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### **Master's thesis**

## **Mathematical Models and Numerical Methods for Reaction-Diffusion Problems in Composite Media**

Supervisor

Dr. Giuseppe Pontrelli  
IAC-CNR, Rome

Author

Sandeep Kumar  
Matricola: 228427

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Università degli Studi dell'Aquila

# Declaration of Authorship

I, Sandeep KUMAR, declare that this thesis titled, “Mathematical Models and Numerical Methods for Reaction-Diffusion Problems in Composite Media” and the work presented in it are my own. I confirm that:

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Signed:

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Date:

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*“Yatha sikha mayuranam, Naganam manayo yatha,  
Tadvedangasastranam, Ganitam murdhani sthitam”*

*As are the crests on the heads of peacocks, as are the gems on head of cobras, so is  
Mathematics, at the top of all Sciences.*

-Yajur Veda, circa 600 B.C.

UNIVERSITÀ DEGLI STUDI DELL'AQUILA

## *Abstract*

Faculty of Science

Department of Information Engineering,  
Computer Science and Mathematics

Master of Science

### **Mathematical Models and Numerical Methods for Reaction-Diffusion Problems in Composite Media**

by Sandeep KUMAR

Today the area of partial differential equation is fascinating because many real world problems can be modelled using these equations. As the system becomes more complicated so becomes the PDE associated with it. For such systems it becomes difficult to get the analytical solution. In the present work, we concentrate on couple of such problems inspired from biological world. We describe a model for a two-phase system which involves a set of reaction-diffusion equations. These equations describes the diffusion and the binding/unbinding processes in both layers. Additional flux continuity at the interface and clearance conditions into systemic circulation are imposed. To solve the system we employ a numerical scheme, compare the numerical results with the analytical ones and later propose a new method which is very efficient in terms of calculations and also solves a nonlinear system (Drug-eluting stent) problem.



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# Chapter 1

## Introduction

### 1.1 Reaction-diffusion systems and their applications

The area of partial differential equation is considered to be the most applied in any branch of Science. All beautiful phenomena in the nature can be modeled using these equations. But, the theory of these equations seems to be even more interesting and insightful. Formally, a partial differential equation can be defined as an equation involving multivariable functions and their partial derivatives. In other words, PDEs are equations that involve rate of change with respect to continuous variables.

The PDEs can be broadly categorized into three parts: linear, semilinear and nonlinear. They can also be divided on the basis of nature of solution such as: elliptic, parabolic and hyperbolic. In the current work we present PDEs called as reaction-diffusion equations.

Reaction-diffusion (RD) equations arise naturally in systems consisting of many interacting components, (e.g., chemical reactions) and are extensively used to describe pattern-formation phenomena in variety of biological, chemical and physical systems. In other words, RD systems are mathematical models which explain how the concentration of one or more substances distributed in space changes under the influence of two processes: local chemical reactions in which the substances are transformed into each other, and diffusion which causes the substances to spread out over a surface in space. Reaction–diffusion systems are naturally applied in chemistry. However, the system is also useful in describing dynamical processes of non-chemical nature. Examples are found in biology, physics, geology and ecology. Mathematically, reaction–diffusion systems take the form of semi-linear parabolic partial differential equations. They can be represented in the general form

$$\partial_t u = D \nabla^2 u + W(u)$$

where  $u(x, t)$  represents the concentration of one material,  $D$  is diffusion coefficient and  $W$  stands for all local reactions. The solutions of RD equations express a wide range of behaviors, including the formation of travelling waves and wave-like phenomena and also some self-organized patterns like stripes, hexagons or more intricate structure like dissipative solitons.

With this introduction to RD equations we proceed to reaction-diffusion equations in composite systems. In the following section, we describe several real life applications where these systems are highly in use.

### 1.1.1 Applications of composite media in real-world problems

There are many applications in physics where the fluxes occur through layers of material. For example, the diffusion of solute, conduction of ion from one side of an epithelium to the other or flow of heat from one body to another. In this section we present 3 applications from the real world, which involves system composed of multiple media.

In the first application, the model describes one dimensional heat flow through a medium consisting of several layers of different materials. The model proposes the measurement of heat production by muscle [1]. The system is composed of a semi-infinite medium, the muscle, in which heat production is spatially uniform and time varying. The heat diffuses through layers of solution and insulation to the center of the thermal element where heat flow is zero. In the systems composed of multiple layers, the solution is algebraically tedious because it involves satisfying two sets of boundary conditions per layer. This complexity makes it difficult to understand physically what is happening, so investigators frequently ignore the layers and analyze the flux as if the medium were homogeneous with a set of effective parameters. However, in this model, no single set of effective parameters are employed that will describe the entire time course when the medium is actually layered. Here the flux of heat from a semi-infinite source, through three finite layers to a central plane where the heat flow is zero, is examined. This geometry represents the experimental measurement of heat production in muscle, where a small thermophile is sandwiched between two relatively large muscles; hence, by symmetry there is no heat flux at the center (Fig. 1.1). To solve this system mathematically, Laplace transforms are employed to derive a series of transfer functions relating the temperature at each interface to that at the next and to the rate of heat production. Moreover, analytic expression are derived for the time course of the initial rate of temperature change and each of these expressions have the same form, regardless of the number of layers, hence these phases of the response can be extrapolated to describe a general system of  $n$  layers.

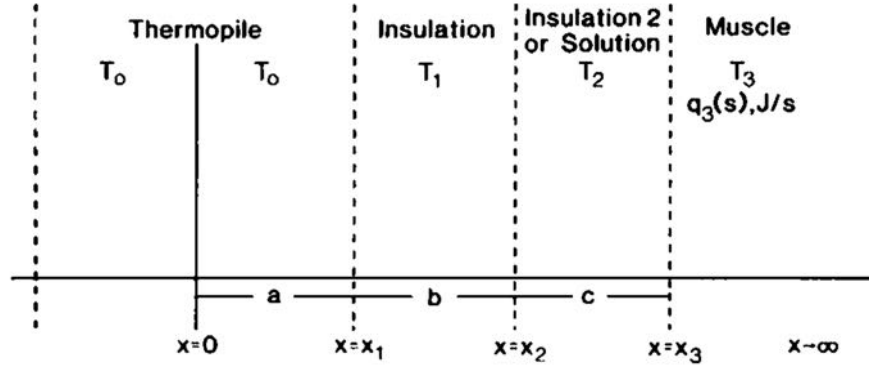


FIGURE 1.1: Geometry of heat diffusion barriers for a thermopile<sup>1</sup> with a muscle mounted on each face. The layers are symmetrical on each side of a plane in the center of the thermal junctions, whose half-thickness is dimension  $a$ . Covering the couples are a layer of insulation (thickness  $b$ ) and an additional layer of insulation or solution (thickness  $c$ )

Another application of composite medium system is heat conduction in one-dimensional heat slab [2]. The three-layer model explains the simplified case in which all heat transfer occurs only by conduction (no radiation, no convection, no heat generation, no combustion). Moreover, by observing the symmetries in the two and three-layer problems, a  $n$ -layer solution for the one-dimensional multi-layer slab is formulated. A composite slab consisting of three parallel layers is shown in the Fig. 1.2. Let  $k_1$ ,  $k_2$ ,  $k_3$  be thermal conductivities,  $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$  be the thermal diffusivities and  $d_1$ ,  $d_2$  and  $d_3$  be the thickness of the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> layers, respectively. Initially at  $t = 0$  the three region plate has specific, uniform temperature  $T_0$ . At time  $t = 0$  the composite slab is suddenly heated such that the temperatures after  $t = 0$  are fixed as  $T_0$  and  $T_1$  at the bottom and top surfaces, respectively. Here  $T_1$  represents the “flame” temperature while  $T_0$  is the cold “substrate” temperature. The central region of thickness  $d_2$  is the heated sample. At the two interfaces ( $x = d_1$ ,  $x = d_1 + d_2$ ), we assume that perfect thermal contact conditions are satisfied. It is assumed that the thermal conductivity and the thermal diffusivity are temperature independent and uniform within each layer. The mathematical model thus given was then solved using eigenfunction expansion method. The main advantage of this method comes when one of the slabs has thermophysical properties radically different from those of other two, or one layer is much narrower than the other two layers.

In the third application we consider the drug delivery problem from mathematical biology which is one of the main subjects in this work [3]. Transdermal drug delivery (TDD) is an approach used to deliver drugs through the skin for therapeutic purposes as an alternative to oral, intravascular, subcutaneous and transmucosal routes. TDD has

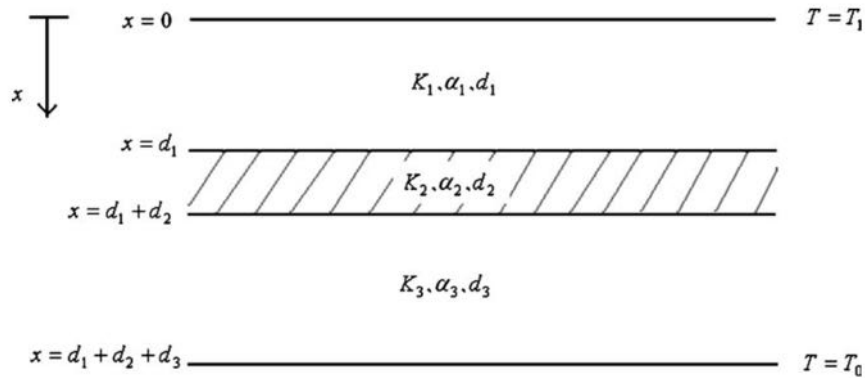


FIGURE 1.2: The three-layer composite slab showing the imposed temperatures on the two sides at the orientation of the coordinate system. The contact between the interfaces is assumed to be thermally perfect, meaning continuity of  $T$  and  $\frac{\partial T}{\partial x}$  at  $x = d_1$  and  $x = d_1 + d_2$ .

several advantages compared to other delivery methods: controlled release rate, noninvasive administration, less frequent dosing, and simple application without professional medical aids. For these reasons it represents a valuable and attractive alternative to oral administration. To describe the model, a system of partial differential equations are used which express the diffusion and the binding/unbinding processes in both layers (skin and drug). Moreover, to connect the both layers an additional flux continuity at the interface and clearance conditions into systemic circulation are imposed. In the next section, we discuss more about the mathematical aspect of the problem.

The last application is a similar problem or can be called mathematically as an extension problem is a drug-eluting stent model and this is also part of the our current work. The model represents drug release from an eluting stent and the subsequent transport in the arterial wall. In order to study the complete process, a two-phase mathematical model describing the transport of a drug between two coupled media of different properties and extensions as a unique release system is presented. To describe the process of dissolution and diffusion in the polymeric matrix and diffusion, convection and binding reaction in the tissue layer, a system of nonlinear partial differential equations has been used.

## 1.2 Thesis layout

The project is composed of four chapters. The first chapter is an introduction to the thesis which contains some real life problems modeled using reaction-diffusion equations in composite medium. One such example is transdermal drug delivery problem which is

one of the main topics to be dealt during the work; an introduction to this problem is also a part of this chapter.

In the second chapter, we solve the system numerically using Crank-Nicolson scheme and obtain the results for individual concentration levels and for total masses. The results obtained are close to the analytical results. In this chapter, we also solve the dimensionless form and from here onwards, for further analysis we use only the dimensionless form.

The challenge in solving the problem numerically lies in finding solution at the interface, as there is a discontinuity in the concentrations. In the third chapter, we introduce a new formulation where the solution at the interface is calculated using a technique involving Taylor's expansion ([4]). We write these equations in system of the form:  $\frac{dU}{dt} = A(U)$ , where  $U$  is the solution vector. We solved it using a MATLAB solver ODE15s and results obtained were more accurate and fast as compared to the previous methods.

In the fourth and last chapter, we plan to use the same technique for a nonlinear problem. As a nonlinear problem can incorporate more functionality of the model problem, solving it numerically would be only way to approach as finding the analytical solution becomes impossible.

### 1.3 A mathematical formulation of transdermal drug delivery problem

In this section we consider the mathematical model of drug delivery problem. We have already introduced the problem in the previous section, thus, in addition to that we have a model TDD, a two-layered system composed of: (i) the vehicle (the transdermal patch or the film of an ointment), and (ii) the skin (the stratum corneum followed by the skin-receptor cells and the capillary bed) (Fig 1.3). The drug is encapsulated in the vehicle, a reservoir consisting of a polymeric matrix. This is enclosed on one side with an impermeable backing and having on the other side an adhesive in contact with the skin. Moreover, a rate-controlling membrane shielding the polymer matrix may exist. In this configuration, the first layer is shaped as a planar slab that is in direct contact with the skin (the second layer). We confine our study to a simplified one-dimensional model as most of the mass dynamics occurs along the direction normal to the skin surface. In particular,  $x$ -axis is assumed to be normal to the skin surface and oriented with the positive direction outwards the skin. Without loss of generality, let  $x = 0$  be the vehicle-skin interface and  $l_0$  and  $l_1$  the thicknesses of the vehicle and skin layers respectively

(Fig 1.3). The vehicle and the skin are both treated from a macroscopic perspective so that they are represented as two homogeneous media.

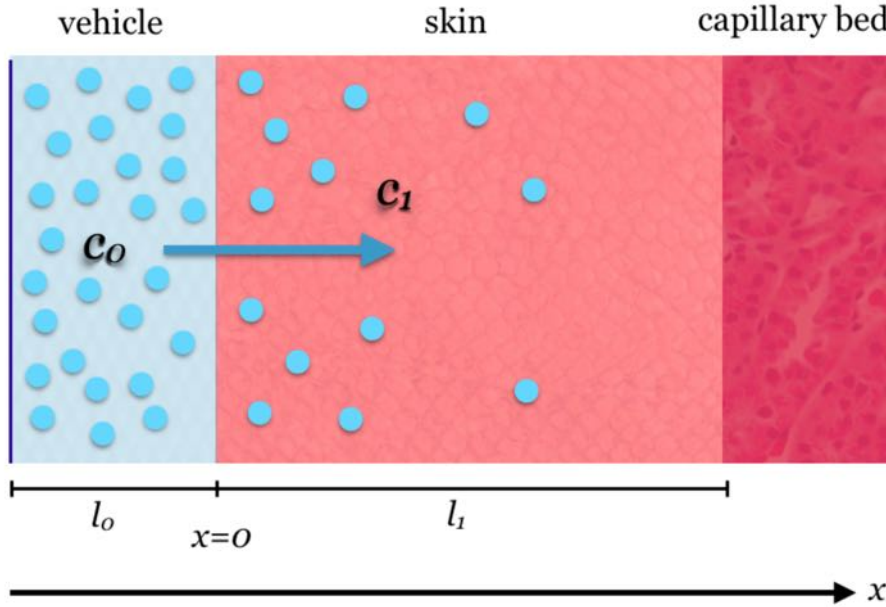


FIGURE 1.3: Cross-section of the vehicle and the skin layers, geometrical configuration and reference system. Due to an initial difference of free drug concentrations  $c_0$  and  $c_1$ , a mass flux is established at the interface and drug diffuses through the skin. At a distance  $x = l_1$  the skin-receptor (capillary bed) is present where all drug is assumed to be absorbed. Figure not to scale.

Initially, the drug is stored at maximum concentration within the vehicle in a bound phase (e.g. nanoparticles or crystalline form) ( $c_e$ ): in such state, it is unable to be delivered to the tissue. Then, a fraction of this drug ( $\beta_0 c_e$ ) is transferred, through a dissolution process, to an unbound – free, biologically available – phase ( $c_0$ ), and conversely, by a binding process, a part of the free drug ( $\delta_0 c_0$ ) may be transferred to the bound state (Fig. 1.4). Also, at the same time, another fraction of free drug ( $c_1$ ) begins to diffuse into the adjacent skin (delivery). Similarly, in the skin – the release medium – a part of the unbound drug ( $\beta_1 c_1$ ) is metabolized by the cell receptors and transformed in a bound state ( $c_b$ ) (absorption), and with the reverse unbinding process ( $\delta_1 c_b$ ) again in a unbound phase. Thus, the drug delivery-absorption process starts from the vehicle and ends to the skin receptors, with bidirectional phase changes in a cascade sequence, as schematically represented in Fig. 1.4. Local mass non-equilibrium processes, such as bidirectional drug binding/unbinding phenomena, play a key role in TDD, with characteristic times faster than those of diffusion. Here, a linear relationship is commonly used, as the density of binding sites far exceeds the local free drug concentration. Thus, we have:

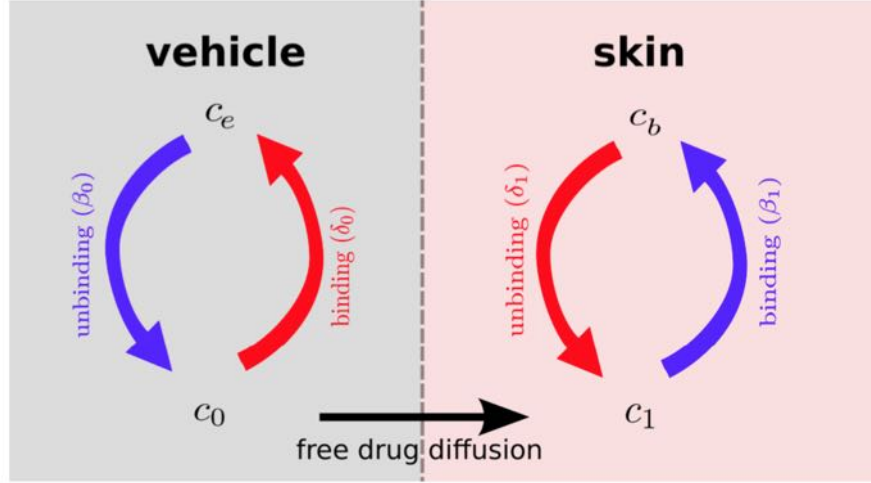


FIGURE 1.4: A diagram sketching the cascade mechanism of drug delivery and percutaneous absorption in the vehicle-skin coupled system. A unbinding (resp. binding) reaction occurs in the vehicle (resp. in the skin) (blue arrows). In both layers, reverse reactions (red arrows) are present in a dynamic equilibrium. Drug diffusion occurs only in the free phases  $c_0$  and  $c_1$ .

## 1.4 The continuum problem

For the given problem, we consider the two layer system with domain  $(-l_0, l_1)$  i.e.  $(-l_0, 0)$  is the layer I(vehicle) and  $(0, l_1)$  is layer II(skin).

The system in  $(-l_0, 0)$  given by

$$\frac{\partial c_e}{\partial t} = -\beta_0 c_e + \delta_0 c_0 \quad (1.1)$$

$$\frac{\partial c_0}{\partial t} = D_0 \frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0 \quad (1.2)$$

Similarly, in the second layer i.e. interval  $(0, l_1)$  the system is given by:

$$\frac{\partial c_1}{\partial t} = D_1 \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b \quad (1.3)$$

$$\frac{\partial c_b}{\partial t} = \beta_1 c_1 - \delta_1 c_b \quad (1.4)$$

where  $D_1$  is the effective diffusivity of unbound drug,  $\beta_1 \geq 0$  and  $\delta_0 \geq 0$  are the binding and unbinding rate constants in the skin, respectively. They can be evaluated experimentally as described in [5, 6], sometimes through the equilibrium constant  $K = \frac{\delta_1}{\beta_1}$ . Moreover, the diffusion coefficient in a composite medium can be assumed as:

$$D(x) = \begin{cases} D_0 & : x \in (-l_0, 0) \\ D_1 & : x \in (0, l_1) \end{cases} \quad (1.5)$$

### 1.4.1 Initial conditions

$$c_e(x, 0) = 1, \quad c_0(x, 0) = 0, \quad c_b(x, 0) = 0, \quad c_1(x, 0) = 0 \quad (1.6)$$

### 1.4.2 Boundary and interface conditions

Since, no mass flux passes between the vehicle and the external surrounding due to the impermeable backing and we impose a no-flux condition at  $x = l_0$  :

$$-D_0 \frac{\partial c_0}{\partial x} = 0 \quad (1.7)$$

For the boundary condition at the skin-receptor (capillary) boundary, the elimination of drug by capillary system follows first-order kinetics. Therefore, at  $x = l_1$ ,

$$K_{cl}c_1 + D_1 \frac{\partial c_1}{\partial x} = 0 \quad (1.8)$$

where  $K_{cl}$  is the skin-capillary clearance per unit area ( $cm/s$ ).

To close the two-layer mass transfer system of eqs. (1.1)-(1.4) a flux continuity condition has to be assigned at the vehicle-skin interface:

$$-D_0 \frac{\partial c_0}{\partial x} = -D_1 \frac{\partial c_1}{\partial x} \quad (1.9)$$

The concentration continuity is not guaranteed because of a different drug partitioning between vehicle and skin. This is taken care by a suitable mass transfer coefficient  $P_r$  [5, 6]. Moreover, a semi-permeable rate-controlling membrane or an adhesive film or a non-perfect vehicle-skin contact, having  $\frac{1}{P_m}$  as mass resistance, might be present at the interface. Thus, a concentration jump may occur:

$$-D_1 \frac{\partial c_1}{\partial x} = P(c_0 - c_1) \quad (1.10)$$

with  $P$  ( $cm/s$ ) the overall mass transfer coefficient:

$$\frac{1}{P} = \frac{1}{P_r} + \frac{1}{P_m}$$

Equations (1.9) and (1.10) are called flux continuity and jump concentration conditions, respectively.



## Chapter 2

# Finite difference method for a composite material

In this chapter, we consider the transdermal drug delivery problem, convert it to dimensionless form and discretize it over space and time using Crank-Nicolson scheme. As explained in the previous chapter, the problems consists of two media i.e. the vehicle and skin; the drug moves from vehicle to skin which is modeled using reaction-diffusion equations. Moreover, the two phases are linked with a flux-continuity equation.

### 2.1 Dimensionless form and its discretization

We use the following variables:

$$\begin{aligned}\bar{x} &= \frac{x}{l_1}, & \bar{t} &= \frac{D_1}{(l_1)^2}t, & \phi &= \frac{Pl_1}{D_1} \\ \bar{l}_0 &= \frac{l_0}{l_1}, & \gamma &= \frac{D_0}{D_1}, & \bar{c}_i &= \frac{c_i}{C_e} \\ K &= \frac{K_{cl}l_1}{D_1}, & \bar{\beta}_i &= \frac{\beta_i(l_1)^2}{D_1}, & \bar{\delta}_i &= \frac{\delta_i(l_1)^2}{D_1} \quad \text{for } i = 0, 1\end{aligned} \quad (2.1)$$

and convert the problem to a dimensionless problem:

### 2.1.1 The continuum problem

By omitting the bar for simplicity, the mass transfer problem (1.1)-(1.4) can be now written in dimensionless form as:

$$\frac{\partial c_e}{\partial t} = -\beta_0 c_e + \delta_0 c_0 \quad \text{in} \quad (-l_0, 0) \quad (2.2)$$

$$\frac{\partial c_0}{\partial t} = \gamma \frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0 \quad \text{in} \quad (-l_0, 0) \quad (2.3)$$

$$\frac{\partial c_1}{\partial t} = \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b \quad \text{in} \quad (0, 1) \quad (2.4)$$

$$\frac{\partial c_b}{\partial t} = \beta_1 c_1 - \delta_1 c_b \quad \text{in} \quad (0, 1) \quad (2.5)$$

### 2.1.2 Initial conditions

$$c_e(x, 0) = 1, \quad c_0(x, 0) = 0 \quad (2.6)$$

$$c_b(x, 0) = 0, \quad c_1(x, 0) = 0 \quad (2.7)$$

### 2.1.3 Boundary conditions

No flux condition at  $x = l_0$  is:

$$\gamma \frac{\partial c_0}{\partial x} = 0 \quad (2.8)$$

At  $x = 1$ ,

$$K c_1 + \frac{\partial c_1}{\partial x} = 0 \quad (2.9)$$

At the interface  $x = 0$  there are two conditions:

$$\gamma \frac{\partial c_0}{\partial x} = \frac{\partial c_1}{\partial x} \quad (2.10)$$

$$-\frac{\partial c_1}{\partial x} = \phi(c_0 - c_1) \quad (2.11)$$

## 2.2 Numerical Discretization

The whole domain  $(-l_0, 1)$  is subdivided in two parts, first is  $(-l_0, 0)$  which is discretized with step size  $h_0$  and  $(0, 1)$  with step size  $h_1$ . The labeling of nodes is as follows:  $x = -l_0$  as  $i = 1$ ,  $(-l_0, 0)$  as  $i = 2, \dots, N - 1$ ,  $x = 0$  as  $i = N$  and  $(0, 1)$  as  $i = N + 1, \dots, M - 1$ ,  $x = 1$  as  $i = M$  (Fig. 2.1). The interval  $(-l_0, 0)$  is discretized into  $N$  points with space step size  $h_0$  and time step size  $k$ , then the nondimensional equations (1.1) and (1.2) in the discretized form are:

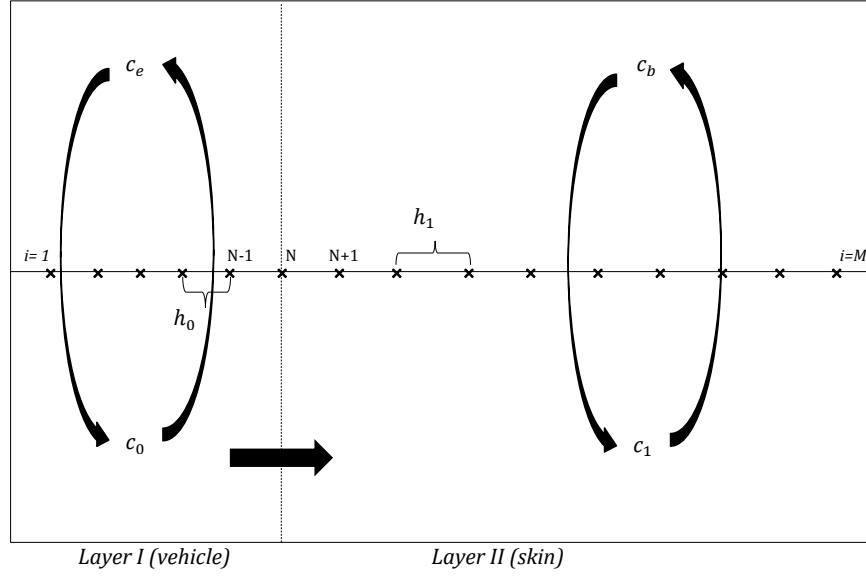


FIGURE 2.1: The two-phase system is divided into  $M$  points:  $N - 1$  points in the first layer with step size  $h_0$  and  $M - N$  points in the second layer with step size  $h_1$ .  $i = N$  is the interface point.

### 2.2.1 Layer I (Vehicle)

$$\frac{c_{e_i}^{n+1} - c_{e_i}^n}{k} = -\beta_0 c_{e_i}^n + \delta_0 c_{0_i}^n$$

$$\implies c_{e_i}^{n+1} = c_{e_i}^n (1 - k\beta_0) + \delta_0 k c_{0_i}^n \quad (2.12)$$

$$\frac{c_{0_i}^{n+1} - c_{0_i}^n}{k} = \left[ \gamma \theta \frac{c_{0_{i+1}}^{n+1} - 2c_{0_i}^{n+1} + c_{0_{i-1}}^{n+1}}{h_0^2} + (1 - \theta) \gamma \frac{c_{0_{i+1}}^n - 2c_{0_i}^n + c_{0_{i-1}}^n}{h_0^2} \right]$$

$$+ \beta_0 c_{e_i}^n - \delta_0 c_{0_i}^n \quad (2.13)$$

$$c_{0_{i-1}}^{n+1} \left( -\frac{k\theta}{h_0^2} \gamma \right) + c_{0_i}^{n+1} \left( 1 + \frac{2k\theta}{h_0^2} \gamma \right) + c_{0_{i+1}}^{n+1} \left( -\frac{k\theta}{h_0^2} \gamma \right)$$

$$= c_{0_{i-1}}^n \left( \frac{k(1-\theta)}{h_0^2} \gamma \right) + c_{0_i}^n \left( 1 - \frac{2k(1-\theta)}{h_0^2} \gamma - \delta_0 k \right) + c_{0_{i+1}}^n \left( \frac{k(1-\theta)}{h_0^2} \gamma \right) + k\beta_0 c_{e_i}^n \quad (2.14)$$

$\forall i = 1, \dots, N-1$  and  $0 < \theta < 1$ .

### 2.2.2 Layer II (Skin)

Next we examine our system in the skin side. The interval  $(0, 1)$  is discretized with step size  $h_1$ . The equations (2.4) and (2.5) in the discretised form are:

$$\begin{aligned} \frac{c_{b_i}^{n+1} - c_{b_i}^n}{k} &= \beta_1 c_{1_i}^n - \delta_1 c_{b_i}^n \\ \Rightarrow c_{b_i}^{n+1} &= c_{b_i}^n (1 - k\delta_1) + k\beta_1 c_{1_i}^n \end{aligned} \quad (2.15)$$

$\forall i = N+1, \dots, M$ .

$$\begin{aligned} &c_{1_{i-1}}^{n+1} \left( -\frac{k\theta}{h_1^2} \right) + c_{1_i}^{n+1} \left( 1 + \frac{2k\theta}{h_1^2} \right) + c_{1_{i+1}}^{n+1} \left( -\frac{k\theta}{h_1^2} \right) \\ &= c_{1_{i-1}}^n \left( \frac{k(1-\theta)}{h_1^2} \right) + c_{1_i}^n \left( 1 - \frac{2k(1-\theta)}{h_1^2} - k\beta_1 \right) + c_{1_{i+1}}^n \left( \frac{k(1-\theta)}{h_1^2} \right) + k\delta_1 c_{b_i}^n \end{aligned} \quad (2.16)$$

$\forall i = N+1, \dots, M$  and  $0 < \theta < 1$ .

### 2.2.3 Initial and boundary conditions

The initial conditions are:

$$\begin{aligned} c_{e_i}^1 &= 1, & c_{0_i}^n &= 0 & \forall i &= 1, \dots, N-1 \\ c_{b_i}^1 &= 0, & c_{1_i}^1 &= 0 & \forall i &= N+1, \dots, M. \end{aligned}$$

**Boundary conditions:** The no flux condition (2.8) at  $x = -l_0$  using central difference scheme can be discretized as (at time step  $n+1$ ):

$$\begin{aligned} \gamma \frac{(c_{0_{i+1}}^{n+1} - c_{0_{i-1}}^{n+1})}{h_0} &= 0 \\ \Rightarrow c_{0_2}^{n+1} &= c_{0_0}^{n+1} \quad \text{at } i = 1 \end{aligned} \quad (2.17)$$

The boundary condition (2.9) at  $x = 1$  i.e.  $i = M$  and at time step  $n+1$  is:

$$\begin{aligned} K c_{1_M}^{n+1} + \left( \frac{c_{1_{M+1}}^{n+1} - c_{1_{M-1}}^{n+1}}{2h_1} \right) &= 0 \\ \Rightarrow c_{1_{M+1}}^{n+1} &= c_{1_{M-1}}^{n+1} - 2Kh_1 c_{1_M}^{n+1} \end{aligned} \quad (2.18)$$

**Conditions at the interface  $x = 0$  :** The flux continuity condition, equation (1.9) at the interface  $x = 0$  i.e.  $i = N$ ,

$$\begin{aligned} \gamma \frac{c_{0_N}^{n+1} - c_{0_{N-1}}^{n+1}}{h_0} &= \frac{c_{1_{N+1}}^{n+1} - c_{1_N}^{n+1}}{h_1} \\ \Rightarrow -\gamma h_1 c_{0_{N-1}}^{n+1} + \gamma h_1 c_{0_N}^{n+1} + h_0 c_{1_N}^{n+1} - h_0 c_{1_{N+1}}^{n+1} &= 0 \end{aligned} \quad (2.19)$$

and the jump concentration, equation (1.10) at  $x = 0$  is:

$$\begin{aligned} -\frac{c_{1_{N+1}}^{n+1} - c_{1_N}^{n+1}}{h_1} &= \phi(c_{0_N}^{n+1} - c_{1_N}^{n+1}) \\ \Rightarrow \phi h_1 c_{0_N}^{n+1} - (1 + \phi h_1) c_{1_N}^{n+1} + c_{1_{N+1}}^{n+1} &= 0 \end{aligned} \quad (2.20)$$

**Note:** All the boundary conditions are evaluated at time step  $n + 1$ .

Moreover, the drug masses are computed as integral of concentration over the corresponding layer:

$$M_i(t) = \int c_i(x, t) dx; \quad i = 0, 1, e, b \quad (2.21)$$

In the discrete version it can be written as:

$$M_j(t) = \sum_i c_j(x_i) * h_0 \quad j = e, 0 \quad (2.22)$$

$$M_j(t) = \sum_i c_j(x_i) * h_1 \quad j = b, 1 \quad (2.23)$$

**The complete system:** We have equation (2.14) for each  $i = 1, \dots, N-1$  and (2.16) for  $i = N+1, \dots, M$ , hence  $N - 1 + M - N = M - 1$  equations. For  $i = N$  we have two equations i.e. (2.19), (2.20) thus making  $M - 1 + 2 = M + 1$  equations system to solve. The values for  $c_{0_0}$  and  $c_{1_{M+1}}$  are substituted from equations (2.17) and (2.18), respectively. A system thus obtained can be written in the following form:

$$AX^{n+1} = BX^n + kZ^n \quad (2.24)$$

where,  $A$  and  $B$  are  $(M+1) \times (M+1)$  size matrices and  $X, Z$  are  $M+1$  dimension vectors with concentration values  $c_0, c_1$  and  $c_e, c_b$  respectively.

$$X = (c_{0_1}^{n+1}, \dots, c_{0_{N-1}}^{n+1}, c_{0_N}^{n+1}, c_{1_N}^{n+1}, c_{1_{N+1}}^{n+1}, \dots, c_{1_M}^{n+1}), Z = (c_{e_1}^n, \dots, c_{e_{N-1}}^n, 0, 0, c_{b_{N+1}}^{n+1}, \dots, c_{b_M}^{n+1}).$$

Moreover, the values of  $c_e$  and  $c_b$  for  $t = n + 1$  are updated using equations (2.12) and (2.15), respectively which are calculated <sup>1</sup> after solving system (2.24).

---

<sup>1</sup>See B.1 for MATLAB code

[illegible]

[illegible]

with  $\Delta_1 = \frac{2k(1-\theta)}{h_0^2}\gamma + \delta_0 k$  and  $\Delta_2 = \frac{2k(1-\theta)}{h_1^2} + \beta_1 k$ .

The matrices on the both sides can be written in the form of tridiagonal matrices as:

$$A = \begin{pmatrix} \overline{A_1} & 0 \\ \begin{matrix} -\gamma h_1 & \gamma h_1 \\ 0 & \phi h_1 \end{matrix} & \begin{matrix} h_0 & -h_0 \\ -\phi h_1 - 1 & 1 \end{matrix} \\ 0 & \overline{A_2} \end{pmatrix}$$

where

$$A_1 = \begin{pmatrix} 1 + \frac{k\theta}{h_0^2}\gamma & -\frac{k\theta}{h_0^2}\gamma & 0 & \cdots & \cdots & 0 \\ -\frac{k\theta}{h_0^2}\gamma & 1 + \frac{2k\theta}{h_0^2}\gamma & -\frac{k\theta}{h_0^2}\gamma & \cdots & \cdots & 0 \\ 0 & -\frac{k\theta}{h_0^2}\gamma & 1 + \frac{2k\theta}{h_0^2}\gamma & -\frac{k\theta}{h_0^2}\gamma & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & \cdots & -\frac{k\theta}{h_0^2}\gamma & 1 + \frac{2k\theta}{h_0^2}\gamma & -\frac{k\theta}{h_0^2}\gamma \end{pmatrix}$$

and

$$A_2 = \begin{pmatrix} -\frac{k\theta}{h_1^2} & 1 + \frac{2k\theta}{h_1^2} & -\frac{k\theta}{h_1^2} & \cdots & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -\frac{k\theta}{h_1^2} & 1 + \frac{2k\theta}{h_1^2} & -\frac{k\theta}{h_1^2} \\ 0 & 0 & \cdots & 0 & -\frac{k\theta}{h_1^2} & 1 + \frac{k\theta}{h_1^2} + \frac{kK_{cl}\theta}{h_1^2} \end{pmatrix}$$

Also,

$$B = \begin{pmatrix} \overline{B_1} & 0 \\ 0 & 0 \\ 0 & \overline{B_2} \end{pmatrix}$$

where

$$B_1 = \begin{pmatrix} 1 - \Delta_1 & \frac{k(1-\theta)}{h_0^2}\gamma & 0 & \cdots & 0 & 0 \\ \frac{k(1-\theta)}{h_0^2}\gamma & 1 - \Delta_1 & \frac{k(1-\theta)}{h_0^2}\gamma & \cdots & \cdots & 0 \\ 0 & \frac{k(1-\theta)}{h_0^2}\gamma & 1 - \Delta_1 & \frac{k(1-\theta)}{h_0^2}\gamma & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & \cdots & \frac{k(1-\theta)}{h_0^2}\gamma & 1 - \Delta_1 & \frac{k(1-\theta)}{h_0^2}\gamma \end{pmatrix}$$

and



$$B_2 = \begin{pmatrix} \frac{k(1-\theta)}{h_1^2} & 1 - \Delta_2 & \frac{k(1-\theta)}{h_1^2} & \cdots & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & \cdots & \frac{k(1-\theta)}{h_1^2} & 1 - \Delta_2 & \frac{k(1-\theta)}{h_1^2} \\ 0 & \cdots & \cdots & 0 & \frac{k(1-\theta)}{h_1^2} & 1 - \Delta_2 - \frac{2kK(1-\theta)}{h_1} \end{pmatrix}$$

## 2.3 Results

The above system was solved in MATLAB using parameters values from table 2.1. Moreover, the space domain was discretized with  $M = 1000$ ,  $N = 50$  and time step was chosen as  $k = 0.1$ . The simulations were run for  $t = 0.01, 0.1, 1$ .

The total drug masses were obtained using the eqns. (2.22), (2.23) and it is seen from the figure (2.2) that only  $M_e$  shows an exponential decay unlike  $M_0$ ,  $M_1$ ,  $M_b$  which increases at initial times upto a peak and later reaches to zero.

In figure (2.3), there are four plots (2.3a, 2.3b, 2.3c, 2.3d), each showing the concentration at different times:  $t = 0.01, 0.1, 1$ . It is seen from that at given time, in the vehicle (Fig. 2.3a, 2.3b) the concentration of drug is almost constant except for the discontinuity at the interface. And, the concentration  $c_e$  reduces as the time progresses whereas  $c_b$  first increases and then starts decreasing.

On the other hand, in the skin side, at any time the drug concentration was found to be decreasing across space (Fig. 2.3c, 2.3d).

It is important to note that the numerical results were found to be very close with the semi-analytical results obtained in the paper [3].

Parameters		
Parameter	Value	Units
$l_0$	$40 * 10^{-4}$	$cm$
$l_1$	0.1	$cm$
$\beta_0$	$10^{-4}$	$s^{-1}$
$\beta_1$	$1.5 * 10^{-4}$	$s^{-1}$
$\delta_0$	$10^{-4}$	$s^{-1}$
$\delta_1$	$10^{-4}$	$s^{-1}$
$D_0$	$5 \times 10^{-7}$	$cm^2/s$
$D_1$	$7 \times 10^{-8}$	$cm^2/s$
$P$	$10^{-6}$	$cm/s$
$K_{cl}$	$3 \times 10^{-3}$	$cm/s$

TABLE 2.1: Parameters for linear problem

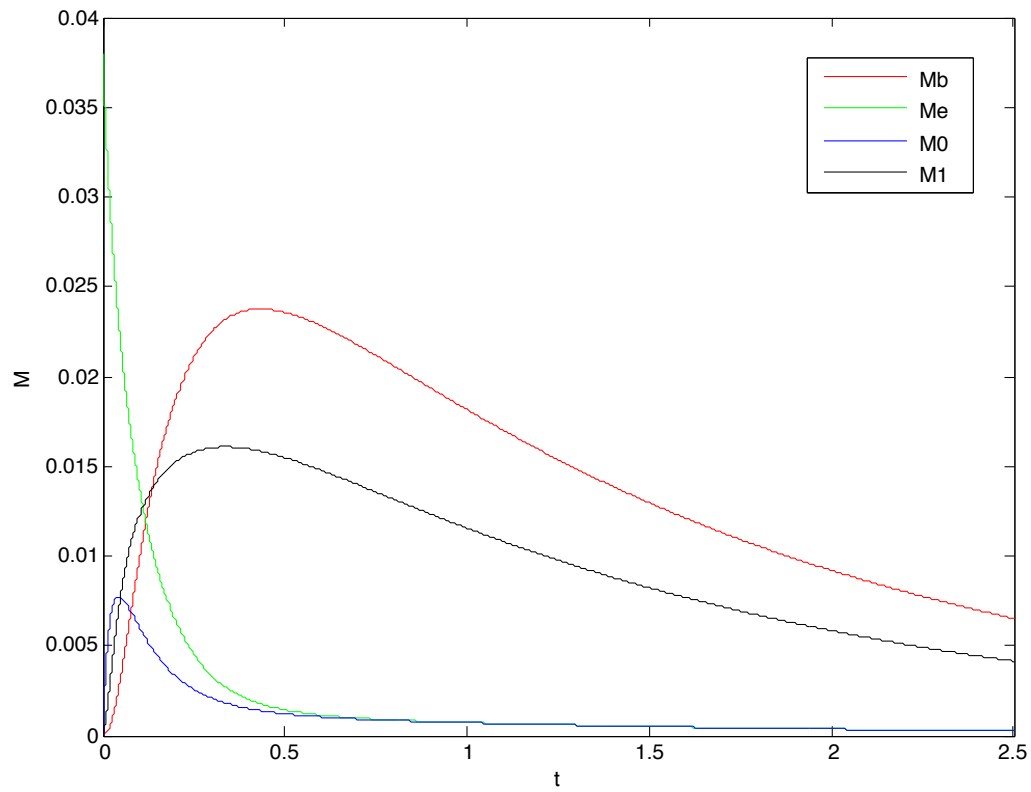
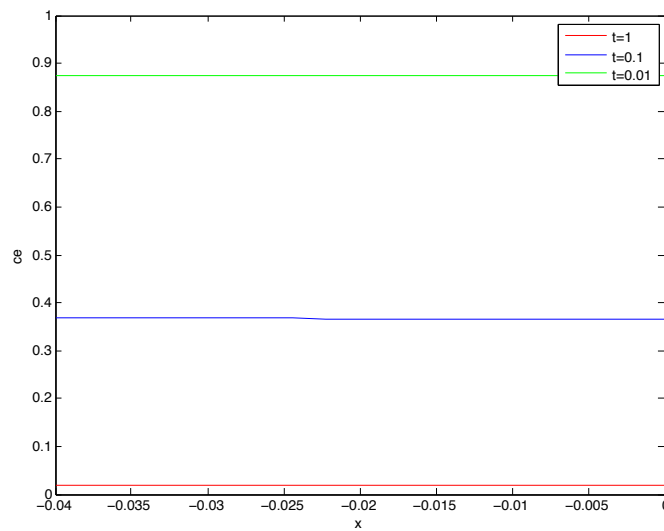


FIGURE 2.2: Time histories of the drug mass in the vehicle ( $M_e$  and  $M_0$ ) and in the skin ( $M_1$  and  $M_b$ ).



(A) Concentration  $c_e$

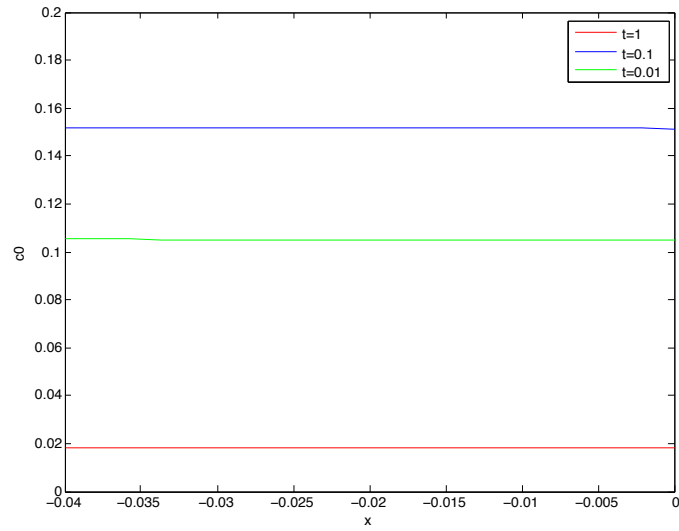
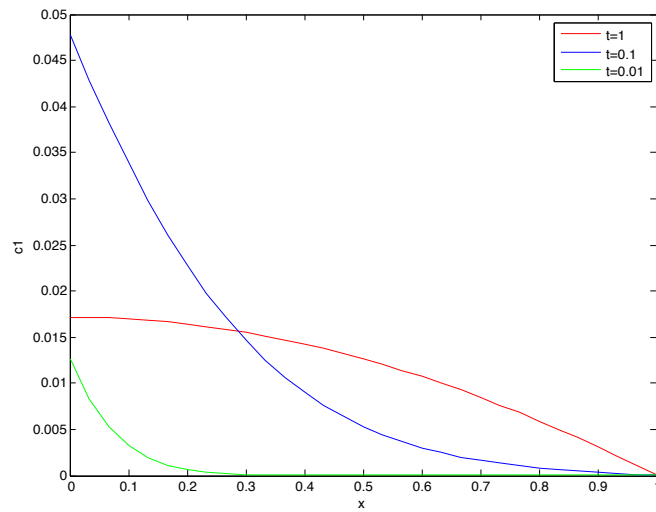
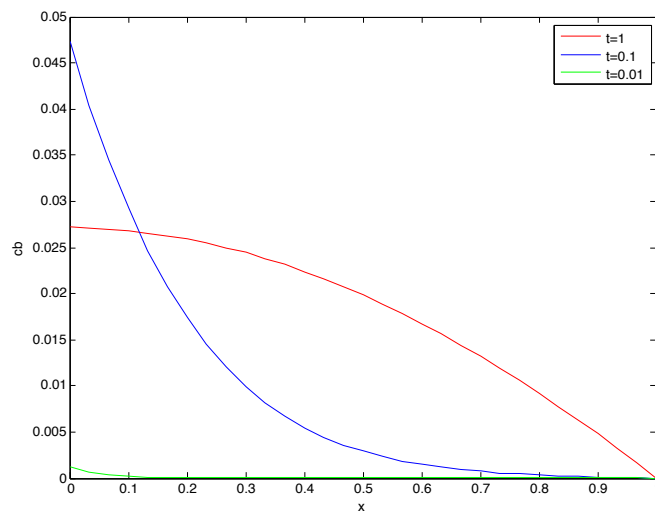
(B) Concentration  $c_0$ (c) Concentration  $c_1$ (D) Concentration  $c_b$ 

FIGURE 2.3: Plots of concentrations at different times



## Chapter 3

# An alternative approach for the linear problem

In this chapter we use a new method to solve our RD problem. We adopt a finite-difference scheme that discretizes the problem spatially, a Runge-Kutta type method with backward differentiation formulas and adaptive time step. In other words, we convert the problem in a form which can be solved using a MATLAB solver ODE15s and compare the results with the ones obtained with the previous methods.

### 3.1 Numerical Discretization

Differently from chapter 2, the whole domain  $(-l_0, 1)$  is subdivided in two parts,  $(-l_0, 0)$  which is discretized with step size  $h_0$  and  $(0, 1)$  with step size  $h_1$ . We denote  $x = -l_0$  as  $i = 1$ ,  $(-l_0, 0)$  as  $i = 2, \dots, N-1$ ,  $(0, 1)$  as  $j = 2, \dots, M-1$ ,  $x = 1$  as  $j = M$ . Moreover, it is important to note that the interface point  $x = 0$  is now considered as (split into) two points i.e.  $i = N$  (left side of interface, in red) and  $j = 1$  (right side of interface, in yellow). Figure 3.1 displays the new discretization with  $N$  grid points on the layer I and  $M$  grid points on the layer II.

### 3.2 ODE15s formulation

In this section we convert our RD system into a form which can further be solved using a MATLAB solver ODE15s. In order to achieve that we discretize the equations with respect to the space as follows:

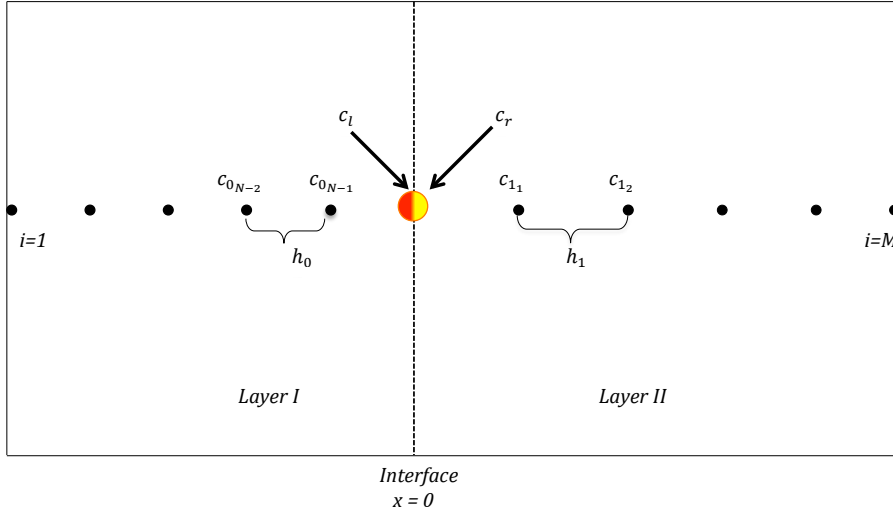


FIGURE 3.1: The two phase domain is divided in  $N+M$  points: layer I in  $N$  points with step size  $h_0$  and layer II in  $M$  points with step size  $h_1$ . Moreover, the discretization differs from the previous one in a manner that the point on the interface is split into two:  $c_l$  on the left side and  $c_r$  on the right side of the interface as seen in two colours.

We consider our ODE system in  $(-l_0, 0)$

$$\frac{dc_{e_i}}{dt} = -\beta_0 c_{e_i} + \delta_0 c_{0_i} \quad (3.1)$$

$$\frac{dc_{0_i}}{dt} = \gamma \frac{c_{0_{i+1}} - 2c_{0_i} + c_{0_{i-1}}}{h_0^2} + \beta_0 c_{e_i} - \delta_0 c_{0_i} \quad (3.2)$$

for  $i = 1, \dots, N-1$  and in the interval  $(0, 1)$ :

$$\frac{dc_{1_j}}{dt} = \frac{c_{1_{j+1}} - 2c_{1_j} + c_{1_{j-1}}}{h_1^2} - \beta_1 c_{1_j} + \delta_1 c_{b_j} \quad (3.3)$$

$$\frac{dc_{b_j}}{dt} = \beta_1 c_{1_j} - \delta_1 c_{b_j} \quad (3.4)$$

for  $j = 2, \dots, M$ . The concentration values of  $c_0$  and  $c_1$  at the interface i.e.  $c_l$  (left side of interface) and  $c_r$  (right side of interface), respectively, were calculated with a method <sup>1</sup> derived by Hickson et al. [4]. The method makes use of the boundary conditions (2.10) and (2.11) and hence we have:

$$\begin{aligned} c_l = & \frac{1}{\Lambda} \{ -c_{0N-2} [\gamma(2\phi h_1 + 3)] + c_{0N-1} [4\gamma(2\phi h_1 + 3)] \\ & + c_{11} (8\phi h_0) - c_{12} (2\phi h_0) \} \end{aligned} \quad (3.5)$$

<sup>1</sup>See appendix A.2

and

$$c_r = \frac{1}{\Lambda} \{-c_{0_{N-2}}(2\phi\gamma h_1) + c_{0_{N-1}}(8\gamma\phi h_1) + c_{1_1}(4(2\phi h_0 + 3\gamma)) - c_{1_2}(2\phi h_0 + 3\gamma)\} \quad (3.6)$$

with  $\Lambda = 9\gamma + 6\phi(h_0 + \gamma h_1)$ .

As now we know the values of  $c_0$  and  $c_1$  at the interface i.e.  $i = N$  and  $j = 1$  therefore, now we can also calculate the bound concentration values at the interface. Hence, with  $c_l$  and  $c_r$  we have:

$$\frac{dc_{e-}}{dt} = -\beta_0 c_{e-} + \delta_0 c_l \quad (3.7)$$

$$\frac{dc_{b+}}{dt} = \beta_1 c_r - \delta_1 c_{b+} \quad (3.8)$$

where  $c_{e-}$  and  $c_{b+}$  are the concentration values at the interface i.e. at  $i = N$  (on the left side of interface) and  $j = 1$  (on the right side of interface), respectively.

Now, with the equations (3.1), (3.2), (3.3), (3.4), (3.7) and (3.8), we get a system of equations of the form:

$$\frac{dU}{dt} = A(U)$$

where the vector  $U = (c_{e_1}, \dots, c_{e_{N-1}}, c_{e-}, c_{0_1}, \dots, c_{0_{N-1}}, c_{1_1}, \dots, c_{1_{M-1}}, c_{b+}, c_{b_2}, \dots, c_{b_M})$ .

### 3.3 The algorithm and advantages of the new method

In this section, we present the algorithm with which we solve our ODE system and the advantages of using the new method.

The algorithm we present, is composed of two parts or procedures. In the first procedure, we define the parameters, assign the initial conditions, time interval. A function call to the ODE solver is also made which in turn calls another routine “ $f$ ”. Output of the procedure is to extract individual concentrations and to plot them.

In the function call “ $f$ ”, we receive parameters, initial data and time interval as inputs and return vector  $\frac{dU}{dt}$  as an output. The system (3.1)-(3.4) is solved for  $i = 1, \dots, M$ . Moreover, the algorithm is given by:

**Algorithm 1** LinearODE algorithm

---

```

1: procedure LINEAR-ODE
2:   para  $\leftarrow$  define parameters
3:    $U_0 \leftarrow$  assign initial conditions
4:    $T \leftarrow$  time interval
5:   Function call  $ODE15s(@f, U_0, para)$ 
6:   Extract the output and plot
7: end procedure
1: procedure  $f(U_0, t, para)$ 
2:   Input:  $U_0, t, para$ 
3:   Output:  $\frac{dU}{dt}$ 
4:   Extract individual concentrations from vector  $U_0$ .
5:   Solve:
        $i = 1$  (boundary condition (2.17))
        $\frac{\partial c_{e_i}}{\partial t} = -\beta_0 c_{e_i} + \delta_0 c_{0_i}$ 
        $\frac{\partial c_{0_i}}{\partial t} = \gamma \frac{2c_{0_{i+1}} - 2c_{0_i}}{h_0^2} + \beta_0 c_{e_i} - \delta_0 c_{0_i}$ 
       for  $i = 2 : M - 1$ 
        $\frac{\partial c_{e_i}}{\partial t} = -\beta_0 c_{e_i} + \delta_0 c_{0_i}$ 
        $\frac{\partial c_{0_i}}{\partial t} = \gamma \frac{c_{0_{i+1}} - 2c_{0_i} + c_{0_{i-1}}}{h_0^2} + \beta_0 c_{e_i} - \delta_0 c_{0_i}$ 
        $\frac{\partial c_{1_i}}{\partial t} = \frac{c_{1_{i+1}} - 2c_{1_i} + c_{1_{i-1}}}{h_1^2} - \beta_1 c_{1_i} + \delta_1 c_{b_i}$ 
        $\frac{\partial c_{b_i}}{\partial t} = \beta_1 c_{1_i} - \delta_1 c_{b_i}$ 
        $i = M$  (boundary condition (2.18))
        $\frac{\partial c_{1_i}}{\partial t} = \frac{2c_{1_{i-1}} - (2+Kh_2)c_{1_i}}{h_1^2} - \beta_1 c_{1_i} + \delta_1 c_{b_i}$ 
        $\frac{\partial c_{b_i}}{\partial t} = \beta_1 c_{1_i} - \delta_1 c_{b_i}$ 
       to obtain  $\frac{dU}{dt}$  for each point in the domain.
6:   Calculate  $c_l$  and  $c_r$  a posteriori using eq. (3.5) and (3.6), respectively.
7:   Return  $\frac{dU}{dt}$ 
8: end procedure

```

---

**3.3.1 Advantages**

The advantages of the current method are the following:

- ◆ We have an ODE even at the interface which is not a relation between fluxes and this allows us to use the MATLAB solver ODE15s. This was not possible with the previous method (chapter2).
- ◆ The system is discretized by standard finite difference scheme only in space and we do not take in account the time (explicit or implicit).
- ◆ The concentrations at the interface are computed more accurately and the convergence of the method is extremely fast compared to the previous methods.



### 3.4 Results

We solved the system of  $M+N-2$  equations with  $M = 1000$ ,  $N = 50$ , the dimensionless parameters and obtain the following results <sup>2</sup>. Moreover, the calculation for  $c_l$  and  $c_r$  is done a posteriori using the equations (3.5) and (3.6). The time interval for the run is  $T = 2.5$ . From the figures, it is seen that the individual concentrations and total masses are almost same as obtained in the semi-analytical case in the previous chapter.

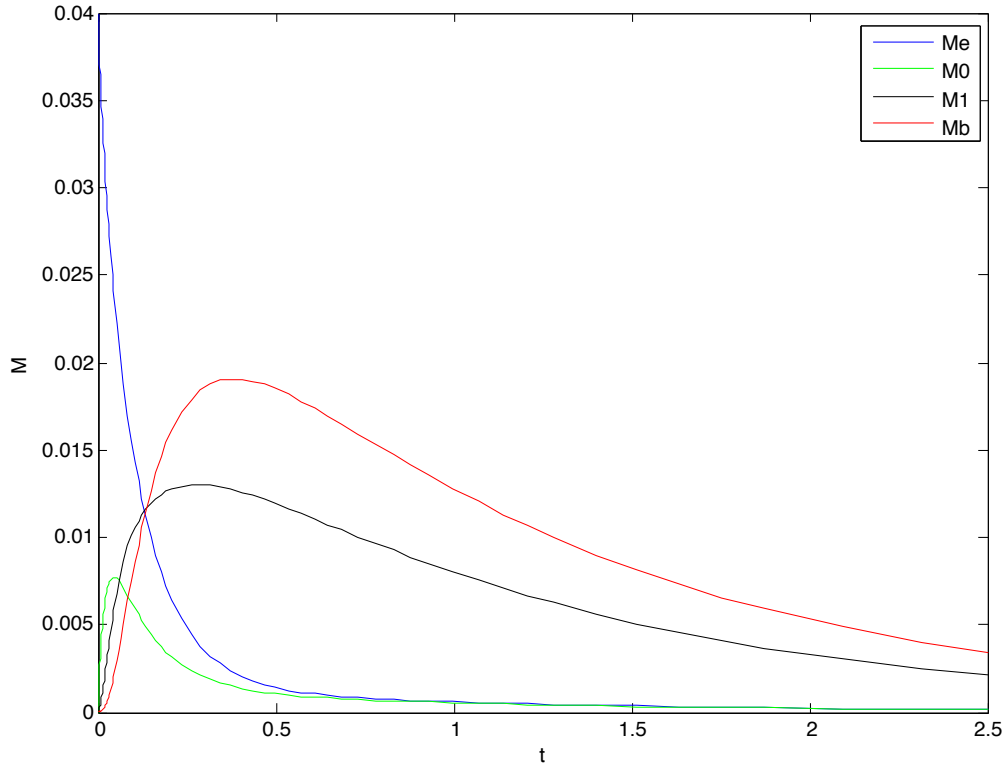
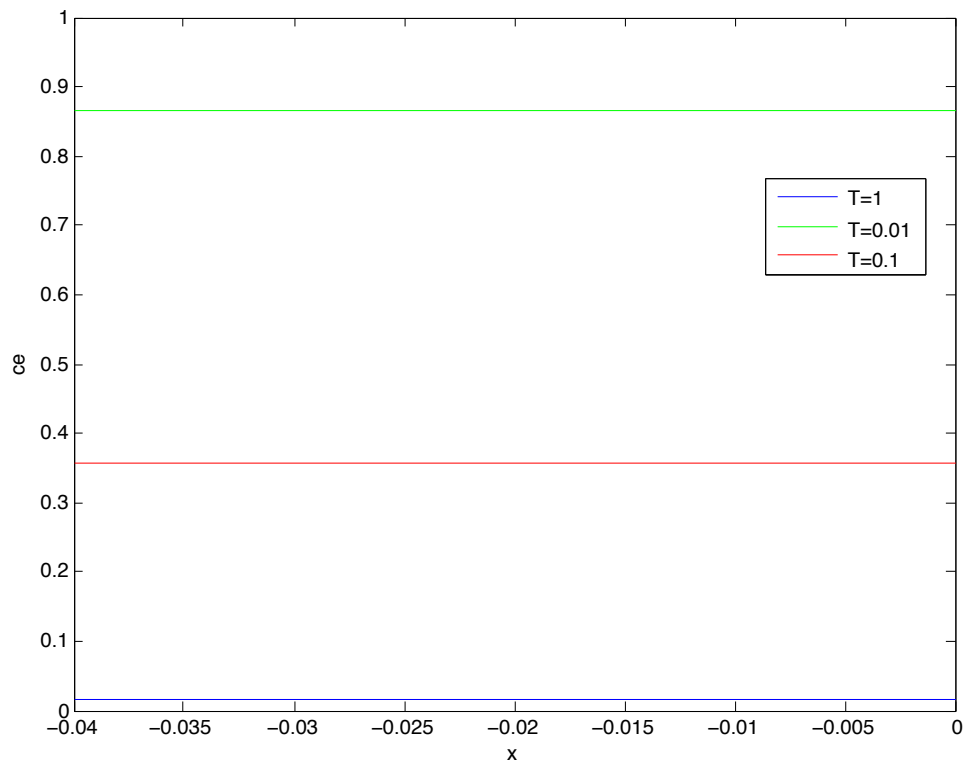
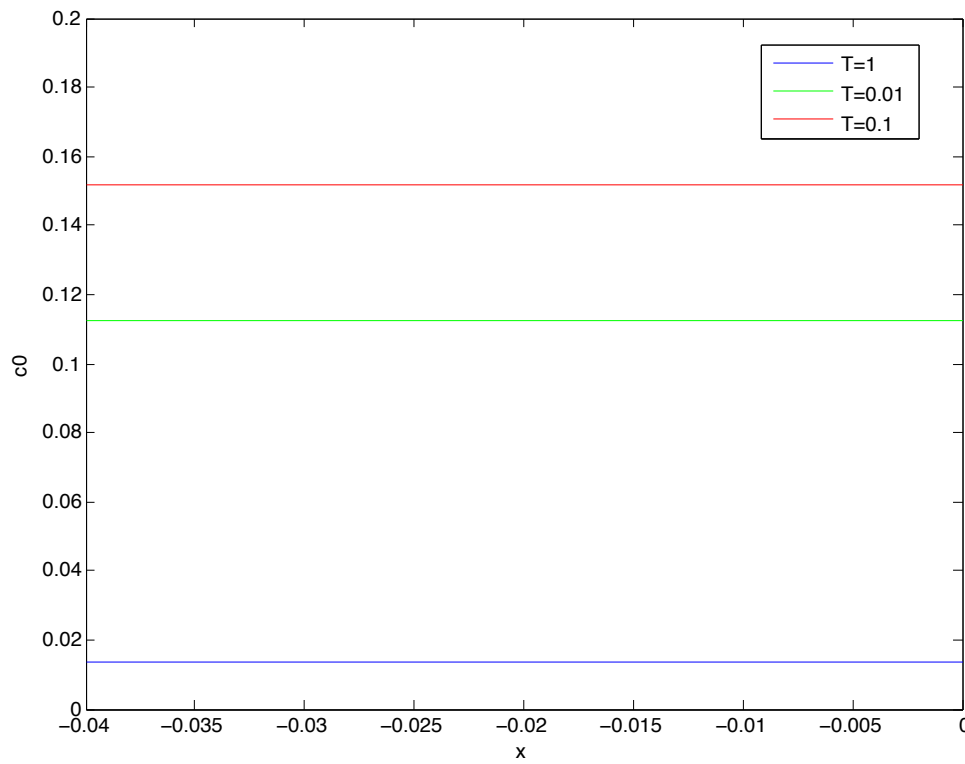


FIGURE 3.2: Time histories of total masses obtained using ODE15s (compare with figure 2.2)

<sup>2</sup>See appendix B.2 for MATLAB code

(A) Concentration  $c_e$ (B) Concentration  $c_0$

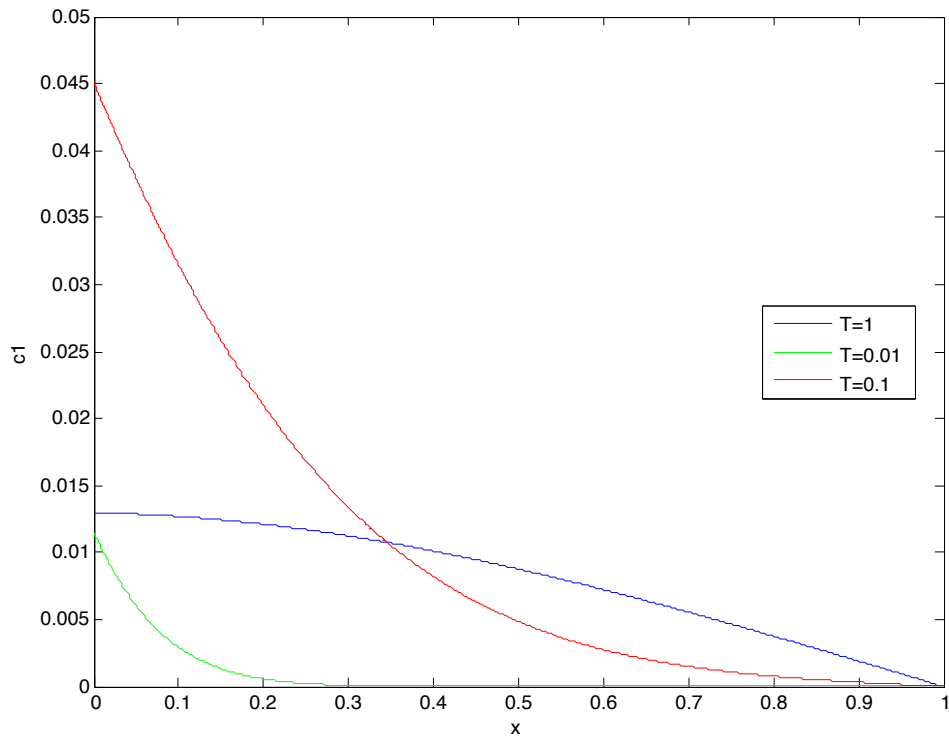
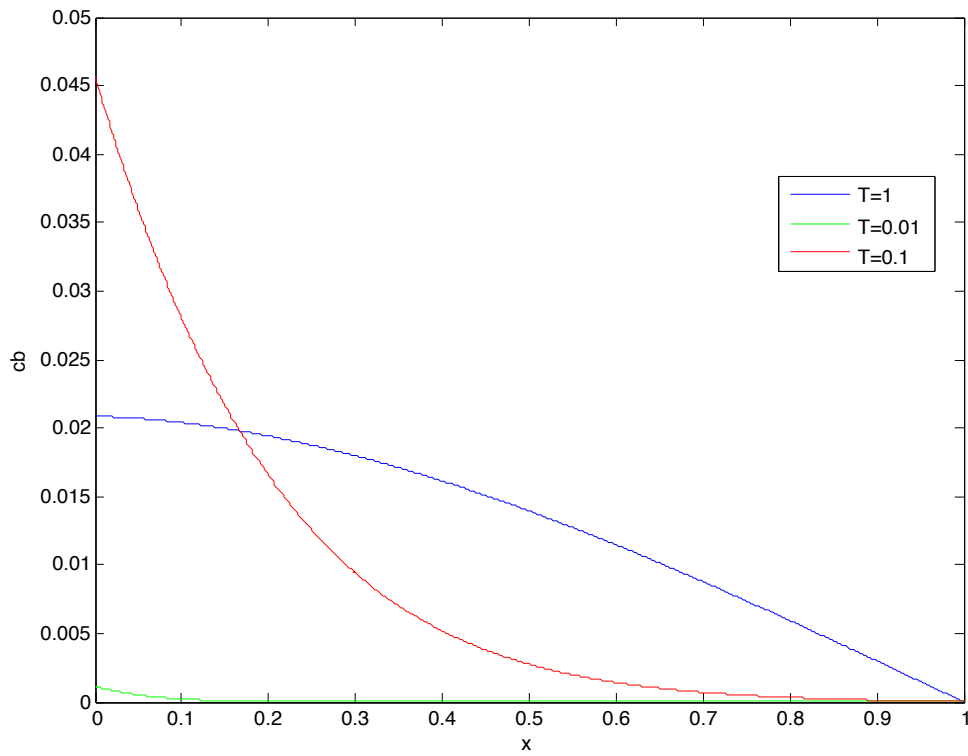
(c) Concentration  $c_1$ (d) Concentration  $c_b$ 

FIGURE 3.3: Plots of individual concentration at different times using ODE15s (compare with figure 2.3)



## Chapter 4

# A nonlinear extension and applications

In this chapter we consider another example of RD problem in composite media. This is a nonlinear problem, an extension to the previous one where we have a mathematical model for a “Drug-eluting stent systems” [7] [8]. The process of drug release from an eluting stent and the subsequent transport in the arterial wall is described using a coupled system of nonlinear RD equations. First we present the continuum model, then discretize it and carry out the same procedure (as done in chapter 2-3) to solve the system.

### 4.1 The mathematical model

A stent consists of a tubular wired mesh consisting of cross-membered struts, inserted and then expanded in a stenosed artery. In a DES, the struts are typically covered with a thin layer of polymer (coating) containing a therapeutic drug. The drug is directed to the vascular wall (the release medium), aimed at healing the vascular tissue or at preventing a possible restenosis by virtue of its antiproliferative action against smooth muscle cells. Therefore, drug delivery occurs between a coupled two-layer system composed of the coating (layer 0) and the wall (layer 1) (Fig. 4.1).

The coating is modelled as a planar slab, enclosed on one side with the impermeable strut and having the other side faced to the wall. A rate-controlling membrane protecting the polymer matrix may exist at the interface. In this configuration, as most of the mass dynamics occurs along the direction normal to the tissue surface, we restrict our study to a simplified one-dimensional case. In particular, since the wall thickness is very small compared to the arterial radius, a Cartesian coordinate system is used, with

the  $x$ -axis normal to the layer surface and pointing outwards. Without loss of generality, we assume that  $x = 0$  is the interface and  $l_0$  and  $l_1$  is the thickness of the coating and wall respectively, with  $l_1 \gg l_0$  Fig. (4.1).

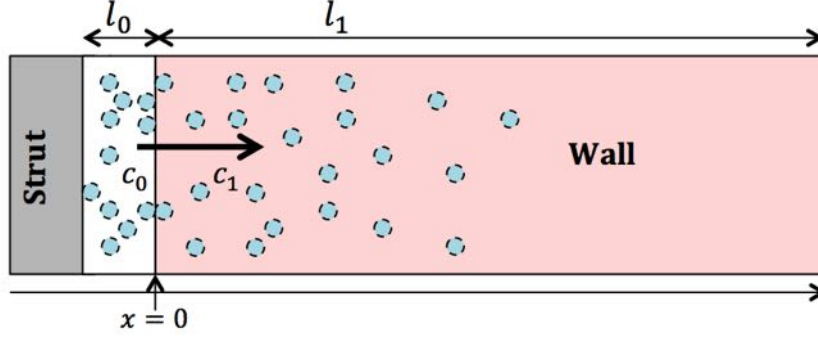


FIGURE 4.1: Cross section of a typical DES, showing the schematic drug release mechanism between coating (layer 0) and wall (layer 1), the geometrical configuration and the reference system. Due to an initial difference of free drug concentrations  $c_0$  and  $c_1$ , a mass flux establishes at the interface and drug diffuses through the wall. Figure not to scale.

#### 4.1.1 Drug dynamics in the coating

Initially, the drug exists in a solid phase, encapsulated within the polymer matrix (e.g. nanoparticles or crystalline form)( $b_0$ ). In such a state, it becomes impossible to be delivered to the tissue [7] [8]. When exposed to biological fluid, as in the in-vivo case, the polymer takes up fluid, initiates the dissolution process, and passes in the free phase ( $c_0$ ), providing a means for the drug to elute from the device. Since the diffusion of drug in the solid phase is negligible, the equations for the drug dynamics in terms of concentrations  $b_0$  and  $c_0$  are given by:

$$\frac{\partial b_0}{\partial t} = -\xi_0 b_0^{\frac{2}{3}}(S - c_0) \quad \text{in } (-l_0, 0) \quad (4.1)$$

$$\frac{\partial c_0}{\partial t} = D_0 \frac{\partial^2 c_0}{\partial x^2} + \xi_0 b_0^{\frac{2}{3}}(S - c_0) \quad \text{in } (-l_0, 0) \quad (4.2)$$

where  $D_0$  ( $cm^2 s^{-1}$ ) is the effective diffusion coefficient of the solute,  $\xi_0$  ( $((mol cm^{-3})^{2/3} s)^{-1}$ ) the dissolution rate and  $S$  is the solubility limit [9].

### 4.1.2 Drug dynamics in the biological tissue

The drug  $c_0$  passes through the interface towards the arterial the wall, the release medium, the free drug ( $c_1$ ) undergoes diffusion and convection due to a pressure difference across the wall. In addition, the drug may bind reversibly to specific components of the cells with a saturable limit. Indeed, a fraction of it ( $b_1$ ) is often targeted to bind to specific receptors on the surface of or within smooth muscle cells. Among several different ways of modelling the binding/unbinding of a drug eluted from DES, we adopt the non-linear saturable binding model presented in [10]. For the purposes of this paper, we make the assumption that the wall comprises a single homogeneous layer with isotropic diffusion properties. The drug transport in the tissue is thus governed by the advection-diffusion reaction equations:

$$\frac{\partial c_1}{\partial t} = D_1 \frac{\partial^2 c_1}{\partial x^2} - v_1 \frac{\partial c_1}{\partial x} - \alpha_1 c_1 (b_{max} - b_1) + \beta_1 b_1 \quad \text{in } (0, l_1) \quad (4.3)$$

$$\frac{\partial b_1}{\partial t} = \alpha_1 c_1 (b_{max} - b_1) - \beta_1 b_1 \quad \text{in } (0, l_1) \quad (4.4)$$

where  $D_1$  is the diffusivity of the unbound drug and  $v_1$  ( $cms^{-1}$ ) is the magnitude of the convection which is assumed to act in the positive  $x$  direction. In the above equations,  $\alpha_1$  ( $(molcm^{-3}s)^{-1}$ ) (resp.  $\beta_1$  ( $s^{-1}$ )) is the forward (resp. backward) rate constant, and  $b_{max}$  the local density of binding sites.

### 4.1.3 Boundary and interface conditions

In order to close the two-layer two-phase mass transfer system of equations (4.1)-(4.4), a matching of fluxes needs to be assigned at the interface between the polymer coating and the tissue i.e.

$$-D_0 \frac{\partial c_0}{\partial x} = -D_1 \frac{\partial c_1}{\partial x} + v_1 c_1 \quad \text{at } x = 0 \quad (4.5)$$

Because of a different drug partitioning between the two layers, the continuity in concentrations is not assured; moreover, a semi-permeable rate-controlling membrane or a non-perfect contact might be present at the interface. Hence, we enforce that the flux is proportional to the concentration jump [3] i.e.

$$-D_1 \frac{\partial c_1}{\partial x} = P(c_0 - c_1) \quad \text{at } x = 0 \quad (4.6)$$

where  $P(\text{cms}^{-1})$  is as defined before, the overall mass transfer coefficient.

No mass flux passes to the outer surrounding due to the impermeable strut ( $x = l_0$ ):

$$-D_0 \frac{\partial c_0}{\partial x} = 0 \quad \text{at } x = -l_0 \quad (4.7)$$

At the other end ( $x = l_1$ ), it is supposed that the concentration vanishes i.e.

$$c_1 = 0 \quad \text{at } x = l_1 \quad (4.8)$$

#### 4.1.4 Initial conditions

For initial conditions, we consider that all drug is at maximum concentration in encapsulated form in the coating, and rest all are zero i.e.

$$b_0(x, 0) = B, \quad c_0(x, 0) = 0, \quad c_1(x, 0) = 0, \quad b_1(x, 0) = 0 \quad (4.9)$$

## 4.2 The dimensionless form

In this section we convert our problem to a dimensionless form which later can be discretized and solved using the same method as used in chapter 2. Therefore, in order to begin we make use of the following dimensionless quantiles:

$$\begin{aligned} \bar{x} &= \frac{x}{l_1}, \quad \bar{t} = \frac{D_1}{(l_1)^2} t, \quad \bar{b}_0 = \frac{b_0}{B}, \quad \bar{S} = \frac{S}{B}, \quad \bar{l}_0 = \frac{l_0}{l_1} \\ \bar{c}_0 &= \frac{c_0}{B}, \quad \bar{b}_1 = \frac{b_1}{B}, \quad \bar{c}_1 = \frac{c_1}{B}, \quad \bar{b}_{max} = \frac{b_{max}}{B}, \quad \phi = \frac{Pl_1}{D_1} \end{aligned} \quad (4.10)$$

Hence, we write eq. (4.1) as :

$$\begin{aligned} \frac{D_1 B}{l_1^2} \frac{\partial \bar{b}_0}{\partial \bar{t}} &= -\xi_0 B^{\frac{2}{3}} \bar{b}_0^{\frac{2}{3}} (B \bar{S} - B \bar{c}_0) \\ \Rightarrow \frac{D_1 B}{l_1^2} \frac{\partial \bar{b}_0}{\partial \bar{t}} &= -\xi_0 B^{\frac{2}{3}} \bar{b}_0^{\frac{2}{3}} B (\bar{S} - \bar{c}_0) \\ \Rightarrow \frac{\partial \bar{b}_0}{\partial \bar{t}} &= \left( -\xi_0 \frac{l_1^2}{D_1} B^{\frac{2}{3}} \right) \bar{b}_0^{\frac{2}{3}} (\bar{S} - \bar{c}_0) \\ \Rightarrow \frac{\partial \bar{b}_0}{\partial \bar{t}} &= -Da \cdot \bar{b}_0^{\frac{2}{3}} (\bar{S} - \bar{c}_0) \end{aligned} \quad (4.11)$$



hence we obtain the dimensionless quantity  $Da = \xi_0 \frac{l_1^2}{D_1} B^{\frac{2}{3}}$  also known as **Damköhler number**<sup>1</sup> and this we use in eq. (4.2) as :

$$\begin{aligned} \frac{BD_1}{l_1^2} \frac{\partial \bar{c}_0}{\partial \bar{t}} &= \frac{BD_0}{l_1^2} \frac{\partial^2 \bar{c}_0}{\partial \bar{x}^2} + \frac{BD_1}{l_1^2} Da \cdot \bar{b}_0^{\frac{2}{3}} (\bar{S} - \bar{c}_0) \\ \Rightarrow \frac{\partial \bar{c}_0}{\partial \bar{t}} &= \frac{D_0}{D_1} \frac{\partial^2 \bar{c}_0}{\partial \bar{x}^2} + Da \cdot \bar{b}_0^{\frac{2}{3}} (\bar{S} - \bar{c}_0) \\ \Rightarrow \frac{\partial \bar{c}_0}{\partial \bar{t}} &= \gamma \frac{\partial^2 \bar{c}_0}{\partial \bar{x}^2} + Da \cdot \bar{b}_0^{\frac{2}{3}} (\bar{S} - \bar{c}_0) \end{aligned} \quad (4.12)$$

from the above equation we get  $\gamma = \frac{D_0}{D_1}$ . Now, from (4.3) we have:

$$\begin{aligned} \frac{BD_1}{l_1^2} \frac{\partial \bar{c}_1}{\partial \bar{t}} &= \frac{BD_1}{l_1^2} \frac{\partial^2 \bar{c}_1}{\partial \bar{x}^2} - v_1 \frac{B}{l_1} \frac{\partial \bar{c}_1}{\partial \bar{x}} - \alpha_1 B \bar{c}_1 (B \bar{b}_{max} - B \bar{b}_1) + \beta_1 B \bar{b}_1 \\ \Rightarrow \frac{\partial \bar{c}_1}{\partial \bar{t}} &= \frac{\partial^2 \bar{c}_1}{\partial \bar{x}^2} - \left( v_1 \frac{l_1}{D_1} \right) \frac{\partial \bar{c}_1}{\partial \bar{x}} - \left( \alpha_1 \frac{l_1^2}{D_1} B \right) \bar{c}_1 (\bar{b}_{max} - \bar{b}_1) + \left( \beta_1 \frac{l_1^2}{D_1} \right) \bar{b}_1 \\ \Rightarrow \frac{\partial \bar{c}_1}{\partial \bar{t}} &= \frac{\partial^2 \bar{c}_1}{\partial \bar{x}^2} - Pe \cdot \frac{\partial \bar{c}_1}{\partial \bar{x}} - \bar{\alpha}_1 \bar{c}_1 (\bar{b}_{max} - \bar{b}_1) + \bar{\beta}_1 \bar{b}_1 \end{aligned} \quad (4.13)$$

Thus, the above equation gives the values for  $\bar{\alpha}_1$ ,  $\bar{\beta}_1$  and another dimensionless quantity  $Pe = v_1 \frac{l_1}{D_1}$  known as **Péclet number**<sup>2</sup>. From the last two terms on the right hand side we get the dimensionless form for eq. (4.4) i.e. :

$$\frac{\partial \bar{b}_1}{\partial \bar{t}} = \bar{\alpha}_1 \bar{c}_1 (\bar{b}_{max} - \bar{b}_1) - \bar{\beta}_1 \bar{b}_1 \quad (4.14)$$

Using the similar calculation we obtain the boundary and interface conditions as:

$$-\gamma \frac{\partial c_0}{\partial x} = -\frac{\partial c_1}{\partial x} + Pe \cdot c_1 \quad \text{at } x = 0 \quad (4.15)$$

$$-\frac{\partial c_1}{\partial x} = \phi(c_0 - c_1) \quad \text{at } x = 0 \quad (4.16)$$

$$\frac{\partial c_0}{\partial x} = 0 \quad \text{at } x = -l_0 \quad (4.17)$$

$$c_1 = 0 \quad \text{at } x = 1 \quad (4.18)$$

<sup>1</sup>The Damköhler number (Da) is a ratio for determining whether diffusion rates or reaction rates are more ‘important’ for defining a steady-state chemical distribution over the length and time scales of interest.

For  $Da \gg 1$  the reaction rate is much greater than the diffusion rate distribution is said to be diffusion limited (diffusion is slowest so diffusion characteristics dominate and the reaction is assumed to be instantaneously in equilibrium). For  $Da \ll 1$  diffusion occurs much faster than the reaction, thus diffusion reaches an ‘equilibrium’ well before the reaction is at equilibrium.

<sup>2</sup> The Péclet number is defined as the ratio of the rate of advection of a physical quantity by the flow to the rate of diffusion of the same quantity.

By omitting the bar for simplicity, we write our system (4.11)-(4.14) as:

$$\frac{\partial b_0}{\partial t} = -Da \cdot b_0^{\frac{2}{3}}(S - c_0) \quad \text{in } (-l_0, 0) \quad (4.19)$$

$$\frac{\partial c_0}{\partial t} = \gamma \frac{\partial^2 c_0}{\partial x^2} + Da \cdot b_0^{\frac{2}{3}}(S - c_0) \quad \text{in } (-l_0, 0) \quad (4.20)$$

$$\frac{\partial c_1}{\partial t} = \frac{\partial^2 c_0}{\partial x^2} - Pe \cdot \frac{\partial c_1}{\partial x} - \alpha_1 c_1(b_{max} - b_1) + \beta_1 b_1 \quad \text{in } (0, 1) \quad (4.21)$$

$$\frac{\partial b_1}{\partial t} = \alpha_1 c_1(b_{max} - b_1) - \beta_1 b_1 \quad \text{in } (0, 1) \quad (4.22)$$

### 4.3 Solving the full coupled system

In this section we convert our problem in a discretized form. As in the chapter 3 we divide our domain  $(-l_0, 0)$  and  $(0, 1)$  with step size  $h_0$  and  $h_1$  respectively (Fig. 3.1). Hence, we have the eq. (4.19)-(4.22) in discrete form as:

$$\frac{\partial b_{0_i}}{\partial t} = -Da \cdot b_{0_i}^{\frac{2}{3}}(S - c_{0_i}) \quad (4.23)$$

$$\frac{\partial c_{0_i}}{\partial t} = \gamma \frac{c_{0_{i+1}} - 2c_{0_i} + c_{0_{i-1}}}{h_0^2} + Da \cdot b_{0_i}^{\frac{2}{3}}(S - c_{0_i}) \quad \forall i = 1, \dots, N-1. \quad (4.24)$$

$$\frac{\partial c_{1_i}}{\partial t} = \frac{c_{1_{i+1}} - 2c_{1_i} + c_{1_{i-1}}}{h_1^2} - Pe \cdot \frac{c_{i+1} - c_{i-1}}{2h_1} - \alpha_1 c_{1_i}(b_{max} - b_{1_i}) + \beta_1 b_{1_i} \quad (4.25)$$

$$\frac{\partial b_{1_i}}{\partial t} = \alpha_1 c_{1_i}(b_{max} - b_{1_i}) - \beta_1 b_{1_i} \quad \forall i = 2, \dots, M. \quad (4.26)$$

At  $x = 0$  no unique value for concentration exists and no derivative can be computed across the interface, due to a possible discontinuity. An alternative procedure is devised to get the concentration values across the interface<sup>3</sup> which makes use of the boundary conditions (4.5) and (4.6) [4] and hence we have:

$$c_l = \frac{1}{\Lambda} \left( \gamma(3 + 2h_1(\phi + Pe))[4c_{0_{N-1}} - c_{0_{N-1}}] + 2h_0\phi[4c_{1_1} - c_{1_2}] \right) \quad (4.27)$$

$$c_r = \frac{1}{\Lambda} \left( (3\gamma + 2h_0\phi)[4c_{1_1} - c_{1_2}] + 2\gamma h_1\phi[4c_{0_{N-1}} - c_{0_{N-1}}] \right) \quad (4.28)$$

where  $\Lambda = 9\gamma + 6\phi(\gamma h_1 + h_0) + 2h_1Pe \cdot (3\gamma + 2h_0\phi)$ . With equations (4.23)-(4.28) our system of PDEs reduces to a system of nonlinear ODE's:

$$\frac{dU}{dt} = A(U)$$

where the vector  $U = (b_{0_1}, \dots, b_{0_{N-1}}, b_{0_-}, c_{0_1}, \dots, c_{0_{N-1}}, c_{1_1}, \dots, c_{1_{M-1}}, b_{1_+}, b_{1_2}, \dots, b_{1_M})$ . Here, the values  $b_{0_-}$  and  $b_{1_+}$  denote the bound concentration values for  $b_0$  (left hand side of interface) and  $b_1$  (right hand side of interface), respectively. Since we know we know  $c_l$

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<sup>3</sup>See appendix A.3.

and  $c_r$  from (4.27) and (4.28) therefore, these values can be easily computed from the following equations:

$$\frac{\partial b_{0-}}{\partial t} = -Da \cdot b_{0-}^{\frac{2}{3}}(S - c_l) \quad (4.29)$$

$$\frac{\partial b_{1+}}{\partial t} = \alpha_1 c_r (b_{max} - b_{1+}) - \beta_1 b_{1+} \quad (4.30)$$

Moreover, the drug masses are computed as integral of concentratoin over the corresponding layer:

$$M_j(t) = \int j(x, t) dx; \quad j = b_0, b_1, c_0, c_1; \quad (4.31)$$

In the discrete version it can be written as:

$$M_j(t) = \sum_i j(x_i) * h_0 \quad j = b_0, c_0 \quad (4.32)$$

$$M_j(t) = \sum_i j(x_i) * h_1 \quad j = b_1, c_1 \quad (4.33)$$

## 4.4 Results

As before, we solve the system of  $M+N-2$  equations with  $M = 1000$ ,  $N = 50$  in MATLAB <sup>4</sup>, the parameters given in the table 4.1 and obtain the results shown in the figures 4.3, 4.2a and 4.2b. Moroeover, the calculation for  $c_l$  and  $c_r$  is done a posteriori using the equations (4.27) and (4.28). The time interval for the run is  $T = T_{max} = 4$  for obtaining the individual concentration profile and for the total masses profile it was chosen as  $T = 100$ . The figures 4.2a and 4.2b show growth and decay of total masses in the coating and in the wall respectively. And, Figure 4.3 has four subfigures, 4.3a, 4.3b, 4.3c and 4.3d showing the concentration profiles of  $c_0$ ,  $b_0$ ,  $c_1$  and  $b_1$  at different times:  $t = 0.1, T_{max}/2, T_{max}$ , respectively.

Moreover, we also examined the dependence of the maximum level of total masses on parameter  $\xi_0$  which in turn determines the Damköhler number (Da). We varied the values of  $\xi_0$  from  $10^{-3}$  to 1  $((molcm^3)^{2/3}s)^{-1}$  and observed that as the value of  $\xi_0$  or Da increases the reaction term gets dominated and hence the accumulation of drug in the wall also increases (Table 4.2).

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<sup>4</sup>See appendix B.3 for MATLAB code

Parameters		
Parameter	Value	Units
$l_0$	$10^{-3}$	$cm$
$l_1$	0.05	$cm$
$B$	$10^{-4}$	$mol\ cm^{-3}$
$S$	$B/10$	$mol\ cm^{-3}$
$b_{max}$	$3.66 \times 10^{-7}$	$mol\ cm^{-3}$
$\alpha_1$	$2 \times 10^6$	$(molcm^{-3}s)^{-1}$
$\xi_0$	1(varied)	$((molcm^3)^{2/3}s)^{-1}$
$\beta_1$	$1.5 * 10^{-4}$	$s^{-1}$
$v_1$	$5 \times 10^{-6}$	$cms^{-1}$
$D_0$	$10^{-12}$	$cm^2/s$
$D_1$	$10^{-7}$	$cm^2/s$
$P$	$10^{-6}$	$cm/s$

TABLE 4.1: Parameters for the nonlinear drug-eluting stent problem

TABLE 4.2: Maximum values for the total masses of drug concentration in coating and wall for different values of  $\xi_0$ .  $M_{b_0}$  ( $= 0.02$ ) is constant and does not have a peak.

Values of peak of total masses w.r.t varying $\xi_0$				
$\xi_0$	$Da$	$Mc_0$	$Mc_1$	$Mb_1$
$10^{-3}$	0.05386	$5.2 \times 10^{-4}$	$3.09 \times 10^{-6}$	$3.55 \times 10^{-4}$
$10^{-2}$	0.5386	0.00152	$3.42 \times 10^{-5}$	0.00184
$10^{-1}$	5.386	0.001829	$8.2194 \times 10^{-5}$	0.00261
1	53.86	0.001929	$8.2617 \times 10^{-5}$	0.00262

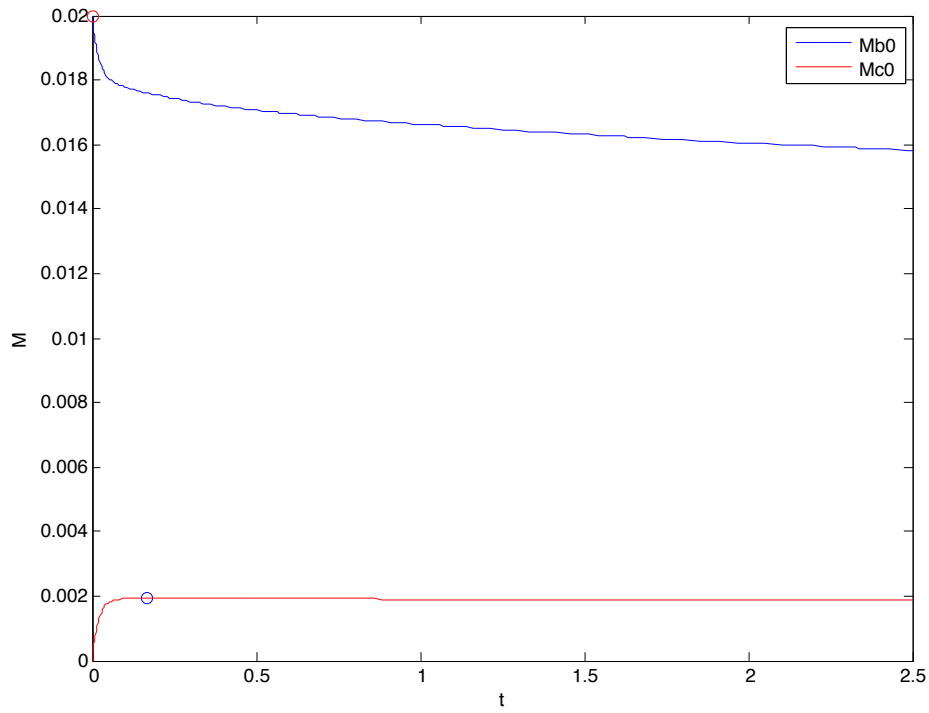
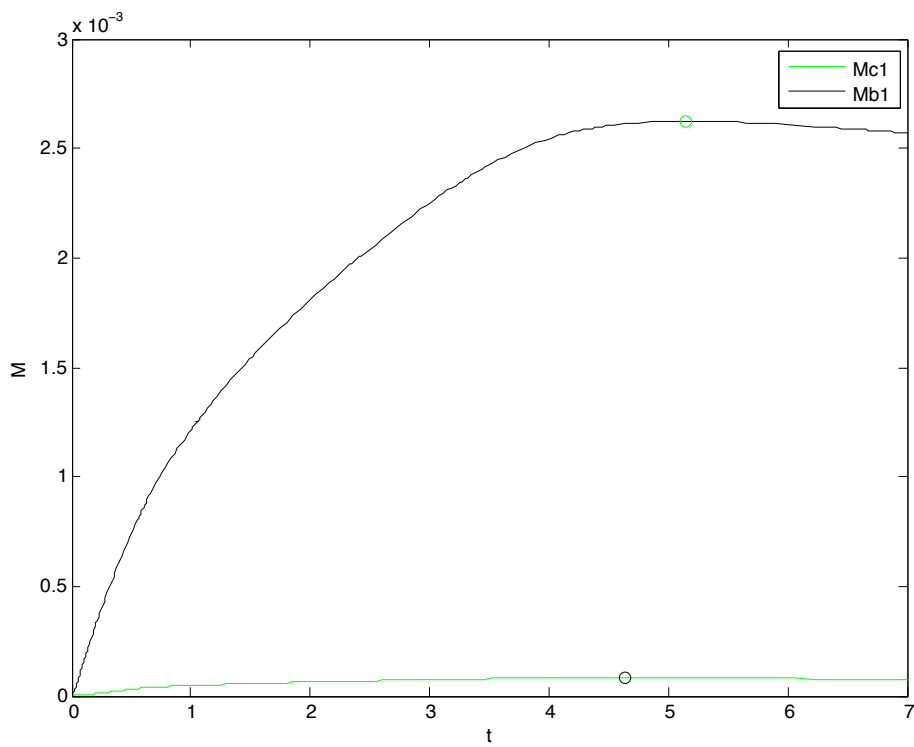
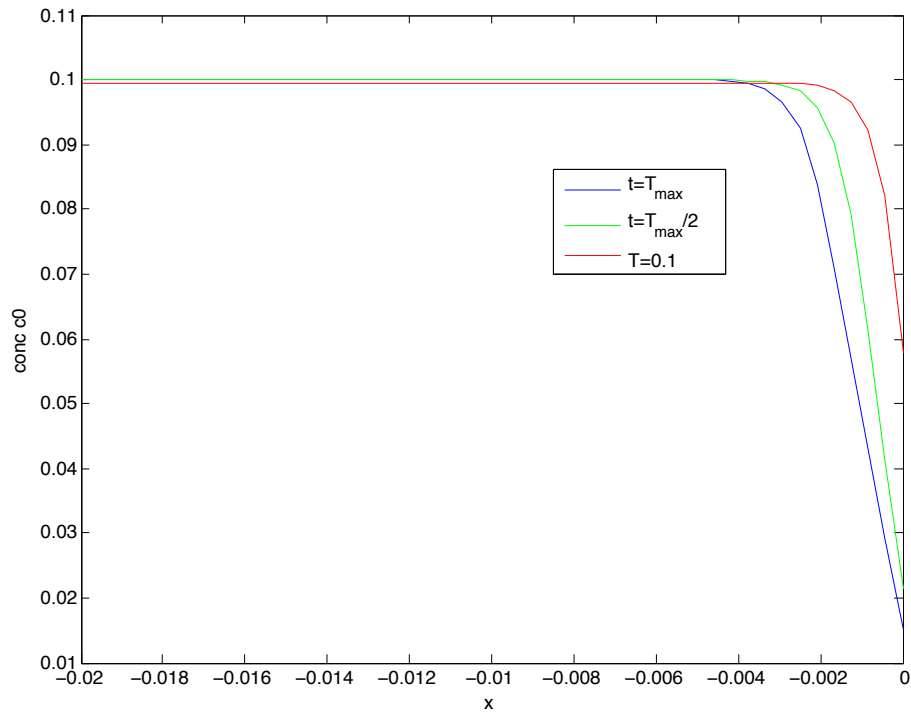
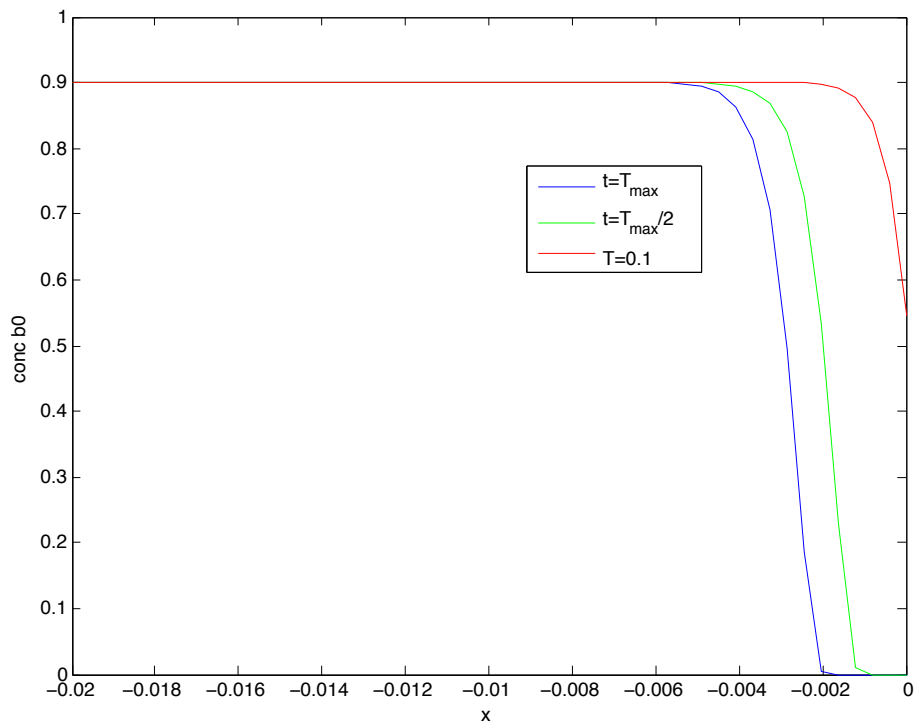
(A) Total masses of  $b_0$  and  $c_0$ (B) Total masses of  $b_1$  and  $c_1$ 

FIGURE 4.2: Time histories of total masses in the wall and in coating.

(A) Concentration  $c_0$ (B) Concentration  $b_0$

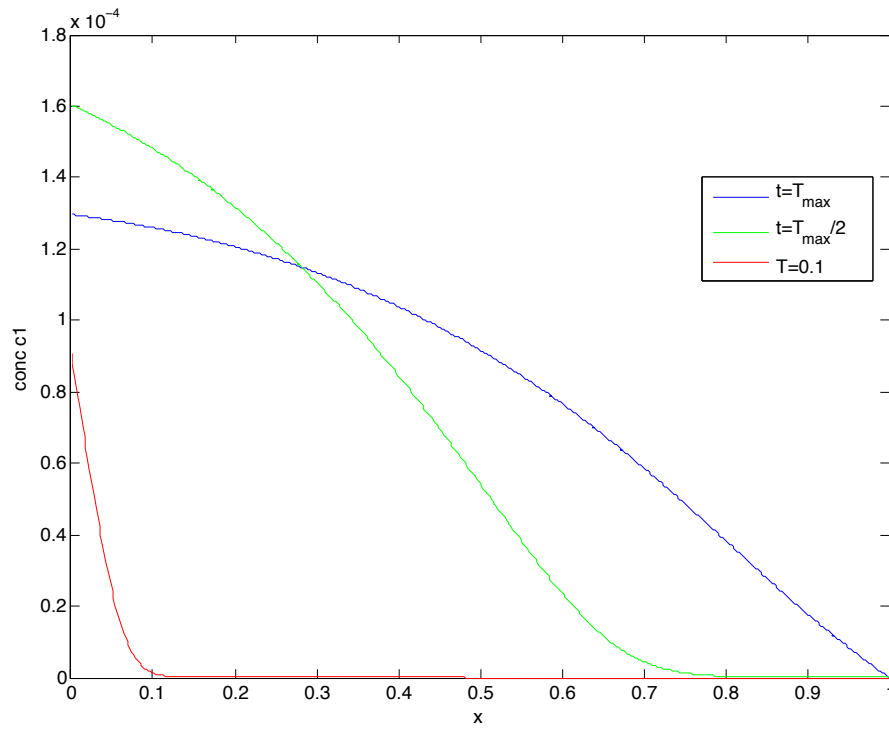
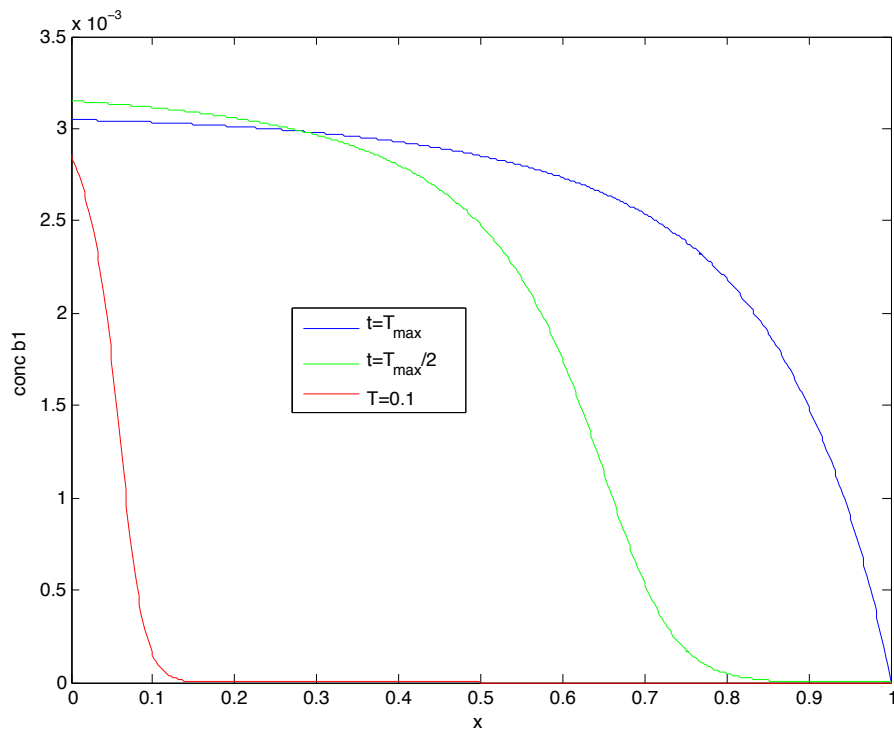
(c) Concentration  $c_1$ (d) Concentration  $b_1$ 

FIGURE 4.3: Plots of individual concentration at different times for the drug eluting stent problem





## Appendix A

# Calculations of the concentration values at interface

### A.1 General case of an interface problem

First we do the calculation steps done for a general problem [4] and then we move on to the drug delivery problem [3] and drug eluting stent problem [8]. Therefore, to begin with we consider the following diagram (Fig. A.1) where we have  $x_i$  as the interface between layer  $i$  and layer  $i+1$ . The domain is discretized with step size  $h_0$ .

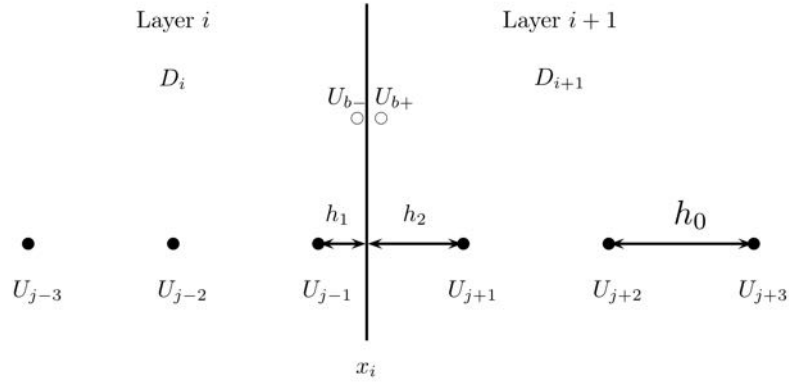


FIGURE A.1: Finite difference scheme indexing, where  $i$  denotes the layer,  $j$  denotes the spatial discretization, and  $b\pm$  denote the points slightly to the positive (right) or negative (left) sides of the interface.  $h_0$  is the distance between the inner spatial discretization,  $h_1$  is the distance between  $U_{j-1}$  and the interface, and  $h_2$  is the distance between the interface and  $U_{j+1}$ .

Now, for this system we have the matching conditions as:

$$k_i \frac{\partial U_i}{\partial x} = H_i (U_{i+1} - U_i) \quad (\text{A.1})$$

$$k_{i+1} \frac{\partial U_{i+1}}{\partial x} = H_i (U_{i+1} - U_i) \quad (\text{A.2})$$

where,  $k_i$  and  $H_i$  are the conductivities and contact transfer coefficient, respectively.

As we see in the figure that the interface point is now split into two points and for these we have two different values of concentrations  $U_{b-}$  and  $U_{b+}$ , values to the left and right side of the interface, respectively. With this convention we write the equations (A.1), (A.2) as:

$$\begin{aligned} k_i \frac{\partial U_{b-}}{\partial x} &= H_i (U_{b+} - U_{b-}) \\ k_{i+1} \frac{\partial U_{b+}}{\partial x} &= H_i (U_{b+} - U_{b-}) \end{aligned} \quad (\text{A.3})$$

Taylor series approximations are taken for  $U_{j-1}$ ,  $U_{j-2}$ ,  $U_{j+1}$  and  $U_{j+2}$  in terms of  $U_{b-}$  and  $U_{b+}$  respectively:

$$\begin{aligned} U_{j-1} &\approx U_{b-} - h_1 \frac{\partial U_{b-}}{\partial x} + \frac{h_1^2}{2} \frac{\partial^2 U_{b-}}{\partial x^2} \\ U_{j-2} &\approx U_{b-} - (h_0 + h_1) \frac{\partial U_{b-}}{\partial x} + \frac{(h_0 + h_1)^2}{2} \frac{\partial^2 U_{b-}}{\partial x^2} \\ U_{j+1} &\approx U_{b+} + h_2 \frac{\partial U_{b+}}{\partial x} + \frac{h_2^2}{2} \frac{\partial^2 U_{b+}}{\partial x^2} \\ U_{j+2} &\approx U_{b+} + (h_0 + h_2) \frac{\partial U_{b+}}{\partial x} + \frac{(h_0 + h_2)^2}{2} \frac{\partial^2 U_{b+}}{\partial x^2} \end{aligned}$$

These, combined with eq. (A.3) give 6 equations with 6 unknowns. We solve this system using MATLAB symbolic calculations<sup>1</sup> that yields:

$$\begin{aligned} U_{b-} = \frac{1}{\Lambda_i} \{ & U_{j-1} [h_0^3 + h_0 h_1^2 + h_0^2 h_1 + 2h_0^2 h_2 + h_1^2 h_2 + h_0^3 h_2 k_2 + h_0^2 h_2^2 k_2 + h_1^2 h_2^2 k_2 + 4h_0 h_1 h_2 \\ & + 2h_0 h_1 h_2^2 k_2 + h_0 h_1^2 h_2 k_2 + 2h_0^2 h_1 h_2 k_2] \\ & + U_{j-2} [-h_0 h_1^2 - 2h_1^2 h_2 - h_1^2 h_2^2 k_2 - h_0 h_1^2 h_2 k_2] \\ & + U_{j+1} [h_0^3 h_1 k_1 + h_0^2 h_1^2 k_1 + h_1^2 h_2^2 k_1 + h_0 h_1 h_2^2 k_1 + 2h_0 h_1^2 h_2 k_1 + 2h_0^2 h_1 h_2 k_1] \\ & + U_{j+2} [-h_1^2 h_2^2 k_1 - h_0 h_1 h_2^2 k_1] \} \end{aligned} \quad (\text{A.4})$$

---

<sup>1</sup>See appendix B.4

with  $\Lambda_i$  is given by:

$$\begin{aligned}\Lambda_i = & h_0\{2h_2(h_0 + 2h_1) + h_0(h_0 + 2h_1) + \frac{H_i}{k_i}[h_0h_1(h_0 + h_1) + 2h_1h_2(h_0 + h_1)] \\ & + \frac{H_i}{k_{i+1}}[h_0h_2(h_0 + h_2) + 2h_1h_2(h_0 + h_2)]\}\end{aligned}\quad (\text{A.5})$$

where  $k_1 = \frac{H_i}{k_i}$  and  $k_2 = \frac{H_i}{k_{i+1}}$  which are different from  $k_i$  and  $k_{i+1}$ .

Similar expression is obtained for  $U_{b+}$ . We simplify the above expression and obtain:

$$\begin{aligned}U_{b-} = & \frac{1}{\Lambda_i}U_{j-1}[(h_0 + h_1)^2(h_2 + h_2^2\frac{H_i}{k_{i+1}}) + h_0h_2\frac{H_i}{k_{i+1}}(h_0^2 + 2h_1^2) + h_0^2(h_0 + h_1 + h_2) + h_0h_1^2 \\ & + 2h_0h_1h_2(1 + h_0\frac{H_i}{k_{i+1}})] \\ & + U_{j-2}[-\frac{h_1^2}{k_{i+1}}\{(k_{i+1} + h_2H_i)(h_0 + h_2) + h_2k_{i+1}\}] \\ & + U_{j+1}[\frac{H_i}{k_{i+1}}\{h_1(h_0 + h_1)(h_0 + h_2)^2\}] \\ & + U_{j+2}[-h_1h_2^2\frac{H_i}{k_i}(h_0 + h_1)]\end{aligned}\quad (\text{A.6})$$

with

$$\begin{aligned}\Lambda_i = & \frac{h_0}{k_ik_{i+1}}\{[(h_0 + h_2)(h_0 + 2h_1)h_2k_i + (h_0 + h_1)(h_0 + 2h_2)h_1k_{i+1}]H_i \\ & + (h_0 + 2h_1)(h_0 + 2h_2)k_ik_{i+1}\}\end{aligned}\quad (\text{A.7})$$

## A.2 Drug delivery problem

This section considers the transdermal drug delivery problem (chapter 2) and describes the similar calculations as done in previous section. The calculations will be different because in the current problem we have different interface conditions as compared to the previous section.

Thus, at the interface from eq. (2.10) and (2.11) we have:

$$\begin{aligned}\gamma\frac{\partial c_0}{\partial x} &= \frac{\partial c_1}{\partial x} \\ -\frac{\partial c_1}{\partial x} &= \phi(c_0 - c_1)\end{aligned}\quad (\text{A.8})$$

where the parameters are same as defined as in chapter 3 . The point on the left hand side of interface corresponding to  $c_0$  is denoted by  $c_{b-}$  and the same on right hand side of interface is called as  $c_{b+}$ . The two-phase domain is discretized with a step size of  $h_0$

and  $h_1$  as shown in the Fig. (3.1). This notation converts eq. (A.8) as:

$$\begin{aligned}\frac{\partial c_{b+}}{\partial x} - \gamma \frac{\partial c_{b-}}{\partial x} &= 0 \\ \frac{\partial c_{b+}}{\partial x} + \phi(c_{b-} - c_{b+}) &= 0\end{aligned}\tag{A.9}$$

As before, the Taylor's series approximatoin is:

$$\begin{aligned}c_{0_{N-1}} &\approx c_l - h_0 \frac{\partial c_l}{\partial x} + \frac{h_0^2}{2} \frac{\partial^2 c_l}{\partial x^2} \\ c_{0_{N-2}} &\approx c_l - 2h_0 \frac{\partial c_l}{\partial x} + 2h_0^2 \frac{\partial^2 c_l}{\partial x^2} \\ c_{1_1} &\approx c_r + h_1 \frac{\partial c_r}{\partial x} + \frac{h_1^2}{2} \frac{\partial^2 c_r}{\partial x^2} \\ c_{1_2} &\approx c_r + 2h_1 \frac{\partial c_r}{\partial x} + 2h_1^2 \frac{\partial^2 c_r}{\partial x^2}\end{aligned}$$

Again, combining the equations above and eq. (A.9) we have a  $6 \times 6$  system which we solve using MATLAB symbolic calculations<sup>2</sup> as we did before and obtain :

$$\begin{aligned}c_l &= \frac{1}{\Lambda} \{-c_{0_{N-2}}[\gamma(2\phi h_1 + 3)] + c_{0_{N-1}}[4\gamma(2\phi h_1 + 3)] \\ &\quad + c_{1_1}(8\phi h_0) - c_{1_2}(2\phi h_0)\}\end{aligned}\tag{A.10}$$

and

$$\begin{aligned}c_r &= \frac{1}{\Lambda} \{-c_{0_{N-2}}(2\phi\gamma h_1) + c_{0_{N-1}}(8\gamma\phi h_1) \\ &\quad + c_{1_1}(4(2\phi h_0 + 3\gamma)) - c_{1_2}(2\phi h_0 + 3\gamma)\}\end{aligned}\tag{A.11}$$

with  $\Lambda = 9\gamma + 6\phi(h_0 + \gamma h_1)$ .

### A.3 Drug-eluting stent problem

In this section, we perform same calculations for the drug-eluting stent problem. As we have seen from chapter 4 that the interface conditions are given from eq. (4.15) and (4.16) as:

$$-\gamma \frac{\partial c_0}{\partial x} = -\frac{\partial c_1}{\partial x} + Pe \cdot c_1 \quad \text{at } x = 0 \tag{A.12}$$

$$-\frac{\partial c_1}{\partial x} = \phi(c_0 - c_1) \quad \text{at } x = 0 \tag{A.13}$$

---

<sup>2</sup>See appendix B.4

The parameters and concentration values  $c_l$ ,  $c_r$  are same as defined in the chapter 4. With this we write the above equations as:

$$-\gamma \frac{\partial c_l}{\partial x} = -\frac{\partial c_r}{\partial x} + Pe \cdot c_r \quad \text{at } x = 0 \quad (\text{A.14})$$

$$-\frac{\partial c_r}{\partial x} = \phi(c_l - c_r) \quad \text{at } x = 0 \quad (\text{A.15})$$

The Taylor series apporixmation for  $c_{0_{N-1}}$ ,  $c_{0_{N-2}}$ ,  $c_{1_1}$  and  $c_{1_2}$  in terms of  $c_l$  and  $c_r$  (Fig. 3.1) are expressed as:

$$\begin{aligned} c_{0_{N-1}} &\approx c_l - h_0 \frac{\partial c_l}{\partial x} + \frac{h_0^2}{2} \frac{\partial^2 c_l}{\partial x^2} \\ c_{0_{N-2}} &\approx c_l - 2h_0 \frac{\partial c_l}{\partial x} + 2h_0^2 \frac{\partial^2 c_l}{\partial x^2} \\ c_{1_1} &\approx c_r + h_1 \frac{\partial c_r}{\partial x} + \frac{h_1^2}{2} \frac{\partial^2 c_r}{\partial x^2} \\ c_{1_2} &\approx c_r + 2h_1 \frac{\partial c_r}{\partial x} + 2h_1^2 \frac{\partial^2 c_r}{\partial x^2} \end{aligned}$$

From these equations and from (A.14), (A.15) we have a system of 6 equations and 6 unknowns, which upon solving with MATLAB symbolic calculations<sup>3</sup> gives:

$$\begin{aligned} c_l &= \frac{1}{\Lambda} \left( \gamma(3 + 2h_1(\phi + Pe))[4c_{0_{N-1}} - c_{0_{N-2}}] + 2h_0\phi[4c_{1_1} - c_{1_2}] \right) \\ c_r &= \frac{1}{\Lambda} \left( (3\gamma + 2h_0\phi)[4c_{1_1} - c_{1_2}] + 2\gamma h_1\phi[4c_{0_{N-1}} - c_{0_{N-2}}] \right) \end{aligned}$$

where  $\Lambda = 9\gamma + 6\phi(\gamma h_1 + h_0) + 2h_1 Pe \cdot (3\gamma + 2h_0\phi)$ .

---

<sup>3</sup>See appendix B.4



## Appendix B

# MATLAB codes

### B.1 Code for chapter 2

Following MATLAB code is used for solving the drug delivery problem and obtaining the results in chapter 2:

---

```
%% The codes solves the dimensionless form drug delivery problem (linear)
%% Results displayed in chapter 2
close all;
clear all;
%% Parameters
tic
fprintf('\n \n Program running...');
M = 1000;           %mesh size
N = 50;
l_0 = 40*10^-4;     %length of domain in layer I in centimeters
l_1 = .1;           %length of domain in layer II in centimeters
h_1 = l_0/N;        % space step size in layer I
h_2 = l_1/(M-N);    % space step size in layer II
k = 0.1;            % time step size
theta = 0.3;
beta_0 = 1*10^-4;
beta_1 = 1.5*10^-4;
delta_0 = 1*10^-4;
delta_1 = 1*10^-4;
D_0 = 5*10^-7;      % Diffusion parameter in layer I
D_1 = 7*10^-8;      % Diffusion parameter in layer II
K_cl = 3*10^-3;
P = 1*10^-6;
T = 2.5*10^5*4/7; % Set Time of run
T = round(T);
Tk = T/k;
TL = D_1*T/l_1^2;
num= 0;
Ce = 1;
ce = ones(N-1,1); % defined with initial data and one dimension less than c0
```

```

                                % since we don't take it's value at the interface
ce = ce*Ce;
c0 = zeros(N,1);    % defined with initial data

cb = zeros(M-N,1);    % one dimension less than c1 because we don't consider it on interface
c1 = zeros(M-N+1,1); % defined with initial data
A1 = zeros(M+1,M+1);  % tridiagonal matrix on LHS
B1 = zeros(M+1,M+1);  % tridiagonal matrix on RHS

mcb = zeros(Tk,1);    % Total mass for cb
mce = zeros(Tk,1);    % Total mass for ce
mc1 = zeros(Tk,1);    % Total mass for c1
mc0 = zeros(Tk,1);    % Total mass for c0

%% dimensionless parameters
h_1L = h_1/l_1;
h_2L = h_2/l_1;
kL = k*D_1/l_1^2;
l_0L = l_0/l_1;
phi = P*l_1/D_1;
gamma = D_0/D_1;
K = K_c1*l_1/D_1;
dum1 = l_1^2/D_1;
beta_0L = beta_0*dum1;
beta_1L = beta_1*dum1;
delta_1L = delta_1*dum1;
delta_0L = delta_0*dum1;
ceL = ce/Ce;
c0L = c0/Ce;
c1L = c1/Ce;
cbL = cb/Ce;

%% Main
%definition of A(for phase I)
dum2 = kL*theta*gamma/h_1L^2;

A1(1,1) = 1 +2*dum2;
A1(1,2) = -2*dum2;
for i = 2 : N-1
    A1(i,i-1) = -dum2;
    A1(i,i) = A1(1,1);
    A1(i,i+1) = A1(i,i-1);
end
% Nth row(for the interface)
dum3 = gamma*h_2L;
A1(N,N-1) = -dum3;
A1(N,N) = dum3;
A1(N,N+1) = h_1L;
A1(N,N+2) = -h_1L;
% N+1 th row(for the interface)
dum4 = phi*h_2L;
A1(N+1,N) = dum4;
A1(N+1,N+1) = -dum4 - 1;
A1(N+1,N+2) = 1;

```



```

% for the remaining part(for phase II)
dum5 = kL*theta/h_2L^2;
for i = N+2:M
    A1(i,i-1) = -dum5;
    A1(i,i) = 1 + 2*dum5;
    A1(i,i+1) = A1(i,i-1);
end
A1(M+1,M) = -2*dum5;
A1(M+1,M+1) = 1+2*dum5+2*kL*K*theta/h_2L;
%% For the RHS matrix B
dum6 = kL*(1-theta)*gamma/h_1L^2;
B1(1,1) = 1 - 2*dum6 - delta_0L*kL;    % use of delta_0
B1(1,2) = 2*dum6;

for i = 2 : N-1
    B1(i,i-1) = dum6;
    B1(i,i) = B1(1,1);    % use of delta_0
    % B1(i,i) = B1(1,1) - dum6;    % use of delta_0
    B1(i,i+1) = B1(i,i-1);
end
% Nth row(for the interface)
% N+1 th row(for the interface)

% for the remaining part(for phase II)
dum7 = kL*(1-theta)/h_2L^2;
for i = N+2:M
    B1(i,i-1) = dum7;
    B1(i,i) = 1 - 2*dum7 - beta_1L*kL;    % use of beta_1
    B1(i,i+1) = B1(i,i-1);
end
B1(M+1,M) = 2*dum7;
B1(M+1,M+1) = 1-beta_1L*kL- 2*dum7 - 2*kL*K*(1-theta)/h_2L;

%% for the vector on the RHS
t = 0;
while t < TL-kL
    z = zeros(M+1,1);
    z(1:N-1) = kL*beta_0L*ceL(1:N-1);    % use of beta_0
    z(N,1) = 0;
    z(N+1,1) = 0;
    z(N+2:M+1) = kL*delta_1L*cbL(1:M-N);    %use of delta_1
    % the unknown vector x
    x = zeros(M+1,1);    %composed of c0 and c1
    x = c0L;
    x(N+1:M+1) = c1L(1:M-N+1);
    %% Final expression
    z;
    x = A1\B1*x + A1\z;
    c0L(1:N) = x(1:N);
    c1L(1:M-N+1) = x(N+1:M+1);

%update cb
for i = 1 : M-N

```

---

```

cbL(i) = cbL(i)*(1-kL*delta_1L)+ kL*beta_1L*c1L(i);
end
%update ce
for i = 1 : N-1
ceL(i) = ceL(i)*(1-kL*beta_0L) + delta_0L *kL*c0L(i);
end
t = t+kL;

num = num+1;

mce(num) = sum(ceL(:))*h_1L;
mc0(num) = sum(c0L(:))*h_1L;
mcb(num) = sum(cbL(:))*h_2L;
mc1(num) = sum(c1L(:))*h_2L;
end
%% Plots
x1=linspace(0,1,M-N+1);
x2=linspace(0,1,M-N);
x3=linspace(-l_0L,0,N-1);
x4=linspace(-l_0L,0,N);
ts = linspace(0,T,Tk);
plot(x1,c1L)
figure;
plot(x2,cbL)
figure;
plot(x3,ceL)
figure;
plot(x4,c0L)
figure;
plot(ts,mcb,'r',ts,mce,'g',ts,mc0,'b',ts,mc1,'k')
axis([0 T 0 0.04])
fprintf('\n \n Program terminated!!');
toc

```

---

## B.2 Code for chapter 3

Following MATLAB code solves the drug delivery problem with the new method that uses the MATLAB solver ODE15s in it:

---

```

%% The program solves the drug delivery problem using MATLAB ode solver ODE 15s
tic;
close all;
clear all;
fprintf('\n \n Program running...');
%% Parameters
N = 50;           % mesh size in layer I
M = 1000;         % mesh size in layer II
l_0 = 40*10^-4;   % length of domain in layer I in centimeters
l_1 = .1;         % length of domain in layer II in centimeters
h_1 = l_0/N;      % space step size in layer I
h_2 = l_1/M;      % space step size in layer II
beta_0 = 1*10^-4;

```

```

beta_1 = 1.5*10^-4;
delta_0 = 1*10^-4;
delta_1 = 1*10^-4;
D_0 = 5*10^-7;      % Diffusion parameter in layer I
D_1 = 7*10^-8;      % Diffusion parameter in layer II
K_cl = 3*10^-3;
P = 1*10^-6;
T = 1;
h1 = h_1/l_1;
h2 = h_2/l_1;
para = [N M l_0 l_1 h_1 h_2 beta_0 beta_1 delta_0 delta_1 D_0 D_1 K_cl P];

%% Setting the Initial condition
v0 = [ones(1,N),zeros(1,N-1),zeros(1,M-1),zeros(1,M)];
tspan = [0; T];

%% Call of the function ODE15s
[t,v] = ode15s(@funlin,tspan,v0,'options',para);

%% recording value at t = 0.01
t1=t(t>0.01);
a=min(t1);
b=find(t==a);
vT1 = v(b,:);
vT1 = vT1';
v1T1=vT1(1:N,:);
v2T1=vT1(N+1:2*N-1,:);
v3T1=vT1(2*N:2*N-1+M-1,:);
v4T1=vT1(2*N-1+M:2*N-2+2*M,:);

%% recording the values for t = 0.1
t1=t(t>0.1);
a=min(t1);
b=find(t==a);
vT2 = v(b,:);
vT2 = vT2';
v1T2=vT2(1:N,:);
v2T2=vT2(N+1:2*N-1,:);
v3T2=vT2(2*N:2*N-1+M-1,:);
v4T2=vT2(2*N-1+M:2*N-2+2*M,:);

%% Recording values of ce and c0 at time T
it = size(t);
vT = v(it(1),:);
vT = vT';
v1T=vT(1:N,:); %ce
v2T=vT(N+1:2*N-1,:); %c0
v3T=vT(2*N:2*N-1+M-1,:); %c1
v4T=vT(2*N-1+M:2*N-2+2*M,:); %cb
v = v';
v1=v(1:N,:);
v2=v(N+1:2*N-1,:);
v3=v(2*N:2*N-1+M-1,:);
v4=v(2*N-1+M:2*N-2+2*M,:);

```

```

%% Plot
x1 = linspace(0,0.04,N);
x2 = linspace(0,0.04,N-1);
x3 = linspace(0,1,M-1);
x4 = linspace(0,1,M);
% subplot(2,2,1);
figure;
x1 = -x1;
v1T = v1T*10^5;
v1T = round(v1T);
v1T = v1T*10^-5;
plot(x1,v1T,'b',x1,v1T1,'g',x1,v1T2,'r');
legend('T=1','T=0.01','T=0.1','Location','Best');
xlabel('x');
ylabel('conc ce');
title('plot for ce');
axis([-0.04 0 0 1])
% xlim([-0.04 0])
figure;
% subplot(2,2,2);
x2 = -x2;
v2T = v2T*10^5;
v2T = round(v2T);
v2T = v2T*10^-5;
plot(x2,v2T,'b',x2,v2T1,'g',x2,v2T2,'r');
legend('T=1','T=0.01','T=0.1','Location','Best');
xlabel('x');
ylabel('conc c0');
title('plot for c0');
axis([-0.04 0 0 0.2])
figure;
% subplot(2,2,3);
plot(x3,v3T,'b',x3,v3T1,'g',x3,v3T2,'r');
legend('T=1','T=0.01','T=0.1','Location','Best');
xlabel('x');
ylabel('conc c1');
title('plot for c1');
axis([0 1 0 0.05])
figure;
% subplot(2,2,4);
plot(x4,v4T,'b',x4,v4T1,'g',x4,v4T2,'r');
legend('T=1','T=0.01','T=0.1','Location','Best');
xlabel('x');
ylabel('conc cb');
title('plot for cb');
axis([0 1 0 0.05])
s1 = sum(v1)*h1;
s2 = sum(v2)*h1;
s3 = sum(v3)*h2;
s4 = sum(v4)*h2;
figure;
plot(t,s1,'b',t,s2,'r',t,s3,'g',t,s4,'k')
legend('Mc0','Mb0','Mc1','Mb1')
xlabel('time');
ylabel('Total mass');

```

---

```

title('Total Mass v/s Time')
fprintf('\n \n Program terminated!!');
toc;

```

---

```

function dUdt = gun(t,U,para)
%% Extract the parameters
N = para(1);
M = para(2);
l_0 = para(3);
l_1 = para(4);
h_1 = para(5);
h_2 = para(6);
beta_0 = para(7);
beta_1 = para(8);
delta_0 = para(9);
delta_1 = para(10);
D_0 = para(11);
D_1 = para(12);
K_cl = para(13);
P = para(14);

%% dimensionaless parameters
h1 = h_1/l_1;
h2 = h_2/l_1;
% k = k*D_1/l_1^2;
% l_0 = l_0/l_1;
phi = P*l_1/D_1;
gamma = D_0/D_1 ;
K = K_cl*l_1/D_1;
dum1 = l_1^2/D_1;
beta_0 = beta_0*dum1;
beta_1 = beta_1*dum1;
delta_1 = delta_1*dum1;
delta_0 = delta_0*dum1;

Lambda = 9*gamma+6*phi*(h1+gamma*h2);
chi = gamma/h1^2;
psi = 1/h2^2;
%% extracting the value of concentration
len1 = N;
len2 = M;
len3 = 2*N;
len4 = 2*M;

ce = U(1:len1,:);
c0 = U(len1+1:len3-1,:);

c1 = U(len3:len3+len2-2,:);
cb = U(len3+len2-1:len3+len4-2,:);

% Main
%% At the boundary i = 1
i = 1;
    dUdt(i,:) = -beta_0*ce(i)+delta_0*c0(i);
    dUdt(len1+i,:) = chi*(2*c0(i+1)-2*c0(i))+beta_0*ce(i)-delta_0*c0(i);

```

---

```

%% Inside the drug layer
for i = 2 : len1-2
    dUdt(i,:) = -beta_0*ce(i)+delta_0*c0(i);
    dUdt(len1+i,:) = chi*(c0(i+1)- 2*c0(i)+ c0(i-1))+beta_0*ce(i)-delta_0*c0(i);
end

%% The LHS interface point N-1
i = len1-1;
dUdt(i,:) = -beta_0*ce(i)+delta_0*c0(i);

c1 = (gamma*(2*phi*h2+3)*(-c0(N-2)+4*c0(N-1))...
      +2*phi*h1*(4*c1(2)-c1(3)))/Lambda;
%the interface point i = N

dUdt(len1+i,:) = chi*(c1- 2*c0(i)+ c0(i-1))+beta_0*ce(i)-delta_0*c0(i); % for i = N-1

%evaluting ce at interface
i = len1;
dUdt(i,:) = -beta_0*ce(i)+delta_0*c1;

%% The RHS interface point 1

cr = (2*gamma*phi*h2*(4*c0(N-1)-c0(N-2))...
      +(2*phi*h1+3*gamma)*(4*c1(1)-c1(2)))/Lambda;

i = 1;
dUdt(len3+len2-2+i,:) = beta_1*cr-delta_1*cb(i);
i = 2;
j = i-1;

dUdt(len3,:) = psi*(c1(j+1)-2*c1(j)+cr)-beta_1*c1(j)+delta_1*cb(i);
dUdt(len3+len2+i-2,:) = beta_1*c1(j)-delta_1*cb(i);

%% Inside the skin layer
for i = 3 : len2-1
    j = i-1;
    dUdt(len3+i-2,:) = psi*(c1(j+1)-2*c1(j)+c1(j-1))-beta_1*c1(j)+delta_1*cb(i);
    dUdt(len3+len2+i-2,:) = beta_1*c1(j)-delta_1*cb(i);
end
%% At boundary i = M
i = len2;
j = i-1;
dUdt(len3+i-2,:) = psi*(2*c1(len2-2)-(2+K*h2)*c1(len2-1))-beta_1*c1(j)+delta_1*cb(i);
dUdt(len3+len2+i-2,:) = beta_1*c1(j)-delta_1*cb(i);

```

---

### B.3 Code for chapter 4

Following code solves the drug eluting stent problem:

---

```

%% Call of function ODE15s
% function RD

```

```

tic
close all;
clear all;
fprintf('\n \n Program running...');
%% Parameters
N = 50;                % mesh size in layer I
M = 1000;              % mesh size in layer II
l_0 = 10^-3;           % length of domain in layer I in centimeters
l_1 = .05;             % length of domain in layer II
h_1 = l_0/N;           % space step size in layer II
h_2 = l_1/M;           % space step size in layer II
bmax = 3.66*10^-7;
B = 10^-4;             %Initial concentration value
S = B/10;
gamma_0 = 1;
D_0 = 10^-12;          % Diffusion parameter in layer I
D_1 = 10^-7;           % Diffusion parameter in layer II in centimeters
alpha_1 = 2*10^6;
beta_1 = 5.2*10^-3;
v_1 = 5*10^-6;
K_cl = 3*10^-3;
P = 1*10^-6;
T = 7;                 % Total time of run
h1 = h_1/l_1;
h2 = h_2/l_1;
para = [N M l_0 l_1 h_1 h_2 alpha_1 beta_1 D_0 D_1 K_cl P bmax ...
        B S gamma_0 v_1]; %17 element array

%% Setting the Initial condition
v0 = [ones(1,N),zeros(1,N-1),zeros(1,M-1),zeros(1,M)];
tspan = [0; T];
options = odeset('RelTol',1e-6,'Abstol',1e-10);

%% Call of the function ODE15s
[t,v] = ode15s(@funNonlin,tspan,v0,'options',para);

%% Recording values of ce and c0 at time T
% recording value at t = T/2
t1=t(t>T/2);
a=min(t1);
b=find(t==a);
vT1 = v(b,:);
vT1 = vT1';
v1T1=vT1(1:N,:);      %b0
v2T1=vT1(N+1:2*N-1,:); %c0
v3T1=vT1(2*N:2*N-1+M-1,:); %c1
v4T1=vT1(2*N-1+M:2*N-2+2*M,:); %b1

% recording value at t = 0.1
t1=t(t>0.1);
a=min(t1);
b=find(t==a);
vT2 = v(b,:);
vT2 = vT2';
v1T2=vT2(1:N,:);      %b0

```

```

v2T2=vT2(N+1:2*N-1,:);          %c0
v3T2=vT2(2*N:2*N-1+M-1,:);      %c1
v4T2=vT2(2*N-1+M:2*N-2+2*M,:);  %b1

% recording the values for t = 0
v0 = v0';
v1T0=v0(1:N,:);
v2T0=v0(N+1:2*N-1,:);
v3T0=v0(2*N:2*N-1+M-1,:);
v4T0=v0(2*N-1+M:2*N-2+2*M,:);

%% Recording values of ce and c0 at time T
it = size(t);
vT = v(it(1),:);
vT = vT';
v1T=vT(1:N,:);                  %ce
v2T=vT(N+1:2*N-1,:);            %c0
v3T=vT(2*N:2*N-1+M-1,:);        %c1
v4T=vT(2*N-1+M:2*N-2+2*M,:);    %cb

v = v';
v1=v(1:N,:);
v2=v(N+1:2*N-1,:);
v3=v(2*N:2*N-1+M-1,:);
v4=v(2*N-1+M:2*N-2+2*M,:);

%% Plots for individual concentrations
x1 = linspace(-0.02,0,N);
x2 = linspace(-0.02,0,N-1);
x3 = linspace(0,1,M-1);
x4 = linspace(0,1,M);

plot(x1,v1T,'b',x1,v1T1,'g',x1,v1T2,'r');
legend('t=T_{max}','t=T_{max}/2','T=0.1','Location','Best');
xlabel('x');
ylabel('conc b0');
title('plot for b0');
axis([-0.02 0 0 1])
figure;

plot(x2,v2T,'b',x2,v2T1,'g',x2,v2T2,'r');
legend('t=T_{max}','t=T_{max}/2','T=0.1','Location','Best');
xlabel('x');
ylabel('conc c0');
title('plot for c0');
figure;

plot(x3,v3T,'b',x3,v3T1,'g',x3,v3T2,'r');
legend('t=T_{max}','t=T_{max}/2','T=0.1','Location','Best');
xlabel('x');
ylabel('conc c1');
title('plot for c1');
figure;

```



---

```

plot(x4,v4T,'b',x4,v4T1,'g',x4,v4T2,'r');
legend('t=T_{max}','t=T_{max}/2','T=0.1','Location','Best');
xlabel('x');
ylabel('conc b1');
title('plot for b1');

s1 = sum(v1)*h1; %b0
s2 = sum(v2)*h1; %c0
s3 = sum(v3)*h2; %b1
s4 = sum(v4)*h2; %c1

%% checking the peaks of total masses
s11 = max(s1);
c = find(s1==s11);
t11 = t(c);

s12 = max(s2);
c = find(s2==s12);
t12 = t(c);

s13 = max(s3);
c = find(s3==s13);
t13 = t(c);

s14 = max(s4);
c = find(s4==s14);
t14 = t(c);

figure;
plot(t,s1,'b',t,s2,'r')
hold on;
plot(t11,s11,'ro',t12,s12,'bo')
legend('Mb0','Mc0')
xlabel('time');
ylabel('Total mass');
title('Total Mass v/s Time')

figure;
plot(t,s3,'g',t,s4,'k')
hold on;
plot(t13,s13,'ko',t14,s14,'go')
legend('Mc1','Mb1')
xlabel('time');
ylabel('Total mass');
title('Total Mass v/s Time')
fprintf('\n \n Program terminated!!');
toc

function dUdt = funNonlin(t,U,para)

%% Extract the parameters
N = para(1);
M = para(2);
l_0 = para(3);
l_1 = para(4);

```

---

```

h_1 = para(5);
h_2 = para(6);
alpha_1 = para(7);
beta_1 = para(8);
D_0 = para(9);
D_1 = para(10);
K_c1 = para(11);
P = para(12);
bmax = para(13);
B = para(14);
S = para(15);
gamma_0 = para(16);
v_1 = para(17);

%% dimensionless parameters
h1 = h_1/l_1;
h2 = h_2/l_1;
l_0 = l_0/l_1;
phi = P*l_1/D_1;
xi = D_0/D_1;
K = K_c1*l_1/D_1;
dum1 = l_1^2/D_1;
alpha_1 = alpha_1*dum1*B;
beta_1 = beta_1*dum1;
v_1 = v_1*l_1/D_1;
exp = 2/3;
gamma_0 = gamma_0*dum1*B^exp;
S = S/B;
bmax = bmax/B;
Lambda = 9*xi+6*phi*(xi*h2+h1)+2*h2*v_1*(3*xi+2*h1*phi);
chi = xi/h1^2;
psi = 1/h2^2;

%% extracting the value of concentration
len1 = N;
len2 = M;
len3 = 2*N;
len4 = 2*M;
b0 = U(1:len1,:);
c0 = U(len1+1:len3-1,:);
c1 = U(len3:len3+len2-2,:);
b1 = U(len3+len2-1:len3+len4-2,:);

% cut off round off errors
for i=1:len1
if (b0(i) <= 10^-12), b0(i)=0; end;
end
dUdt = zeros(len4,size(U,2));

%% Main
% At the boundary i = 1
i = 1;
dUdt(i,:) = -gamma_0*(b0(i).^exp).*(S-c0(i));
dUdt(len1+i,:) = chi*(2*c0(i+1)-2*c0(i))+gamma_0*(b0(i).^exp).*(S-c0(i));

```

---

```

%% Inside the drug layer
for i = 2 : len1-2
    dUdt(i,:) = -gamma_0*(b0(i).^exp).*(S-c0(i));
    dUdt(len1+i,:) = chi*(c0(i+1)- 2*c0(i)+ c0(i-1))+gamma_0*(b0(i).^exp).*(S-c0(i));
end

%% The LHS interface point N-1
i = len1-1;
dUdt(i,:) = -gamma_0*(b0(i).^exp).*(S-c0(i));

argl1 = (3+2*h2*(phi+v_1))*xi/Lambda;
argl2 = 2*h1*phi/Lambda;
cl=argl1*(4*c0(N-1)-c0(N-2))+argl2*(4*c1(2)-c1(3));

%the interface point i = N

dUdt(len1+i,:) = chi*(cl- 2*c0(i)+ c0(i-1))+gamma_0*(b0(i).^exp).*(S-c0(i));

%evaluting ce at interface
i = len1;
dUdt(i,:) = -gamma_0*(b0(i).^exp).*(S-cl);

%% The RHS interface point 1
argr2 = (3*xi+2*h1*phi)/Lambda;
argr1 = 2*xi*h2*phi/Lambda;
cr=argr2*(4*c1(1)-c1(2))+argr1*(4*c0(N-1)-c0(N-2));
i = 1;
dUdt(len3+len2-2+i,:) = alpha_1*cr.*(bmax-b1(i))-beta_1*b1(i);
i = 2;
j = i-1;
dUdt(len3,:) = psi*(c1(j+1)-2*c1(j)+cr)-v_1*(c1(j+1)-cr)/(2*h2)-alpha_1*c1(j)...
    .*(bmax-b1(i))+beta_1*b1(i);
dUdt(len3+len2+i-2,:) = alpha_1*c1(j).*(bmax-b1(i))-beta_1*b1(i);

%% Inside the skin layer
for i = 3 : len2-1
    j = i-1;
    dUdt(len3+i-2,:) = psi*(c1(j+1)-2*c1(j)+c1(j-1))-v_1*(c1(j+1)-c1(j-1))...
        /(2*h2)-alpha_1*c1(j).*(bmax-b1(i))+beta_1*b1(i);
    dUdt(len3+len2+i-2,:) = alpha_1*c1(j).*(bmax-b1(i))-beta_1*b1(i);
end
%% At boundary i = M
i = len2;
j = i-1;
dUdt(len3+i-2,:) = -alpha_1*c1(j).*(bmax-b1(i))+beta_1*b1(i);
dUdt(len3+len2+i-2,:) = alpha_1*c1(j).*(bmax-b1(i))-beta_1*b1(i);

```

---

## B.4 Code for symbolic calculations

Following code is used for solving the  $6 \times 6$  system of unknowns:

---

```

%% The program solves the linear system with enteries of matrix as variables

```

---

```

syms g p h0 h1 h2 h3 a b c d H k1 k2
%k1 = k_i and k2 = k_{i+1}, the conductivities
% for the Hickson's paper
A = [-H H -k1 0 0 0; -H H 0 -k2 0 0;...
      1 0 -h1 0 h1^2/2 0; 1 0 -(h0+h1) 0 (h0+h1)^2/2 0;...
      0 1 0 h2 0 h2^2/2; 0 1 0 h0+h2 0 (h0+h2)^2/2];

% for the drug delivery problem
% g = gamma and p = phi (in the dimensionless form)
C = [0 0 -g 1 0 0; p -p 0 1 0 0;...
      1 0 -h1 0 h1^2/2 0; 1 0 -(h0+h1) 0 (h0+h1)^2/2 0; ...
      0 1 0 h3 0 h3^2/2; 0 1 0 (h3+h2) 0 (h3+h2)^2/2];

% a = U_{j-1}, b = U_{j-2}, U_{j+1}, U_{j+2},
B = [ 0; 0; a; b; c; d];
% The solution vector is composed of U_b-(1st element), U_b+, dU_b-/dx,...
% dU_b+/dx, d^2U_b-/dx^2, d^2U_b+/dx^2(last element of the vector)

A\B; %Solves A*x = B system and yields the solution vector
C\B; %Solves C*y = B system and yields the solution vector

```

---

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