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MASTER THESIS

A two-layer reaction-diffusion model for transdermal drug delivery: a semi-analytical approach

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Declaration of Authorship

I, Mauricio Garcia Vergara, declare that this thesis titled, 'A two-layer reaction-diffusion model for transdermal drug delivery: a semi-analytical approach' and the work presented in it are my own. I confirm that:

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"Mathematical analysis is as extensive as nature itself; it defines all perceptible relations, measures times, spaces, forces, temperatures ; this difficult science is formed slowly, but it preserves every principle which it has once acquired; it grows and strengthens itself incessantly in the midst of the many variations and errors of the human mind.
It's chief attribute is clearness; it has no marks to express confused notations. It brings together phenomena the most diverse, and discovers the hidden analogies which unite them."

Jean Baptiste Joseph Fourier

UNIVERSITY OF L'AQUILA

Abstract

Faculty of Science
Department of Information Engineering, Computer Science and Mathematics

Master of Science

A two-layer reaction-diffusion model for transdermal drug delivery: a semi-analytical approach

by Mauricio Garcia Vergara

We present a two-phase two-layer mathematical model for transdermal drug delivery and percutaneous absorption. A set of coupled partial differential equations describes the reaction diffusion process in both layers. Using the Method of Eigenfunctions Expansion with shifted data and solving a Volterra Integral Equation of Second Kind we obtain a solution in the form of an infinite series.

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A mis padres Blanca y Modesto y a mis hermanos Monica y Ricardo por todo su cariño, apoyo, por estar conmigo siempre y por nunca dejar de creer en mi aún cuando yo empezaba a dudar. Ustedes son mi ejemplo y lo que me hace seguir adelante. Muchas gracias por todo, los quiero mucho.

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A Josslyn por su amistad, por siempre estar ahí, por cuidarme y darme ánimo. Tu es mon étoile.

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To my parents Blanca Vergara Antonio and Modesto Garcia Rojas,
everything that is good in me is because of you.

Chapter 1

The Mathematical Model

1.1 Introduction

Transdermal drug delivery (TDD for short) is an approach used to deliver drugs through the skin for therapeutic purposes as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Various TDD technologies are possible including the use of suitable drug formulations, carriers such as nanoparticles and penetration enhancers to facilitate drug delivery and transcutaneous absorption[1]. TDD offers several advantages compared to other traditional delivery methods: controlled release rate, noninvasive administration, less frequent dosing, and simple application without professional medical aids, improving patient compliance. For these reasons it represents a valuable and attractive alternative to oral administration [4].

Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application (*topical delivery*) or to be effective after distribution through the circulatory system (*systemic delivery*). While there are many advantages to TDD, the skin's barrier properties provide a significant challenge.To this aim, it is important to understand the mechanism of drug permeation from the delivery device (or vehicle, typically a transdermal patch or medicated plaster, fig. 1.1) across the skin [25]. In TDD, the drug should be absorbed to an adequate extent and rate in order to achieve and maintain uniform, systemic, effective levels throughout the duration of use.TDD must be carefully tailored to achieve the optimal therapeutic effect and to deliver the correct dose in the required time [20]. The pharmacological effects of the drug,tissue accumulation, duration and distribution could potentially have an effect on its efficacy and a delicate balance between an adequate amount of drug delivered over an extended

[1]The term "drug delivery" refers to the release of drug from a polymeric platform where it is initially contained. The name "percutaneous absorption" is generally related to the same process viewed from the perspective of the living tissue where the drug is directed to.

period of time and the minimal local toxicity should be found [29]. Most drugs do not penetrate skin at rates sufficient for therapeutic efficacy and this restrictive nature limits the use of the transdermal route to molecules of low molecular weight and with moderate lipophilicity. In general, the first skin layer, the stratum corneum, presents most of the resistance to diffusive transport into skin. Thus, once the drug molecules cross it, transfer into deeper dermal layers and systemic uptake occurs in a relatively short time. In order to speed up transdermal permeation of drugs in the stratum corneum, new delivery techniques are currently underinvestigation, for example the use of chemical enhancers or microneedles and techniques such as ultrasound, electroporation and iontophoresis [19, 20].

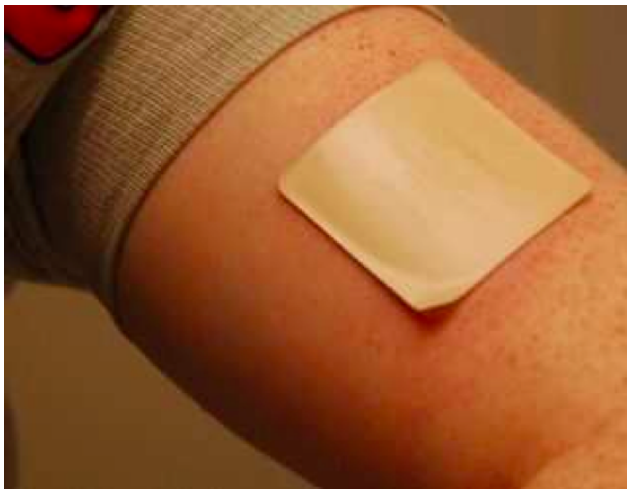


FIGURE 1.1: The transdermal patch, a typical vehicle in transdermal drug delivery.

Mathematical modelling for TDD constitutes a powerful predictive tool for the fundamental understanding of biotransport processes, and for screening processes and stability assessment of new formulations. In the absence of experiments, a number of mathematical models and numerical simulations have been carried out regarding TDD, its efficacy and the optimal design of devices [13, 14, 23, 27]. Recent extensive reviews deal with various aspects of transdermal delivery at different scales [1, 6, 10, 25, 30]. In general, drug absorption into the skin occurs by passive diffusion and most of the proposed models consider this effect only. On the other hand, there is a limited effort to explain the drug delivery mechanism from the vehicle platform.This is a very important issue indeed, since the polymer matrix acts as a drug reservoir, and an optimal design of its microstructural characteristics would improve the release performances [15]. For example, in the vehicle, the dissolution of the drug from encapsulated to free phase occurs at

a given reaction rate. Another relevant feature in TDD is the similar binding/unbinding process through the receptor sites in the skin. These drug association-dissociaton aspects are often neglected or underestimated by most authors who consider purely diffusive systems in the skin or in the vehicle [16, 18]. One exception is the work of Anissimov et al.[25, 29], where a linear reversible binding is considered, but the vehicle is taken into account only through a boundary condition of the first kind.

The method used in the present thesis follows the mathematical approach developed in a series of previously published papers by G. Pontrelli and F. de Monte which successfully describe drug dynamics form an eluting stent embedded in an arterial wall [7–11]. In these papers, it is proposed a number of models of increasing complexity to explain the diffusion-advection-reaction release mechanismof a drug from the stent coating to the wall, constituted of a number of contiguous homogeneous media of different properties and extents. Separation of variables leads to an eigenvalue problem with discontinuous coefficients and an exact solution is given in terms of infinite series expansion and is based on a two- or multi-layer diffusion model.

In the present thesis we extend the above study and remove some of the simplifying assumptions on the interface condition, obtaining a solution in a more general form. Together with diffusive effects, the drug dissolution process in the polymer constituting the vehicle platform and the reversible drug binding process in the skin are also addressed. A solution of the Sturm-Liouville problem serves as the building block to construct a space-time dependent solution for the general equations using the Eigenfunctions expansion method [3]. The interface condition is obtained as the solution of a Volterra integral equation of second kind with a difference kernel [22, 26]. A major issue in modelling TDD is the assessment of the key parameters defining skin permeability, diffusion coefficients, drug dissociation and association rates. The results of the simulations provide valuable insights into local TDD and can be used to assess experimental procedures to evaluate drug efficacy, for an optimal control strategy in the design of technologically advanced transdermal patches.

1.2 Formulation of the problem

To model TDD, let us consider 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. 1.2). The drug is stored 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. A rate-controlling membrane protecting 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. As most of the mass dynamics occurs along the direction normal to the skin surface, we restrict our study to a simplified one-dimensional model. In particular, we consideras x-axis the normal to the skin surface and oriented with the positive direction outwards the skin. Without loss of generality, let $x_0 = 0$ be the vehicle-skin interface and l_0 and l_1 the thicknesses of the vehicle and skin layers respectively (fig. 1.2). The vehicle and the skin are both treated from a macroscopic perspective so that they are represented as two homogeneous media.

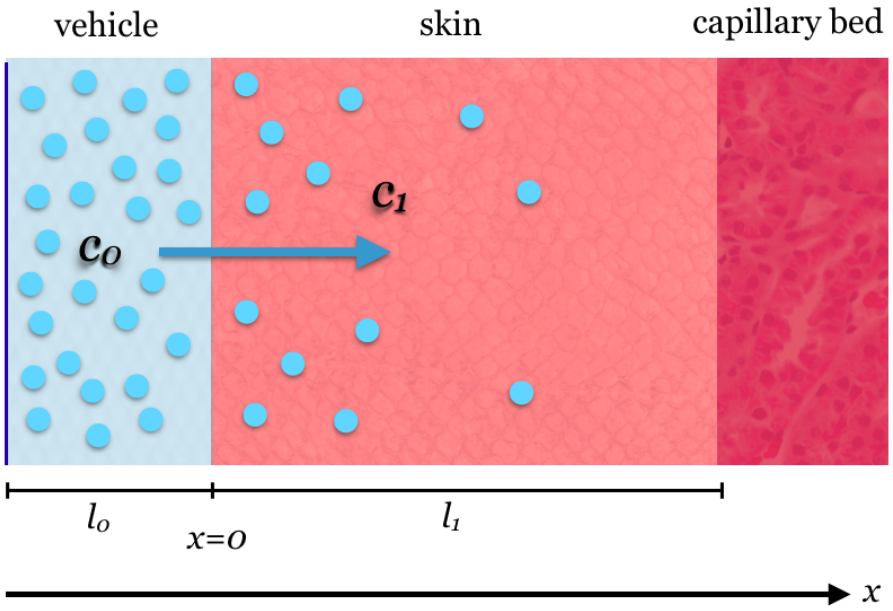


FIGURE 1.2: Cross-section of the vehicle and the skin layers, geometrical configuration and reference system. Due to an initial difference of free drug concentrations c_0 and c_1, a mass flux is established at the interface and drug diffuses through the skin. At a distance $x = l_1$ the skin-receptor (capillary bed) is present where all drug is assumed to be absorbed. Figure not to scale.

Initially, the drug is encapsulated at maximum concentration within the vehicle in a bound phase (e.g. nanoparticles or crystalline form) (c_e): in a such state, it is unable to be delivered to the tissue. Then, a fraction of this drug ($\beta_0 c_e$) is transferred, through an unbinding process, to an unbound – free, biologically available – phase (c_0), and conversely, a part of the free drug ($\delta_0 c_0$) is transferred by a binding process to the bound state, in a dynamic equilibrium (fig. 1.3). 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. 1.3.

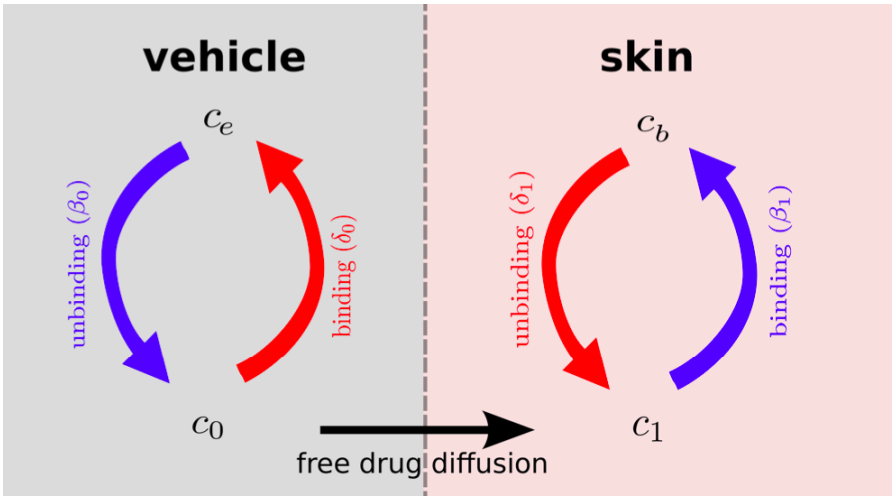


FIGURE 1.3: A diagram sketching the cascade mechanism of drug delivery and percutaneous absorption in the vehicle-skin coupled system. A unbinding (resp. binding) reaction occurs in the vehicle (resp. in the skin) (blue arrows). In both layers, reverse reactions (red arrows) are present in a dynamic equilibrium. Drug diffusion occurs only in the free phases c_0 and c_1.

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. In other cases of drug delivery, such as in eluting stents, a second-order saturable reversible binding model has been proposed [2]: this comprehensive model includes a number of drug dependent parameters which are difficult to measure experimentally and, nevertheless, does not necessarily apply to TDD. Here, a linear relationship is commonly used, as the density of binding sites far exceeds the local free drug concentration [10, 25, 29]. In the first layer the process is described by the following equations:

$$\frac{\partial c_e}{\partial t} = -\beta_0 c_e + \delta_0 c_0 \qquad \text{in } (-l_0, 0) \tag{1.1}$$

$$\frac{\partial c_0}{\partial t} = D_0 \frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0 \qquad \text{in } (-l_0, 0) \tag{1.2}$$

where D_0 (cm^2/s) is the effective diffusion coefficient of the unbound solute, $\beta_0 \geq 0$ and $\delta_0 \geq 0$ (s^{-1}) are the unbinding and binding rate constants in the vehicle, respectively. In detail, the rate of release of encapsulated drug into its free state is implied by the dissociation rate constant β_0, while δ_0 provides a representation of the rate at which the free solute re-associates in the bound state.

Similarly, in the second layer, the drug dynamics is governed by similar reaction-diffusion equations:

$$\frac{\partial c_1}{\partial t} = D_1 \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b \qquad \text{in } (0, l_1) \tag{1.3}$$

$$\frac{\partial c_b}{\partial t} = \beta_1 c_1 - \delta_1 c_b \qquad \text{in } (0, l_1) \tag{1.4}$$

where D_1 is the effective diffusivity of unbound drug, $\beta_1 \geq 0$ and $\delta_1 \geq 0$ are the binding and unbinding rate constants in the skin, respectively, defined similarly as above for the vehicle. They can be evaluated experimentally as described in [14, 29], sometimes through the equilibrium dissociation constant $K = \dfrac{\delta_1}{\beta_1}$. To close the previous bi-layered mass transfer system of eqns. (1.1)–(1.4), a flux continuity condition has to be assigned at the vehicle-skin interface:

$$-D_0 \frac{\partial c_0}{\partial x} = -D_1 \frac{\partial c_1}{\partial x} \qquad \text{at } x = 0 \tag{1.5}$$

As far as the concentration continuity is concerned, this is not guaranteed because of a different drug partitioning between vehicle and skin. This is taken into account through an appropriate mass transfer coefficient P_r [6, 14]. Additionally, a semi-permeable rate-controlling membrane or an adhesive film or a non-perfect vehicle-skin contact, having $1/P_m$ as mass resistance, might be present at the interface. Thus, a jump concentration may occur:

$$-D_1 \frac{\partial c_1}{\partial x} = P(c_0 - c_1) \qquad \text{at } x = 0 \tag{1.6}$$

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

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

Estimation of the partition coefficient or of its derived quantity P_r is a very difficult task. The recent review of Mitragotri et al. [25] provides an excellent overview of the current methods used for its representation. The usually met condition $c_0 \propto c_1$ does not apply, in our opinion, to time dependent cases.

No mass flux passes between the vehicle and the external surrounding due to the impermeable backing and we impose a no-flux condition :

$$D_0 \frac{\partial c_0}{\partial x} = 0 \qquad \text{at } x = -l_0 \tag{1.7}$$

Finally, a boundary condition has to be imposed at the skin-receptor (capillary) boundary. At this point the elimination of drug by capillary system follows first-order kinetics:

$$K_{cl}c_1 + D_1\frac{\partial c_1}{\partial x} = 0 \qquad \text{at } x = l_1 \tag{1.8}$$

where K_{cl} is the skin-capillary clearance per unit area (cm/s). The initial conditions are:

$$c_e(x,0) = C_e \qquad c_0(x,0) = 0 \qquad c_1(x,0) = 0 \qquad c_b(x,0) = 0 \tag{1.9}$$

1.2.1 Dimensionless equations

All the variables and the parameters are now normalized to get easily computable dimensionless quantities as follows:

$$\begin{aligned}
&\bar{x} = \frac{x}{l_1} && \bar{t} = \frac{D_1}{(l_1)^2}t && \Phi = \frac{Pl_1}{D_1} \\
&\bar{l}_0 = \frac{l_0}{l_1} && \gamma = \frac{D_0}{D_1} && \bar{c}_i = \frac{c_i}{C_e} \\
&k = \frac{K_{cl}l_1}{D_1} && \bar{\beta}_i = \frac{\beta_i(l_1)^2}{D_1} && \bar{\delta}_i = \frac{\delta_i(l_1)^2}{D_1} \qquad i = 0,1
\end{aligned} \tag{1.10}$$

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

$$\frac{\partial c_e}{\partial t} = -\beta_0 c_e + \delta_0 c_0 \qquad \text{in } (-l_0, 0) \tag{1.11a}$$

$$\frac{\partial c_0}{\partial t} = \gamma\frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0 \qquad \text{in } (-l_0, 0) \tag{1.11b}$$

$$\frac{\partial c_1}{\partial t} = \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b \qquad \text{in } (0, 1) \tag{1.11c}$$

$$\frac{\partial c_b}{\partial t} = \beta_1 c_1 - \delta_1 c_b \qquad \text{in } (0, 1) \tag{1.11d}$$

and the interface and boundary conditions (1.5)–(1.8) read:

$$\left.\frac{\partial c_0}{\partial x}\right|_{x=-l_0} = 0 \tag{1.12a}$$

$$\gamma\left.\frac{\partial c_0}{\partial x}\right|_{x=0} = \left.\frac{\partial c_1}{\partial x}\right|_{x=0} = R(t) \tag{1.12b}$$

$$-\left.\frac{\partial c_1}{\partial x}\right|_{x=0} = \Phi(c_0 - c_1)\Big|_{x=0} \tag{1.12c}$$

$$kc_1\Big|_{x=1} + \left.\frac{\partial c_1}{\partial x}\right|_{x=1} = 0 \tag{1.12d}$$

Here $R(t)$ is a matching interface function designed to model the temporal evolution of the drug flux between the two layers.

Finally, the initial conditions are:

$$c_e(x,0) = 1 \qquad c_0(x,0) = 0 \qquad c_1(x,0) = 0 \qquad c_b(x,0) = 0 \quad (1.13)$$

In the next chapter we will develop the techniques necessary to solve this system of PDE's.

Chapter 2

Solution by Method of Eigenfunctions Expansion

In order to solve the coupled PDE's problem, we are going to use the Method of eigenfunctions expansion that consists of building up the solution of our boundary value problem as a sum of eigenfunctions of a related Helmholtz problem with time dependent coefficients in order to reduce the problem to a system of ODE's [3, 12]. The success of this method on a given region depends on whether the eigenfunctions of the Helmholtz problem on that region form a complete set, in the sense that a function defined on that region can be expanded in a series in terms of the eigenfunctions, called an eigenseries expansion. The interface condition given by (1.12b) will be handle by considering that the partial derivatives of c_e, c_0, c_1 and c_b can also be expressed in terms of an eigenfunctions expansion, the result of this approach will give us a non homogeneous system of ODE's [26].

2.1 First layer

For the domain $(-l_0, 0)$ we want to solve equations (1.11a) and (1.11b)

$$\frac{\partial c_e}{\partial t} = -\beta_0 c_e + \delta_0 c_0$$
$$\frac{\partial c_0}{\partial t} = \gamma \frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0$$

with the interface/boundary conditions given by (1.12a) (1.12b)

$$\left.\frac{\partial c_0}{\partial x}\right|_{x=-l_0} = 0, \qquad \gamma \left.\frac{\partial c_0}{\partial x}\right|_{x=0} = R(t)$$

We assume that c_e also satisfies the same interface/boundary conditions.

The initial conditions are given by (1.13)

$$c_e(x,0) = 1, \qquad c_0(x,0) = 0.$$

Using the Method of eigenfunctions expansion we propose that $c_e(x,t)$ and $c_0(x,t)$ can be expressed in the following way

$$c_e(x,t) = \sum_{n=0}^{\infty} T_e^n(t) X_0^n(x) \qquad \text{and} \qquad c_0(x,t) = \sum_{n=0}^{\infty} T_0^n(t) X_0^n(x), \tag{2.1}$$

with the spatial eigenfunctions for $(-l_0, 0)$ given by

$$X_0^n(x) = \cos[\lambda_0^n(l_0 + x)] \qquad \text{where} \qquad \lambda_0^n = \frac{n\pi}{l_0} \qquad n \geq 0 \tag{2.2}$$

These eigenfunctions satisfy the following orthogonality relation

$$\int_{-l_0}^{0} X_0^n X_0^m dx = \delta_n^m (N_0^n)^2 \tag{2.3}$$

here δ_n^m is the usual Kronecker's delta and $(N_0^n)^2$ is the square $L^2(-l_0, 0)$ norm of $X_0^n(x)$ given by

$$(N_0^n)^2 = \frac{l_0}{2 - \delta_0^n}. \tag{2.4}$$

(See Appendix A). In figure (2.1) we can see some of eigenfunctions given by (2.2).

Using orthogonality we know that the coefficients $T_e^n(t)$, $T_0^n(t)$ can be written as

$$T_e^n(t) = \frac{1}{(N_0^n)^2} \int_{-l_0}^{0} c_e(x,t) X_0^n(x) dx, \qquad T_0^n(t) = \frac{1}{(N_0^n)^2} \int_{-l_0}^{0} c_0(x,t) X_0^n(x) dx.$$

In the same way as for (2.1) we can write the partial derivatives with respect to time as the expansions

$$\frac{\partial c_e}{\partial t} = \sum_{n=0}^{\infty} \frac{dT_e^n}{dt} X_0^n(x) \qquad \text{and} \qquad \frac{\partial c_0}{\partial t} = \sum_{n=0}^{\infty} \frac{dT_0^n}{dt} X_0^n(x) \tag{2.5}$$

For the diffusion term of (1.11b) we propose also an eigenfunctions expansion

$$\frac{\partial^2 c_0}{\partial x^2} = \sum_{n=0}^{\infty} W_0^n(t) X_0^n(x) \tag{2.6}$$

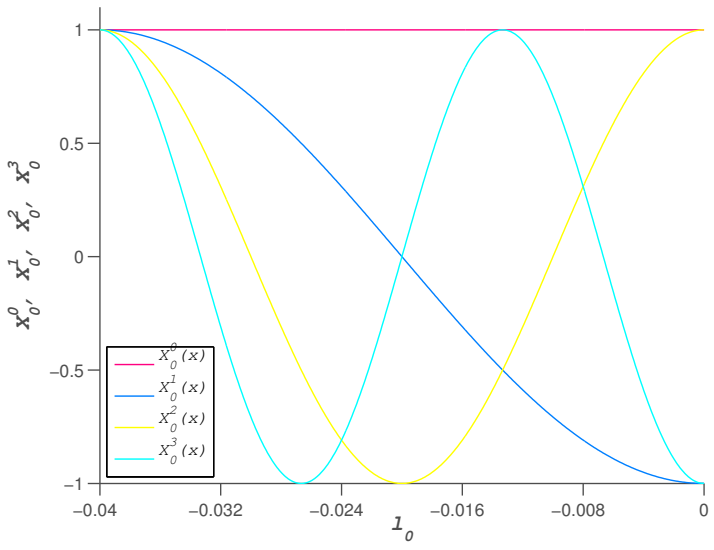


FIGURE 2.1: The first four eigenfunctions for layer 0 with $l_0 = 0.04$.

with its coefficients

$$W_0^n(t) = \frac{1}{(N_0^n)^2} \int_{-l_0}^{0} \frac{\partial^2 c_0}{\partial x^2} X_0^n(x) dx$$

Using integration by parts we have that

$$\begin{aligned} W_0^n(t) &= \frac{1}{(N_0^n)^2} \left(X_0^n \frac{\partial c_0}{\partial x}\bigg|_{x=-l_0}^{x=0} - c_0 \frac{dX_0^n}{dx}\bigg|_{x=-l_0}^{x=0} + \int_{-l_0}^{0} c_0(x,t) \frac{d^2 X_0^n}{dx^2} dx \right) \\ &= \frac{1}{(N_0^n)^2} \left(\frac{(-1)^n}{\gamma} R(t) - (\lambda_0^n)^2 \int_{-l_0}^{0} c_0(x,t) X_0^n(x) dx \right) \\ &= \frac{(-1)^n}{(N_0^n)^2 \gamma} R(t) - (\lambda_0^n)^2 T_0^n(t) \end{aligned} \tag{2.7}$$

Notice that in this term we have included the information corresponding with the interface condition (1.12b). Now with the help of (2.7) we can rewrite (2.6) as

$$\frac{\partial^2 c_0}{\partial x^2} = \sum_{n=0}^{\infty} \left(\frac{(-1)^n}{(N_0^n)^2 \gamma} R(t) - (\lambda_0^n)^2 T_0^n(t) \right) X_0^n(x) \tag{2.8}$$

Plugging equations (2.1), (2.5) and (2.8) into (1.11a) - (1.11b) we have

$$\sum_{n=0}^{\infty} \left(\frac{dT_e^n}{dt} + \beta_0 T_e^n(t) - \delta_0 T_0^n(t) \right) X_0^n(x) = 0$$

$$\sum_{n=0}^{\infty}\left(\frac{dT_0^n}{dt}-\beta_0 T_e^n(t)+(\delta_0+\gamma(\lambda_0^n)^2)T_0^n(t)-\frac{(-1)^n}{(N_0^n)^2}R(t)\right)X_0^n(x)=0$$

Given that the family of functions $X_0^n(x)$ is a complete basis in $L^2(-L_0,0)$ we know that every time dependent term in the previous expression is equal to zero. Therefore it is only necessary to solve the system

$$\begin{pmatrix}\frac{dT_e^n}{dt}\\ \\ \frac{dT_0^n}{dt}\end{pmatrix}=\begin{pmatrix}-\beta_0 & \delta_0\\ \\ \beta_0 & -\epsilon_0^n\end{pmatrix}\begin{pmatrix}T_e^n(t)\\ \\ T_0^n(t)\end{pmatrix}+\begin{pmatrix}0\\ \\ \frac{(-1)^n}{(N_0^n)^2}R(t)\end{pmatrix} \tag{2.9}$$

with

$$\epsilon_0^n=\delta_0+\gamma(\lambda_0^n)^2 \tag{2.10}$$

and the initial conditions

$$T_e^0(0)=1,\qquad T_e^n(0)=0\qquad \text{for } n>1,\qquad T_0^n(0)=0\qquad \text{for } n\geq 0.$$

The solutions of the system (2.9) are given by

$$T_e^0(t)=\frac{1}{\rho_0}\left[\delta_0+\beta_0 e^{-t\rho_0}+\frac{\delta_0}{(N_0^0)^2}\int_0^t R(\tau)\left(1-e^{-(t-\tau)\rho_0}\right)d\tau\right] \tag{2.11}$$

$$T_0^0(t)=\frac{1}{\rho_0}\left[\beta_0(1-e^{-t\rho_0})+\frac{1}{(N_0^0)^2}\int_0^t R(\tau)\left(\beta_0+\delta_0 e^{-(t-\tau)\rho_0}\right)d\tau\right] \tag{2.12}$$

$$T_e^n(t)=\frac{(-1)^n}{(N_0^n)^2\rho_n}\int_0^t 2\delta_0 R(\tau)e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n)}\sinh\left(\frac{1}{2}(t-\tau)\rho_n\right)d\tau \tag{2.13}$$

$$\begin{aligned}T_0^n(t)=&\frac{(-1)^n}{(N_0^n)^2\rho_n}\int_0^t \rho_n R(\tau)e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n)}\cosh\left(\frac{1}{2}(t-\tau)\rho_n\right)d\tau\\ &+\frac{(-1)^n}{(N_0^n)^2\rho_n}\int_0^t(\beta_0-\epsilon_n)R(\tau)e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n)}\sinh\left(\frac{1}{2}(t-\tau)\rho_n\right)d\tau\end{aligned} \tag{2.14}$$

where

$$\rho_n=\sqrt{(\epsilon_n-\beta_0)^2+4\beta_0\delta_0} \tag{2.15}$$

2.2 Second Layer

For the domain $(0, 1)$, we want to solve (1.11c) and (1.11d)

$$\frac{\partial c_1}{\partial t} = \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b$$
$$\frac{\partial c_b}{\partial t} = \beta_1 c_1 - \delta_1 c_b$$

with the interface/boundary conditions (1.12b) and (1.12d)

$$\left.\frac{\partial c_1}{\partial x}\right|_{x=0} = R(t), \qquad \left. kc_1\right|_{x=1} + \left.\frac{\partial c_1}{\partial x}\right|_{x=1} = 0$$

which are also satisfied by $c_b(x, t)$

The initial conditions are given by (1.13)

$$c_1(x, 0) = 0, \qquad c_b(x, 0) = 0.$$

Analogously to the procedure with the First layer, we propose an expansion for the domain (0.1) given by

$$c_b(x, t) = \sum_{n=1}^{\infty} T_b^n(t) X_1^n(x), \qquad c_1(x, t) = \sum_{n=1}^{\infty} T_1^n(t) X_1^n(x), \tag{2.16}$$

with the eigenfunctions

$$X_1^n(x) = \cos(\lambda_1^n x), \tag{2.17}$$

where λ_1^n is the n-th rooth of the trascendental equation

$$k\cos(\lambda_1^n) - \lambda_1^n \sin(\lambda_1^n) = 0. \tag{2.18}$$

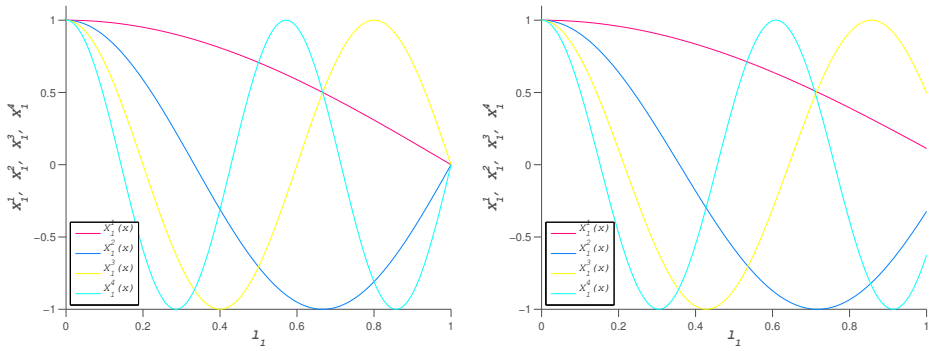
Figure (2.3) illustrates (2.18) for $k = 12.85$, while fig (2.2) shows the first four eigenfunctions for layer 1 with different values of k.

Also as with layer 0 functions $X_1^n(x)$ satisfies the following relation

$$\int_0^1 X_1^n(x) X_1^m(x) dx = \delta_n^m (N_1^n)^2 \tag{2.19}$$

with $(N_1^n)^2$ the square $L^2(0, 1)$ norm of $X_1^n(x)$ given by (See Appendix A).

$$(N_1^n)^2 = \frac{(\lambda_1^n)^2 + k\cos^2(\lambda_1^n)}{2(\lambda_1^n)^2} \tag{2.20}$$



(A) (B)

FIGURE 2.2: First four eigenfunctions for layer 1 with (A) $k = 12857.$ and (B) $k = 12.85$

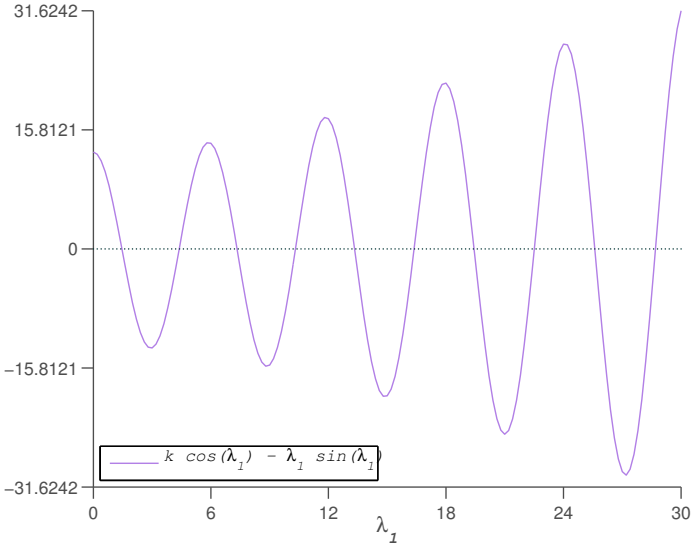


FIGURE 2.3: The roots of this trascendental function with $k = 12.85$ are the eigenvalues λ_1

The coefficients $T_1^n(t)$ and $T_b^n(t)$ can be written as

$$T_b^n(t) = \frac{1}{(N_1^n)^2}\int_0^1 c_b(x,t)X_1^n(x)dx, \qquad T_1^n(t) = \frac{1}{(N_1^n)^2}\int_0^1 c_0(x,t)X_1^n(x)dx$$

In the same way as in the previous subsection, we can write the partial derivatives with respect to time as the expansions

$$\frac{\partial c_b}{\partial t} = \sum_{n=1}^{\infty}\frac{dT_b^n}{dt}X_1^n(x), \qquad \frac{\partial c_1}{\partial t} = \sum_{n=1}^{\infty}\frac{dT_1^n}{dt}X_1^n(x). \tag{2.21}$$

For the diffusion term of (1.11c) we propose

$$\frac{\partial^2 c_1}{\partial x^2} = \sum_{n=1}^{\infty} W_1^n(t)X_1^n(x), \tag{2.22}$$

with coefficients

$$W_1^n(t) = \frac{1}{(N_1^n)^2}\int_0^1 \frac{\partial^2 c_1}{\partial x^2}X_1^n(x)dx.$$

Using integration by parts in order to rewrite $W_1^n(t)$ we have

$$\begin{aligned} W_1^n(t) &= \frac{1}{(N_1^n)^2}\left(X_1^n\frac{\partial c_1}{\partial x}\bigg|_{x=0}^{x=1} - c_1\frac{dX_1^n}{dx}\bigg|_{x=0}^{x=1} + \int_0^1 c_1(x,t)\frac{d^2X_1^n}{dx^2}dx\right) \\ &= \frac{1}{(N_1^n)^2}\left(-R(t) - (\lambda_1^n)^2\int_0^1 c_1(x,t)X_1^n(x)dx\right) \\ &= -\frac{1}{(N_1^n)^2}R(t) - (\lambda_1^n)^2 T_1^n(t) \end{aligned} \tag{2.23}$$

Then, the diffusion term can be written as

$$\frac{\partial^2 c_1}{\partial x^2} = \sum_{n=1}^{\infty}\left(-\frac{1}{(N_1^n)^2}R(t) - (\lambda_1^n)^2 T_1^n(t)\right)X_1^n(x). \tag{2.24}$$

Upon substitution of equations (2.16), (2.21) and (2.22) into (1.11c) - (1.11d) we have

$$\sum_{n=1}^{\infty}\left(\frac{dT_b^n}{dt} + \delta_1 T_b^n(t) - \beta_1 T_1^n(t)\right)X_1^n(x) = 0$$

and

$$\sum_{n=1}^{\infty}\left(\frac{dT_1^n}{dt} - \delta_1 T_b^n(t) + (\beta_1 + (\lambda_1^n)^2)T_1^n(t) + \frac{1}{(N_1^n)^2}R(t)\right)X_1^n(x) = 0$$

Puttying everything in matrix form as before we have

$$\begin{pmatrix} \dfrac{dT_b^n}{dt} \\ \\ \dfrac{dT_1^n}{dt} \end{pmatrix} = \begin{pmatrix} -\delta_1 & \beta_1 \\ \\ \delta_1 & -\eta_1^n \end{pmatrix} \begin{pmatrix} T_b^n(t) \\ \\ T_1^n(t) \end{pmatrix} + \begin{pmatrix} 0 \\ \\ -\frac{1}{(N_1^n)^2} R(t) \end{pmatrix} \tag{2.25}$$

with

$$\eta_1^n = \beta_1 + (\lambda_1^n)^2 \tag{2.26}$$

and the initial conditions

$$T_b^n(0) = 0 \qquad \text{for } n \geq 1, \qquad T_1^n(0) = 0 \qquad \text{for } n \geq 1.$$

The solutions of system (2.25) are given by

$$T_b^n(t) = \frac{-1}{(N_1^n)^2 \sigma_n} \int_0^t 2\beta_1 R(\tau) e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_1^n)} \sinh\left(\frac{1}{2}(t-\tau)\sigma_n\right) d\tau \tag{2.27}$$

$$\begin{aligned} T_1^n(t) =& \frac{-1}{(N_1^n)^2 \sigma_n} \int_0^t \sigma_n R(\tau) e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_1^n)} \cosh\left(\frac{1}{2}(t-\tau)\sigma_n\right) d\tau \\ &+ \frac{-1}{(N_1^n)^2 \sigma_n} \int_0^t (\delta_1 - \eta_1^n) R(\tau) e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_1^n)} \sinh\left(\frac{1}{2}(t-\tau)\sigma_n\right) d\tau \end{aligned} \tag{2.28}$$

with

$$\sigma_n = \sqrt{(\eta_1^n - \delta_1)^2 + 4\delta_1\beta_1} \tag{2.29}$$

2.3 Working with the interface condition

As we can see from (2.12), (2.14), (2.27) and (2.28) once the compatibility time dependent interface function $R(t)$ is founded, all the time dependent cofficients are completely determinated and c_e, c_0, c_1 and c_b can be obtained by equations (2.1) and (2.16). This idea is similar to the one used by McGinty et al in [24], how ever they need to consider a new problem with an overdetermined system with pure diffusion equations. In our case we arrive directly to the Volterra equation without considering any kind of auxiliary problem.

Using the interface condition (1.12c) we can find $R(t)$ as solution of.

$$R(t) = \Phi\left(\sum_{n=1}^{\infty}(T_1^n(t) - (-1)^n T_0^n(t)) - T_0^0(t)\right) \tag{2.30}$$

For numerical purposes we are going to truncate the sum in (2.30) up to certain N. Then we will see that this equation can be written as a Volterra integral equation of second kind in the Uryshon's form [22]. With this starting point we will use two numerical methods to find the solution of this integral equation: i) *Adomian decomposition method* [28] and iii) *A quadrature method with trapezoidal rule* [21]. This procedure is more general than the one used by G. Pontrelli and F. de Monte in [9, 11]. The fact that we don't use the Laplace transform to solve the integral equation is because in our case is difficult to find the inverse Laplace transform for the resolvent of our particular integral equation [22].

2.3.1 The interface condition as a Volterra integral equation

In order to see (2.30) as an integral equation we just need to plug in it the equations (2.12), (2.14), (2.27) and (2.28). Then truncate the infinite sum up to certain number N. Rewriting the hyperbolic sine and cosine in terms of the exponential function we have.

$$\begin{aligned}
R_N(t) = -\frac{\Phi}{\rho_0}\Bigg[&\beta_0(1-e^{-t\rho_0}) + \frac{1}{(N_0^0)^2}\int_0^t R_N(\tau)\left(\beta_0 + \delta_0 e^{-(t-\tau)\rho_0}\right)d\tau\Bigg] \\
&-\Phi\sum_{n=1}^{N}\Bigg[\frac{\rho_n - \epsilon_n + \beta_0}{2(N_0^n)^2\rho_n}\int_0^t R_N(\tau)e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n-\rho_n)}d\tau \\
&\quad + \frac{\rho_n + \epsilon_n - \beta_0}{2(N_0^n)^2\rho_n}\int_0^t R_N(\tau)e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n+\rho_n)}d\tau \\
&\quad + \frac{\sigma_n - \eta_n + \delta_1}{2(N_0^n)^2\sigma_n}\int_0^t R_N(\tau)e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_n-\sigma_n)}d\tau \\
&\quad + \frac{\sigma_n + \eta_n - \delta_1}{2(N_0^n)^2\sigma_n}\int_0^t R_N(\tau)e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_n+\sigma_n)}d\tau\Bigg]
\end{aligned} \tag{2.31}$$

If now we interchange the sum with the integral sign and defining the following functions

$$f(t) = -\Phi\frac{\beta_0}{\rho_0}(1-e^{-t\rho_0}) \tag{2.32}$$

and

$$K_N(t-\tau) = -\frac{\Phi}{(N_0^0)^2\rho_0}\left(\beta_0 + \delta_0 e^{-(t-\tau)\rho_0}\right) - \Phi\sum_{n=1}^{\infty}\left[\frac{\rho_n - \epsilon_n + \beta_0}{2(N_0^n)^2\rho_n}e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n-\rho_n)}\right.$$
$$+ \frac{\rho_n + \epsilon_n - \beta_0}{2(N_0^n)^2\rho_n}e^{-\frac{1}{2}(t-\tau)(\beta_0+\epsilon_n+\rho_n)} + \frac{\sigma_n - \eta_n + \delta_1}{2(N_0^n)^2\sigma_n}e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_n-\sigma_n)}$$
$$\left. + \frac{\sigma_n + \eta_n - \delta_1}{2(N_0^n)^2\sigma_n}e^{-\frac{1}{2}(t-\tau)(\delta_1+\eta_n+\sigma_n)}\right] \tag{2.33}$$

we arrive to the next expression

$$R_N(t) - \int_0^t R_N(\tau)K_N(t-\tau)d\tau = f(t). \tag{2.34}$$

As we can appreciate, equation (2.34) is a Volterra integral equation of second kind in the Uryshon's form [17] with a difference degenerated kernel $K_N(t-\tau)$ [22]. Due to the fact that $f(t)$ and $R_N(t)$ are continuous on $[0,T]$ we know that solution $R_N(t)$ of (2.34) exists and it is unique (see Appendix B). Let's notice that equation (2.34) carries the information that is interchanged between layers 0 and 1. In fact the kernel $K_N(t,\tau)$ (2.33) contains all the physical constants involved in the phenomenon and the eigenvalues λ_0^n, λ_1^n of both layers.

2.3.2 Adomian Decomposition Method

The Adomian decomposition method [28] consists of decomposing the unknown function $R_N(t)$ of any equation into a sum of an infinite number of components defined by the decomposition series

$$R_N(t) = \sum_{m=0}^{\infty} R_N^m(t), \tag{2.35}$$

where the components $R_N^m(t)$, $m \geq 0$ are to be determinated in a recursive manner, The decomposition method concerns itself with finding the components $R_N^0, R_N^1, R_N^2, \ldots$ individually.

To establish the recurrence relation, we substitute (2.35) into the Volterra integral equation (2.34) to obtain

$$\sum_{m=0}^{\infty} R_N^m(t) = f(t) + \int_0^t \left(\sum_{m=0}^{\infty} R_N^m(\tau)\right) K_N(t-\tau)d\tau \tag{2.36}$$

The zeroth component $R_n^0(t)$ is indentified by all terms that are not included under the integral sign. Consequently, teh components $R_N^m(t)$, $m \geq 1$ of the unknown function

$R_N(t)$ are completely determinated by setting the recurrence relation:

$$\begin{aligned} R_N^0(t) &= f(t), \\ R_N^{m+1} &= \int_0^t R_N^m(\tau) K_N(t-\tau) d\tau. \end{aligned} \tag{2.37}$$

In view of (2.37) the components $R_N^0(t), R_N^1(t), R_N^2(t), \ldots$ are completely determinated. As a result, the solution $R_N(t)$ of the Volterra integral equation (2.34) in a series form is obtained by using the series assumption in (2.35). For a real problem, where a closed form is not obtainable, a truncated number of terms is used for numerical purposes. The more components we use the higher accuracy we obtain [5]. In this case we are going to use a trapezoidal rule in order to compute the numerical integrations.

2.3.3 A Quadrature Method

We develop a numerical scheme by choosing a constant integration step h and consider the discrete set of points $t_i = h(i-1)$, $i =, 1 \ldots, n$ in the time domain. We assume that the kernel $K_N(t-\tau)$ and $f(t)$ are continuos functions. From equation (2.34) we find that $R_N(0) = f(0) = 0$ and for $t = t_i$ equation (2.34) acquires the form

$$R_N(t_i) - \int_0^{t_i} K_N(t_i - \tau) R_N(\tau) d\tau = f(t_i), \qquad i = 1, \ldots, n. \tag{2.38}$$

Applying the quadrature formula with the trapezoidal rule [22] to the integral in (2.38) and choosing t_j $(j = 1 \ldots i)$ to be the nodes in τ, we arrive at the system of equations

$$R_N(t_1) = f(t_1), \qquad R_N(t_i) = \frac{f(t_i) + h\sum_{j=1}^{i-1} B_j K_N(t_i - t_j) R_N(t_j)}{1 - \frac{1}{2} h K_N(0)} \qquad i = 2, \ldots, n \tag{2.39}$$

with

$$t_i = (i-1)h, \qquad n = \frac{T}{h} + 1, \qquad B_j = \begin{cases} \frac{1}{2} & \text{for } j = 1 \\ 1 & \text{for } j > 1. \end{cases} \tag{2.40}$$

Chapter 3

Numerical Simulations and Results

In this chapter we are going to show the results for our numerical simulations. First, we will show some numerical results for the interface condition $R_N(t)$ and make a comparison between the Quadrature Method and the Adomian method. Second, we present the results of our simulations for c_e, c_0, c_1 and c_b.

Let's emphasize that the physical problem depends on a large number of parameters, each of them may vary in a finite range, with a variety of combinations and limiting cases. The model constants cannot be chosen independently from each other and there is a compatibility condition among them and the binding/unbinding constants. In our case all the numerical schemes where implemented for $l_0 = 4 \times 10^{-2}$, with the physical constants fixed for simulations as in [6, 10, 16, 18, 30] and using (1.10) we get the following dimensionless quantities

$$\gamma = 7.14, \qquad \Phi = 4.28, \qquad k = 12857 \tag{3.1}$$

and the binding/unbinding constants

$$\beta_0 = 128.57, \qquad \delta_0 = 128.57, \qquad \beta_1 = 192.85, \qquad \delta_1 = 128.57. \tag{3.2}$$

3.1 Numerical results for $R_N(t)$

The aim of this section is to show some results for $R_N(t)$ with the Adomian method and the Quadrature Method using trapezoidal rule. The results were computed for a time interval of length $T = 0.6$, the integration step was $h = 2.5 \times 10^{-5}$ and in the

case of the Adomian method the number of terms in the decomposition is $M = 10$. In figure (3.1) we can appreciate how the solutions obtained with both methods show the same qualitative behaviour but without being exactly the same solution, in particular the minimum is slightly different.

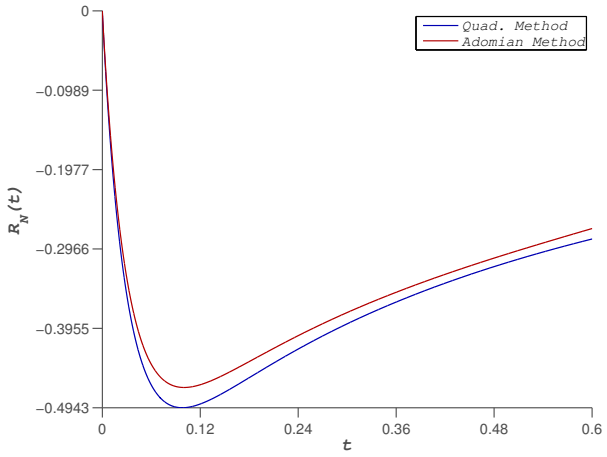


FIGURE 3.1: $R_N(t)$ with Quad. Method and Adomian Method with $M = 10$

However if now we increase the length of the time interval to $T = 1.0$ we can see in fig 3.2 how the behaviour of $R_N(t)$ with the Adomian method starts to diverge from the Quadrature method. However this can be fixed if we add more terms $R_N^m(t)$ (fig 3.2).

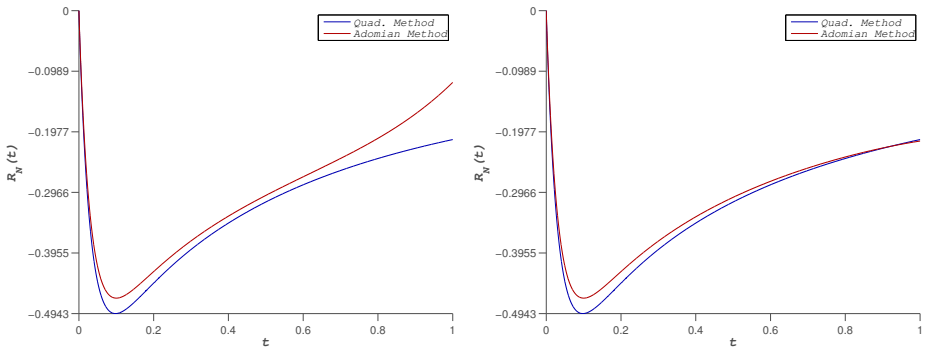


FIGURE 3.2: Comparison between the Quadrature method with trapezoidal rule and the Adomian method for (A) $M = 10$ and (B) $M = 15$. The lenght of time interval is given by $T = 1.0$

The fact that each time that the length of time interval is increased we have the necessity to add more terms, is one of the reasons that make us choose the Quadrature method

with trapezoidal rule over the Adomian decomposition method. The second reason, which is very related with the first one, is the big difference between the computation times for both methods. As an illustrative example table 3.1 shows the computation times and the percentage change for different values of T. From now on we will only use the Quadrature method with trapezoidal rule.

T	Quad. Method	Ad. Method with $M = 15$	% change
0.2	1.42	17.32	91.80
0.4	5.71	69.53	91.78
0.6	12.70	179.96	92.94
0.8	24.08	502.71	95.20
1.0	35.63	862.56	95.86

TABLE 3.1: Comparison between computation times for Quad. Method and Adomian Method with $M = 15$

3.2 Numerical results for c_e, c_0, c_1 and c_b

Once we computed $R_N(t)$ numerically we can obtain the time dependent coefficientes $T_i^n(t)$, $i = e, o, 1, b$ using equations (2.11)-(2.14) and (2.27)-(2.28), these integrals were obtained numerically using the trapezoidal rule with $h = 2.5 \times 10^{-5}$. Using the previous results we can get the solutions for $c_i(x,t)$ $i = e, o, 1, b$ via (2.1) and (2.16). All the series were truncated up to 50 terms.

In fig 3.3 we can see the evolution for $c_e(x,t)$ and $c_0(x,t)$ for different times. The concentration profiles are almost flat in the vehicle, because of its small size, and have a decreasing behaviour in the skin layer. At the beginning the bound phase c_e starts to be transferred to the unbound phase c_0 until the dynamic equilibrium is reached. And at the same time one fraction of the drug is passing to the skin layer, this process continues until the concentrations vanish.

In the case of the skin layer the evolution of $c_1(x,t)$ and $c_b(x,t)$ can be seen in fig 3.4, a part of the unbound drug c_1 is metabolized by the cell receptors and transformed in the bound state c_b and again to an unbound phase with the reverse unbindign process. Also, we can see how at the beginning the concentration of c_1 is bigger than c_b but as the time passes c_b increases and overcomes c_1 this means that a bigger quantity of the drug is metabolized.

3.3 Conclusions

- Currently TDD is one of the most promising method for drug administration and an increasing number of drugs are being added to the list of therapeutic agents that can be delivered topically or systemically through the skin. One of the approaches to evaluate the characteristics of drug elution from the transdermal patch into the skin and to optimize the physico-chemical parameters is the mathematical modelling and the numerical simulation.

- Local mass non-equilibrium processes, such as bidirectional drug binding/unbinding phenomena, play a key role in TDD. We consider a coupled linear system of reaction-diffusion PDE's in order to model the kinetics of a drug in the delivery device together with the percutaneous absorption in the skin, as a unique system.

- Using the Eigenfunctions expansion method with shifted data, we reduced the PDE's system to an non homogeneous system of ODE's. The solutions obtained for the time-dependent coefficients are in terms of the matching interface condition $R_N(t)$.

- In order to get $R_N(t)$ we solved a Volterra Integral Equation of second kind with two numerical methods: A quadrature method with trapezoidal rule and the Adomian decomposition method. The best numerical result between these two methods was chosen for the further coming simulations.

- The simulations obtained capture the essential physics of drug release and percutaneous absorption and it helps in identify and quantify the effects in TDD. Because of the large space of parameters, a crucial step is the experimental assessment of the key parameters which the model is based on

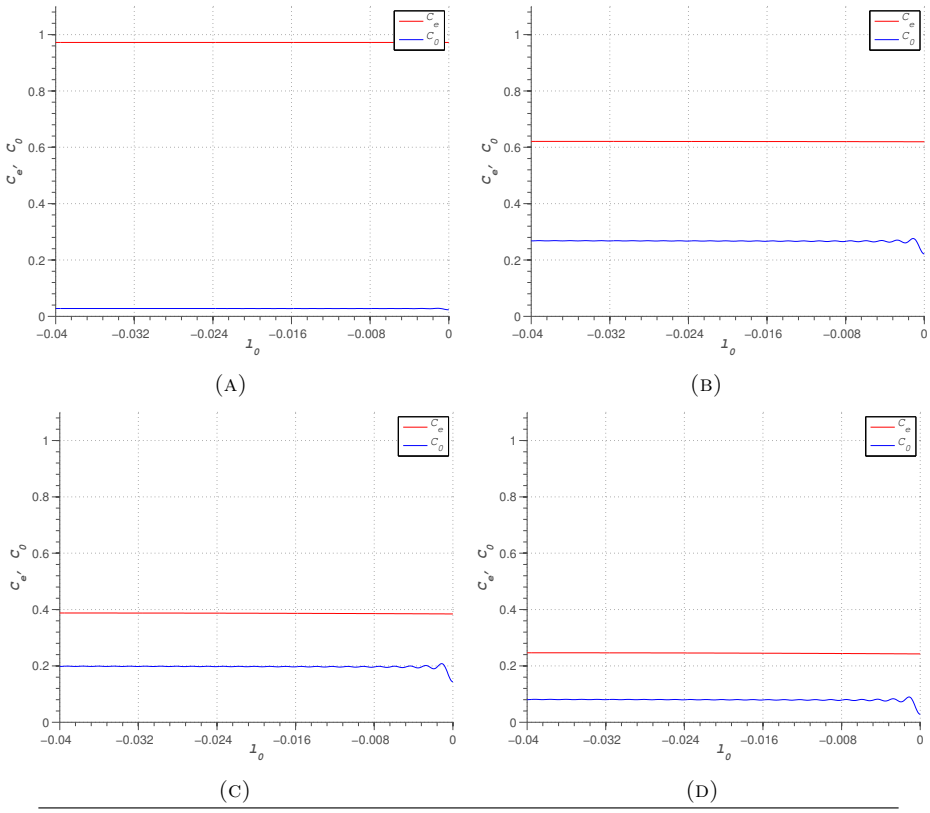


FIGURE 3.3: Concentration profiles for c_e and c_0 with dimensionless time : (A) $t = 2.23 \times 10^{-4}$, (B) $t = 0.012$, (C) $t = 0.049$, (D) $t = 0.018$

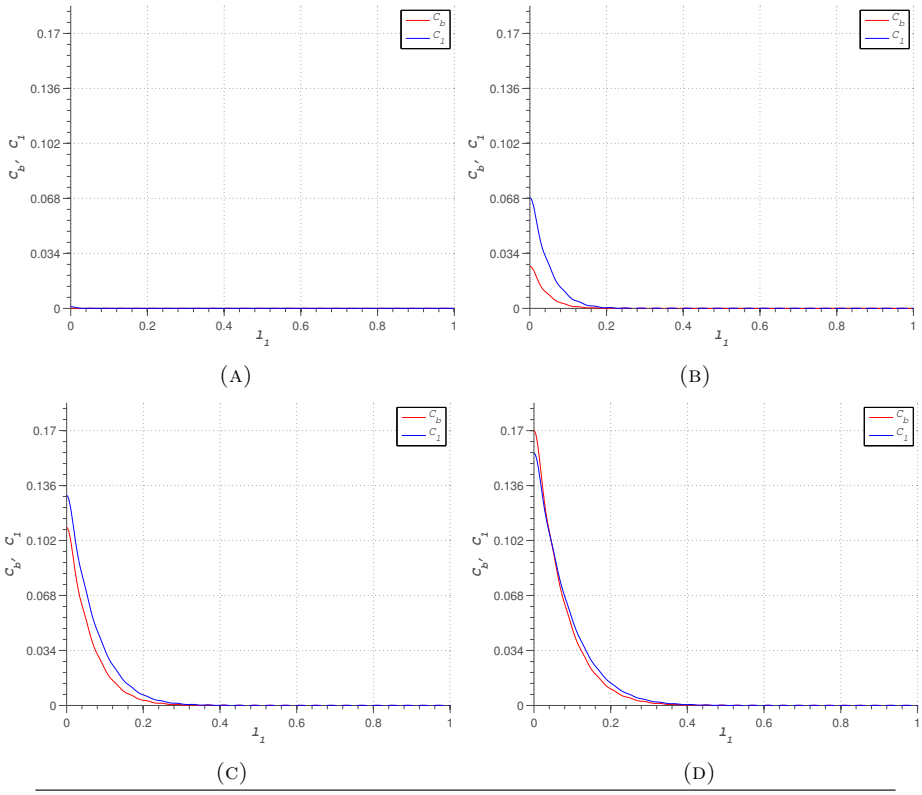


FIGURE 3.4: Concentration profiles for c_1 and c_b with dimensionless time: (A) $t = 2.23 \times 10^{-4}$, (B) $t = 0.012$, (C) $t = 0.049$, (D) $t = 0.018$

Appendix A

Eigenfunctions for the domains $(-l_0, 0)$ and $(0, 1)$

A.1 Solution of the Helmholtz Problem in $(-l_0, 0)$

In order to find the right eigenfunctions for the domain $(-l_0, 0)$ let's consider the associated 1D Helmholtz problem given by the equation

$$\frac{d^2X_0}{dx^2} + (\lambda_0)^2 X_0 = 0 \tag{A.1}$$

and the boundary conditions

$$\left.\frac{dX_0}{dx}\right|_{x=-l_0} = 0 \tag{A.2a}$$

$$\left.\frac{dX_0}{dx}\right|_{x=0} = 0 \tag{A.2b}$$

We know that the solution of (A.1) is

$$X_0(x) = A\cos(\lambda_0 x) + B\sin(\lambda_0 x)$$

Applying the first boundary condition (A.2a) we get

$$\lambda_0(B\cos(\lambda_0 l_0) + A\sin(\lambda_0 l_0)) = 0$$

If now we pick $A = cos(\lambda_0 l_0)$ and $B = -\sin(\lambda_0 l_)$ we can rewrite the solution of (A.1) in a much more compact way as

$$X_0(x) = \cos[\lambda_0(l_0 + x)] \tag{A.3}$$

Using the second boundary condition (A.2b) we arrive to the expression

$$-\lambda_0 \sin(\lambda_0 l_0) = 0$$

this implies

$$\lambda_0^n = \frac{n\pi}{l_0} \qquad \text{for } n \geq 0 \tag{A.4}$$

Therefore the solution of (A.1)-(A.2) is given by (A.3) with (A.4)

A.1.1 Orthogonality of $X_0^n(x)$

The next step is to prove the orthogonality of (A.3).

Theorem A.1. *Let* $X_0^n(x)$ *and* $X_0^m(x)$ *two different solutions of (A.1)-(A.2) with* $(n \neq m)$ *and* λ_0^n, λ_0^m *the corresponding eigenvalues, then*

$$\int_{-l_0}^{0} X_0^n(x) X_0^m(x) dx = 0 \tag{A.5}$$

Proof. As we know $X_0^n(x)$ and $X_0^m(x)$ satisfy

$$-(\lambda_0^n)^2 X_0^n = \frac{d^2 X_0^n}{dx^2} \tag{A.6}$$

$$-(\lambda_0^m)^2 X_0^m = \frac{d^2 X_0^m}{dx^2} \tag{A.7}$$

Multiplying (A.6) by $-X_0^m$ and (A.7) by X_0^n and then adding them we get

$$((\lambda_0^n)^2 - (\lambda_0^m)^2) X_0^n X_0^m = \frac{d^2 X_0^m}{dx^2} X_0^n - \frac{d^2 X_0^n}{dx^2} X_0^m$$

Integrating now from $-l_0$ to 0

$$\begin{aligned}((\lambda_0^n)^2 - (\lambda_0^m)^2) \int_{-l_0}^{0} X_0^n X_0^m dx &= \int_{-l_0}^{0} \frac{d^2 X_0^m}{dx^2} X_0^n - \frac{d^2 X_0^n}{dx^2} X_0^m dx \\ &= \frac{dX_0^m}{dx} X_0^n \Big|_{-l_0}^{0} - \frac{dX_0^n}{dx} X_0^m \Big|_{-l_0}^{0} \\ &= 0\end{aligned}$$

Finally we just need to remember that $\lambda_0^n \neq \lambda_0^m$ and (A.5) follows. □

A.1.2 Square $L^2(-l_0,0)$ norm of $X_0^n(x)$

In order to find the square $L^2(-l_0,0)$ norm of $X_0^n(x)$ we have the following theorem

Theorem A.2. *The square* $L^2(-l_0,0)$ *norm of* $X_0^n(x)$ *is given by*

$$\int_{-l_0}^{0}(X_0^n(x))^2dx=\frac{l_0}{2-\delta_{n,0}} \tag{A.8}$$

with $\delta_{n,0}$ *the usual Kronecker Delta*

Proof. We should proced by cases

$n=0$ This case is very easy

$$\begin{aligned}\int_{-l_0}^{0}(X_0^0(x))^2dx&=\int_{-l_0}^{0}1dx\\&=l_0\end{aligned}$$

$n\geq 0$ For this case we multiply (A.6) by $X_0^n(x)$ and then we integrate from $-l_0$ to 0

$$\begin{aligned}-(\lambda_0^n)^2\int_{-l_0}^{0}(X_0^n(x))^2dx&=\int_{-l_0}^{0}\frac{d^2X_0^n}{dx^2}X_0^ndx\\&=\frac{dX_0^n}{dx}X_0^n\Big|_{-l_0}^{0}-\int_{-l_0}^{0}\left(\frac{dX_0^n}{dx}\right)^2dx\\&=-\int_{-l_0}^{0}\left(\frac{dX_0^n}{dx}\right)^2dx\end{aligned} \tag{A.9}$$

Adding $-(\lambda_0^n)^2\int_{-l_0}^{0}(X_0^n(x))^2dx$ to both sides of (A.9) and dividing over $-2(\lambda_0^n)^2$ we get

$$\begin{aligned}\int_{-l_0}^{0}(X_0^n(x))^2dx&=\frac{1}{2}\int_{-l_0}^{0}\frac{1}{(\lambda_0^n)^2}\left(\frac{dX_0^n}{dx}\right)^2+(X_0^n(x))^2dx\\&=\frac{1}{2}\int_{-l_0}^{0}\frac{1}{(\lambda_0^n)^2}(-\lambda_0^n\sin[\lambda_0^n(l_0+x)])^2+\cos^2[\lambda_0^n(l_0+x)]dx\\&=\frac{l_0}{2}\end{aligned}$$

this finishes the proof □

A.2 Solution of the Helmholtz Problem in $(0,1)$

As with the previous domain in order to find the right eigenfunctions for the domain $(0,1)$ we consider the 1D Boundary Value Problem given by the equation

$$\frac{d^2X_1}{dx^2} + (\lambda_1)^2 X_1 = 0 \tag{A.10}$$

and the boundary conditions

$$\left.\frac{dX_1}{dx}\right|_{x=0} = 0 \tag{A.11a}$$

$$kX_1\Big|_{x=1} + \left.\frac{dX_1}{dx}\right|_{x=1} = 0 \tag{A.11b}$$

Again we have that the solution of (A.10) is

$$X_1(x) = C\cos(\lambda_1 x) + D\sin(\lambda_1 x)$$

Applying the first boundary condition (A.11a) we get $D = 0$ and without loss of generality we can choose $C = 1$. Then we just rewrite the solution of (A.10) as

$$X_1(x) = \cos(\lambda_1 x) \tag{A.12}$$

Using the second boundary condition (A.11b) we obtain that λ_1^n should be the n-th root of the trascendental equation

$$\cot(\lambda_1^n) - \lambda_1^n = 0 \tag{A.13}$$

Therefore the solution of (A.10)-(A.11) is given by (A.12) with λ_1^n the solution of (A.13)

A.2.1 Orthogonality of $X_1^n(x)$

The next step is to prove the orthogonality of (A.12).

Theorem A.3. *Let* $X_0^n(x)$ *and* $X_0^m(x)$ *two different solutions of (A.10)-(A.11) with* $(n \neq m)$ *and* λ_0^n, λ_0^m *the corresponding eigenvalues, then*

$$\int_0^1 X_1^n(x) X_1^m(x) dx = 0 \tag{A.14}$$

Proof. As we know $X_1^n(x)$ and $X_1^m(x)$ satisfy

$$-(\lambda_1^n)^2 X_1^n = \frac{d^2 X_1^n}{dx^2} \tag{A.15}$$

$$-(\lambda_1^m)^2 X_1^m = \frac{d^2 X_1^m}{dx^2} \tag{A.16}$$

Multiplying (A.15) by $-X_1^m$ and (A.16) by X_1^n and then adding them we get

$$((\lambda_1^n)^2 - (\lambda_1^m)^2) X_1^n X_1^m = \frac{d^2 X_1^m}{dx^2} X_1^n - \frac{d^2 X_1^n}{dx^2} X_1^m$$

Integrating now from 0 to 1

$$\begin{aligned}((\lambda_1^n)^2 - (\lambda_1^m)^2) \int_0^1 X_1^n X_1^m dx &= \int_0^1 \frac{d^2 X_1^m}{dx^2} X_1^n - \frac{d^2 X_1^n}{dx^2} X_1^m dx \\ &= \frac{dX_1^m}{dx} X_1^n \Big|_0^1 - \frac{dX_1^n}{dx} X_1^m \Big|_0^1 \\ &= -k X_1^m X_1^n \Big|_1 + X_1^n X_1^m \Big|_1 \\ &= 0\end{aligned}$$

Finally we just need to remember that $\lambda_1^n \neq \lambda_1^m$ and (A.14) follows. □

A.2.2 Square $L^2(0,1)$ norm of $X_1^n(x)$

In order to find the square $L^2(0,1)$ norm of $X_1^n(x)$ we have the following theorem

Theorem A.4. *The square* $L^2(0,1)$ *norm of* $X_1^n(x)$ *is given by*

$$\int_0^1 (X_1^n(x))^2 dx = \frac{(\lambda_1^n)^2 + k\cos^2(\lambda_1^n)}{2(\lambda_1^n)^2} \tag{A.17}$$

Proof. As before we multiply (A.15) by $X_1^n(x)$ and then we integrate from 0 to 1

$$\begin{aligned}-(\lambda_1^n)^2 \int_0^1 (X_1^n(x))^2 dx &= \int_0^1 \frac{d^2 X_1^n}{dx^2} X_1^n dx \\ &= \frac{dX_1^n}{dx} X_1^n \Big|_0^1 - \int_0^1 \left(\frac{dX_1^n}{dx}\right)^2 dx \\ &= -k(X_1^n(1))^2 - \int_0^1 \left(\frac{dX_1^n}{dx}\right)^2 dx \end{aligned} \tag{A.18}$$

Adding $-(\lambda_1^n)^2 \int_0^1 (X_1^n(x))^2 dx$ to both sides of (A.18) and dividing over $-2(\lambda_1^n)^2$ we get

$$\begin{aligned}
\int_0^1 (X_0^n(x))^2 dx &= \frac{k\cos^2(\lambda_1^n)}{2(\lambda_1^n)^2} + \frac{1}{2}\int_0^1 \frac{1}{(\lambda_1^n)^2}\left(\frac{dX_1^n}{dx}\right)^2 + (X_1^n(x))^2 dx \\
&= \frac{k\cos^2(\lambda_1^n)}{2(\lambda_1^n)^2} + \frac{1}{2}\int_0^1 \frac{1}{(\lambda_1^n)^2}(-\lambda_1^n \sin(\lambda_1^n x))^2 + \cos^2(\lambda_1^n x) dx \\
&= \frac{k\cos^2(\lambda_1^n)}{2(\lambda_1^n)^2} + \frac{1}{2} \\
&= \frac{(\lambda_1^n)^2 + k\cos^2(\lambda_1^n)}{2(\lambda_1^n)^2}
\end{aligned}$$

this finishes the proof □

Appendix B

The Volterra integral equation of second kind

B.1 Banach's fixed point theorem

Banach'e fixed point theorem assures the existence and uniqueness of fixed points of certain functions of a metric space on itself. This theorem gives a constructive method to obtain a fixed point trought a iteration method.

Let $X = (X, d)$ a metric space.

Definition B.1. A function $\phi_\lambda : X \longrightarrow X$ is called a **contraction** if exists $\alpha \in (0, 1)$ such that

$$d(\phi(t), \phi(\tau)) \leq \alpha d(t, \tau) \qquad \forall t, \tau \in X \tag{B.1}$$

This is, a contraction it is a function of a metric space in itself that is Lipschitz continuous with Lipschitz constant strictly less than 1.

Definition B.2. A point $x^* \in X$ is called a fixed point of function $\phi : X \longrightarrow X$ if $\phi(x^*) = x^*$.

We deonte by ϕ^k the composition

$$\phi^k = \underbrace{\phi \circ \cdots \circ \phi}_{ktimes} \text{ if } k \in \mathbb{N} \qquad \phi^0 = id_X, \tag{B.2}$$

where $id_X : X \longrightarrow X$ is the identity function.

Theorem B.3. *Let X a complete metric space, non empty, and let $\phi : X \longrightarrow X$ a contraction. Then the following is true*

1. *ϕ has a unique fixed point x^*.*
2. *For any $x_0 \in X$ the succession $(\phi^k(x_0))$ converges to x^* in X, and it follows that*

$$d(\phi^k(x_0), x) \leq \frac{\alpha^k}{1-\alpha} d(\phi(x_0), x_0), \tag{B.3}$$

where $\alpha \in (0,1)$ satisfies (B.1).

Proof. Let x_0 any point of X_0 and let's denote by

$$x_k = \phi^k(x_0).$$

We will proof first that the sequence (x_k) is Cauchy in X. Note that, if ϕ satisfies (B.1), then

$$d(x_{k+1}, x_k) = d(\phi^k(x_1), \phi^k(x_0)) \leq \alpha^k d(x_1, x_0) \qquad \forall k \in \mathbb{N}.$$

Also, for any y, $z \in \mathbb{N}$, it follows that

$$\begin{aligned} d(y,z) &\leq d(y, \phi(y)) + d(\phi(y), \phi(z)) + d(\phi(z), z) \\ &\leq d(y, \phi(y)) + \alpha d(y,z) + d(\phi(z), z), \end{aligned}$$

this is

$$(1-\alpha) d(y,z) \leq d(y, \phi(y)) + d(\phi(z), z).$$

Tomando $y = x_k$ and $z = x_j$ we get

$$d(x_k, x_j) \leq \frac{d(x_{k+1}, x_k) + d(x_{j+1}, x_j)}{1-\alpha} \leq \frac{\alpha^k + \alpha^j}{1-\alpha} d(x_1, x_0). \tag{B.4}$$

Let $\epsilon > 0$. Because $\alpha \in (0,1)$ exists $k_0 \in \mathbb{N}$ such that

$$\frac{\alpha^k}{1-\alpha} d(x_1, x_0) < \frac{\epsilon}{2} \qquad \forall k \geq k_0.$$

As a consequence,

$$d(x_k, x_j) < \epsilon \qquad \forall j, k \geq k_0.$$

This proofs that the succession (x_k) is Cauchy in X. As X is complete, exists $x^* \in X$ such that $x_k \longrightarrow x^*$ in X and, due that ϕ is continuous, then we have that $x_{k+1} = \phi(x_k) \longrightarrow \phi(x^*)$ in X. Because the limit of a succession is unique, we conclude that $\phi(x^*) = x^*$, that is, x^* is a fixed point of ϕ.

Let's see that x^* is unique. If x_1^* and x_2^* are fixed points of ϕ then

$$d(x_1^*, d_2^*) = d(\phi(x_1^*, x_2^*)) \leq \alpha d(x_1^*, x_2^*).$$

Because $\alpha < 1$, this inequality inplies that $d(x_1^*, x_2^*) = 0$, this is, $x_1^* = x_2^*$. Finally, making $j \longrightarrow \infty$ in (B.4) we get that

$$d(x_k, x^*) = \lim_{j \longrightarrow \infty} \leq \frac{\alpha^k}{1-\alpha} d(x_1, x_0) \qquad \forall k \in \mathbb{N}.$$

This concludes the proof. □

B.2 Existence and Uniqueness of the solution

Let's consider the equation

$$\lambda y(t) - \int_0^t K(t,\tau) y(\tau) d\tau = f(t) \qquad \forall\ t \in [a,b] \tag{B.5}$$

where $K : [a,b] \times [a,b] \longrightarrow \mathbb{R}$ and $y : [a,b] \longrightarrow \mathbb{R}$ are given continuous functions and λ is a real number. A equation of this type is called a Volterra integral equation of second kind.

We want to express the solutions of (B.5) as fixed points of a function $\phi_\lambda : \mathcal{C}^0[a,b] \longrightarrow \mathcal{C}^0$. In order to do that , for each function $y(t) \in \mathcal{C}^0[a,b]$ we associate the function $\mathfrak{D}y : [a,b] \longrightarrow \mathbb{R}$ given by

$$(\mathfrak{D}y)(t) := \int_a^t K(t,\tau) y(\tau) d\tau \tag{B.6}$$

In terms of this function, equation (B.5) is written as

$$\lambda y - \mathfrak{D}y = f \tag{B.7}$$

We will prove that $\mathfrak{D} \in [a,b]$ If $\lambda \neq 0$ we can then define a function of $\mathcal{C}^0[a,b]$ in itself as follows

$$\phi_\lambda : \mathcal{C}^0[a,b] \longrightarrow \mathcal{C}^0[a,b], \qquad \phi_\lambda(y) = \frac{1}{\lambda}(\mathfrak{D}y + f) \tag{B.8}$$

The fixed points of this operator are the solutions of (B.5). We are going to prove that for each $\lambda \neq 0$ there exists $k \in N$ such that ϕ_λ^k is a contraction. Then by Banach fixed point theorem, ϕ_λ has a unique fixed point, i.e. equation (B.5) has a unique solution.

Theorem B.4. *For each $y \in \mathcal{C}^0[a,b]$, the operator $\mathfrak{D}y : [a,b] \longrightarrow \mathbb{R}$ given by*

$$(\mathfrak{D}y)(t) = \int_0^t K(t,\tau)y(\tau)d\tau \tag{B.9}$$

is continuous

Proof. Let $y \in \mathcal{C}^0[a,b]$. If $y = 0$ then $\mathfrak{D}y = 0$. If $y \neq 0$, then due that in any compact metric space every continuous function is uniform continuous, we have that for each $\epsilon > 0$ there exists $\delta > 0$ such that

$$|K(t_1,\tau_1) - K(t_2,\tau_2)| < \frac{\epsilon}{2(b-a)\left\|y\right\|_\infty} \qquad \text{if } \|(t_1,\tau_1) - (t_2,\tau_2)\| < \delta \tag{B.10}$$

In consequence, if $|t_1 - t_2| < \min\left\{\delta, \frac{\epsilon}{2\|K\|_\infty \|y\|_\infty}\right\}$ and $t_1 \leq t_2$ we have that

$$\begin{aligned}
|(\mathfrak{D}y)(t_1) - (\mathfrak{D}y)(t_2)| &= \left| \int_a^{t_1} (K(t_1,\tau) - K(t_2,\tau))y(\tau)d\tau - \int_{t_1}^{t_2} K(t_2,\tau)|y(\tau)|d\tau \right| \\
&\leq \int_a^{t_1} |K(t_1,\tau) - K(t_2,\tau)||y(\tau)|d\tau + \int_{t_1}^{t_2} |K(t_2,\tau)||y(\tau)|d\tau \\
&< (t_1 - a)\frac{\epsilon}{2(b-a)\left\|y\right\|_\infty}\left\|y\right\|_\infty + \frac{\epsilon}{2\left\|K\right\|_\infty \left\|y\right\|_\infty}\left\|K\right\|_\infty \left\|y\right\|_\infty \\
&\leq \frac{\epsilon}{2} + \frac{\epsilon}{2} = \epsilon.
\end{aligned}$$

This proves $\mathfrak{D}y$ is continuous. □

Given $\lambda \neq 0$ and $f \in \mathcal{C}^0[a,b]$, we define $\phi_\lambda : \mathcal{C}^0[a,b] \longrightarrow \mathcal{C}^0[a,b]$ as

$$\phi_\lambda(y) = \frac{1}{\lambda}(\mathfrak{D}y + f).$$

The previous Theorem assures that ϕ_λ is, in fact, a function of $\mathcal{C}^0[a,b]$ in itself. Let's prove the following result

Theorem B.5. *The function ϕ_λ satisfies the inequality*

$$\left\|\phi_\lambda^k(y_1) - \phi_\lambda^k(y_2)\right\|_\infty \leq |\lambda|^{-k}\left\|K\right\|_\infty^k \frac{(b-a)^k}{k!}\left\|y_1 - y_2\right\|_\infty, \tag{B.11}$$

with $\phi^k = \phi \circ \cdots \circ \phi$ (k times) and for all $y_1, y_2 \in \mathcal{C}^0[a,b]$, $k \in \mathbb{N}$.

Proof. We will prove that

$$|\phi_\lambda^k(y_1)(t) - \phi_\lambda^k(y_2)(t)| \leq \frac{(|\lambda|^{-1} \|K\|_\infty (t-a))^k}{k!} \|y_1 - y_2\|_\infty \qquad \forall t \in [a,b]. \quad \text{(B.12)}$$

For $k = 1$ we have that

$$\begin{aligned} |\phi_\lambda^k(y_1)(t) - \phi_\lambda^k(y_2)(t)| &\leq \frac{1}{|\lambda|} \int_a^t |K(t,\tau)||y_1(\tau) - y_2(\tau)| d\tau \\ &\leq \frac{1}{|\lambda|} \|K\|_\infty (t-a) \|y_1 - y_2\|_\infty . \end{aligned}$$

Let's suppose that the inequality (B.12) is valid for $k-1$. Then

$$\begin{aligned} |\phi_\lambda^k(y_1)(t) - \phi_\lambda^k(y_2)(t) &\leq \frac{1}{|\lambda|} | \int_a^t |K(t,\tau)||\phi_\lambda^{k-1}(y_1)(\tau) - \phi_\lambda^{k-1}(y_2)(\tau)| d\tau \\ &\leq \frac{\|K\|_\infty}{|\lambda|} \int_a^t |\phi_\lambda^{k-1}(y_1)(\tau) - \phi_\lambda^{k-1}(y_2)(\tau)| d\tau \\ &\leq \frac{\|K\|_\infty^k}{|\lambda|^k} \|y_1 - y_2\|_\infty \frac{(t-a)^k}{k!}. \end{aligned}$$

This proves inequality (B.12). From it follows that

$$|\phi_\lambda^k(y_1)(t) - \phi_\lambda^k(y_2)(t)| \leq |\lambda|^{-k} \|K\|_\infty \frac{(b-a)^k}{k!} \|y_1 - y_2\|_\infty \qquad \forall t \in [a,b]$$

and, in consequence

$$\left\| \phi_\lambda^k(y_1) - \phi_\lambda^k(y_2) \right\|_\infty \frac{(|\lambda|^{-1} \|K\|_\infty (b-a))^k}{k!} \|y_1 - y_2\|_\infty ,$$

as the Theorem states. □

Theorem B.6. *If $\lambda \neq 0$ then, for each $f \in \mathcal{C}^0[a,b]$, the Volterra integral equation (B.5) has a unique solution.*

Proof. We know that there exists $k_0 \in \mathbb{N}$ such that

$$\frac{(\|\lambda|^{-1} \|K\|_\infty (b-a))^k}{k!} < 1 \qquad \forall k \geq k_0.$$

By the previous theorem, for each $k \geq k_0$, the function $\phi_\lambda^k : \mathcal{C}^0[a,b] \longrightarrow \mathcal{C}^0[a,b]$ is a contraction. From Banach's fixed point theorem it follows that ϕ_λ has a unique fixed point, i.e. equation (B.5) has a unique solution. □

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