Mathematical Models of Facilitated Diffusion Processes in Physiology

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Declaration of Originality

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

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Abstract

Combining diffusion and chemical reactions introduces many interesting effects in nature, particularly in physiology. Diffusion by itself, called simple diffusion, can occur in gases, liquids and solids. A simple example of diffusion in gases is when we spray a perfume and after a few minutes its smell spreads throughout the room. The diffusion process can be observed in liquids as well: for instance, when we put a small drop of food colouring into a cup of water, after a while, the colour of the water changes. Simple diffusion also occurs continuously in the human body while we breathe, since gas exchange occurs between our lungs and the air that we breathe. The reason behind the diffusion process is the movement of molecules from areas of high concentration to areas of lower concentration to achieve an equilibrium situation of uniform concentration between those two areas. The more complex case where diffusion occurs simultaneously as a chemical or other reaction between the component substances is called reaction–diffusion.
The facilitated diffusion process is a special case of reactiondiffusion and it affects many aspects of life, making it one of the most important processes in all of biology. During facilitated diffusion, a molecule (the ligand) joins another molecule (the carrier), which is typically a large protein, to form a ligand–carrier complex. This complex then provides an alternative way for the ligand to move or diffuse. Facilitated diffusion and simple diffusion are similar in that both involve the movement of molecules from a high-concentration region to a low-concentration region. They are also both passive processes since the molecules transport is performed without any energy input. However, in facilitated diffusion, the transport of molecules will only occur if it is facilitated or assisted by an appropriate carrier. Facilitated diffusion has two transport pathways, the direct and the facilitated. Further, facilitated diffusion requires both a forward reaction and a backward reaction to occur easily, the first one to associate the ligand with the carrier and the second to dissociate it from the carrier. The most common example of facilitated diffusion in the human body is that of oxygen by haemoglobin in red blood cells or by myoglobin in muscle tissues. In this thesis, a mathematical model of the facilitated diffusion of oxygen within muscle cells is studied. In this case, the carrier molecule is myoglobin. This dissertation has many goals, and one is to solve the second-order partial differential equation that expresses the mathematical model in two ways. This first is to solve the equation by using an equilibrium approximation. The second way is to solve the full partial differentiation equations numerically using the FEniCS program. We explore the extent to which various system parameters affect the enhancement of transport in some simple situations and compare the results of the two different solution methods. We show that a balance between the forward reaction and backward reaction rates is important to ensure maximum enhanced transport.

Acknowledgment

First, I would like to thank God Almighty since without His will and blessings throughout my research phase, I would not have been able to complete my research successfully. Next, I am deeply grateful to Dr. Tony Miller, who assisted me throughout the research and made it possible for me to complete it. I really am thankful to him for his guidance, patience and encouragement. I would also like to thank Professor Murk Bottema for his valuable feedback and careful analysis of the dissertation. Finally, I would like to thank my entire family, my parents, my husband and my children, for their continued support and love.

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Preface

Mathematics is a vital field in the sciences, and it can be considered a prologue to different sciences. At present, the utilisation of natural science incorporates the entire human body. The science of mathematics is utilised to depict a few wonders and practices in scientific ways. Estimating the blood sugar level, the quantity of red and white blood cells and platelets and the body's development and weight are, in effect, indications of using mathematics in science. Physiological science or physiology is the science that reviews the elements of all organs of the body, how these functions are working, the degree of utilitarian relationships between every part of the body and different organs and additionally, factors influencing the execution of body organs. For instance, the nervous system is a vital part of our body that manages and controls all our organs. It demonstrates how signals move from the brain to various parts of the body through mathematical equations. The science framework is incredibly mind boggling and understanding this many-sided quality is testing. The objective of this exploration is to utilise mathematics to comprehend the riddles of life. To this end, the analysis in this study focuses on the diffusion and reaction equation to clarify the functioning of the body.
The technique used for this analysis is to consider a biological process and clarify it in a scientific way. The key example of the facilitated diffusion equation in our bodies is oxygen transportation in muscle tissues and between cell membranes by haemoglobin and myoglobin. In biology, this procedure is imperative since it gives cells oxygen to feast upon and keeps them alive. Hence, this thesis considers this process and is divided into five chapters, including the first chapter that focuses on presenting the thesis problem background. In particular, Chapter 1 discusses the diffusion and reaction–diffusion equations since the facilitated diffusion equation is obtained from these two equations. Chapter 2 explains facilitated diffusion processes in detail and presents some biological examples of facilitated diffusion. Chapter 3 considers a mathematical model of facilitated diffusion processes for oxygen, specifically, diffusion facilitated by haemoglobin, the example mentioned in many studies and the common example. In Chapter 4, a similar mathematical model is considered but, in this model, myoglobin is the carrier molecule for oxygen. In addition, this research includes a new case, that is, when oxygen is consumed within muscle tissue especially when the body is practicing or exercising. The goals of this dissertation can be categorised into three main parts. The first goal of this research is to use mathematics to understand the mysteries of life. The second is to use a mathematical model to understand how the various system parameters affect or facilitate diffusion. The third is to compare the simple equilibrium model with the full partial diffusion model. The related results are discussed in the final chapter in which the FEniCS program is used to find the full solution for the model's equations. In this thesis, I attempt to refer to the most recent literature but I also cite earlier studies that are worthy.

Chapter 1

Diffusion and Reaction Equations

1.1 Introduction

Two important equations are used to describe various genuine physical and chemical processes occurring around us in this world. Most common processes incorporate the variety of the concentration of at least one substance in time and in space under the impact of two responses, which are, as the name suggests, diffusion and reaction [10]. The diffusion equation is for the procedure that makes things, for example, molecules, atoms and heat, move from a high-concentration part to a low-concentration part to achieve balanced concentration [6]. The term reaction refers to the procedure to change the concentration of the concerned substance, and diffusion indicates the procedure to oversee the movement of the substance in space [10]. The most effortless case to show dispersion is the one in which we pour an iodine solution into an empty glass container and then add water to it gradually, we observe the colour at the base of the container changing in shading in light of the impact of iodine molecules at the base of the glass. Later, iodine atoms gradually move and spread out until blended with the water. At this point, the shade of the water in the container becomes blue; see Figure from [28] (has been removed due to copyright restrictions) [6]. The purpose for this adjustment in water shading is the movement of ions from a higher concentration to a lower concentration keeping in mind the end goal to achieve equilibrium, at which stage the diffusion procedure stops; see Figure 1.1 [7].

1.2 Diffusion equation

The diffusion equation is a partial differential equation and it depicts the movement of microparticles. The mathematical expression of the diffusion process can be communicated scientifically using Fick's Law, proposed by Adolf Fick in the nineteenth century, which basically expresses the rate of diffusion across a surface as follows:

$$F = -D\nabla C, \tag{1.2.0.1}$$

where F is the rate of transfer per unit area (in $mol.m^{-2}.s^{-1}$), D is the diffusion coefficient (in $m^2.s^{-1}$) and C is the concentration (in $mol.m^{-3}$) [10] ,[36] and [19]. The negative sign indicates that the diffusion occurs in the opposite direction of increasing concentration [6]. In one dimension, the previous equation reduces to

$$F_i = -D\frac{\partial C}{\partial x_i}, \tag{1.2.0.2}$$

since the subscript i denotes the i-th position (in m)[12].

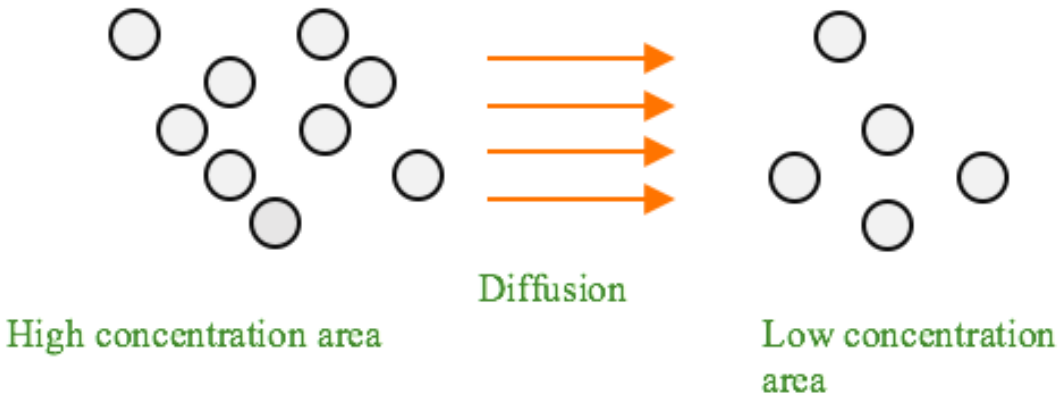

Figure 1.1: Movement of molecules from high-concentration region to low-concentration region.

1.3 Derivation of diffusion equation from balance equation

The diffusion equation is a partial differential equation and it depicts the movement of microparticles [21]. Let us consider interior volume as shown in Figure 1.2. Here, we use the summation convention where repeated indices in a term denote summation over all the values of the indices. We also use the comma notation to denote derivation with respect to coordinates. For example, if ϕ is a scalar function of $x = x_1, x_2, x_3$ then $\phi_{,i} = \frac{d\phi}{dx_i}$. The net rate of flow of molecules into volume V^* from outside V^* across the boundary ∂V^* is

$$-\int_{\partial V^*} f_i n_i ds,$$

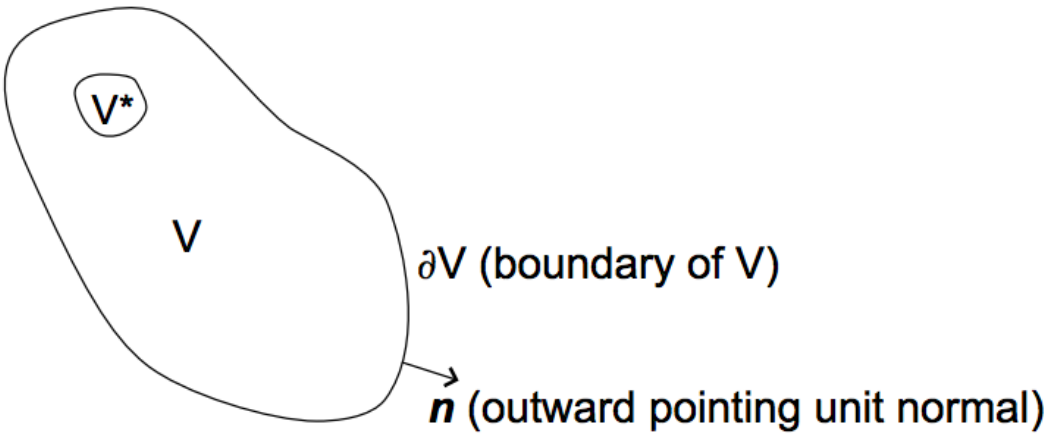

Figure 1.2: An arbitraray volume V with an interior subvolume V^*.

here, n indicates outward pointing unit normal and f indicates the flux vector inside volume V^*. This rate should balance the rate of time for the collection of molecules inside V^*. This is expressed mathematically in the stuff balance relationship:

$$-\int_{\partial V^*} f_i n_i \, dS = \frac{\partial}{\partial t}\int_{V^*} C \, dV = \int_{V^*} \frac{\partial C}{\partial t} \, dV, \tag{1.3.0.1}$$

where t represents time. The partial derivative is calculated for the terms inside the integral, and this yields a valid result since the upper or lower limits of the integration do not involve t. The concentration c represents the amount of molecules (i.e., the concentration) per unit volume, and therefore, its volume integral over V^* will yield the total amount of stuff (total concentration) in the volume. To convert the surface integral to volume integral, the divergence theorem can be applied on the terms on the left-hand side. Re-arranging the terms yields the following equation:

$$\int_{V^*} (\frac{\partial C}{\partial t} + f_{i,i}) dV = 0. \tag{1.3.0.2}$$

V* is arbitrary, and thus, on the basis of (1.3.0.2) it can be argued that the integrand must be zero at every point inside V. However, if in some subregion of V the integrand is positive, V* is chosen to represent that subregion. In this case, the integrand in (1.3.0.2) would be strictly positive and it will lead to a contradictory result. The same argument can be developed if, in any subregion, the integrand is negative. Therefore, the equation must be

$$\frac{\partial C}{\partial t} = -f_{i,i}$$

everywhere inside V. This applies to every point and region inside V. Using Fick's Law (isotropic), it can be written as follows:

$$\frac{\partial C}{\partial t} = (DC_{,i}),i = \nabla(D\nabla C).$$

The above equation is a usual form of the diffusion equation. If the diffusivity coefficient D is a constant, it can be shifted out of the differentiation without affecting the result since D does not depend on x. Hence, the equation can be written as:

$$\frac{\partial C}{\partial t} = DC_{,ii} = D\nabla^2 C.$$

Some such cases may also occur where the stuff is being created or destroyed inside the volume. For example, a reaction may occur that can destroy the stuff or can create more stuff within

the region. To deal with this issue, another source term R(x) is introduced in the equation. R(x) describes how much more stuff is being produced per unit volume per unit time. Its value may be positive or negative, and the former indicates that the stuff is being produced and the latter that stuff is being destroyed [30].

1.4 Reaction–diffusion process

The reaction–diffusion process of diffusion involves a reaction by adding to the previous equation the reaction term; at that point, the condition will turn into the reaction–diffusion equation. These equations occur normally in frameworks that have interconnected components, such as chemical reactions (see Figure 1.3), and are utilised broadly to portray pattern-formation phenomena in an assortment of physical, chemical and biological systems [10],[36] and [41].

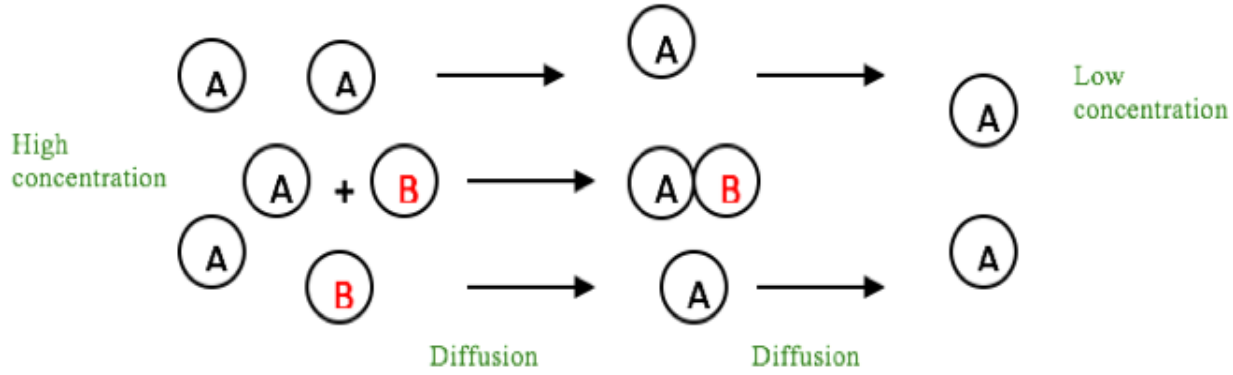

Figure 1.3: Diffusion process when two components interact. Here components A and B are diffusing and at the same time they are reacting to produce a complex AB which itself also diffuses.

A generalised formulation of the reaction–diffusion equation for a single substance in one spatial dimension (x-axis) is as follows:

$$\frac{\partial}{\partial t}C(x,t) = D\frac{\partial}{\partial x^2}C(x,t) + R(C), \tag{1.4.0.1}$$

here C(x,t) is the concentration of the substance at a specified x-coordinate and time t, R(C) is the reaction function and D is the diffusion constant. This simple case of the reaction–diffusion equation is known as the Kolmogorov–Petrovsky–Piskunov equation, or more easily, the KPP reaction–diffusion equation [42][3]. This equation is derived from the diffusion equation as given by Fick's Second Law and the reaction equation refers to the various physical phenomena; for example, Fisher's equation is derived by setting $R(C) = C(1-C)$ which yields

$$\frac{\partial}{\partial t}C(x,t) = D\frac{\partial}{\partial x^2}C(x,t) + C(1-C). \tag{1.4.0.2}$$

Fishers equation explains the wavelike spreading of biological populations with advantageous genes [9]. If $R(C) = C(1-C^2)$ the equation derived is known as the Rayleigh–Benard convection equation:

$$\frac{\partial}{\partial t}C(x,t) = D\frac{\partial}{\partial x^2}C(x,t) + C(1-C^2). \tag{1.4.0.3}$$

This equation shows the behaviour of natural convection as observed when a horizontal layer of fluid is heated, which results in the creation of convection cells known as Benard cells. Similarly, many other natural phenomena can be modelled using this equation simply by finding the

appropriate reaction function. Examples include a large number of phenomena in chemistry as well as a significant number of processes in biology, geology, physics and ecology [11] [14] [15]. Alan Turing 'The father of computing' wrote an article in 1952 on the chemical basis of morphogenesis, in which he described how patterns accrued in the world are formed from relatively stable initial states. This theory used reaction–diffusion equations as the mathematical basis of his argument where he showed how a large number of natural phenomena can be explained by the reaction–diffusion equation [43].

1.5 Mechanism of reaction

The mechanism of reaction is that it gives a new chemical identification for a substance by transforming it into a new one. These reactions are classified into three types: :
1. synthesis reactions, when at least two substances join to form another substance:

$$A + B \rightarrow AB.$$

2. decomposition reactions, when one substance separates into two components, as demonstrated using the following equation:

$$AB \rightarrow A + B.$$

3.exchange reactions, when two substances exchange their atoms to create two new products:

$$AB + CD \rightarrow AD + BC$$

[34].

1.6 Factors affecting diffusion rate

The diffusion rate can be affected by several factors. The first and the most obvious factor is the Fixation Inclination, that is, the rate of diffusion is increased because of the increased difference in the concentrations. The second factor affecting the rate of diffusion is the mass of the molecules. Heavier molecules tend to move slowly, and thus, they diffuse at a lower rate. The opposite holds true for lighter molecules [5]. The third factor is the temperature. Higher temperature increases the kinetic energy of molecules, which results in an increased rate of diffusion. Similarly, lower temperatures reduce the kinetic energy of molecules and thus reduce the movement of the molecules, which decreases the rate of diffusion. The fourth factor is density. Higher density makes the solvent thicker and, as a result, molecules slow down because they face higher resistance in movement, thus reducing the rate of diffusion. Conversely, if the density of the medium is less, the rate of diffusion will be higher since the molecules can move through the medium easily without facing much resistance. The primary movement of materials within the cytoplasm of cells is via diffusion. The increase in the density of cytoplasm will slow down the movement of the materials inside the cell. Dehydration is a perfect example of this scenario. During dehydration, the body faces a shortage of water. Owing to the decreased water content in the body, the density of cytoplasm increases, thus reducing the rate of diffusion and the cell functions. The most prominent effect of this can be observed in neurons because they are very sensitive to this effect. Dehydration can cause unconsciousness and, in severe cases, may cause individuals to fall into a coma because of the slower rate of diffusion within the cells [5]. The fifth factor affecting the rate of diffusion is the solubility of the material. Nonpolar or lipid-soluble materials can easily pass through the cell membranes compared with polar materials, thus increasing the diffusion rate. Other factors

affecting the rate are the surface area and the thickness of the plasma membranes. The more the surface area, the higher the rate of diffusion since the molecules will have more space to pass to the other side. However, the higher the thickness, the lower the rate of diffusion because more thickness means a larger distance and thus more resistance to the molecules. The more the distance a substance has to travel, the slower its rate of diffusion. This places a limit on the maximum possible cell size. A spherical-shaped cell will die if nutrients or waste materials cannot be transported in and out of the cell respectively [5].

Chapter 2

Facilitated Diffusion

2.1 Facilitated diffusion

Facilitated diffusion is a special case of reaction–diffusion and it is the process that makes substances move through the membrane by the assistance of an intermediary or a facilitator. It is a type of facilitated transport involving the passive movement of molecules down their concentration gradient influenced by the presence of another molecule, usually an integral membrane protein shaping a pore or channel [5]. Facilitated diffusion can be described by the three following steps; see Figure 2.1:
First, the molecule called the ligand associates with a carrier molecule to form a ligand–carrier complex. Typically, the carrier molecule, as well as the ligand–carrier complex, is much larger than the ligand molecule.
Second, the ligand–carrier complex is transported across the cell membrane.

Third, the ligand is separated from the ligand–carrier complex [38].

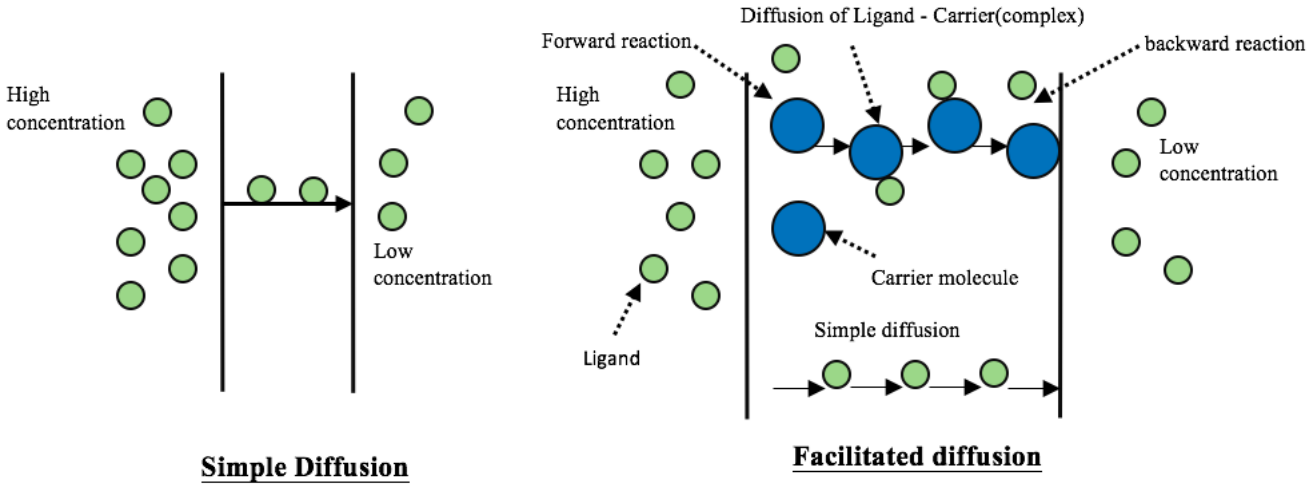

Figure 2.1: This figure shows the difference between simple and facilitated diffusion. Both include the movement of substances but facilitated diffusion is enhanced by a carrier molecule and has two transport pathways, the simple and the facilitated.

2.2 Formula for facilitated diffusion

Let us denote the carrier molecular species by C . The carrier is confined to the cell membrane of uniform thickness L in which it is able to diffuse. A ligand S in the surrounding medium, which is both extracellular and intracellular, reacts with C in a reversible manner to form a complex SC as follows:

$$S + C \underset{k^-}{\overset{k^+}{\rightleftarrows}} SC,$$

$$\text{ligand+carrier molecule} \underset{k^-}{\overset{k^+}{\rightleftarrows}} \text{ligand–carrier complex.}$$

Here, k^+ and k^- denote the forward and backward reaction rate constants respectively [38].

Reaction rate:

The reaction rate indicates how quickly the reactants of a chemical reaction are being converted into products and can be measured in two ways. The first way is to measure the rate at which the reactants of the chemical reaction are being consumed and the second is to measure the rate at which the products of the reaction are being produced. By using either way, the rate of the reaction can be found. The association and dissociation rate can be defined as follows:

$$\text{the forward rate} = k^+[S][C],$$
$$\text{the backward rate} = k^-[S][C],$$

where the square brackets mean concentration. The total rate equal to the forward rate less the inverse rate as follows:

$$\text{total rate} = k^+[S][C] - k^-[SC],$$

here k^+,k^- are the reaction rate coefficients [40].

2.3 Facilitated diffusion through cell membranes

The human body is built with millions of cells and every single cell is surrounded by a membrane called the plasma membrane. These membranes contain pores through which substances transport into and out of a cell. Some of the cells need substances that are not generally used by most other cells, and they have to acquire it somehow from extracellular fluids. This can be achieved if there is some mechanism to facilitate such movement from outside the cells to inside. Substances such as sugar and amino acids become permeable very rapidly, which forms the basis of facilitated diffusion [38]. The plasma membrane must be able to allow the movement of some substances into and out of the cell. It should also be able to restrict harmful substances from entering cells and some basic substances from leaving cells. Plasma membranes are made exactly the same way, that is, they only allow a few substances to cross through. If the plasma membrane somehow loses this property, this would soon result in the death of the cells [5]. Only a very small group of molecules can move across cell membranes. These molecules are usually small in size and are nonpolar. This allows the substances the cells need, such as oxygen, water and carbon dioxide, to diffuse through the membranes while preventing the movement of materials such as biopolymers, most of the nutrients and several small molecules. Consider the example of glucose. It is a relatively big molecule and cannot pass through the cell membrane directly or via simple diffusion. In such cases, facilitated diffusion using the membranes proteins plays a vital role. Usually, two types of these protein membranes act as carriers and form the channels across the membranes for the transport of materials [12]. In the process of facilitated diffusion, carrier proteins form a corridor that helps molecules to move across membranes and into cells. The carrier molecules just attach to a specific set of molecules, for example, only to some sugars and amino acids. Once the molecule is attached to the carrier

protein, the protein changes its shape in such a way that the molecule is pushed down through the channel and into the cell where it is released. Simple and facilitated diffusion are identical in that both make molecules move from higher concentration to lower without making use of any energy. However, facilitated diffusion only occurs if there is a carrier molecule to help the substance move through the membrane. Channel proteins and carrier proteins move materials at different rates. Channel proteins tend to move materials at a faster pace since the diffusion through them occurs at a rate of innumerable molecules per second, while in carrier proteins the rate is only a few thousand to a million molecules per second [5].

2.4 Biological examples of facilitated diffusion

2.4.1 Facilitated calcium diffusion by intestinal calcium binding protein

Calcium is the most plentiful metal in the human body and is important for several functions. One of the most important is bone building during growth and maintenance throughout life. Vitamin D is fundamental in helping the body retain and utilise this calcium [8]. Vitamin D's role is to form a protein that helps facilitate calcium diffusion across intestinal walls when calcium binds with this protein inside the intestine [8]. This protein is denoted as CaBP and is found in the cells that constitute the intestinal wall. The two types of CaBP, avian and mammalian, differ in weight. The relationship between this protein, CaBP, and calcium absorption is very strong and it occurs under several physiological conditions [8]. This relationship can be expressed as follows:

$$Ca + CaBP \rightarrow Ca_2BP.$$

Calcium is the ligand, CaBP is the carrier molecule and the medium is the intestinal wall cell cytoplasm.
This was examined experimentally by [8] .In that experiment, an aqueous compartment was used to provide evidence that CaBP enhances Ca absorption. In the experiment, two flow dialysis apparatus made of plexiglas were used with a dialysis membrane to separate the middle compartments from the two outer compartments and then, a solution located in the middle compartment was examined. The results show that the flux of calcium increased by 50 per cent on adding CaBP to the solution in the middle compartment and this is owing to the protein's role of facilitating calcium diffusion.

2.4.2 Facilitated diffusion of oxygen in plants

Every nodule in a plant's roots can be thought of as a manufacturing unit where several millions of bacteria live in around a hundred thousand diverse plant cells. These bacteria require basic nutrients from the plant, such as oxygen. Oxygen is carried to the bacteria by assistance from a protein called leghaemoglobin, which contains tenfold affinity of oxygen [45] [13]. Plants make leghaemoglobin, which is basically similar to haemoglobin in our red platelets, which helps to carry oxygen across cell walls. Bacteria require oxygen to increase the energy they obtain from photosynthesis and determine that the plant nourishes the bacterium considering the end goal to have the capacity to complete biological nitrogen fixation [45] [13]. To explain the mathematical model which is:

$$O_2 + LH \rightarrow LHO_2,$$

leghaemoglobin, LH, is the carrier molecule which joins the ligand oxygen, O_2, and medium, which is the root nodule cell, cytoplasm, to facilitate oxygen diffusion to feed bacteria. (Figure from [27] has been removed due to copyright restrictions)

2.4.3 Facilitated diffusion of glucose

Glucose transport is a good example of facilitated diffusion since glucose is an important resource that the body needs to create energy. Glucose is a sugar formed by 6 atoms of carbon, 12 atoms of hydrogen and 6 atoms of oxygen, $C_6H_{12}O_6$. A glucose molecule is mainly absorbed in the small intestine, is present in many foods and is consumed in our diet. Its molecule is not able to pass directly through cell membranes and hence needs a transporter protein. Most mammal cells have membrane proteins that enhance and facilitate glucose transport between blood and cell membrane. The human body contains five types of proteins specialised in facilitating glucose diffusion, namely, GLUE1,GLUE2,GLUE3,GLUE4 and GLUE5, and the differences between them are related to the tissues in which they are located. In this example, glucose is the ligand and the carrier molecule is the protein, regardless of whether it is GLUE1 or the others [20]; see Figure 2.3 from [20] (has been removed due to copyright restrictions).

2.4.4 Facilitated diffusion of oxygen inside the eyes

Retina is one the highest oxygen consuming tissues of the body because vision-related processes in the eyes of vertebrates consume substantial oxygen. Neuroglobin (Ngb) is a respiratory protein specific to neurons and is related to haemoglobin and myoglobin. Ngb is found not only in the brain but also in the peripheral nervous system and the endocrine system and has been identified as the intercellular respiratory protein [37]. Ngb is believed to increase the delivery of oxygen to mitochondria, the powerhouse of the cell. It has also been detected in photoreceptors, where it helps protein molecules with facilitated oxygen metabolism in the outer region of the retina [33]. The mathematical model of oxygen when facilitated by neuroglobin is expressed as follows:

$$Ngb + O_2 \rightarrow NgbO_2,$$

here, Ngb is the carrier protein, oxygen is the ligand and the medium is the mitochondria of eye cells.

2.4.5 Oxygen-facilitated diffusion by myoglobin or haemoglobin

Facilitated diffusion of oxygen in muscle tissues is one of the most well-known, well-researched examples of diffusion. The most common example in these studies is the transport of oxygen by the carrier molecule haemoglobin or myoglobin. Haemoglobin and myoglobin are two proteins, of which the first is abundant in muscles and the other in red cells. The two play a major role in enhancing oxygen transport across tissues in mammals. Haemoglobin is four times greater in size than myoglobin, which contains a fourth iron atom at a binding site with a very large affinity for oxygen; myoglobin has one iron atom at a binding site with a very large affinity for oxygen, but the affinities differ between these two proteins in terms of quantity [46]. The mathematical model when we suppose myoglobin is the carrier molecule is as follows:

$$O_2 + Mb \rightleftarrows MbO_2,$$

where O_2 is the ligand, myoglobin is the carrier molecule and the medium is the cytoplasm (sarcoplasm) of muscle cells (myocytes and cardiocytes) [13]; see Figure for across-section of muscle tissue (has been removed due to copyright restrictions).

Discussion:

The good, classic illustration in physiology for the role of myoglobin in the body's muscles is its providing these muscles with oxygen. This function of myoglobin is considered very important in diving mammals, for example whales, dolphins and seals, because myoglobin is present in

abundance in these mammals [35]. Recently, many proposals mentioned that the essential role of myoglobin is to enhance oxygen transport. Facilitated diffusion of oxygen by haemoglobin and myoglobin comes after the proposal which give a principally through the explore of Scholander (1960) and of Wittenberg (1959), and many quantitative realisations after that [38]. The basic experiment that was performed was Wittenberg's experiment where mentioned in [4] and [44] were used a water-tight diffusion chambers during this experiment. The results of this experiment can be summarised as follows: The first result that he obtained is that the diffusion of oxygen flux is a function of partial pressure of oxygen at the upstream end of the framework. He proved that that the flux of oxygen in the presence of haemoglobin is more noteworthy than that in the absence of haemoglobin , approximately by a constant value. The following figure shows the result; the closed circle demonstrates the flux in the presence of haemoglobin and the open circle demonstrates the flux with myoglobin.

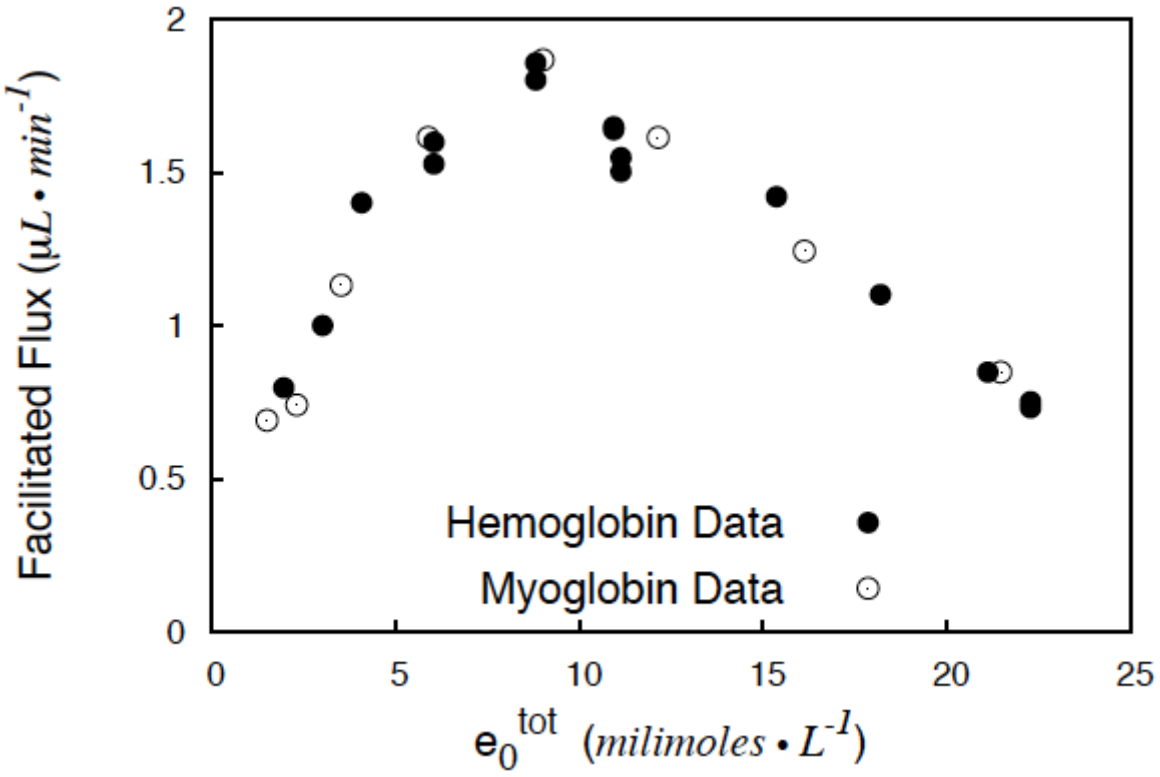

Figure 2.2: One of the figures mentioned in [4], which shows the effect of facilitated diffusion of oxygen in the presence of haemoglobin or myoglobin. In this Figure the horizontal axis represent the concentration of the carrier.

2.5 Active and passive transport diffusion

The difference between active transport and facilitated diffusion must be noted since these are two different processes that help materials move to their specified locations. Facilitated diffusion can occur in either direction depending on the concentration gradient. It transports the materials from higher concentration to a lower concertation with the help of carrier proteins. If the concentration of a material inside the cell is higher, the carrier proteins would move them out of the cell via facilitated diffusion. However, in active transport the molecules move from a place of lower concentration to a place of higher concentration and this process uses energy

through molecules such as adhenosine triphospate (ATP) or guanosine triphosphate (GTP) [12][5]. An example of active transport is the diffusion in the kidneys, the human kidney is used to filter out waste products that enter the body. To reabsorb the vital substances, namely, amino acids, water and salts, into the bloodstream, the process of active transport is required [26].

Chapter 3

Mathematical Model

Mathematical modelling is an effective way to explain some worldwide phenomena [29]. A mathematical model utilises the properties of easiness and abstraction to portray something identified with our world and is made for a particular reason [1]. The mathematical models of facilitated diffusion are basically classified as steady-state reaction–diffusion partial differential equation models. In these models, the diffusing of ligands, carrier molecules and ligand-carrier complexes under Fick's law, and the responses, reveal the affiliation and separation of the ligand-carrier complexes. In 1965–1966, numerous authors explained reaction–diffusion models for facilitated diffusion and most such research was based on that of Wyman and subsequently, that of Murray [4].
A mathematical model presented in [4] and [44] for oxygen binding with haemoglobin as carrier molecule. This model considered a framework in which oxygen is the ligand and haemoglobin is the carrier molecule that transform in the x direction. The chemical reaction between oxygen and haemoglobin is given by

$$O_2 + Hb \underset{k-}{\overset{k+}{\leftrightarrows}} HbO_2, \tag{3.0.0.1}$$

where O_2 is the ligand and Hb is the carrier molecule.
The facilitated diffusion model's equations are:

$$\frac{\partial(mc_pY(x,t))}{\partial t} = D_p\frac{\partial^2(mc_pY(x,t))}{\partial x^2} + \rho, \tag{3.0.0.2}$$

$$\frac{\partial c(x,t)}{\partial t} = D_c\frac{\partial^2(c(x,t))}{\partial x^2} - \rho. \tag{3.0.0.3}$$

Equation (3.0.0.2) is for the diffusion of oxygen, which combines with the carrier molecule, and equation (3.0.0.3) is for the diffusion of free oxygen.

Here:

$c(x,t)$ is the concentration of free oxygen.
c_p is the (constant) concentration of the carrier molecule.
m represents the number of sites on the carrier that can bind oxygen which is equal to four in the case of haemoglobin.
$Y(x,t)$ is the fractional saturation of the carrier molecule with the ligand.
$c_pY(x,t)$ represents the concentration of the bound oxygen in the model.
ρ represents the rate of the reaction.
D_p is the diffusion coefficients of bound oxygen.
D_c is the diffusion coefficients of free oxygen.

We know that in the steady state (which is a stable condition and means stability over time without any changes $\frac{\partial}{\partial t} = 0$), and in the previous model case

$$\frac{\partial(mc_pY(x,t))}{\partial t} = \frac{\partial c(x,t)}{\partial t} = 0. \tag{3.0.0.4}$$

From now onwards only the steady state will be considered and therefore c and Y will only depend on x. By combining (3.0.0.2) and (3.0.0.3), we have

$$D_p\frac{\partial^2(mc_pY(x))}{\partial x^2} + D_c\frac{\partial^2(c(x))}{\partial x^2} = 0,$$

and after one integration this becomes

$$D_p\frac{\partial(mc_pY(x))}{\partial x} + D_c\frac{\partial c(x)}{\partial x} = -F,$$

where F is an arbitrary constant of integration and for later convenience a minus sign has been used. Integration a second time yields

$$D_p(mc_pY(x)) + D_cc(x) = -Fx + B, \tag{3.0.0.5}$$

where the constant F symbolises the total flux of free and bound oxygen and B is the integration constant in the system. This system has been studied in one dimension in the x direction with boundaries at x = 0 and x = L.

The boundary conditions are

$c(0) = c_0, \quad , \quad c(L) = c_L.$

The chemical reaction term is defined as

$$\rho_f = k^+mc_p(1 - Y(x))c(x),$$

$$\rho_b = k^-mc_pY(x),$$

where ρ_f is the forward reaction, which is proportional to the product of concentration of free oxygen and concentration of unsaturated carrier $c_p(1 - Y(x))$. The backward reaction ρ_b is proportional to the amount of saturated carrier $c_pY(x)$. The reaction rate constants are k^+ and k^-. For the moment it will be assumed that equilibrium hold through the domain that is , $\rho_f = \rho_b$, which leads to:

$$k^+mc_p(1 - Y)c(x) - k^-mc_pY(x) = 0, \tag{3.0.0.6}$$

where k^+ is the denoted the association rate and k^- is denoted the dissociation rate for the oxygen–haemoglobin complex. Expanding (3.0.0.6) becomes

$$k^+mc_pc(x) - k^+mc_pY(x)c(x) - k^-mc_pY(x) = 0.$$

Dividing by k^+mc_p to simplify this equation

$$c(x) - Y(x)c(x) - \frac{k^-}{k^+}Y(x) = 0,$$

then

$$Y(x)\left[c(x) + \frac{k^-}{k^+}\right] = c(x),$$

$$Y(x) = \frac{c(x)}{c(x) + k^-/k^+},$$

$$Y(x) = \frac{c(x)}{c(x) + k_{eq}}, \tag{3.0.0.7}$$

where $k_{eq} = \frac{k^-}{k^+}$ and this is the equilibrium approximation that this study uses to compare some of equilibrium solutions and the full solution derived from the FEniCS program. Equilibrium approximation can be obtained by singular perturbation, which is discussed later in this thesis.

From (3.0.0.5)

$$mc_p Y(x) = \big(\frac{1}{D_p}\big)[-Fx + B - D_c c(x)],$$

and by using (3.0.0.7)

$$mc_p\left(\frac{c(x)}{c(x) + k_{eq}}\right) + (\frac{1}{D_p})[Fx - B + D_c c(x)] = 0,$$

and so

$$mc_p c(x) + \left(\frac{c(x) + k_{eq}}{D_p}\right)[Fx - B + D_c c(x)] = 0. \tag{3.0.0.8}$$

Despite extensive calculations, Wyman could not demonstrate that facilitated diffusion of oxygen in the presence of haemoglobin or myoglobin is principally because of translational diffusion of the carrier molecules. A significant contribution of Wyman is determining the rotational diffusion of carrier molecules which considered the opposite of the transnational diffusion as it is involved in establishing the spatial balance of the particles' position. He then stated that a numerical answer for (3.0.0.8) could be derived using experimental values for the physical parameters mentioned. In Ref [22], Kreuzer and Hoofd obtain such a numerical solution.

Chapter 4

Solutions of the Mathematical Model

4.1 Introduction

In the previous chapter, in Equation (3.0.0.1), haemoglobin is the carrier and oxygen the ligand, but any other ligand and carrier combination that has reverse correlation can be used, as in the present study, which considers myoglobin the carrier molecule. Undoubtedly, myoglobin plays an essential role in carrying oxygen to stimulate the physiological function of cardio and skeletal muscles [13]. Myoglobin is a protein that contains one iron atom at a binding site with a very great affinity for oxygen [38].
In this chapter, two basic models in one-dimensional geometry are considered, one to study the facilitated diffusion of myoglobin across cell membranes and the other, facilitated diffusion of oxygen across muscle tissues. The difference between these two models is in the boundary conditions; further, in the second model respiration of oxygen is assumed.

4.2 Facilitated diffusion of myoglobin across cell membranes

The mathematical model is

$$O_2 + Mb \underset{k-}{\overset{k+}{\leftrightarrows}} MbO_2.$$

Hence, we obtain the same equation as in (3.0.0.8) but in myoglobin case the binding site m = 1. The equation will be

$$c_p c(x) + \left(\frac{c(x) + k_{eq}}{D_p}\right)(D_c c(x) + Fx - B) = 0.$$

In order to solve this equation and find the value of F and B, we use the boundaries conditions which are

$$c(0) = c_0 \quad , \quad c(L) = c_L \quad , \quad Y'(0) = 0 \quad , \quad Y'(L) = 0.$$

The third and fourth boundaries conditions means no flux of the carrier out of the region; see Figure (4.1).
After applying the first condition $c(0) = c_0$, we obtain B as follows:

$$B = \frac{c_p c_o D_p}{c_0 + k_{eq}} + D_c c_0. \tag{4.2.0.1}$$

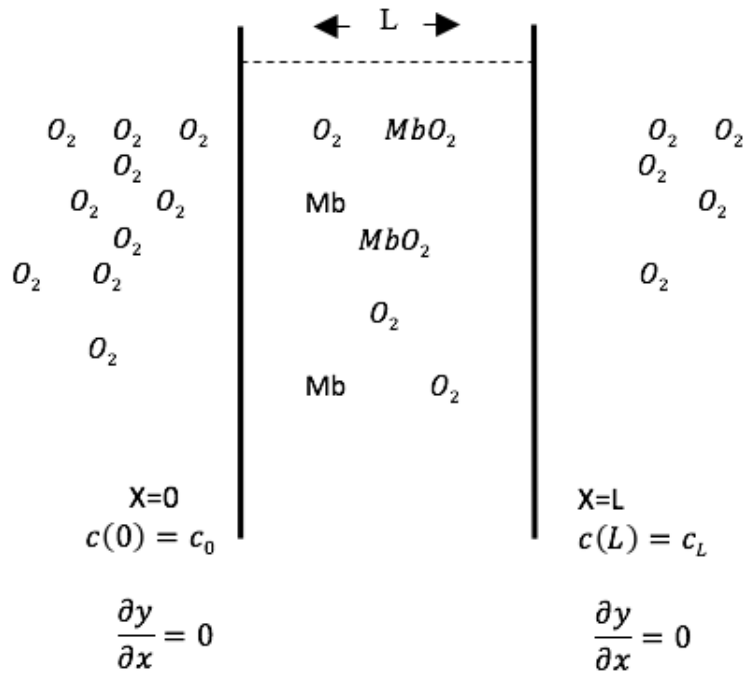

Figure 4.1: Mathematical model of oxygen diffusion between cell membranes, which differs in concentration at the edges

By applying the second boundary condition $c(L) = c_L$, we obtain F as follows:

$$F = \frac{1}{L}\left(\frac{-c_p c_L D_p}{c_L + k_{eq}} - D_c c_L + \frac{c_p c_0 D_p}{c_0 + k_{eq}} + D_c c_0\right). \tag{4.2.0.2}$$

Equation (4.2.0.2) can simplified to be the sum of two functions F_f and F_d since F_d is the flux equation without the concentration of the carrier molecule c_p and F_f is the flux equation with the concentration of the carrier molecule as follows

$$F = F_d + F_f,$$

$$F_d = \frac{D_c}{L}(c_0 - c_L)$$

and

$$F_f = \frac{1}{L}\left[\frac{-c_p c_L D_p}{c_L + k_{eq}} + \frac{c_p c_0 D_p}{c_0 + k_{eq}}\right].$$

Moreover, we have to find the concentration as a function of F and B as follows

$$c_p c(x) + \left(\frac{c(x) + k_{eq}}{D_p}\right)(D_c c(x) + F(x) - B) = 0,$$

$$c_p c(x) + \frac{D_C}{D_P}[c(x)]^2 + \frac{k_{eq} D_c}{D_p} c(x) + \frac{Fx}{D_p} c(x) + \frac{k_{eq}}{D_p} Fx - \frac{B}{D_p} c(x) - \frac{k_{eq}}{D_p} B = 0,$$

$$\frac{D_C}{D_P}[c(x)]^2 + \left[c_p + \frac{k_{eq} D_c}{D_p} + \frac{Fx}{D_p} - \frac{B}{D_p}\right] c(x) + \frac{k_{eq}}{D_p} F(x) - \frac{k_{eq}}{D_p} B = 0.$$

By using the square root method;

$$Ac(x)^2 + Gc(x) + E = 0,$$

$$c(x) = \frac{-G \pm \sqrt{G^2 - 4AE}}{2A}.$$

Since:

$$A = \frac{D_C}{D_P},$$

$$G = \left[c_p + \frac{k_{eq} D_c}{D_p} + \frac{Fx}{D_p} - \frac{B}{D_p} \right]$$

and

$$E = \frac{k_{eq}}{D_p} Fx - \frac{k_{eq}}{D_p} B.$$

Clearly only the positive solution will make sense physically. The values of the parameters in the following table are from [32] and [31].

Parameters	Murray 1974	Murray 1971
c_p	$2.8\times10^{-7} mol\ cm^{-3}$	$1.2\times10^{-5} mol\ cm^{-3}$
c_0	$3.5\times10^{-8} mol\ cm^{-3}$	$1\times10^{-7} mol\ cm^{-3}$
D_p	$1.86\times10^{-6} cm^2 s^{-1}$	$4.35\times10^{-7} cm^2 s^{-1}$
D_c	$2\times10^{-5} cm^2 s^{-1}$	$1.2\times10^{-5} cm^2 s^{-1}$
m	1	1
L	2.5×10^{-3}cm	2.2×10^{-2}cm
k^-	$65 s^{-1}$	$11 S^{-1}$
k^+	$2.4\times10^{10} cm^3 mol^{-1} s^{-1}$	$14\times10^{9} cm^3 mol^{-1} s^{-1}$

Table 4.1: Parameters values for myoglobin- facilitated diffusion of oxygen in cells, from Murray 1974 and Murray 1971.

Some of the results:

The result now described have used the (Muarry 1971) parameters from the table above. Plot

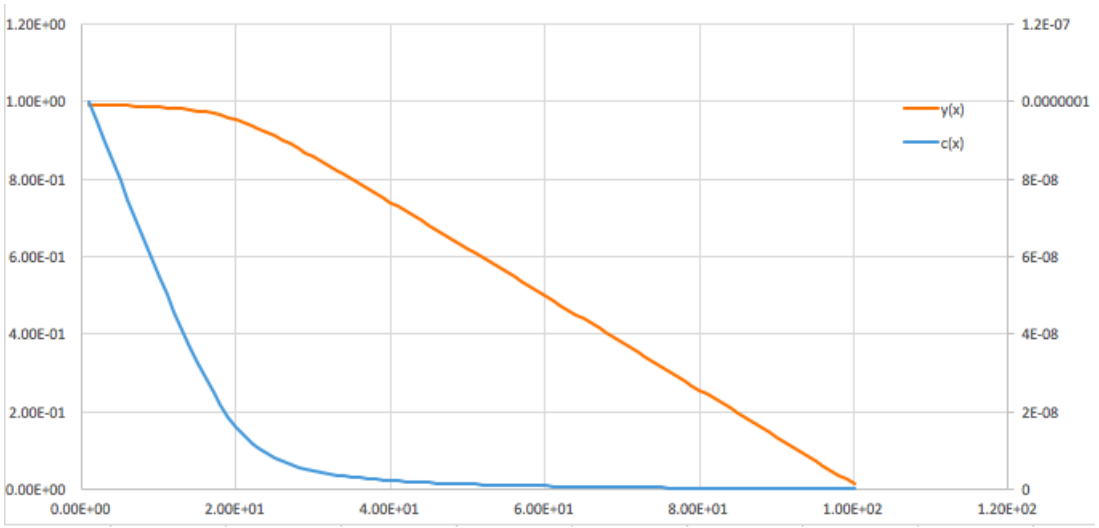

Figure 4.2: Profiles of c and Y in the presence of a carrier molecule

4.2 for c(x) and Y(x) when there is a carrier molecule, which shows that both c(x) and Y(x) decrease and the decrease in c(x) is faster than that in Y(x). Initially the decrease in c(x) is linear, but after a point becomes curvilinear. Conversely, the initial decrease in Y(x) is curvilinear, but after a point becomes linear. The point at which the decrease in c(x) changes from linear to curvilinear and the decrease in Y(x) changes from curvilinear to linear is the same (as illustrated in the graph above).

In Figure 4.3, where there is no carrier, the decrease is linear (constant rate), as depicted by

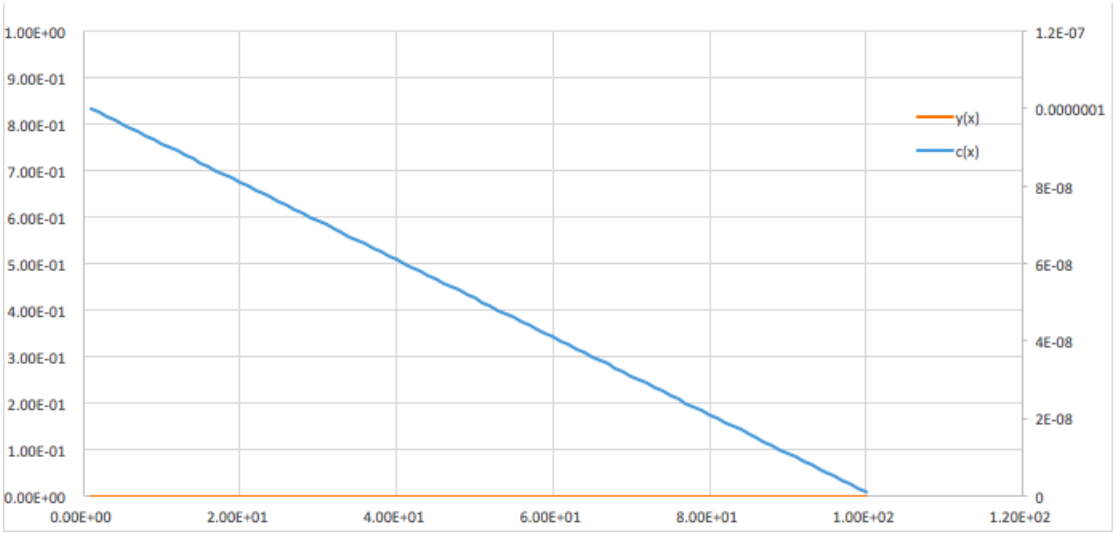

Figure 4.3: Profiles of c and Y in the absence of a carrier molecule

the blue line in the chart above. The red line represents zero (constant). Rate of diffusion is not linear when a carrier protein reacts with a molecule while the rate in simple diffusion is linear [18].

Rate of diffusion:

Now, the rate of diffusion is calculated, which is the fraction between the facilitated diffusion in the presence of the carrier molecule and that in the absence of the carrier molecule, such that:

$$\frac{1}{L}\left[\frac{-c_p c_L D_p}{c_L + k_{eq}} - D_c c_L + \frac{c_p c_0 D_p}{c_0 + k_{eq}} + D_c c_0\right] \div \frac{D_c}{L}(c_0 - c_L) = 1 + \frac{F_f}{F_d}.$$

The rate of the flux of oxygen when there is a carrier myoglobin equals 5.3; however, the rate of flux when is no carrier molecule equals 1, which means the increased flux of oxygen when it is facilitated by myoglobin is greater by five times.

Calculating the flux at different values of c_0 and c_L, the result is as follows since c_L<c_0. From Figure 4.4, it is observed that the flux attains its maximum value at the beginning for every series after which it decreases.

cL \ c0	1.00E-07	5.00E-08	2.50E-08	1.00E-08	5.00E-09	2.50E-09	1.00E-09	5.00E-10	2.50E-10
5.00E-08	1.07E+00								
2.50E-08	1.13E+00	1.26E+00							
1.00E-08	1.31E+00	1.62E+00	2.23E+00						
5.00E-09	1.59E+00	2.16E+00	3.29E+00	6.48E+00					
2.50E-09	2.03E+00	3.05E+00	5.03E+00	1.06E+01	1.90E+01				
1.00E-09	2.90E+00	4.77E+00	8.42E+00	1.87E+01	3.41E+01	5.93E+01			
5.00E-10	3.64E+00	6.23E+00	1.13E+01	2.56E+01	4.69E+01	8.19E+01	1.50E+02		
2.50E-10	4.27E+00	7.50E+00	1.38E+01	3.16E+01	5.80E+01	1.01E+02	1.86E+02	2.58E+02	
1.00E-10	4.83E+00	8.60E+00	1.60E+01	3.68E+01	6.77E+01	1.18E+02	2.17E+02	3.01E+02	3.74E+02
0.00E+00	5.32E+00	9.57E+00	1.79E+01	4.13E+01	7.62E+01	1.33E+02	2.45E+02	3.39E+02	4.21E+02

Table 4.2: Flux ratio for different values of c_0 andc_L

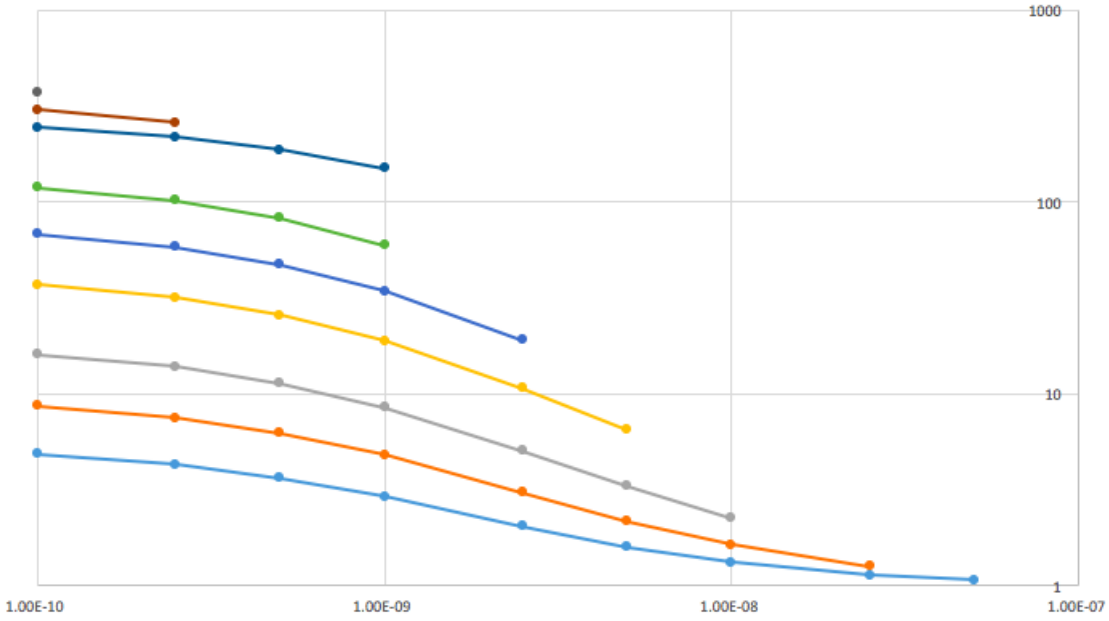

Figure 4.4: Plot of the data in table 4.2. The horizontal axis is c_L. The various curves represent the columns of table 4.2, that is they corresponds to fixed values of c_0.

4.3 Facilitated diffusion of myoglobin across muscle tissues

During exercises, muscles' demand for oxygen increases and must be fulfilled. Myoglobin can be characterised as a portable carrier of oxygen and it is created in response to the heart and muscle demand [45]. Essentially, all of the oxygen is consumed by skeletal muscles and the heart [45]. We now consider a new case when there is respiration of oxygen within the muscle tissue; see Figure 4.5. The facilitated diffusion equations of this model are as follows:

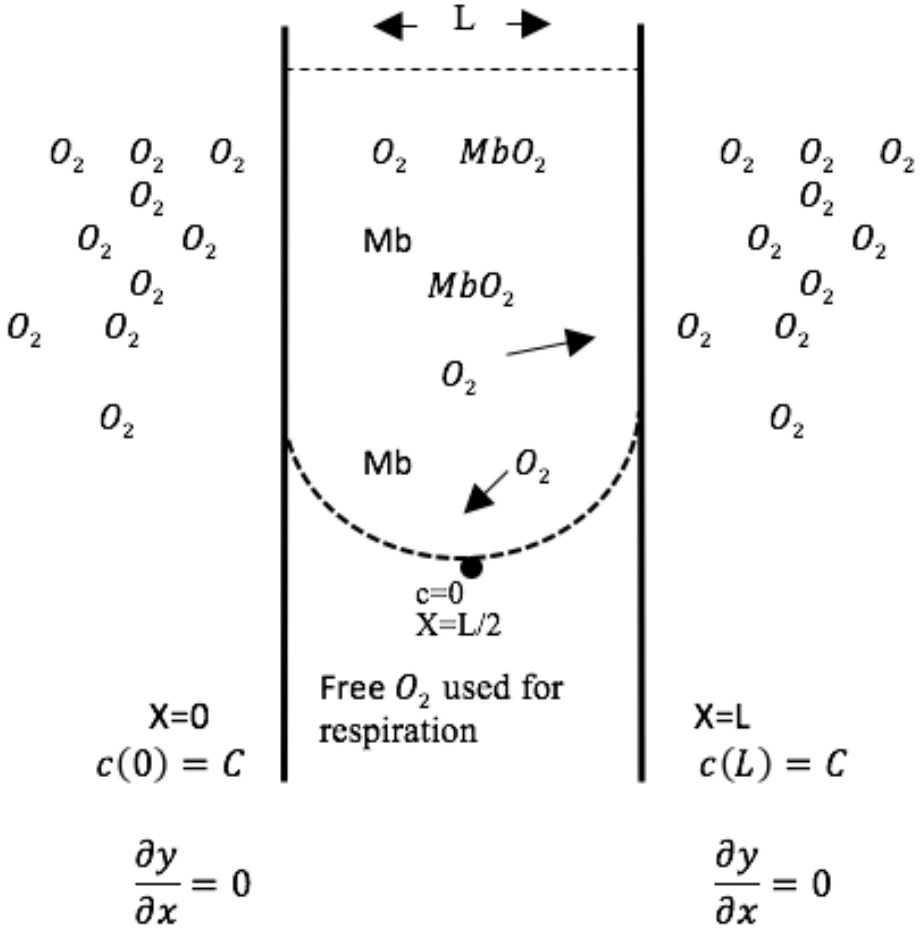

Figure 4.5: Mathematical model of oxygen diffusion within muscle tissue; the concentration at the edges is the same and respiration of oxygen occurs inside the muscles

$$\frac{\partial c(x,t)}{\partial t} = D_c \frac{\partial^2 (c(x,t))}{\partial x^2} - \rho - Q, \tag{4.3.0.1}$$

$$\frac{\partial (c_p Y(x,t))}{\partial t} = D_p \frac{\partial^2 (c_p Y(x,t))}{\partial x^2} + \rho, \tag{4.3.0.2}$$

Q here is the respiration term. The same steps in the previous model are repeated with some differences. In the steady state, combining the previous two equations we obtain:

$$D_p \frac{\partial^2 (c_p Y(x,t))}{\partial x^2} + D_c \frac{\partial^2 (c(x,t))}{\partial x^2} = Q, \tag{4.3.0.3}$$

by integrating the previous equation twice we obtain:

$$(D_p c_p Y(x) + D_c c(x) = \frac{1}{2}Qx^2 + Fx + B, \tag{4.3.0.4}$$

by using the equilibrium assumption which is:

$$Y(x) = \frac{c(x)}{c(x) + k_{eq}}, \tag{4.3.0.5}$$

we obtain that:

$$c_p Y(x) = \frac{1}{D_p}\left[\frac{1}{2}Qx^2 + Fx + B - D_c c(x)\right], \tag{4.3.0.6}$$

$$c_p c(x) + \frac{c(x) + k_{eq}}{D_p}\left[\frac{-1}{2}Qx^2 - Fx - B + D_c c(x)\right] = 0. \tag{4.3.0.7}$$

By using the boundary conditions $c(0) = C$ and $c(L) = C$, we find the values of B and F respectively as follows:

$$B = D_c C + \frac{c_p D_p C}{C + k_{eq}}, \tag{4.3.0.8}$$

$$F = \frac{1}{L}\left(D_c C + \frac{c_p D_p C}{C + (k_{eq})} - \frac{1}{2}QL^2 - B\right),$$

by using the value of B we have

$$F = \frac{1}{L}\left(D_c C + \frac{c_p D_p C}{C + k_{eq}} - \frac{1}{2}QL^2 - D_c C - \frac{c_p D_p C}{C + k_{eq}}\right). \tag{4.3.0.9}$$

We can express the concentration as a function of F, B and Q as follows:

$$\frac{D_c}{D_p}c(x)^2 + \left[c_p - \frac{1}{2}\frac{Qx^2}{D_p} - \frac{Fx}{D_p} - \frac{B}{D_p} + k_{eq}\frac{D_c}{D_p}\right]c(x) + \left[\frac{-k_{eq}}{2}\frac{Qx^2}{D_p} - k_{eq}\frac{Fx}{D_p} - k_{eq}\frac{B}{D_p}\right] = 0.$$

By using the square root method we have

$$Ac(x)^2 + Gc(x) + E = 0,$$

$$c(x) = \frac{-G \pm \sqrt{G^2 - 4AE}}{2A}.$$

Since:

$$A = \frac{D_C}{D_P},$$

$$G = \left[c_p - \frac{1}{2}\frac{Qx^2}{D_p} - \frac{Fx}{D_p} - \frac{B}{D_p} + k_{eq}\frac{D_c}{D_p}\right]$$

and

$$E = \left[\frac{-k_{eq}}{2}\frac{Qx^2}{D_p} - \frac{k_{eq}Fx}{D_p} - \frac{k_{eq}B}{D_p}\right].$$

We calculate how big we can make respiration Q before the concentration begins to be negative by using the equilibrium approximation. We obtain the big respiration when $x = \frac{L}{2}$ and $c(x) = 0$, and this make equation (4.3.0.4) be:

$$\frac{1}{2}Q\frac{L^2}{4} + F\frac{L}{2} + B = 0,$$

by using the value of F

$$\frac{1}{2}Q\frac{L^2}{4} + \frac{L}{2}\left[\frac{1}{L}\left(D_cC + \frac{c_pD_pC}{C + k_{eq}} - \frac{1}{2}QL^2 - B\right) + B\right] = 0,$$

then

$$\frac{1}{8}QL^2 + \frac{1}{2}D_cC + \frac{c_pD_pC}{c + k_{eq}} - \frac{1}{4}QL^2 - \frac{1}{2}B + B = 0,$$

$$\frac{-1}{8}QL^2 = \frac{-1}{2}D_cC - \frac{1}{2}\frac{c_pD_pC}{C + k_{eq}} - \frac{1}{2}B,$$

by using B

$$Q = \frac{4}{L^2}\left[D_cC + \frac{c_pD_pC}{c + k_{eq}} + D_cC + \frac{c_pD_pC}{C + k_{eq}}\right].$$

The ratio of Q is the fraction between Q when there is a carrier molecule and when there is no carrier molecule. From Figure 4.6, the decrease in rate of consumption is curvilinear initially; however, the decrease becomes linear later

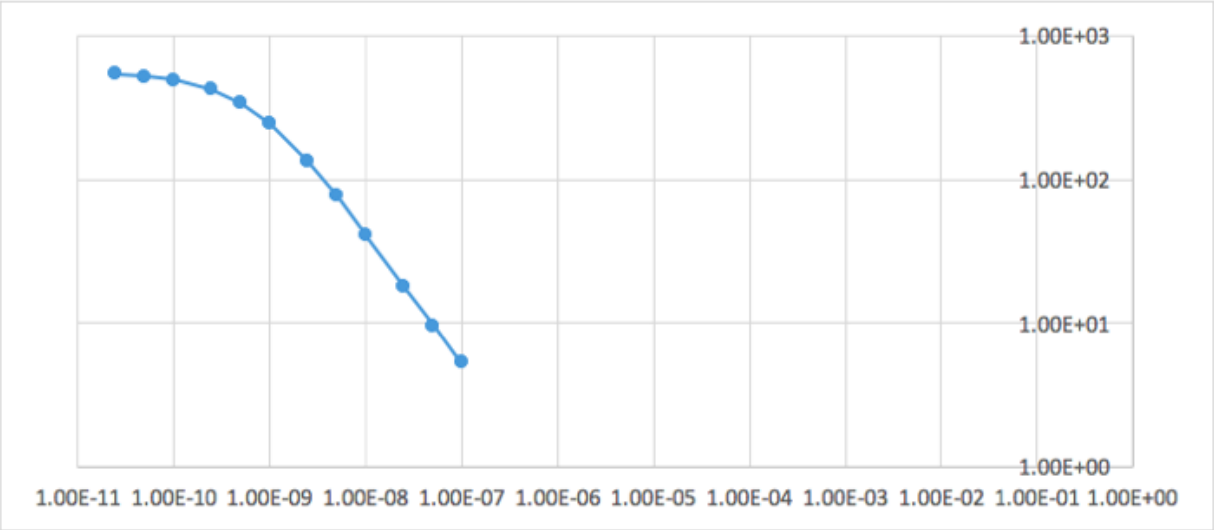

Figure 4.6: The maximum respiration rate plotted against the external concentration C.

4.4 Numerical solution

4.4.1 Full solution using FEniCS

FEniCS
Partial differential equations can be easily solved using the FEniCS tool [25]. FEniCS is a powerful software-based platform that can be used to create complex mathematical models as well as software for automated computational mathematical modelling. This places in users hands an easy-to-use, natural, reliable software for solving partial differential equations using finite element methods. FEniCS was developed in 2003 as the result of collaboration between researchers from various universities and research centres worldwide [24].

The following steps are used to solve any physical problem using FEniCS:

1. Identify the domain over which the computations are to be performed, the partial differential equation along with the boundary conditions and the source terms.
2. Change the identified problem to a finite element variational problem.
3. Using the code in Python, define the domain of the problem, the variational problem that is to be resolved, the boundary conditions of the problem and the source terms using the relevant FEniCS abstractions.
4. Using FEniCS, solve the problem for the given boundary values, calculate the derived quantities, such as averages, and, finally, visualise the results.

4.4.2 Nondimensionalization and scaling

Nondimensionalization, as the name indicates, is the transformation of a problem so that it no longer has dimensions, that is, it acquires a dimensionless form. Nondimensionalization and scaling are useful since several approximation methods used in reducing the complexity of a problem are based on comparisons. For example, the variable of interest in a problem may be larger, slower or faster in comparison with other terms/variables in the problem. Regardless of the comparison to be made, it is crucial to know the way in which the terms are interrelated and to be compared with each other. For this, the concept of scaling is helpful [16].
Working on Equations (4.3.0.1) and (4.3.0.2) which are;

$$\frac{\partial}{\partial t}c = D_c\frac{\partial^2 c}{\partial x^2} - \rho - Q, \tag{4.4.2.1}$$

$$\frac{\partial}{\partial t}c_pY = D_pc_p\frac{\partial^2 Y}{\partial x^2} + \rho, \tag{4.4.2.2}$$

since ρ is the chemical reaction and equal to

$$\rho = k^+c_p(1-Y)c - k^-c_pY. \tag{4.4.2.3}$$

By substituting it in the two previous equations we have

$$\frac{\partial}{\partial t}c = D_c\frac{\partial^2 c}{\partial x^2} - k^+c_p(1-Y)c + k^-c_pY - Q, \tag{4.4.2.4}$$

$$\frac{\partial}{\partial t}c_pY = D_pc_p\frac{\partial^2 Y}{\partial x^2} + k^+c_p(1-Y)c - k^-c_pY. \tag{4.4.2.5}$$

By performing scaling to simplify such that:

$$\tilde{c} = \frac{c}{c_0} \Longrightarrow c = \tilde{c}c_0,$$

$$\tilde{x} = \frac{x}{L} \Longrightarrow x = \tilde{x}L$$

and

$$\tilde{t} = t\frac{D_p}{L^2} \Longrightarrow t = \frac{L^2\tilde{t}}{D_p}.$$

By substituting the previous values of $\tilde{c}$, $\tilde{x}$ and $\tilde{t}$ on Equations (4.4.2.4) and (4.4.2.5); we have

$$\frac{L^2 c_0}{D_p}\frac{\partial \tilde{c}}{\partial \tilde{t}} = \frac{D_C c_0}{L^2}\frac{\partial^2 \tilde{c}}{\partial \tilde{x}^2} - k^+ c_0 c_p (1-Y)\tilde{c} + k^- c_p Y - Q,$$

$$\frac{D_p c_p}{L^2}\frac{\partial Y}{\partial \tilde{t}} = \frac{D_p c_p}{L^2}\frac{\partial^2 Y}{\partial \tilde{x^2}} + k^+ c_0 c_p (1-Y)\tilde{c} - k^- c_p Y.$$

in the steady state, the previous two equations become:

$$\frac{D_C c_0}{L^2}\frac{\partial^2 \tilde{c}}{\partial \tilde{x}^2} - k^+ c_0 c_p (1-Y)\tilde{c} + k^- c_p Y - Q = 0,$$

$$\frac{D_p c_p}{L^2}\frac{\partial^2 Y}{\partial \tilde{x^2}} + k^+ c_0 c_p (1-Y)\tilde{c} - k^- c_p Y = 0.$$

Multiply the previous two equations by $\frac{L^2}{D_c c_0}$ as follows:

$$\frac{\partial^2 \tilde{c}}{\partial \tilde{x}^2} - \frac{k^+ L^2 c_p}{D_c}(1-Y)\tilde{c} + \frac{k^- c_p L^2}{D_c c_0}Y - \frac{QL^2}{D_c c_0} = 0,$$

$$\frac{D_p c_p}{D_c c_0}\frac{\partial^2 Y}{\partial \tilde{x^2}} + \frac{k^+ c_p L^2}{D_c}(1-Y)\tilde{c} - \frac{k^- c_p L^2}{D_c c_0}Y = 0,$$

and that yields

$$\frac{\partial^2 \tilde{c}}{\partial \tilde{x}^2} - K^+(1-Y)\tilde{c} + K^- Y - Q_{new} = 0, \tag{4.4.2.6}$$

$$D\frac{\partial^2 Y}{\partial \tilde{x^2}} + K^+(1-Y)\tilde{c} - K^- Y = 0. \tag{4.4.2.7}$$

The above equations are the non-dimensional form that we will work with from now on. Note that there are four non-dimensional parameters which are:

$$K^+ = \frac{k^+ L^2 c_p}{D_c},$$

$$K^- = \frac{k^- c_p L^2}{D_c c_0},$$

$$Q_{new} = \frac{QL^2}{D_c c_0}$$

and

$$D = \frac{D_p c_p}{D_c c_0}.$$

Weak formulation

Now, convert (4.4.2.6) and (4.4.2.7) to weak formulation by multiplying by test function and integration by parts.
Starting with Equation (4.4.2.6), we have

$$\int_0^1 \frac{\partial^2 \tilde{c}}{\partial \tilde{x^2}} * \phi_1 dx - \int_0^1 K^+(1-Y)\tilde{c} * \phi_1 dx + \int_0^1 K^- Y * \phi_1 dx - \int_0^1 Q_{new} * \phi_1 dx = 0,$$

$$\left[\phi_1 * \frac{\partial \tilde{c}}{\partial \tilde{x}}\right]_0^1 - \int_0^1 \frac{\partial \tilde{c}}{\partial \tilde{x}} \frac{d\phi_1}{d\tilde{x}} dx - \int_0^1 K^+(1-Y)\tilde{c} * \phi_1 dx + \int_0^1 K^- Y * \phi_1 dx - \int_0^1 Q_{new} * \phi_1 dx = 0,$$

since $\phi_1 = 0$ on the boundary

$$-\int_0^1 \frac{\partial \tilde{c}}{\partial \tilde{x}} \frac{d\phi_1}{d\tilde{x}} dx - \int_0^1 K^+(1-Y)\tilde{c} * \phi_1 dx + \int_0^1 K^- Y * \phi_1 dx - \int_0^1 Q_{new} * \phi_1 dx = 0. \quad (4.4.2.8)$$

Convert Equation (4.4.2.7) to weak formulation by multiplying by ϕ_2 and perform integration by parts as follows:

$$D\int_0^1 \frac{\partial^2 Y}{\partial \tilde{x^2}} * \phi_2 dx + \int_0^1 K^+(1-Y)\tilde{c} * \phi_2 dx - \int_0^1 K^- Y * \phi_2 dx = 0,$$

$$D\left[\frac{\partial Y}{\partial \tilde{x}} * \phi_2\right]_0^1 - D\int_0^1 \frac{\partial Y}{\partial \tilde{x}} * \frac{\partial \phi_2}{\partial \tilde{x}} * dx + \int_0^1 K^+(1-Y)\tilde{c}\phi_2 dx - \int_0^1 K^- Y \phi_2 dx = 0,$$

on the boundaries $\frac{\partial Y}{\partial \tilde{x}} = 0$, there is no restriction on ϕ_2, and hence, the weak formulation is

$$-D\int_0^1 \frac{\partial Y}{\partial \tilde{x}} * \frac{\partial \phi_1}{\partial \tilde{x}} * dx + \int_0^1 K^+(1-Y)\tilde{c}\phi_2 dx - \int_0^1 K^- Y \phi_2 dx = 0. \quad (4.4.2.9)$$

Picard iteration

Nonlinear partial differentiation equations (PDEs) can be easily solved using the Picard iteration. A previously known solution is used to convert nonlinear terms to linear terms with an unknown u. The resulting linearized equations can be written in the variational form: Find an admissible function u for all admissible variations ϕ such that

$$a(u, \phi) = L(\phi),$$

where $a(u, \phi)$ is the bilinear form, while $L(\phi)$ is a linear form. To solve every linear problem, the terms with unknown u are identified and collected in the bilinear form $a(u, \phi)$ and the terms with known functions are collected in the form $L(\phi)$. The formulas of a and L are then directly entered into FEniCS software. (For further details see [24].) Note that to write a FEniCS program for solving PDEs, two steps must be performed first:
Step 1: Formulate the discrete variation problem from the partial differential equation and find u such that the equation is valid: $a(u, \phi) = L(\phi)$
Step 2: Specify the type of meshing and the finite elements to be used for the problem. In the present problem, we have

$$u = \begin{cases} u_1 \\ u_2 \end{cases}$$

since

$u_1 = Y,$

$u_2 = \tilde{c} = \frac{c}{c_0},$

and

$$\phi = \begin{cases} \phi_1 \\ \phi_2 \end{cases}$$

Combining (4.4.2.8) and (4.4.2.9) gives the overall weak formulation as follows:

$$-\int_0^1 \Big(\frac{du_1}{dx}\frac{d\phi_1}{dx} + \Big(\frac{D_c c_0}{D_p c_p}\Big)\frac{du_2}{dx}\frac{d\phi_2}{dx}\Big)dx + \int_0^1 K^+(1-u_1)u_2\phi_1 dx - \int_0^1 K^- u_1\phi_1 dx$$
$$-\int_0^1 K^+(1-u_1)u_2\phi_2 dx + \int_0^1 K^- u_1\phi_2 dx - \frac{L^2}{C_p D_p}\int_0^1 Q\phi_2 dx = 0. \qquad (4.4.2.10)$$

The FEniCS code that is used to solve this is provided in the Appendix along with some details.

Figure 4.7: Geometry used in FEniCS code since the size of the element is much smaller near the boundaries at x = 0 and x = 1 because the solution for c and Y may change very rapidly at those locations

Singular perturbation

4.5 Concept of singular perturbation

The term perturbation in mathematics is a concept that reflects a very simple fact, which is to take a set of complicated equations and reduce them to their simplest form so that a better equation or a better solution can be derived. The concept is used in many important areas and its origin is extraordinary [2].
The fact on which this theory is based is that it studies an ideal system to provide an authentic description for the current system under study. Perturbation consists of a perturbation series that basically requires the forming of small parameters. Perturbation reduces complex equations into simpler ones; as each step towards simplification is achieved, a correction is made. However, the correction is not always perfect and several iterations may be required to reach an approximate solution [39].
The concept of singular perturbation is used in many branches of mathematics and engineering and applied in aerodynamics, among other fields. Singular perturbations, unlike regular perturbation, reduce the equations to the point where they are simple and can be solved analytically. A singular perturbation's boundary possesses an interior layer (inner layer) and an exterior one (outer layer). The interior layer has a width of 0(1) as $\epsilon \to 0$ [23].

A singular perturbation is used whenever the regular perturbation limit $y_\epsilon(x) \to y_0(x)$ fails. Another difference between a regular and singular perturbation is that when a regular perturbation is defined, it has a power series in ϵ with a nonvanishing radius of convergence. However, in singular perturbation a power series is not formed and even if it does occur, it has a vanishing radius of convergence. When a solution ceases to exist, ϵ becomes $\epsilon = 0$ [17].

Example 1:

Consider the equation:

$$y^n + y + \epsilon y^3 = 0 \qquad y(0) = 1, \qquad y'(0) = 0$$

This equation is an example of a regular perturbation because when $\epsilon \to 0$, no changes occur in the order of the equation and the approximate answer to the parameters (0) approaches the solution smoothly.

Example 2:

Consider the following boundary value problem:

$$\epsilon y^n - y' = 0 \qquad y(0) = 0, \qquad y(1) = 1$$

The above equation is a singular perturbation because $y' = 0, y(0) = 0$ and $y(1) = 1$ cannot be solved. It does not satisfy the boundary conditions and hence is considered a singular perturbation. Singular perturbation is an extremely useful and rich concept that encourages mathematicians and engineers alike to investigate the field.

4.6 Using singular perturbation to reach equilibrium assumption

Solving (4.4.2.6) and (4.4.2.7) by singular perturbation method:
First, let us denote $\tilde{x}$ and $\tilde{c}$ as x and c

$$\frac{\partial^2 c}{\partial x^2} - K^+(1-Y)c + K^- Y - Q_{new} = 0,$$

$$D\frac{\partial^2 Y}{\partial x^2} + K^+(1-Y)c - K^- Y = 0.$$

The previous equations become with their boundaries conditions:

$$c'' - K^+(1-Y)c + K^- Y - Q_{new} = 0 \qquad c(0) = 1 \qquad c(1) = c_1 \qquad (4.6.0.1)$$

$$DY'' + K^+(1-Y)c - K^- Y = 0 \qquad y'(0) = 0 \qquad y'(1) = 0 \qquad (4.6.0.2)$$

In Equation (4.6.0.2), we find K^+ and K^- are big numbers compared with the factor of Y'', which is D, using (Murray 1974) parameters we find

$$K^+ = 2.10 \times 10^3,$$

$$K^- = 1.63 \times 10^2$$

and

$$D = 7.44 \times 10^{-1}.$$

To reduce this problem, we divide the equation by the value of K^+ such that

$$\epsilon y'' + (1 - Y)c - \frac{K^-}{K^+}Y = 0,$$

$\epsilon = \frac{D}{K^+}$ is very small number which equal 3.54×10^{-4}, so we neglect the term with ϵ, so the equation becomes:

$$(1 - Y)c - \frac{K^-}{K^+}Y = 0,$$

then

$$c - cY - \alpha Y = 0.$$

Since

$$\alpha = \frac{K^-}{K^+},$$

and that makes

$$Y = \frac{c}{c + \alpha} \qquad \leftrightarrow \qquad Y = \frac{c}{c + K_{eq}}$$

which is the equilibrium approximation.

Chapter 5

Results and Discussion

5.1 Equilibrium Solution

For comparison purposes, we solve the equations after scaling by combining the nondimensional Equations (4.6.0.1) and (4.6.0.2), perform integration by parts twice and then apply the new boundary conditions, which are:

$$c(x=0) = \frac{c_0}{c_0} = 1,$$

$$c(x=1) = c_L.$$

The values of B, F and C are obtained as follows:

$$B = (1 + \frac{D}{1+K_{eq}}),$$

$$F = c_L + D(\frac{c_L}{c_L + K_{eq}}) - \frac{1}{2}Q - 1 - \frac{D}{1+K_{eq}},$$

and

$$C(x)^2 + [K_{eq} + D - \frac{1}{2}Qx^2 - Fx - B]C(x) - [\frac{1}{2}K_{eq}Qx^2 + K_{eq}Fx + K_{eq}B] = 0,$$

$$Ac(x)^2 + Gc(x) + E = 0.$$

Since

$$A = 1,$$

$$G = (K_{eq} + D - \frac{1}{2}Qx^2 - Fx - B),$$

and

$$E = (K_{eq}\frac{Qx^2}{2} + K_{eq}Fx + K_{eq}B)$$

In the following figures, we calculate the total flux against K_{eq} when D = 50, D = 10, D = 5 and D = 0 (which corresponds to the case of no facilitation) and when $c(L) = 0.01$ and $c(L) = 0$ and $Q = 0$.

When $c(L) = 0.01$ Figure 5.1 the flux increases as D increases. Moreover, when D = 0, the flux is constant throughout. As D increases from D = 0 to D = 50, the flux increases until $K_eq = 0.1$; after which it decreases. For all the values of D, the flux attains its maximum value at $K_eq = (0.1)$. Thus, the flux has a bell-shaped curve for $D > 0$. Remember that at D = 0, the flux does not have a bell-shaped curve.

From Figure 5.2, we can observe that when $c(L) = 0$, the flux increases as D increases. However, when D = 0, the flux is constant throughout. It does not have a bell-shaped curve for a particular value of D; initially, the flux is more or less constant and then decreases linearly and the maximum value of flux is achieved when $K_{eq} = 0$. The flux is almost linear (for $D > 0$) from Keq = 0.001 to Keq = 0.1, after which it drops. This drop after Keq = 0.1 is steeper as the value of D increases.

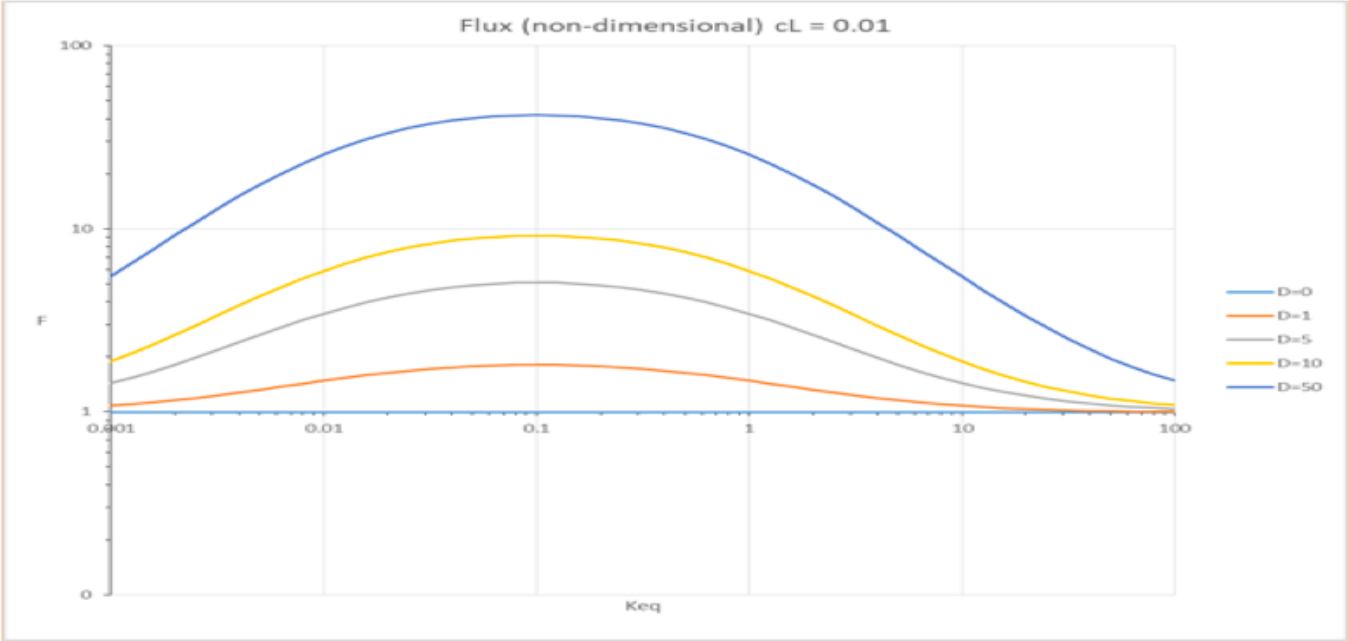

Figure 5.1: Flux at different values of D and K_{eq}

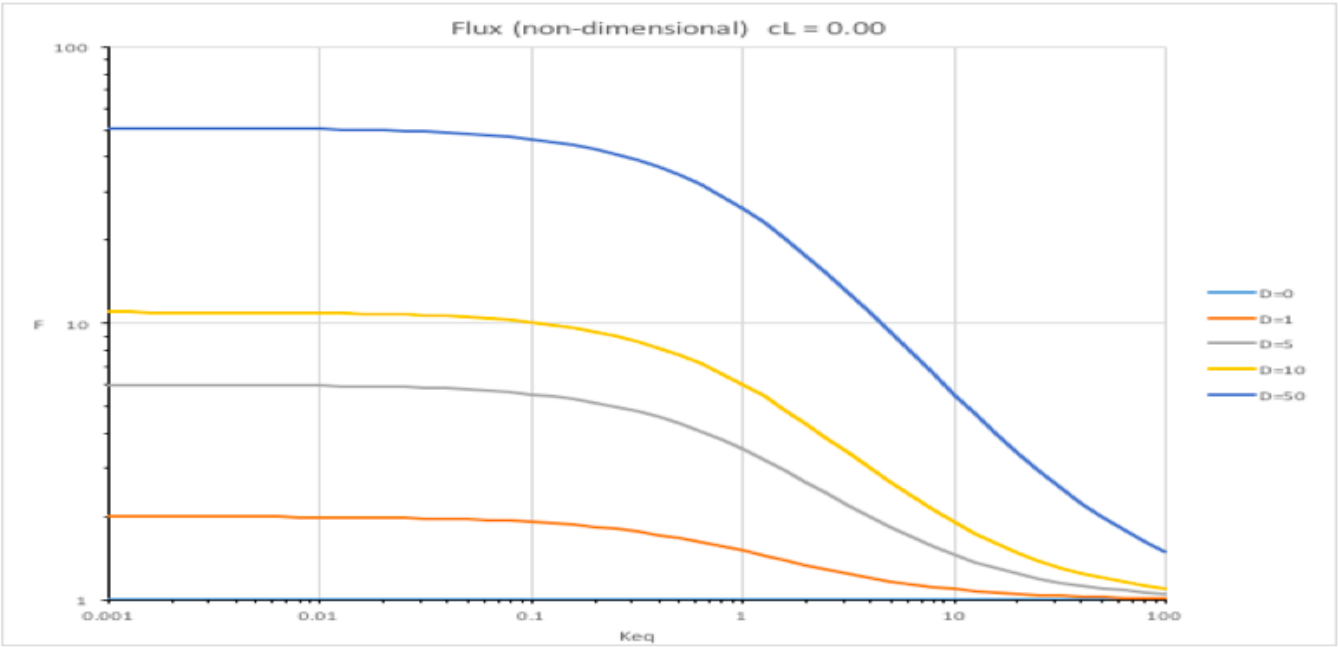

Figure 5.2: Flux at different values of D and K_{eq}

To investigate the previous result, we differentiate the equation of F with respect to K_{eq} and make it equal zero to find the maximum value of at K_{eq}

$$\frac{d}{dK_{eq}}\Big[c_L + D(\frac{c_L}{c_L + K_{eq}}) - \frac{1}{2}Q - 1 - \frac{D}{1 + K_{eq}}\Big] = 0,$$

$$Dc_L\frac{d}{dK_{eq}}\big(\frac{1}{c_L + K_{eq}}) - D\frac{d}{dK_{eq}}(\frac{1}{1 + K_{eq}}) = 0,$$

$$Dc_L\left[\frac{-\frac{d}{dK_{equ}}(c_L + K_{eq})}{(c_L + K_{eq})^2}\right] + D\left[\frac{\frac{d}{dK_{eq}}(1 + K_{eq})}{(1 + K_{eq})^2}\right] = 0,$$

$$\left[\frac{-Dc_L}{(c_L + K_{eq})^2}\right] + \left[\frac{D}{(1 + K_{eq})^2}\right] = 0,$$

$$\frac{D(c_L + K_{eq})^2 - Dc_L(1 + K_{eq})^2}{(1 + K_{eq})^2(c_L + K_{eq})^2} = 0,$$

$$D(c_L + K_{eq})^2 - Dc_L(1 + K_{eq})^2 = 0,$$

$$Dc_L^2 + 2Dc_LK_{eq} + DK_{eq}^2 - Dc_L - 2Dc_LK_{eq} - Dc_LK_{eq}^2 = 0,$$

$$K_{equ}^2(D - Dc_L) = c_L(D - Dc_L),$$

$$K_{equ}^2 = c_L,$$

$$K_{equ} = \sqrt{c_L}.$$

Thus, the maximum value of K_{eq}, which is equal to the square root of c_L, proved the results obtained in the previous two figures since $\sqrt{0.01} = 0.1$ and $\sqrt{0} = 0$.

5.2 Comparison of equilibrium solution and full solution

Table 5.1 presents a comparison of the two results, which shows the value of the flux from the equilibrium solution and the FEniCS solution (when $K^+ = 10^4$) at different values of D and K_{eq}. As shown in the table, the flux from the equilibrium position is approximately the same as the flux from the full solution when $K_{eq} = 1$ and D = 10. However, the former differs significantly from the latter if K_{eq} is changed to 0.1 or 0.01 and D = 10. When D = 5, the former is approximately the same as the flux from the full solution when $K_{eq} = 1$. However, the flux from the equilibrium position differs significantly from the latter if K_{eq} is changed to 0.1 or 0.01. The value of the flux from both is considerably lower at D = 5 compared with that at D = 10. When D = 1, the flux from the equilibrium position is approximately the same as the flux from the full solution when $K_{eq} = 1$. However, the former differs significantly from the latter if K_{eq} is changed to 0.1 or 0.01 and D = 1. The value of the flux from both is considerably lower at D = 1 compared with that at D = 5 and D = 10. The result obtained is that the flux increases with an increase in D. The difference between the full solution and the equilibrium solution are small for large K_{eq} but become greater as K_{eq} becomes smaller. For the fixed D, both the full solution and equilibrium solution show maximum flux in the middle.

parameters / cases	K_eq	D	Flux from equilibrium solution	Flux from the full solution
Case 1	1	10	5.89	5.25
Case 2	0.1	10	9.17	5.45
Case 3	0.01	10	5.89	2.15
Case 4	1	5	3.44	3.25
Case 5	0.1	5	5.08	3.72
Case 6	0.01	5	3.44	1.75
Case 7	1	1	1.48	1.47
Case 8	0.1	1	1.81	1.68
Case 9	0.01	1	1.48	1.21

Table 5.1: Table of comparison

In the following figures, we study each case individually to compare the full and the equilibrium solutions.

Case one:

Figure 5.3 illustrates the case when D = 10 and $k_{eq} = 1$, confirming the observation that the equilibrium slope and full solution are not too different for this case. Further, the equilibrium solution does not satisfy the zero-slope boundary condition for Y. However, the full solution does satisfy this boundary condition; see the expanded plots (5.4), (5.5) and (5.6). This correction occurs close to the boundary, particularly on the low-concentration side, and shows a bit of boundary layer with sudden increase in the slope of c. Saturation Y is never greater than 0.5, and c is not too different from linear.

Case two:

Figure 5.7 for the second case when $K_{eq} = 0.1$ and D = 10 shows bigger differences than before, especially in Y. Again, notice that the boundary layer is near x = 1. In addition, Y varies from near 1 to less than 0.5, c is quite different from the linear. For $x > 0.5$, the slope of c is quite low; most of the transport is from Y.

Case three:

Figure 5.8 when D = 10 and $k_{eq} = 0.01$ shows the continuous trend observed in Cases 1 and 2. Y is now higher overall, and c deviates more from the linear. Equilibrium slope and full solution slope differ significantly. Boundary conditions are satisfied for c, but not for y. Again, notice

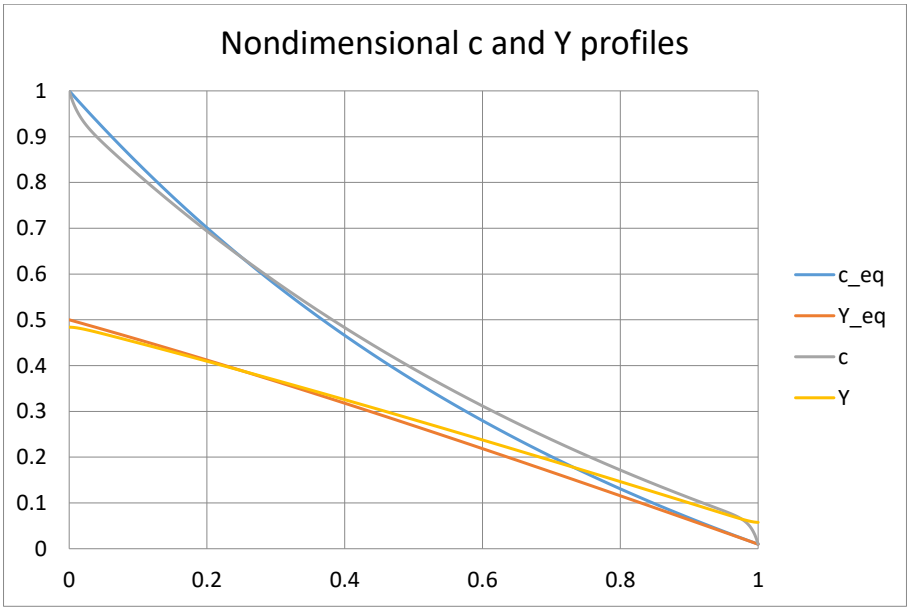

Figure 5.3: Case 1 of comparison when D=10 and $K_{eq} = 1$

the boundary layer near x = 1. Further, Y varies from near 1 to less than 0.5 and c is not linear.

Case four:

Equilibrium slope and full solution slope are almost similar in Figure 5.9 when D = 5 and $k_{eq} = 1$. Further, the equilibrium solution does not satisfy the zero-slope boundary condition for Y. However, the full solution does satisfy this boundary condition. This correction occurs close to the boundary, particular on the low-concentration side, and shows a bit of a boundary layer with sudden increase in the slope of c. Saturation Y is never greater than 0.5 and c is almost linear. In the expansion of Case 4, figure 5.10 we can notice that equilibrium slope and full solution slope are almost parallel to start with. Boundary conditions are satisfied for c but not for Y. c as well as Y is linear to from x = 0.7 to x = 0.95. After x = 0.95, Y increases and c drops.

Case five:

In case of Figure 5.11, when D = 5 and $K_{eq} = 0.1$ the equilibrium slope and full solution slope differ considerably. The slopes for Y are almost identical initially ($0 < x < 0.01$). However, the slopes for c differ. Boundary conditions are satisfied for c. Notice the boundary layer near x = 1. Moreover, Y varies from near 1 to less than 0.5; c is not linear.

Case six:

The equilibrium slope and full solution slope differ significantly in Figure 5.12 when D = 5 and $k_{eq} = 0.01$. Boundary conditions are satisfied for c but not for y. Notice the boundary layer near x = 1. Further, Y varies from near 1 to less than 0.5, and c is not linear. For $x > 0.6$ the slope of Y is linear.

Case seven:

The slopes are almost the same in Figure 5.13 when D = 1 and $K_{eq} = 1$. Boundary conditions are satisfied for c as well as Y; notice the boundary layer near x = 1. Further, Y varies from near 1 to less than 0.5 and c is almost linear. In the expansion Figure 5.14, the equilibrium slope and full solution slope are almost parallel initially. Boundary conditions are satisfied for c but not for Y; c as well as Y is linear from x = 0.975 to x = 0.995. Later, Y increases and c

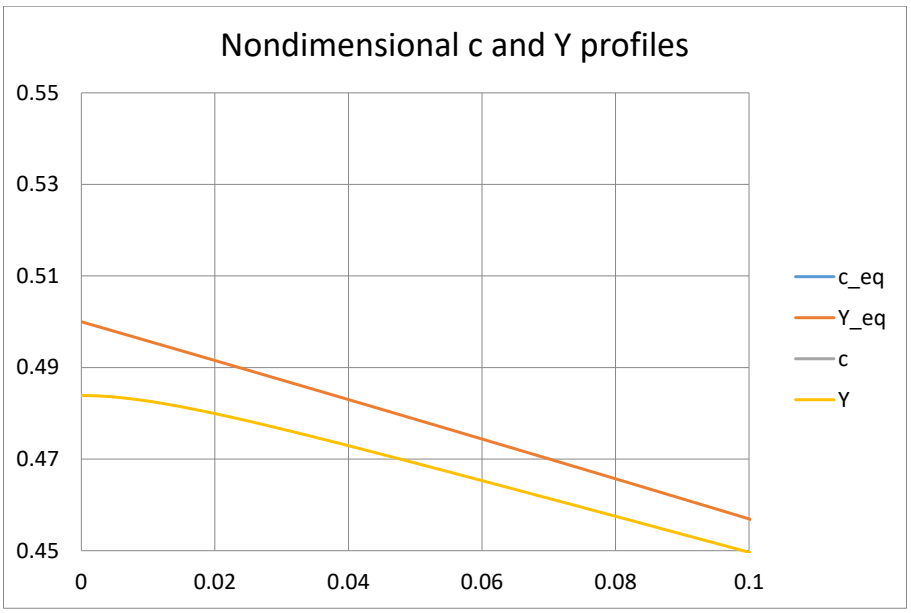

Figure 5.4: Expansion of case 1 of comparison when D = 10 and $K_{eq} = 1$

decreases.

Case eight:

In Case 8, Figure 5.15, when D = 1 and $K_{eq} = 0.1$ the equilibrium slope and full solution slope are different. Moreover, the equilibrium solution does not satisfy the zero-slope boundary condition for Y. However, the full solution does satisfy this boundary condition.

Case nine:

The equilibrium slope and full solution slope are different in Figure 5.16 when D = 1 and $K_{eq} = 1$. Additionally, the equilibrium solution does not satisfy the zero-slope boundary condition for Y. However, the full solution does satisfy this boundary condition. This correction occurs close to the boundary, particular on the low-concentration side, and shows a bit of a boundary layer with sudden decrease in slope of c.

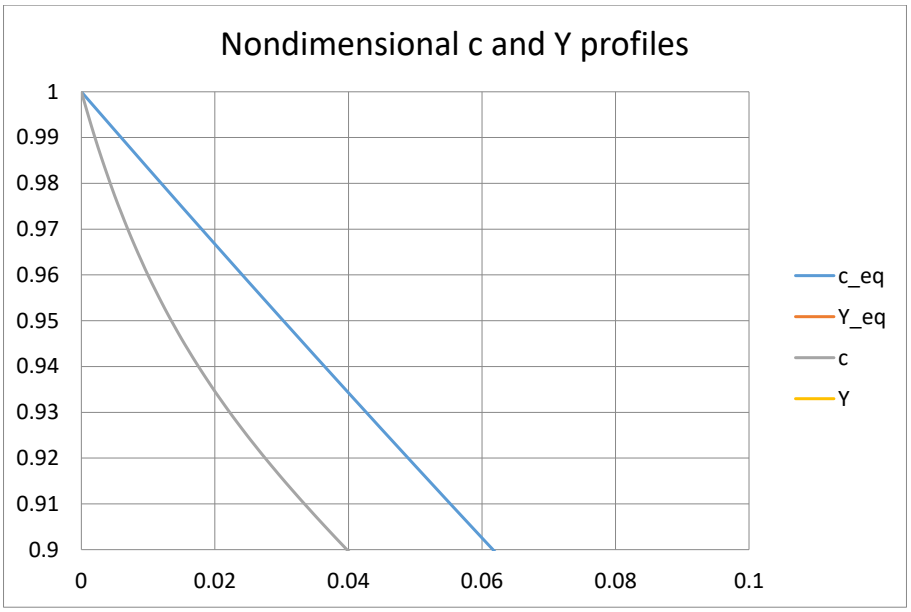

Figure 5.5: Expansion of case 1 of comparison when D = 10 and $K_{eq} = 1$

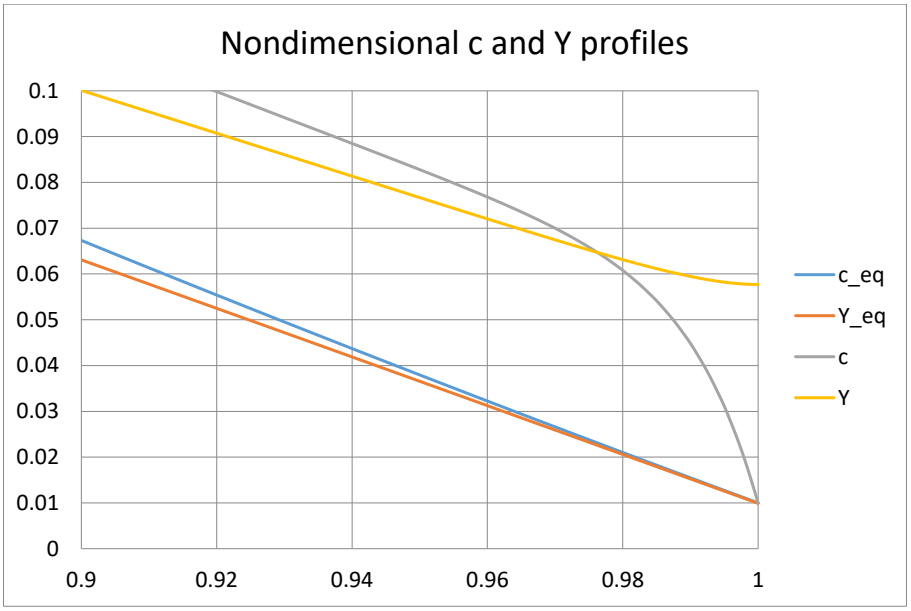

Figure 5.6: Expansion of case 1 of comparison when D = 10 and $K_{eq} = 1$

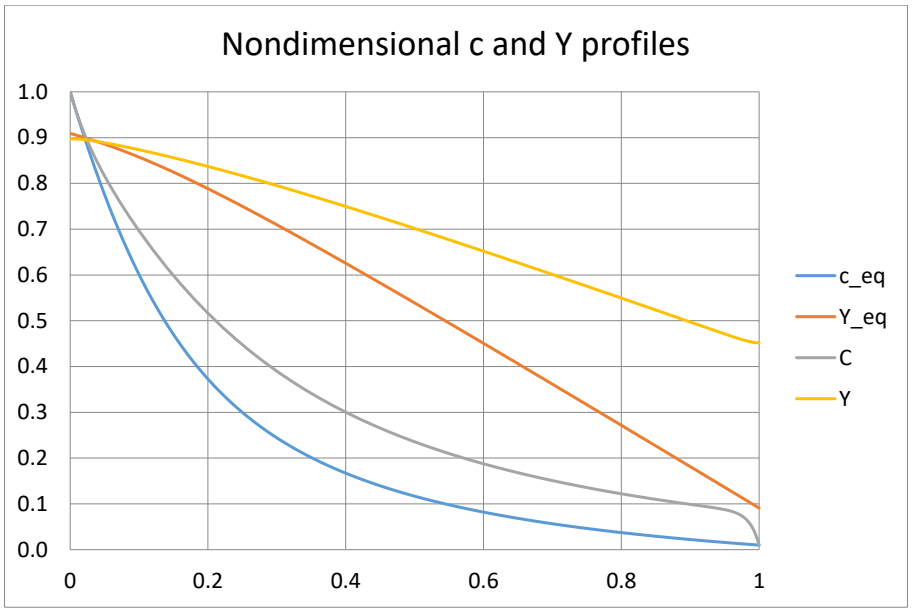

Figure 5.7: Case 2 of comparison when D = 10 and $K_{eq} = 0.1$

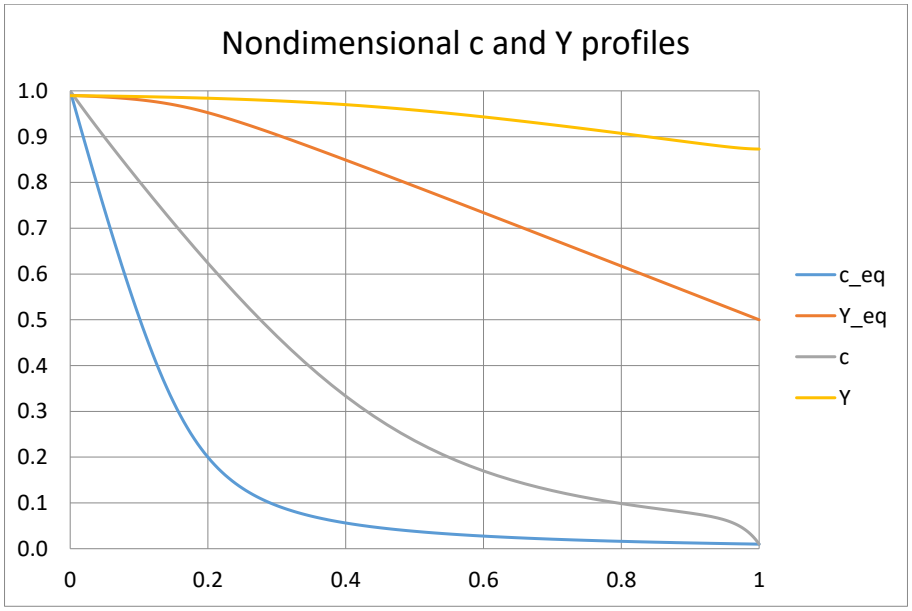

Figure 5.8: Case 3 of comparison when D = 10 and $K_{eq} = 0.01$

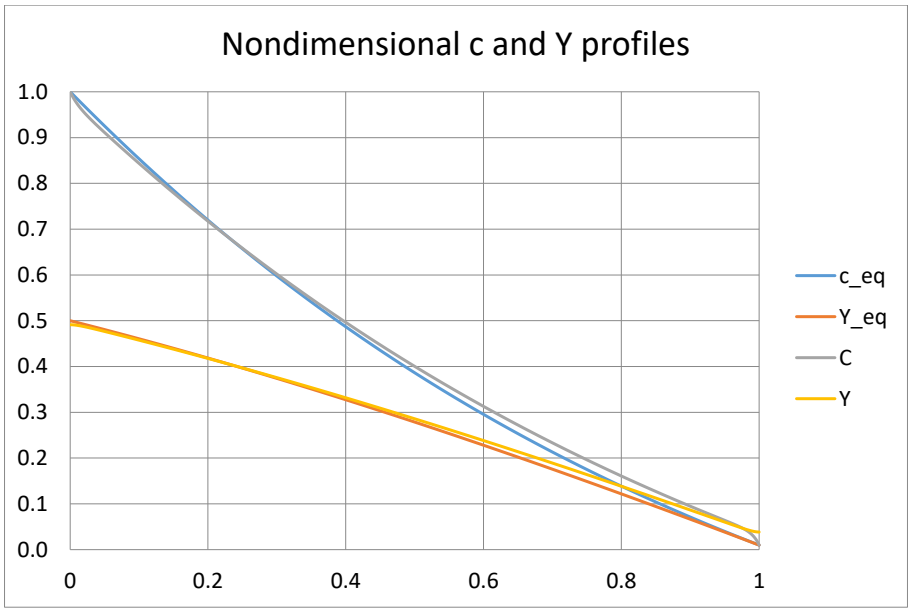

Figure 5.9: Case 4 of comparison when D = 5 and $K_{eq} = 1$

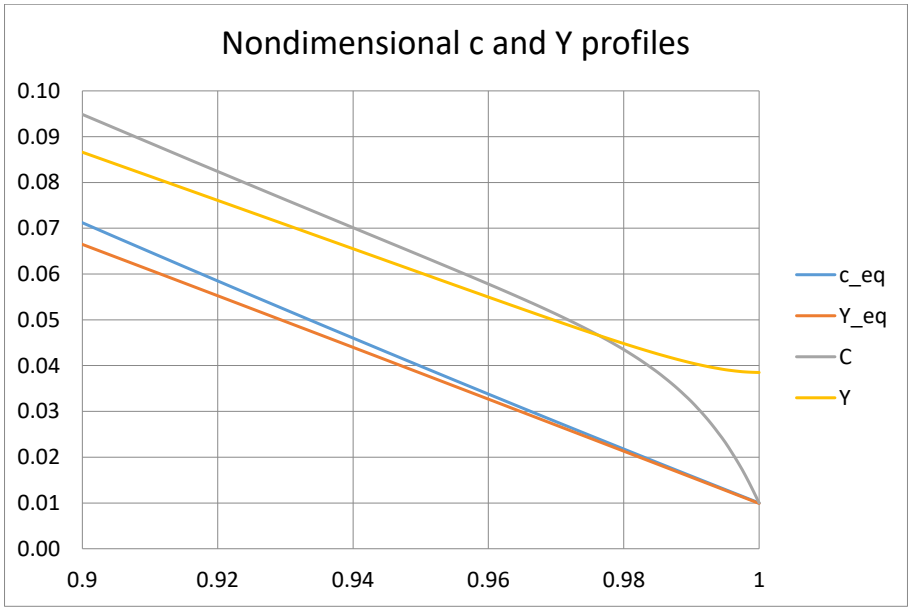

Figure 5.10: Expansion of Case 4 of comparison when D = 5 and $K_{eq} = 1$

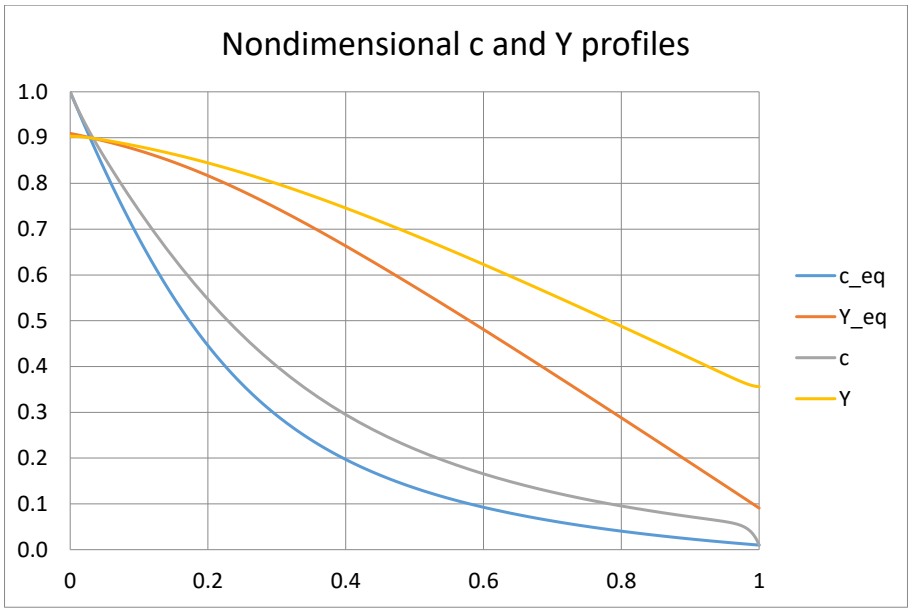

Figure 5.11: Case 5 of comparison when D = 5 and $K_{eq} = 0.1$

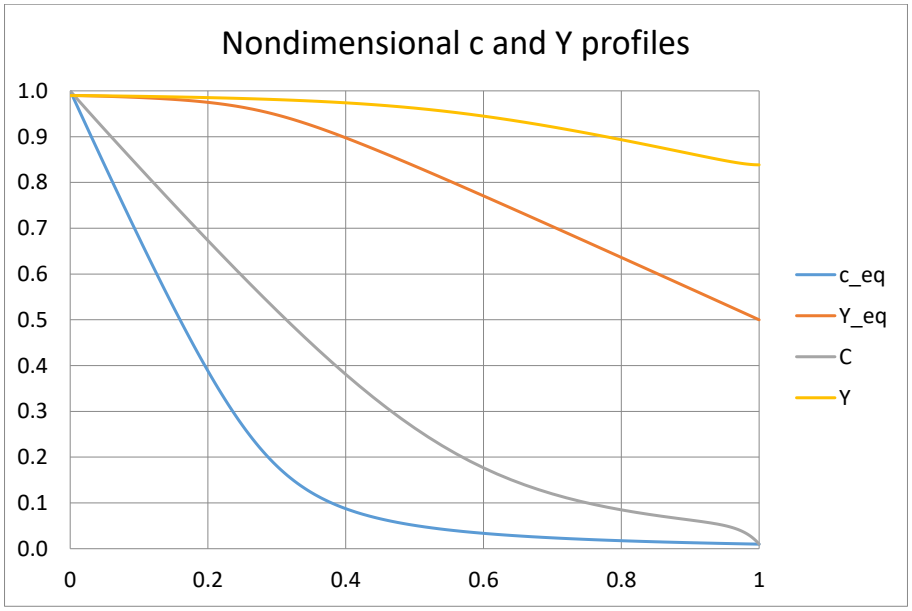

Figure 5.12: Case 6 of comparison when D = 5 and $K_{eq} = 0.01$

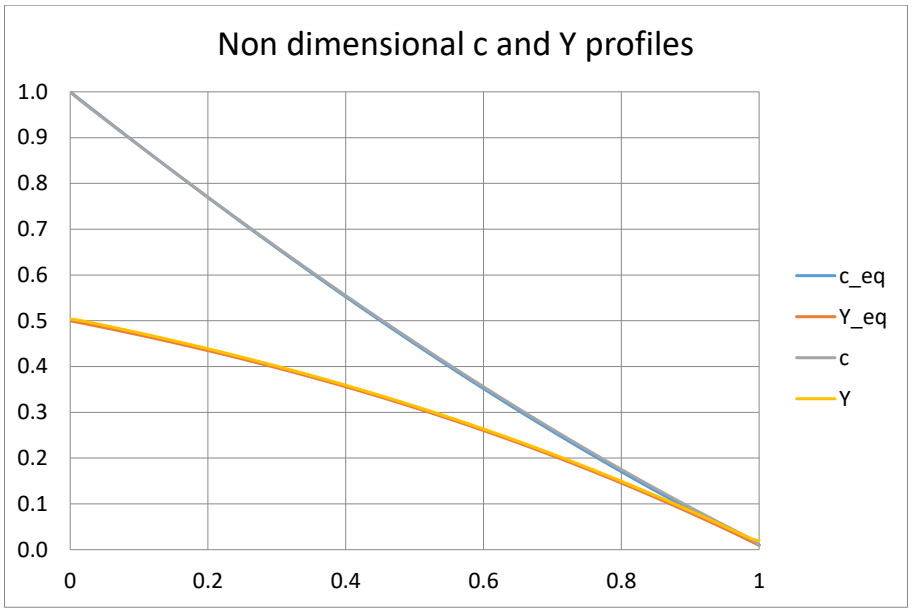

Figure 5.13: Case 7 of comparison when D = 1 and $K_{eq} = 1$

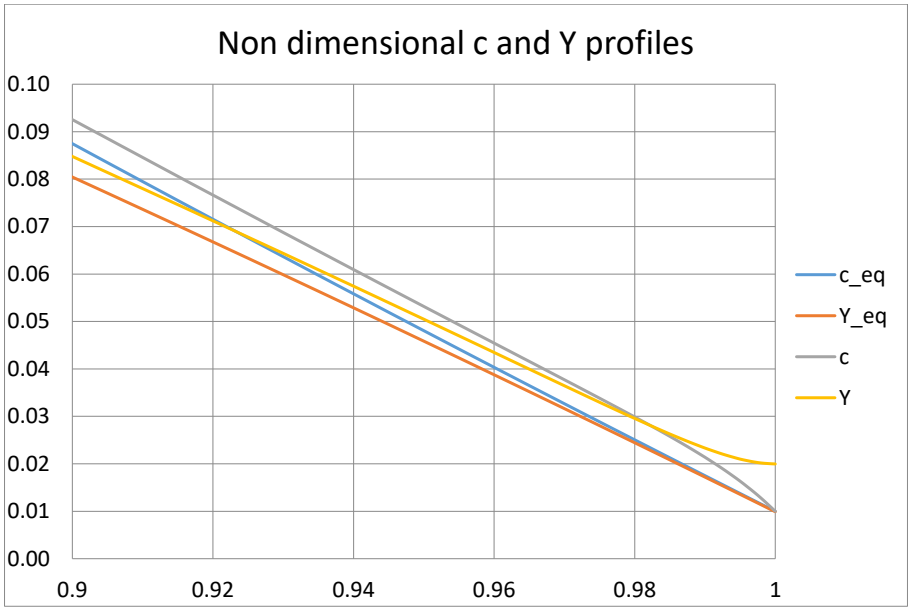

Figure 5.14: Expansion of Case 7 of comparison when D = 1 and $K_{eq} = 1$

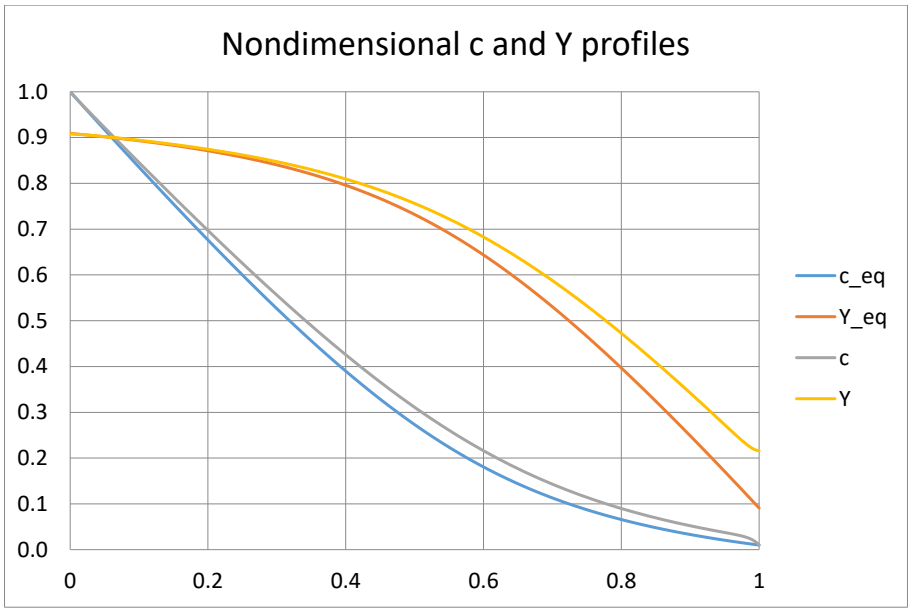

Figure 5.15: Case 8 of comparison when D = 1 and $K_{eq} = 0.1$

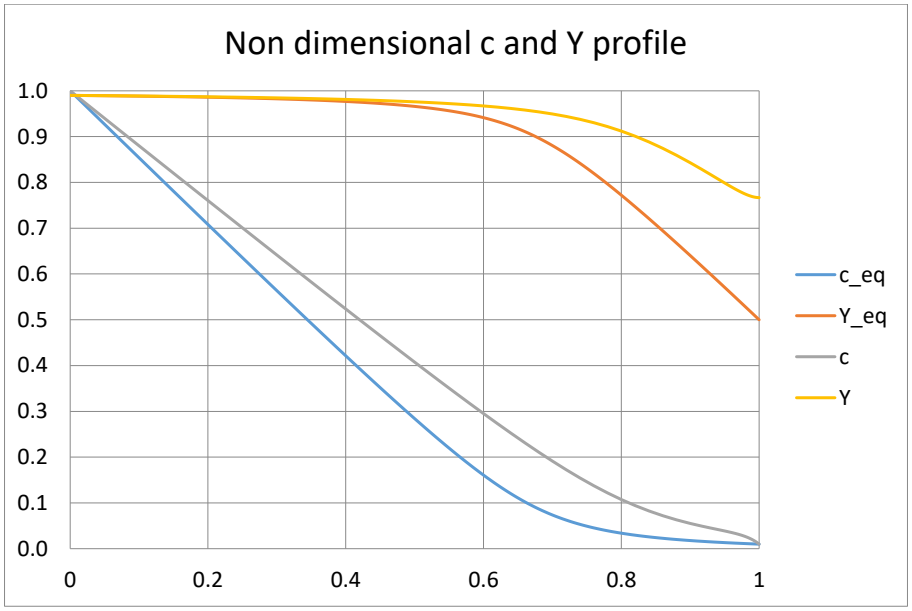

Figure 5.16: Case 9 of comparison when D = 1 and $K_{eq} = 0.01$

5.3 Discussion and Conclusion

This thesis showed that the link between reaction and diffusion is important because it introduces many interesting effects in nature and in physiology in particular. The facilitated diffusion process has biologically significant affects, such as the stimulation that haemoglobin, myoglobin and other proteins perform to facilitate oxygen transportation across membranes. Chapter 1 of this thesis indicated two basic equations of facilitated diffusion, that is, diffusion and reaction—diffusion. Facilitated diffusion is considered an example of diffusion that allows substances to move between two areas, varying according to the concentration, and this movement is accompanied by an interaction between the substance components. Many biological examples have been mentioned in Chapter 2, which prove the strength of the link between facilitated diffusion and the biological role it plays. One of the most important examples is oxygen transportation by myoglobin between muscle tissues and between cell membranes. A mathematical model of oxygen enhanced by myoglobin was studied in Chapter 4. The model's equation was solved in two different ways, through equilibrium approximation and the FEniCS program, and the results obtained in the last chapter can be summarised as follows:

1. The absolute value of flux increases as D increases.

2. The difference between the flux from the equilibrium solution and full solution is small for large values of K_{eq}; however, this difference becomes greater as K_{eq} becomes smaller.

3. For fixed D, the equilibrium approximation and full solution both show maximum flux at middle values of K_{eq}, which is 0.1, indicating that balance between the forward reaction and backward reaction rates is important for maximum enhanced transport.

To conclude, I believe that the relationship between facilitated diffusion and biology is firm which has allowed us to understand how the mystery of the life.

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Appendix A

FEniCS Code

In the FEniCS code below the variational formulation in 4.4.2.10 has been written in the form of the Picard iteration

$$a(u, \phi) = L(\phi),$$

where

$$a(u, \phi) = \int_0^1 \left(\frac{du_1}{dx}\frac{d\phi_1}{dx} + D\frac{du_2}{dx}\frac{d\phi_2}{dx} + A_1 u_1 \phi_1 + A_2 u_2 \phi_1 - A_1 u_1 \phi_2 - A_2 u_2 \phi_2 \right) dx,$$

$$L(\phi) = \left(A_1 u_1^* + A_2 u_2^* - \left(K^+(1 - u_2^*)u_1^* - K^- u_2^* \right)(\phi_1 - \phi_2) \right).$$

Here (u_1^*, u_2^*) is the solution from the previous iteration (called u_{old} in the FEniCS code) and $A_1 = -A_2 = max(K^+, K^-)$.

```
from __future__ import print_function
from fenics import *
import numpy as np

#Define various model parameters
Kplus = 10000.0
Keq = 0.01
Q = Constant(0.0)
Dfacil = 1.0
cL = Constant(0.01)
#

# Derived parameters
Kminus = Kplus*Keq

#Define iteration parameters
A1 = max(Kplus,Kminus)
A2 = -A1
MAX_ITER = 200

# Read in the mesh and define function space and trial and test functions
mesh = Mesh('mesh.xml')
#mesh = UnitIntervalMesh(100)
U = VectorFunctionSpace(mesh, 'Lagrange', 1,dim=2)
print('U =',U)
u1, u2 = TrialFunctions(U)
phi1, phi2 = TestFunctions(U)


# Define boundary conditions
def Endpoint0(x, on_boundary):
    return on_boundary and x[0] < 0.1

def Endpoint1(x, on_boundary):
    return on_boundary and x[0] > 0.9

# will have different bc on different components
bc0 = DirichletBC(U.sub(0), Constant(1.0), Endpoint0)
bc1 = DirichletBC(U.sub(0), cL, Endpoint1)




#  Set up functions for current and previous solutions for u2
unow = Function(U)
uold = Function(U)

```

Figure A.1: FEniCS code

```
47
48  #Initialise uold to start the iteration, only the second component matters)
49  uold = interpolate(Constant((1.0, 1.0)),U)
50
51
52  #define the variational problem
53
54  def rho(u):
55      return Kplus*(1.0 - u[1])*u[0] - Kminus*u[1]
56  def error(u):
57      return A1*u[0] + A2*u[1] - rho(u)
58
59  a = dot(grad(u1),grad(phi1))*dx +A1*u1*phi1*dx + A2*u2*phi1*dx \
60      + Dfacil*dot(grad(u2),grad(phi2))*dx - A1*u1*phi2*dx - A2*u2*phi2*dx
61  L = Q*phi1*dx + error(uold)*phi1*dx -error(uold)*phi2*dx
62  # perform the iterations
63  vtkfile = File('test.pvd')
64  vtkfile << uold
65  for iter in range(MAX_ITER):
66      solve(a==L, unow,[bc0,bc1])
67      #check residual of the iteration
68      resid1 = dot(grad(unow[0]),grad(phi1))*dx + rho(unow)*phi1*dx
69      resid2 = Dfacil*dot(grad(unow[1]),grad(phi2))*dx - rho(unow)*phi2*dx
70      R1 = assemble(resid1).get_local()
71      R1_size = np.size(R1)
72  #   print('R1-size: ', R1_size)
73  #   info(R1,verbose=False)
74      R2 = assemble(resid2).get_local()
75      print('iteration, R1, R2 ', iter, np.linalg.norm(np.abs(R1[2:R1_size-3])), np.linalg.norm(np.abs(R2)))
76      print('flux = ', R1[0])
77      vtkfile << unow
78      #update previous solution
79      uold.assign(unow)
80  # print('Residuals: ', R1,R2)
81
82
83
84
85
```

Figure A.2: FEniCS code