Analytical and Numerical Study of a Coupled Cardiovascular Drug Delivery Model

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Abstract

A two dimensional coupled model of drug delivery in the cardiovascular tissue using biodegradable drug eluting stents is developed. Qualitative behavior, stability analysis as well as simulations of the model have been presented. Numerical results computed with an implicit explicit finite element method show a complete agreement with the expected physical behaviour.

Keywords:: Implicit-Explicit Finite Element Method, Drug eluting stent, Coupled model
Mathematics Subject Classification (2010): $65M60$, $76R50$, $76Z05$.

1 Introduction

A stent is a metallic scaffold that is inserted in a restricted part of a narrowed blood vessel. A drug eluting stent (DES) consists of a stent coated with a polymeric layer that encapsulates a therapeutic drug to reduce smooth muscle cell growth and to prevent an inflammatory response. These are the predominant causes of neointimal proliferation and in-stent restenosis that is the re-narrowing of blood vessels after stent implantation. Application of DES for prevention of restenosis is a promising technology which combines the mechanical support of the vessel with local drug delivery.

Drug release depends on many factors, such as the geometry and location of the vessel, the geometry of the stent, the coating properties as its chemical composition and porosity, and drug characteristics as for example its diffusivity. Due to the involvement of so many factors, prediction of drug release represents an important issue and mathematical models are a useful tool to design an appropriate drug delivery system [3, 11]. The use of mathematical models and numerical simulation can give further insight on the pharmacokinetics of cardiovascular drug

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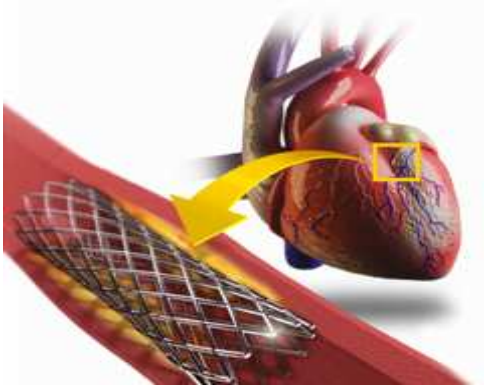


Figure 1: Drug Eluting Stent (DES) implanted in the blood artery, http://www.michaelrowecardiologist.com.au/coronary-stenting-michael-rowe.html.

release leading to optimized clinical results.

During the last years, a number of studies have proposed mathematical models to describe drug delivery in the cardiovascular tissues. We refer without being exhaustive $[3-10, 13]$ and also [11] as a review paper. Most of these studies address the release of drug and its numerical behavior in one dimension, while the behaviour of the biodegradable materials is disregarded.

Pontrelli and de Monte $[7-9]$ developed a mathematical model for drug release through a drug eluting stent in contact with the vessel wall as a coupled cardiovascular drug delivery system. They analyzed numerically and analytically the drug release from the coating into both an homogeneous mono-layer wall [7] and an heterogenous multi-layered wall [9] in one dimension. Despite their interesting results, the biodegradation process of the carrier polymer, the penetration of the biological fluid into the coating and the egression of materials from the coating have not been taken into account.

Prabhu and Hossainy [10] developed a mathematical model to predict the transport of drug with simultaneous degradation of the biodegradable polymer in the aqueous media. These authors use a simplified wall-free condition, in which the influence of the arterial wall is modeled through the coupling with a *Robin* boundary condition. An important feature of this model, which differentiates it from other models, are the conditions used to represent the polymer degradation. It is assumed that a set of oligomers can be identified as one compartment, characterized by a certain molecular weight range, whose their diffusion characteristics and degradation kinetics can be considered to be identical. Furthermore, the model in [10] takes into account the underlying chemical reactions responsible for degradation in a more detailed form than the models presented by other researchers. It also accounts for the increase of diffusivity of the different species involved as time evolves. In this paper, while following the approach in [10], we have completed the model with the dynamics of the drug in the arterial vessel.

The geometrical and mechanical effects of the metalic part of the stent in degradation and drug release as well as the penetration of the oligomer and lactic acid into the vessel wall are considered

negligible. As the transport properties through the glycocalyx (the coverage of endothelium) are unknown, we have considered the values of the parameters in the endothelium layer. A perfect sink condition at the interface between the vascular wall and the vascular lumen are considered. The paper is organized as follows. Section 2 is devoted to the description of the model and its initial, boundary and interface conditions. In Section 3 we briefly explain the mass behaviour of the materials. In Section 4 we present a variational formulation and we establish a stability result for the continuous model and in Section 5, using an implicit explicit finite element method, we establish a discrete variational form of the problem. Numerical simulations are discussed in Section 6.

2 Description of the model

We consider a stent S coated with polylactic acid (PLA) containing the drug and in contact with the vessel wall V (Figure 2). In the stent S, Γ_1 is the boundary between the coated stent and the metalic part of the stent that is stent structure while Γ_2 and Γ_3 are the boundaries which separate the coated stent and the lumen. Γ_4 is an interface boundary which separates the coated stent from the arterial wall. In the vessel wall V, Γ_5 and Γ_6 are the boundaries between the vessel wall and the lumen while Γ_7 is the boundary between the vessel wall and the tissue (outer part of the vessel wall). Finally Γ_8 and Γ_9 are virtual boundaries where symmetry conditions are imposed to simplify the model.

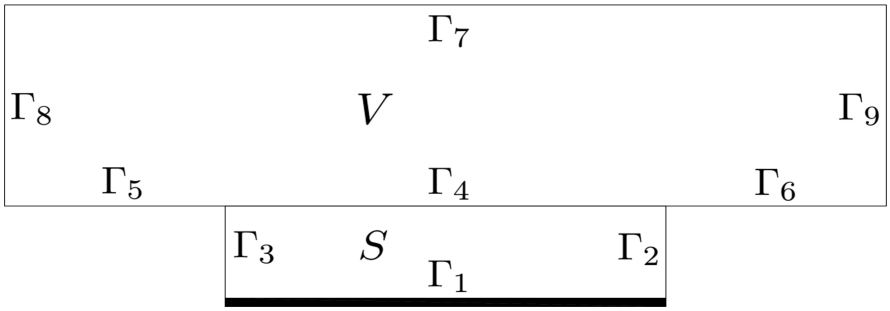


Figure 2: Polymeric stent S in contact with the vessel wall V.

When the coated stent is immersed in the artery and enters in contact with the vessel wall, a mass transport process and a series of chemical reactions occur. We assume that two main reactions are responsible for the degradation of PLA into lactic acid and oligomers. The first reaction is the hydrolyzing of the PLA, producing molecules with smaller molecular weights, $2 \times 10^4\ g/mol \leq M_W \leq 1.2 \times 10^5\ g/mol$ for oligomers and $M_W \leq 2 \times 10^4\ g/mol$ for lactic acid. The second reaction is the hydrolyzing of the oligomers giving lactic acid. These reactions are

represented by

$$\begin{aligned} &\text{Reaction 1: } C_{1,S} + C_{2,S} \xrightarrow{\kappa_{1,S}} C_{3,S} + C_{4,S}, \\ &\text{Reaction 2: } C_{1,S} + C_{3,S} \xrightarrow{\kappa_{2,S}} C_{4,S}, \end{aligned} \tag{1}$$

where $C_{1,S}, C_{2,S}, C_{3,S}$ and $C_{4,S}$ represent the concentrations of the fluid, PLA, oligomers and lactic acid in the coating respectively, that are defined in $(x, y, t) \in \bar{S} \times \mathbb{R}^+$. The constants $\kappa_{1,S}$ and $\kappa_{2,S}$ stand for the reaction rates of the first and second reactions respectively.
In the coating, the problem is described by the following nonlinear reaction diffusion equations

$$\frac{\partial C_{m,S}}{\partial t} = \nabla.\big(D_{m,S}\nabla C_{m,S}\big) + F_{m,S}(C_{1,S}, \ldots, C_{4,S}) \ \text{ in } S \times \mathbb{R}^+, \ m = 1, \ldots, 5, \tag{2}$$

where $C_{5,S}$ denotes the concentration of the drug in the coating, and the reaction terms are defined by

$$F_{m,S}(C_{1,S}, \ldots, C_{4,S}) = \begin{cases} -\sum\limits_{i=1,2} \mathcal{F}_i(C_{1,S}, \ldots, C_{4,S}), & \text{m=1,} \\ -\mathcal{F}_1(C_{1,S}, \ldots, C_{4,S}), & \text{m=2,} \\ \sum\limits_{i=1,2} (-1)^{i-1}\mathcal{F}_i(C_{1,S}, \ldots, C_{4,S}), & \text{m=3,} \\ \sum\limits_{i=1,2} \mathcal{F}_i(C_{1,S}, \ldots, C_{4,S}), & \text{m=4,} \\ 0, & \text{m=5.} \end{cases} \tag{3}$$

In (3), $\mathcal{F}_1$ and $\mathcal{F}_2$ are defined by

$$\begin{aligned} \mathcal{F}_1(C_{1,S}, \ldots, C_{4,S}) &= \kappa_{1,S} C_{1,S} C_{2,S}\big(1 + \alpha C_{4,S}\big), \\ \mathcal{F}_2(C_{1,S}, \ldots, C_{4,S}) &= \kappa_{2,S} C_{1,S} C_{3,S}\big(1 + \beta C_{4,S}\big), \end{aligned} \tag{4}$$

where α and β are positive dimensional constants (see the Annex for more details).
The diffusivities of the fluid, oligomers, lactic acid and drug will evolve with time. This variation occurs due to the progressive degradation of the polymer as well as to the swelling of the polymer. The diffusivities $D_{m,S}$ of the species in the stent coating, will attain a lower bound in the PLA and an upper bound in the fluid. It is therefore assumed that the diffusion coefficients increase exponentially with the extent of the hydrolysis of PLA. We represent these diffusivity coefficients in the coated stent by

$$D_{m,S} = D^0_{m,S} \mathrm{e}^{\alpha_{m,S} \frac{C^0_{2,S} - C_{2,S}}{C^0_{2,S}}} \ \text{ in } \bar{S} \times \mathbb{R}^+, \ m = 1, \ldots, 5, \tag{5}$$

where $D^0_{m,S}$ is the diffusivity of the specie m in the unhydrolyzed PLA and $C^0_{2,S}$ is the unhydrolyzed polymer concentration at the initial time.

For the vessel wall, a diffusion equation with constant diffusion coefficient D_V is considered

$$\frac{\partial C_V}{\partial t} = \nabla.\big(D_V \nabla C_V\big) \text{ in } V \times \mathbb{R}^+, \tag{6}$$

where C_V stands for the drug concentration in the vessel wall. Although the concentrations depend on time and space, we will consider often explicitly the time variable, omitting the space variable. Since the degradation starts at $t = 0$, we assume there is no initial concentration of oligomers and lactic acid in the coating and that the drug and PLA are uniformly distributed. In the coated stent and the vessel wall, the initial conditions are defined by

$$\begin{cases} C_{1,S}(0) = C_{3,S}(0) = C_{4,S}(0) = 0,\ C_{2,S}(0) = C_{5,S}(0) = 0 \text{ in } S, \\ C_V(0) = 1 \text{ in } V. \end{cases} \tag{7}$$

We also assume that the boundary Γ_1, interface between the coating and the stent structure, is impermeable to the materials which means that no mass flux crosses it, that is

$$D_{m,S} \nabla C_{m,S}.\eta_S = 0 \quad \text{ on } \Gamma_1 \times \mathbb{R}^+,\ m = 1, \ldots, 5, \tag{8}$$

where η_S is the exterior unit normal to Γ_1.
We assume that the blood flow in the arterial lumen does not significantly influence the drug release and the transport in the arterial wall tissue. In Γ_2 and Γ_3, the boundary conditions are defined by

$$\begin{cases} D_{1,S} \nabla C_{1,S}.\eta_S = \gamma_{1,S}(1 - C_{1,S}) & \text{on} \quad (\Gamma_2 \cup \Gamma_3) \times \mathbb{R}^+, \\ D_{m,S} \nabla C_{m,S}.\eta_S = -\gamma_{m,S} C_{m,S} & \text{on} \quad (\Gamma_2 \cup \Gamma_3) \times \mathbb{R}^+,\ m = 2, \ldots, 5, \end{cases} \tag{9}$$

where $\gamma_{m,S},\ m = 1, \ldots, 5$, represent partition coefficients.
To couple the transport od drug in the coated stent and the vessel wall, the continuity of the mass flux and the concentration are assumed, that is

$$\begin{cases} D_{5,S} \nabla C_{5,S}.\eta_S = -D_V \nabla C_V.\eta_V & \text{on } \Gamma_4 \times \mathbb{R}^+, \\ C_{5,S} = C_V & \text{on } \Gamma_4 \times \mathbb{R}^+, \end{cases} \tag{10}$$

where $\eta_S = -\eta_V$. We also assume that Γ_4 is impermeable to other compounds.
In what concerns the interface layer between intima and media, a *Robin* condition of type

$$D_V \nabla C_V.\eta_V = -\gamma_v C_V \quad \text{ on } \Gamma_7 \times \mathbb{R}^+, \tag{11}$$

is considered.
On Γ_8 and Γ_9, a homogeneous Neumann boundary condition $D_V \nabla C_V.\eta_V = 0$ is assumed which

represents a no flux condition. The flux of drug from the arterial wall to the blood is given by

$$D_V \nabla C_V . \eta_V = -\gamma_b C_V \quad \text{on } (\Gamma_5 \cup \Gamma_6) \times \mathbb{R}^+, \tag{12}$$

where γ_b is such that the endothelium offers a small resistance to the drug transport.
Summarizing, the boundary and interface conditions of the problem are defined by the following set of equations:

$$\begin{cases} D_{m,S} \nabla C_{m,S} . \eta_S = 0 & \text{on } \Gamma_1 \times \mathbb{R}^+, \ m = 1, \dots, 5, \\ D_{1,S} \nabla C_{1,S} . \eta_S = \gamma_{1,S}(1 - C_{1,S}) & \text{on } (\Gamma_2 \cup \Gamma_3) \times \mathbb{R}^+, \\ D_{m,S} \nabla C_{m,S} . \eta_S = -\gamma_{m,S} C_{m,S} & \text{on } (\Gamma_2 \cup \Gamma_3) \times \mathbb{R}^+, \ m = 2, \dots, 5, \\ D_{m,S} \nabla C_{m,S} . \eta_S = 0 & \text{on } \Gamma_4 \times \mathbb{R}^+, \ m = 1, \dots, 4, \\ C_{5,S} = C_V & \text{on } \Gamma_4 \times \mathbb{R}^+, \\ D_{5,S} \nabla C_{5,S} . \eta_S = -D_V \nabla C_V . \eta_V & \text{on } \Gamma_4 \times \mathbb{R}^+, \\ D_V \nabla C_V . \eta_V = -\gamma_b C_V & \text{on } (\Gamma_5 \cup \Gamma_6) \times \mathbb{R}^+, \\ D_V \nabla C_V . \eta_V = -\gamma_v C_V & \text{on } \Gamma_7 \times \mathbb{R}^+, \\ D_V \nabla C_V . \eta_V = 0 & \text{on } (\Gamma_8 \cup \Gamma_9) \times \mathbb{R}^+. \end{cases} \tag{13}$$

The meaning and units of all variables and parameters used in the model are presented in Table 2 (Annex).

3 Qualitative behaviour of the total mass of the system

In what follows we analyse the time behaviour of the total mass

$$\mathcal{M}(t) = \sum_{m=1}^{5} \int_S C_{m,S}(t) dS + \int_V C_V(t) dV,$$

where S and V stand for the stent and the vessel wall domains.
As we have

$$\mathcal{M}'(t) = \sum_{m=1}^{5} \int_S \frac{\partial C_{m,S}}{\partial t}(t) dS + \int_V \frac{\partial C_V}{\partial t}(t) dV,$$

considering (2) and (6), and taking into account the boundary conditions we obtain

$$\begin{aligned} \mathcal{M}'(t) \ &= \gamma_{1,S} \int_{\Gamma_2 \cup \Gamma_3} (1 - C_{1,S}(t)) ds - \sum_{m=2}^{4} \gamma_{m,S} \int_{\Gamma_2 \cup \Gamma_3} C_{m,S}(t) ds - \gamma_b \int_{\Gamma_5 \cup \Gamma_6} C_V(t) ds \\ &+ \int_{\Gamma_4} D_{5,S} \nabla C_{5,S}(t) . \eta_S ds + \int_{\Gamma_4} D_V \nabla C_V(t) . \eta_V ds - \gamma_{5,S} \int_{\Gamma_2 \cup \Gamma_3} C_{5,S}(t) ds - \gamma_v \int_{\Gamma_7} C_V(t) ds \\ &- \int_S \kappa_{2,S} C_{1,S}(t) C_{3,S}(t) \big(1 + \beta C_{4,S}(t)\big) \, dS, \end{aligned}$$

where the measures of the boundaries are defined by the length.
The coupling conditions (10) lead to

$$\mathcal{M}'(t) = -\Delta M_\Gamma(t) - \Delta M_H(t) + \gamma_{1,S}\Big|\Gamma_2 \cup \Gamma_3\Big|,$$

where

$$\Delta M_\Gamma(t) = \sum_{m=1}^{5} \gamma_{m,S} \int_{\Gamma_2\cup\Gamma_3} C_{m,S}(t)ds + \gamma_v \int_{\Gamma_7} C_V(t)ds + \gamma_b \int_{\Gamma_5\cup\Gamma_6} C_V(t)ds,$$

and

$$\Delta M_H(t) = \int_S \kappa_{2,S} C_{1,S}(t) C_{3,S}(t)\big(1 + \beta C_{4,S}(t)\big)\, dS.$$

We note that $\Delta M_\Gamma(t)$ represents the mass of molecules that enters, per unit time, in the lumen; $\Delta M_H(t)$ stands for the mass of lactic acid produced by unit time, and resulting from the hydrolysis of oligomers. Finally, integrating in time we deduce

$$\mathcal{M}(t) = \mathcal{M}(0) + \gamma_{1,S}\Big|\Gamma_2 \cup \Gamma_3\Big| t - \int_0^t \Delta M_H(\mu)\, d\mu - \int_0^t \Delta M_\Gamma(\mu)\, d\mu.$$

This equality means that the total mass in the system at time t is given by the difference between the initial mass added with the mass of fluid that enters in the system until time t and the mass of hydrolyzed oligomers until time t, the mass of the components that are on the boundary until time t: fluid ($C_{1,S}$), PLA ($C_{2,S}$), oligomers and lactic acid ($C_{3,S}, C_{4,S}$) respectively, and drug, $C_{5,S}$, and C_V.

4 Weak formulation of the coupled problems

In this section, we introduce a variational problem induced by the initial boundary value problem (IBVP) (2) − (6) and (13). We start by introducing some notations.
Let Ω be a bounded domain in $\mathbb{R}^2$ with boundary $\partial\Omega$. By $L^2(\Omega)$, $H^1(\Omega)$ and $L^2(\partial\Omega)$ we denote the usual Sobolev spaces endowed with the usual inner products $(.,.)$, $(.,.)_1$, and $(.,.)_{\partial\Omega}$, respectively, and norms $\|.\|_{L^2(\Omega)}$ and $\|.\|_{H^1(\Omega)}$, $\|.\|_{L^2(\partial\Omega)}$, respectively. By $L^\infty(\Omega)$ we represent the space of functions $v : \Omega \to \mathbb{R}$ such that

$$\big\|v\big\|_{L^\infty(\Omega)} = \operatorname*{ess\,sup}_{\Omega} |v| < \infty.$$

Let $T > 0$ be fixed. The space of functions $v : (0,T) \longrightarrow H^1(\Omega)$ such that

$$\int_0^T \big\|v(t)\big\|^2_{H^1(\Omega)} dt < \infty,$$

will be denoted by $L^2(0,T;H^1(\Omega))$ and $L^\infty(0,T;L^\infty(\Omega))$ represents the space of functions $v : (0,T) \longrightarrow L^\infty(\Omega)$ such that

$$\operatorname*{ess\,sup}_{(0,T)} \left\|v(t)\right\|_{L^\infty(\Omega)} < \infty.$$

Let $\Omega_{S,V} = S \cup V \cup \Gamma_4$ and C, γ, D and C^* be defined by

$$C = \begin{cases} C_{5,S} & \text{in } \bar{S} \times [0,T], \\ C_V & \text{in } \bar{V} \times [0,T], \end{cases} \tag{14}$$

$$\gamma = \begin{cases} \gamma_{5,S} & \text{on } \Gamma_2 \cup \Gamma_3, \\ \gamma_b & \text{on } \Gamma_5 \cup \Gamma_6, \\ \gamma_v & \text{on } \Gamma_7, \end{cases} \tag{15}$$

$$D = \begin{cases} D^0_{5,S} e^{\alpha_{5,S} \frac{C^0_{2,S} - C_{2,S}}{C^0_{2,S}}} & \text{in } \bar{S} \times (0,T], \\ D_V & \text{in } \bar{V} \times (0,T], \end{cases} \tag{16}$$

and $C^* = (C_{1,S}, C_{2,S}, C_{3,S}, C_{4,S})$.
In what follows we consider the weak solution of the initial boundary value problem (IBVP) $(2)-(6)$ and (13) defined by the variational problem:
VP: Find $(C^*, C) \in \left(L^2(0,T;H^1(S))\right)^4 \times L^2(0,T;H^1(\Omega_{S,V}))$ such that $\frac{\partial C^*}{\partial t} \in \left(L^2(0,T;L^2(S))\right)^4$, $\frac{\partial C}{\partial t} \in L^2(0,T;L^2(\Omega_{S,V}))$ and

$$\begin{cases} \displaystyle\sum_{m=1}^{4} \left(\frac{\partial C_{m,S}}{\partial t}(t), v_m\right)_S + \left(\frac{\partial C}{\partial t}(t), w\right)_{\Omega_{S,V}} = -\sum_{m=1}^{4} \left(D_{m,S} \nabla C_{m,S}(t), \nabla v_m\right)_S \\ \qquad\qquad -\left(D \nabla C(t), \nabla w\right)_{\Omega_{S,V}} + \displaystyle\sum_{m=1}^{4} \left(F_{m,S}(C^*(t)), v_m\right)_S \\ \qquad\qquad +\gamma_{1,S}\left(1 - C_{1,S}(t), v_1\right)_{\Gamma_2 \cup \Gamma_3} - \displaystyle\sum_{m=2}^{4} \gamma_{m,S}\left(C_{m,S}(t), v_m\right)_{\Gamma_2 \cup \Gamma_3} \\ \qquad\qquad -\left(\gamma C(t), w\right)_{\Gamma} \\ \qquad\qquad \text{a.e. in } (0,T), \text{ for all } v_m \in H^1(S),\ m = 1, \ldots, 4,\ w \in H^1(\Omega_{S,V}), \\ C_{m,S}(0) = 0,\ m = 1,3,4,\ C_{m,S}(0) = 1,\ m = 2,5,\ C_V(0) = 0, \end{cases} \tag{17}$$

where $\Gamma = \Gamma_2 \cup \Gamma_3 \cup \Gamma_5 \cup \Gamma_6 \cup \Gamma_7$.
In what follows we study the behaviour of the solution of the initial value problem **VP**. Let the

energy functional $\mathcal{E}_\nabla(t)$ be defined by

$$\begin{aligned}\mathcal{E}_\nabla(t) &= \sum_{m=1}^{4}\left(\left\|C_{m,S}(t)\right\|^2_{L^2(S)} + 2\int_0^t \left\|\sqrt{D_{m,S}}\nabla C_{m,S}(s)\right\|^2_{L^2(S)} ds\right) + \left\|C(t)\right\|^2_{L^2(\Omega_{S,V})} \\ &+2\int_0^t \left\|\sqrt{D}\nabla C(s)\right\|^2_{L^2(\Omega_{S,V})} ds, \quad t\in[0,T],\end{aligned} \tag{18}$$

where $\mathcal{E}_\nabla(0)$ is the initial mass of PLA and drug. In the following, the space $L^\infty(0,T,L^\infty(\Omega))$ will be represented by $L^\infty(L^\infty)$.

Theorem 4.1 *If (C^*,C) is a solution of the variational problem **VP** such that $C_{m,S}(t)\in H^2(S)$, $m=1,\ldots,4$, then there exists a positive constant $\mathcal{K}$ depending on $\|C^*\|_{L^\infty(L^\infty)} = \max\limits_{m=1,\ldots,4}\|C_{m,S}\|_{L^\infty(L^\infty)}$ such that the following holds*

$$\mathcal{E}_\nabla(t) \le e^{2\mathcal{K}t}\mathcal{E}_\nabla(0) + \tfrac{\gamma_{1,S}}{2\mathcal{K}}\left|\Gamma_2\cup\Gamma_3\right|\left(e^{2\mathcal{K}t}-1\right),\ t\in[0,T], \tag{19}$$

where $|\Gamma_2\cup\Gamma_3|$ is the length of the boundary $\Gamma_2\cup\Gamma_3$.

Proof. Taking in (17), $v_m = C_{m,S}(t)$ and $w = C(t)$ we obtain

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\mathcal{E}_\nabla(t) &\le \sum_{m=1}^{4}\Big(F_m(C^*(t)),C_{m,S}(t)\Big)_S + \gamma_{1,S}\Big(1-C_{1,S}(t),C_{1,S}(t)\Big)_{\Gamma_2\cup\Gamma_3} \\ &-\sum_{m=2}^{4}\gamma_{m,S}\left\|C_{m,S}(t)\right\|_{L^2(\Gamma_2\cup\Gamma_3)} - \gamma\left\|C(t)\right\|_{L^2(\Gamma)},\end{aligned} \tag{20}$$

that leads to

$$\frac{1}{2}\frac{d}{dt}\mathcal{E}_\nabla(t) \le \sum_{m=1}^{4}\Big(F_{m,S}(C^*(t)),C_{m,S}(t)\Big)_S + \tfrac{\gamma_{1,S}}{4}\left|\Gamma_2\cup\Gamma_3\right|. \tag{21}$$

As $H^2(S)$ is embedded in the space of continuous bounded functions in S ([1]), it can be shown that there exists a positive constant $\mathcal{K}$, that depends on $\|C^*\|_{L^\infty(L^\infty)} = \max\limits_{m=1,\ldots,4}\|C_{m,S}\|_{L^\infty(L^\infty)}$, such that

$$\sum_{m=1}^{4}\Big(F_{m,S}(C^*(t)),C_{m,S}(t)\Big)_S \le \mathcal{K}\sum_{m=1}^{4}\left\|C_{m,S}(t)\right\|^2_{L^2(S)}. \tag{22}$$

Inequality (21) leads to the differential inequality

$$\frac{d}{dt}\mathcal{E}_\nabla(t) \le 2\mathcal{K}\mathcal{E}_\nabla(t) + \tfrac{\gamma_{1,S}}{2}\left|\Gamma_2\cup\Gamma_3\right|,$$

and consequently we deduce (19). □

In order to simplify the presentation, we assume in what follows that the diffusion coefficients $D_{m,S},\ m = 1, \ldots, 5$, are constant. To study the stability of the initial value problem **VP**, we consider two solutions $\mathcal{C} = (C^*, C)$ and $\tilde{\mathcal{C}} = (\tilde{C}^*, \tilde{C})$ with different initial conditions $\mathcal{C}(0)$ and $\tilde{\mathcal{C}}(0)$. To establish an inequality of form

$$\begin{aligned}\Big\|C^*(t) - \tilde{C}^*(t)\Big\|^2_{L^2(S)} \quad &+\Big\|C(t) - \tilde{C}(t)\Big\|^2_{L^2(\Omega_{S,V})} \\ &\leq B(t)\Big(\Big\|C^*(0) - \tilde{C}^*(0)\Big\|^2_{L^2(S)} + \Big\|C(0) - \tilde{C}(0)\Big\|^2_{L^2(\Omega_{S,V})}\Big), \quad t \in [0,T],\end{aligned} \tag{23}$$

where $B(t)$ must be bounded in time, that leads to the stability a system of quasi-linear reaction-diffusion equations, it is sufficient to assume that the reaction terms have bounded partial derivatives. As reaction terms (3) are nonlinear functions unbounded partial derivative, an estimate of type (23) can not be established. To gain some insight on the stability behaviour of the initial value problem **VP**, we study in what follows the stability of a linearization of **VP** in the neighborhood of a soloution $\mathcal{C}(t)$.

We recall that $C^*(t) = \Big(C_{m,S}(t)\Big)_{m=1,\ldots,4}$, and $C(t)$ and D are defined by (14) and (16) respectively. Then, the system of equations (2) and (6) can be rewritten in the following form

$$\begin{cases} \dfrac{d\mathcal{C}}{dt}(t) = \mathbb{F}(\mathcal{C}(t)),\ t > 0, \\ \mathcal{C}(0) \ \text{ is given,} \end{cases} \tag{24}$$

where $\mathcal{C}(t) = \big(C^*(t), C(t)\big)$, $\mathbb{F}(\mathcal{C}(t)) = \Big(\mathbb{F}_m(\mathcal{C}(t))\Big)_{m=1,\ldots,5}$ is defined by

$$\begin{cases} \mathbb{F}_m(\mathcal{C}(t)) = \nabla.\big(D_{m,S}\nabla C_{m,S}(t)\big) + F_{m,S}(C^*(t)),\ m = 1, \ldots, 4, \\ \mathbb{F}_5(\mathcal{C}(t)) = \nabla.\big(D\nabla C(t)\big), \end{cases} \tag{25}$$

and $F_{m,S}(C^*(t)), m = 1, \ldots, 4$, are given by (3) and (4).

The linearization of the initial value problem (24) in $\mathcal{C}(t)$ is then written in the following form

$$\begin{cases} \dfrac{d\tilde{\mathcal{C}}}{dt}(t) = \mathbb{L}\tilde{\mathcal{C}}(t)\,, t > 0, \\ \tilde{\mathcal{C}}(0) \ \text{ is given,} \end{cases} \tag{26}$$

where $\mathbb{L}\tilde{\mathcal{C}}(t) = \Big(\mathbb{L}_m\tilde{\mathcal{C}}(t)\Big)_{m=1,\ldots,5}$ is defined by

$$\begin{cases} \mathbb{L}_m\tilde{\mathcal{C}}(t) = \nabla.\big(D_{m,S}\nabla\tilde{C}_{m,S}(t)\big) + \mathbb{F}_{J,m}(\mathcal{C}(t))\tilde{C}(t),\ m = 1, \ldots, 4, \\ \mathbb{L}_5\tilde{\mathcal{C}}(t) = \nabla.\big(D\nabla\tilde{C}(t)\big), \end{cases} \tag{27}$$

with $\tilde{\mathcal{C}}(t) = (\tilde{C}^*(t), \tilde{C}(t))$, $\tilde{C}^*(t) = \left(\tilde{C}_{m,S}(t)\right)_{m=1,\ldots,4}$ and

$$\mathbb{F}_{J,m}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) = \begin{cases} -\sum\limits_{i=1,2} \mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t), & \text{m=1,} \\ -\mathcal{F}_{J,1}(\mathcal{C}(t))\tilde{\mathcal{C}}(t), & \text{m=2,} \\ \sum\limits_{i=1,2} (-1)^{i-1}\mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t), & \text{m=3,} \\ \sum\limits_{i=1,2} \mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t), & \text{m=4.} \end{cases} \tag{28}$$

In (28), $\mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t),\ i = 1, 2$, represent Fréchet derivatives defined by

$$\begin{cases} \mathcal{F}_{J,1}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & = \kappa_{1,S}C_{2,S}(t)(1 + \alpha C_{4,S}(t))\tilde{C}_{1,S}(t) + \kappa_{1,S}C_{1,S}(t)(1 + \alpha C_{4,S}(t))\tilde{C}_{2,S}(t) \\ & \quad +\kappa_{1,S}\alpha C_{1,S}(t)C_{2,S}(t)\tilde{C}_{4,S}(t), \\ \mathcal{F}_{J,2}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & = \kappa_{2,S}C_{3,S}(t)(1 + \beta C_{4,S}(t))\tilde{C}_{1,S}(t) + \kappa_{2,S}C_{1,S}(t)(1 + \beta C_{4,S}(t))\tilde{C}_{3,S}(t) \\ & \quad +\kappa_{2,S}\beta C_{1,S}(t)C_{3,S}(t)\tilde{C}_{4,S}(t). \end{cases} \tag{29}$$

Let $\tilde{\mathcal{C}}$ and $\tilde{\tilde{\mathcal{C}}}$ be solutions of the variational problem associated with the initial boundary value problem defined by (26) and the conditions (13), with initial conditions $\tilde{\mathcal{C}}(0)$ and $\tilde{\tilde{\mathcal{C}}}(0)$. We suppose that $\tilde{\mathcal{C}}(t), \tilde{\tilde{\mathcal{C}}}(t) \in \left(H^2(S)\right)^4$.

We establish in what follows an upper bound for the functional $\mathcal{E}_{\mathcal{W}}(t)$ defined by

$$\mathcal{E}_{\mathcal{W}}(t) = \sum_{m=1}^{4} \left\| W_{m,S}(t) \right\|^2_{L^2(S)} + \left\| W(t) \right\|^2_{L^2(\Omega_{S,V})},\ t \in [0, T], \tag{30}$$

where $W_{m,S} = \tilde{C}_{m,S} - \tilde{\tilde{C}}_{m,S},\ m = 1, \ldots, 4$, and

$$W = \begin{cases} \tilde{C}_{5,S} - \tilde{\tilde{C}}_{5,S} & \text{in } \bar{S} \times [0, T], \\ \tilde{C}_V - \tilde{\tilde{C}}_V & \text{in } \bar{V} \times [0, T]. \end{cases} \tag{31}$$

It can be shown that

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\mathcal{E}_{\mathcal{W}}(t) \leq & -\sum_{m=1}^{4} \left\| \sqrt{D_{m,S}}\nabla W_{m,S}(t) \right\|^2_{L^2(S)} - \left\| \sqrt{D}\nabla W(t) \right\|^2_{L^2(\Omega_{S,V})} \\ & + \sum_{m=1}^{4} \left(\mathbb{F}_{J,m}(\mathcal{C}(t))W_{m,S}(t), W_{m,S}(t) \right)_S. \end{aligned} \tag{32}$$

Consequently, there exists a positive constant $\mathcal{K}'$ depending on $\left\| C^* \right\|_{L^\infty(L^\infty)}$ such that

$$\frac{d}{dt}\mathcal{E}_{\mathcal{W}}(t) \leq 2\mathcal{K}'\mathcal{E}_{\mathcal{W}}(t),\ t > 0. \tag{33}$$

This inequality leads to

$$\mathcal{E}_{\mathcal{W}}(t) \leq e^{2\mathcal{K}'t}\mathcal{E}_{\mathcal{W}}(0), \tag{34}$$

which allow us to conclude the stability of the linearization of **VP** for bounded time intervals.

5 Finite dimensional approximation

To define a finite dimensional approximation for the solution of **VP** we fix $h > 0$ and we introduce in $\Omega_{S,V}$ an admissible triangulation $\mathcal{T}_h$, depending on $h > 0$, such that the corresponding admissible triangulations induced in S and V, respectively $\mathcal{T}_{h_S}$ and $\mathcal{T}_{h_V}$, are compatible on Γ_4 (see Figure 3).
To compute the semi-discrete Ritz-Galerkin aproximation $\mathcal{C}_h = (C_h^*, C_h)$ for the weak solution $\mathcal{C} = (C^*, C)$ defined by **VP**, we introduce the finite dimensional spaces

$$\mathcal{P}_Q^n = \left\{ u \in C^0(\bar{Q}) : u\big|_\Delta = P_n,\, \Delta \in \mathcal{T}_{h_Q} \right\},$$

where $Q = S, \Omega_{S,V}$ and P_n denotes a polynomial with degree at most n.
Let $C_h^* = (C_{1,S,h}, C_{2,S,h}, C_{3,S,h}, C_{4,S,h})$ and

$$C_h = \begin{cases} C_{5,S,h} & \text{in } \bar{S} \times [0,T], \\ C_{V,h} & \text{in } \bar{V} \times [0,T], \end{cases} \tag{35}$$

The Ritz-Galerkin approximation $\mathcal{C}_h = (C_h^*, C_h)$ for the weak solution $\mathcal{C} = (C^*, C)$ defined by **VP**, is computed solving the following variational problem:
FEVP: Find $(C_h^*(t), C_h(t)) \in \left(\mathcal{P}_S^n\right)^4 \times \mathcal{P}_{\Omega_{S,V}}^n$ such that

$$\begin{cases} \displaystyle\sum_{m=1}^{4}\left(\frac{\partial C_{m,S,h}}{\partial t}(t), v_{m,h}\right)_S + \left(\frac{\partial C_h}{\partial t}(t), w_h\right)_{\Omega_{S,V}} = -\sum_{m=1}^{4}\left(D_{m,S,h}\nabla C_{m,S,h}(t), \nabla v_{m,h}\right)_S \\ \qquad -\left(D\nabla C_h(t), \nabla w_h\right)_{\Omega_{S,V}} + \displaystyle\sum_{m=1}^{4}\left(F_{m,S}(C_h^*(t)), v_{m,h}\right)_S \\ \qquad +\gamma_{1,S}\left(1 - C_{1,S,h}(t), v_{1,h}\right)_{\Gamma_2\cup\Gamma_3} - \displaystyle\sum_{m=2}^{4}\gamma_{m,S}\left(C_{m,S,h}(t), v_{m,h}\right)_{\Gamma_2\cup\Gamma_3} \\ \qquad -\left(\gamma C_h(t), w_h\right)_\Gamma \\ \qquad \text{in } (0,T], \text{ for all } v_{m,h} \in \mathcal{P}_S^n, m = 1,\ldots,4, \text{ and } w_h \in \mathcal{P}_{\Omega_{S,V}}^n, \\ C_{m,S,h}(0) = 0,\ m = 1,3,4,\ C_{m,S,h}(0) = 1,\ m = 2,5,\ C_{V,h}(0) = 0. \end{cases} \tag{36}$$

In (36), $D_{m,S,h} = D_{m,S}^0 e^{\alpha_{m,S}\frac{C_{2,S}^0 - C_{2,S,h}}{C_{2,S}^0}}$ in $\bar{S} \times (0,T]$, $m = 1,\ldots,4$, and

$$D_h = \begin{cases} D_{5,S}^0 e^{\alpha_{5,S}\frac{C_{2,S}^0 - C_{2,S,h}}{C_{2,S}^0}} & \text{in } \bar{S} \times (0,T], \\ D_V & \text{in } \bar{V} \times (0,T]. \end{cases}$$

Following the proof of Theorem 4.1 it can be shown that $\mathcal{E}_\nabla(t)$ defined with the Ritz-Galerkin

approximation $\mathcal{C}_h = (C_h^*, C_h)$ satisfies an inequality analogous to (19). Moreover, for the linearization of **FEVP** around $\mathcal{C}_h = (C_h^*, C_h)$ it can be shown an inequality analogous to (34).

6 Numerical Experiments

In this section, we analyse the material behavior and the influence of the parameters of the model in the release rate. All experiments have been done with the open source partial differential equation solver freeFEM++ with 10096 elements (5224 vertices) for $\Omega_{S,V}$ and 3250 elements (1751 vertices) for the stent S, and using IMEX backward integrator with time step size $\Delta t = 10^{-3}$. Several choices of finite element spaces can be made, but we consider here the piecewise linear finite element space P_1.

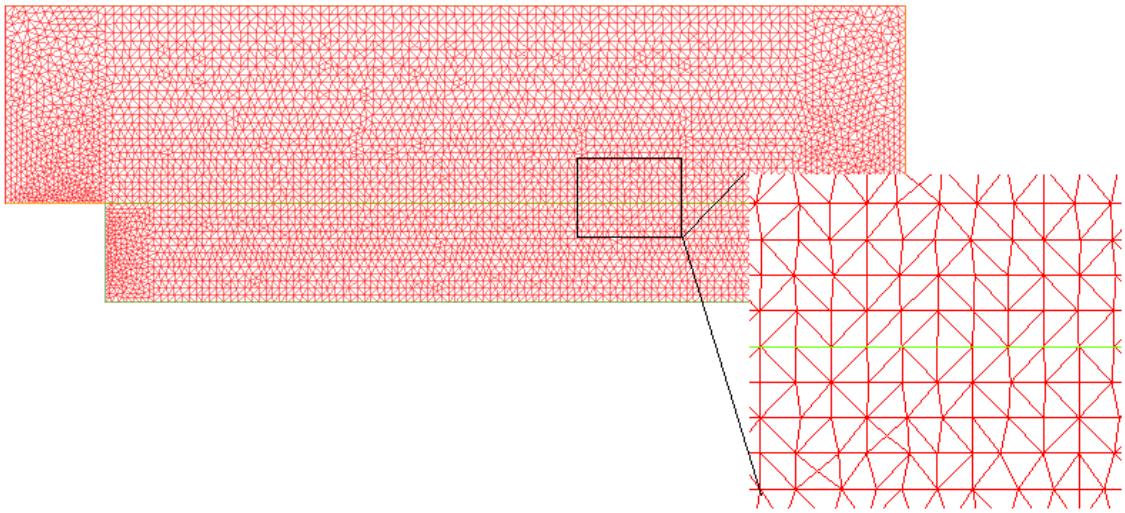
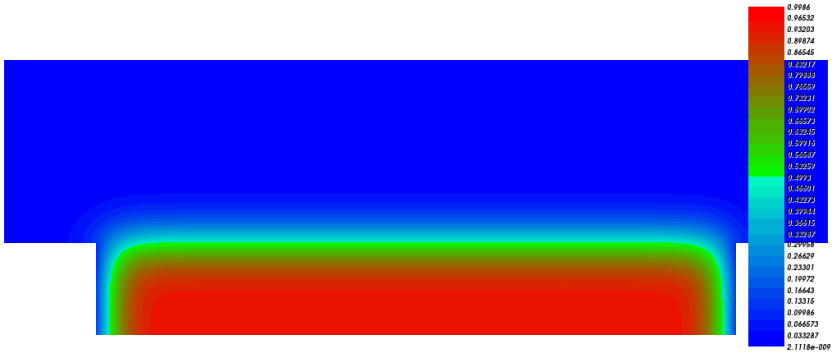
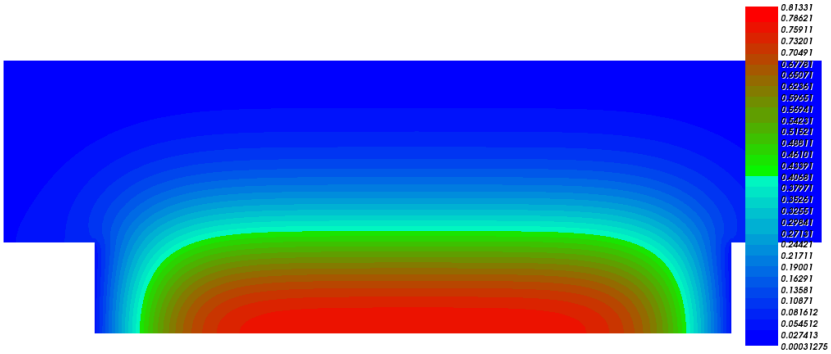


Figure 3: Triangulation in the stent and in the vessel wall.

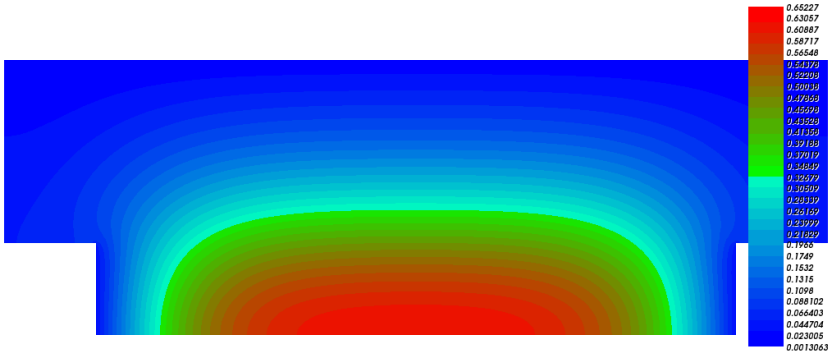
The IMEX method is defined by integrating (36) with an implicit Euler method where the diffusion terms are considered implicitly with implicit diffusion coefficients explicit. The discretization of the reaction terms, is explicit which convert each nonlinear reaction into a linear one.
The following parameters have been used in the simulation of the drug release from the drug eluting stent into the arterial wall:
$\gamma_{m,S} = 10^5\ cm/s,\ m = 1,\dots,5,\ \gamma_v = 10^5\ cm/s,\ \gamma_b = 10^{10}\ cm/s,\ \alpha_{m,S} = 9,\ m = 1,\dots,4,$
$\alpha_{5,S} = 0.9,\ \kappa_{1,S} = 1 \times 10^{-6}\ cm^2/g.s,\ \kappa_{2,S} = 1 \times 10^{-8}\ cm^2/g.s,\ \alpha = 1\ s/cm^2,\ \beta = 10\ s/cm^2,$
$D^0_{1,S} = 5{\times}10^{-7}\ cm^2/s,\ D^0_{2,S} = 1{\times}10^{-15}\ cm^2/s,\ D^0_{3,S} = 5{\times}10^{-12}\ cm^2/s,\ D^0_{4,S} = 3{\times}10^{-12}\ cm^2/s,$
$D^0_{5,S} = 2 \times 10^{-8}\ cm^2/s,\ D_V = 5 \times 10^{-8}\ cm^2/s.$



(a) 1 day.



(b) 7 days.



(c) 14 days.

Figure 4: Evolution of drug distribution in the coating and in the vessel wall.

In Figure 4, we plot the drug distribution in the stent and in the arterial wall after 1 day, 7 and 14 days. When the drug reaches Γ_4 (See Figure 2), it crosses the arterial wall through the interface boundary as mathematically described by (10). When the drug reaches the boundary Γ_7, it enters the media as described by Robin boundary conditions (11).

(a) 1 day.

(b) 7 days.

(c) 14 days.

Figure 5: Evolution of concentration of fluid in the coating.

In Figure 5, we exhibit the penetration of the fluid into the coated stent. We observe that the fluid penetrates into the PLA until it reaches a steady state level.

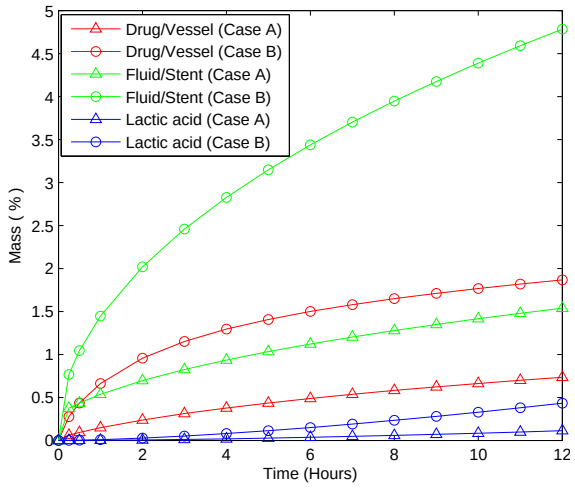
(a) 1 day.

(b) 7 days.

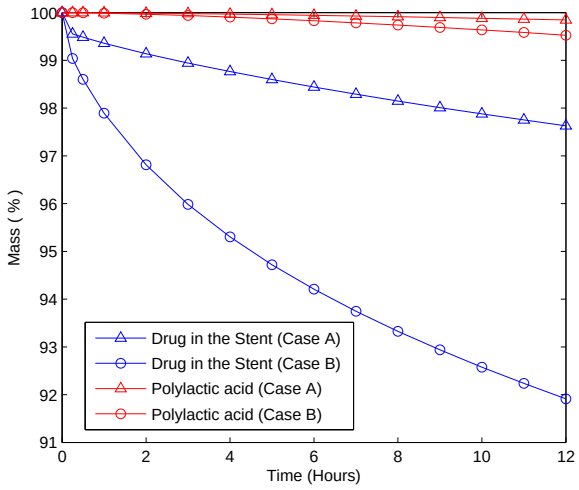
(c) 14 days.

Figure 6: Evolution of concentration of PLA in the coating.

In Figure 6, the degradation of PLA into smaller molecules which are released into the lumen is shown. It is assumed that the penetration of the PLA and also its reaction products, oligomers and lactic acid, into the arterial wall is negligible. The evolution of PLA concentration is compatible with erosion during degradation.



(a) Mass of drug in the vessel wall, fluid and lactic acid in the stent during the first 12 hours of the process.



(b) Mass of drug and PLA in the stent during the first 12 hours of the process.

Figure 7: Diffusion of fluid, drug, lactic acid and PLA, $D_{1,S} = 5 \times 10^{-8}\ cm^2/s, D_{5,S} = 2 \times 10^{-9}\ cm^2/s, D_V = 5 \times 10^{-9}\ cm^2/s$ (Case A) and $D_{1,S} = 5 \times 10^{-7}\ cm^2/s, D_{5,S} = 2 \times 10^{-8}\ cm^2/s, D_V = 5 \times 10^{-8}\ cm^2/s$ (Case B).

In Figure 7, we exhibit the mass of drug both in the coating and in the vessel wall as well as the mass of the fluid, PLA and lactic acid in the coating during the first 12 hours using different diffusion coefficients. We observe in Figure 7 (a) that small diffusion coefficients will increase accumulation of the drug in the vessel wall resulting in higher drug residence time and also will increase the mass of fluid and lactic acid in the stent. In Figure 7 (b), an increase in the PLA degradation and drug release is observed when the diffusion coefficients of the drug and the fluid decrease.

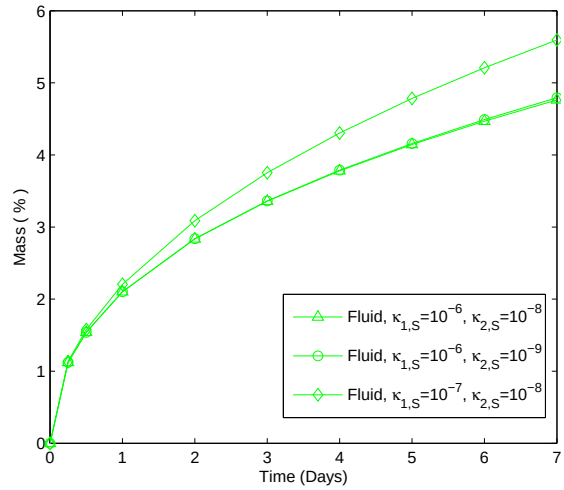
We compute the mass fractions retained in the coating by

$$M_{m,S}(t) = \frac{1}{|S|}\int_S C_{m,S}(t)dS, \quad m = 1, \ldots, 5, \tag{37}$$

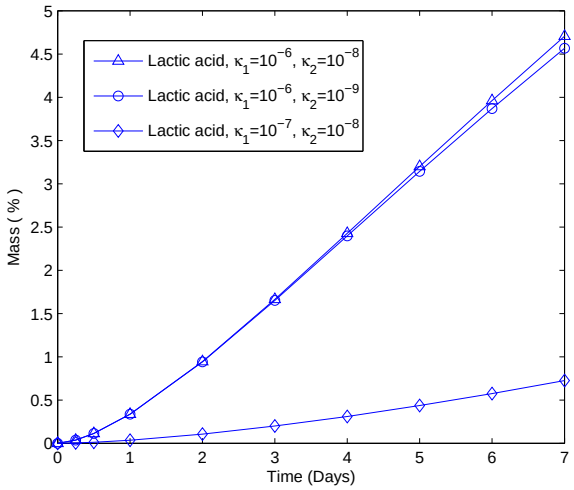
where $|S|$ represents the area of S. The mass of drug in the vessel is defined by

$$M_V(t) = \frac{1}{|V|}\int_V C_V(t)dV, \tag{38}$$

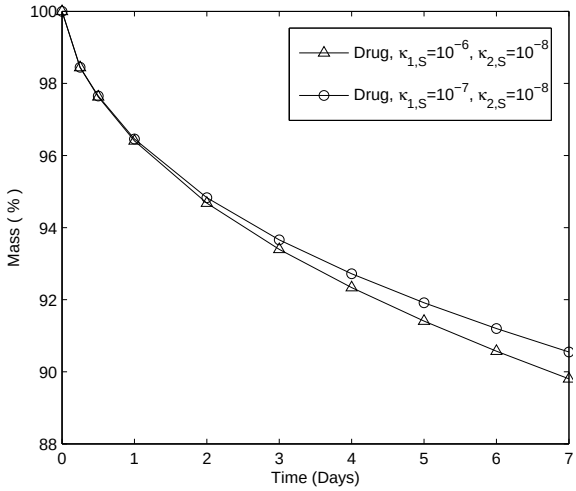
where $|V|$ stands for the area of the vessel wall.



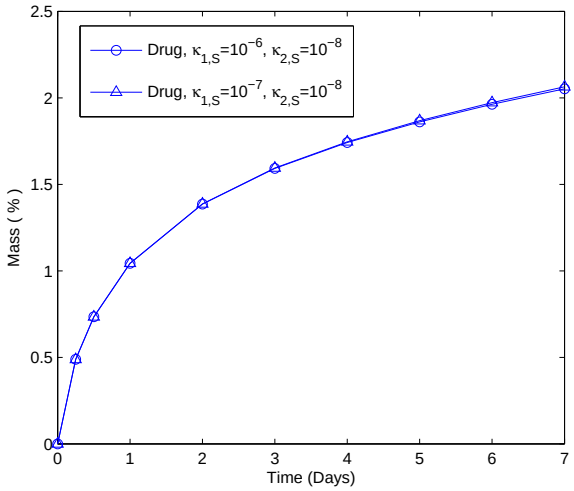
(a) Mass of fluid in the stent.



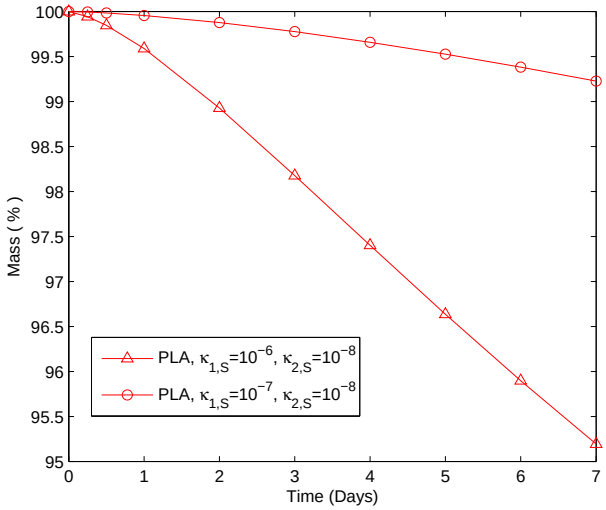
(b) Mass of lactic acid in the stent.



(c) Mass of drug in the stent.



(d) Mass of drug in the vessel wall.



(e) Mass of PLA in the stent.

Figure 8: Mass of fluid, drug, lactic acid and PLA during 7 days with different reaction rates $\kappa_{1,S}$ and $\kappa_{2,S}$ $(cm^2/g.s)$.

Figure 8 shows the influence of reaction rates on the release process. In Figure 8 (a) we observe that when the reaction rate $\kappa_{1,S}$ decreases, more fluid enters the stent. A little increment will also accur when we decrease $\kappa_{2,S}$. As it is seen in Figure 8 (b), when both the values of the reaction rates $\kappa_{1,S}$ and $\kappa_{2,S}$ are decreased, some reduction in lactic acid production is observed. Figures 8 $(c)-(e)$ indicate that the changes in $\kappa_{2,S}$ do not have any effect on the masses of drug in the stent and the vessel wall. The same insensitivity occurs with PLA. The decrease of $\kappa_{1,S}$ will decelerate the speed of drug release and PLA degradation in the stent and will accelerate slightly the speed of drug in the vessel wall.

α and β	Fluid	PLA	Oligomers	Polylactic Acid
$\alpha = 0, \beta = 0$	2.1177	99.9631	0.0309	0.0313
$\alpha = 1, \beta = 1$	2.1176	99.9629	0.0311	0.0315
$\alpha = 10, \beta = 1$	2.1171	99.9612	0.0328	0.0332
$\alpha = 1, \beta = 10$	2.1176	99.9629	0.0311	0.0315
$\alpha = 10, \beta = 10$	2.1170	99.9612	0.0328	0.0332
$\alpha = 100, \beta = 10$	2.1060	99.9322	0.0608	0.0616

Table 1: Behaviour of the mass of the fluid, PLA, oligomers and lactic acid for different valuse of α and β (s/cm^2) after 24 hours.

Table 1 shows the effect of the autocatalysis coefficients on the degradation of the polymer. As it can be observed, the polymer degrades slightly faster at higher values of the autocatalysis coefficients α. The amounts of oligomers and lactic acid are also influenced by α. The mass does not seem very sensitive to changes in β.

7 Conclusion

In recent years, mathematical modeling has become an effective tool to simulate drug delivery processes in DES leading to a deeper understanding of the drug release mechanism both in biodegradable polymers and in the arteries.

In this paper, a two dimensional mathematical model of in vivo drug delivery from an eluting stent has been developed. Numerical simulations as well as a sensitivity analysis of the parameters have been done using freeFEM++. The degradation of the PLA into oligomers and lactic acid has been taken into account. The process of penetration of the fluid into a biodegradable polymer as well as the process of drug diffusion into the blood and the vessel wall have been analyzed from a numerical viewpoint. The sensitivity of the model to the perturbations of the effective parameters such as diffusion coefficients, reaction rates and autocatalytic parameters is also analyzed. The interplay between these parameters can be used as an efficient tool in the design of the coating polymer in such a way that a predefined drug delivery profile can be obtained.

The cardiovascular drug delivery process is not well understood because it depends on a huge number of complex biochemical and physical phenomena. However a simplified release model as

the one presented in this paper can help to give some insight of the dependence of the release profiles on the parameters involved. The introduction of the mechanical properties of the stent and the vessel wall as the coupling with blood flow in the vessel are important aspects that we plan to consider in the near future.

Annex

Parameter/Variable	Unit	Equation
$\kappa_{1,S}, \kappa_{2,S}$	$cm^2/g.s$	(1)
α, β	s/cm^2	(4)
$C_{m,S}, C_V$	g/cm^2	(2), (6)
$D^0_{m,S}, D_V$	cm^2/s	(5), (6)
$\gamma_{m,V}$	cm/s	(9)
γ_b, γ_v	cm/s	(11), (12)

Table 2: Parameters of the model in the drug eluting stent and vessel wall.

In the column Equation, we indicate the first equation in the paper where the parameter or variable appear.

Acknowledgements

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