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Diffusion, viscoelasticity and erosion: Analytical study and medical applications

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0. ABSTRACT

The aim of this thesis, consisting of four chapters, is the mathematical analysis of transport in viscoelastic and biodegradable materials and their application in controlled drug release in ophthalmology.

From the physical point of view the problem lies in understanding the mechanisms that regulate absorption of a solvent by a polymeric matrix and/or the release of a dispersed solute. These transport phenomena are classically described by Fick's Law. In the case of polymeric materials, experimental results show that it doesn't provide an accurate description. Many researchers, experimentalists and theoreticians, consider this lack of accuracy is justified by the neglecting of the rheological properties of the materials and that Fick's law must be modified to include the influence of viscoelasticity. When the polymer is biodegradable, transport is governed in addition by degradation, which is characterized by the breaking of the bonds between the polymeric chains.

In Chapter 1 the problem of transport in viscoelastic and biodegradable materials is presented.

In Chapter 2 a model that describes *in vitro* transport of a solute through a viscoelastic, biodegradable material is studied. The model is based on three partial differential equations which include Fickian diffusion, viscoelasticity and material degradation. The stability of the continuous model and of the discrete model are proved, under a mathematical condition that hides a solid physical sense.

In Chapter 3 the transport of a drug *in the vitreous chamber of the eye* is addressed. A mathematical model obtained by coupling the system studied in Chapter 2, with another system which describes the transport of drug into the vitreous humor is used to describe *in vivo* delivery.

In Chapter 4 a complete model of *in vitro* drug delivery is presented. It comprises the sorption of a solvent, the dissolution of a drug and its release. The model is defined by a system of quasi-linear partial differential equations. The stability of an initial value problem associated with the system is studied.

For all models studied in this thesis, numerical simulations that illustrate their dynamic behaviour and their dependence on the parameters involved are exhibited.

In Chapter 5 we present some concluding remarks and describe issues that were raised in the course of the work of recent years and that we plan to address in the near future.

0. RESUMO

O objectivo desta tese, composta por quatro capítulos, é a análise matemática da difusão em materiais viscoelásticos e biodegradáveis e a sua aplicação em libertação controlada de fármacos no campo da oftalmologia.

Do ponto de vista físico o problema que importa conhecer é a absorção de um solvente através de uma matriz polimérica e/ou a libertação de um soluto disperso nessa matriz. Estes fenómenos de transporte são classicamente descritos pela Lei de Fick. No caso dos materiais poliméricos os resultados experimentais mostram que o comportamento da difusão se afasta muito do comportamento prescrito pela Lei de Fick. Muitos investigadores consideram que este afastamento se justifica pelas propriedades mecânicas dos materiais e que a Lei de Fick deve ser modificada de modo a incluir a influência da viscoelasticidade. Quando o polímero é biodegradável a difusão é governada também pela degradação do polímero que caracterizada pela ruptura das ligações entre as suas cadeias.

No Capítulo 1 introduz-se o problema da difusão em meios viscoelásticos e biodegradáveis.

No Capítulo 2 apresenta-se um modelo que descreve o transporte *in vitro* de um soluto através de um material viscoelástico e biodegradável. O modelo baseia-se num sistema de três equações de derivadas parciais que incluem difusão Fickiana, viscoelasticidade e degradação. A estabilidade, do modelo contínuo e de um modelo discreto, é provada, através da imposição de uma condição de carácter matemático, que se revela com sólido sentido físico.

No capítulo 3 aborda-se o transporte de um fármaco *in vivo*. O problema que se estuda é a libertação de um fármaco através de um implante biodegradável que é colocado no vítreo. O sistema que descreve o fenómeno resulta do acoplamento do sistema estudado no Capítulo 2, com um outro que descreve o transporte de fármaco no tecido vivo.

No capítulo 4 apresenta-se um modelo completo de libertação *in vitro*. A matriz, contendo um fármaco disperso, entra em contacto com o solvente e inicia-se o processo de degradação, com a progressiva diminuição do peso

molecular. O modelo é definido por um sistema de equações de derivadas parciais quase-lineares. É estudada a estabilidade de um problema de valor inicial associado ao sistema.

São exibidas simulações numéricas que ilustram o comportamento dinâmico de todos os modelos apresentados e a sua dependência em relação aos parâmetros envolvidos.

No capítulo 5 apresentamos algumas observações finais e descrevemos problemas suscitados ao longo do trabalho dos últimos anos e que planeamos abordar num futuro próximo.

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1. INTRODUCTION

In the past few decades diffusion through viscoelastic materials has attracted the attention of many researchers ([1, 2, 3, 4, 5]). Apart from the mathematical interest of the topic such research focus is also explained by the increasing practical use of polymer in coatings, packaging, membranes for transdermal drug delivery or more generally in controlled drug delivery ([3, 6]). There is a huge literature in the field of controlled drug delivery. Some of these studies have an experimental character, others are completed with mathematical models. We mention without being exhaustive [7, 8, 9, 10] for the first type of studies and [9, 11, 12, 13, 14] for the second type of approach. Mathematical modeling of drug delivery is a domain of great academic and industrial importance because the computational simulation of new drug delivery systems significantly increases their accuracy and avoids costly laboratorial experiments.

In this dissertation we address the analytical and numerical study of the diffusion of a solute in a viscoelastic degradable material and its release to an external medium. The mathematical results established will be used to study the pharmacokinetics of drug eluting from ophtalmic intravitreal implants. Our study has a theoretical character in the sense that the results obtained have not yet been compared with *in vitro or in vivo* experiments.

It is well known that the diffusion of a solute through a viscoelastic material does not obey Fick's law [5, 14, 15, 16, 17]. Though all the mechanisms that affect Brownian motion are not completely known, many scientists consider that the building up of a viscoelastic stress in the material is a determinant factor. In fact the viscoelastic matrix opposes a resistance to the Brownian motion of molecules that can be quantified by the stress response to the strain induced by these molecules (Figure 1.1). Several authors ([1, 2, 3, 4, 5, 9, 13, 14, 18, 19]) have proposed a general model where the flux is caused by two separate phenomena: a concentration gradient of a solute dispersed in a polymeric matrix and a stress gradient developed by

the matrix. This flux is represented by

$$J = -D_1 \nabla C_1 - D_v \nabla \sigma, \tag{1.1}$$

where C_1 is a solute concentration, σ represents the stress response of the matrix to the strain exerted by drug molecules, D_1 stands for the diffusion tensor of the solute and D_v is a stress driven tensor whose meaning will be clarified in Chapter 2. Equation (1.1) replaces the classical Fick's first law, that is obtained considering $D_v = 0$. Equation (1.1) is coupled with the mass conservation equation

$$\frac{\partial C_1}{\partial t} = -\nabla \cdot J. \tag{1.2}$$

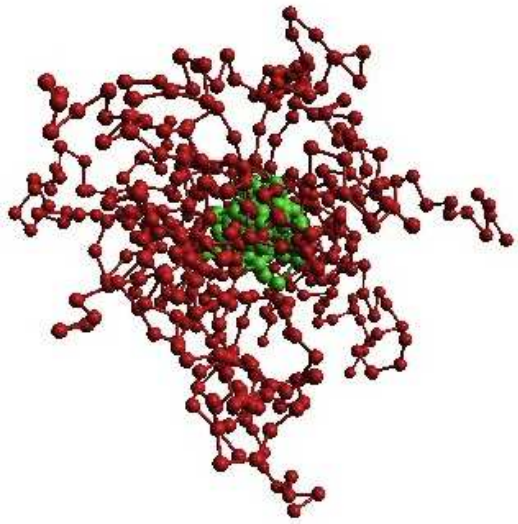


Fig. 1.1: Drug molecules dispersed in a viscoelastic matrix (http://itn-snal.net/2013/12/01/polymer-micelles-drug-carriers/)

The viscoelastic stress σ is related to the concept of relaxation time, τ, that is defined as the time it takes a polymeric chain to react to a change in another chain. To have a better insight of the delaying effect of the relaxation time we can interpret the non Fickian part of the flux (1.1), J_{NF},

$$J_{NF} = -D_v \nabla \sigma, \tag{1.3}$$

under that viewpoint. As the non Fickian flux acts as a counterflux which represents the opposition of the polymer to the release of the solute, and for

this reason it points in the direction of higher concentrations, we can write

$$J_{NF}(t+\tau) = -\widetilde{D}_1 J_F(t), \tag{1.4}$$

where $\widetilde{D}_1$ is a positive constant and J_F represents the Fickian flux with

$$J_F = -D_1 \nabla C_1.$$

For τ small enough and for one dimensional situation, equation (1.4) leads to an ordinary differential equation whose approximated solution can be expressed by the memory term

$$J_{NF} = -\frac{\widetilde{D}_1}{\tau} \int_0^t e^{-\frac{t-s}{\tau}} J_F(s) ds, \tag{1.5}$$

where $J_F(0) = 0$. Equations (1.3) and (1.5) suggest that, for a homogeneous initial stress, we have

$$\nabla \sigma = -\frac{\widetilde{D}_1 D_1}{D_v \tau} \int_0^t e^{-\frac{t-s}{\tau}} \nabla C_1(s) ds. \tag{1.6}$$

An analogous explanation holds to describe the stress response of a viscoelastic material to the strain exerted by the molecular of an incoming solvent. We postpone until Chapter 2 an explanation of the relation existing between this approach and the direct use of mechanistic models to define the stress in function of the strain exerted by the molecules of drug.

In recent years the need to control polymer waste has become a great concern. The replacement of synthetic polymers by biodegradable polymers which degrade due to microbial action can give a contribution to soften the problem. When the polymeric matrix is biodegradable the transport of molecules is no more described by (1.1)-(1.2) and a more complex system must be considered. In the case of medical applications, as drug eluting implants for ophtalmic drug delivery to the vitreous or implants to deliver drugs to other specific sites, the use of biodegradable matrices avoids the need of an a *posteriori* surgery to remove the device after the drug has been released.

In this case a biodegradable device containing a drug is implanted in the human body (Figure 1.2). When the polymeric implant containing a drug contacts with a biological fluid, the first event that occurs is solvent uptake,

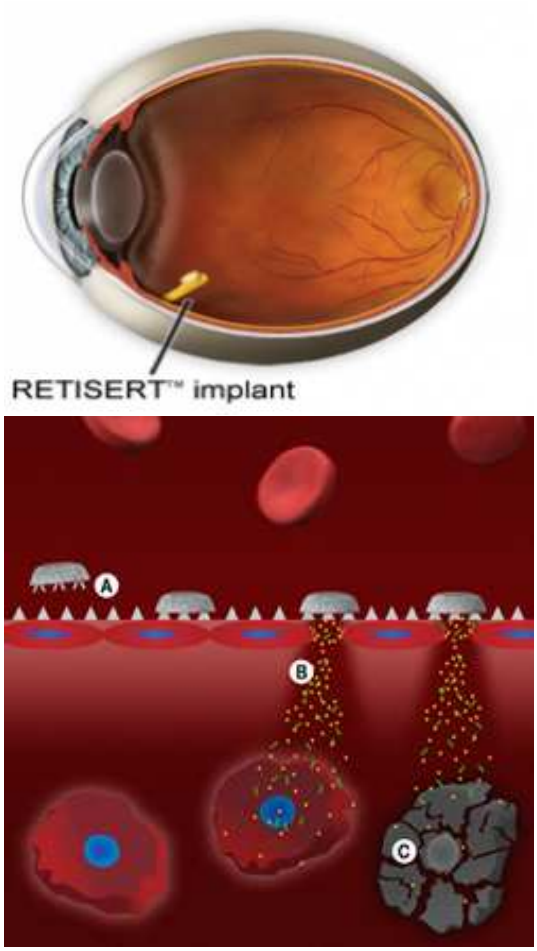


Fig. 1.2: -Top: An intravitreal implant(http://retinavitreouscenter.net /wbcntntprd/wp-content/uploads/Retisert-300x234.png)
-Bottom: A subcutaneous implant with an anticancerigenous drug ($http://www.nanotech-now.com/news.cgi?story_id=27008$)

that can be accompanied by the swell of the matrix. The molecules of the solute (drug) begin then to diffuse by the coupled action of Brownian motion and the opposition of the polymer chains as described by (1.1)-(1.2). Simultaneously an irreversible phenomenon called hydrolisis- the cleavage of chemical bonds by the addition of water or other solvent- causes the progressive breakage of the chemical bonds between polymeric chains, enhancing the release of the solute. This is followed by bioassimilation of the polymer fragments. This bioassimilation explains why a surgery is not required to remove the implant.

The enhancement of drug release has two causes. One is due to the fact that the cleavage of bonds creates more void spaces inside the polymer and consequently the drug has new paths to diffuse; another is that as the chains have a smaller molecular weight they can more easily migrate from the matrix core dragging the molecules of drug. The delivery of a drug dispersed in a polymeric matrix is then governed by:

- the Fickian diffusion of the molecules in the void spaces of the polymer;
- the opposition of the polymeric chains that exerts a stress on the molecules as a response to the strain they induce in the polymeric structure;
- the enhancement caused by the material degradation.

As degradation proceeds the polymer molecular weight decreases and the new diffusional paths opened through the matrix create void spaces that is increase the permeability of the matrix. The diffusion tensor of the solute is no more constant and its dependence on the molecular weight must be considered ([20]). A first order reaction term that describes the degradation of the polymeric chains is then added to (1.1), (1.2). The equation that describes the diffusion of a solute dispersed in a polymeric degradable matrix is then

$$\frac{\partial C_1}{\partial t} = \nabla \cdot (D_1(M)\nabla C_1 + D_v \nabla \sigma) - k_1 C_1, \tag{1.7}$$

where k_1 represents the degradation rate. In (1.7) $D_1(M)$ represents a diffusion tensor depending on the molecular weight M of the polymer. Degradation can occur homogeneously in the matrix bulk or only in the surface (Figure 1.3) [20, 21, 22, 23]. In the first case- bulk degradation- the penetration of the solvent is much faster than polymer degradation; in the second

case- surface erosion- polymer degradation proceeds at a faster rate than the water uptake.

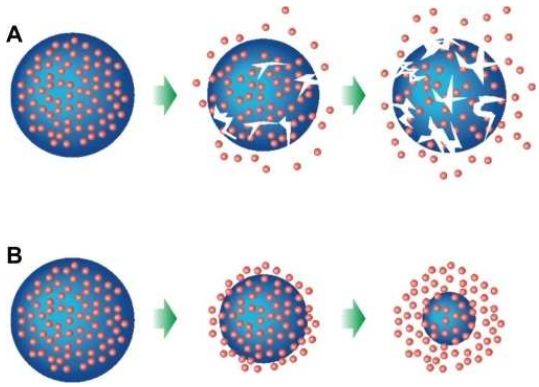


Fig. 1.3: Bulk erosion (A) and surface erosion (B) ($http : //openi.nlm.nih.gov/imgs/512/203/3124394/3124394_i jn - 6 - 877f3.png$)

All degradable polymers can undergo surface erosion or bulk erosion. Following [24] the way a matrix degrades depends on the diffusivity of the solvent inside the matrix, the degradation rate of the polymeric chains and also the matrix dimension. The release of a solute from a bulk degrading polymer is mainly driven by diffusion; in the case of a surface- degrading polymer it is not possible to indicate which of the three phenomenon, diffusion, visco-elasticity and erosion is dominant. It depends on the properties of the polymer and the solute.

To describe diffusion from a biodegradable polymeric matrix, equation (1.7) is completed with two other equations: one that describes the mechanistic behaviour of the polymer, that is a relation between stress and strain; and another equation that represents the evolution of the polymer molecular weight as the solute concentration evolves. The model composed by these three equations is completed with initial and boundary conditions. To the best of our knowledge the simultaneous effect of diffusion, viscoelasticity and degradation has not been studied in the mathematical literature.

The description we have previously presented assumes an instantaneous uptake of the matrix after contact with a solvent. However instantaneous uptake represents an approximation of the real phenomenon. To model accurately the release of a solute we consider the sorption of the solvent and

evolution of its concentration inside the matrix. The system of three partial differential equation considered in Chapter 2, which variables are solute concentration, stress and molecular weight, must be completed with a fourth equation that describes the evolution of solvent concentration.

This thesis is organized in four chapters where we address the pharmacokinetics of a solute dispersed in a biodegradable viscoelastic matrix in progressively more complex frameworks. In Figure 1.4 we summarize the content of Chapters 2, 3 and 4. We remark that the existence and regularity of the solution will not be addressed in this thesis. In all the problems treated we assume that the solutions exist and have the regularity required by the mathematical techniques used.

In Chapter 2 a mathematical model of the diffusion of a solute through a viscoelastic biodegradable material is presented. The qualitative behaviour of the released mass of solute is studied through an a priori energy estimate. We show that the continuous model is stable, under initial perturbations, and for bounded intervals of time, by imposing some conditions on the parameters. These conditions which at a first sight appear as a technical tool, in the sense that they represent mathematical constraints needed to establish the result, revealed to have a sound physical meaning. In fact they essentially say that if the Fickian diffusion dominates the non Fickian one, the mathematical model is stable. If we translate this constraint in physical terms it indicates that to have an effective release of the solute, the Fickian diffusion must overcome the opposition of the polymer represented by the stress it exerts on the solute molecules. Following an approach first introduced in [25] we obtain a sharper stability inequality which holds for any time. We consider a semi-discrete version of the model by discretizing the spatial derivatives with finite differences operators and we establish energy estimates which are semi-discrete versions of the continuous ones. Finally a fully discrete method is analyzed and an energy estimate analogous to the continuous one, from a formal viewpoint, is obtained. To illustrate the behaviour of the model and to give some insight on the dependence of the solution on the parameters, we exhibit several numerical simulations. Physical and physiological values of the parameters are used in these numerical simulations. These values satisfy the constraints assumed to establish the theoretical stability results. This fact suggests that such constraints are not artificial mathematical artifacts but represent natural conditions.

The results presented in Chapter 2 are extensions of the results included in the work:

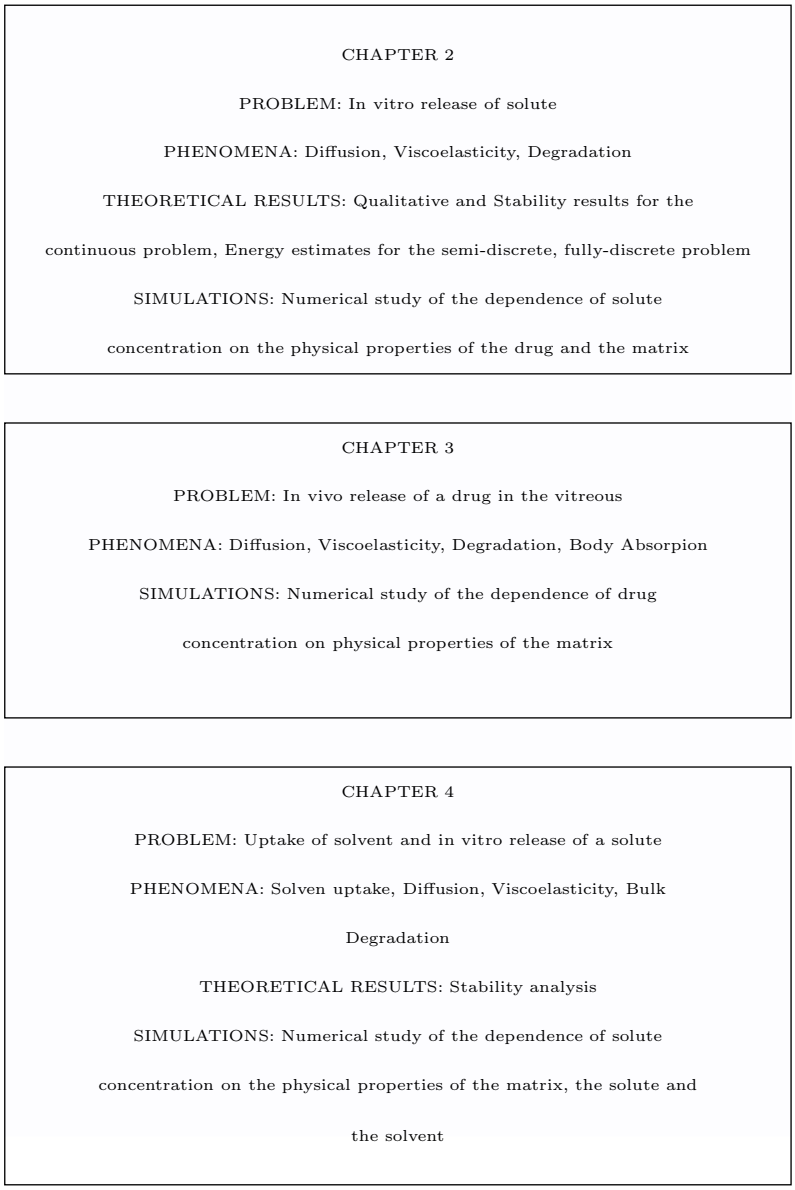


Fig. 1.4: Content of chapters

E. Azhdari, J.A. Ferreira, P. de Oliveira, P.M. da Silva, Analytical and numerical study of diffusion through biodegradable viscoelastic materials, Proceedings of the 13th International Conference on Computational and Mathematical Methods in Science and Engineering, CMMSE 2013, I (2013), 174-184.

In Chapter 3 a medical application in the field of controlled drug delivery is addressed. In a drug delivery process the main actors are the living system, the composition of the drug, the polymeric matrix where it is dispersed and the external conditions of release as for example the presence of an electric field or a heat source.

To obtain a predefined release profile, the mechanisms of control can act essentially on the polymeric matrix and the external conditions. Delivering drugs to the vitreous chamber of the eye assumes a crucial role and is a challenging problem due to the presence of various physiological and anatomical barriers. Classical ocular drug delivery systems for segment diseases fall under one of the following categories:

- Systemic delivery: systemic administration of drugs to the blood stream directly, in the form of injections, or by absorption into the blood stream in the form of pills.

- Topical delivery: topical delivery in the form of ophthalmic drops which is the most common method used to treat ocular diseases.

However none of these drug delivery systems are effective. In fact systemic delivery is not effective because the drug concentration carried by the blood stream is not enough, which means that it does not reach the therapeutic window. With topical delivery just a small fraction of drug reaches the posterior segment of the eye due to physiological barriers. These classical drug delivery systems are being replaced by direct intravitreal injection or intravitreal implants of drug (Figure 1.5). As vitreal injections imply several treatments and can cause deleterious side effects, intravitreal implants have deserved much attention these last years ([26, 27, 28]). In fact there are a number of severe diseases that can affect the vitreous and the retina, which must be treated over long periods of time and where drugs must be maintained in their therapeutic windows . Among these diseases we mention:

- Age-related macular degeneration which is a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field because of damage to the retina;

- Glaucoma that is an eye disease in which the optic nerve is damaged and that is normally associated with an increased fluid pressure in the anterior chamber of the eye;

- Diabetic retinopathy which is a retinopathy caused by complications of diabetes, that affect the blood vessels of the retina. Usually affects older adults and results in a loss of vision in the center of the visual field because of damage to the retina.

Many drugs have a narrow concentration window of effectiveness and may be toxic at higher concentration ([29]), so the ability to predict local drug concentrations is necessary for proper designing of the delivery system. A big challenge in the drug delivery field is the study of the mathematical models that describe the simultaneous processes of drug release and absorption by the human body. Mathematical models which couple drug delivery from a device with the transport in the living system play a central role because not only they can be used to explain the kinetics of the delivery by describing the interplay of the different phenomena but also they quantify the effect of physical and physiological parameters in the delivery trend. Several authors have studied Fickian mathematical models to describe transport and elimination of drugs in the vitreous [29, 30, 31, 32, 33, 34]. However at the best of our knowledge the *in vivo* delivery of drug from a viscoelastic biodegradable implant has not yet been addressed.

In Chapter 3 we will propose a model to simulate intravitreal delivery of drug through viscoelastic biodegradable implants (Figure 1.6). The model consists of coupled systems of partial differential equations linked by interface conditions. One of the systems describes the diffusion of drug in the polymeric biodegradable implant; the other models the transport of drug in the vitreous, which is a porous medium. The geometry of the vitreous chamber of the eye and of the intravitreal implant are described and the mathematical coupled model is presented. We briefly explain the mass behaviour of the materials in the phenomenological approach. We present a variational formulation for the continuous model and using an implicit- explicit finite element method, we establish a discrete variational form. Finally, numerical simulations that illustrate the kinetics of the drug release and show the effect of degradation and viscoelasticity are exhibited in the last section.

The results presented in Chapter 3 are generalizations of the results included in the works:

Fig. 1.5: Applicator used to insert an implant in the vitreous
(*http* : *//eyewiki.aao.org/File* : *Ozurdex.ipg*)

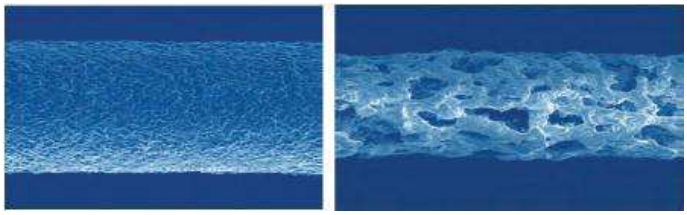


Fig. 1.6: An intravitreal implant composed of a biodegradable polymer
(*http* : *//eyewiki.aao.org/images*/1/8/85/*Device.ipg*)

- E. Azhdari, J.A. Ferreira, P. de Oliveira, P.M. da Silva, Drug delivery from an ocular implant into the vitreous chamber of the eye. Proceedings of the 13th International Conference on Computational and Mathematical Methods in Science and Engineering, CMMSE 2013, I (2013) 185-195.

- E. Azhdari, J.A. Ferreira, P. de Oliveira, P.M. da Silva, Diffusion, viscoelasticity and erosion: analytical study and medical applications, accepted for publication in Journal of Computational and Applied Mathematics (2014).

In Chapters 2 and 3 the uptake of solvent, by the polymeric matrix, that initiates the kinetics of drug is not taken into account. In these chapters we assume that the sorption of solvent has already taken place which means that the sorption of the solvent is much faster than the degradation rate and consequently that a bulk erosion is occurring. In Chapter 4 we present a detailed model of *in vitro* release, where the kinetics of the solvent is coupled with the kinetics of drug. We consider a biodegradable viscoelastic polymeric matrix with a limited amount of drug which is in contact with water. As the water diffuses into the matrix, a hydration process takes place and the viscoelastic properties of the polymer are modified. In contact with water, the polymeric weight decreases and the drug dissolves and diffuses. The whole model is composed by a set of partial differential equations that describe the entrance of water into the polymer, the hydrolysis process, the decreasing of the molecular weight, the evolution of the stress and strain, the dissolution process and the diffusion of the dissolved drug. Numerical simulations that illustrate the evolution of drug concentration in the case of bulk erosion are exhibited.

2. ANALYTICAL AND NUMERICAL STUDY OF DIFFUSION, VISCOELASTICITY AND DEGRADATION

In this chapter the transport of a drug through a biodegradable viscoelastic material is studied. The phenomenon is described by a set of three coupled partial differential equations that take into account passive diffusion, stress driven diffusion and the degradation of the material. The qualitative behaviour of the released mass is studied through an *a priori* energy estimate. A semi-discrete and a fully-discrete version of this energy estimate is also studied. We show that the solution of the continuous model is bounded for bounded intervals of time. By following [25] and imposing some conditions on the parameters we obtain a sharper inequality which holds for any time. By using energy estimates we also establish the stability of the model under initial perturbations. When Dirichlet boundary conditions for concentration are replaced by Robin boundary conditions we prove that the solution of the problem presents the same boundedness properties. Finally, in the last section, numerical simulations that illustrate the influence of diffusion, viscoelasticity and degradation parameters are exhibited. In these simulations, as in several other numerical experiments that have been carried on, qualitative agreement with the expected physical behaviour is observed. These findings suggest the effectiveness of our approach.

2.1 Mathematical model

We consider a biodegradable viscoelastic material filling a bounded domain $\Omega_1 \subset \mathbb{R}^2$ with boundary $\partial\Omega_1$. A certain amount of drug is dispersed in Ω_1. We suppose that when Ω_1 enters in contact with a penetrant solvent an instantaneous swelling occurs. The drug then dissolves in the solvent and its transport through Ω_1 is driven by diffusion, viscoelasticity and degradation. We describe these phenomena by the system of

$$\begin{cases} \dfrac{\partial C_1}{\partial t} = \nabla \cdot (D_1(M)\nabla C_1) + \nabla \cdot (D_v \nabla \sigma) - k_1 C_1 & \text{in } \ \Omega_1 \times (0,T], \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E}{\mu}\sigma = \overline{E} C_1 & \text{in } \ \Omega_1 \times (0,T], \\ \dfrac{\partial M}{\partial t} + \beta_1 M = \beta_2 C_1 & \texttt{in } \ \Omega_1 \times (0,T]. \end{cases} \tag{2.1}$$

In (2.1) C_1 represents the unknown concentration of the drug inside the material, σ is the unknown stress response of the material to the strain exerted by the dissolved drug and M is the unknown molecular weight of the material. The viscoelastic influence in the drug transport is represented by the term $\nabla \cdot (D_v \nabla \sigma)$ where D_v is a viscoelastic tensor. The term $-k_1 C_1$ describes the degradation of drug inside the material and the positive constant k_1 represents the degradation rate. The viscoelastic term states that the polymer acts as a barrier to the diffusion of the drug: as the drug strains the polymer it reacts with a stress of opposite sign ([35, 36, 37, 38, 39, 40]). To account for the increasing permeability of the system upon degradation, the diffusion tensor is defined by ([20])

$$D_1(M) = D_0 e^{\bar{k}\frac{M_0 - M}{M_0}}, \tag{2.2}$$

where D_0 is the diffusion tensor of the drug in the non hydrolyzed polymer, $\bar{k}$ is a positive constant and M_0 is the initial molecular weight of the polymeric matrix.

The second equation in (2.1) defines the viscoelastic behaviour of the polymer as described by the Maxwell fluid model ([1, 2, 18, 19, 41])

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu}\sigma = E\frac{\partial \epsilon}{\partial t}, \tag{2.3}$$

where E represents the Young modulus of the material, μ is its viscosity and ϵ is the strain produced by the drug molecules. Assuming that the polymer acts as a barrier to the release of the drug, σ and ϵ are of opposite sign, and a minus sign should be considered in the right hand side of (2.3). To eliminate the strain ϵ in (2.3) we assume

$$\epsilon(x,t) = k \int_0^t C_1(x,s) ds, \tag{2.4}$$

where k is a dimensional positive constant ([3]). We note that the strain ϵ is a function of x and t. Whenever no confusion case arise we will omit in this thesis the arguments in the variables. Consequently we will write equation (2.4) as

$$\epsilon = k \int_0^t C_1(s)ds.$$

Replacing (2.4) in (2.3) and considering the minus sign in the right hand side of (2.3) we obtain the second equation in (2.1) where $\overline{E} = -Ek$. The solution of the second equation in (2.1) gives

$$\sigma = -Ek \int_0^t e^{-\frac{t-s}{\tau}} C_1(s)ds + \sigma(0)e^{-\frac{1}{\tau}t}, \tag{2.5}$$

where the relaxation τ is defined as $\tau = \frac{\mu}{E}$ ([41]). We remark that the expression of $\nabla\sigma$ obtained from (2.5) coincides in the one dimensional case with the expression in equation (1.6) for $k = \frac{\widetilde{D_1}D_1}{D_v\mu}$. The viscoelastic tensor D_v has a precise physical meaning that has been established in [38] and for a one dimensional model it can be proved that $D_v > 0$ ([35, 38]). In [9, 13, 14] the authors considered $D_v < 0$ and the stress σ and the strain ϵ with the same sign. Underlying this approach we can find the same physical idea of the polymeric matrix as a barrier to diffusion.

In the third equation of (2.1), β_1 and β_2 are positive constants that characterize the degradation properties of the material ([22]). The meaning and units of all variables and parameters used along the work are presented in the Appendix.

System (2.1) is completed with the initial conditions

$$\begin{cases} C_1(0) = C_0 & \text{in} \quad \Omega_1, \\ \sigma(0) = \sigma_0 & \text{in} \quad \Omega_1, \\ M(0) = M_0 & \text{in} \quad \Omega_1, \end{cases} \tag{2.6}$$

where C_0 represents the initial concentration of the drug in the polymeric matrix and σ_0 is the initial stress response of the polymer to the strain exerted by the initial dissolved drug. The boundary condition

$$C_1 = 0 \quad \text{on} \quad \partial\Omega_1 \times (0, T], \tag{2.7}$$

which means that the drug is immediately removed as it attains the boundary, closes the model.

2.2 Qualitative behaviour of the solution

In this section we study the qualitative behaviour of the energy functional

$$Q(t) = \left\| C_1(t) \right\|^2, \quad t \geq 0, \tag{2.8}$$

where $\left\| \cdot \right\|$ represents the usual norm in $L^2(\Omega_1)$ which is induced by the corresponding inner product $(\cdot, \cdot)$.

The following lemma, Gronwall's Lemma, will be used in the proof of Theorem 1.

Lemma 1. *(Gronwall's Lemma([42])) Let u and g be non-negative functions on $[0,T]$ having one-sided limits for every $t \in [0,T]$, and K a non-negative constant. If for every $0 \leq t \leq T$ we have*

$$u \leq K + \int_0^t g(s)u(s)ds,$$

then

$$u \leq K \exp\Big(\int_0^t g(s)ds \Big),$$

for all $0 \leq t \leq T$.

In what follows we establish a qualitative result for the solution C_1 of system (2.1). We begin by deducing an estimate that holds in bounded intervals of time $(0,T]$. This result is then sharpened in Theorem 1 for any T.

From the second equation of (2.1) we easily get

$$\sigma = \overline{E} \int_0^t e^{-\frac{E}{\mu}(t-s)} C_1(s)ds + \sigma(0)e^{-\frac{E}{\mu}t}, \quad t \geq 0,$$

with $\overline{E} = -Ek$. Replacing this last expression in the first equation of (2.1) and assuming that σ_0 is constant, we obtain for C_1

$$\begin{aligned} \frac{\partial C_1}{\partial t} = \nabla \cdot (D_1(M)\nabla C_1) \quad &- \quad Ek \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_v \nabla C_1(s))ds \\ &- \quad k_1 C_1 \quad in \quad \Omega_1 \times (0,T]. \end{aligned} \tag{2.9}$$

In what follows we assume that D_1 and D_v are diagonal matrices where the nonzero entries of D_1, $(D_1)_{ii}$, $i = 1, 2$, satisfy $(D_1)_{ii} \geq \overline{D_0} > 0, i = 1, 2$, and the nonzero entries of D_v, $(D_v)_{ii}$, $i = 1, 2$, satisfy $|(D_v)_{ii}| \leq \overline{D_v}$. As $\frac{1}{2}\frac{dQ}{dt} = (C_1, \frac{\partial C_1}{\partial t})$ we deduce, from (2.9), after multiplying scalarly by C_1 and using the equation (2.7), the following equation:

$$\begin{aligned} \frac{1}{2}\frac{dQ}{dt} &= -\left\| \sqrt{D_1(M)}\nabla C_1 \right\|^2 \\ &+ \left(Ek \int_0^t e^{-\frac{E}{\mu}(t-s)} D_v \nabla C_1(s) ds, \nabla C_1 \right) \\ &- k_1 \left\| C_1 \right\|^2, \end{aligned} \tag{2.10}$$

where $\sqrt{D_1(M)}$ is defined as the matrix which entries are the square root of the entries of $D_1(M)$. In (2.10) the inner product in $(L^2(\Omega_1))^2$ and the corresponding norm $\left\| \cdot \right\|$ are denoted as the inner product in $L^2(\Omega_1)$ and its associated norm, respectively. From (2.10) and using Cauchy-Schwarz inequality, we have

$$\begin{aligned} \frac{1}{2}\frac{dQ}{dt} + \overline{D_0}\left\| \nabla C_1 \right\|^2 &\leq \frac{Ek}{4\delta^2}\left\| \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla C_1(s) ds \right\|^2 \\ &+ \overline{D_v}^2 Ek\delta^2 \left\| \nabla C_1 \right\|^2 - k_1 Q, \end{aligned} \tag{2.11}$$

where $\delta \neq 0$ is an arbitrary constant. We note that in the application of Cauchy- Schwarz inequality the factors have been defined as to be dimensionally sound. From the previous inequality we deduce

$$\frac{1}{2}\frac{dQ}{dt} + k_1 Q + (\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\left\| \nabla C_1 \right\|^2 \leq$$

$$\frac{Ek}{4\delta^2} \int_0^t e^{-2\frac{E}{\mu}(t-s)} ds \int_0^t \left\| \nabla C_1(s) \right\|^2 ds,$$

and then, by considering

$$\int_0^t e^{-2\frac{E}{\mu}(t-s)} ds \leq \frac{1}{2\frac{E}{\mu}},$$

we have

$$Q + 2k_1 \int_0^t Q(s)ds + 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2) \int_0^t \left\| \nabla C_1(s) \right\|^2 ds \leq$$

$$\frac{Ek}{4\delta^2 \frac{E}{\mu}} \int_0^t \int_0^s \left\| \nabla C_1(\mu) \right\|^2 d\mu ds + Q(0).$$

If δ^2 is such that

$$\overline{D_0} - \overline{D_v}^2 Ek\delta^2 > 0, \tag{2.12}$$

we obtain

$$Q + \int_0^t Q(s)ds + \int_0^t \left\| \nabla C_1(s) \right\|^2 ds \leq$$

$$\frac{k\mu}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}4\delta^2} \int_0^t \int_0^s \left\| \nabla C_1(\mu) \right\|^2 d\mu ds$$

$$+ \quad \frac{1}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}} Q(0).$$

Finally using Gronwall's Lemma we obtain

$$Q + \int_0^t Q(s)ds + \int_0^t \left\| \nabla C_1(s) \right\|^2 ds \leq$$

$$\frac{1}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}} Q(0) e^{\bar{c}t}, \tag{2.13}$$

where

$$\bar{c} = \frac{k\mu}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}4\delta^2}. \tag{2.14}$$

This last inequality establishes that Q, $\int_0^t Q(s)ds$ and $\int_0^t \left\| \nabla C_1(s) \right\|^2 ds$ are bounded for bounded intervals of time. Inequality (2.13) can be improved by eliminating the exponential factor in its right hand side. Following [25] we multiply (2.9) by $e^{\gamma t}$, where γ is a positive constant to be selected, obtaining

$$e^{\gamma t}\frac{\partial C_1}{\partial t} = \nabla\cdot(D_1(M)\nabla C_1)e^{\gamma t} - Ek\int_0^t e^{-\frac{E}{\mu}(t-s)}e^{\gamma t}\nabla\cdot(D_v\nabla C_1(s))ds - k_1 e^{\gamma t}C_1. \quad (2.15)$$

Adding $\gamma e^{\gamma t}C_1$ to both sides of (2.15) we have

$$\frac{\partial C_{1,\gamma}}{\partial t} = \nabla\cdot(D_1(M)\nabla C_{1,\gamma}) - Ek\int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)}\nabla\cdot(D_v\nabla C_{1,\gamma}(s))ds + (\gamma-k_1)C_{1,\gamma}, \quad (2.16)$$

where $C_{1,\gamma} = e^{\gamma t}C_1$. The last equation leads to

$$\left(\frac{dC_{1,\gamma}}{dt}, C_{1,\gamma}\right) + (D_1(M)\nabla C_{1,\gamma}, \nabla C_{1,\gamma}) = Ek\left(\int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)}D_v\nabla C_{1,\gamma}(s)ds, \nabla C_{1,\gamma}\right) + (\gamma-k_1)(C_{1,\gamma}, C_{1,\gamma}).$$

Using the Cauchy-Schwarz inequality, equation (2.7) and the notation $Q_\gamma = \left\|C_{1,\gamma}\right\|^2$, we easily deduce that

$$\frac{d}{dt}Q_\gamma + 2k_1Q_\gamma - 2\gamma Q_\gamma + 2\overline{D_0}\left\|\nabla C_{1,\gamma}\right\|^2 \leq 2\overline{D_v}^2 Ek\int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)}\left\|\nabla C_{1,\gamma}(s)\right\|\left\|\nabla C_{1,\gamma}\right\|ds \leq 2\delta^2\overline{D_v}^2 Ek\left\|\nabla C_{1,\gamma}\right\|^2 + \frac{\beta_\gamma Ek}{2\delta^2}\int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)}\left\|\nabla C_{1,\gamma}(s)\right\|^2 ds,$$

for an arbitrary positive constant δ and γ such that $\gamma - \frac{E}{\mu} < 0$, where β_γ is defined by

$$\int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)}ds < \frac{1}{\frac{E}{\mu}-\gamma} = \beta_\gamma. \quad (2.17)$$

Since $\left\|C_{1,\gamma}\right\| \leq K_\Omega \left\|\nabla C_{1,\gamma}\right\|$, where K_Ω represents the Poincaré's constant ([43]), we have

$$Q_\gamma + 2k_1 \int_0^t Q_\gamma(s)ds + (2\overline{D_0} - 2\gamma K_\Omega^2 - 2\delta^2 \overline{D_v}^2 Ek) \int_0^t \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds \leq$$

$$Q(0) + \frac{\beta_\gamma Ek}{2\delta^2} \int_0^t \int_0^\eta e^{(\gamma - \frac{E}{\mu})(\eta - s)} \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds d\eta. \qquad (2.18)$$

Changing the order of integration in the double integral on the right hand side of (2.18) we have

$$Q_\gamma + 2k_1 \int_0^t Q_\gamma(s)ds + (2\overline{D_0} - 2\gamma K_\Omega^2 - 2\delta^2 \overline{D_v}^2 Ek) \int_0^t \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds \leq$$

$$Q(0) + \frac{\beta_\gamma Ek}{2\delta^2} \int_0^t \int_s^t e^{(\gamma - \frac{E}{\mu})(\eta - s)} d\eta \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds. \qquad (2.19)$$

Computing now the interior integral in the right hand side of (2.19) and considering (2.17) we obtain

$$Q_\gamma + 2k_1 \int_0^t Q_\gamma(s)ds + (2\overline{D_0} - 2\gamma K_\Omega^2 - 2\delta^2 \overline{D_v}^2 Ek) \int_0^t \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds \leq$$

$$Q(0) + \frac{\beta_\gamma^2 Ek}{2\delta^2} \int_0^t \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds. \qquad (2.20)$$

As $Q_\gamma = e^{2\gamma t} Q$ we have from (2.20)

$$Q + 2k_1 \int_0^t e^{-2\gamma(t-s)} Q(s)ds$$

$$+ \left(2\overline{D_0} - 2\gamma K_\Omega^2 - 2\delta^2 \overline{D_v}^2 Ek - \frac{Ek}{2\delta^2(\frac{E}{\mu} - \gamma)^2}\right) \int_0^t e^{-2\gamma(t-s)} \left\|\nabla C_1(s)\right\|^2 ds$$

$$\leq e^{-2\gamma t} Q(0).$$

We now look for a positive γ such that

$$2\overline{D_0} - 2\gamma K_\Omega^2 - 2\delta^2 \overline{D_v}^2 Ek - \frac{Ek}{2\delta^2(\frac{E}{\mu} - \gamma)^2} > 0,$$

with $\dfrac{E}{\mu} - \gamma > 0$.

The parameter δ is arbitrary so we select $\delta = 1$. The function f defined by

$$f(\gamma) = 2\overline{D_0} - 2\gamma K_\Omega^2 - 2\overline{D_v}^2 Ek - \frac{Ek}{2(\frac{E}{\mu} - \gamma)^2},$$

is a continuous function for $\gamma \in [0, \frac{E}{\mu})$. We have

$$f(0) = 2\overline{D_0} - 2\overline{D_v}^2 Ek - \frac{\mu^2 k}{2E},$$

and $\lim\limits_{\gamma \to \frac{E}{\mu}} f(\gamma) < 0$. If we impose

$$\overline{D_0} - \overline{D_v}^2 Ek - \frac{\mu^2 k}{4E} > 0, \tag{2.21}$$

the non linear equation

$$f(\gamma) = 0,$$

has a positive root in $(0, \frac{E}{\mu})$.

We have then proved the following result for the energy functional defined in (2.8).

Theorem 1. *If $\overline{D_0}$, $\overline{D_v}$, E, k and μ are such that* (2.21) *holds, then there exists $\gamma \in (0, \frac{E}{\mu})$ such that*

$$Q + \int_0^t e^{-2\gamma(t-s)} Q(s) ds + \int_0^t e^{-2\gamma(t-s)} \left\| \nabla C_1(s) \right\|^2 ds \leq C e^{-2\gamma t} Q(0), \quad t \geq 0, \tag{2.22}$$

where

$$C = \frac{1}{\min\left\{1, 2k_1, 2\left(\overline{D_0} - \gamma K_\Omega^2 - \overline{D_v}^2 Ek - \frac{Ek}{4(\frac{E}{\mu} - \gamma)^2}\right)\right\}}. \tag{2.23}$$

□

We note that the restriction on the parameters imposed in Theorem 1 have a physical meaning. In fact if we make a dimensional analysis of (2.21) for the one dimensional case with $\Omega_1 = (0,1)$, we conclude that all the terms are consistent with dimension $\frac{L^2}{T}$, where L^2 stands for the square length and T for the time. The condition establishes that the Fickian contribution dominates the non Fickian one, which is a physically sound restriction.

In what follows we analyze the stability and the uniqueness of the solution of (2.1), (2.6) and (2.7).

Let $\tilde{C}_1$, $\tilde{M}$ and $\tilde{\sigma}$ be another solution of the initial boundary value problem (2.1), (2.7) with the initial conditions

$$\begin{cases} \tilde{C}_1(0) = \tilde{C}_0 & \text{in } \Omega_1, \\ \tilde{\sigma}(0) = \tilde{\sigma_0} & \text{in } \Omega_1, \\ \tilde{M}(0) = \tilde{M}_0 & \text{in } \Omega_1. \end{cases}$$

Let E_C, E_M and E_σ be defined by

$$E_C = C_1 - \tilde{C}_1, \quad E_M = M - \tilde{M}, \quad E_\sigma = \sigma - \tilde{\sigma}.$$

It can be shown that E_C, E_M and E_σ satisfy

$$\begin{aligned} \frac{\partial E_C}{\partial t} &= \nabla \cdot (D_1(M)\nabla C_1 - D_1(\tilde{M})\nabla \tilde{C}_1) \\ &- Ek \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_v \nabla E_C(s)) ds \\ &- k_1 E_C + e^{-\frac{E}{\mu}t} \nabla \cdot (D_v \nabla E_\sigma(0)) \quad in \quad \Omega_1 \times (0,T], \end{aligned}$$

$$\frac{\partial E_M}{\partial t} + \beta_1 E_M = \beta_2 E_C \quad in \quad \Omega_1 \times (0,T],$$

with initial conditions

$$\begin{cases} E_C(0) = C_1(0) - \tilde{C}_1(0) & \text{in } \Omega_1, \\ E_M(0) = M(0) - \tilde{M}(0) & \text{in } \Omega_1, \\ E_\sigma(0) = \sigma(0) - \tilde{\sigma}(0) & \text{in } \Omega_1, \end{cases}$$

and boundary conditions

$$E_C = 0 \text{ on } \partial\Omega_1 \times (0,T].$$

In what follows we use the notations

$$Q_C = \left\| E_C \right\|^2, \quad Q_M = \left\| E_M \right\|^2.$$

For Q_C and Q_M we have

$$\begin{aligned} \frac{1}{2}\frac{dQ_C}{dt} &= -(D_1(M)\nabla C_1 - D_1(\tilde{M})\nabla \tilde{C}_1, \nabla E_C) \\ &+ Ek\int_0^t e^{-\frac{E}{\mu}(t-s)}(D_v \nabla E_C(s), \nabla E_C)ds \\ &- k_1 Q_C + e^{-\frac{E}{\mu}t}(\nabla \cdot (D_v \nabla E_\sigma(0)), E_C) \text{ in } (0,T], \end{aligned} \tag{2.24}$$

$$\frac{1}{2}\frac{dQ_M}{dt} + \beta_1 Q_M = \beta_2(E_C, E_M) \text{ in } (0,T]. \tag{2.25}$$

As

$$\begin{aligned} D_1(M)\nabla C_1 - D_1(\tilde{M})\nabla \tilde{C}_1 &= E_M D_{1,d}(\tilde{\tilde{M}})\nabla C_1 \\ &+ D_1(\tilde{M})\nabla E_C, \end{aligned}$$

where $D_{1,d}$ is the diagonal matrix of the derivatives of entries of D_1 and $\tilde{\tilde{M}} = \theta\tilde{M} + (1-\theta)M, \theta \in [0,1]$. Taking this representation in (2.24) we get

$$\begin{aligned} &\frac{1}{2}\frac{dQ_C}{dt} + k_1 Q_C + (\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\left\|\nabla E_C\right\|^2 \leq \\ &\frac{\mu k}{8\delta^2}\int_0^t \left\|\nabla E_C(s)\right\|^2 ds + D_{1,d_{max}}\left\|\nabla C_1\right\|_\infty \left\|E_M\right\|\left\|\nabla E_C\right\| \\ &+e^{-\frac{E}{\mu}t}\left\|\nabla \cdot (D_v \nabla E_\sigma(0))\right\|\left\|E_C\right\| \text{ in } (0,T], \end{aligned} \tag{2.26}$$

where $D_{1,d_{max}} \geq \left|(D_{1,d})_{ii}\right|$, $i = 1,2$, $\left\|\cdot\right\|_\infty$ denotes the usual norm and $\delta \neq 0$ is an arbitrary constant. Inequality (2.26) leads to

$$\begin{aligned} &\frac{1}{2}\frac{dQ_C}{dt} + (k_1 - \epsilon_2^2)Q_C + (\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2)\left\|\nabla E_C\right\|^2 \leq \\ &\frac{\mu k}{8\delta^2}\int_0^t \left\|\nabla E_C(s)\right\|^2 ds + \frac{D_{1,d_{max}}^2}{4\epsilon_1^2}\left\|\nabla C_1\right\|_\infty^2 \left\|E_M\right\|^2 \\ &+e^{-2\frac{E}{\mu}t}\frac{1}{4\epsilon_2^2}\left\|\nabla \cdot (D_v \nabla E_\sigma(0))\right\|^2 \text{ in } (0,T], \end{aligned} \tag{2.27}$$

where $\epsilon_i \neq 0$ $i = 1, 2$, are arbitrary constants.

As from (2.25) we have

$$\frac{1}{2}\frac{dQ_M}{dt} + \beta_1 Q_M \leq \frac{\beta_2^2}{4\epsilon_3^2} Q_M + \epsilon_3^2 Q_C \quad \text{in} \quad (0, T], \tag{2.28}$$

where $\epsilon_3 \neq 0$ is an arbitrary constant, we deduce from (2.27) and (2.28)

$$\begin{aligned} & \frac{dQ_C}{dt} + \frac{dQ_M}{dt} + 2(k_1 - \epsilon_2^2 - \epsilon_3^2) Q_C + 2\beta_1 Q_M \\ + \quad & 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2) \left\| \nabla E_C \right\|^2 \leq \\ & \frac{\mu k}{4\delta^2} \int_0^t \left\| \nabla E_C(s) \right\|^2 ds + \Big(\frac{D_{1,d_{max}}^2}{2\epsilon_1^2} \left\| \nabla C_1 \right\|_\infty^2 \\ + \quad & \frac{\beta_2^2}{2\epsilon_3^2} \Big) Q_M + e^{-2\frac{E}{\mu}t} \frac{1}{2\epsilon_2^2} \left\| \nabla \cdot (D_v \nabla E_\sigma(0)) \right\|^2 \quad \text{in} \quad (0, T]. \end{aligned}$$

Consequently

$$\begin{aligned} & Q_C + Q_M + 2(k_1 - \epsilon_2^2 - \epsilon_3^2) \int_0^t Q_C(s) ds + 2\beta_1 \int_0^t Q_M(s) ds \\ + \quad & 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2) \int_0^t \left\| \nabla E_C(s) \right\|^2 ds \leq \\ & Q_C(0) + Q_M(0) + \frac{\mu k}{4\delta^2} \int_0^t \int_0^s \left\| \nabla E_C(\nu) \right\|^2 d\nu ds \\ + \quad & \int_0^t \Big(\frac{\beta_2^2}{2\epsilon_3^2} + \frac{D_{1,d_{max}}^2}{2\epsilon_1^2} \left\| \nabla C_1(s) \right\|_\infty^2 \Big) Q_M(s) ds \\ + \quad & \frac{\mu}{4\epsilon_2^2 E} \left\| \nabla \cdot (D_v \nabla E_\sigma(0)) \right\|^2. \end{aligned} \tag{2.29}$$

Fixing in (2.29) $\epsilon_i \neq 0$, $i = 1, 2, 3$, such that

$$k_1 - \epsilon_2^2 - \epsilon_3^2 > 0,$$

$$\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2 > 0,$$

we obtain

$$
\begin{aligned}
& Q_C + Q_M + \int_0^t \Big(Q_C(s) + Q_M(s)\Big)ds + \int_0^t \Big\|\nabla E_C(s)\Big\|^2 ds \leq \\
& \frac{1}{\min\Big\{1, 2(k_1 - \epsilon_2^2 - \epsilon_3^2), 2\beta_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2)\Big\}}\Big(Q_C(0) \\
+ \quad & Q_M(0) + \frac{\mu}{4\epsilon_2^2 E}\Big\|\nabla\cdot(D_v\nabla E_\sigma(0))\Big\|^2\Big) \\
+ \quad & \frac{\max\Big\{\frac{\mu k}{4\delta^2}, \frac{\beta_2^2}{2\epsilon_3^2} + \frac{D_{1,d_{max}}^2}{2\epsilon_1^2}\big\|\nabla C_1\big\|_\infty^2\Big\}}{\min\Big\{1, 2(k_1 - \epsilon_2^2 - \epsilon_3^2), 2\beta_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2)\Big\}}\int_0^t \Big(Q_M(s) \\
+ \quad & \int_0^s \Big\|\nabla E_C(\nu)\Big\|^2 d\nu\Big)ds, \qquad (2.30)
\end{aligned}
$$

where $\big\|\nabla C_1\big\|_\infty = \max\limits_{[0,T]}\big\|\nabla C_1(t)\big\|_\infty$.

Finally, applying the Gronwall's Lemma to inequality (2.30) we deduce

$$
\begin{aligned}
& Q_C + Q_M + \int_0^t \Big(Q_C(s) + Q_M(s)\Big)ds + \int_0^t \Big\|\nabla E_C(s)\Big\|^2 ds \leq \\
& \frac{1}{\min\Big\{1, 2(k_1 - \epsilon_2^2 - \epsilon_3^2), 2\beta_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2)\Big\}}\Big(Q_C(0) \\
+ \quad & Q_M(0) + \frac{\mu}{4\epsilon_2^2 E}\Big\|\nabla\cdot(D_v\nabla E_\sigma(0))\Big\|^2\Big)e^{\bar{c}t}, \quad t \in [0,T], \qquad (2.31)
\end{aligned}
$$

where

$$
\bar{c} = \frac{\max\Big\{\frac{\mu k}{4\delta^2}, \frac{\beta_2^2}{2\epsilon_3^2} + \frac{D_{1,d_{max}}^2}{2\epsilon_1^2}\big\|\nabla C_1\big\|_\infty^2\Big\}}{\min\Big\{1, 2(k_1 - \epsilon_2^2 - \epsilon_3^2), 2\beta_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2 - \epsilon_1^2)\Big\}}.
$$

Inequality (2.31) allows us to conclude the stability of the initial boundary value problem (2.1), (2.6), (2.7) in bounded time intervals, provided that this problem has a solution with the smoothness required in the establishment of (2.31). Moreover, (2.31) implies the uniqueness of the solution of (2.1), (2.6) and (2.7). The results in this section, namely Theorem 1, also hold for $\Omega \subset \mathbb{R}^3$.

2.3 Qualitative behaviour of the solution in the case of Robin boundary conditions

To simulate *in vivo* the drug release, the polymeric matrix is coupled with a living system. In this case the Dirichlet boundary conditions for C_1, (2.7), should be replaced by a Robin boundary condition of type

$$J \cdot \eta = A_c C_1 \text{ on } \partial\Omega_1 \times (0,T], \tag{2.32}$$

where J stands for the flux, η is the unit outward normal to $\partial\Omega_1$ and A_c is a positive constant. The problem to be solved is then

$$\begin{cases} \dfrac{\partial C_1}{\partial t} = \nabla \cdot (D_1(M)\nabla C_1) - Ek \displaystyle\int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_v \nabla C_1(s))ds \\ \qquad\qquad -k_1 C_1 \quad \texttt{in } \ \Omega_1 \times (0,T], \\ \dfrac{\partial M}{\partial t} + \beta_1 M = \beta_2 C_1 \quad \texttt{in } \ \Omega_1 \times (0,T], \end{cases}$$

coupled with initial condition (2.6) and the equation (2.32), where J is given by

$$J = -D_1(M)\nabla C_1 + D_v Ek \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla C_1(s)ds, \tag{2.33}$$

provided that σ_0 is a constant.

The arguments used in the proof of Theorem 1 still hold. In fact equation (2.9) is of form

$$\frac{\partial C_1}{\partial t} = -\nabla \cdot J - k_1 C_1, \tag{2.34}$$

and multiplying scalarly by C_1 we have

$$\frac{1}{2}\frac{dQ}{dt} = -\Big(J \cdot \eta, C_1\Big)_{\partial\Omega_1} + \Big(J, \nabla C_1\Big) - k_1 \Big\| C_1 \Big\|^2,$$

where the scalar product in $\partial\Omega_1$ is defined by

$$\Big(J \cdot \eta, C_1\Big)_{\partial\Omega_1} = \int_{\partial\Omega_1} J \cdot \eta C_1 ds.$$

From (2.32) we obtain, instead of (2.10), the inequality

$$\frac{1}{2}\frac{dQ}{dt} \leq (J, \nabla C_1) - k_1 \Big\| C_1 \Big\|^2,$$

and replacing J defined in (2.33) in the last inequality we have

$$\frac{1}{2}\frac{dQ}{dt} \leq \Big(- D_1(M)\nabla C_1 + D_v E k \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla C_1(s) ds, \nabla C_1 \Big) - k_1 Q.$$

So we easily obtain

$$\begin{aligned} \frac{1}{2}\frac{dQ}{dt} \leq & -\left\| \sqrt{D_1(M)} \nabla C_1 \right\|^2 \\ & + \quad \Big(E k \int_0^t e^{-\frac{E}{\mu}(t-s)} D_v \nabla C_1(s) ds, \nabla C_1 \Big) - k_1 Q, \end{aligned}$$

and estimate (2.13) then follows.

To eliminate the exponential factor we multiply (2.32) and (2.34) by $e^{\gamma t}$, where γ is a positive constant, obtaining

$$J \cdot \eta e^{\gamma t} = A_c C_1 e^{\gamma t}, \tag{2.35}$$

and

$$e^{\gamma t}\frac{\partial C_1}{\partial t} = -\nabla \cdot J e^{\gamma t} - k_1 C_1 e^{\gamma t}, \tag{2.36}$$

respectively, where J is defined by (2.33). Adding $\gamma e^{\gamma t} C_1$ to both sides of (2.36) we have

$$\frac{\partial C_{1,\gamma}}{\partial t} = -\nabla \cdot J e^{\gamma t} + \gamma C_{1,\gamma} - k_1 C_{1,\gamma},$$

where $C_{1,\gamma} = e^{\gamma t} C_1$. Multiplying the last equality scalarly by $C_{1,\gamma}$ we get

$$\begin{aligned} \Big(\frac{dC_{1,\gamma}}{dt}, C_{1,\gamma} \Big) &= -(J \cdot \eta e^{\gamma t}, C_{1,\gamma})_{\partial\Omega_1} + (J e^{\gamma t}, \nabla C_{1,\gamma}) \\ &+ \gamma \left\| C_{1,\gamma} \right\|^2 - k_1 \left\| C_{1,\gamma} \right\|^2. \end{aligned} \tag{2.37}$$

Using (2.35) in (2.37) we obtain

$$\frac{1}{2}\frac{dQ_\gamma}{dt} \leq (J e^{\gamma t}, \nabla C_{1,\gamma}) + \gamma Q_\gamma - k_1 Q_\gamma.$$

By replacing J from (2.33) in the last inequality and using the Cauchy-Schwarz inequality we easily deduce

$$\frac{dQ_\gamma}{dt} + 2k_1 Q_\gamma - 2\gamma Q_\gamma + 2\overline{D_0}\left\|\nabla C_{1,\gamma}\right\|^2 \leq$$
$$2\overline{D_v}Ek \int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)} \left\|\nabla C_{1,\gamma}(s)\right\| \left\|\nabla C_{1,\gamma}\right\| ds \leq$$
$$2\delta^2 \overline{D_v}^2 Ek \left\|\nabla C_{1,\gamma}\right\|^2 + \frac{\beta_\gamma Ek}{2\delta^2} \int_0^t e^{(\gamma-\frac{E}{\mu})(t-s)} \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds,$$

for any $\delta \neq 0$, where γ is such that $\gamma - \frac{E}{\mu} < 0$ and β_γ is defined by (2.17). Integrating and rearranging the terms we get

$$Q_\gamma + 2(k_1-\gamma)\int_0^t Q_\gamma(s)ds + 2(\overline{D_0} - \delta^2\overline{D_v}^2 Ek)\int_0^t \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds \leq$$
$$Q_\gamma(0) + \frac{\beta_\gamma Ek}{2\delta^2}\int_0^t \int_0^\eta e^{(\gamma-\frac{E}{\mu})(\eta-s)} \left\|\nabla C_{1,\gamma}(s)\right\|^2 ds d\eta. \qquad (2.38)$$

Following the proof of Theorem 1, by assuming $k_1 - \gamma > 0$, we conclude the following result.

Theorem 2. *If $\overline{D_0}$, $\overline{D_v}$, E, k and μ are such that* (2.21) *holds and*

$$\frac{E}{\mu} < k_1$$

then there exists $\gamma \in (0, \frac{E}{\mu})$ such that

$$Q + \int_0^t e^{-2\gamma(t-s)} Q(s)ds + \int_0^t e^{-2\gamma(t-s)} \left\|\nabla C_1(s)\right\|^2 ds \leq Ce^{-2\gamma t}Q(0), \quad t \geq 0, \qquad (2.39)$$

where

$$C = \frac{1}{\min\left\{1, 2(k_1-\gamma), 2\left(\overline{D_0} - \overline{D_v}^2 Ek - \frac{Ek}{4(\frac{E}{\mu}-\gamma)^2}\right)\right\}}.$$

□

Estimate (2.39) is formally analogous to estimate (2.22). The constants that appear in the right hand side of these estimates are only slightly different but its comparison in a general framework can not be done.

2.4 Energy estimates for the semi-discrete approximation

In this section we consider semi-discrete approximations for C_1 and M, defined by the **IBVP** (2.9), the third equation of (2.1), the first and third equations of (2.6) and equation (2.7). For such semi-discrete approximations we establish a discrete version of Theorem 1. We start by considering $\Omega_1 = (0, L)$ and then we analyze the case $\Omega_1 = (0, L) \times (0, L)$.

2.4.1 One dimensional case

Let us consider in $\overline{\Omega}_1 = [0, L]$ a grid $I_h = \{x_i, i = 0, \ldots, N\}$ with $x_0 = 0$, $x_N = L$ and $x_i - x_{i-1} = h$. By $\partial\Omega_{1h}$ we represent the boundary points. We introduce the following finite-difference operators

$$D_{-x}u_h(x_i) = \frac{u_h(x_i) - u_h(x_{i-1})}{h},$$

and

$$D_x u_h(x_i) = \frac{u_h(x_{i+1}) - u_h(x_i)}{h}.$$

We denote by $L^2(I_h)$ the space of grid functions u_h defined in I_h and by $L_0^2(I_h)$ the subspace of $L^2(I_h)$ such that $u_h = 0$ on $\partial\Omega_{1h}$. In $L_0^2(I_h)$ we consider the discrete inner product

$$(u_h, v_h)_h = \sum_{i=1}^{N-1} h u_h(x_i) v_h(x_i), \qquad u_h, v_h \in L_0^2(I_h).$$

We denote by $\left\| \cdot \right\|_h$ the norm induced by the above inner product. For $u_h, v_h \in L^2(I_h)$ we introduce the notations

$$(u_h, v_h)_+ = \sum_{i=1}^{N} h u_h(x_i) v_h(x_i),$$

and

$$\left\| u_h \right\|_+^2 = \sum_{i=1}^{N} h \Big(u_h(x_i) \Big)^2.$$

Let

$$\Big\|u_h\Big\|_1 = \Big(\Big\|u_h\Big\|_h^2 + \Big\|D_{-x}u_h\Big\|_+^2\Big)^{1/2}, \qquad u_h \in L^2(I_h).$$

We note that $\Big\|\cdot\Big\|_1$ represents a norm which can be viewed as a discretization of the usual Sobolev norm of the space $H^1(0,1)$.

To discretize the spatial derivative in (2.9) we introduce the finite difference operator

$$D_x^*(D_1(v_h)D_{-x}u_h)(x_i) = \frac{1}{h}\Big(D_1(A_hv_h(x_{i+1}))D_{-x}u_h(x_{i+1}) - D_1(A_hv_h(x_i))D_{-x}u_h(x_i)\Big), \quad i = 1,\dots,N-1,$$

where v_h and u_h are grid functions and A_h denotes the average operator

$$A_hv_h(x_i) = \frac{1}{2}\Big(v_h(x_i) + v_h(x_{i-1})\Big).$$

Using summation by parts, it can be shown that, for $v_h \in L^2(I_h)$, $u_h, w_h \in L_0^2(I_h)$, we have

$$\Big(D_x^*(D_1(v_h)D_{-x}u_h), w_h\Big)_h = -\Big(D_1(v_h)D_{-x}u_h, D_{-x}w_h\Big)_+. \tag{2.40}$$

Semi-discrete approximations for C_1 and M are then defined by the system of differential equations

$$\frac{dC_{1h}}{dt} = D_x^*\Big(D_1(M_h)D_{-x}C_{1h}\Big) - Ek\int_0^t e^{\frac{-E}{\mu}(t-s)}D_x^*(D_vD_{-x}C_{1h}(s))ds - k_1C_{1h} \quad \text{in} \quad \Omega_{1h}\times(0,T], \tag{2.41}$$

and

$$\frac{dM_h}{dt} + \beta_1M_h = \beta_2C_{1h} \quad \text{in} \quad \Omega_{1h}\times(0,T], \tag{2.42}$$

which is complemented by the following conditions

$$C_{1h}(0) = R_hC_0, \quad M_h(0) = R_hM_0 \quad \text{in} \quad \Omega_{1h}, \tag{2.43}$$

and

$$C_{1h} = 0 \quad \text{on} \quad \partial\Omega_{1h}\times(0,T], \tag{2.44}$$

where $R_h : C^0(\overline{\Omega}_1) \to L^2(I_h)$ denotes the restriction operator.

To complete the finite difference equation (2.41) for $i = 1, \ldots, N$, the values M_h on $\partial\Omega_{1h}$ are needed. We assume that

$$M_h = M_0 e^{-\beta_1 t} \quad \text{on} \quad \partial\Omega_{1h} \times (0, T]. \tag{2.45}$$

We remark that this condition was obtained by extending the differential equation for the molecular weight to the boundary points.

In what follows we study the qualitative behaviour of the energy functional

$$Q_h(t) = \left\| C_{1h}(t) \right\|_h^2, \quad t \geq 0. \tag{2.46}$$

Multiplying (2.41) by C_{1h}, with respect to the inner product $(\cdot, \cdot)_h$, and using (2.40) and the boundary condition (2.44) we obtain

$$\begin{aligned} \Big(\frac{dC_{1h}}{dt}, C_{1h}\Big)_h &+ \Big(D_1(M_h) D_{-x} C_{1h}, D_{-x} C_{1h}\Big)_+ \\ &= Ek\Big(\int_0^t e^{-\frac{E}{\mu}(t-s)} D_v D_{-x} C_{1h}(s) ds, D_{-x} C_{1h}\Big)_+ \\ &- k_1 (C_{1h}, C_{1h})_h. \end{aligned} \tag{2.47}$$

Using in (2.47) Cauchy-Schwarz inequality, we have

$$\begin{aligned} \frac{1}{2}\frac{dQ_h}{dt} + \overline{D_0}\left\| D_{-x} C_{1h} \right\|_+^2 &\leq \frac{Ek}{4\delta^2}\left\| \int_0^t e^{-\frac{E}{\mu}(t-s)} D_{-x} C_{1h}(s) ds \right\|_+^2 \\ &+ \overline{D_v}^2 Ek\delta^2 \left\| D_{-x} C_{1h} \right\|_+^2 - k_1 Q_h, \end{aligned}$$

where $\delta \neq 0$ is an arbitrary constant. From the previous inequality we deduce

$$\begin{aligned} \frac{1}{2}\frac{dQ_h}{dt} + k_1 Q_h + (\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\left\| D_{-x} C_{1h} \right\|_+^2 \leq \\ \frac{Ek}{4\delta^2}\int_0^t e^{-2\frac{E}{\mu}(t-s)} ds \int_0^t \left\| D_{-x} C_{1h}(s) \right\|_+^2 ds, \end{aligned}$$

and then

$$Q_h + 2k_1 \int_0^t Q_h(s) ds + 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2) \int_0^t \left\| D_{-x} C_{1h}(s) \right\|_+^2 ds \leq$$

$$\frac{Ek}{4\delta^2\frac{E}{\mu}}\int_0^t\int_0^s\left\|D_{-x}C_{1h}(\mu)\right\|_+^2 d\mu ds + Q_h(0).$$

If δ^2 is such that (2.12) holds we obtain

$$\begin{aligned} Q_h + \int_0^t Q_h(s)ds + \int_0^t \left\|D_{-x}C_{1h}(s)\right\|_+^2 ds \leq \\ \frac{k\mu}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}4\delta^2}\int_0^t\int_0^s\left\|D_{-x}C_{1h}(\mu)\right\|_+^2 d\mu ds \\ + \frac{1}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}}Q_h(0). \end{aligned}$$

Finally Gronwall's Lemma leads to

$$\begin{aligned} Q_h + \int_0^t Q_h(s)ds + \int_0^t \left\|D_{-x}C_{1h}(s)\right\|_+^2 ds \leq \\ \frac{1}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}}Q_h(0)e^{\bar{c}t}, \end{aligned} \tag{2.48}$$

where $\bar{c}$ is defined by (2.14). This last inequality establishes that Q_h, $\int_0^t Q_h(s)ds$ and $\int_0^t \left\|D_{-x}C_{1h}(s)\right\|_+^2 ds$ are bounded for bounded intervals of time. Inequality (2.48) can be improved by eliminating the exponential factor in its right hand side. Following the proof of Theorem 1, Theorem 3 can be proved.

Theorem 3. *If $\overline{D_0}$, $\overline{D_v}$, E, k and μ are such that* (2.21) *holds, then there exists $\gamma \in (0, \frac{E}{\mu})$ such that*

$$\begin{aligned} Q_h + \int_0^t e^{-2\gamma(t-s)}Q_h(s)ds + \int_0^t e^{-2\gamma(t-s)}\left\|D_{-x}C_{1h}(s)\right\|_+^2 ds \\ \leq Ce^{-2\gamma t}Q_h(0), \quad t \geq 0, \end{aligned}$$

where C is defined by (2.23). □

2.4.2 Two dimensional case

In $\overline{\Omega}_1 = [0, L] \times [0, L]$ we introduce the grid

$$\overline{\Omega_1}_H = \Big\{(x_i, y_j), i = 0, \ldots, N, j = 0, \ldots, M, x_0 = y_0 = 0, x_N = y_M = L\Big\},$$

where

$$H = (h_1, h_2), x_i - x_{i-1} = h_1, y_j - y_{j-1} = h_2, \quad \text{for} \quad i = 1, \ldots, N, j = 1, \ldots, M.$$

Let Ω_{1H} be the set of grid points of $\overline{\Omega}_{1H}$ which are in Ω_1 and let $\partial\Omega_{1H}$ be the set of grid points on $\partial\Omega_1$. By $\mathcal{C}$ we denote the set of corner points $\Big\{(0,0), (0,L), (L,0), (L,L)\Big\}$. We introduce the following notations

$$(w_H, q_H)_{\Omega_{1H}} = \sum_{i=1}^{N-1}\sum_{j=1}^{M-1} h_1 h_2 w_H(x_i, y_j) q_H(x_i, y_j),$$

$$(w_H, q_H)_x = \sum_{i=1}^{N}\sum_{j=1}^{M-1} h_1 h_2 w_H(x_i, y_j) q_H(x_i, y_j),$$

$$(w_H, q_H)_y = \sum_{i=1}^{N-1}\sum_{j=1}^{M} h_1 h_2 w_H(x_i, y_j) q_H(x_i, y_j),$$

where $w_H,\ q_H$ are grid functions defined in $\overline{\Omega}_{1H}$. Let $\nabla_H u_H$ be the discrete gradient $\nabla_H u_H = (D_{-x}u_H, D_{-y}u_H)$. We use also the notations

$$(\nabla_H w_H, \nabla_H q_H)_H = (D_{-x}w_H, D_{-x}q_H)_x + (D_{-y}w_H, D_{-y}q_H)_y,$$

and $\Big\|\nabla_H w_H\Big\|_H^2 = (\nabla_H w_H, \nabla_H w_H)_H$, where D_{-x} and D_{-y} denote the usual backward finite difference operators in the x and y directions, respectively. To discretize the spatial partial derivatives of (2.9) we introduce the second order finite difference operator

$$\begin{aligned} D_x^*(a(v_H)D_{-x}u_H)(x_i, y_j) &= \frac{1}{h_1}\Big(a(A_{H,x}v_H(x_{i+1}, y_j))D_{-x}u_H(x_{i+1}, y_j) \\ &- a(A_{H,x}v_H(x_i, y_j))D_{-x}u_H(x_i, y_j)\Big), \end{aligned}$$

$i = 1, \ldots, N-1,\ j = 1, \ldots, M-1$, where $A_{H,x}$ is the average operator

$$A_{H,x}v_H(x_l, y_j) = \frac{1}{2}\Big(v_H(x_l, y_j) + v_H(x_{l-1}, y_j)\Big).$$

The finite difference operator $D_y^*(b(v_H)D_{-y}u_H)$ is defined analogously, considering the average operator $A_{H,y}$ which is defined as $A_{H,x}$ but considering the y direction.

The discretization of $\nabla \cdot (D_1(M)\nabla C_1)$ is made with the finite difference operator

$$\nabla_H^* \cdot (B(v_H)\nabla_H u_H) = D_x^*(a(v_H)D_{-x}u_H) + D_y^*(b(v_H)D_{-y}u_H),$$

where B is the diagonal matrix with entries a and b.

Using summation by parts it can be shown the following equality

$$\begin{aligned}\Big(\nabla_H^* \cdot (B(v_H)\nabla_H u_H), w_H\Big)_{\Omega_{1H}} &= -\Big(a(A_{H,x}v_H)D_{-x}u_H, D_{-x}w_H\Big)_x \\ &- \Big(b(A_{H,y}v_H)D_{-y}u_H, D_{-y}w_H\Big)_y \\ &= -\Big(B(A_H v_H)\nabla_H u_H, \nabla_H w_H\Big)_H \end{aligned} \quad (2.49)$$

where $B(A_H v_H)$ is the diagonal matrix whose entries are $a(A_{H,x}v_H)$ and $b(A_{H,y}v_H)$.

Let us consider the semi-discrete approximation for (2.8) defined by

$$Q_H(t) = \Big\| C_{1H}(t) \Big\|^2_{\Omega_{1H}}, \quad t \geq 0, \quad (2.50)$$

where $\Big\| \cdot \Big\|_{\Omega_{1H}}$ denotes the norm induced by the inner product $(\cdot, \cdot)_{\Omega_{1H}}$.

The semi-discrete approximations C_{1H} and M_H of the solution of the system composed by the **IBVP** (2.9), the third equation in (2.1), with initial condition defined by the first and third equations of (2.6) and boundary condition (2.7) are then defined by the following system of differential equations

$$\begin{aligned}\frac{dC_{1H}}{dt} &= \nabla_H^* \cdot \Big(D_1(M_H)\nabla_H C_{1H}\Big) \\ &- Ek \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla_H^* \cdot (D_v \nabla_H C_{1H}(s)) ds \\ &- k_1 C_{1H} \ \text{ in } \ \Omega_{1H} \times (0, T], \end{aligned} \quad (2.51)$$

and

$$\frac{dM_H}{dt} + \beta_1 M_H \;=\; \beta_2 C_{1H} \;\text{ in }\; \Omega_{1H} \times (0,T]. \tag{2.52}$$

The initial and boundary semi-discrete conditions are defined respectively by

$$C_{1H}(0) = R_H C_1(0), \quad M_H(0) = R_H M(0) \;\text{ in }\; \Omega_{1H}, \tag{2.53}$$

and

$$C_{1H} = 0 \;\text{ on }\; \partial\Omega_{1H} \times (0,T]. \tag{2.54}$$

In (2.53) R_H denotes the restriction operator defined from $C^0(\overline{\Omega}_1)$ into the space of gird functions defined in $\overline{\Omega}_{1H}$.

Analogously to the one dimensional case, to give sense to the finite difference equation (2.51) for $i = 1, \ldots, N$ and $j = 1, \ldots, M$ we need to define M_H on $\partial\Omega_{1H}$. We assume that

$$M_H = M_0 e^{-\beta_1 t} \;\text{ on }\; \partial\Omega_{1H} \times (0,T]. \tag{2.55}$$

Multiplying (2.51), with respect to the inner product $(\cdot,\cdot)_{\Omega_{1H}}$, by C_{1H} and using (2.49) and (2.54) we easily establish

$$\begin{aligned}\left(\frac{dC_{1H}}{dt}, C_{1H}\right)_{\Omega_{1H}} &+ (D_1(M_H)\nabla_H C_{1H}, \nabla_H C_{1H})_H \\ &= Ek\Big(\int_0^t e^{-\frac{E}{\mu}(t-s)} D_v \nabla_H C_{1H}(s)ds, \nabla_H C_{1H}\Big)_H \\ &- k_1 (C_{1H}, C_{1H})_{\Omega_{1H}}. \end{aligned}\tag{2.56}$$

Considering in (2.56), Cauchy-Schwarz inequality, the conditions imposed on the entries of the diagonal matrices D_1 and D_v and following the proof of (2.11) it can be shown that

$$\begin{aligned}\frac{1}{2}\frac{dQ_H}{dt} + \overline{D_0}\left\|\nabla_H C_{1H}\right\|_H^2 &\le \frac{Ek}{4\delta^2}\left\|\int_0^t e^{-\frac{E}{\mu}(t-s)}\nabla_H C_{1H}(s)ds\right\|_H^2 \\ &+ \overline{D_v}^2 Ek\delta^2\left\|\nabla_H C_{1H}\right\|_H^2 - k_1 Q_H,\end{aligned}$$

where $\delta \neq 0$ is an arbitrary constant.

From the previous inequality we deduce

$$\frac{1}{2}\frac{dQ_H}{dt} + k_1 Q_H + (\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\left\|\nabla_H C_{1H}\right\|_H^2 \leq \frac{Ek}{4\delta^2}\int_0^t e^{-2\frac{E}{\mu}(t-s)}ds \int_0^t \left\|\nabla_H C_{1H}(s)\right\|_H^2 ds,$$

and then

$$Q_H + 2k_1\int_0^t Q_H(s)ds + 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\int_0^t \left\|\nabla_H C_{1H}(s)\right\|_H^2 ds \leq \frac{Ek}{4\delta^2\frac{E}{\mu}}\int_0^t\int_0^s \left\|\nabla_H C_{1H}(\mu)\right\|_H^2 d\mu ds + Q_H(0).$$

If δ^2 is such that (2.12) holds, we obtain

$$Q_H + \int_0^t Q_H(s)ds + \int_0^t \left\|\nabla_H C_{1H}(s)\right\|_H^2 ds \leq \frac{k\mu}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}4\delta^2}\int_0^t\int_0^s \left\|\nabla_H C_{1H}(\mu)\right\|_H^2 d\mu ds + \frac{1}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}}Q_H(0).$$

Finally Gronwall's Lemma leads to

$$Q_H + \int_0^t Q_H(s)ds + \int_0^t \left\|\nabla_H C_{1H}(s)\right\|_H^2 ds \leq \frac{1}{\min\{1, 2k_1, 2(\overline{D_0} - \overline{D_v}^2 Ek\delta^2)\}}Q_H(0)e^{\bar{c}t}, \tag{2.57}$$

where $\bar{c}$ is defined by (2.14).

This last inequality establishes that Q_H, $\displaystyle\int_0^t Q_H(s)ds$ and $\displaystyle\int_0^t \left\|\nabla_H C_{1H}(s)\right\|_H^2 ds$ are bounded for bounded intervals of time. Inequality (2.57) can be improved by eliminating the exponential factor in its right hand side. Analogously as in the previous section, following [25] and the proof of the Theorem 1 the next result can be proved.

Theorem 4. *If* $\overline{D_0}$, $\overline{D_v}$, E, k *and* μ *are such that* (2.21) *holds, then there exists* $\gamma \in (0, \frac{E}{\mu})$ *such that*

$$Q_H + \int_0^t e^{-2\gamma(t-s)} Q_H(s) ds + \int_0^t e^{-2\gamma(t-s)} \left\| \nabla_H C_{1H}(s) \right\|_H^2 ds \leq$$

$$C e^{-2\gamma t} Q_H(0), \quad t \geq 0,$$

where C *is defined by* (2.23). □

2.5 Energy estimates for the fully discrete implicit-explicit approximation

In this section, following [44], we analyze a fully discrete FDM that can be obtained by combining the spatial discretization introduced in the last section with an implicit-explicit Euler's method to integrate in time and a rectangular rule to discretize the time integral term in (2.51). An essential tool is the following lemma:

Lemma 2. *(Discrete Gronwall inequality (Lemma 4.3 of [45])) Let* $\{\eta_n\}$ *be a sequence of nonnegative real numbers satisfying*

$$\eta_n \leq \sum_{j=0}^{n-1} w_j \eta_j + \beta_n \qquad for \quad n \geq 1,$$

where $w_j \geq 0$ *and* $\{\beta_n\}$ *is a nondecreasing sequence of nonnegative numbers. Then*

$$\eta_n \leq \beta_n \exp(\sum_{j=0}^{n-1} w_j) \qquad for \quad n \geq 1.$$

□

We introduce in $[0, T]$ a uniform grid $\{t_n, n = 0, \ldots, N_{\Delta t}\}$ with $t_0 = 0$, $t_{N_{\Delta t}} = T$ and $t_n - t_{n-1} = \Delta t$.

Let D_{-t} be the backward finite-difference operator. Then the fully discrete approximation for the concentration C_1, C_{1H}^m, and for the molecular

weight M, M_H^m, are defined by the following set of equations

$$\begin{aligned} D_{-t}{C_1}_H^{m+1} &= \nabla_H^* \cdot (D_1(M_H^m)\nabla_H {C_1}_H^{m+1}) \\ &- \Delta t Ek \sum_{j=0}^{m} e^{-\frac{E}{\mu}(t_{m+1}-t_j)} \nabla_H^* \cdot (D_v \nabla_H {C_1}_H^{j}) \\ &- k_1 {C_1}_H^{m+1} \text{ in } \Omega_{1H}, \end{aligned} \tag{2.58}$$

$$D_{-t}M_H^{m+1} + \beta_1 M_H^m = \beta_2 C_{1H}^{m+1} \text{ in } \Omega_{1H}, \tag{2.59}$$

for $m = 0, \ldots, N_{\Delta t} - 1$, with initial conditions

$$C_{1H}^0 = R_H C_0, \quad M_H^0 = R_H M_0 \text{ in } \Omega_{1H}, \tag{2.60}$$

and the boundary conditions

$$C_{1H}^m = 0 \text{ on } \partial\Omega_{1H} \text{ for } m = 1, \ldots, N_{\triangle t}, \tag{2.61}$$

$$M_H^m = M_0 e^{-\beta_1 t_m} \text{ on } \partial\Omega_{1H} \text{ for } m = 1, \ldots, N_{\triangle t}. \tag{2.62}$$

We study in what follows the qualitative behaviour of the energy functional

$$Q_H^n = \left\| {C_1}_H^n \right\|_{\Omega_{1H}}^2, \quad n = 0, \ldots, N_{\Delta t}. \tag{2.63}$$

Multiplying (2.58) by C_{1H}^{m+1}, with respect to the inner product $(\cdot,\cdot)_{\Omega_{1H}}$, we obtain

$$\begin{aligned} ({C_1}_H^{m+1}, C_{1H}^{m+1})_{\Omega_{1H}} - ({C_1}_H^{m}, C_{1H}^{m+1})_{\Omega_{1H}} + \Delta t \Big(D_1(M_H^m)\nabla_H {C_1}_H^{m+1}, \nabla_H C_{1H}^{m+1} \Big)_H \\ = \Delta t^2 Ek \sum_{j=0}^{m} e^{-\frac{E}{\mu}(t_{m+1}-t_j)} (D_v \nabla_H {C_1}_H^{j}, \nabla_H C_{1H}^{m+1})_H \\ -\Delta t k_1 ({C_1}_H^{m+1}, C_{1H}^{m+1})_{\Omega_{1H}}, \end{aligned} \tag{2.64}$$

for $m = 0, \ldots, N_{\Delta t} - 1$.

Considering Cauchy-Schwarz inequality and the conditions on D_1 and D_v as in the previous section, we establish

$$\left\| {C_1}_H^{m+1} \right\|_{\Omega_{1H}}^2 - \left\| {C_1}_H^{m} \right\|_{\Omega_{1H}}^2 + 2\Delta t \overline{D_0} \left\| \nabla_H {C_1}_H^{m+1} \right\|_H^2 \leq$$

$$2\Delta t^2 Ek\overline{D_v}\sum_{j=0}^{m} e^{-\frac{E}{\mu}(t_{m+1}-t_j)}\left\|\nabla_H C_{1H}^{\,j}\right\|_H\left\|\nabla_H C_{1H}^{\,m+1}\right\|_H$$
$$- \quad 2\Delta t k_1\left\|C_{1H}^{\,m+1}\right\|^2_{\Omega_{1H}}. \tag{2.65}$$

As we have

$$\Delta t Ek\overline{D_v}\sum_{j=0}^{m} e^{-\frac{E}{\mu}(t_{m+1}-t_j)}\left\|\nabla_H C_{1H}^{\,j}\right\|_H\left\|\nabla_H C_{1H}^{\,m+1}\right\|_H \leq$$

$$Ek\overline{D_v}^2\delta^2\left\|\nabla_H C_{1H}^{\,m+1}\right\|^2_H$$
$$+ \quad \frac{TEk\Delta t}{4\delta^2}\sum_{j=0}^{m}\left\|\nabla_H C_{1H}^{\,j}\right\|^2_H,$$

where $\delta \neq 0$ is an arbitrary constant, from (2.65) we deduce

$$\left\|C_{1H}^{\,m+1}\right\|^2_{\Omega_{1H}} - \left\|C_{1H}^{\,m}\right\|^2_{\Omega_{1H}} + 2\overline{D_0}\Delta t\left\|\nabla_H C_{1H}^{\,m+1}\right\|^2_H \leq$$

$$2\Delta t Ek\overline{D_v}^2\delta^2\left\|\nabla_H C_{1H}^{\,m+1}\right\|^2_H$$
$$+ \quad \frac{Ek\Delta t^2 T}{2\delta^2}\sum_{j=0}^{m}\left\|\nabla_H C_{1H}^{\,j}\right\|^2_H - 2\Delta t k_1\left\|C_{1H}^{\,m+1}\right\|^2_{\Omega_{1H}}.$$

So we have

$$\left\|C_{1H}^{\,m+1}\right\|^2_{\Omega_{1H}} - \left\|C_{1H}^{\,m}\right\|^2_{\Omega_{1H}} + 2\Delta t k_1\left\|C_{1H}^{\,m+1}\right\|^2_{\Omega_{1H}}$$
$$+ \quad 2\Delta t(\overline{D_0} - Ek\overline{D_v}^2\delta^2)\left\|\nabla_H C_{1H}^{\,m+1}\right\|^2_H \leq$$
$$\frac{Ek\Delta t^2 T}{2\delta^2}\sum_{j=0}^{m}\left\|\nabla_H C_{1H}^{\,j}\right\|^2_H. \tag{2.66}$$

Summing (2.66) over $m = 0, \ldots, n-1$, we get

$$\left\|C_{1H}^{\,n}\right\|_{\Omega_{1H}}^2 - \left\|C_{1H}^{\,0}\right\|_{\Omega_{1H}}^2 + 2\Delta t k_1 \sum_{m=0}^{n-1} \left\|C_{1H}^{\,m+1}\right\|_{\Omega_{1H}}^2 + 2\Delta t(\overline{D_0} - Ek\overline{D_v}^{\,2}\delta^2) \sum_{m=0}^{n-1} \left\|\nabla_H C_{1H}^{\,m+1}\right\|_H^2 \leq \frac{Ek\Delta t^2 T}{2\delta^2} \sum_{m=0}^{n-1}\sum_{j=0}^{m} \left\|\nabla_H C_{1H}^{\,j}\right\|_H^2,$$

and consequently

$$\left\|C_{1H}^{\,n}\right\|_{\Omega_{1H}}^2 + 2\Delta t k_1 \sum_{m=0}^{n} \left\|C_{1H}^{\,m}\right\|_{\Omega_{1H}}^2 + 2\Delta t(\overline{D_0} - Ek\overline{D_v}^{\,2}\delta^2) \sum_{m=0}^{n} \left\|\nabla_H C_{1H}^{\,m}\right\|_H^2 \leq (1 + 2\Delta t k_1)\left\|C_{1H}^{\,0}\right\|_{\Omega_{1H}}^2 + 2\Delta t(\overline{D_0} - Ek\overline{D_v}^{\,2}\delta^2)\left\|\nabla_H C_{1H}^{\,0}\right\|_H^2 + \sum_{m=0}^{n-1} \frac{Ek\Delta t T}{2\delta^2} \Delta t \sum_{j=0}^{m} \left\|\nabla_H C_{1H}^{\,j}\right\|_H^2. \tag{2.67}$$

Choosing in (2.67) δ such that (2.12) holds, we obtain

$$\left\|C_{1H}^{\,n}\right\|_{\Omega_{1H}}^2 + \Delta t \sum_{m=0}^{n} \left\|C_{1H}^{\,m}\right\|_{\Omega_{1H}}^2 + \Delta t \sum_{m=0}^{n} \left\|\nabla_H C_{1H}^{\,m}\right\|_H^2 \leq \sum_{m=0}^{n-1} \phi_1 \Delta t \sum_{j=0}^{m} \left\|\nabla_H C_{1H}^{\,j}\right\|_H^2 + \phi_2 \left((1 + 2\Delta t k_1)\left\|C_{1H}^{\,0}\right\|_{\Omega_{1H}}^2 + 2\Delta t(\overline{D_0} - Ek\overline{D_v}^{\,2}\delta^2)\left\|\nabla_H C_{1H}^{\,0}\right\|_H^2 \right)$$

with

$$\phi_1 = \frac{\frac{EkT\Delta t}{2\delta^2}}{\min\left\{1, 2k_1, 2(\overline{D_0} - Ek\overline{D_v}^{\,2}\delta^2)\right\}}, \tag{2.68}$$

and

$$\phi_2 = \frac{1}{\min\left\{1, 2k_1, 2(\overline{D_0} - Ek\overline{D_v}^2\delta^2)\right\}}. \tag{2.69}$$

An application of the discrete Gronwall's Lemma, leads to the following theorem for the energy functional defined by (2.63).

Theorem 5. *If $\overline{D_0}, \overline{D_v}, E$ and k are such that equation* (2.12) *holds, then the energy functional defined by* (2.63) *satisfies*

$$Q_H^n + \Delta t \sum_{m=0}^{n} Q_H^m + \Delta t \sum_{m=0}^{n} \left\| \nabla_H C_{1H}^{\,m} \right\|_H^2 \leq$$

$$\widetilde{C}\left((1 + 2\Delta t k_1) Q_H^0 + 2\Delta t(\overline{D_0} - Ek\overline{D_v}^2\delta^2) \left\| \nabla_H C_{1H}^{\,0} \right\|_H^2 \right), \tag{2.70}$$

with

$$\widetilde{C} = \phi_2 \exp(\phi_2 \frac{EkT^2}{2\delta^2}), \tag{2.71}$$

where ϕ_2 is defined by (2.69). □

2.6 Numerical simulations

In this section we present some numerical results that illustrate the behaviour of the system composed by the **IBVP** (2.9) and the third equation in (2.1). The influence of the parameters of the model is also analyzed.

2.6.1 One dimensional case

In order to study the influence of the parameters and the behaviour of the model we consider in what follows $\Omega_1 = (0, 1)$. The results are obtained with the one dimensional version **IMEX** method (2.58) defined by using an implicit-explicit Euler method to integrate (2.41)-(2.45) and a rectangular rule to integrate the time integral in (2.41).

The values used for the parameters and initial values of the variables are presented in Table 2.1. We observe that the values in Table 2.1 satisfy the

Variable/ Parameter	Unit	Value	Equation
C_0	mol/mm^3	1	(2.6)
M_0	Da	5×10^{-1}	(2.2)
D_0	mm^2/s	10^{-2}	(2.6)
D_v	$mol/(mm.s.Pa)$	10^{-4}	(2.1)
k_1	$1/s$	10^{-3}	(2.1)
k	mm^3/mol	1	(2.4)
$\bar{k}$	–	1	(2.2)
μ	$Pa.s$	10^{-3}	(2.1)
E	Pa	10^{-4}	(2.1)
β_1	$1/s$	10^{-1}	(2.1)
β_2	$Da.mm^3/(mol.s)$	10^{-3}	(2.1)
Δt	s	10^{-3}	(2.58)
h	mm	10^{-2}	(2.41)

Tab. 2.1: Values of the parameters and variables at $t = 0$. The column on the right display the number of the equation where they first appear.

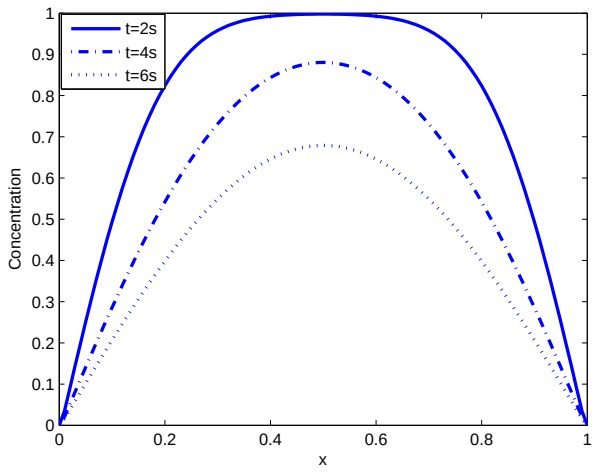


Fig. 2.1: Concentration at different times.

constraints in Theorem 1.

In Figure 2.1 the evolution of C_1 in time is illustrated. As expected the drug concentration decreases in time.

The evolution of M is plotted in Figure 2.2. The decrease in time of the molecular weight is a consequence of the polymer degradation. In fact as a solvent penetrates a degradable matrix the polymeric chains are broken and consequently they loose molecular weight. To observe that the evolution inside the polymer is not spatially homogeneous, a zoom of the plot of the molecular weight at $t = 6s$ is presented in Figure 2.2 (right).

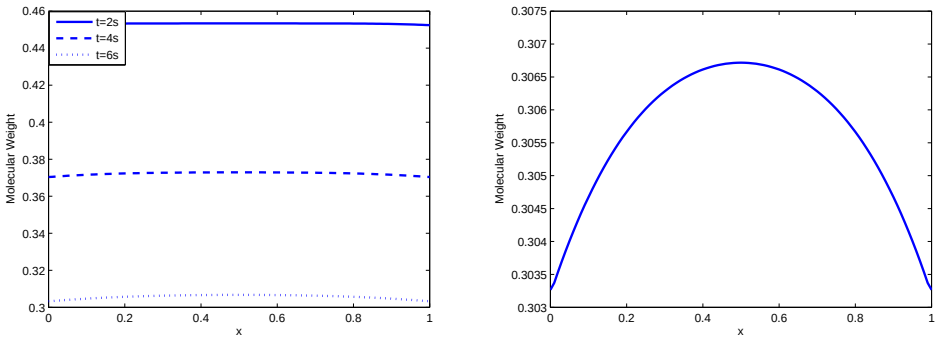


Fig. 2.2: Molecular weight at different times (left) and a zoom of molecular weight at $t = 6s$ (right).

In Figure 2.3 the influence of the diffusion coefficient on the released mass is shown. As the diffusion coefficient of the drug in the non hydrolyzed polymer, D_0, increases the released mass increases because the diffusion process becomes faster. Consequently, as D_0 increases, the concentration inside the polymer decreases.

The influence of the degradation rate is presented in Figure 2.4. As expected if the degradation rate increases the delivery rate of the drug also increases. In Figure 2.4 (right) we observe that the increase of the degradation rate is closely related with the loss of molecular weight.

In Figure 2.5 we illustrate the dependence of the released mass on the viscoelastic diffusion coefficient D_v. We observe that the polymer acts as a barrier that difficults drug diffusion. The drug molecules strain the polymer and it exerts a stress of opposite sign. The non Fickian flux $-D_v\nabla\sigma$ is, in a certain sense an antiflux which decreases the Fickian flux $-D_1\nabla C_1$.

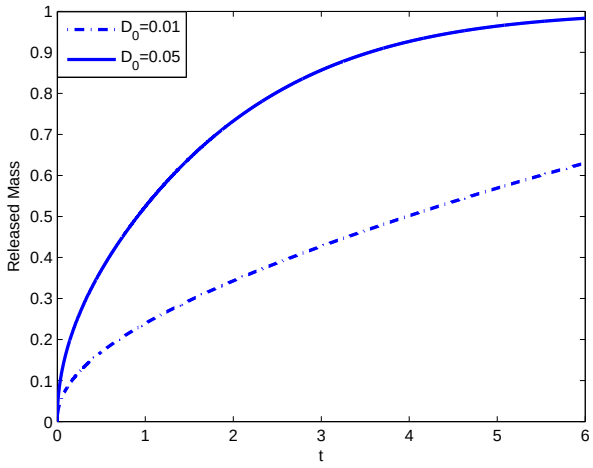


Fig. 2.3: Influence of the diffusion D_0 on the released mass.

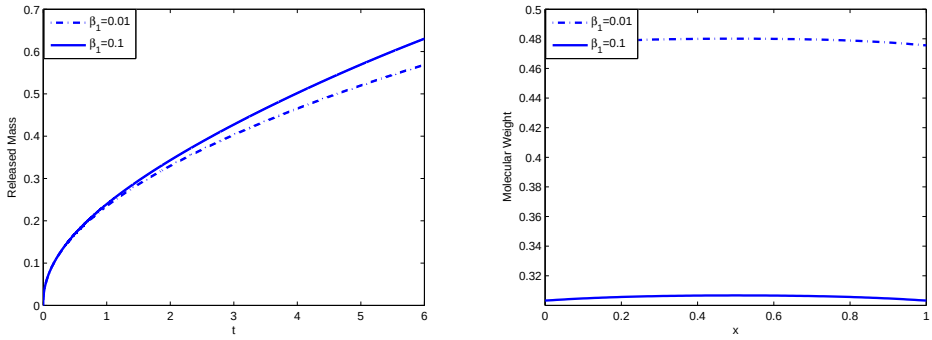


Fig. 2.4: Influence of the degradation rate β_1 on the released mass (left) and molecular weight at $t = 6s$ (right).

In agreement with this description, the increase of D_v represents a large opposition of the polymer and consequently leads to a delay in the release.

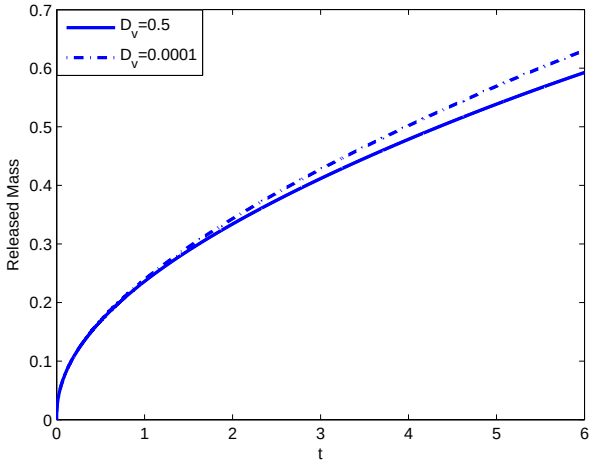


Fig. 2.5: Influence of viscoelastic diffusion D_v on the released mass.

In Figure 2.6 the influence of Young modulus, E, on the drug concentration inside the polymer is presented at $t = 6s$. To explain the behaviour in Figure 2.6 we must consider the relation existing between Young modulus and the crosslinks between the polymeric chains. These crosslinks are bonds that link the polymeric chains. More crosslinks exist in a polymeric material and less flexible in the material. The crosslink density of a polymer is proportional to Young modulus E and consequently as this constant increases the polymer offers more resistance to the exit of the drug, which is delayed.

2.6.2 Two dimensional case

We consider $\overline{\Omega_1} = [0,1] \times [0,1]$ and $h_1 = h_2$. The numerical results that we presented in what follows were obtained with the **IMEX** method (2.58)-(2.62) and with the diffusion tensor of the drug in the non hydrolyzed polymer $D_0 I_2$ and with the viscoelastic tensor $D_v I_2$ where I_2 is the identity matrix. The values of the parameters presented in Table 2.1 have been used.

In Figure 2.7 we present plots of the concentration of drug at $t = 0.1s$, $t = 1s$, $t = 5s$ and $t = 10s$. As expected the concentration decreases as time increases.

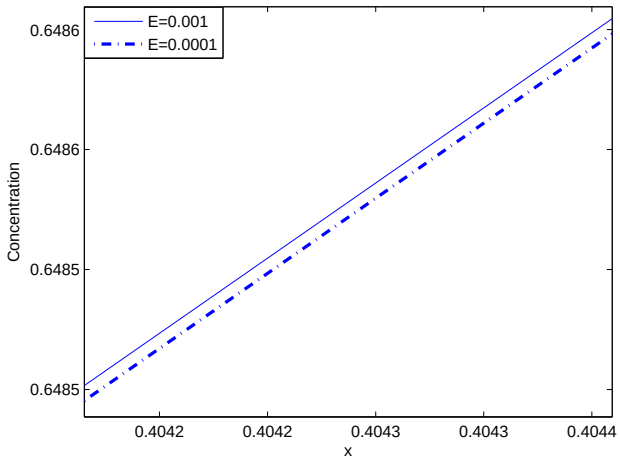


Fig. 2.6: Influence of Young modulus E on the drug concentration in the polymeric matrix at $t = 6s$.

In Figure 2.8 we present the molecular weight for different times. We observe that due to polymer degradation the molecular weight decreases.

2.7 Final comments

A model to simulate transport through a biodegradable viscoelastic material is studied. The analytical treatment of the system of partial differential equations lead to the establishment of stability results. The influence of mechanistic and degradation parameters is analyzed, showing agreement with the physical behaviour. We believe that with future improvements the model can be used as a tool to design biodegradable polymers with predefined properties.

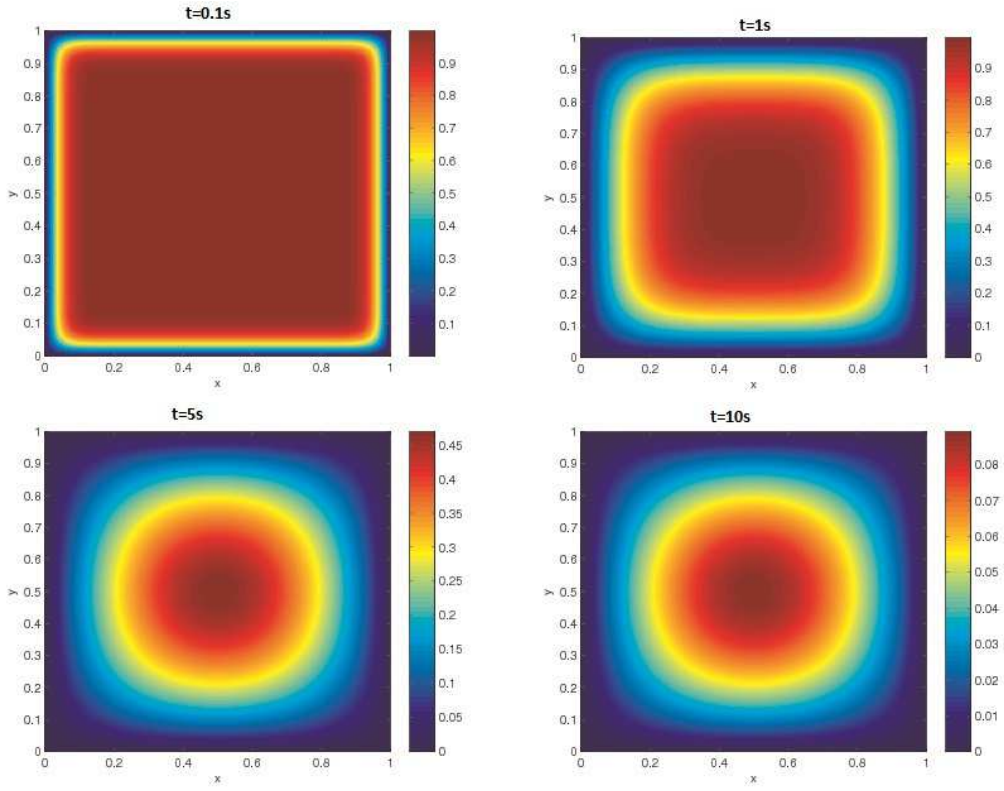


Fig. 2.7: Concentration of drug at different times.

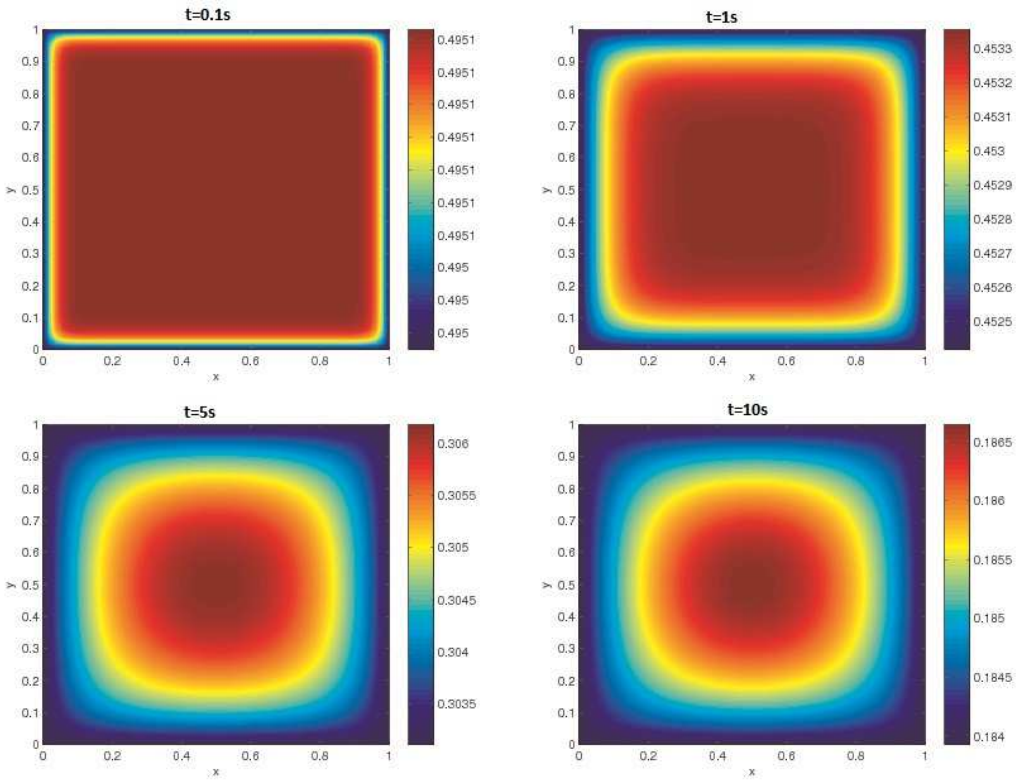


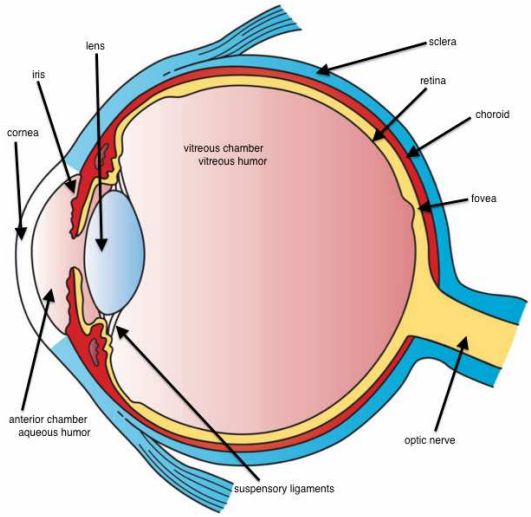
Fig. 2.8: Molecular weight of the polymer at different times.

3. DRUG DELIVERY FROM AN OCULAR IMPLANT INTO THE VITREOUS CHAMBER OF THE EYE

In this chapter we present a medical application of a biodegradable viscoelastic drug eluting implant. As described in Chapter 1 this type of implant is used for instance in the vitreous chamber of the eye to release drug to the retina ([27]). The model presented here describes *in vivo* drug delivery as it couples system (2.1) with the kinetics of drug in the vitreous chamber of the eye. The geometry of the vitreous chamber of the eye and of the intravitreal implant are described and the mathematical coupled model is presented. We briefly explain the mass behaviour of the materials within a phenomenological approach. We present a variational formulation for the continuous model and using an implicit-explicit finite element method, we establish a discrete variational form. Finally, numerical simulations that illustrate the kinetics of the drug release and show the effect of degradation and viscoelasticity are exhibited in the last section.

3.1 Geometry

The 2D geometric model of the human eye adopted in the present study is shown in Figure 3.1 and is based on physiological dimensions ([31]). The vitreous chamber, Ω_2, is mainly composed by vitreous humor and it occupies about two-thirds of the eye. The lens is located behind the iris and is modeled here as an ellipsoid. The hyaloid membrane and the lens separate the anterior chamber and the posterior chamber of the eye from the vitreous chamber. The retina forms the boundary of the vitreous on the posterior surface and is modeled as a spherical surface with a radius of 11 mm. The intravitreal implant, Ω_1, is placed into the vitreous, as shown in Figure 3.1, and it is geometrically represented by a cylinder with radius 0.023 mm and height 0.6 mm.



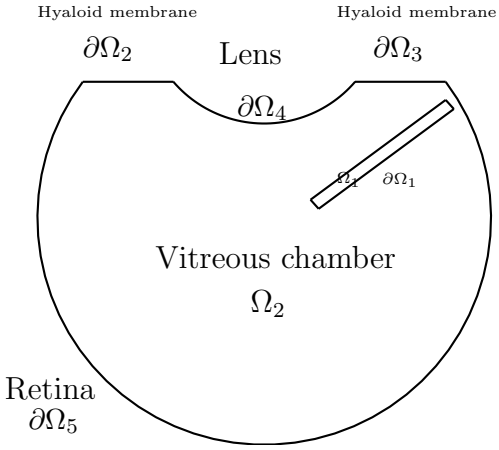


Fig. 3.1: Top: Anatomy of the human eye(http://marcelohosoume.blogspot.pt /2010/10/iluvien-and-future-of-ophthalmic-drug.html)
Bottom: Geometry of the vitreous chamber of the human eye(Ω_2), hyaloid membrane($\partial\Omega_2$, $\partial\Omega_3$), lens ($\partial\Omega_4$), retina($\partial\Omega_5$), ocular implant (Ω_1) and its boundary ($\partial\Omega_1$).

3.2 Mathematical model

The implant, Ω_1, containing dispersed drug, is placed into the vitreous, near the retina (Figure 3.1-Bottom). The drug is released in a controlled manner through the vitreous which is a porous media, and its target is the retina affected by an inflammatory process.

The diffusion-reaction equation that describes the drug kinetics in the polymeric implant is represented by system (2.1), completed with initial conditions (2.6). We couple with this system the drug dynamics in the vitreous, where the diffusion of drug occurs from the polymer towards the vitreous and the retina. Mass transport in the vitreous is described by diffusion and convection. Convection is due to the steady permeation of the aqueous humor through the vitreous, and diffusion is driven by the concentration gradient ([31]). To simulate the kinetics of the drug in the vitreous we use a diffusion-convection equation where the permeation velocity of the aqueous humor is given by Darcy's law ([29, 31, 32, 34, 46, 47]), as follows:

$$\frac{\partial C_2}{\partial t} + \nabla \cdot (C_2 \mathbf{v}) - \nabla \cdot (D_2 \nabla C_2) = 0 \qquad \texttt{in } \Omega_2 \times (0, T], \tag{3.1}$$

and

$$\begin{cases} \mathbf{v} = -\dfrac{K}{\mu_1} \nabla p & \text{in } \ \Omega_2 \times (0, T], \\ \nabla \cdot \mathbf{v} = 0 & \text{in } \ \Omega_2 \times (0, T]. \end{cases} \tag{3.2}$$

In equation (3.1) C_2 represents the concentration of the drug in the vitreous, D_2 is the diffusion tensor of the drug in the vitreous and $\mathbf{v}$ is the velocity of aqueous humor permeation given by (3.2). In this last system K is the permeability of the vitreous and μ_1 is the viscosity of the permeating aqueous humour ([31]). The term $\dfrac{K}{\mu_1}$ is referred to as the hydraulic conductivity.

3.3 Initial and boundary conditions

Equations (2.1), (3.1) and (3.2) are completed with initial conditions represented by

$$\begin{cases} C_1(0) = C_0 & \text{in } \Omega_1, \\ \sigma(0) = \sigma_0 & \text{in } \Omega_1, \\ M(0) = M_0 & \text{in } \Omega_1, \\ C_2(0) = 0 & \text{in } \Omega_2. \end{cases} \tag{3.3}$$

Boundary conditions of different types will be used in the model:

- Boundary conditions for the pressure:

$$p = 2000 \text{ Pa} \quad \texttt{on } (\partial\Omega_2 \cup \partial\Omega_3) \times (0, T],$$

and

$$p = 1200 \text{ Pa} \quad \texttt{on } \partial\Omega_5 \times (0, T].$$

We note that $\partial\Omega_2 \cup \partial\Omega_3$ represents the hyaloid membrane and $\partial\Omega_5$ represents the retina. The two previous values of the pressure that we have considered correspond to a limit value of an healthy intraocular pressure in the anterior chamber near the lens and a normal pressure of the blood system, respectively.

- As the retina is a permeable membrane, a realistic boundary condition can be defined by

$$J_2 \cdot \eta = A_r C_2 \quad \texttt{on } \partial\Omega_5 \times (0, T],$$

where $J_2 = -D_2 \nabla C_2 + \mathbf{v} C_2$ stands for the flux, η is the unit outward normal to $\partial\Omega_5$ and A_r is the permeability constant of the retina. The convective part of the flux is due to a convective field generated by the porous structure of the vitreous.

As the lens and the hyaloid membrane are not permeable to the drug then

$$J_2 \cdot \eta = 0 \quad \texttt{on } (\partial\Omega_2 \cup \partial\Omega_3 \cup \partial\Omega_4) \times (0, T],$$

where η is the unit outward normal to $\partial\Omega_2 \cup \partial\Omega_3 \cup \partial\Omega_4$.

- Wall conditions for the velocity: we assume a no slip condition for the velocity

$$\mathbf{v} \cdot \eta = 0, \tag{3.4}$$

on the boundary $\partial\Omega_4$ of the vitreous chamber Ω_2 and on the boundary $\partial\Omega_1$ of the implant Ω_1 (Figure 3.1-Bottom), that is the fluid has zero velocity with respect to the normal to the boundary $\partial\Omega_1 \cup \partial\Omega_2 \backslash \partial\Omega_5$.

- Interface boundary conditions for the flux of drug: on the boundary of the implant

$$J_1 \cdot \eta_\theta = A_c(C_1 - C_2) \quad \texttt{on } \partial\Omega_1 \times (0,T],$$
$$J_1 \cdot \eta_\theta = -J_2 \cdot \eta_i \quad \texttt{on } \partial\Omega_1 \times (0,T],$$

where $J_1 = -D_1(M)\nabla C_1 - D_v \nabla\sigma$, A_c is the permeability constant and η_θ and η_i are the unit outward and inward normals to $\partial\Omega_1$. As $\eta_\theta = -\eta_i$, the last equation represents the continuity of the flux on $\partial\Omega_1$.

The previous boundary and interface conditions are summarized as follows:

$$\begin{cases} J_2 \cdot \eta = A_r C_2 & \text{on } \partial\Omega_5 \times (0,T], \\ p = 2000 & \text{on } (\partial\Omega_2 \cup \partial\Omega_3) \times (0,T], \\ p = 1200 & \text{on } \partial\Omega_5 \times (0,T], \\ \mathbf{v} \cdot \eta = 0 & \text{on } (\partial\Omega_1 \cup \partial\Omega_4) \times (0,T], \\ J_2 \cdot \eta = 0 & \text{on } (\partial\Omega_2 \cup \partial\Omega_3 \cup \partial\Omega_4) \times (0,T], \\ J_1 \cdot \eta_\theta = A_c(C_1 - C_2) & \text{on } \partial\Omega_1 \times (0,T], \\ J_1 \cdot \eta_\theta = -J_2 \cdot \eta_i & \text{on } \partial\Omega_1 \times (0,T]. \end{cases} \tag{3.5}$$

3.4 Qualitative behaviour of the total mass

In what follows we analyze the time behaviour of the total mass of drug,

$$\mathcal{M}(t) = \int_{\Omega_1} C_1 dX + \int_{\Omega_2} C_2 dX,$$

where Ω_1 and Ω_2 stand for the implant and the vitreous chamber, respectively.
As we have

$$\mathcal{M}'(t) = \int_{\Omega_1} \frac{\partial C_1}{\partial t} dX + \int_{\Omega_2} \frac{\partial C_2}{\partial t} dX,$$

for C_1 and C_2 regular enough considering the first equation of (2.1), equation (3.1) and integrating by parts, we obtain

$$\begin{aligned} \mathcal{M}'(t) &= \int_{\partial\Omega_1} \Big(D_1(M)\nabla C_1 + D_v \nabla\sigma \Big)\eta ds - \int_{\Omega_1} k_1 C_1 dX \\ &+ \int_\Gamma \Big(D_2 \nabla C_2 - C_2 \mathbf{v} \Big)\eta ds, \end{aligned}$$

where $\Gamma = \bigcup_{i=1}^{5} \partial\Omega_i$. Taking into account the boundary conditions (3.5), we get

$$\mathcal{M}'(t) = -k_1 \int_{\Omega_1} C_1 dX - A_r \int_{\partial\Omega_5} C_2 ds,$$

that leads to

$$\mathcal{M}(t) + \int_0^t \int_{\Omega_1} k_1 C_1(\tau) dX d\tau + \int_0^t \int_{\partial\Omega_5} A_r C_2(\tau) ds d\tau = \mathcal{M}(0).$$

Phenomenologically, we can assume that the second and third terms of the left side of the last equality are positive. We can then conclude that $\mathcal{M}(t) \leq \mathcal{M}(0)$.

3.5 Weak formulation

3.5.1 Weak formulation of Darcy's Law

To introduce a variational formulation of the boundary value problem defined by the system (3.2) we start by writing such system in the following form:

$$-\nabla \cdot (\frac{K}{\mu_1} \nabla p) = 0 \quad \text{in } \Omega_2,$$

which is complemented by the boundary conditions

$$p = 2000 \ \ Pa \ \text{ on } \partial\Omega_2 \cup \partial\Omega_3,$$
$$p = 1200 \ \ Pa \ \text{ on } \partial\Omega_5,$$
$$\nabla p \cdot \eta = 0 \ \text{ on } \partial\Omega_1 \cup \partial\Omega_4.$$

Let

$$V = \Big\{ v \in H^1(\Omega_2) : \nabla v \cdot \eta = 0 \text{ on } \partial\Omega_1 \cup \partial\Omega_4 \Big\},$$

and

$$V_D = \Big\{ v \in H^1(\Omega_2) : \ v = 0 \text{ on } \partial\Omega_2 \cup \partial\Omega_3 \cup \partial\Omega_5 \Big\}.$$

We then consider the following variational problem:
Find $p \in V$ such that

$$\begin{cases} p = 2000 \quad \text{on } \partial\Omega_2 \cup \partial\Omega_3, \ \ p = 1200 \quad \text{on } \partial\Omega_5, \\ (\frac{K}{\mu_1} \nabla p, \nabla u) = 0, \ \ \forall u \in V_D. \end{cases} \tag{3.6}$$

3.5.2 Weak formulation of the coupled problems

We introduce a variational problem induced by the concentration equations (2.1), (3.1), (3.3) and (3.5). Let C in $\Omega = \Omega_1 \cup \Omega_2$ be defined by

$$C = \begin{cases} C_1 & \text{in } \Omega_1, \\ C_2 & \text{in } \Omega_2, \end{cases} \tag{3.7}$$

and the diffusion tensor of the drug by

$$D = \begin{cases} D_0 e^{\bar{k}\frac{M_0 - M}{M_0}} & \text{in } \Omega_1, \\ D_2 & \text{in } \Omega_2. \end{cases} \tag{3.8}$$

We replace (2.1), (3.1), (3.3) and (3.5) by the following variational problem:
Find $C \in H^1(\Omega)$, $\sigma \in H^1(\Omega_1)$ and $M \in L^2(\Omega_1)$, such that $\dfrac{\partial C}{\partial t} \in L^2(\Omega)$, $\dfrac{\partial \sigma}{\partial t}, \dfrac{\partial M}{\partial t} \in L^2(\Omega_1)$ and

$$\begin{cases} \left(\dfrac{\partial C}{\partial t}, v\right)_\Omega + \left(\dfrac{\partial \sigma}{\partial t}, w_1\right)_{\Omega_1} + \left(\dfrac{\partial M}{\partial t}, w_2\right)_{\Omega_1} = -(D\nabla C, \nabla v)_\Omega \\ \qquad -(D_v \nabla \sigma, \nabla v)_{\Omega_1} - k_1(C, v)_{\Omega_1} + (\mathbf{v}C, \nabla v)_{\Omega_2} \\ \qquad -\dfrac{E}{\mu}(\sigma, w_1)_{\Omega_1} + \overline{E}(C, w_1)_{\Omega_1} - \beta_1(M, w_2)_{\Omega_1} \\ \qquad +\beta_2(C, w_2)_{\Omega_1} - \Big(A_r C, v\Big)_{\partial\Omega_5}, \\ \qquad \forall v \in H^1(\Omega), \forall w_1 \in H^1(\Omega_1), \forall w_2 \in L^2(\Omega_1), \\ C(0) = \widehat{C}_0, \quad \sigma(0) = \sigma_0, \quad M(0) = M_0, \end{cases} \tag{3.9}$$

where

$$\widehat{C}_0 = \begin{cases} C_0 & \text{in } \Omega_1, \\ 0 & \text{in } \Omega_2. \end{cases}$$

3.6 Finite element approximation

To define a finite element approximation for the solution of (3.6) coupled with (3.9), we introduce in $\Omega = \overline{\Omega}_1 \cup \Omega_2$ an admissible triangulation J_h defining in $\overline{\Omega}_1$ and $\overline{\Omega}_2$ two compatible triangulations $J_{h,1}$ and $J_{h,2}$, respectively, that is, triangulations that share the same edges on $\partial\Omega_1$ (Figure 3.2-Bottom).

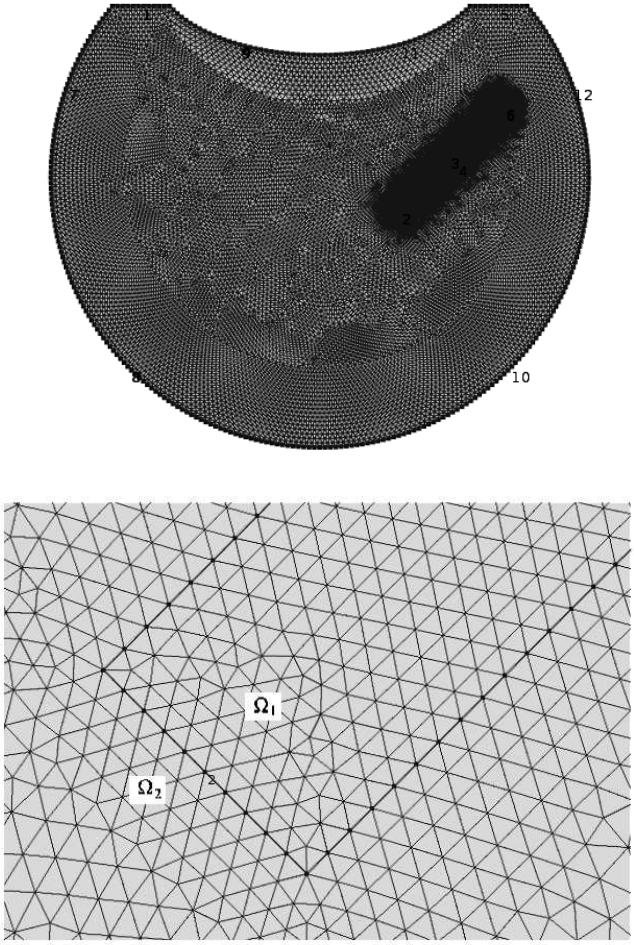


Fig. 3.2: Admissible triangulation with 30042 elements (top) and a zoom of the mesh near the implant (bottom).

3.6.1 Darcy's Law

To define a finite dimensional approximation for the solution of the variational problem (3.6) we introduce

$$V_h(\Omega_2) = \Big\{ v \in C^0(\overline{\Omega}_2) : \ v\mid_k \ \text{is linear, } k \in J_{h,2}, \ \nabla v \cdot \eta = 0 \text{ on } \partial\Omega_1 \cup \partial\Omega_4 \Big\},$$

$$V_{D,h}(\Omega_2) = \Big\{ v \in C^0(\overline{\Omega}_2) : \ v\mid_k \ \text{is linear, } k \in J_{h,2}, v = 0 \text{ on } \partial\Omega_2 \cup \partial\Omega_3 \cup \partial\Omega_5 \Big\},$$

then the finite dimensional approximation for the pressure is obtained solving the variational problem:
Find $p_h \in V_h$ such that

$$\begin{cases} p_h = 2000 \ \ Pa \ \ \text{on} \ \ \partial\Omega_2 \cup \partial\Omega_3, \ \ p_h = 1200 \ \ Pa \ \ \text{on} \ \ \partial\Omega_5, \\ (\dfrac{K}{\mu_1}\nabla p_h, \nabla v_h) = 0, \ \ \forall v_h \in V_{D,h}(\Omega_2). \end{cases}$$

The finite dimensional approximation for the velocity is then obtained considering $\mathbf{v}_h = -\dfrac{K}{\mu_1}\nabla p_h$.

3.6.2 Coupled problems

To compute the numerical approximations for the concentration, stress and molecular weight we introduce the following finite dimensional spaces

$$V_h^0(\Omega_1) = \Big\{ v : \ \overline{\Omega}_1 \mapsto \mathbb{R}, v\mid_k \ \text{is constant, } k \in J_{h,1} \Big\},$$

$$V_h(\Omega_1) = \Big\{ v \in C^0(\overline{\Omega}_1) : \ v\mid_k \ \text{is linear, } k \in J_{h,1} \Big\},$$

$$V_h(\Omega) = \Big\{ v \in H^1(\Omega) : \ v\mid_k \ \text{is linear, } k \in J_h \Big\}.$$

So, the variational problem (3.9) is replaced by the finite dimensional variational problem:

Find $C_h \in V_h(\Omega)$, $\sigma_h \in V_h(\Omega_1)$, $M_h \in V_h^0(\Omega_1)$ such that

$$\begin{cases} \Big(\dfrac{\partial C_h}{\partial t}, v_h\Big)_\Omega + \Big(\dfrac{\partial \sigma_h}{\partial t}, w_1\Big)_{\Omega_1} + \Big(\dfrac{\partial M_h}{\partial t}, w_2\Big)_{\Omega_1} \\ \qquad = -(D_h \nabla C_h, \nabla v_h)_\Omega - (D_v \nabla \sigma_h, \nabla w_1)_{\Omega_1} \\ \qquad -k_1 (C_h, v_h)_{\Omega_1} + (\mathbf{v}C, \nabla v_h)_{\Omega_2} \\ \qquad -\dfrac{E}{\mu}(\sigma_h, w_1)_{\Omega_1} + \overline{E}(C_h, w_1)_{\Omega_1} - \beta_1 (M_h, w_2)_{\Omega_1} \\ \qquad +\beta_2 (C_h, w_2)_{\Omega_1} - \Big(A_r C_h, v_h\Big)_{\partial\Omega_5}, \\ \qquad \forall v_h \in V_h(\Omega),\ \forall w_1 \in V_h(\Omega_1),\ \forall w_2 \in V_h^0(\Omega_1), \\ C_h(0) = P_{C,h}\widehat{C}_0, \quad \sigma_h(0) = P_{\sigma,h}\sigma_0, \quad M_h(0) = P_{M,h}M_0, \end{cases} \tag{3.10}$$

where $P_{C,h}$, $P_{\sigma,h}$ and $P_{M,h}$ denote the projection operators in the spaces $V_h(\Omega)$, $V_h(\Omega_1)$ and $V_h^0(\Omega_1)$, respectively.

In (3.10) D_h is defined by

$$D_h = \begin{cases} D_0 e^{\bar{k}\frac{M_0 - M_h}{M_0}} & \text{in } \Omega_1, \\ D_2 & \text{in } \Omega_2. \end{cases}$$

3.7 Numerical simulations

In this section we illustrate the behaviour of drug concentration in the implant and in the vitreous chamber. In the time integration of the differential problem for the finite element solutions an adaptive Backward Differentiation Formula with order between 1 and 2, with adaptive time step, has been used ([48]). The results that we present in this section were obtained using the software Comsol (v4.2a).

The values of some of the constants used to model the implant are not available in the literature. In these cases we use values that make physical sense but that may not correspond to the exact characteristics of the intravitreous implants in the market. For this reason the present study has, for the moment, mainly a qualitative character.

The numerical simulations have been obtained with $C_0 = 1.7887 \times 10^{-6}$ mol/mm^3, $M_0 = 0.5 \times 10^{-6}\, Da$ and $\sigma_0 = 0.5 \times 10^{-6}\, Pa$, representing the initial drug concentration, initial stress and the initial molecular weight in the implant, respectively. All the units of the variables and parameters are listed in Table 3.1. The units are selected such that the equations are dimensionally correct.

The diffusion tensor of the drug in the implant is defined considering $D_0 = 1 \times 10^{-11} I_2$ in (3.8), where I_2 is the identity matrix, and its diffusion tensor in the vitreous is defined by $D_2 = 1 \times 10^{-8} I_2$. We recall that the diffusion tensor in the polymer will increase as the molecular weight decreases that is as degradation occurs. We took the viscoelastic tensor $D_v I_2$. We

Variable/ Parameter	Unit	Value	Equation
k_1	$1/s$	10^{-10}	(3.9)
β_1	$1/s$	5×10^{-4}	(3.9)
β_2	$Da.mm^3/(mol.s)$	10^{-9}	(3.9)
μ	$Pa.s$	2×10^{-8}	(3.9)
E	Pa	10^{-7}	(3.9)
k	mm^3/mol	10^{-4}	(3.9)
$\bar{k}$	–	1	(3.8)
A_c	mm/s	5×10^{-5}	(3.5)
D_v	$mol/(mm.s.Pa)$	10^{-11}	(3.5)
$\frac{K}{\mu_1}$	$mm^2/(Pa.s)$	8.4×10^{-8}	(3.2)
A_r	mm/s	5×10^{-3}	(3.5)

Tab. 3.1: Values of the parameters. The column on the right display the number of the equation where they first appear.

observe that the parameters which are used in the numerical simulations are in agreement with condition (2.21) imposed in Theorem 1.

In Figure 3.3 the drug concentration at time $t = 5\,min$ and $t = 2\,h$ are presented. It can be observed that as time evolves the drug is released and less drug concentration is inside the implant. As expected the concentration for $t = 5\,min$ is higher than the concentration for $t = 2\,h$.

The pressure in the vitreous chamber is shown in Figure 3.4. The evolution of the pressure from the top ($p = 2000\,Pa$) to the boundary of the vitreous chamber, that is in contact with the retina ($p = 1200\,Pa$), can be observed.

In Figure 3.5 the drug concentration in the vitreous chamber is plotted for $t = 5\,min$ and $t = 2\,h$.

During the first instants of the delivery process, no drug is observed in the vitreous, except near the ocular implant, and as time increases more drug concentration is available to diffuse. For a better understanding of the

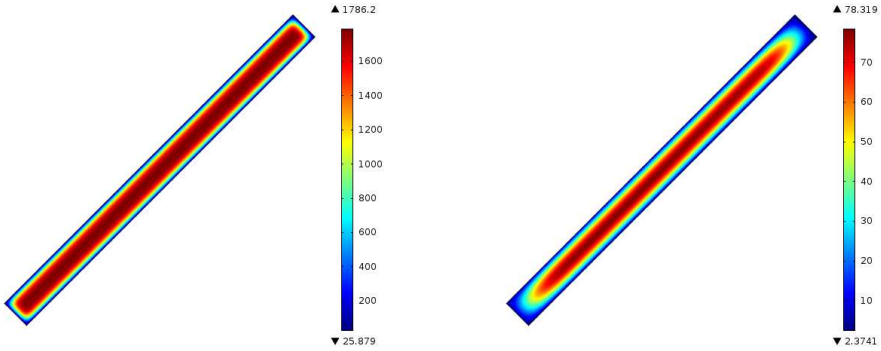


Fig. 3.3: Drug concentration in the implant at $t = 5\,min$ (left) and $t = 2\,h$ (right).

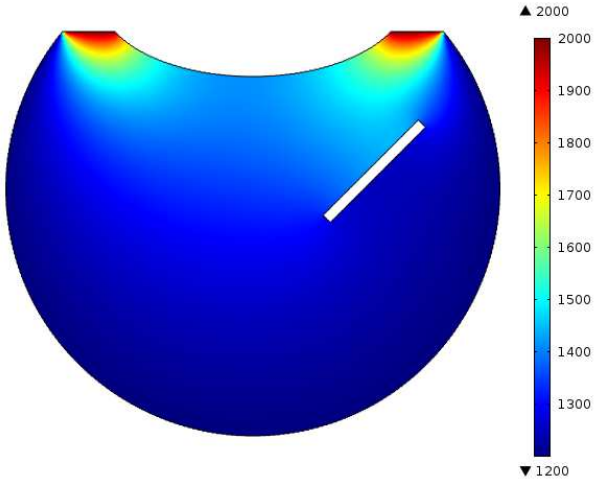


Fig. 3.4: Steady pressure in the vitreous chamber.

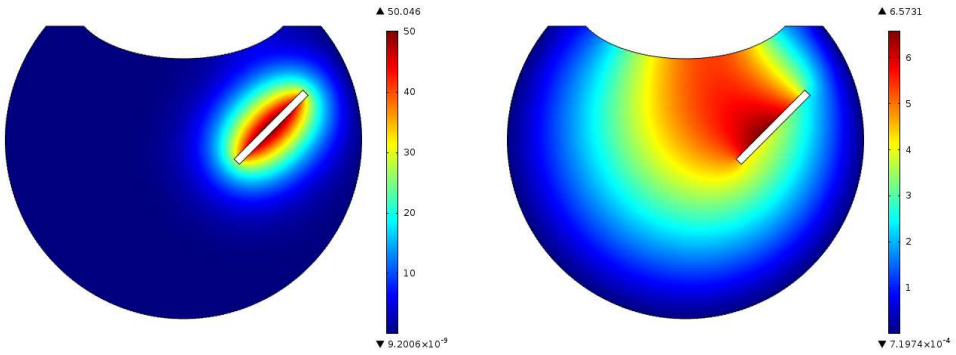


Fig. 3.5: Drug concentration in the vitreous chamber at $t = 5\,min$ (left) and $t = 2\,h$ (right).

qualitative behaviour of the drug concentration in the vitreous chamber, we present in Figure 3.6, the plot of the mean drug concentration *vs* time inside the implant and the vitreous chamber. It can be observed that the drug concentration in the vitreous chamber increases until it attains a maximum value at $t = 30\,min$; for $t > 30\,min$ the drug concentration decreases until no drug concentration is present in the ocular implant. This qualitative behaviour is in agreement with medical data, which suggest that for a duration of T units of time the maximum concentration of drug is attained for $\overline{T}$, where $\frac{T}{4} < \overline{T} < \frac{T}{3}$.

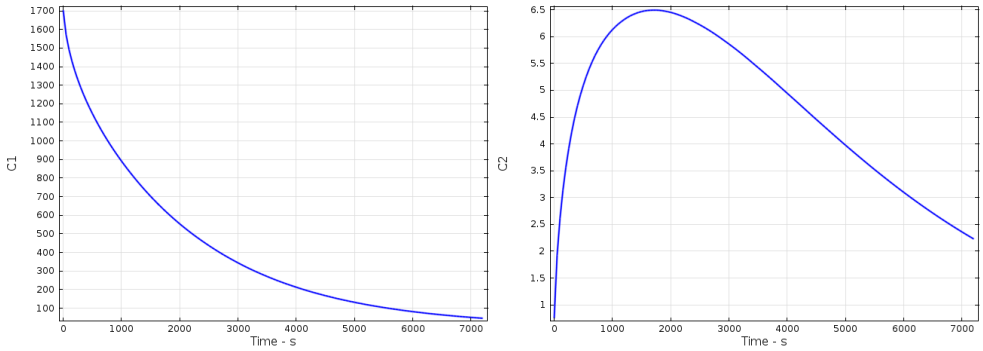


Fig. 3.6: Mean drug concentration in the implant (left) and in the vitreous chamber (right) during two hours.

In Figure 3.7 the influence of the degradation rate is illustrated: a smaller value of β_1 leads to a slower degradation process and consequently more

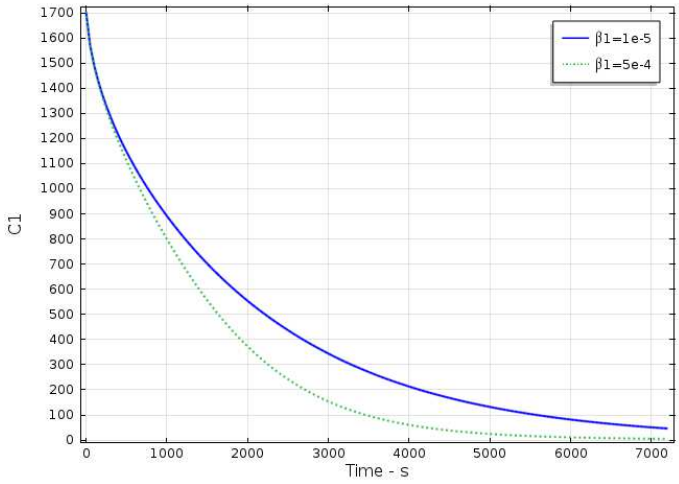


Fig. 3.7: Mean drug concentration in the implant during two hours- influence of degradation rate.

concentration is observed inside the polymeric implant.

In Figure 3.8 the influence of Young's modulus is illustrated. As expected the increase of Young's modulus, E, delays the drug release and consequently more drug concentration is observed inside the polymer. In fact as crosslinking density is proportional to E, the larger is this parameter, the stiffer is the material and a more significant barrier difficults the release of drug.

In Figure 3.9 the influence of the diffusion tensor of drug in the non hydrolyzed polymer, $D_0 I_2$, on the mean drug concentration in the vitreous is shown. We observe that as D_0 increases the drug concentration increases because the diffusion process becomes faster.

In Figure 3.10 we observe that increasing the diffusion coefficient D_2 of drug in the vitreous, the drug concentration is decreasing as expected.

3.8 Final comments

A coupled model to simulate *in vivo* drug delivery from an intravitreal viscoelastic biodegradable implant has been developed. The whole process is described by a set of partial differential equations that take into account passive diffusion, convection resulting from the permeation of aqueous humor, stress driven diffusion and the degradation of the polymer. To the best of

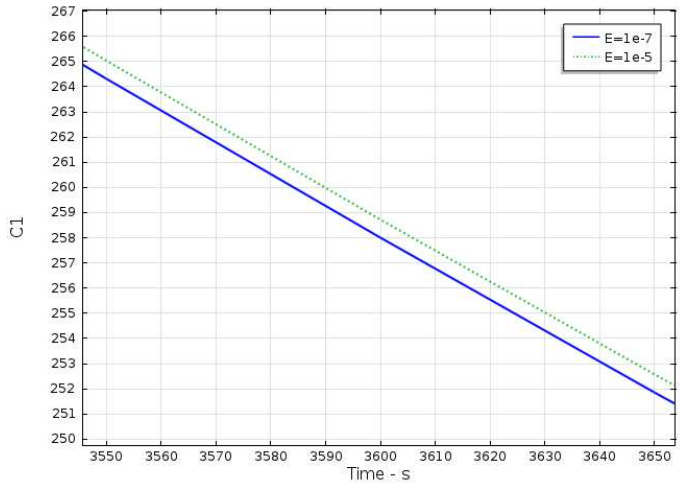


Fig. 3.8: Influence of E on the mean drug concentration in the implant around $t = 1h$.

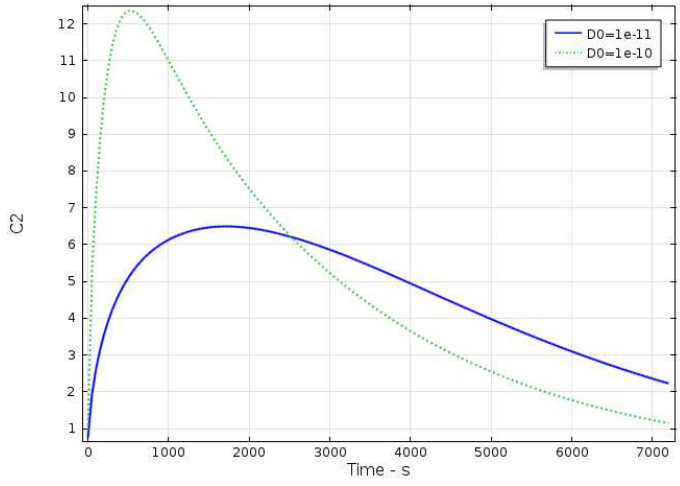


Fig. 3.9: Influence of parameter D_0 on the mean drug concentration in the vitreous.

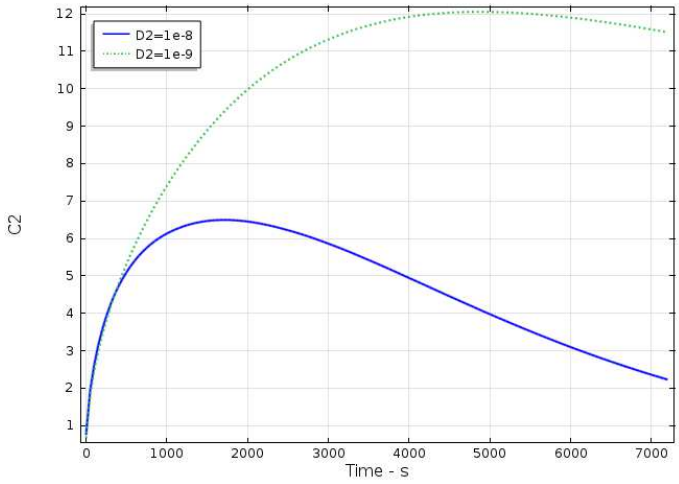


Fig. 3.10: Influence of parameter D_2 on the mean drug concentration in the vitreous.

our knowledge the dynamics of drug desorption has not been described so far in the literature considering the simultaneous interplay between mechanical, physical and chemical effects. The numerical simulations show qualitative agreement with the physical expected behaviour. The model clarifies the large influence of the degradation parameter in sustained drug delivery. The viscoelastic properties of the polymeric implant are also shown to be an effective control mechanism to delay or to speed up the release of drug. Mathematical modeling is a unique tool to explain transport mechanisms, and to help in implant design, avoiding expensive and extensive experimentation. In future work physical values for all the parameters of the model should be retrieved. Also more realistic mechanical models will be considered and the heterogeneous structure of the vitreous, that is characteristic of elderly patients, should be taken into account.

4. A COMPLETE MODEL OF IN VITRO DELIVERY: FROM SOLVENT SORPTION TO DRUG RELEASE

In this chapter we present a mathematical model for drug delivery from viscoelastic polymers characterized by bulk erosion. In the previous chapters we study the process assuming that solvent uptake was instantaneous and we assumed that the swell of the polymer under contact with the solvent was instantaneous. In this chapter we describe mathematically the whole process: the solvent uptake, drug dissolution, followed by drug diffusion, the progressive bulk degradation of the polymer, and the release of drug from the polymer in the external medium. The interplay between these phenomena is described by a system of partial differential equations linked by interface conditions. We study the stability of the mathematical model studying linearized versions for small and large times. An IMEX method is proposed and its convergence is numerically studied. The qualitative behaviour of the model will be also analyzed numerically.

In [22] the authors address the problem of drug delivery from a biodegradable polymer. However the rheological behaviour of the matrix is not considered. Moreover the authors in [22] are not concerned with the theoretical study of the model they propose.

4.1 Mathematical model

We consider a biodegradable viscoelastic polymeric matrix $\Omega \subset \mathbb{R}^2$ with boundary $\partial\Omega$, and with a limited amount of drug dispersed. The matrix is in contact with a solvent. As the solvent diffuses into the matrix, an hydratation process takes place that modifies the viscoelastic properties of the polymer, and its molecular weight that decreases. The drug dissolves, diffuses and is released in the external medium.

In what follows we consider a set of partial differential equations that describe the entrance of a solvent, as for example water, into the polymer

and its consumption in the hydrolysis process, the decreasing of the molecular weight, the evolution of the stress and strain, the dissolution process and the diffusion of the dissolved drug:

$$\begin{cases} \dfrac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) - k C_W M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial M}{\partial t} = -k C_W M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E(M)}{\mu(M)}\sigma = -E(M)\dfrac{\partial C_W}{\partial t} & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_S}{\partial t} = -k_{dis} C_{Sn} C_{An} C_{Wn} & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_A}{\partial t} = \nabla \cdot (D(M) \nabla C_A) + k_{dis} C_{Sn} C_{An} C_{Wn} & \text{in } \Omega \times (0,T]. \end{cases} \tag{4.1}$$

In (4.1) C_W, C_S and C_A represent the concentration of solvent, let us say water, solid drug and dissolved drug in the polymeric matrix, respectively, M is the molecular weight of the polymer and σ is the stress response to the strain exerted by the water molecules. We remark that in the partial differential system considered in [22] the viscoelastic response of the polymer to the uptake of water was not considered (see for instance [49, 50, 51, 52, 53, 54]).

The first diffusion-reaction equation of (4.1) describes the diffusion of water into the matrix and its consumption in the hydrolysis of the polymer matrix. In this equation D_W represents the diffusion tensor of water in the polymeric matrix. The viscoelastic behaviour of the matrix is taken into account by the term $\nabla \cdot (D_v \nabla \sigma)$, where D_v is a viscoelastic tensor and σ is the stress response of the matrix to the strain exerted by the incoming molecules of solvent. This term represents the opposition of the polymer to the entrance of the solvent. In the previous chapters the viscoelastic behaviour of the polymer is also taken into account but as a response of the polymeric matrix to the strain exerted by the dispersed drug. No other type of strain was considered because our description of the process begin, in those chapters, with a polymer completely swelled. In (4.1) we assume that the main viscoelastic response is due to the strain exerted by the incoming fluid and the strain of the diffusing drug is neglected. This is the case of drug molecules, which are much smaller than the void spaces in the matrix. For this reason in the last equation of (4.1) which represents the dissolved drug, C_A, we just include Fickian diffusion and a source term that quantifies the dissolution of solid drug as we detail in what follows.

Since water diffuses into the polymeric matrix the molecules of water react with the molecules of polymer and polymer bonds are broken leading to a decrease in the molecular weight of the polymeric matrix. This process is described by the second equation of (4.1). The term $-kC_W M$ represents the degradation of the polymer in contact with the water, with rate k, due to the hydrolysis of the polymer matrix.

As in Chapter 2, the viscoelastic behaviour of the polymer can be modelled by equation (2.3), where ϵ is the strain produced by the incoming water molecules. As the polymer acts as a barrier to the entrance of the water, then σ and ϵ are of opposite sign, and a minus sign should be considered in the right hand side of (2.3) ([35, 36, 37, 38, 39, 40]). We assume that the strain and the concentration of water are proportional, that is, there is $k_1 > 0$ such that $\epsilon = k_1 C_W$.

In chapters 2 and 3 the Young modulus E and the viscosity μ are considered constants. In this chapter we assume that the Young modulus and the viscosity depend on the molecular weight ([49, 50, 51, 52, 53, 54]). In fact the Young modulus varies significantly in a biodegradable polymeric matrix due to the heterogeneous nature of the hydrolysis reaction that leads to the polymer-chain cleavages. As the degradation processes evolves, the Young modulus decreases ([55]). We remark that Mark-Houwink equation ([56]) establishes a functional relation between the viscosity and the molecular weight. We consider the particular expressions $E(M) = E_0 M^\alpha$ and $\mu(M) = \mu_0 M^\beta$, where E_0, μ_0, α and β are constant (see [55, 56]).

The evolution in time of the solid drug is described by the fourth equation of (4.1) where k_{dis} is the dissolution rate, C_{Sn} is the normalized concentration of solid drug in the polymeric matrix, C_{An} is the difference between the dissolved drug concentration and its maximum solubility (C_{Amx}), normalized by C_{Amx} and C_{Wn} is the normalized concentration of water ($\frac{C_W}{C_{Wout}}$). In this case C_{Wout} is the concentration of water outside of the polymeric matrix. As already mentioned the evolution of the concentration of dissolved drug in the polymeric matrix is defined by the last equation of (4.1) where only Fick's second law and the dissolution source were taken into account.

Analogously, as in Chapter 2, the diffusion tensor of the dissolved drug is defined by

$$D(M) = D_A e^{\bar{k}\frac{M_0 - M}{M_0}}, \tag{4.2}$$

where D_A is the diffusion tensor of the drug in the non hydrolyzed polymer,

M_0 is its initial molecular weight and $\bar{k}$ is a positive constant.

System (4.1) is completed with the initial conditions

$$\begin{cases} C_W(0) = 0 & \text{in } \Omega, \\ \sigma(0) = \sigma_0 & \text{in } \Omega, \\ M(0) = M_0 & \text{in } \Omega, \\ C_S(0) = C_{S0} & \text{in } \Omega, \\ C_A(0) = 0 & \text{in } \Omega, \end{cases} \tag{4.3}$$

where σ_0 represents the initial stress of the molecules of the polymer and C_{S0} is the initial solid drug concentration in the polymeric matrix.

Degradation of the polymeric matrix can be one of the two types: surface and bulk. Surface degradation occurs because the degradation is faster than the entrance of water in the system. The break of polymer chains occurs mainly in the outermost polymer layers. Bulk degradation occurs when the degradation is slower than the water uptake. The entirely system is rapidly hydrated and polymer chains are cleaved through all polymer structure ([20, 21, 22, 23]).

In this chapter we consider that bulk degradation occurs. In this case the physical domain will be maintained in time and system (4.1) is completed with initial conditions (4.3) and the following boundary conditions

$$\begin{cases} J \cdot \eta = A_c(C_W - C_{W out}) & \text{on } \partial\Omega \times (0,T], \\ C_A = 0 & \text{on } \partial\Omega \times (0,T]. \end{cases} \tag{4.4}$$

In (4.4) J represents the flux of solvent defined by $J = -D_W \nabla C_W - D_v \nabla \sigma$, η is the unit outward normal to $\partial\Omega$ and A_c is the permeability constant. The second condition in (4.4) means that the dissolved drug that attains the boundary is immediately removed. We will study the stability of the mathematical model (4.1), (4.3) and (4.4). Numerical simulations will be used to illustrate the qualitative behaviour of the model.

4.2 Stability analysis

In order to simplify the presentation, we assume in this section that E and μ are constant. We also assume that the diffusion tensor is only space dependent.

To gain some insight on the stability behaviour of the initial value problem (4.1),(4.3) and (4.4) we study in what follows the stability of a linearization of (4.1) for short and long times. For short times we linearize the system in the neighborhood of the initial state; for large times the system is linearized in the neighborhood of the steady state solution. Let $\tilde{C}_W$, $\tilde{M}$, $\tilde{C}_A$ and $\tilde{C}_S$ be a solution of (4.1). The linearized system at this solution can be written in the following form

$$\begin{cases} \dfrac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) - k\tilde{C}_W M - k\tilde{M} C_W, \\ \dfrac{\partial M}{\partial t} = -k\tilde{C}_W M - k\tilde{M} C_W, \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E}{\mu}\sigma = -E\dfrac{\partial C_W}{\partial t}, \\ \dfrac{\partial C_S}{\partial t} = -K\Big((C_{Amx} - \tilde{C}_A)\tilde{C}_W C_S - \tilde{C}_W \tilde{C}_S C_A \\ \qquad\qquad + \tilde{C}_S (C_{Amx} - \tilde{C}_A) C_W\Big), \\ \dfrac{\partial C_A}{\partial t} = \nabla \cdot (D \nabla C_A) + K\Big((C_{Amx} - \tilde{C}_A)\tilde{C}_W C_S \\ \qquad\qquad - \tilde{C}_W \tilde{C}_S C_A + \tilde{C}_S (C_{Amx} - \tilde{C}_A) C_W\Big), \end{cases} \tag{4.5}$$

where $K = \dfrac{k_{dis}}{C_{S0} C_{Amx} C_{Wout}}$ is a constant.

For small times the concentration of water and dissolved drug is very small so we consider

$$\tilde{C}_W = 0,\ \tilde{C}_A = 0,\ \tilde{C}_S = C_{S0}, \tilde{M} = M_0. \tag{4.6}$$

For large times, that is when the matrix is practically degraded and the drug released, we assume

$$\tilde{M} = 0, \tilde{C}_W = C_{Wout}, \tilde{C}_S = 0, \tilde{C}_A = 0. \tag{4.7}$$

Solution (4.6) defines the state of the system as $t \to 0$. So for small times, the stability of system (4.1) is obtained studying the stability of (4.5) and (4.4) when (4.6) is considered. When $t \to +\infty$, the solution of system (4.1) approaches the steady solution (4.7). In fact, phenomenologically, the molecular weight decreases and vanishes, the concentration of water goes to the equilibrium, that is C_{Wout}, the concentrations of solid and dissolved drug inside of the polymeric matrix vanish.

Stability for short times: To study the stability of (4.4) and (4.5), we consider in this case

$$\begin{cases} \dfrac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) & \\ \qquad\qquad\qquad\qquad -kM_0 C_W & \text{in } \ \Omega \times (0,T], \\ \dfrac{\partial M}{\partial t} = -kM_0 C_W & \text{in } \ \Omega \times (0,T], \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E}{\mu}\sigma = -E\dfrac{\partial C_W}{\partial t} & \text{in } \ \Omega \times (0,T], \\ \dfrac{\partial C_S}{\partial t} = -\dfrac{k_{dis}}{C_{Wout}} C_W & \text{in } \ \Omega \times (0,T], \\ \dfrac{\partial C_A}{\partial t} = \nabla \cdot (D \nabla C_A) + \dfrac{k_{dis}}{C_{Wout}} C_W & \text{in } \ \Omega \times (0,T], \end{cases} \tag{4.8}$$

where $T > 0$ is fixed, with the boundary conditions

$$\begin{cases} J \cdot \eta = A_c C_W & \text{on } \ \partial\Omega \times (0,T], \\ C_A = 0 & \text{on } \ \partial\Omega \times (0,T]. \end{cases} \tag{4.9}$$

In what follows we use the energy method to analyze (4.8) and (4.9) complemented with the initial condition

$$\begin{cases} C_W(0) = C_{W0} & \text{in } \ \Omega, \\ \sigma(0) = \sigma_0 & \text{in } \ \Omega, \\ M(0) = M_0 & \text{in } \ \Omega, \\ C_S(0) = C_{S0} & \text{in } \ \Omega, \\ C_A(0) = C_{A0} & \text{in } \ \Omega. \end{cases} \tag{4.10}$$

From the third equation of (4.8) we easily get

$$\begin{aligned} \sigma = \frac{E^2}{\mu} \int_0^t e^{-\frac{E}{\mu}(t-s)} C_W(s) ds \ &- \ EC_W + EC_W(0) e^{-\frac{E}{\mu}t} \\ &+ \ \sigma(0) e^{-\frac{E}{\mu}t}, \ t \geq 0, \end{aligned} \tag{4.11}$$

and using this equality in the first equation of (4.8) we obtain for C_W the following equation

$$\begin{aligned} &\frac{\partial C_W}{\partial t} = \nabla \cdot (D_1 \nabla C_W) + \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_2 \nabla C_W(s)) ds - kM_0 C_W \\ &+ Ee^{-\frac{E}{\mu}t} \nabla . (D_v \nabla C_W(0)) + e^{-\frac{E}{\mu}t} \nabla . (D_v \nabla \sigma(0)), \end{aligned} \tag{4.12}$$

where

$$D_1 = D_W - ED_v, \quad D_2 = \frac{E^2}{\mu} D_v. \tag{4.13}$$

We assume that, in (4.13), D_W, D_v and D are 2×2 diagonal matrices and E and μ are such that the entries of D_1 and D_2 are positive and satisfy the following conditions:

$$D_{1,jj} \geq D_{min}, \quad D_{2,jj}, D_{v,jj} \leq D_{max}, \quad D_{jj} \geq D_0, \quad \text{for} \quad j = 1, 2. \tag{4.14}$$

Let $V = H^1(\Omega) \times \Big(L^2(\Omega)\Big)^2 \times H_0^1(\Omega)$ and let $(C_W, M, C_S, C_A) \in V$ be such that $\frac{\partial C_W}{\partial t}, \frac{\partial M}{\partial t}, \frac{\partial C_S}{\partial t}, \frac{\partial C_A}{\partial t} \in L^2(\Omega)$ and (4.10) holds and

$$\begin{cases} \Big(\frac{\partial C_W}{\partial t}, v_1\Big) = -(D_1 \nabla C_W, \nabla v_1) \\ \qquad - \int_0^t e^{-\frac{E}{\mu}(t-s)} (D_2 \nabla C_W(s), \nabla v_1) ds \\ \qquad -(A_c C_W, v_1)_{\partial\Omega} - k M_0 (C_W, v_1) \\ \qquad + e^{-\frac{E}{\mu}t} E(\nabla \cdot (D_v \nabla C_W(0)), v_1) \\ \qquad + e^{-\frac{E}{\mu}t} (\nabla \cdot (D_v \nabla \sigma(0)), v_1), \quad \forall v_1 \in H^1(\Omega), \\ \Big(\frac{\partial M}{\partial t}, v_2\Big) = -k(M_0 C_W, v_2), \quad \forall v_2 \in L^2(\Omega), \\ \Big(\frac{\partial C_S}{\partial t}, v_3\Big) = -\frac{k_{dis}}{C_{Wout}} (C_W, v_3), \quad \forall v_3 \in L^2(\Omega), \\ \Big(\frac{\partial C_A}{\partial t}, v_4\Big) = -(D \nabla C_A, \nabla v_4) \\ \qquad + \frac{k_{dis}}{C_{Wout}} (C_W, v_4), \quad \forall v_4 \in H_0^1(\Omega), \end{cases} \tag{4.15}$$

where the same notation is used to represent the usual inner products in $L^2(\Omega)$ and $\Big(L^2(\Omega)\Big)^2$.
We establish in what follows an estimate for the energy functional

$$\mathcal{E}(t) = E_{CM}(t) + \int_0^t \left(\Big\| \nabla C_W(s) \Big\|^2 + \Big\| \nabla C_A(s) \Big\|^2 \right) ds, \quad t \in [0, T], \tag{4.16}$$

with

$$E_{CM}(t) = \Big\| C_W(t) \Big\|^2 + \Big\| M(t) \Big\|^2 + \Big\| C_S(t) \Big\|^2 + \Big\| C_A(t) \Big\|^2, \tag{4.17}$$

where the same notation $\|.\|$ was used to represent the norm induced by the usual inner products in $L^2(\Omega)$ and $\Big(L^2(\Omega)\Big)^2$.

Theorem 6. *Let $(C_W, M, C_S, C_A) \in V$ be a solution of the variational problem (4.15). Then*

$$\mathcal{E}(t) \leq \frac{1}{\min\Big\{1, 2(D_{min}-\epsilon_1^2), 2D_0\Big\}}\Big(\frac{\mu}{4E\epsilon_2^2}\Big(E^2\Big\|\nabla\cdot(D_v\nabla C_W(0))\Big\|^2 + \Big\|\nabla\cdot(D_v\nabla\sigma(0))\Big\|^2\Big) + E_{CM}(0)\Big)e^{\overline{c}t} \quad (4.18)$$

where $\epsilon_1 \neq 0$ satisfies

$$D_{min} - \epsilon_1^2 > 0, \quad (4.19)$$

and

$$\overline{c} = \frac{\max\Big\{\frac{D_{max}^2\mu}{4\epsilon_1^2E}, 2\epsilon_3^2\Big(k^2M_0^2 + 2\frac{k_{dis}^2}{C_{Wout}^2}\Big) + 4\epsilon_2^2 - 2kM_0, \frac{1}{2\epsilon_3^2}\Big\}}{\min\Big\{1, 2(D_{min}-\epsilon_1^2), 2D_0\Big\}} \quad (4.20)$$

with $\epsilon_2, \epsilon_3 \neq 0$ arbitrary constants.

Proof. Taking in (4.15) $v_1 = C_W, v_2 = M, v_3 = C_S$ and $v_4 = C_A$, we easily obtain from the first equation

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\Big\|C_W\Big\|^2 &= -(D_1\nabla C_W, \nabla C_W)\\ &\quad - \int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla C_W(s), \nabla C_W)ds\\ -A_c\Big\|C_W\Big\|_{\partial\Omega}^2 &+ e^{-\frac{E}{\mu}t}E(\nabla\cdot(D_v\nabla C_W(0)), C_W)\\ +e^{-\frac{E}{\mu}t}(\nabla\cdot(D_v\nabla\sigma(0)), C_W) &- kM_0\Big\|C_W\Big\|^2,\end{aligned}$$

where $\|.\|_{\partial\Omega}$ denotes the usual norm in $L^2(\partial\Omega)$. The remaining three equations of (4.15) lead to

$$\frac{1}{2}\frac{d}{dt}\Big\|M\Big\|^2 = -kM_0(C_W, M),$$

$$\frac{1}{2}\frac{d}{dt}\Big\|C_S\Big\|^2 = -\frac{k_{dis}}{C_{Wout}}(C_W, C_S),$$

and

$$\frac{1}{2}\frac{d}{dt}\Big\|C_A\Big\|^2 = -(D\nabla C_A, \nabla C_A) + \frac{k_{dis}}{C_{Wout}}(C_W, C_A).$$

For any non zero constants ϵ_1, ϵ_2 and ϵ_3 we have the following inequalities

$$\begin{aligned} -\int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla C_W(s), \nabla C_W)ds &\leq \epsilon_1^2\Big\|\nabla C_W\Big\|^2 \\ &+ \frac{D_{max}^2\mu}{8\epsilon_1^2 E}\int_0^t \Big\|\nabla C_W(s)\Big\|^2 ds, \end{aligned}$$

$$\begin{aligned} &+e^{-\frac{E}{\mu}t}E(\nabla\cdot(D_v\nabla C_W(0)), C_W) + e^{-\frac{E}{\mu}t}(\nabla\cdot(D_v\nabla\sigma(0)), C_W) \\ &\leq \frac{1}{4\epsilon_2^2}e^{-2\frac{E}{\mu}t}\Big(E^2\Big\|\nabla\cdot(D_v\nabla C_W(0))\Big\|^2 + \Big\|\nabla\cdot(D_v\nabla\sigma(0))\Big\|^2\Big) + 2\epsilon_2^2\Big\|C_w\Big\|^2, \end{aligned}$$

$$kM_0(C_W, M) \leq k^2M_0^2\epsilon_3^2\Big\|C_W\Big\|^2 + \frac{1}{4\epsilon_3^2}\Big\|M\Big\|^2,$$

$$\frac{k_{dis}}{C_{Wout}}(C_W, C_S) \leq \frac{k_{dis}^2}{C_{Wout}^2}\epsilon_3^2\Big\|C_W\Big\|^2 + \frac{1}{4\epsilon_3^2}\Big\|C_S\Big\|^2,$$

$$\frac{k_{dis}}{C_{Wout}}(C_W, C_A) \leq \frac{k_{dis}^2}{C_{Wout}^2}\epsilon_3^2\Big\|C_W\Big\|^2 + \frac{1}{4\epsilon_3^2}\Big\|C_A\Big\|^2.$$

Summing up the preceeding three equations we obtain

$$\begin{aligned} \frac{d}{dt}E_{CM} &+ 2(D_{min} - \epsilon_1^2)\Big\|\nabla C_W\Big\|^2 + 2D_0\Big\|\nabla C_A\Big\|^2 \\ &\leq \frac{D_{max}^2\mu}{4\epsilon_1^2 E}\int_0^t \Big\|\nabla C_W(s)\Big\|^2 ds \\ &+ \Big(2\epsilon_3^2\Big(k^2M_0^2 + 2\frac{k_{dis}^2}{C_{Wout}^2}\Big) + 4\epsilon_2^2 - 2kM_0\Big)\Big\|C_W\Big\|^2 \\ &+ \frac{1}{2\epsilon_3^2}\Big(\Big\|M\Big\|^2 + \Big\|C_S\Big\|^2 + \Big\|C_A\Big\|^2\Big) \\ &+ \frac{1}{2\epsilon_2^2}e^{-2\frac{E}{\mu}t}\Big(E^2\Big\|\nabla\cdot(D_v\nabla C_W(0))\Big\|^2 + \Big\|\nabla\cdot(D_v\nabla\sigma(0))\Big\|^2\Big), \end{aligned}$$

where E_{CM} is defined in (4.17). If we fix ϵ_1 satisfying (4.19) then

$$\mathcal{E}(t) \leq \overline{c} \int_0^t \mathcal{E}(s)ds + \frac{1}{\min\Big\{1, 2(D_{min} - \epsilon_1^2), 2D_0\Big\}}\Big(\frac{\mu}{4E\epsilon_2^2}$$
$$\Big(E^2\Big\|\nabla \cdot (D_v \nabla C_W(0))\Big\|^2 + \Big\|\nabla \cdot (D_v \nabla \sigma(0))\Big\|^2\Big) + E_{CM}(0)\Big),$$

where $\overline{c}$ is defined by (4.20). Finally by using Gronwall's Lemma we obtain (4.18). □

The energy estimate (4.18) leads to the uniqueness of solution of the variational problem (4.15) and (4.10). It enables also to conclude the stability of such solution in bounded time intervals. These results hold provided that the initial data are smooth enough.

Stability for large times: To analyze the stability of the initial boundary value problem (4.1),(4.3) and (4.4) for large times we consider system (4.5), that arise from the linearization of system (4.1) in the neighborhood of the steady solution defined by (4.7). That is, we study the stability of the initial boundary value problem

$$\begin{cases} \dfrac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) & \\ \qquad -kC_{W\,out}M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial M}{\partial t} = -kC_{W\,out}M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E}{\mu}\sigma = -E\dfrac{\partial C_W}{\partial t} & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_S}{\partial t} = -\dfrac{k_{dis}}{C_{S0}}C_S & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_A}{\partial t} = \nabla \cdot (D\nabla C_A) + \dfrac{k_{dis}}{C_{S0}}C_S & \text{in } \Omega \times (0,T], \end{cases} \tag{4.21}$$

where $T > 0$ is fixed, with initial conditions

$$\begin{cases} C_W(0) = C_{W,\infty} & \text{in } \Omega, \\ \sigma(0) = \sigma_\infty & \text{in } \Omega, \\ M(0) = M_\infty & \text{in } \Omega, \\ C_S(0) = C_{S\infty} & \text{in } \Omega, \\ C_A(0) = C_{A,\infty} & \text{in } \Omega, \end{cases} \tag{4.22}$$

and boundary conditions (4.9).

From the third equation of (4.21) we easily get an expression for the stress σ analogous to (4.11). Replacing then that expression in the first equation of (4.21) we obtain

$$\begin{cases} \dfrac{\partial C_W}{\partial t} = \nabla \cdot (D_1 \nabla C_W) \\ \qquad + \displaystyle\int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_2 \nabla C_W(s)) ds \\ \qquad - k C_{W out} M + E e^{-\frac{E}{\mu} t} \nabla . (D_v \nabla C_W(0)) \\ \qquad + e^{-\frac{E}{\mu} t} \nabla . (D_v \nabla \sigma(0)) & \text{in } \Omega \times (0,T], \\ \dfrac{\partial M}{\partial t} = -k C_{W out} M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_S}{\partial t} = -\dfrac{k_{dis}}{C_{S0}} C_S & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_A}{\partial t} = \nabla \cdot (D \nabla C_A) + \dfrac{k_{dis}}{C_{S0}} C_S & \text{in } \Omega \times (0,T], \end{cases} \tag{4.23}$$

where D_1 and D_2 are given by (4.13). The original initial boundary value problem (4.21), (4.9) and (4.22) is then replaced by (4.23), completed with (4.22) and (4.9).

In what follows we consider the weak formulation of (4.23), (4.22) and (4.9) defined by the variational problem:
Find $(C_W, M, C_S, C_A) \in V$ such that $\dfrac{\partial C_W}{\partial t}$, $\dfrac{\partial M}{\partial t}$, $\dfrac{\partial C_S}{\partial t}$, $\dfrac{\partial C_A}{\partial t} \in L^2(\Omega)$, and

(4.22) holds and

$$\begin{cases} \left(\dfrac{\partial C_W}{\partial t}, v_1\right) = -(D_1\nabla C_W, \nabla v_1) \\ \qquad\qquad - \displaystyle\int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla C_W(s), \nabla v_1)ds \\ \qquad\qquad -(A_c C_W, v_1)_{\partial\Omega} - kC_{Wout}(M, v_1) \\ \qquad\qquad +Ee^{-\frac{E}{\mu}t}(\nabla\cdot(D_v\nabla C_W(0)), v_1) \\ \qquad\qquad +e^{-\frac{E}{\mu}t}(\nabla\cdot(D_v\nabla\sigma(0)), v_1), \quad \forall v_1 \in H^1(\Omega), \\ \left(\dfrac{\partial M}{\partial t}, v_2\right) = -kC_{Wout}(M, v_2), \quad \forall v_2 \in L^2(\Omega), \\ \left(\dfrac{\partial C_S}{\partial t}, v_3\right) = -\dfrac{k_{dis}}{C_{S0}}(C_S, v_3), \quad \forall v_3 \in L^2(\Omega), \\ \left(\dfrac{\partial C_A}{\partial t}, v_4\right) = -(D\nabla C_A, \nabla v_4) \\ \qquad\qquad +\dfrac{k_{dis}}{C_{S0}}(C_S, v_4), \quad \forall v_4 \in H_0^1(\Omega). \end{cases} \tag{4.24}$$

Following the proof of Theorem 6 it can be shown an upper bound for $\mathcal{E}(t)$ analogous to the one defined by (4.16).

Theorem 7. *If $(C_W, M, C_S, C_A) \in V$ is a solution of the variational problem (4.24), then*

$$\begin{aligned} \mathcal{E}(t) \;&\leq\; \frac{1}{\min\left\{1, 2(D_{min}-\epsilon_1^2), 2D_0\right\}}\Big(E_{CM}(0) \\ &+\; \frac{\mu}{4E\epsilon_2^2}\Big(E^2\Big\|\nabla\cdot(D_v\nabla C_W(0))\Big\|^2 + \Big\|\nabla\cdot(D_v\nabla\sigma(0))\Big\|^2\Big)\Big)e^{\bar{c}t},\ t\geq 0, \end{aligned}$$

where ϵ_1 is fixed by (4.19),

$$\bar{c} = \frac{\max\left\{\frac{\mu D_{max}^2}{4\epsilon_1^2 E},\ 2kC_{Wout}\left(\frac{kC_{Wout}}{4\epsilon_2^2}-1\right), 2\frac{k_{dis}}{C_{S0}}\left(\frac{k_{dis}}{C_{S0}}\epsilon_3^2-1\right), \frac{1}{2\epsilon_3^2}, 6\epsilon_2^2\right\}}{\min\left\{1, 2(D_{min}-\epsilon_1^2), 2D_0\right\}},$$

and ϵ_2, ϵ_3 are arbitrary nonzero constants. □

From Theorem 7 we conclude the uniqueness of the solution of (4.24) and (4.22) and its stability for bounded time intervals, provided that the initial data are smooth enough.

4.3 Qualitative behaviour of the model

Let $\Omega = (0, L) \times (0, L)$. In this section in order to study numerically the qualitative behaviour of the model we discretize the initial boundary value problem (4.1), (4.3) and (4.4) with the **IMEX** method

$$\begin{cases} D_{-t}C_{W,H}^{n+1} = \nabla_H^* \cdot \Big(D_W \nabla_H C_{W,H}^{n+1}\Big) + \nabla_H^* \cdot \Big(D_v \nabla_H \sigma_H^n\Big) \\ \qquad\qquad -kC_{W,H}^n M_H^n \ \text{ in } \Omega_H, \\ D_{-t}M_H^{n+1} = -kC_{W,H}^{n+1} M_H^n \ \text{ in } \overline{\Omega}_H, \\ D_{-t}\sigma_H^{n+1} + \dfrac{E_0 (M_H^{n+1})^\alpha}{\mu_0 (M_H^{n+1})^\beta}\sigma_H^n = -E_0 (M_H^{n+1})^\alpha D_{-t}C_{W,H}^{n+1} \text{ in } \overline{\Omega}_H, \\ D_{-t}C_{S,H}^{n+1} = -\dfrac{k_{dis}}{C_{S0}C_{Amx}C_{Wout}} C_{S,H}^n (C_{Amx} - C_{A,H}^n) C_{W,H}^{n+1} \ \text{ in } \overline{\Omega}_H, \\ D_{-t}C_{A,H}^{n+1} = \nabla_H^* \cdot \Big(D(M_H^{n+1}) \nabla_H C_{A,H}^{n+1}\Big) \\ \qquad\qquad + \dfrac{k_{dis}}{C_{S0}C_{Amx}C_{Wout}} C_{S,H}^{n+1} \Big(C_{Amx} - C_{A,H}^n\Big) C_{W,H}^{n+1} \ \text{ in } \Omega_H, \end{cases} \tag{4.25}$$

where $H = (h, h)$ and Ω_H denotes the rectangular grid defined in Ω for $n = 0, \ldots, N_{\Delta t} - 1$. The **IMEX** method (4.25) is completed with initial conditions

$$\begin{cases} C_{W,H}^0 = 0 & \text{in } \ \Omega_H, \\ \sigma_H^0 = R_H \sigma(0) & \text{in } \ \Omega_H, \\ M_H^0 = R_H M(0) & \text{in } \ \Omega_H, \\ C_{S,H}^0 = R_H C_S(0) & \text{in } \ \Omega_H, \\ C_{A,H}^0 = 0 & \text{in } \ \Omega_H. \end{cases} \tag{4.26}$$

In (4.26) R_H represents the restriction operator defined from the space of continuous functions in $\overline{\Omega}$ into the space of grid functions defined in $\overline{\Omega}_H$.

The boundary conditions are given by

$$\begin{cases} J_H^{n+1}.\eta = A_c (C_{W,H}^{n+1} - C_{Wout}) & \text{on } \ \partial\Omega_H, \\ C_{A,H}^{n+1} = 0 & \text{on } \ \partial\Omega_H, \end{cases} \tag{4.27}$$

where

$$J_H^{n+1} \cdot \eta = -D_w \mathfrak{D}_\eta C_{W,H}^{n+1} - D_v \mathfrak{D}_\eta \sigma_H^n,$$

and $\mathfrak{D}_\eta$ represents the boundary operator

$$\mathfrak{D}_\eta v_H(x_i, y_j) = \begin{cases} -D_x v_H(x_0, y_j) & i = 0, \\ D_{-x} v_H(x_N, y_j) & i = N, \\ -D_y v_H(x_i, y_0) & j = 0, \\ D_{-y} v_H(x_i, y_N) & j = N, \end{cases} \tag{4.28}$$

for $(x_i, y_j) \in \partial\Omega_H$. In (4.27), $\partial\Omega_H$ denotes the set of grid points placed on $\partial\Omega$.

The numerical results that we present were obtained considering the parameters listed in Table 4.1.

To illustrate the convergence behaviour of method (4.25), (4.26) and (4.27) we present in Table 4.2 the errors of C, $C = C_W, C_A$, with these errors defined by

$$Error(C) = \max_{n=1,\ldots,N_{\Delta t}} \left\| C_H^n - \overline{C}_H^n \right\|_{\Omega_H},$$

where $\overline{C}_H^n$ is a reference solution obtained with $\Delta t = 10^{-5}$ and $h = 0.001$. The results exhibited in Table 4.2 show the convergence rates given by

$$\text{rate} = \frac{\ln \frac{\text{Error}_{h_1}(C)}{\text{Error}_{h_2}(C)}}{\ln \frac{h_1}{h_2}},$$

where h_1 and h_2 are two consecutive step sizes.

The last part of this section is devoted to the study of the dependence of the solution of the problem on different physical parameters. We take that the diffusion tensors and the viscoelastic tensor are given by $D_w I$, DI and $D_v I$, respectively, where I is the identity matrix of order 2.

To analyze the behaviour of the mass of dissolved drug and water inside the polymer we define it

$$\mathcal{M}_i(t) = \int_\Omega C_i(t) dX,$$

where $i = W, A$, for each $t \in [0, T]$, which are numerically computed at each time level using the trapezoidal rule.

In Figure 4.1 we plot the mass of water in the polymeric matrix for different values of D_v. We observe that the polymer acts as a barrier to the

Variable/ Parameter	Unit	Value	Equation
D_A	mm^2/s	5.94×10^{-2}	(4.2)
D_v	$mol/(mm.s.Pa)$	2×10^{-4}	(4.1)
D_W	mm^2/s	4.61×10^{-2}	(4.1)
k	$1/s$	10^{-2}	(4.1)
σ_0	Pa	5×10^{-2}	(4.3)
C_{Amx}	mol/mm^3	2.184×10^{-2}	(4.5)
C_{S0}	mol/mm^3	288.42×10^{-2}	(4.3)
β	$-$	7×10^{-1}	(4.25)
E_0	Pa	10^{-4}	(4.25)
μ_0	$Pa.s$	10^{-1}	(4.25)
k_{dis}	$mol/(mm^3.s)$	4.6×10^{-2}	(4.1)
M_0	Da	8.3×10^{-2}	(4.2)
C_{Wout}	mol/mm^3	5.55×10^{-1}	(4.5)
A_c	mm/s	10^{-2}	(4.4)
α	$-$	2×10^{-1}	(4.25)
h	mm	10^{-2}	(4.25)
Δt	s	10^{-4}	(4.25)

Tab. 4.1: Values of the parameters and variables at $t = 0$. The column on the right display the number of the equation where they first appear.

h	$Error(C_W)$	P_W	$Error(C_A)$	P_A
0.01	3.23×10^{-5}	1.38	5.29×10^{-10}	1.08
0.005	1.24×10^{-5}	1.35	2.50×10^{-10}	1.30
0.004	9.17×10^{-6}	2.01	1.87×10^{-10}	1.61
0.002	2.28×10^{-6}		6.13×10^{-11}	

Tab. 4.2: Convergence orders for C_W and C_A, respectively, P_W and P_A.

entrance of water. In other words, the norm of non Fickian flux, $\left\|D_v \nabla \sigma\right\|$, decreases the Fickian flux, $\left\|D_w \nabla C_W\right\|$. According to this description the increase of D_v leads to the decreasing of the mass of water in the polymeric matrix.

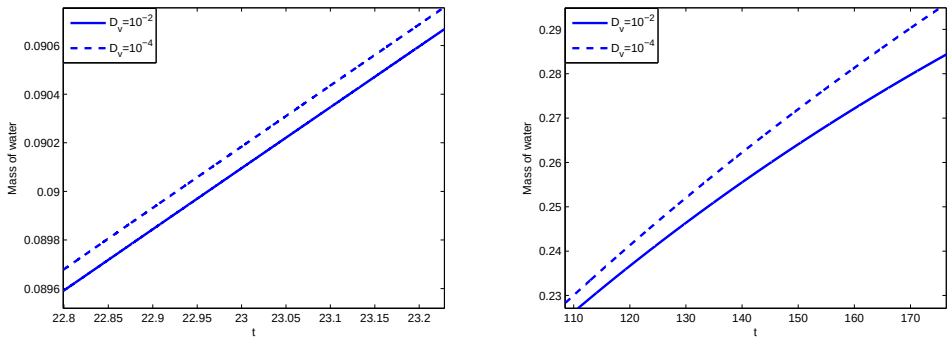


Fig. 4.1: Influence of D_v on the mass of the water for short times (left) and larger times (right).

The influence of Young modulus, E, on the mass of water is presented in Figure 4.2 near $t = 2$. The crosslink density of the polymer is proportional to the Young modulus E. Consequently, as this constant increases the polymer offers more resistance to the entrance of water and then the water concentration is lower.

The behaviour of the mass of dissolved drug for different dimensions of the matrix is presented in Figure 4.3. As the thickness increases more mass of drug is initially in the polymer and consequently more time is needed to attain the steady state.

In Figure 4.4 we illustrate the behaviour of the mass of water uptaken by the polymeric matrix when the thickness of the polymeric matrix increases. We also observe that the value of the steady mass in the polymer with $L = 0.1$ is 0.0555 while in the polymer with $L = 0.5$ is 0.2769.

The influence of the degradation rate, k, is presented in Figure 4.5. As expected, if the degradation rate increases the delivery rate of the dissolved drug also increases. Consequently, we have less concentration of the dissolved drug inside the polymeric matrix.

In Figure 4.6 we exhibit the behaviour of the concentration of water in the polymeric matrix at different times. We observe that the concentration

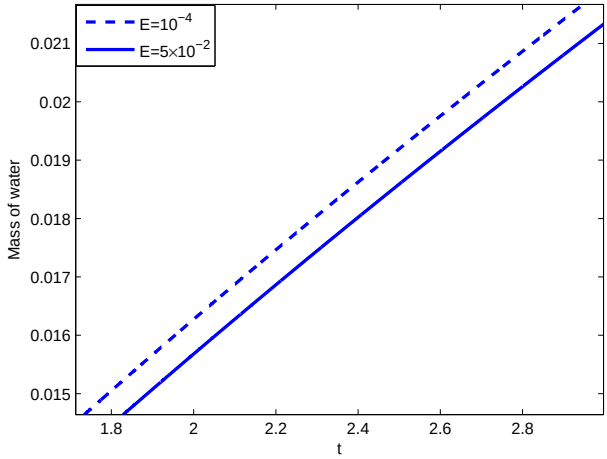


Fig. 4.2: Influence of E on the mass of the water.

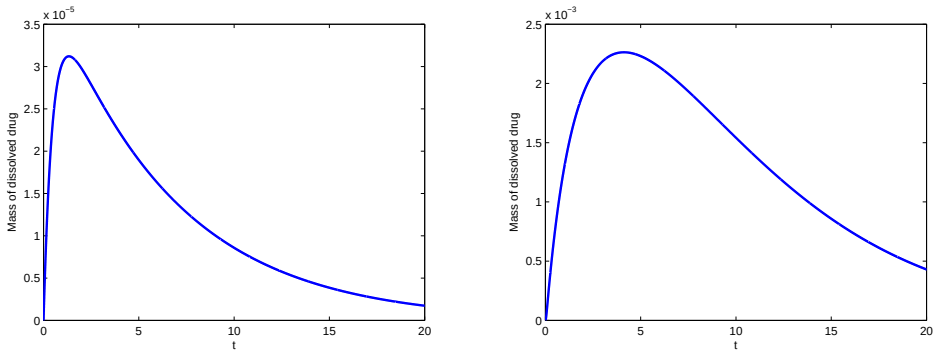


Fig. 4.3: Mass of dissolved drug inside the polymer with $L = 0.1$ (left) and $L = 0.5$ (right).

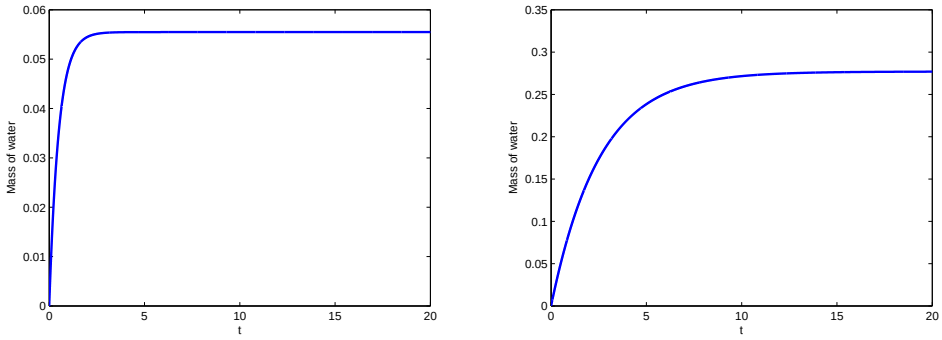


Fig. 4.4: Mass of water inside the polymer with $L = 0.1$ (left) and $L = 0.5$ (right).

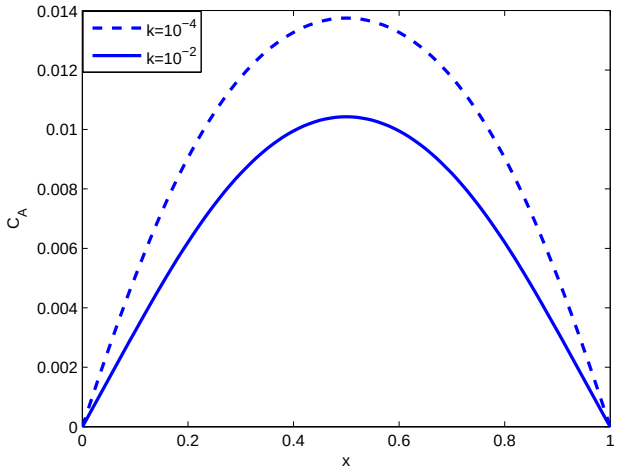


Fig. 4.5: Influence of k on the concentration of dissolved drug.

of water increases as time increases and the behaviour is homogeneous in the polymeric matrix since the diffusion coefficient is assumed constant.

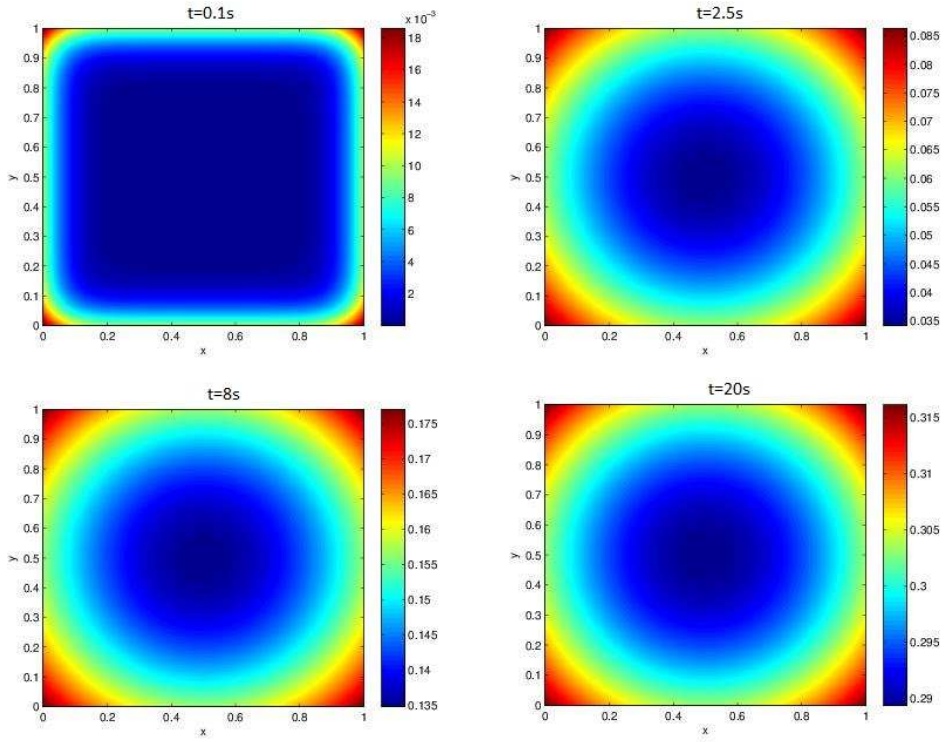


Fig. 4.6: Concentration of water for different times.

In Figures 4.7 and 4.8 the concentrations of solid drug and dissolved drug, respectively, at different times are shown. We observe that regions where the concentration of the water is high correspond to regions where the concentration of solid drug is low and dissolved drug is high. We also observe that when the concentration of solid drug decreases, the concentration of dissolved drug increases.

4.4 Final comments

The whole process of sorption of a solvent by a biodegradable polymeric matrix and release of a drug, which is dispersed in the matrix, is described in Chapter 4. Theoretical and numerical results are presented. As far as theoretical results are concerned we establish stability results for short and

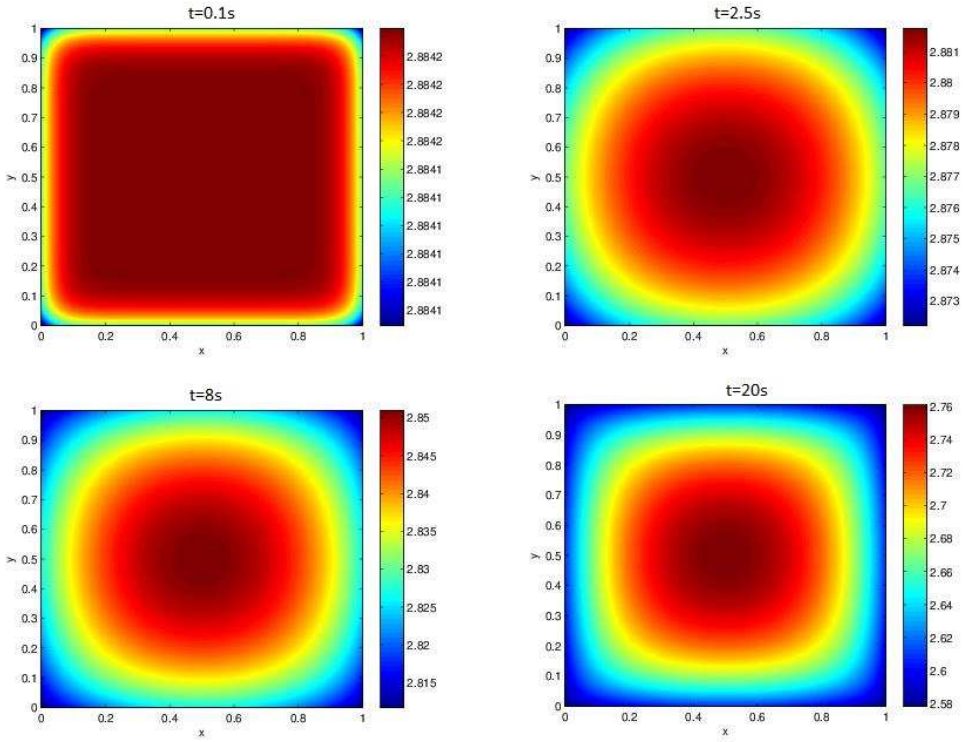


Fig. 4.7: Concentration of solid drug for different times.

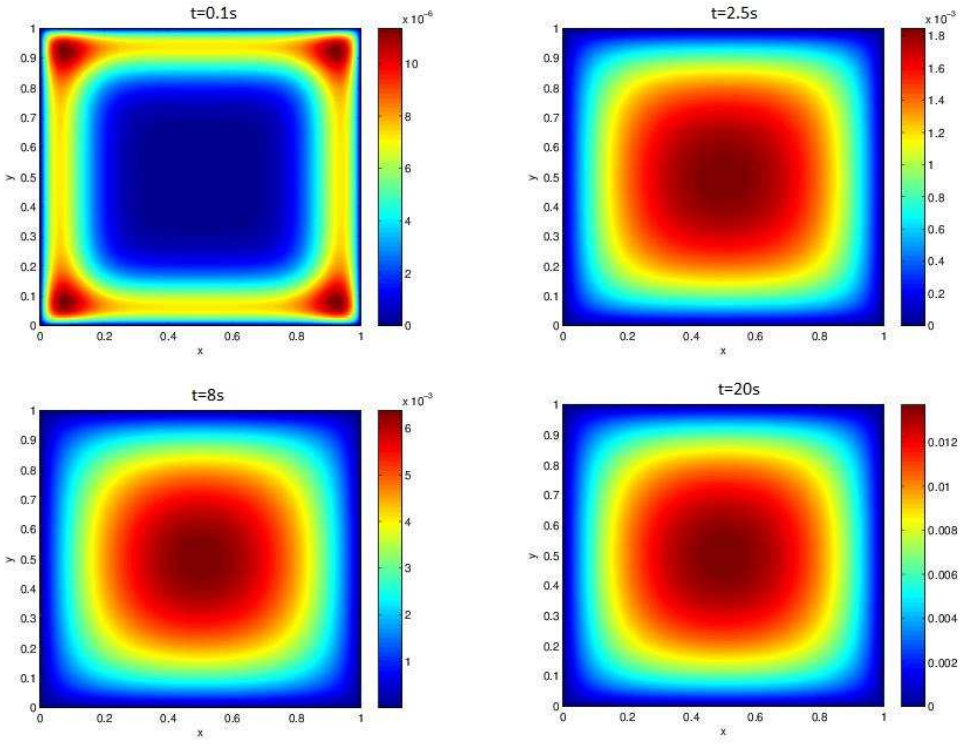


Fig. 4.8: Concentration of dissolved drug for different times.

long times. The technique used consists essentially in applying the energy method to a linearized system. In the case of short times this system is a linearization of the initial problem in the neighborhood of the initial state. For long times the initial system is linearized in the neighborhood of the steady state. The estimates, presented in theorems 6 and 7 hold for bounded intervals of time. The positivity imposed to all entries of D_1, (4.13), which assume that solvent effectively penetrates the matrix, is used to select the parameters in Table 4.1. Concerning the numerical simulations that illustrate the behaviour of the model we obtained sound physical results. The influence of the crosslinking density of the polymer is shown to delay the drug release. In fact a large Young modulus induces a longer opposition to the solvent penetration. As the solvent enters slowly, the degradation process are also delayed.

5. CONCLUSIONS AND FUTURE WORK

In this thesis we study mathematical models that describe transport *in vitro and in vivo*, of solvents and solutes, through a viscoelastic biodegradable material.

From a theoretical point of view we analyze the qualitative behaviour of the solutions and we establish a number of results on stability, under initial perturbations. These theoretical results, proved for the continuous models, are extended to semi-discrete models and fully discrete models. In the proofs, we present, some conditions on the parameters, involved in the models, are imposed. We observe that these conditions which at a first sight appear as technical tools, in the sense they represent mathematical constraints needed to establish the results, have a sound physical meaning because they essentially say that the models are stable if the Fickian diffusion dominates the non Fickian one. To illustrate the behaviour of the solutions and to give some insight into the dependence of the solutions on the parameters of the models several numerical simulations are exhibited.

One of the main areas where transport through a viscoelastic biodegradable polymer is used is controlled drug delivery. Mathematical models assume a central role in controlled drug delivery because they can be used to predict the behaviour of materials avoiding time consuming and very expensive laboratorial experiments. Under the viewpoint of a personalized medicine mathematical models can be used to match the characteristics of the implant to the special needs of the patient. We address the problem of intravitreal drug delivery through a viscoelastic biodegradable implant. In this case the release of drug *in vivo* is described by two coupled systems of partial differential equations linked by interface conditions: one of the systems takes into account the kinetics of drug in the implant while the other considers the transport in the living system. We exhibit several numerical simulations that illustrate the effect of viscoelastic and degradation properties of the implant. Nowadays implants that deliver drug to target sites in the human body are used in several areas of medicine. Our model can be adapted to study differ-

ent types of release by changing the geometry of the implant and the specific characteristics of the target site. We mention for example implants used to deliver opioids, antibiotics or highly potent drugs in oncology.

The release of drug *in vitro or in vivo* takes place when the matrix contacts with a solvent. In Chapter 2 and 3 we considered that the uptake of solvent was instantaneous. The models presented there describe the processes immediately after this initial uptake. In some situations this approach is accurate. However depending on the characteristics of the material and the solvent in many situations uptake is not an instantaneous phenomenon. Those parameters should not be prescribed as they depend on the evolution of solvent and solute concentrations. In Chapter 4 we address a release problem in this more general framework: the entrance of solvent in the polymeric matrix, the hydrolysis process, the decreasing of molecular weight, the evolution of stress and strain, the dissolution of dispersed drug, and its diffusion enhanced by bulk erosion. Surface erosion which implies that a vanishing polymeric matrix is considered is not addressed in this thesis.

Several issues were raised in the course of our work which we plan to address in the near future.

From the modelling point of view the swelling of the polymer, due to the uptake of solvent, and its shrinking, due to surface erosion, are very challenging problems. Both are related with moving boundary domains. These two phenomena should be considered in realistic three dimensional geometries. As far as the implants are considered the problem does not seem very difficult because cylindrical coordinates or spherical coordinates, coupled with symmetry arguments, can reduce the dimension of the equations. The three dimensional geometry of the target site in the living system is more complex. In our future work we are planning to complete the models in Chapter 3 and 4 by considering swelling, surface erosion and three dimensionality.

From an analytical point of view the convergence analysis of the **IMEX** methods used in the simulations will deserve our attention in the near future.

APPENDIX

A. APPENDIX

Symbol	Definition (unities)
C_1	Drug concentration in the implant (mol/mm^3)
C_2	Drug concentration in the vitreous (mol/mm^3)
σ	Stress (Pa)
M	Polymer molecular weight (Da)
D_0	Diffusion coefficient of the drug in the non hydrolysed polymer (mm^2/s)
D_1	Diffusion function depending on M (mm^2/s)
D_2	Diffusion coefficient of drug in the vitreous (mm^2/s)
D_v	Stress-driven diffusion coefficient ($mol/(mm.s.Pa)$)
E	Young modulus (Pa)
ϵ	Strain
μ	Viscosity ($Pa \cdot s$)
$\frac{K}{\mu_1}$	Hydraulic conductivity ($mm^2/(Pa \cdot s)$)
p	Pressure (Pa)
v	Velocity of the aqueous humor (mm/s)
A_c	Permeability constant (mm/s)
A_r	Permeability of the retina (mm/s)
k_1	Degradation rate of the drug ($1/s$)
β_1, β_2	Degradation rate of the polymer ($1/s$, $Da.mm^3/(mol.s)$)

Symbol	Definition (unities)
C_A	Concentration of dissolved drug in the polymeric matrix (mol/mm^3)
C_S	Concentration of solid drug (mol/mm^3)
C_W	Concentration of water in the polymeric matrix (mol/mm^3)
C_{Amx}	Maximum concentration of dissolved drug in the polymeric matrix (solubility limit) (mol/mm^3)
C_{A0}	Initial concentration of dissolved drug (mol/mm^3)
C_{S0}	Initial concentration of solid drug in the polymeric matrix (mol/mm^3)
C_{W0}	Initial concentration of water in the polymeric matrix (mol/mm^3)
C_{Wout}	Concentration of water outside of the polymeric matrix (mol/mm^3)
M_0	Initial polymer molecular weight (Da)
D_A	Diffusivity of drug through the non hydrolysed polymeric matrix (mm^2/s)
D_W	Diffusivity of water through the polymeric matrix (mm^2/s)
k	Polymer degradation rate (mm^3/mol)
k_{dis}	Drug dissolution rate ($mol/(mm^3.s)$)
L	Thickness of the polymeric matrix (mm)
t	Time(s)

BIBLIOGRAPHY

[1] D. Cohen and A. White, "Sharp fronts due to diffusion and viscoelastic relaxation in polymers," *SIAM Journal of Applied Mathematics*, vol. 51, pp. 472–483, 1991.

[2] D. Cohen, A. White, and T. Witelski, "Shock formation in a multidimensional viscoelastic diffusive system," *SIAM Journal of Applied Mathematics*, vol. 55, pp. 348–368, 1995.

[3] D. Edwards, "Non-fickian diffusion in thin polymer films," *Journal of Polymer Science: Part B: Polymer Physics*, vol. 34, pp. 981–997, 1996.

[4] D. Edwards and R. Cairncross, "Desorption overshoot in polymer-penetrant systems, asymptotic and computational results," *SIAM Journal of Applied Mathematics*, vol. 63, pp. 98–115, 2002.

[5] D. Edwards and D. Cohen, "A mathematical model for a dissolving polymer," *AIChE Journal*, vol. 18, pp. 2345–2355, 1995.

[6] J. Ferreira, P. de Oliveira, P. da Silva, and J. Murta, "Numerical simulation of aqueous humor flow: from healthy to pathologic situations," *Applied Mathematics and Computation*, vol. 226, pp. 777–792, 2014.

[7] L. Cheong, P. Heng, and L. Wong, "Relationship between polymer viscosity and drug release from a matrix system," *Pharmaceutical Research Journal*, pp. 9–11, 1992.

[8] S. Cypes, W. Saltzman, and E. Gianneli, "Organosilicate polymer drug delivery systems: controlled release and enhanced machanical properties," *Journal of Controlled Release*, vol. 90, pp. 163–169, 2003.

[9] J. Ferreira, P. de Oliveira, P. da Silva, and L. Simon, "Flux tracking in drug delivery," *Applied Mathematical Modelling*, vol. 35, pp. 4684–4696, 2011.

[10] S. Xiao, C. Moresoll, J. Bovenkamp, and D. D. Kee, "Sorption and permeation of organic environmental contaminants through PVC geomembranes," *Journal of Applied Polymer Science*, vol. 63, pp. 1189–1197, 1997.

[11] A. Raval, J. Parikh, and C. Engineer, "Mechanism of controlled release kinetics from medical devices," *Brazilian Journal of Chemical Engineering*, vol. 27, no. 2, pp. 211–225, 2010.

[12] G. Grassi and M. Grassi, "Mathematical modelling and controlled drug delivery: matrix systems," *Current Drug Delivery Journal*, vol. 2, no. 1, pp. 97–116, 2005.

[13] Q. Liu and D. D. Kee, "Modeling of diffusion through polymeric membranes," *Rheolgica Acta*, vol. 44, pp. 287–294, 2005.

[14] Q. Liu, X. Wang, and D. D. Kee, "Mass transport through swelling membranes," *International Journal of Engineering Science*, vol. 43, pp. 1464–1470, 2005.

[15] T. Alfrey, E. Gurnee, and W. Lloyd, "Diffusion in glassy polymers," *Journal of Polymer Science Part C: Polymer Symposia*, vol. 12, pp. 249–261, 1966.

[16] ASTM, "Test method f739-99a standard test method for resistance of protective clothing materials to permeation by liquids or gases under conditions of continuous contact," 1999.

[17] N. Thomas and A. Windle, "Diffusion mechanics of the system **pmma**-methanol," *Polymer*, vol. 22, pp. 627–639, 1981.

[18] J. Ferreira, P. de Oliveira, and P. da Silva, "Analytic and numerics of drug release tracking," *Journal of Computational and Applied Mathematics*, vol. 236, pp. 3572–3583, 2012.

[19] J. Ferreira, P. de Oliveira, and P. da Silva, "Reaction-diffusion in viscoelastic materials," *Journal of Computational and Applied Mathematics*, vol. 236, pp. 3783–3795, 2012.

[20] J. Siepmann and A. Göpferich, "Mathematical modeling of bioerodible polymeric drug delivery systems," *Advanced Drug Delivery Reviews*, vol. 48, pp. 229–247, 2001.

[21] R. Langer and N. Peppas, "Chemical and physical structure of polymers as carriers for controlled release of bioactive agents a review," *Reviews in Macromolecular Chemistry and Physics*, vol. C23, pp. 61–126, 1983.

[22] S. Rothstein, W. Federspiel, and S. Little, "A unified mathematical model for the prediction of controlled release from surface and bulk eroding polymer matrices," *Biomaterials*, vol. 30, pp. 1657–1664, 2009.

[23] S. Rothstein, W. Federspiel, and S. Little, "A simple model framework for the prediction of controlled release from bulk eroding polymer matrices," *Journal of Materials Chemistry*, vol. 18, pp. 1873–1880, 2008.

[24] F. Burkersroda, L. Schedl, and A. Gopferich, "Why degradable polymers undergo surface erosion or bulk erosion," *Biomaterials*, vol. 23, pp. 4221–31, 2002.

[25] V. Thomée and L. Wahlbin, "Long-time numerical solution of a parabolic equation with memory," *Mathematics of Computation*, vol. 62, pp. 477–496, 1994.

[26] U. Kompella, R. Kadam, and V. Lee, "Recent advances in ophthalmic drug delivery," *National Institute of Health, Therapeutic Delivery*, vol. 1, pp. 435–456, 2010.

[27] S. Lee, P. Hughes, A. Ross, and M. Robinson, "Biodegradable implants for sustained drug release in the eye," *Pharmaceutical Research*, vol. 27, pp. 2043–2053, 2010.

[28] S. Shah, L. Denham, J. Elison, P. Bhattacharjee, C. Clement, T. Huq, and J. Hill, "Drug delivery to the posterior segment of the eye for pharmacologic therapy," *National Institute of Health, Therapeutic Delivery*, vol. 1, pp. 75–93, 2010.

[29] M. Stay, J. Xu, T. Randolph, and V. Barocas, "Computer simulation of convective and diffusive transport of controlled-release drug in the vitreous humor," *Pharmaceutical Research*, vol. 20, pp. 96–102, 2003.

[30] R. Balachandran and V. Barocas, "Finite element modeling of drug distribution in the vitreous humor of the rabbit eye," *Annals of Biomedical Engineering*, vol. 25, pp. 303–314, 1997.

[31] R. Balachandran and V. Barocas, "Computer modeling of drug delivery to the posterior eye: effect of active transport and loss to choroidal blood flow," *Pharmaceutical Research*, vol. 25, pp. 2685–2696, 2008.

[32] D. Cox, R. Phipps, B. Levine, A. Jacobs, and D. Fowler, "Distribution of phencyclidine into vitreous humor," *Journal of Analytical Toxicology*, vol. 31, pp. 537–539, 2007.

[33] J. Kathawate and S. Acharya, "Computational modeling of intravitreal drug delivery in the vitreous chamber with different vitreous substitutes," *International Journal of Heat and Mass Transfer*, vol. 51, pp. 5598–5609, 2008.

[34] C. Misner, K. Thorne, and J. Wheeler, "Computer modeling of drug delivery to the posterior eye: effect of active transport and loss to choroidal blood flow," *Freeman, San Francisco, 1970.*

[35] J. Ferreira, M. Grassi, E. Gudino, and P. de Oliveira, "A 3d mechanistic model for drug release in swelling polymers," *accepted for publication in SIAM Journal of Applied Mathematics.*

[36] P. Flory, "Thermodynamics of high polymer solutions," *Journal of Chemical Physics*, vol. 10, pp. 51–61, 1942.

[37] G. Franceschini, *The mechanics of humain brain tissue.* PhD Thesis, University of Trento, Italy, 2006.

[38] E. Gudino, *Recent developments in non-Fickian diffusion: a new look at viscoelastic materials.* PhD thesis, University of Coimbra, Portugal, 2014.

[39] J. Ferreira, M. Grassi, E. Gudino, and P. de Oliveira, "A mathematical model for controlled drug delivery in swelling polymers," *CMMSE 2013: Proceedings of the 13th International Conference on Mathematical Methods in Science and Engineering*, vol. 2, pp. 630–641, 2013.

[40] J. Ferreira, M. Grassi, E. Gudino, and P. de Oliveira, "A new look to non-fickian diffusion," *Preprint n: 13-05, Department of Mathematics, University of Coimbra, Portugal*, 2013.

[41] H. Brinson and L. Brinson, *Polymer Engineering Science and Viscoelasticity: An Introduction.* Springer, 2008.

[42] T. Gronwall, "Note on the derivative with respect to a parameter of the solutions of a system of differential equations," *Annals of Mathematics*, vol. 20, pp. 292–296, 1919.

[43] L. Evans, *Partial Differential Equations.* American Mathematial Society, Second Edition (Graduate Series in Mathematics), V.19, 2010.

[44] J. Ferreira, L. Pinto, and G. Romanazzi, "Supraconvergence and supercloseness in volterra equations," *Applied Numerical Mathematics*, vol. 62, pp. 1718–1739, 2012.

[45] C. Chuanmiao and S. Tsimin, *Finite Element Methods for Integrodifferential Equations.* World Scientific Publishers (Series on Applied Mathematics), 1998.

[46] R. Avtar and D. Tandon, "A mathematical analysis of intravitreal drug transport," *Journal of Pharmaceutical Research*, vol. 7, pp. 867–877, 2008.

[47] N. Haghjou, M. Abdekhodaie, Y. Cheng, and M. Saadatmand, "Computer modeling of drug distribution after intravitreal administration," *World Academy of Science, Engineering and Tecnology*, vol. 53, pp. 706–716, 2011.

[48] G. Smith, *Numerical Solution of Partial Differential Equations: Finite Difference Methods*. Third Edition, Oxford University Press, New York, 1985.

[49] R. Al-Itry, K. Lamnawar, and A. Maazouz, "Improvement of thermal stability, rheological and mechanical properties of pla, pbat and their blends by reactive extrusion with functionalized epoxy," *Polymer Degradation and Stability*, vol. 97, pp. 1898–1914, 2012.

[50] M. Al-Nasassrah, F. Podczeck, and J. Newton, "The effect of an increase in chain length on the mechanical properties of polyethylene glycols," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 46, pp. 31–38, 1998.

[51] S. Baruah and N. Laskar, "Relation between molecular weight and viscosity for polydispersed pol(n-docosyl acrylate)," *Polymer Journal*, vol. 28, pp. 893–895, 1996.

[52] A. Izuka, H. Winter, and T. Hashimoto, "Molecular weight dependence of viscoelasticity of polycaprolactone critical gels," *Macromolecules*, vol. 25, pp. 2422–2428, 1992.

[53] T. Rushing and R. Hester, "Intrinsic viscosity dependence on polymer molecular weight and fluid temperature," *Journal of Applied Polymer Science*, vol. 89, pp. 2831–2835, 2003.

[54] J. Torres, C. Stafford, and B. Vogt, "Impact of molecular mass on the elastic modulus of polystyrene thin films," *Polymers*, vol. 51, pp. 4211–4217, 2010.

[55] Y. Wang, X. Han, J. Pan, and C. Sinka, "An entropy spring model for the young's modulus change of biodegradable polymers during biodegradation," *Journal of the Mechanical Behavior of Biomedical Materials*, vol. 3, pp. 14–21, 2010.

[56] S. Luo, D. Grubba, and A. Netravali, "The effect of molecular weight on the lamellar structure, thermal and mechanical properties of poly (hydroxybutyrate-co-hydroxyvalerates)," *Polymer*, vol. 43, pp. 4159–4166, 2002.