathbb{R}^n \rightarrow \mathbb{R}$ such that $V(0) = 0, h(0) = 0$ and

$$0 < V(x) < 1, \quad x \in \mathfrak{D}, \quad x \neq 0 \quad (4.16)$$

$$V(x) \rightarrow 1 \quad \text{as} \quad x \rightarrow \partial\mathfrak{D}, \quad (4.17)$$

$$h(x) > 0, \quad x \in \mathbb{R}^n, \quad x \neq 0, \quad (4.18)$$

$$V'(x)f(x) = h(x)[1 - V(x)]. \quad (4.19)$$

Then the zero solution $x(t) \equiv 0$ is asymptotically stable with domain of attraction \mathfrak{D} .

Example: Consider the second-order nonlinear dynamical system

$$\begin{aligned} \dot{x}_1 &= f_1(x_1) + f_2(x_2), & x_1(0) &= x_{10}, \\ \dot{x}_2 &= -f_3(x_1), & x_2(0) &= x_{20}, \end{aligned} \quad (4.20)$$

where, $f_i(0) = 0$, $\sigma f_i(0) > 0$, $\sigma \in (-a_i, b_i)$ for $i = 1, 2, 3$, $a_1 = a_3$, $b_1 = b_3$, and $\int_0^y f_i(s)ds \rightarrow \infty$ as $y \rightarrow -a_i$ or $y \rightarrow b_i$, for $i = 2, 3$.
Next, let $h(x) = f_1(x_1)f_3(x_1)$ and let $V(x)$ be of the form $V(x) = 1 - Y_1(x_1)V_2(x_2)$, where $V_i : \mathbb{R} \rightarrow \mathbb{R}$, $V_i(0) = 1$, $i = 1, 2$.
Now, it follows from (4.19) that

$$[V_1'(x_1) + f_3(x_1)]V_2(x_2)f_1(x_1) + [V_2'(x_2)V_1(x_1)f_3(x_1) - V_1'(x_1)V_2(x_2)f_2(x_1)] = 0, \quad (4.21)$$

which can be satisfied by setting

$$V_1'(x_1) = -f_3(x_1)V_1(x_1),$$

and

$$V_2'(x_2) = -f_2(x_2)V_2.$$

Hence (4.19) holds with

$$V(x) = 1 - \exp \left[- \left(\int_0^{x_1} f_3(s)ds + \int_0^{x_2} f_2(s)ds \right) \right]. \quad (4.22)$$

Note that (4.22) satisfies $V(0) = 0$, (4.16), (4.17) for all $x \in \mathfrak{D} = \{x \in \mathbb{R}^2 : -a_i < x_i < b_i\}, i = 1, 2$.

Moreover, it can be easily shown that $V(x) = -f_1(x_1)f_3(x_1)[1 - V(x)] \leq 0$ which proves that it is Lyapunov stable (4.20).

To show asymptotically stability, we consider that $\dot{V}(x) = 0$, which implies that $f_1(x_1)f_3(x_1) = 0$. This further implies $x_1 = 0$. Furthermore $x_1(t) \equiv 0$ implies $f_2(x_2(t)) \equiv 0$, which suggests $x_2(t) \equiv 0$.

Hence, with $\mathfrak{D}_C = \bar{\mathfrak{D}}$, it follows that the zero solution $(x_1(t), x_2(t)) \equiv (0, 0)$ to (4.20), which means it is asymptotically stable in the domain of attraction $\bar{\mathfrak{D}}$.

Theorem 7. Consider the nonlinear system where $f : \mathfrak{D} \rightarrow \mathbb{R}^n$ is Lipschitz continuous on \mathfrak{D} . Let $x_e \in \mathfrak{D}$ be an equilibrium point and let $C_i : \mathfrak{D} \rightarrow \mathbb{R}, i = 1, \dots, r$ be a Casimir function. Assume that the vectors $C_i'(x_e), i = 2, \dots, r$ are linearly independent and suppose that there exists $\mu = [\mu_1, \dots, \mu_r]^T \in \mathbb{R}^r$ such that $\mu_1 \neq 0, E'(x_e) = 0$, and $x^T E''(x_e)x > 0, x \in \mathfrak{M}$ where $\mathfrak{M} \triangleq \{x \in \mathfrak{D} : c_i'(x_e)x = 0, i = 2, \dots, r\}$. Then there exists $\alpha \geq 0$ such that

$$E''(x_e) + \alpha \sum_{i=2}^r \left(\frac{\sigma C_i}{\sigma x}(x_e) \right)^T \left(\frac{\sigma C_i}{\sigma x} \right) > 0. \quad (4.23)$$

Furthermore, the equilibrium solution $x(t) \equiv x_e$ is Lyapunov stable with Lyapunov function

$$V(x) = E(x) - E(x_e) + \frac{\alpha}{2} \sum_{i=2}^r [C_i(x) - C_i(x_e)]^2. \quad (4.24)$$

This is known as the Energy-Casimir theorem.

Example: Consider the nonlinear dynamical system representing a rigid spacecraft given by

$$\begin{aligned}\dot{x}_1(t) &= I_{23}x_2(t)x_3(t), & x_1(0) &= x_{10}, & t &\geq 0 \\ \dot{x}_2(t) &= I_{31}x_3(t)x_1(t), & x_2(0) &= x_{20}, \\ \dot{x}_3(t) &= I_{12}x_1(t)x_2(t), & x_3(0) &= x_{30}.\end{aligned}\tag{4.25}$$

To show that the equilibrium solution $x(t) \equiv x_e$, where $x_e = [0, 0, x_{3e}]^T$ to (4.25) is Lyapunov stable, we must consider the fact that

$$C_1(x) = \frac{1}{2}(I_1x_1^2 + I_2x_2^2 + I_3x_3^2),\tag{4.26}$$

$$C_2(x) = \frac{1}{2}(I_1^2x_1^2 + I_2^2x_2^2 + I_3^2x_3^2),\tag{4.27}$$

are Cashmir functions for (4.25).

Now letting $E(x) = \mu_1 C_1(x) + \mu_2 C_2(x)$, it follows that $E'(x_e) = 0$ and $x^T E''(x_e)x > 0, x \in M, x \neq (0)$ are satisfied with $\mu_1 = -I_3$ and $\mu_2 = 1$.

Next, using

$$V(x_1, x_2, x_3) = E(x_1, x_2, x_3) - E(0, 0, x_{3e}) + \frac{\alpha}{2}[C_2(x_1, x_2, x_3) - C_2(0, 0, x_{3e})]^2,\tag{4.28}$$

it follows that Q in $V''(x_e) = S^T \begin{bmatrix} E_1 & E_{12} \\ E_{12}^T & E_2 + \alpha N \end{bmatrix} S \triangleq S^T Q S$ is given by

$$Q = \begin{bmatrix} I_1(I_1 - I_3) & 0 & 0 \\ 0 & I_2(I_2 - I_3) & 0 \\ 0 & 0 & \alpha I_3^4 x_{3e}^2 \end{bmatrix}.\tag{4.29}$$

Note that $Q > 0$ for every $\alpha > 0$. Hence it follows from Energy-Casimir theorem that the equilibrium solution $x(t) \equiv x_e$ to (4.25) is Lyapunov stable with Lyapunov function (4.28).

Theorem 8. Suppose that G is a bounded domain in \mathbb{R}^n with boundary ∂G , and that $V : cl(G) \rightarrow \mathbb{R}$ is a Lyapunov function. If there exists $x_0 \in G$ such that $V(x) > V(x_0)$ for all $x \in \partial G$ then

$$S(x_0) = \{x \in cl(G) | V(x) \leq V(x_0)\}$$

is bounded set in G and $\varphi(x_0, t) \in S(x_0)$ for all $t \geq 0$.

4.2 Lyapunov First Stability Theorem

One way in which Lyapunov believed that stability could be determined was by his First Stability Theorem.

Theorem 9. Suppose that a Lyapunov function can be defined on a neighbourhood of the origin $x = 0$, which is a stationary point of differential equation $\dot{x} = f(x)$.

Example: Considering the differential equation

$$\begin{aligned}\dot{x} &= -x + x^3 - 3xy, \\ \dot{y} &= -3y - 4xy + 3y^2,\end{aligned}\tag{4.30}$$

we know that the origin is a stationary point. However, we want to see whether or not it is Lyapunov stable. Firstly, we assume that the trial function is $V(x, y) = \frac{1}{2}(x^2 + y^2)$ which gives

$$\dot{V}(x, y) = x\dot{x} + y\dot{y} = x(-x + x^3 - 3xy) + y(-3y - 4xy + y^2),\tag{4.31}$$

or

$$\dot{V}(x, y) = -x^2(1 - x^2 + 3y) - y^2(3 + 4x - y).\tag{4.32}$$

This has proved that $V(x, y)$ is a Lyapunov function, provided $(1 - x^2 + 3y)$ and $(3 + 4x - y)$ are positive on some neighbourhood of $(x, y) = (0, 0)$. This is true, so we can set G to be any open bounded subset containing $(0, 0)$

$$\{(x, y) | x^2 - 3y < 1, \quad 4x - y > 3\}.\tag{4.33}$$

4.3 Lyapunov Second Stability Theorem

Theorem 10. Suppose $x = 0$ is a stationary point $\partial x = f(x)$ and let $V(x, y)$ be a Lyapunov function on a neighbourhood G of $x = 0$. If $\dot{V}(x, y) < 0$ for all $x \in G \setminus \{0\}$, then $x = 0$ is asymptotically stable.

In other words, using the system from (4.2) and (4.3) we can then say that there exists a function $V(x, y)$ such that

1. If $\frac{dV}{dt} = \frac{\partial V}{\partial x}f(x, y) + \frac{\partial V}{\partial y}g(x, y)$ is a negative semi definite which means the steady state is stable.
2. If $\frac{dV}{dt} = \frac{\partial V}{\partial x}f(x, y) + \frac{\partial V}{\partial y}g(x, y)$ is negative definite which means the steady state is asymptotically stable.
3. If $\frac{dV}{dt} = \frac{\partial V}{\partial x}f(x, y) + \frac{\partial V}{\partial y}g(x, y)$ is positive definite which means the steady state is unstable.

Example: Given the system

$$\frac{dx}{dt} = -y + \alpha x(x^2 + y^2), \quad \alpha \in \mathbb{R}\tag{4.34}$$

$$\frac{dy}{dt} = x + \alpha y(x^2 + y^2),\tag{4.35}$$

suppose that $V(x, y) = x^2 + y^2$, then

$$\frac{\partial v}{\partial t} = \frac{\partial v}{\partial x}f + \frac{\partial v}{\partial y}g.\tag{4.36}$$

Substituting in the values to (4.36)

$$\begin{aligned}
 \frac{dV}{dt} &= 2x[-y + \alpha x(x^2 + y^2)] + 2y[x + \alpha y(x^2 + y^2)] \\
 &= \alpha x(x^2 + y^2) + \alpha y(x^2 + y^2) \\
 &= \alpha x(x^2 + y^2)^2.
 \end{aligned} \tag{4.37}$$

We can conclude that $\frac{dV}{dt} < 0$ and Lyapunov's theorem ensures that the origin is:

1. **Asymptotically stable** when $\alpha < 0$, which can be seen in Figure (4.1),
2. **Stable** if $\alpha = 0$.
3. **Unstable** if $\alpha > 0$ which can be in seen Figure (4.2).

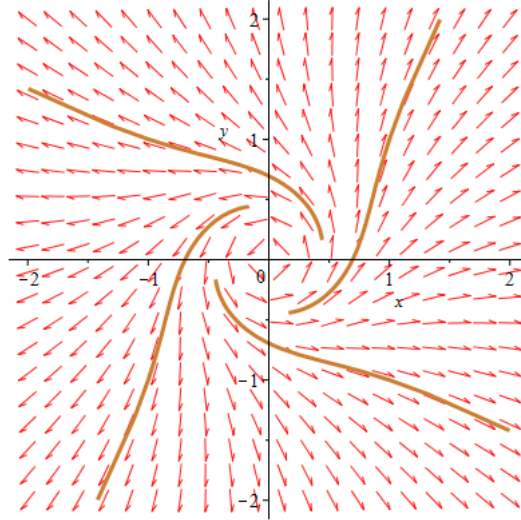


Figure 4.1: Shows a phase portrait when $\alpha < 0$ and the steady state is asymptotically stable. The maple calculations for this graph can be seen in the appendix.

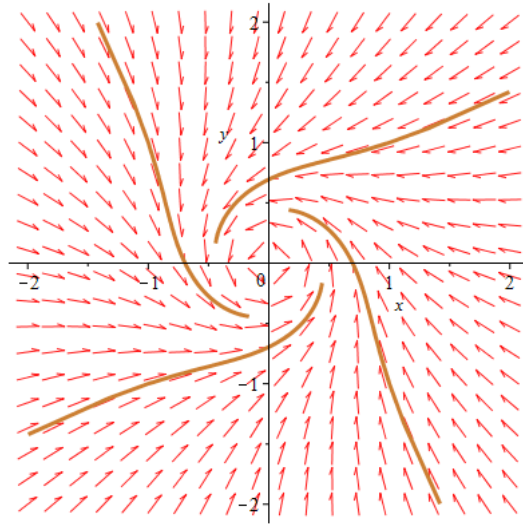


Figure 4.2: Shows a phase portrait when $\alpha > 0$ and the steady state is asymptotically stable. The maple calculations

Chapter 5

Scalar Equations and Stability

In this chapter we will be exploring the concept of scalar equations and what effect scalar equations have on nonlinear systems. We will also explore what a scalar equation is and how it relates to stability and also, steady states. In this chapter we will be using information from Stability is very hard to define due to the vast amount of problems it can be applied to. One focus of this chapter will be to explore the key definitions of steady states and an in depth analysis of what these definitions mean. Another aspect of this chapter will be to explore the stability of steady states and how they can be worked out using various methods. In this chapter, we will use the sources of [3], [4], [7], [11] and [12] to help provide us with information for this chapter.

Definition 11. A steady state of a differential equation is the solution which does not vary with t .

General case: Consider the first order differential equation

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \quad (5.1)$$

then the steady state of this equation is

$$\dot{x} = 0 \implies \dot{x} = x^* \in \mathbb{R}. \quad (5.2)$$

Example: Looking at the equation

$$\dot{x} = 3x - 1, \quad (5.3)$$

we then replace x with x^* , which denotes the steady state

$$-3x^* + 1 = 0, \quad (5.4)$$

this result in

$$x^* = \frac{1}{3}. \quad (5.5)$$

5.1 Phase Plane Analysis of First Order Differential Equations

Phase planes are very useful in visualising the dynamics (behaviours) of a ODE system. They are extremely useful in Mathematical Biology. There are many processes in chemical reactions that can be applied to a phase plane. They can be used to determine whether the dynamics are stable or unstable in an ODE. Phase planes can be easily applied to Chemical Kinetics due to the fact that we can formulate them as an ODE system and visualize them onto a phase plane. They help map out the rise and fall of a reactant and the concentration of a substance.

Given A is a diagonalizable matrix, the determinant $\det(A - \lambda I) = 0$ results in us getting the characteristic polynomial

$$\lambda^2 - \text{tr}(A)\lambda + \det(A) = 0. \quad (5.6)$$

The solution of each eigenvalue is given by the quadratic equation;

$$\lambda = \frac{1}{2}(\text{tr}(A) \pm \sqrt{\Delta}). \quad (5.7)$$

Rearranging (5.7), we get

$$\Delta = (\text{tr}(A))^2 - 4 \cdot \det(A). \quad (5.8)$$

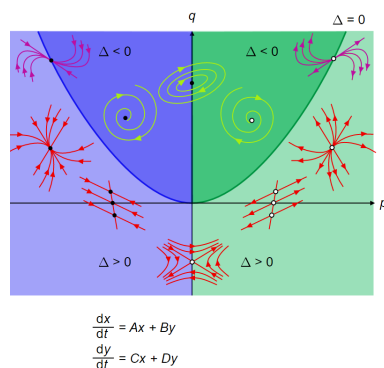


Figure 5.1: Behaviour of different types of equilibrium points of a linear autonomous system.[13]

We can see an example of a **phase portrait** in Figure(5.1). Usually phase portraits only include the trajectories of the solutions. To set up a phase plane, we need to sketch two straight lines which represent the two eigenvectors. We know that the system either converges or diverges towards these eigenvalues. The direction of the phase plane is plotted by using full lines. By determining whether the eigenvalues are positive or negative, we can see the dynamics of the system. The dynamics of the system can be defined by the following descriptions:

- The intersection of the eigenvectors is said to be a **saddle point** if the eigenvalues are positive and negative.

- The intersection is said to be an **unstable node**, if the eigenvalues are both positive. The eigenvectors represent stable situations in which the system diverges away.
- The intersection is said to be a **stable node** if the eigenvalues are both negative. The eigenvectors represent stable situations such that the system converges.

An important fact to be considered is that this is the linear case.

5.2 Bifurcation Diagram for First Order Differential Equations

In the next section, we will be using this basic understanding of phase planes to obtain a Bifurcation Diagram. In last section, we talked about phase planes, however, in this section we will see how stability can be combined with phase planes to create a diagram called the bifurcation diagram. Bifurcation diagrams can predict the long term behaviour of the system, when its parameter is varied. Along with the bibliographical reference we referred to in the beginning of this chapter, we will also be using [6], [8] and [13] in this section.

We can apply Bifurcation diagram in Biology to give us a basic idea of understanding the behaviour of a biological system. The ability to make dramatic changes in the output system is essential to organism functionality. In this section, we will be focusing on the first order linear and nonlinear case. We will talk about the meaning of x^* in chapter 3.

5.2.1 First Order Linear Case

Considering k as the parameter of the ODE model $\frac{dx}{dt} = kx$, then we can clearly see that this is linear.

Let us consider $k < 0$,

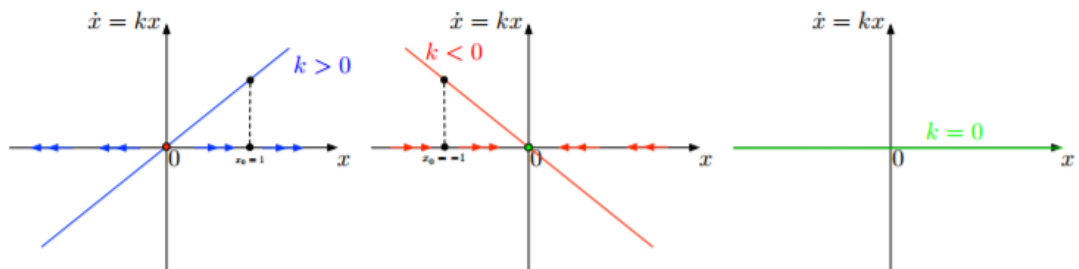


Figure 5.2: This outline the case when a) $k > 0$, b) $k < 0$, c) $k = 0$ [3]

a) When $k > 0$:

- When $x_0 > 0$, $\frac{dx}{dt} > 0$, as x increases when $x \rightarrow \infty$.
- When $x_0 = 0$, $\frac{dx}{dt} = 0$, x stays at 0. If x is perturbed, it diverge to $\pm \rightarrow \infty$
- When $x_0 < 0$, $\frac{dx}{dt} < 0$, x decreases when $x \rightarrow -\infty$.

The graph indicates that $k > 0$ which means it is unstable

- $x_0 > 0$, $\frac{dx}{dt} < 0$, as x decreases when $x \rightarrow \infty$.
- $x_0 = 0$, $\frac{dx}{dt} = 0$, x stays at 0.
- $x_0 < 0$, $\frac{dx}{dt} > 0$, x increases when $x \rightarrow -\infty$.

The graph indicates that $k < 0$ which mean it is stable.

c) When $k = 0$, then $\frac{dx}{dt}$ will always be 0.

If we combine these 3 pictures together, we get the following diagram

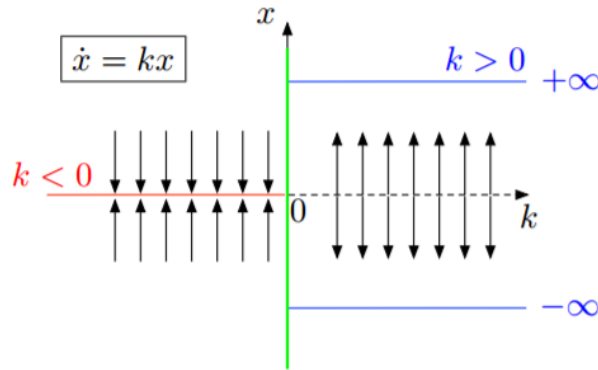


Figure 5.3: This graph shows a combination of $k > 0$, $k = 0$ and $k < 0$. [3]

5.2.2 First Order Nonlinear Case

In the nonlinear case, there are 3 types of bifurcation. These are: **Saddle node**, **Transcritical** and **Pitchfork**. Here we will use the parameter of r to avoid the confusion with the first order linear case.

a) **Saddle-node Bifurcation**: Consider the model,

$$\dot{x} = r + x^2. \quad (5.9)$$

Similar to the first order linear case, we can consider different values of the parameter r and express them onto a phase plane.

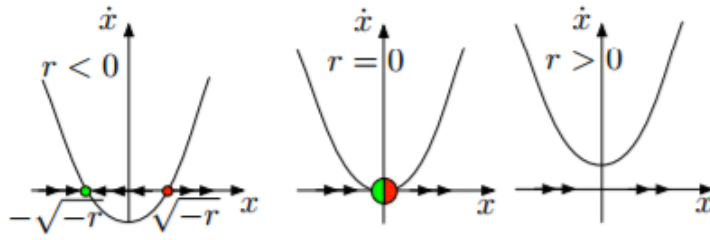


Figure 5.4: These 3 diagrams show the behaviour for $r < 0$, $r = 0$ and $r > 0$. [3]

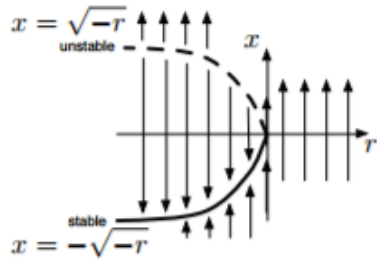


Figure 5.5: Shows Saddle-node Bifurcation. When r is increasing from negative to positive values, the two fixed points merge at $r = 0$ and disappear for $r > 0$. The saddle-node bifurcation is formed by combining a stable and an unstable fixed point. [3]

b) Transcritical Bifurcation Consider the model

$$\dot{x} = x(r - x). \quad (5.10)$$

There are always two fixed points in this case, one at $x = 0$ and the another at $x = r$.

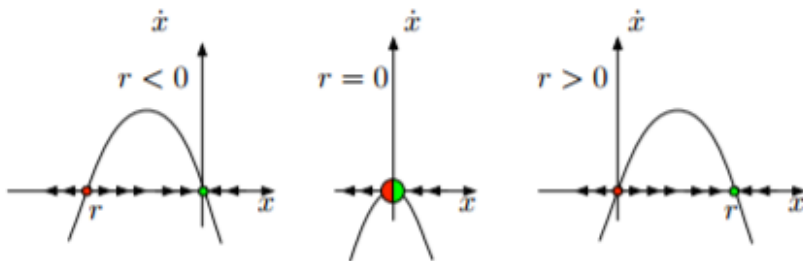


Figure 5.6: These 3 diagrams shows the behaviour for $r < 0$, $r = 0$ and $r > 0$. [3]

The Pitchfork bifurcation diagram is shown below. This has fixed points at $x = \pm\sqrt{r}$.

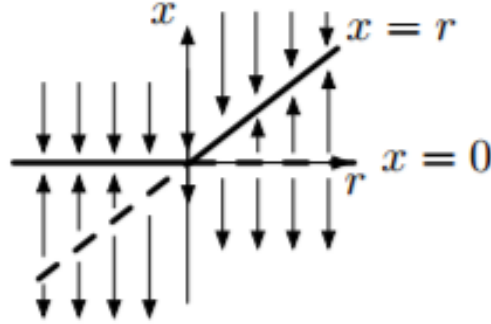


Figure 5.7: **Pitchfork bifurcation diagram.** At $r = 0$, there is a reversal in the stability of the fixed points, where everything that used was stable becomes unstable and vice versa.[3]

c) Pitchfork Bifurcation

Consider the model

$$\dot{x} = x(r \pm x^2). \quad (5.11)$$

In this model we have 2 cases,

For r negative, there is always a fixed point at $x = 0$. While for $r > 0$, there are two fixed points at $x = \pm\sqrt{r}$ as shown below.

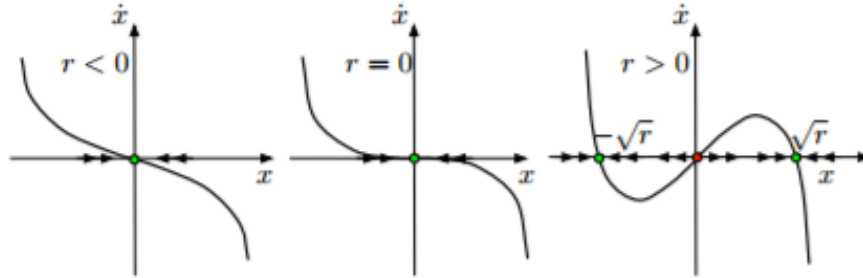


Figure 5.8: These 3 diagrams are showing the behaviour when $r < 0$, $r = 0$ and $r > 0$. [3]

If we combine the 3 diagrams together, we get that diagram in Figure 6.11.

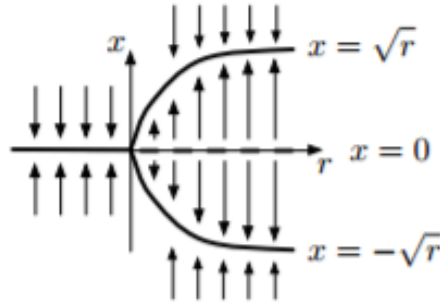


Figure 5.9: This is Pitchfork Bifurcation, when the value of the parameter is changing, 2 new fixed stable points are created whilst the third fixed point becomes unstable. This type of pitchfork bifurcation is said to be supercritical.[3]

Considering the positive case,

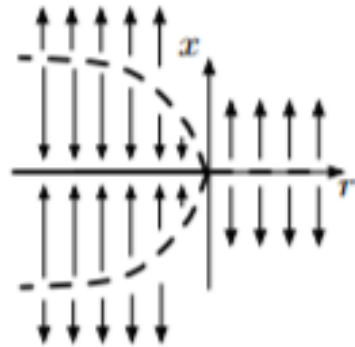


Figure 5.10: **Pitchfork Bifurcation** occurs when the parameter is changing. Two new unstable fixed points are created while the first fixed point becomes unstable. [3]

5.3 Meaning of Stability

To explore differential equations and their stability, we have to take into consideration the type of stability we are looking for from the differential equation itself.

We can apply this basic concept to equations that dictate the paths in which a particle moves in order to get a better understanding of stability. First we take a particle positioned at the origin. If the particle is not in the correct position, then this will result in the particle not getting any better overtime due to the fact that it does not get any better overtime as it stays the same distance from the origin. This tells us that the equation is unstable. This causes us to come

to the conclusion that a stationary point is always stable due to the fact that solutions near to the point tend to it. Similarly, if we place the particle close to the origin and a small error causes no impact on the overall outcome, then the stationary point is stable because it stays near the origin throughout its whole motion. These two types of stability will be explored in further detail during this section. Note that that we have used information and visual representations from pages 25-46 from [7] to write this section and further proofs of definitions used in this chapter can be here.

In the beginning of this section we described two types of stability. The first one described **Lyapunov stability** which occurs when points that start nearby stay nearby. The other definition described is called **quasi-asymptotic stability**. This means that any points that stay nearby the stationary point tend to it. If a point is quasi-asymptotically stable and Lyapunov stable then we say it is asymptotically stable. Examples of these different types of stability will be seen in further detail in this section when they are described in more detail. Note that φ denotes the flow of an autonomous differential system such that φ is the solution to the differential equation.

Definition 12. A point x is quasi-asymptotically stable('tends to eventually') if and only if there exists $\delta > 0$ such that $|x - y| < \delta$ then stable (starts near stay near') if for all $\varepsilon > 0$ there exists $\delta > 0$ such that if $|x - y| < \delta$, then

$$|\varphi(x, t) - \varphi(y, t)| \rightarrow 0, \quad (5.12)$$

as $t \rightarrow \infty$. A further point to be considered is that this definition only considers the limit when t tends to ∞ . This definition is illustrated in (5.11b)

Definition 13. A point x is asymptotically stable('tends to directly') if and only if it is both Lyapunov stable and quasi-asymptotically stable. This is illustrated in (5.11c)

A further point to be considered is that if a stationary point is asymptotically stable, then a neighbourhood of the stationary point must exist. This means that all the points inside this neighbourhood must tend to the stationary point. The largest neighbourhood in which this is satisfied is known as the basin of attraction.

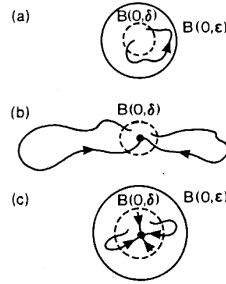


Figure 5.11: Shows visual representations of a) Lyapunov, b) quasi-asymptotic and c) asymptotic stability when it follows the path of a particle.

5.4 Strong Linear Stability

Sometimes, constructing a Lyapunov function can be a complicated task. This can be done by finding the stationary points of the differential equation and then by substituting these points into the Jacobian matrix, created from the differential equation, in order to find the eigenvalues. From the eigenvalues we obtain, we can see whether the system is asymptotically stable or not.

Theorem 14. Suppose $\dot{x} = f(x)$ has linearisation $\dot{x} = Ax$ at $x = 0$. If A has n distinct eigenvalues, each of which has strictly negative real part then, $x = 0$ is asymptotically stable.

Theorem 14 is true, even if the eigenvalues of A are not distinct. It is sufficient that A has eigenvalues with strictly negative real parts

Example:

$$\dot{x} = x(y + 1) \quad (5.13)$$

$$\dot{y} = 6x - 3y + x^2 - 3y^2 \quad (5.14)$$

We look for the stationary points using $\dot{x} = 0$ and $\dot{y} = 0$. By looking at equation (5.13), we can see that $x = 0$ or $y = -1$. By substituting $x = 0$ into (5.14) with $\dot{y} = 0$ gives $y = 0$ or $y = -1$. Also, when $y = -1$ results in us getting $x = 0$ and $x = -6$. From these values we deduce that there are three stationary points which are $(x, y) = (0, 0), (0, -1), (-6, -1)$. The Jacobian matrix

$$\begin{pmatrix} y - 1 & x \\ 3 + 2x & -2 - 4y \end{pmatrix}. \quad (5.15)$$

We need this matrix in order to find the eigenvalues of the matrix at the three stationary points. At $(0, 0)$ the matrix becomes

$$\begin{pmatrix} -1 & 0 \\ 3 & -2 \end{pmatrix}. \quad (5.16)$$

Due to the fact that the eigenvalues are -1 and -2 , we see that both values are negative, so we can expect the origin to be asymptotically stable. At the other two stationary points, one eigenvalue value is positive and the other is negative meaning that we cannot say that these points are asymptotically stable.

Chapter 6

Reaction Kinetics

6.1 Basic Enzyme Kinetics

Enzymes play a central role in many biological processes. An example of this is when enzymes are used breakdown food in our digestive system. Many diseases are caused by the deficiency of enzyme whilst, on the other hand, many treatments act by interacting with enzymes. The **Law of Mass Action** is the basic idea of Enzyme Kinetics. Its aim is to analyse more complex reactions and involves two or more elements in a reaction step. For this to be valid, we need to keep the temperature constant, the number of molecules must be large and mixed very well. Most of the information in this chapter will be based on the book stated in [1], however, the sources of [2],[5],[6] and [7] have also provided us with the necessary help.

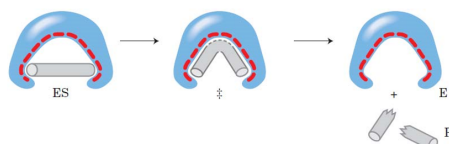


Figure 6.1: The graph shows that the complex ES which is a formed when a substrate and an enzyme is combined. It also show when E and P are broken into two elements again.

This will be discussed in way more detail in Section(6.3).

6.2 Non-Reversible Kinetic Reaction

The Transition State Theory(TST) is one of the best known examples of first order DE in Biology.

TST is the reaction rate of elementary chemical reactions. The theory indicates a special type of chemical equilibrium (known as quasi-equilibrium) between elements and activated in transition state complexes. TST is used to understand qualitatively how chemical reactions work.

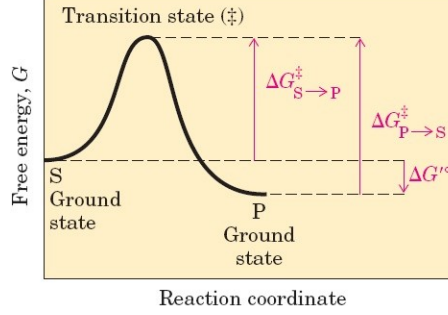


Figure 6.2: The equilibrium of a reaction is linked to the variation of biochemical standard free energy ΔG . However, the velocity depends on the activation energy, $\Delta G_{s \rightarrow p}$.

Consider a model of reaction



where S and P are the ground state of substrate of 2 elements respectively. The notation " \rightarrow " means that the reaction would only go one way. A constant parameter associated with these rates of the reaction is known as k . The reaction rate k , is affected by the concentration of reaction. From the TST it is possible to derive the relation

$$k = \frac{KT}{h} \exp \left[\frac{\Delta G}{RT} \right], \quad (6.2)$$

where K is Boltzmann constant¹, h is Plank constant², R is the universal gas constant³ and T is thermodynamic temperature.

This rate of reaction is proportional to the concentrations of the reactant. We use the lower case letter to denote the concentrations of the reactants

$$s = [S], \quad p = [P], \quad (6.3)$$

where $[]$ denotes the concentrations. We now apply it into ODE system, we obtain

$$V = \frac{dp}{dt} = ks. \quad (6.4)$$

¹Boltzmann constant is a physical constant relating energy at the individual particle level with temperature, which equals to $1.38064852 \times 10^{-23} m^2 kg s^{-2} K^{-1}$

²Planck constant is a physical constant that is the quantum of action, which equals to $6.62607004 \times 10^{-34} m^2 kg/s$

³Gas Constant is the constant in the equation for the Ideal Gas Law: $PV = nRT$. where P is pressure, V is volume, n is number of moles, and T is temperature. The value of the gas constant ' R ' depends on the units used for pressure, volume and temperature. $R = 0.0821 liter \Delta atm / mol \Delta K$

This equation is referring to the velocity, V .

If S is turning P , then each molecule of S which appears must correspond to a molecule of P , which disappeared. Thus, we have

$$\frac{ds}{dt} = -ks. \quad (6.5)$$

To obtain the future behaviour, the initial value of the variables have to be found. We integrate (6.5) by using the idea (2.7) and (2.6). We have

$$s(t) = s(0) \exp(-kt). \quad (6.6)$$

Then we can also solve p by substituting (6.6) into (6.4). We obtain

$$p(t) = P(0) + s(0)(1 - \exp(-kt)), \quad (6.7)$$

from (6.7), (6.6), we know that s decays exponentially to 0 which means p rises exponentially to its steady states.

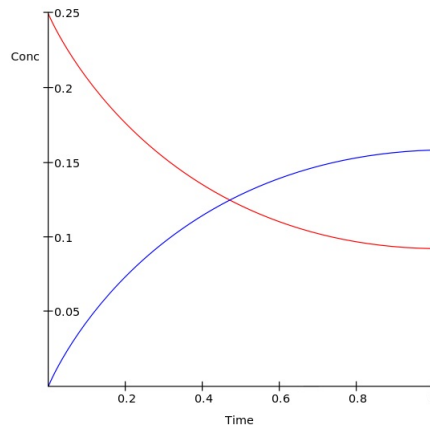


Figure 6.3: Dynamics of the concentrations in first order, $s \rightarrow p$.

6.3 Reversible Kinetic Reaction

As we have mentioned in Chapter 1, the component of a linear ODE is determined by the number of dependent variables. If we assume that the equation is a reversible reaction, such that



Similar to previous section, k_1 and k_{-1} are constant parameters. The double arrow \rightleftharpoons is a concise notation for the forward and backward reactions. We now

express this as the following



We should be able to obtain the same equation as (2.1), which is

$$\begin{pmatrix} \frac{ds}{dt} \\ \frac{dp}{dt} \end{pmatrix} = \begin{pmatrix} -1 & 1 \\ 1 & -1 \end{pmatrix} \begin{pmatrix} s \\ p \end{pmatrix}. \quad (6.10)$$

If we apply the method we used in (2.3), we will obtain the same solution as (2.20) where

$$X(t) = \frac{1}{\sqrt{2}} \left(\begin{pmatrix} 1 \\ 1 \end{pmatrix} + \begin{pmatrix} 1 \\ -1 \end{pmatrix} \right) e^{-2t}. \quad (6.11)$$

6.4 Michaelis–Menten Model

Enzyme Catalysed Reactions

Enzymes are the proteins that convert substrates into products and remain unchanged. Additionally, the rate of production depends nonlinearly on the concentration as

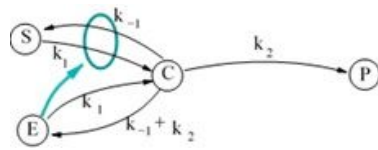
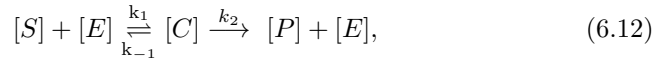


Figure 6.4: The graph indicates the mass of law between $[S]$, $[E]$, $[C]$, $[P]$.

where $[S]$ is the substrate, $[E]$ is the enzyme, $[C]$ is the complex $[ES]$ and $[P]$ is the Product.

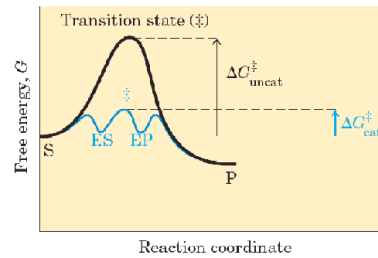


Figure 6.5: The graph shows the transition state between $[S] + [E]$ and $[P] + [E]$.

As well as (6.3) we use the lower case letter s, e, c, p respectively. We then express it in the ODE

$$\begin{aligned}\frac{ds}{dt} &= -k_1se + k_{-1}c, & \frac{de}{dt} &= -k_1se + (k_{-1} + k_2)c, \\ \frac{dc}{dt} &= k_1se - (k_{-1} + k_2)c, & \frac{dp}{dt} &= k_2c,\end{aligned}\tag{6.13}$$

with initial conditions

$$S(0) = s_0, \quad e(0) = e_0, \quad C(0) = 0, \quad p(0) = 0.\tag{6.14}$$

We can simplify by eliminating the ODEs, then $\frac{dp}{dt}$ is uncoupled from the others. However, we can obtain $p(t)$ by integration when we have $c(t)$. By the conservation of mass, $\frac{de}{dt}$ and $\frac{dc}{dt}$ can be eliminated by each other.

$$\frac{de}{dt} + \frac{dc}{dt} = 0 \Rightarrow e(t) + c(t) = e_0 = \text{constant}.\tag{6.15}$$

Using the initial conditions from (6.14), we reduced to only two ODEs $\frac{ds}{dt}$ and $\frac{dc}{dt}$, namely

$$\begin{aligned}\frac{ds}{dt} &= -k_1e_0s + (k_1s + k_{-1})c, \\ \frac{dc}{dt} &= k_1e_0s - (k_1s + k_{-1} + k_2)c,\end{aligned}\tag{6.16}$$

where its initial conditions are

$$s(0) = S_0, \quad c(0) = 0.\tag{6.17}$$

We then now use the initial conditions to solve the equations $\frac{dc}{dt}$ and $\frac{dp}{dt}$. An equilibrium state is essential for a fast complex [C] formation, implying that

$$\frac{dc}{dt} = 0 \Rightarrow c(t) = \frac{e_0s}{s + K_m}, \quad K_m = \frac{k_{-1} + k_2}{k_1},\tag{6.18}$$

substituting into $\frac{ds}{dt}$ gives

$$\frac{ds}{dt} = \frac{V_ms}{s + K_m}, \quad \text{where } V_m = -k_2e_0.\tag{6.19}$$

We called K_m the Michaelis constant. The enzyme is considered to be present in small amounts compared with substrate. The assumption is that the substrate concentration does not change during this initial transient stage. The approximation is governed by (6.19), with the initial condition s_0 . This is known as

quasi-steady state approximation which will be discussed later on. We are now solving (6.19), we obtain

$$s(t) + k_m \ln s(t) = s_0 + k_m \ln(s_0). \quad (6.20)$$

We have an expression for the complex $c(t)$. It is unable to satisfy the initial condition on $c(t)$ when substituting (6.20) this into (6.18). However, it involves time-scales in that system, one is the initial transient time-scale near $t = 0$ and the other is the longer time-scale t_c . The three important questions which face us when we consider the Michaelis-Menten Model are:

- How fast is the initial transient?
- For what range of the parameters to make the approximation of (6.18) and (6.20) sufficiently.
- if the enzyme concentration is bigger then substrate concentration?

To solve these problems, we have a new method called non-dimensionalisation. Since the problems depend on how short transient period is, we know that the dimensionless quantity is time. The normal way to do the quasi-state analysis is to use the change of variables (dimensionless quantities). A change of variables is often used in biochemical models, in order to obtain dimensional normalized parameters. This helps in analysing the behaviour of the system for different values of the parameters. Furthermore, dimensionalization reduces the number of parameters. For the Michaelis-Menten (M-M) reaction we can use the following change of variables

$$\begin{aligned} \tau &= k_1 e_0 t, & u(\tau) &= \frac{s(t)}{s_0}, & v(\tau) &= \frac{c(t)}{e_0}, \\ \lambda &= \frac{k_2}{k_1 s_0}, & K &= \frac{k_{-1} + k_2}{k_1 s_0} = \frac{K_m}{s_0}, & \varepsilon &= \frac{e_0}{s_0}. \end{aligned} \quad (6.21)$$

It is reasonable non-dimensionalisation if $\frac{e_0}{s_0} \ll 1$. Note, \ll denotes much less than. We are substituting the dimensionless quantities into (6.16). The simplified model reduces to

$$\frac{du}{d\tau} = -u + (u + K - \lambda)v, \quad \varepsilon \frac{dv}{d\tau} = u - (u + K)v, \quad (6.22)$$

where the initial conditions are $u(0) = 1$ and $v(0) = 0$. Note that $K - \lambda > 0$ from (6.22).

The reaction (6.16) converts S into the product P . We therefore have the steady state where $u = 0$ and $v = 0$, which means that the substrate and the substrate-enzyme complex concentrations are zero. We need the solution of (6.22) to find out the time evolution of the reaction. Since $\tau = 0$, we can say $\frac{du}{d\tau} < 0$ which means that u decreases from $u = 1$. Furthermore, if $\frac{dv}{d\tau} > 0$, then we say that v increases from $v = 0$ and continuous to do until

$$v = \frac{u}{u + K}, \quad \text{where} \quad \frac{dv}{d\tau} = 0. \quad (6.23)$$

From the initial condition of (6.22), u is decreasing. When v has reached its maximum. It starts to decrease towards zero and so does u for all values of t . The concentration of the dimensional enzyme $e(t)$ decreases from e_0 and then increase again to e_0 as $t \rightarrow \infty$.

6.5 Transient Time Estimates and Non-dimensionalisation

In the last section, we discussed how the Michaelis-Menten model is in dimensionless form when $\frac{e_0}{s_0} \ll 1$, but it is not always dimensionless in this case. We will now extend this analysis, with a new non-dimensionalisation which regards the situation of $\frac{e_0}{s_0} \ll 1$ and $\frac{e_0}{s_0} = O(1)$. As in the last section, we are interested in the two time-scales, the fast transient t_c and the slow time t_s . The complex $c(t)$ increases while $s(t)$ does not change. If the time-scale is obtained from the second equation of (6.16) with the initial condition s_0 , we have

$$\frac{dc}{dt} = k_1 e_0 s_0 - k_1 (s_0 + K_m) c. \quad (6.24)$$

If we solve (6.24), we obtain an exponential solution

$$t_c = \frac{1}{k_1 (s_0 + K_m)}. \quad (6.25)$$

As we have mentioned, t_c is the fast transient. We are now going to estimate the slow time-scale, t_s . While $s(t)$ changes significantly, we take the maximum change in the substrate, s_0 , to be divided by the size of the maximum rate of change of $s(t)$ given by setting $s = s_0$. This gives the approximation

$$t_s \approx \frac{s_0}{\left| \frac{ds}{dt} \right|_{max}} \approx \frac{s_0 + K_m}{k_2 s_0}. \quad (6.26)$$

For this to be valid, the fast initial transient time needs to be (much) smaller than the slow time-scale when $s(t)$ changes. This shows us that $t_c \ll t_s$. We can give analytical conditions for the validity of the simplified model in terms of t_c and t_s

$$\frac{k_2 e_0}{k_1 (s_0 + K_m)^2} \ll 1. \quad (6.27)$$

The amount of s consumed during the initial transient can be considered negligible. This means that the substrate $\Delta s(t)$, during the fast transient, is only a small fraction of s_0 . The overestimate of $\Delta s(t)$ is given by the maximum rate which is possible from the start of (6.17), that is $k_1 e_0 s_0$ multiplied by t_c . If we divide this by s_0 , it gives

$$\varepsilon = \frac{e_0}{s_0 + K_m} \ll 1. \quad (6.28)$$

Combine (6.27), with K_m from (6.18), can be written as

$$\frac{e_0}{(s_0 + K_m)(1 + (k_{-1}/k_2) + (s_0 k_1/k_2))} \ll 1. \quad (6.29)$$

The latter assumption is satisfied for large values of K_m , which is when the reaction is slow. A condition of (6.28) can be satisfied even if K_m is large. In experimental practice, not all the kinetic parameters of the reaction are measured, but rather

- the M-M constant, K_m ,
- the maximum reaction rate.

$$Q = [R_0]_{max} = k_2 e_0, \quad R_0 = \frac{k_2 e_0 s_0}{s_0 + K_m} = \frac{Q s_0}{s_0 + K_m}. \quad (6.30)$$

We will explore these equations in much greater detail later on in this chapter. The non-dimensionalisation depends on the two time-scales t_c and t_s . From the previous section, the solution we used depended on the fast transient t_c . However, we conceded the slow time-scale t_s when $s(t)$ changed significantly. We use t_c from (6.25) as new variable. We obtain

$$\begin{aligned} \tau = \frac{t}{t_c} &= k_1(s_0 + K_m)t, \quad u(\tau) = \frac{s(t)}{s_0}, \quad v(\tau) = \frac{(s_0 + K_m)c(t)}{e_0 s_0}, \\ \lambda &= \frac{k_2}{k_1 s_0}, \quad K_m = \frac{k_{-1} + k_2}{k_1}, \quad \varepsilon = \frac{e_0}{s_0 + K_m}, \quad \rho = \frac{k_{-1}}{k_2}, \quad \sigma = \frac{s_0}{K_m}. \end{aligned} \quad (6.31)$$

If we substitute these variables into (6.17) and (6.16), we get

$$\begin{aligned} \frac{du}{d\tau} &= \varepsilon \left[-u + \frac{\sigma}{1 + \sigma} uv + \frac{\rho}{(1 + \sigma)(1 + \rho)} v \right], \\ \frac{dv}{d\tau} &= u - \frac{\sigma}{1 + \sigma} uv - \frac{v}{1 + \sigma}, \\ u(0) &= 1, v(0) = 0. \end{aligned} \quad (6.32)$$

We are now non-dimensionalising the time with the fast or slow time-scale with t_s by setting

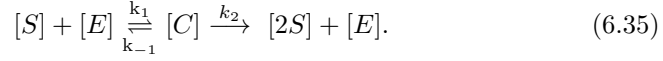
$$T = \frac{(1 + \rho)t}{t_s} = \frac{(1 + \rho)k_2 e_0}{s_0 + K_m} t = \varepsilon(1 + \rho)k_2 t. \quad (6.33)$$

With the dimensionless variables from (6.31) and dimensionless variables (6.33), the model equations (6.16) become the following,

$$\begin{aligned} \frac{du}{dT} &= -(1 + \sigma)U + \sigma UV + \frac{\rho}{1 + \rho} V, \\ \varepsilon \frac{dv}{dT} &= (1 + \sigma)u - \sigma uv - v. \end{aligned} \quad (6.34)$$

We need to remember that equation (6.16) is being investigated. However, the three equation systems (6.22), (6.32) and (6.34) are a bit different, since they are non-dimensionalised. The parameter ε in these three equation is small and comes up in different places. The analytical procedure we use is determined by ε . We also have to know what to do in case ε in (6.31) is not small. This happens when we have various enzyme reactions but also appears in a quite different situation involving T-cell proliferation in response in an antigen.

In our case, the substrate is a replacement of the cell. The enzyme site on the antigen-presenting cell is bound by T-cell and antigen-presenting cell. The kinetics is shown as following



We should be able to see that P is in (6.12) and is replaced by $2S$. This reaction system can be extended and analysed further by the uniformly valid asymptotic solution.

6.6 Michaelis-Menten Quasi-Steady State Analysis

In this section we will be using graphs and information from the text book [1] in the bibliography and the lecture notes from [10]. To give a basic insight into this section, we will try singular perturbation analysis on a dimensionless equation we used before. We are going to use the equation (6.22) and a process called pedagogical analysis to explain the background reasoning for singular perturbation analysis. This results in an asymptotic solution to (6.22) between $0 < \varepsilon \ll 1$. In this section we will analyse a complex system which arises in practical enzyme reactions. We are going to be using the fact that $\frac{e_0}{s_0}$ is not as small as stated in the previous section and the Michaelis constant K_m is drastically larger. Also, ε used in (6.22) is small. Although, using a large Michaelis constant is rare, we will also see it applied later on in this chapter when we discuss Suicide Substrate Kinetics.

Considering the system in (6.22), we can use the Taylor expansion solution to u and v :

$$u(\tau; \varepsilon) = \sum_{n=0} \varepsilon^n u_n(\tau), \quad v(\tau; \varepsilon) = \sum_{n=0} \varepsilon^n v_n(\tau). \quad (6.36)$$

Substituting this into (6.22) and equating the powers of ε gives us a the differential equations for the $u_n(\tau)$ and $v_n(\tau)$. This means that $u(\tau; \varepsilon)$ and $v(\tau; \varepsilon)$ are analytic functions of ε as $\varepsilon \rightarrow 0$.

The $O(1)$ equations are

$$\frac{du_0}{d\tau} = -u_0 + (u_0 + K - \lambda)v_0, \quad 0 = u_0 - (u_0 + K)v_0, \quad (6.37)$$

when $u(0) = 1$ and $v(0) = 0$. However, by examining both of these equations, we can see that the second one is algebraic and therefore cannot satisfy the initial condition. However, solving (6.37) results in

$$v_0 = \frac{u_0}{u_0 + K} \Rightarrow \frac{du_0}{d\tau} = -u_0 + (u_0 + K - \lambda) \frac{u_0}{u_0 + K} = -\lambda \frac{u_0}{u_0 + K}. \quad (6.38)$$

This leads to

$$u_0(\tau) + K \ln u_0(\tau) = A - \lambda\tau. \quad (6.39)$$

We can then solve this by using the result that when $u_0(0) = 1$, then $A = 1$. This causes us to get

$$u_0(\tau) + K \ln u_0(\tau) = 1 - \lambda\tau, \quad v_0 = \frac{u_0\tau}{u_0\tau + K}. \quad (6.40)$$

However, this is not a valid solution for all $\tau \geq 0$ due to the fact $v_0(0) \neq 0$ and the only derivative was found by setting $\varepsilon = 0$. In this case we can see that a small parameter, $0 < \varepsilon \ll 1$, is used in the derivative in (6.22), which indicates that it is immediately recognised because when we set $\varepsilon = 0$, the order of the system of differential equations is immediately reduced and a reduced system is unable to satisfy all the initial conditions. Singular perturbation methods are very important in determining asymptotic solutions of systems that involve ε being small. We will be exploring this technique behind the singular perturbation method in detail and the asymptotic solution to (6.22) for when $0 < \varepsilon \ll 1$. An important fact to be considered is that in order for us to have derived the solution (6.37) from the equation given to us in (6.22), we would have had to assume that $v(\tau; \varepsilon)$ is analytical. This is due to the fact that the initial condition could not be satisfied and by assuming that $\varepsilon \frac{dv}{dt}$ is $O(e)$ can only be satisfied when we have neglected $v(\tau; \varepsilon)$. This causes us to retain this term in our analysis near $\tau = 0$. This means we can focus more on the time scale of 'near $\tau = 0$ ' rather than just $\tau = 0$. This can be denoted by $\sigma = \frac{\tau}{\varepsilon}$ rather than $\tau = 0$ which results in $\varepsilon \frac{dv}{dt} = \frac{dv}{d\sigma}$.

The reason why we changed our timescale is because it magnifies the neighbourhood of $\tau = 0$ and allows us to have a more in-depth look at the region for a fixed $0 < \tau \ll 1$, where we have $\sigma \gg 1$ as $\varepsilon \rightarrow 0$. This is a very small neighbourhood near $\tau = 0$, which relates to a very large domain σ . We now apply this to (6.22) near $\tau = 0$. This will result in us getting a solution away from $\tau = 0$ and this can be shown in how to get a valid solution for all $\tau \geq 0$ using the time scale $\sigma \frac{\tau}{\varepsilon} = 0$, where the transformations become

$$u(\tau; \varepsilon) = U(\sigma; \varepsilon), \quad v(\tau; \varepsilon) = V(\sigma; \varepsilon). \quad (6.41)$$

This results in the equation in (6.22) becoming

$$\frac{dU}{d\sigma} = -\varepsilon U + \varepsilon(U + K - \lambda)V, \quad \frac{dV}{d\sigma} = U - (U + K)V, \quad (6.42)$$

Where $U(0) = 1$ and $V(0) = 0$.

Furthermore, if we again set $\varepsilon = 0$ and $O(1)$ in the system, we get the solution

$$u(\sigma; \varepsilon) = \sum_{n=0} \varepsilon^n U_n(\sigma), \quad v(\sigma; \varepsilon) = \sum_{n=0} \varepsilon^n V_n(\sigma). \quad (6.43)$$

This results in

$$\frac{dU_0}{d\sigma} = 0, \quad \frac{dV_0}{d\sigma} = U_0 - (U_0 + K)V_0. \quad (6.44)$$

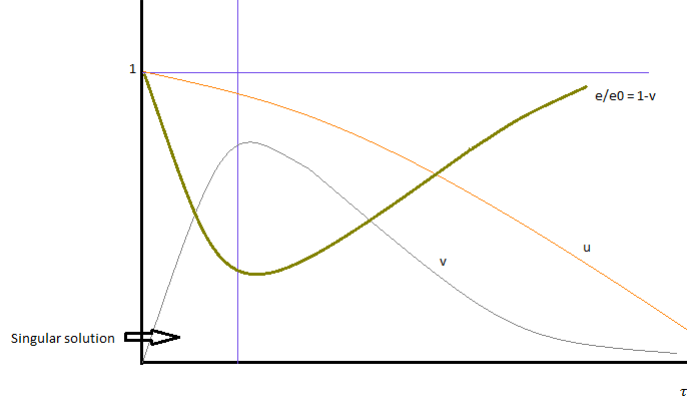


Figure 6.6: Displays the behaviour of the solution of $u(\tau)$ and $v(\tau)$ with dimensionless enzyme concentration $\frac{\varepsilon}{\varepsilon_0}$ also included in the graph.

with the conditions $U(0) = 1, V(0) = 0$. However, this is not of lower than the initial system which is (6.42). The solution for (6.44) is

$$U_0(\sigma) = 1, \quad V_0(\sigma) = \frac{1}{1+K}(1 - \exp[-(1+K)\sigma]). \quad (6.45)$$

We don't expect solution (6.45), to hold for all $\tau \geq 0$ due to the fact that this results in $\frac{dv}{d\sigma} = \varepsilon \frac{dv}{d\tau}$ is $O(1)$, for all τ . The solution we found (6.40) is known as the singular/inner solution for u and v and is valid for $0 \leq \tau \ll 1$ while (6.40) is the non-singular/outer solution which is valid for all τ that is not in the immediate neighbourhood of $\tau = 0$. Furthermore, if we let $\varepsilon \rightarrow 0$ then we have a fixed $0 < \tau \ll 1$ whilst $\varepsilon \rightarrow \infty$. This means that the limit $\varepsilon \rightarrow 0$, we can expect the solution of (6.40) as $\tau \rightarrow 0$ to be equal to the solution (6.45) as $\sigma \rightarrow \infty$. In other words, the singular solution as $\tau \rightarrow 0$, will be equal to the non-singular solution. This is known as the matching in singular perturbation theory. This can be shown in relation to (6.45) and (6.40) below:

$$\lim_{\sigma \rightarrow \infty} U_0(\sigma)V_0(\sigma) = \left[1, \frac{1}{1+K}\right] = \lim_{\tau \rightarrow \infty} U_0(\tau)V_0(\tau) \quad (6.46)$$

We can also see this visually in Fig(6.6). A further point to be considered is that sometimes a thin layer $O(\varepsilon)$ near $\tau = 0$ is formed. This is known as the boundary layer and is found in the τ -domain where there are very sharp changes in the solution. Using (6.45) we get the equation:

$$\frac{dV}{d\tau}]_{\tau=0} \sim \varepsilon^{-1} \frac{dV_0}{d\sigma}]_{\sigma} = \varepsilon^{-1} \gg 1. \quad (6.47)$$

To further enhance our knowledge on singular perturbation, we must look for the outer solution of (6.22) using the Taylor expansions we used in (6.36). this

results in the equations becoming

$$O(1) : \frac{du_0}{d\tau} = -u_0 + (u_0 + K - \lambda)v_0, \quad 0 = u_0 - (u_0 + K)v_0, \quad (6.48)$$

$$O(\varepsilon) : \frac{du_1}{d\tau} = u_1(v_0 - 1) + (u_0 + K - \lambda)v_1, \quad \frac{dv_0}{d\tau} = u_1(1 - v_0) - (u_0 + K)v_1. \quad (6.49)$$

These are all valid for $\tau > 0$ and the solutions include undetermined constants of integration, which means we have to use matching in singular perturbation. We do this by matching all the solutions as $\tau \rightarrow 0$ with the singular solutions as $\sigma \rightarrow 0$.

We can find the sequence of equations for the singular part of the solution by substituting (6.43) into (6.42) when valid for $0 \leq \tau \ll 1$ and equating powers ε . This gives us

$$O(1) : \frac{dU_0}{d\sigma} = 0 \quad \frac{dV_0}{d\sigma} = U_0 - (U_0 + K)V_0, \quad (6.50)$$

$$O(\varepsilon) : \frac{dU_1}{d\sigma} = U_0 + (V_0 + K - \lambda)V_0, \quad \frac{dV_1}{d\sigma} = (1 - V_0)U_1 - (V_0 + K)V_1. \quad (6.51)$$

All these equations must satisfy the initial conditions $\sigma = 0$, which is $\tau = 0$. This results in

$$1 = U(0; \varepsilon) = \sum_{n=0} \varepsilon^n U_n(0) \implies U_0(0) = 1, \quad U_{n \geq 1}(0) = 0 \quad (6.52)$$

$$0 = V(0; \varepsilon) = \sum_{n=0} \varepsilon^n V_n(0) \implies V_{n \geq 0}(0) = 0. \quad (6.53)$$

Unusually, the singular solutions have been determined completely which rarely ever happens. A more generalised way of showing matching of singular perturbation can be seen by the following equation:

$$\lim_{\sigma \rightarrow \infty} [U(\sigma; \varepsilon)V(\sigma; \varepsilon)] = \lim_{\tau \rightarrow \infty} [u(\tau; \varepsilon)v(\tau; \varepsilon)] \quad (6.54)$$

This is for all orders of ε and it shows the matching of the inner and outer solution. Using the equation from

$$u_0(\tau) + K \ln u_0(\tau) = A - \lambda\tau, \quad v_0(\tau) = \frac{u_0(\tau)}{u_0(\tau) + K}. \quad (6.55)$$

Here we must use matching of singular perturbation in order to find out what A is. A represents the constant of integration. This process occurs by applying the limiting process which is what we denoted by (6.54) to (6.45). This results in equations

$$\lim_{\sigma \rightarrow \infty} V_0(\sigma) = \frac{1}{1 + K} = \lim_{\tau \rightarrow 0} v_0(\tau) \quad (6.56)$$

$$\implies v_0(0) = \frac{1}{1 + K} = \frac{u_0(0)}{u_0(0) + K} \quad (6.57)$$

$$\implies u_0(0) = 1 \implies A = 1. \quad (6.58)$$

This is an example of an asymptotic solution $0 < \varepsilon \ll 1$ to $O(1)$. Due to the fact that most of the biological application occurs when $0 < \varepsilon \ll 1$, we only need to evaluate the terms when $O(1)$ rather than $O(\varepsilon)$. This is because $O(\varepsilon)$ terms' contributions are negligible. Furthermore, a rapid change in the equation $v(\tau; \varepsilon)$, takes places in a dimensionless time, $\tau = O(\varepsilon)$, which is minute. Also, the dimensional time, t , is very small and in most experiments it is unable to be measured. This means that in many experiments, $u(\tau)$ and $v(\tau)$ are never observed. This happens in (6.40). We got this from the kinetic system in (6.22) by setting $\varepsilon = 0$ and by satisfying the initial condition on $u(\tau)$, the substrate concentration. In simpler terms, this means the reaction for $v(\tau)$ is in a steady state or in mathematical terms, $\varepsilon \frac{dv}{dt} \approx 0$, which basically means the v -reaction is so fast that it is more or less at the equilibrium point at all times. This is known as Michaelis-Menten Quasi-Steady State hypothesis.

This can further be applied to Reaction Kinetics and the rate of reactions that occur. Michaelis-Menten Quasi-Steady State hypothesis can be determined by measuring the dimensional substrate concentration denoted by $s(t)$ at different times and then seeing the magnitude of the initial rate $\frac{ds}{dt}$. The dimensional terms of the rate of reaction can be deduced by (6.21), with the $O(1)$ rate of reaction of R_0 is

$$R_0 = \frac{k_2 e_0 s_0}{s_0 + K_m} = \frac{Q s_0}{s_0 + K_m}, \quad K_m = \frac{k_{-1} + k_2}{k_1}, \quad Q = [R_0]_{max} = k_2 e_0, \quad (6.59)$$

where $Q = \text{maximum/rate}$.

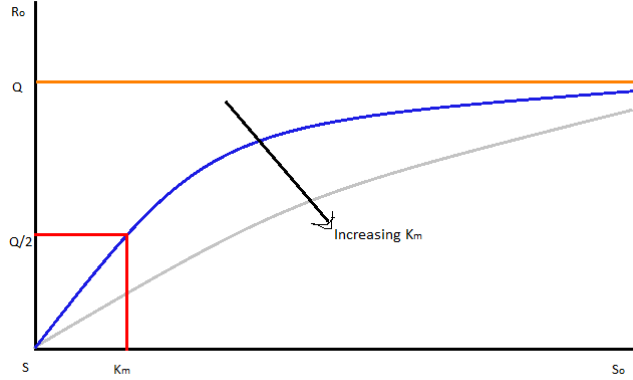


Figure 6.7: Michaelis-Menten rate of uptake. Q is the maximum rate and K_m is the Michaelis constant.

This rate of reaction is seen in (Figure 6.7) which is typical for a biological point of view. Applying these dimensional terms to (6.22), the exact initial rate of the substrate is $\left[\frac{du}{d\tau} \right]_{\tau=0} = -1$ while for the complex rate ,it is $\left[\frac{dv}{d\tau} \right]_{\tau=0} = \frac{1}{\varepsilon}$.

Using (6.59) we can deduce that the rate of reaction, which depends on time, is the magnitude of $\frac{ds}{dt}$ from the outer solution $\frac{du_0}{d\tau}$ and written in dimensional form

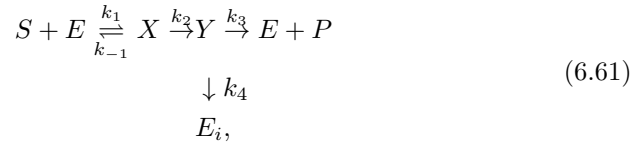
$$\frac{ds}{dt} = -\frac{Qs}{K_m + s}. \quad (6.60)$$

An important fact to be considered is that the maximum rate from (6.59), which is denoted by $Q = k_2e_0$, is reliant on the rate constant k_2 of the product reaction $SE \rightarrow P + E$. This is known as the rate limiting step in a reaction mechanism.

Overall, an important fact to be considered is that when we use the Michaelis-Menten Quasi-Steady State hypothesis we lose a degree of accuracy due to the fact we have considered $\varepsilon \frac{dv}{dt}$ to be negligible in (6.22), and also, the accuracy is lost when the results from the experiment cannot satisfy the initial conditions. However, this hypothesis is compensated by the Michaelis-Menton theory, which allows us to create a curve similar to (Figure 6.7). From this curve, we can deduce the maximum rate Q and the Michaelis constant K_m .

6.7 Suicide Substrate Kinetics

The suicide substrate system is an enzyme system represented by



where E, S and P respectively indicate enzyme, substrate and product, X and Y enzyme-substrates. E_i is the inactivated enzyme and ks indicate the positive rate constants.

In this model, Y can follow two different paths:

- The k_3 path leads to $E + P$,
- The k_4 that leads to E_i .

Suicides substrates are key to provide a way to target a specific enzyme for inactivation. In the real world, they are useful in drug administration as when suicide substrates are in there common form, they are not harmful and can only be activated by a designated enzyme. They can be used to treat illnesses like depression, epilepsy and some sort of tumours.

By the laws of mass attraction, we can get the rate equations from (6.61), which

are:

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[X], \quad (6.62)$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[X] + k_3[Y], \quad (6.63)$$

$$\frac{d[X]}{dt} = k_1[E][S] - k_{-1}[X] - k_2[X], \quad (6.64)$$

$$\frac{d[Y]}{dt} = k_2[X] - k_3[Y] - k_4[Y], \quad (6.65)$$

$$\frac{d[E_i]}{dt} = k_4[Y], \quad (6.66)$$

$$\frac{d[P]}{dt} = k_3[Y], \quad (6.67)$$

where $[]$ indicates the concentrations and t is the time. Usually, the initial conditions that complete the formulation are

$$\begin{aligned} [E(0)] &= e_0, \quad [S(0)] = s_0, \\ [X(0)] &= [Y(0)] = [E_i(0)] = [P(0)] = 0. \end{aligned} \quad (6.68)$$

Here (6.67) is uncoupled, hence $[P]$ can be found by integration after $[Y]$ has been evaluated.

By adding the equations (6.62)-(6.66), the system can be further reduced using conservation of enzyme, giving

$$\frac{d}{dt}\{[E] + [X] + [Y] + [E_i]\} = 0, \quad (6.69)$$

$$\Rightarrow [E] + [X] + [Y] + [E_i] = e_0. \quad (6.70)$$

From (6.70), $[E]$ can be eliminated, obtaining a reduced system

$$\begin{aligned} \frac{d[S]}{dt} &= -k_1(e_0 - [X] - [Y] - [E_i])[S] + k_{-1}[X], \\ \frac{d[X]}{dt} &= k_1(e_0 - [X] - [Y] - [E_i])[S] - (k_{-1} + k_2)[X], \\ \frac{d[Y]}{dt} &= k_2[X] - (k_3 + k_4)[Y], \\ \frac{d[E_i]}{dt} &= k_4[Y]. \end{aligned} \quad (6.71)$$

This system can be non-dimensionalised in many ways. Since $\frac{e_0}{s_0} = O(1)$, following the procedure of a section mentioned previously c, it is equivalent to (6.31) for the outer region and (6.33) for the inner region.

The variables are non-dimensionalised by setting

$$\begin{aligned} [S] &= s_0 s, \quad [X] = \frac{e_0 s_0}{s_0 + K_m} x, \\ [Y] &= e_0 y, \quad [E_i] = e_0 e_i. \end{aligned} \quad (6.72)$$

Here,

$$K_m = \frac{k_{-1} + k_2}{k_1}. \quad (6.73)$$

The fast-transient time-scale is (cf. (6.31)) taken as

$$\tau = \frac{t}{t_c} = tk_1(s_0 + K_m), \quad (6.74)$$

and the quasi-steady state time-scale as

$$T = (1 + \rho) \frac{t}{t_s} = t\varepsilon(k_{-1} + k_2)(1 + \rho), \quad (6.75)$$

with ρ as in (6.78) below and

$$\varepsilon = \frac{e_0}{e_0 + K_m}. \quad (6.76)$$

Using the scaling in (6.72) with τ as the time-scale, equations equals (6.77) for the fast-transient phase are

$$\begin{aligned} \frac{ds}{d\tau} &= \varepsilon \left[-s + \frac{\sigma}{1 + \sigma} sx + sy + se_i + \frac{\rho}{(1 + \rho)(1 + \sigma)} x \right], \\ \frac{dx}{d\tau} &= s - \left(\frac{\sigma}{1 + \sigma} \right) sx - sy - se_i - \frac{x}{1 + \sigma}, \\ \frac{dy}{d\tau} &= \left(\frac{\sigma}{(1 + \sigma)^2(1 + \rho)} \right) x - \left(\frac{\psi}{(1 + \sigma)} \right) y, \\ \frac{de_i}{d\tau} &= \left(\frac{\phi}{1 + \sigma} \right) y, \end{aligned} \quad (6.77)$$

where

$$\sigma = \frac{s_0}{k_m}, \quad \rho = \frac{k_{-1}}{k_2}, \quad \psi = \frac{k_3 + k_4}{k_{-1} + k_2}, \quad \phi = \frac{k_4}{k_{-1} + k_2}. \quad (6.78)$$

The previous initial conditions (6.68), after applying (6.72), become

$$s(0) = 1, \quad x(0) = 0, \quad y(0) = 0, \quad e_i(0) = 0. \quad (6.79)$$

The inner solutions are given from the equations (6.77), which are equivalent to (6.32) from before.

While, given T as the time-scale, the rate equations for the outer quasi-steady state phase are;

$$\begin{aligned} \frac{ds}{dT} &= -s[(\sigma + 1) - \sigma x - (\sigma + 1)y - (\sigma + 1)e_i] + \frac{\rho}{1 + \rho} x, \\ \varepsilon \frac{dx}{dT} &= s[(\sigma + 1) - \sigma x - (\sigma + 1)y - (\sigma + 1)e_i] - x, \\ \varepsilon \frac{dy}{dT} &= \left(\frac{\sigma}{(1 + \sigma)(1 + \rho)} \right) x - \psi y, \\ \varepsilon \frac{de_i}{dT} &= \phi y, \end{aligned} \quad (6.80)$$

where ε , σ , ρ , ϕ and ψ are given by (6.78), and they are equivalent to (6.34). We will determine these parameters with the asymptotic technique method, that we will explore in more depth now.

Asymptotic Technique and Solutions

We now exploit the fact that in the equation (6.76) ε is almost zero ($0 < \varepsilon \ll 1$) and solve the equation by the singular perturbation model.

Consider the inner solutions first, we start with the fast-transient phase equation analysed in (6.77), with initial conditions from (6.79). As ε is almost zero, we have to search for a Taylor series solution in the form

$$s(\tau) = s^{(0)}(\tau) + \varepsilon s^{(1)}(\tau) + \varepsilon^2 s^{(2)}(\tau) + \dots, \quad (6.81)$$

for the variables s , x , y and e_i . Once we substitute this in the equations (6.77) and equate the powers of ε , we find

$$\frac{ds^{(0)}}{d\tau} = 0, \quad \frac{dy^{(0)}}{d\tau} = -\frac{\psi}{1+\sigma} y^{(0)}. \quad (6.82)$$

When combined with (6.79), gives the unique solutions $s^{(0)}(\tau) \equiv 1$, $y^{(0)}(\tau) \equiv 0$. Like the last equation from (6.77) yields for $O(1)$,

$$\frac{de_i^{(0)}}{d\tau} = -\frac{\phi}{1+\sigma} y^{(0)} = 0. \quad (6.83)$$

This implies that $e_i^{(0)} \equiv 0$, since $e_i(0) = 0$. Substituting these series of solution into the last equation of (6.77), we get the result

$$\frac{dx^{(0)}}{d\tau} = s^{(0)} - s^{(0)}y^{(0)} - s^{(0)}e_i^{(0)} - \frac{x^{(0)}}{1+\sigma} - \frac{\sigma s^{(0)}x^{(0)}}{1+\sigma}. \quad (6.84)$$

Using the solutions for $s^{(0)}$, $y^{(0)}$ and $e_i^{(0)}$, the above equation will become

$$\frac{dx^{(0)}}{d\tau} = 1 - x^{(0)}, \quad (6.85)$$

given $x(0) = 0$. This results in $x^{(0)}(\tau) = 1 - e^{-\tau}$.

If we want to get nonzero solutions for y and e_i , the $O(\varepsilon)$ terms, $y^{(0)}(\tau)$ and $e_i^{(0)}(\tau)$ have to be determined. To do such thing the terms of $O(\varepsilon)$ have to be matched.

Combining (6.76) with (6.78)

$$\varepsilon = \frac{e_0}{s_0(1 + K_m/s_0)} = \frac{e_0}{s_0} \frac{\sigma}{1 + \sigma}, \quad (6.86)$$

which implies that

$$\sigma = \left(\frac{s_0}{e_0}\right)\varepsilon + O(\varepsilon^2). \quad (6.87)$$

Thus, as $\frac{s_0}{e_0} = O(1)$, it is implied that $\sigma = O(\varepsilon)$. Here we introduce a similarity variable for σ , where

$$\sigma = \varepsilon p. \quad (6.88)$$

Also p is a constant of $O(1)$. We show the ε factor explicitly so that it can be matched with the $O(\varepsilon)$ term. We can equate the terms of $O(\varepsilon)$ by substituting (6.88) for σ in the third equation of (6.77):

$$y^{(1)}(\tau) = \frac{p}{\psi(1+\rho)} \left(\frac{1 - e^{-\psi\tau}}{\psi} + \frac{e^{-\psi\tau} - e^{-\tau}}{\psi - 1} \right). \quad (6.89)$$

Thus, matching the coefficients from the last equation of (6.77) to $O(\varepsilon)$ gives an equation for $\frac{de_i}{d\tau}$ in terms of $y^{(1)}$. Therefore, the solution will be

$$e_i^{(1)} = \frac{\phi p}{(1+p)} \left(\frac{\tau}{\psi} + \frac{e^{-\tau} - 1}{\psi - 1} + \frac{1 - e^{-\psi\tau}}{\psi^2(\psi - 1)} \right). \quad (6.90)$$

In order to get $e_i^{(1)}$, it is assumed that $\phi = O(1)$. In the case where $\phi = O(\varepsilon)$, another similarity variable, $q = \varepsilon\phi$, should have been used, and found that $e_i^{(1)}(\tau)$, but that $e_i^{(2)}(\tau)$ gives the same result as $e_i^{(1)}(\tau)$ above.

The coefficients of higher-order can be found in a similar way, for example, the $O(\varepsilon)$ terms of the first equation of (6.77) give

$$s^{(1)}(\tau) = -\frac{\tau}{1+\rho} + \frac{\rho}{1+\rho}(e^{-\tau} - 1). \quad (6.91)$$

The initial conditions in (6.79) are satisfied by all these solutions.

For the outer solutions, we proceed by looking in the long time-scale which gives the quasi-steady state approximation. Firstly, we have to match the two time period solutions. Generally, the initial conditions are not satisfied in these long time-scale solutions.

Here we look for solutions to (6.80) in the form

$$s(T) = s_0(T) + \varepsilon s_{(1)}(T) + \varepsilon^2 s_{(2)} + \dots, \quad (6.92)$$

for each of the variables s , x , y and e_i . We have to substitute this into the equations (6.80) and again equate the coefficients of ε . Here, to solve the undetermined constants of integration, we have to use the method of matched asymptotic expansions. This is when the inner solution as $\tau \rightarrow \infty$ has to be matching the outer solution as $T \rightarrow 0$.

Now, as $\sigma = \varepsilon p = O(\varepsilon)$ from (6.88), and taking the $O(1)$ terms, we get

$$0 = s_{(0)} - s_{(0)}y_{(0)} - x_{(0)} - s_{(0)}e_{i(0)}, \quad (6.93)$$

from the second equation of (6.80). Also assuming from the last equation of the set (6.80), $\phi = O(1)$ and $y_{(0)} = 0$, then we get

$$x_{(0)} = s_{(0)}(1 - e_{i(0)}). \quad (6.94)$$

Similarly, it can be obtained

$$y_{(1)} = \frac{p}{\phi(1+\rho)}x_{(0)}. \quad (6.95)$$

In order to equate coefficients further, the order of the magnitude of each of the terms has to be determined. There are only two possible outcomes, either all of the substrate is exhausted or all of the enzyme is inactivated. This corresponds to $\phi = O(1)$ with $\psi = O(1)$, and $\psi = O(1)$ with $\phi = O(\varepsilon)$ (referring to (6.78) for the parameter relations). We must solve the equations for each of these sets of constraints.

Case 1: $\rho = O(1), \quad \psi = O(1), \quad \phi = O(1)$

In this case, all the rate constants are of the same order of magnitude.

By assuming that $\phi = O(1)$, the first equation in (6.80) with (6.88), (6.92) and (6.94) give

$$\frac{ds_{(0)}}{dT} = -\frac{1}{1+\rho}s_{(0)}(1-e_{i(0)}). \quad (6.96)$$

From the second equation in (6.80) with (6.88), (6.92), (6.94) and (6.95), we get

$$\frac{de_{i(0)}}{dT} = \frac{\phi\rho}{\psi(1+\rho)}s_{(0)}(1-e_{i(0)}). \quad (6.97)$$

By dividing and integrating the last two equations we get

$$e_{i(0)}(T) = \frac{1}{\beta}(B - s_{(0)}(T)), \quad (6.98)$$

where B is an constant of integration and

$$\beta = \frac{\psi}{\phi\rho}. \quad (6.99)$$

To determine B , we use the matching condition discussed in the previous section. This is the condition that $s_{(0)}(T), x_{(0)}(T), y_{(0)}(T)$ and $e_{i(0)}(T)$ as $T \rightarrow 0$ must match the values, respectively, of $s^{(0)}(\tau), x^{(0)}(\tau), y^{(0)}(\tau)$ and $e_i^{(0)}(\tau)$ as $\tau \rightarrow \infty$. We know that $s^{(0)}(\tau) \equiv 1, x^{(0)}(\tau) \equiv 1 - e^{-\tau}, y^{(0)}(\tau) \equiv 0, e_i^{(0)}(\tau) \equiv 0$ so the conditions on the $O(1)$ outer solution are

$$s_{(0)}(T) \rightarrow 1, \quad x_{(0)}(T) \rightarrow 1, \quad y_{(0)}(T) \rightarrow 0, \quad \text{and} \quad se_{i(0)}(T) \rightarrow 0, \quad \text{as} \quad T \rightarrow 0. \quad (6.100)$$

From this, we see that $B = 1$ from (6.98). By substituting into (6.96), we get

$$\frac{ds_{(0)}}{dT} = -\frac{(\beta-1)}{\beta(1+\rho)}s_{(0)}\left[1 - \frac{s_{(0)}}{1-\beta}\right]. \quad (6.101)$$

After integration and after applying the conditions as $T \rightarrow 0$ from (6.100) gives $s_{(0)}(T)$ and $e_{i(0)}(T)$ as

$$\begin{aligned} s_{(0)}(T) &= \frac{1-\beta}{1-\beta e^{T[1-(1/\beta)]/(1+\rho)}}, \\ e_{i(0)}(T) &= \frac{1-s_{(0)}(T)}{\beta}. \end{aligned} \quad (6.102)$$

Case 2: $\rho = O(1)$, $\psi = O(1)$, $\phi = O(\varepsilon)$

Assuming $\phi = O(\varepsilon)$, this gives

$$s_{(0)}(T) = e^{-T/(1+\rho)}, \quad e_{i(0)} = 0, \quad \varepsilon e_{i(1)}(T) = \frac{1 - e^{-T/(1+\rho)}}{\beta}, \quad (6.103)$$

where yet again the inner solutions are matched.

We can find more inner and outer solutions to solve for terms of higher-order of ε in the series (6.81) and (6.92). These solutions will be linear, but they get more complicated.

Uniformly Valid Solution for all Time

As we now have a solution for the fast transient and quasi-steady state time periods, we can obtain composite solutions, which are valid for all time $t \geq 0$ by a simple method. We add the first inner solution term with the corresponding outer solution term and we subtract their common part, the limit of the inner solution as time (τ) goes to infinity, which is the same as the limit of the outer solution as time (T) tends to zero. Both these limits are equal to 1, therefore the composite solution will be

$$s_c^0 = 1 + e^{-T/(1+\rho)} - 1 = e^{-t/t_s} = e^{-\varepsilon(k_{-1}+k_2)t}. \quad (6.104)$$

on using (6.75).

As we continue doing this for the other solutions we get two sets of composite solutions: Set 1 and Set 2. They are both valid for all time.

Set 1:

$$\begin{aligned} s_c^0(t) &= \frac{1 - \beta}{1 - \beta e^{(1-1/\beta)/t_s}}, \quad e_{i\ c}^0(t) = \frac{1 - s_c^0}{\beta}, \\ x_c^0(t) &= s_c^0(1 - e_{i\ c}^0) - e^{-t/t_c}, \quad y_c^0 = 0, \\ \varepsilon y_c^1(t) &= \frac{\sigma}{\psi(1+\rho)} \left(\frac{e^{-\psi t/t_c} - \psi e^{-t/t_c}}{\psi - 1} + s_c^0(1 - e_c^0) \right). \end{aligned} \quad (6.105)$$

Set 2:

$$\begin{aligned} s_c^0(t) &= e^{-t/t_s}, \quad e_{i\ c}^0(t) = 0, \quad \varepsilon e_{i\ c}^1(t) = \frac{1 - s_c^0}{\beta}, \\ x_c^0(t) &= s_c^0 - e^{-t/t_c}, \quad y_c^0(t) = 0, \\ \varepsilon y_c^1 &= \frac{\sigma}{\psi(1+\rho)} \left(\frac{e^{-\psi t/t_c} - \psi e^{-t/t_c}}{\psi - 1} + s_c^0 \right). \end{aligned} \quad (6.106)$$

Where $\beta = \frac{\psi}{\phi p}$ and σ , ρ and ψ are the same as (6.78).

Note that if $\beta < 1$ Set 1 holds, while if $\beta > 1$ then Set 2 holds. These directly relate to the amount of inactivated enzyme discussed previously.

Numerical solutions and Comparison with Analytic Solutions

To highlight their accuracy, we have approximate asymptotic solutions to the non-dimensionalised systems to compare with the numerical solutions.

To get the numerical solution, the dimensional system (6.77), has to be solved numerically. Since the analysis was brought out on the dimensional system, we have to multiply the non-dimensional concentrations by their scale factors.

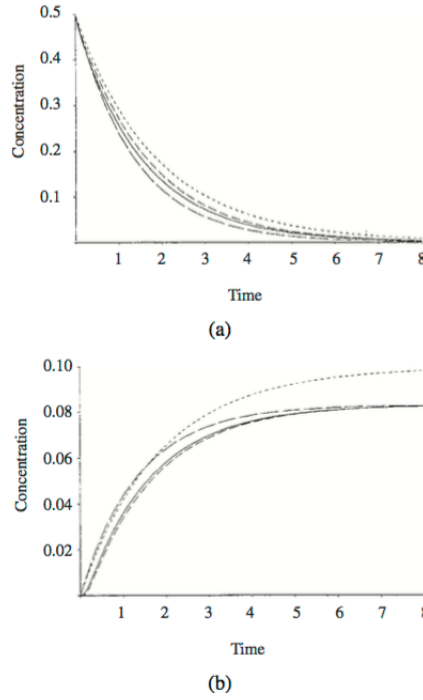


Figure 6.8: (a) represents the substrate concentration for the various solutions, while (b) is the inactive enzyme concentrations.

From the graphs we get the parameters $k_1 = 2, k_{-1} = 4, k_2 = 12, k_3 = 10, k_4 = 2, e_0 = 0.5, s_0 = 0.5$. These give $\varepsilon = 5.88 \times 10^{-2}, \rho = 0.333, \beta = 5.647$. These intermediate results, X and Y , are more accurate than any quasi-steady state method can achieve.

The above results show how analytical solutions are a good approximation of the suicide substrate kinetics represented by (6.61). The analysis is much more involved than the basic enzyme reaction in (6.12), but the reaction is more complicated compared to it.

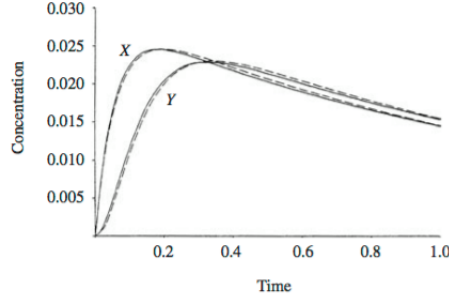
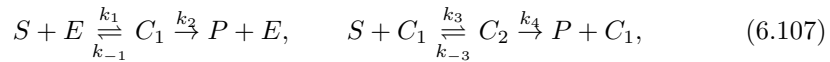


Figure 6.9: This represent the composite solutions compared the numerical ones, for X and Y , the intermediate concentrations. Assuming the parameters are the same as the previous figure.

6.8 Cooperative Phenomena

In the model $S + E \xrightleftharpoons[k_{-1}]{k_1} SE \xrightarrow{k_2} P + E$, an enzyme molecule combines with a substrate molecule. A reaction between these two molecules is called cooperative if an enzyme can bind with a substrate molecule at a site after having bound with a different substrate molecule at a different site. This is a common phenomena. Another important cooperative behaviour, is known as the allosteric effect, or allostery, which is when an enzyme that has bound with several substrate molecules, can affect the binding activity of other substrate molecules at different sites. The enzyme displaying this behaviour is known as allosteric enzyme. A substrate is known as an activator if it binds at one site it increases the activity of binding at a different site. On the other hand, if it decreases the activity then it is an inhibitor. Consider the example where an enzyme has 2 binding sites, this model consists of an enzyme E which binds a substrate molecule S . This forms a single bond substrate-enzyme complex, C_1 . When this complex breaks down it forms a product P and again the enzyme. It can also join with a different substrate molecule to form a new dual bound substrate-enzyme complex C_2 , which breaks down to form the product and the complex C_1 . As represented by the equation:



where k 's are the rate constants as indicated.

Applying the law of mass attraction to (6.107) with the concentrations, denoted with the lower case, we get;

$$\begin{aligned}
\frac{ds}{dt} &= -k_1 s e + (k_{-1} - k_3 s) c_1 + k_3 c_2, \\
\frac{dc_1}{dt} &= k_1 s e - (k_{-1} + k_2 + k_3 s) c_1 + (k_{-3} + k_4) c_2, \\
\frac{dc_2}{dt} &= k_3 s c_1 - (k_{-3} + k_4) c_2, \\
\frac{de}{dt} &= -k_1 s e + (k_{-1} + k_2) c_1, \\
\frac{dp}{dt} &= k_2 c_1 + k_4 c_2.
\end{aligned} \tag{6.108}$$

The initial conditions are

$$s(0) = s_0, \quad e(0) = e_0, \quad c_1(0) = c_2(0) = p(0) = 0. \tag{6.109}$$

By adding the 2nd, 3rd and 4th equations in (6.108) and using the initial conditions we get

$$\frac{dc_1}{dt} + \frac{dc_2}{dt} + \frac{de}{dt} = 0 \quad \Rightarrow \quad e + c_1 + c_2 = e_0. \tag{6.110}$$

The equation for the product $p(t)$ is given by integration once c_1 and c_2 have been found. This results in us getting the system:

$$\begin{aligned}
\frac{ds}{dt} &= -k_1 e_0 s + (k_{-1} + k_1 s - k_3 s) c_1 + (k_1 s + k_{-3}) c_2, \\
\frac{dc_1}{dt} &= k_1 e_0 s - (k_{-1} + k_2 + k_1 s + k_3 s) c_1 + (k_3 + k_4 - k_1 s) c_2, \\
\frac{dc_2}{dt} &= k_3 s c_1 - (k_{-3} + k_4) c_2,
\end{aligned} \tag{6.111}$$

applying the initial conditions from (6.108).

Like in the previous cases, the system has to be non-dimensionalised. There are many ways to do this, but if we take $\frac{e_0}{s_0} \ll 1$, we write

$$\begin{aligned}
\tau &= k_1 e_0 t, \quad u = \frac{s}{s_0}, \quad v_1 = \frac{c_1}{s_0}, \quad v_2 = \frac{c_2}{e_0}, \\
a_1 &= \frac{k_{-1}}{k_1 s_0}, \quad a_2 = \frac{k_2}{k_1 s_0}, \quad a_3 = \frac{k_3}{k_1}, \\
a_4 &= \frac{k_{-3}}{k_1 s_0}, \quad a_5 = \frac{k_4}{k_1 s_0}, \quad e = \frac{e_0}{s_0}.
\end{aligned} \tag{6.112}$$

Therefore, (6.111) becomes

$$\frac{du}{d\tau} = -u + (u - a_3 u + a_1) v_1 + (a_4 + u) v_2 = f(u, v_1, v_2), \tag{6.113}$$

$$\varepsilon \frac{dv_1}{d\tau} = u - (u + a_3 u + a_1 + a_2) v_1 + (a_4 + a_5 - u) v_2 = g_1(u, v_1, v_2), \tag{6.114}$$

$$\varepsilon \frac{dv_2}{d\tau} = a_3 u v_1 - (a_4 + a_5) v_2 = g_2(u, v_1, v_2), \tag{6.115}$$

with the following initial conditions

$$u(0) = 1, \quad v_1(0) = v_2(0) = 0. \tag{6.116}$$

6.9 Multiple Steady States, Mushrooms and Isolals

Multiple Steady States

Multiple steady states take place when a parameter in the model passes through a bifurcation value, whereas one steady state occurs and behaves qualitatively when the model passes through fixed values. These types of steady states were explored in chapter 5. The comparison between one steady state and multiple steady states can be seen in Figure(6.10a), where the dotted line shows the change in behaviour of the curve when the line goes through the bifurcation value and multiple steady states are formed, whilst a typical steady state dependent on the parameter can be seen by the solid line.

Mushrooms

Figure 6.10 displays the early transition of the generic form of the disparity of a steady state, from when the model passes through a standard parameter to when it passes through a bifurcation value, which cause multiple steady states to be formed. This is because the behaviour of the graph becomes more erratic. The development of a curve from a basic a standard curve to a mushroom like curve can be seen in Figure(6.10b) where two regions in the p -space are being formed meaning that multiple steady states are also being formed. In this case we can see there are 3 steady states formed in (Figure 6.10b). Branches CD and GH have unstable steady states on them.

Isolas

The word Isola comes from the term isolated closed curves which can be seen in Figure(6.10c), where a separate breakaway region has been formed as a continuation of the mushroom like shape formed in Figure (6.10b). The name given to this type of behaviour is an Isola.

The behaviour of Isolals is rather different to a Mushroom. The first fact to be considered is that there is no hysteresis. Hysteresis occurs when there are abrupt changes in the value of u_s . Since U_s stay on the branch $ABIJ$ as the parameter p increases from $p < p_1$ to $p > p_2$. In fact, u_s just stays on the branch on the return sweep through the multi-steady state region $p_1 < p < p_2$. Isolals can only form on branches and can only be formed of solutions of nonlinear equations.

Another fact to be considered is that in Figure 6.10, if u_s lies on BI , then it could only possibly move onto the other stable branch which is DFG . However, this can only happen if u_s has a finite perturbation so that u_s moves in the domain of attraction which we explored in chapter 4.

We just explored the analytical approach to multiple steady states. Dellwo et al (1982) presented a theory on the analytical structure of Isolals. He believed that Isolals tend to a point, as some parameters tend to a critical value. Application of Isolals to the real World, can be seen in chemical reactions. Gray and Scott (1983,1986) shared a kinetic model system which included multi-steady

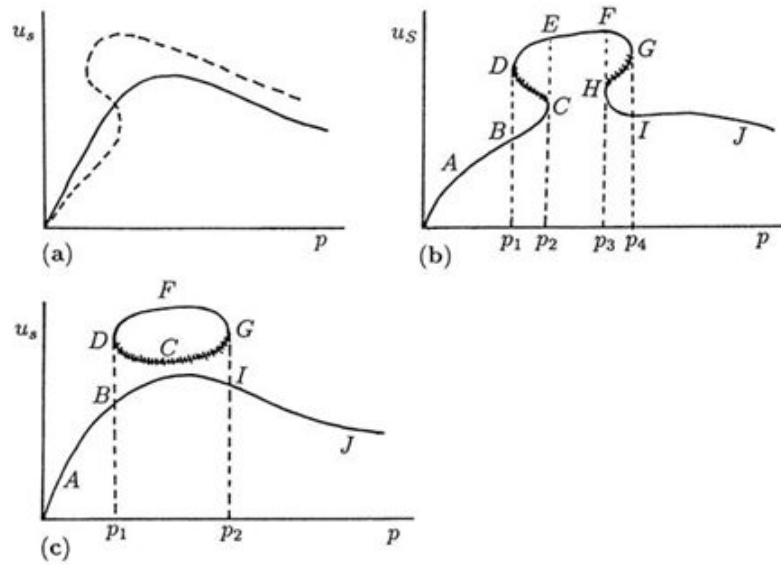


Figure 6.10: a) Shows a steady state dependent on a parameter. b) Shows Mushroom dependence of the steady states as a function of parameter p . c) Continuation of Mushroom independence leading to an Isola being formed.

states with Mushrooms and Isolals in a reaction that involves auto-catalysis in a continuously stirred tank reactor (CSTR). This can be seen in further detail in book [1] referred in the bibliography.

Chapter 7

Conclusion

Overall, we understand that Mathematical Biology is a very complex system. In this project, we have explored this through Reaction Kinetics in different cases. Normally, Reaction Kinetics can be formulated into a nonlinear ODE system. The idea behind Reaction Kinetics is the Law of Mass Action. To estimate the time scales, we have to non-dimensionalise the system to satisfy the quasi-steady state estimate.

By visualising the ODE system, a phase plane can be used to determine whether the systems are stable or not. We have learnt that Bifurcation diagram is a combination of a phase plane with a changing value of parameter, which gives the future behaviour of the system. Therefore, it is always a benefit to visualise Mathematics to understand systems.

Leading on, we went into a lot of detail regarding many different types of stability and how, by determining the steady states, we can derive the stability of a nonlinear system. We tried to define stability, but realised that there are many different types, therefore we only considered three types. However, we also gained a further insight into Lyapunov's theorems in stability, which he created in order to determine whether a stationary point is stable or unstable. This provided us with information for the section regarding Michaelis-Menten Quasi-Steady states hypotheses. On the other hand, we learnt that this hypothesis may be flawed due to the fact the changes of these reactions take place in a dimensionless time, where the time frame is small. Many experiments are unable to measure these rapid changes which suggests that calculating this is pointless because it is never observed. This means that many systems only satisfy the initial conditions of the reaction which means it is in a steady state. However, when using Michaelis-Menten Quasi-Steady State hypothesis, we lose a significant level of accuracy due to the fact that we consider $\varepsilon = \frac{dv}{dt}$ to be negligible when it is not. Here, we see how the basic concept of steady states is applied to complex biological processes.

Another topic we explored was generic multiple steady states and how these

compare to the generic cases of steady states with qualitative parameters to more complex cases. We see that if the parameter in the model goes through a bifurcation value, then it would cause multiple steady states to be formed. This is seen in biochemical processes with regards to auto-catalysis in continuously stirred tank [CSTR].

We have now learnt how the rate equations for the Kinetics of Suicide Substrate are a set of nonlinear equations. We have also learnt the technique to find asymptotic solutions for both inner and outer solutions. This allows us to form uniformly valid solutions for all time.

Although, we have discussed a lot on ODE systems in Reaction Kinetics, there is still a lot of application of it in the real World. Examples of this are: Biological Oscillates, Belousov-Zhabotinskii Reaction and Perturbed and Coupled Oscillators. For additional reading we could study more in detail about Partial Differential Equations(PDE), as it can be applied to biochemical and biological processes, which will further enhance this study. Examples of this application are s Structured Population Dynamics, Pattern Formation and Chemotaxis.

Chapter 8

Appendix

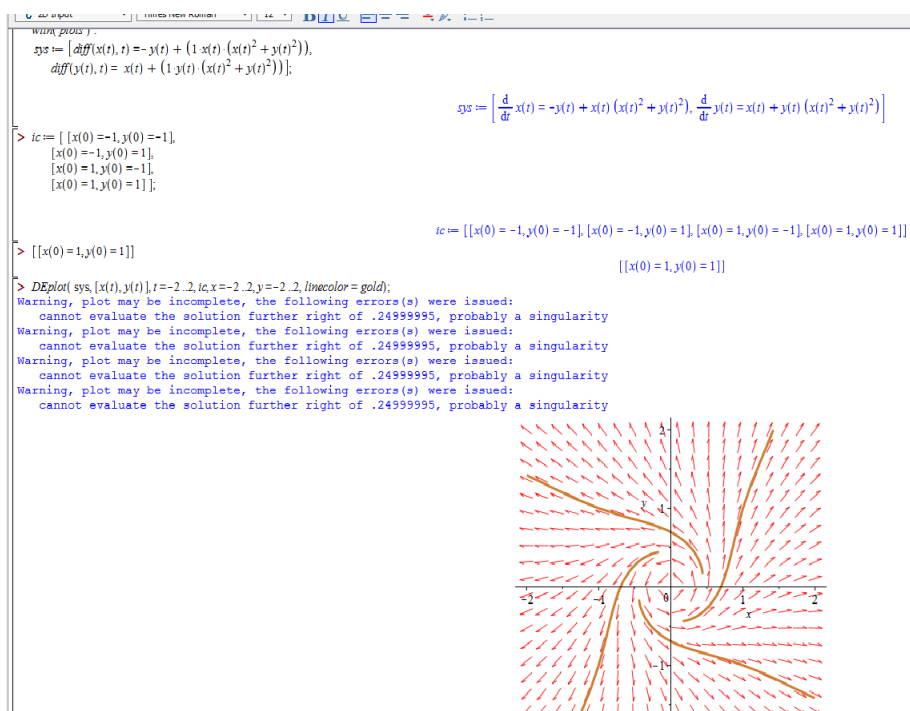


Figure 8.1: Maple calculations for (4.1)

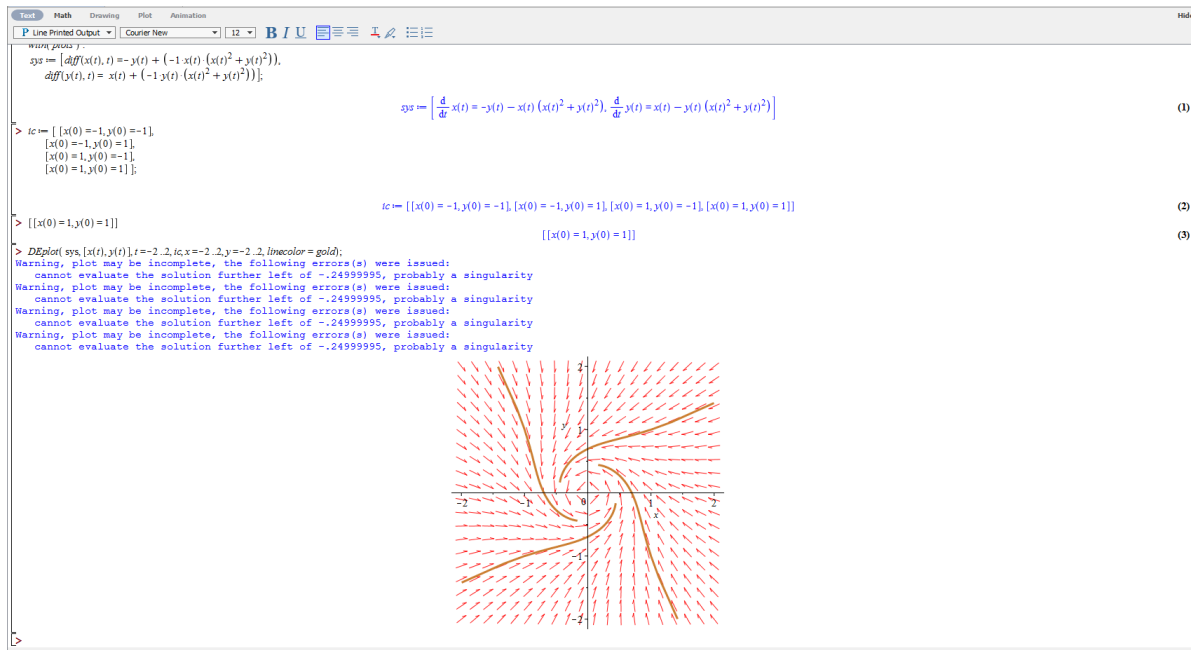


Figure 8.2: Maple calculations for (4.2)

Bibliography

- [1] J.D.Murray *Mathematical Biology*. Berlin: Springer-Verlag, 2003. Print
- [2] *Mathematical Biology: I. An Introduction*. New York, NY: Springer New York, 2004. Print.
- [3] Dr Guy-Bart Stan http://www.bg.ic.ac.uk/research/g.stan/2010_Course_MiB_article.pdf Imperial College accessed 12/12/2016
- [4] William A. Adkins, Mark G. Davidson *Ordinary Differential Equations*
- [5] Singh, Vikram. *Systems and Synthetic Biology*. Dordrecht: Springer, 2015. Print.
- [6] Murray, James Dickson. *Mathematical Biology* Berlin: Springer, 1989. Print.
- [7] Glendinning, Paul. *Stability, Instability and Chaos*. N.p.: Cambridge UP, 1993. Print.
- [8] Wassim M. Haddad *Nonlinear Dynamical Systems and Control: A Lyapunov-Based Approach* 02/28/2008
- [9] Philip G. Drazin *Nonlinear Systems* Cambridge Univ. Press Cambridge 2002
- [10] Dr.J.P.Wang *Mathematical Biology University of Kent MA591 Lecture Notes* 2015
- [11] Dr Steffen Krusch, Dr Pavlos Xenitidis *Mathematical Modelling University of Kent Lecture MA590 Notes* 2015
- [12] Dr John Pearson, Dr Kuan Xu *Numerical Solution of Differential Equations University of Kent Lecture MA587 Notes* 2016
- [13] *PhasePlane* https://upload.wikimedia.org/wikipedia/commons/thumb/3/35/Phase_plane_nodes.svg/300px-Phase_plane_nodes.svg.png. Last Accessed 01 march 2017
- [14] *Predator-Prey* <http://www.bapp.org/images/science/puma-prey-graph.png>. Last accessed 01 March 2017.
- [15] *Harvesting Population Model* <http://tashian.com/car1/docs/harvesting/Image33.gif> Last accessed 01 March 2017.

- [16] *Logistic Growth* <https://figures.boundless-cdn.com/21346/large/figure-45-03-01.jpe> Last accessed 01 march 2017.