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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.

Key words: Implicit-Explicit Finite Element Method, Drug eluting stent, Coupled model.

Mathematics Subject Classification (2000): 65M60, 76R50, 76Z05.

1. Introduction

Application of drug eluting stent (DES) for prevention of restenosis, that is the re-narrowing of the blood vessel after stent implantation, is a promising technology which combines a stent, that is a mechanical support of restricted lumen with local drug delivery. Mathematical modelling and numerical simulation are useful tools in the design of DES that lead to optimized clinical results and give further insight on the pharmacokinetics of the cardiovascular drug release.

A DES (Figure 1), consists of a metallic stent strut coated with a polymeric layer that encapsulates a therapeutic drug to reduce smooth muscle cell growth and to prevent inflammatory response which are the predominant causes of neointimal proliferation and in-stent restenosis.

Drug release depends on many factors, such as the strut geometry and location, the coating properties and drug characteristics such as porosity and diffusivity. Due to the involvement of so many factors, prediction of drug release appears as an important issue and mathematical models are a useful predictive tool to design an appropriate drug delivery system [3, 12].

During the last years, a number of studies have proposed mathematical models for coupled drug delivery in the cardiovascular tissues. We refer without being exhaustive [3 − 11, 14] and also [12] as a review paper. Most of these

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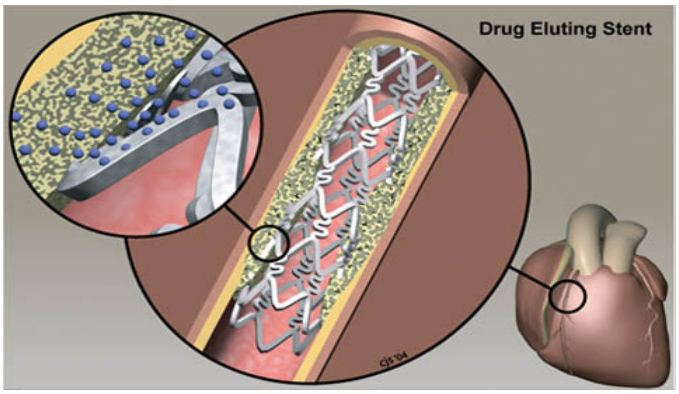

FIGURE 1. Drug Eluting Stent (DES) implanted in the blood artery

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 [8 – 10], 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 [8] and an heterogenous multi-layered wall [10] 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 polymer's materials from the coating have not been taken into account.

Prabhu and Hossainy [11] 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 *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, for which their diffusion characteristics and degradation kinetics can be considered to be identical. Furthermore, the model in [11] 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 different species involved as time evolves. In this

paper, while following the approach in [11], we have completed the model with the dynamics of the drug in the arterial vessel. Preliminary results were obtained in [5].

The geometrical and mechanical effects of the stent strut 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 values in the endothelium layer. A perfect sink condition, a fixed zero concentration 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 the phenomenological approach. In section 4 we present a variational formulation and 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. Numerical simulations are discussed in section 6.

2. Description of the model

We consider a stent coated with PLA containing the drug and in contact with the arterial wall. 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 start.

We assume that two main reactions are responsible for the degradation of

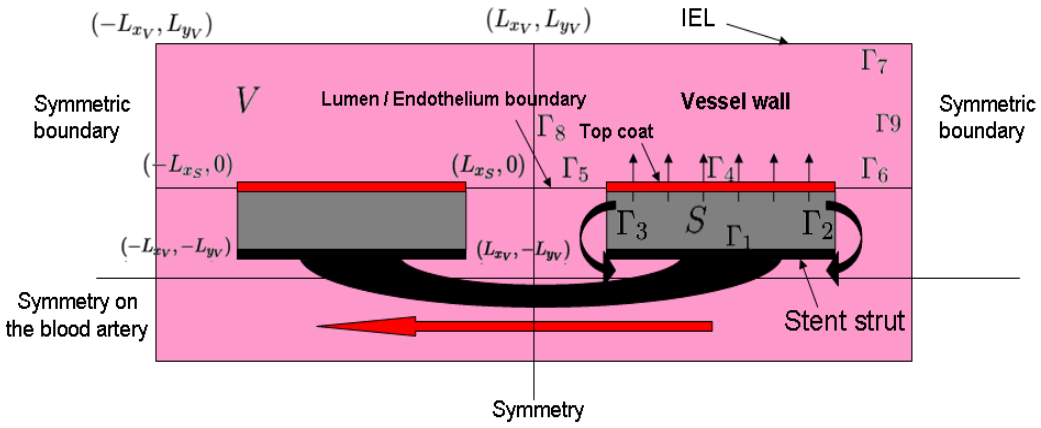

FIGURE 2. xy-cross section of the physical model

PLA into lactic acid and oligomers. The first reaction is the hydrolyzing of

the PLA producing molecules with smaller molecular weights, $20K \leq M_W \leq 120K$ for oligomers and $M_W \leq 20K$ for lactic acid; second reaction is the hydrolyzing of the oligomers giving lactic acid. The reactions are represented by

$$\begin{cases} \text{Reaction 1: } C_{1,S} + C_{2,S} \xrightarrow{\kappa_1} C_{3,S} + C_{4,S}, \\ \text{Reaction 2: } C_{1,S} + C_{3,S} \xrightarrow{\kappa_2} C_{4,S}, \end{cases} \tag{1}$$

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. The constants κ_1 and κ_2 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

$$\frac{\partial C_{m,S}}{\partial t} = \nabla.\big(D_{m,S}\nabla C_{m,S}\big) + F_m(C_{1,S}, \ldots, C_{4,S}),\ m = 1, \ldots, 5 \tag{2}$$

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

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

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

$$\begin{cases} \mathcal{F}_1(C_{1,S}, \ldots, C_{4,S}) = \kappa_1 C_{1,S} C_{2,S}\big(1 + \alpha C_{4,S}\big), \\ \mathcal{F}_2(C_{1,S}, \ldots, C_{4,S}) = \kappa_2 C_{1,S} C_{3,S}\big(1 + \beta C_{4,S}\big). \end{cases} \tag{4}$$

We will simulate the model in two dimensions. Accordingly the concentration $C_{m,S},\ m = 1, \ldots, 5$ are real functions defined in $[0, \infty) \times [-L_{x_S}, L_{x_S}] \times [-L_{y_S}, 0]$.

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 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.
The diffusivity coefficients in the coated stent are represented by

$$D_{m,S} = D^0_{m,S} e^{\alpha_{m,S} \frac{C^0_{2,S} - C_{2,S}}{C^0_{2,S}}}, \ m = 1, \ldots, 5, \tag{5}$$

where $D^0_{m,S}$ (cm^2/s) is the diffusivity of the respective species in the unhydrolyzed PLA and $C^0_{2,S}$ is the unhydrolyzed polymer concentration at the initial time.
For the vessel wall, the following simplified model of diffusion equation with constant diffusion coefficient D_d is assumed

$$\frac{\partial C_d}{\partial t} = \nabla.\big(D_d \nabla C_d\big), \tag{6}$$

where C_d stands for the drug concentration in the vessel wall and is defined in $[0, \infty) \times [-L_{x_V}, L_{x_V}] \times [0, L_{y_V}]$.
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

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

We also assume that the boundary Γ_1 is impermeable to the materials which means no mass flux crosses it, that is

$$D_{m,S} \nabla C_{m,S} \eta_S = 0, \ m = 1, \ldots, 5 \text{ on } \Gamma_1, \tag{8}$$

where η_S is the unit exterior 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

$$\begin{cases} D_{1,S} \nabla C_{1,S} \eta_S = \gamma_{1,S}(1 - C_{1,S}) & \text{on } \Gamma_2, \Gamma_3, \\ D_{m,S} \nabla C_{m,S} \eta_S = -\gamma_{m,S} C_{m,S} \ m = 2, \ldots, 5 & \text{on } \Gamma_2, \Gamma_3, \end{cases} \tag{9}$$

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

$$\begin{cases} D_{5,S} \nabla C_{5,S} \eta_S = -D_d \nabla C_d \eta_V & \text{on } \Gamma_4, \\ C_{5,S} = C_d, & \text{on } \Gamma_4. \end{cases} \tag{10}$$

Concentration jumps may occur at the interface Γ_4 in presence of a second thin layer in the stent named *topcoat* that is used to slow down the release rate. In this case, the boundary conditions on Γ_4 are represented by

$$\begin{cases} D_{5,S}\nabla C_{5,S}\eta_S = -D_d\nabla C_d\eta_V & \text{on } \Gamma_4, \\ D_{5,S}\nabla C_{5,S}\eta_S = P_c\big(\frac{C_{5,S}}{\varepsilon_1} - \frac{C_d}{\varepsilon_2}\big) & \text{on } \Gamma_4, \end{cases} \tag{11}$$

where P_c is the permeability of the topcoat, ε_1 and ε_2 are the porosity of the coating and the vessel wall respectively. We have also assumed that Γ_4 is impermeable to all other components.
In what concerns Γ_7, the interface layer between intima and media named IEL a *Robin* condition of type

$$D_d\nabla C_d\eta_V = -\gamma_d C_d \text{ on } \Gamma_7, \tag{12}$$

is considered.
In the symmetric boundary layers of the vessel wall, Γ_8 and Γ_9, which are considered sufficiently far away from the domain of interest, a no-flux condition, $D_d\nabla C_d\eta_V = 0$ is assumed. We assume that the drug flux from the arteria wall to the blood is given by

$$D_d\nabla C_d\eta_V = -\gamma_b C_d \text{ on } \Gamma_5 \cup \Gamma_6, \tag{13}$$

where γ_b is such that the endothelium offers a small resistance to the drug transport.

Since the drug goes directly from the arterial wall to the blood and is transported very fast away from the region of interest, we may assume a perfect washout of the drug, $C_d = 0$, for the lumen-arterial wall boundaries Γ_5 and Γ_6. The boundary conditions on lumen-arterial wall assume that the endothelium does not offer any resistance to the drug transport from the wall to the artery.
Summarizing, the various boundary and interface conditions are defined by

$$\begin{cases} D_{m,S}\nabla C_{m,S}\eta_S = 0, \ m = 1,\dots,5 & \text{on } \Gamma_1, \\ D_{1,S}\nabla C_{1,S}\eta_S = \gamma_{1,S}(1 - C_{1,S}) & \text{on } \Gamma_2 \cup \Gamma_3, \\ D_{m,S}\nabla C_{m,S}\eta_S = -\gamma_{m,S}C_{m,S}, \ m = 2,\dots,5 & \text{on } \Gamma_2 \cup \Gamma_3, \\ D_{m,S}\nabla C_{m,S}\eta_S = 0, \ m = 1,\dots,4 & \text{on } \Gamma_4, \\ C_{5,S} = C_d, \ D_{5,S}\nabla C_{5,S}\eta_S = -D_d\nabla C_d\eta_V & \text{on } \Gamma_4, \\ D_d\nabla C_d\eta_V = -\gamma_b C_d & \text{on } \Gamma_5 \cup \Gamma_6, \\ D_d\nabla C_d\eta_V = -\gamma_d C_d & \text{on } \Gamma_7, \\ D_d\nabla C_d\eta_V = 0 & \text{on } \Gamma_8 \cup \Gamma_9. \end{cases} \tag{14}$$

3. Qualitative behaviour of the total mass of the system

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

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

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

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

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

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

The coupling conditions (10) lead to

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

where

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

and the mass of hydrolyzed oligomers is given by

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

and $\Big| \Gamma_2 \cup \Gamma_3 \Big|$ represents the length of the boundary segment $\Gamma_2 \cup \Gamma_3$. Finally, integrating in time we deduce

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

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_d.

4. Weak formulation of the coupled problems

In this section, we introduce a variational problem induced by the initial boundary value problem (2) − (6) and (14). 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 os functions $v : \Omega \to \mathbb{R}$ such that

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

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

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

Let C, γ, D and C^* be defined by

$$C = \begin{cases} C_{5,S} & \text{in } S, \\ C_d & \text{in } V, \end{cases} \tag{15}$$

$$\gamma = \begin{cases} \gamma_{5,S} & \text{on } \Gamma_2 \cup \Gamma_3, \\ \gamma_b & \text{on } \Gamma_5 \cup \Gamma_6 \\ \gamma_d & \text{on } \Gamma_7, \end{cases} \tag{16}$$

$$D = \begin{cases} D^0_{5,S} e^{\alpha_{5,S} \frac{C^0_{2,S} - C_{2,S}}{C^0_{2,S}}} & \text{in } S, \\ D_d & \text{in } V. \end{cases} \tag{17}$$

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 (14) defined by the variational problem:
Find $(C^*, C) \in \Big(L^2(0,T;H^1(S))\Big)^4 \times L^2(0,T;H^1(S\cup V))$ such that $\frac{\partial C^*}{\partial t} \in \Big(L^2(0,T;L^2(S))\Big)^4$ and $\frac{\partial C}{\partial t} \in L^2(0,T;L^2(S\cup V))$ and

$$\begin{cases} \sum_{m=1}^{4}\Big(\frac{\partial C_{m,S}}{\partial t}(t), v_m\Big)_S + \Big(\frac{\partial C}{\partial t}(t), w\Big)_{S\cup V} = -\sum_{m=1}^{4}\Big(D_{m,S}\nabla C_{m,S}(t), \nabla v_m\Big)_S \\ \qquad -\Big(D\nabla C(t), \nabla w\Big)_{S\cup V} + \sum_{m=1}^{4}\Big(F_m(C^*(t)), v_m\Big)_S \\ \qquad +\gamma_{1,S}\Big(1 - C_{1,S}(t), v_1\Big)_{\Gamma_2\cup\Gamma_3} - \sum_{m=2}^{4}\gamma_{m,S}\Big(C_{m,S}(t), v_m\Big)_{\Gamma_2\cup\Gamma_3} \\ \qquad -\Big(\gamma C(t), w\Big)_{\Gamma} \\ \qquad \text{a.e. in } (0,T), \text{ for all } (v_1,\dots,v_4) \in \prod_{m=1}^{4} H^1(S), w \in H^1(S\cup V), \\ C_{i,S}(0) = 0,\ i = 1,3,4, \\ C_{i,S}(0) = 1,\ i = 2,5, \\ C_d(0) = 0. \end{cases} \tag{18}$$

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 (18). We start to study the energy functional

$$\begin{aligned} \mathcal{E}_\nabla(t) &= \sum_{m=1}^{4}\Big(\Big\|C_{m,S}(t)\Big\|^2_{L^2(S)} + 2\int_0^t \Big\|\sqrt{\mathcal{D}_{m,S}}\nabla C_{m,S}(s)\Big\|^2_{L^2(S)} ds\Big) + \Big\|C(t)\Big\|^2_{L^2(S\cup V)} \\ &\quad +2\int_0^t \Big\|\sqrt{D}\nabla C(s)\Big\|^2_{L^2(S\cup V)} ds,\ t\in[0,T] \end{aligned} \tag{19}$$

Theorem 1. *If* $(C^*, C) \in \Big(L^2(0,T;H^1(S))\Big)^4 \times L^2(0,T;H^1(S\cup V))$ *in which* $\frac{\partial C^*}{\partial t} \in \Big(L^2(0,T;L^2(S))\Big)^4$ *and* $\frac{\partial C}{\partial t} \in L^2(0,T;L^2(S\cup V))$, *is a solution of the variational problem* (18) *such that* $C_{m,S}(t) \in H^2(S)$, $m = 1,\dots,4$, *then there exists a positive constant* $\mathcal{K}(\|C^*\|_{L^\infty(L^\infty)})$ *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*

$$\mathcal{E}_\nabla(t) \leq e^{2\mathcal{K}(\|C_*\|_{L^\infty(L^\infty)})t}\mathcal{E}_\nabla(0) + \frac{\gamma_{1,S}}{4\mathcal{K}(\|C_*\|_{L^\infty(L^\infty)})}\Big|\Gamma_2 \cup \Gamma_3\Big|\Big(e^{2\mathcal{K}(\|C_*\|_{L^\infty(L^\infty)})t} - 1\Big),\ t \in [0,T], \quad (20)$$

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

Proof: Taking in (18), $v_m = C_{m,S}(t)$ and $w = C(t)$ we obtain

$$\begin{aligned} \tfrac{1}{2}\tfrac{d}{dt}\mathcal{E}_\nabla(t) \ &\leq \sum_{m=1}^{4}\Big(F_m(C^*(t)), C_{m,S}(t)\Big)_S + \gamma_{1,S}\Big(1 - C_{1,S}(t), C_{1,S}(t)\Big)_{\Gamma_2\cup\Gamma_3} \\ &\quad -\sum_{m=2}^{4}\gamma_{m,S}\Big\|C_{m,S}(t)\Big\|_{L^2(\Gamma_2\cup\Gamma_3)} - \gamma\Big\|C(t)\Big\|_{L^2(\Gamma)} \end{aligned} \quad (21)$$

that leads to

$$\tfrac{1}{2}\tfrac{d}{dt}\mathcal{E}_\nabla(t) \leq \sum_{m=1}^{4}\Big(F_m(C^*(t)), C_{m,S}(t)\Big)_S + \tfrac{\gamma_{1,S}}{4}\Big|\Gamma_2 \cup \Gamma_3\Big|. \quad (22)$$

As $H^2(S)$ is embedded in the space of continuous bounded functions in S, $C_B^0(S)$ [1], it can be shown that there exists a positive constant $\mathcal{K}(\|C_*\|_{L^\infty(L^\infty)})$ that depends on $\|C_*\|_{L^\infty(L^\infty)} = \max\limits_{m=1,\ldots,4} \|C_{m,S}\|_{L^\infty(L^\infty)}$ such that

$$\sum_{m=1}^{4}\Big(F_m(C^*(t)), C_{m,S}(t)\Big)_S \leq \mathcal{K}(\|C_*\|_{L^\infty(L^\infty)})\sum_{m=1}^{4}\Big\|C_{m,S}(t)\Big\|^2_{L^2(S)} \quad (23)$$

Inequality (22) leads to the differential inequality

$$\tfrac{d}{dt}\mathcal{E}_\nabla(t) \leq 2\mathcal{K}(\|C_*\|_{L^\infty(L^\infty)}\mathcal{E}_\nabla(t) + \tfrac{\gamma_{1,S}}{2}\Big|\Gamma_2 \cup \Gamma_3\Big|.$$

and consequently we deduce (20) ■

In (20), $\mathcal{E}_\nabla(0)$ is the initial mass of the materials which is twice of the stent area.
In order to simplify the presentation, we assume in what follows that diffusion coefficients $\mathcal{D}_m,\ m = 1,\ldots,5$ are constant. To study the stability of the initial value problem (18) we need to consider two solutions $\mathcal{C} = (C^*, C)$ and $\tilde{\mathcal{C}} = (\tilde{C}^*, \tilde{C})$ with different initial conditions $\mathcal{C}(0)$ and $\tilde{\mathcal{C}}(0)$, respectively, and

we need to establish

$$\left\|C^*(t)-\tilde{C}^*(t)\right\|^2_{L^2(S)} + \left\|C(t)-\tilde{C}(t)\right\|^2_{L^2(S\cup V)} \leq B(t)\Big(\left\|C^*(0)-\tilde{C}^*(0)\right\|^2_{L^2(S)} + \left\|C(0)-\tilde{C}(0)\right\|^2_{L^2(S\cup V)}\Big),\ t\in[0,T], \tag{24}$$

where $B(t)$ must be bounded in time. To establish the last inequality for a system of quasi-linear diffusion-reaction equations it is sufficient to assume that the reaction term has bounded partial derivatives. In our case is not possible to use these arguments because we aren't able to establish such bound. To gain some insight on the stability behaviour of the of the initial value problem (18) we study in what follows the stability of the linearization of (18) in the solution of this problem. Taking $\mathcal{C} = (C^*, C)$, system of equations $(2)-(6)$ can be rewritten in the following form

$$\begin{cases} \dfrac{d\mathcal{C}}{dt}(t) = \mathbb{F}(\mathcal{C}(t)),\ t>0, \\ \mathcal{C}(0) \text{ is given,} \end{cases} \tag{25}$$

where $\mathbb{F}(\mathcal{C}(t)) = (\mathbb{F}_m(\mathcal{C}(t)))_{m=1,\dots,5}$,

$$\begin{cases} \mathbb{F}_m(\mathcal{C}(t)) = \nabla.\big(\mathcal{D}_m\nabla C_m(t)\big) + F_m(C^*(t)),\ m=1,\dots,4, \\ \mathbb{F}_5(\mathcal{C}(t)) = \nabla.\big(\mathcal{D}\nabla C(t)\big), \end{cases}$$

and $F_m(C^*(t)), m=1,\dots,4$, are defined by $(3)-(4)$. In (25) we consider $\mathbb{F}$ with domain $\left\{v\in\big(H^2(S)\big)^4\times H^2(S\cup V):\ v \text{ satisfies } (14)\right\}$.

The linearization of the initial value problem (25) in $\mathcal{C}$ can be written in the following form

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

where $\mathbb{L}\tilde{\mathcal{C}}(t) = (\mathbb{L}_m\tilde{\mathcal{C}}(t))_{m=1,\dots,5}$ with domain $\left\{v\in\big(H^2(S)\big)^4\times H^2(S\cup V):\ v \text{ satisfies } (14)\right\}$. is defined by

$$\mathbb{L}_m\tilde{\mathcal{C}}(t) = \nabla.\big(\mathcal{D}_m\nabla\tilde{C}_m(t)\big) + \mathbb{F}_{J,m}(\mathcal{C}(t))\tilde{\mathcal{C}}(t)$$

and

$$\mathbb{F}_{J,m}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) = \begin{cases} -\sum\limits_{i=1,2} \mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & \text{m=1} \\ -\mathcal{F}_{J,1}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & \text{m=2} \\ \sum\limits_{i=1,2} (-1)^{i-1}\mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & \text{m=3} \\ \sum\limits_{i=1,2} \mathcal{F}_{J,i}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & \text{m=4} \\ 0 & \text{m=5.} \end{cases} \tag{27}$$

In (27), $\mathcal{F}_{J,1}(\mathcal{C}(t))\tilde{\mathcal{C}}(t)$ and $\mathcal{F}_{J,2}(\mathcal{C}(t))\tilde{\mathcal{C}}(t)$ are defined by

$$\begin{cases} \mathcal{F}_{J,1}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & = \kappa_1 C_{2,S}(t)(1+\alpha C_{4,S}(t))\tilde{C}_{1,S}(t) + \kappa_1 C_{1,S}(t)(1+\alpha C_{4,S}(t))\tilde{C}_{2,S}(t) \\ & \quad +\kappa_1\alpha C_{1,S}(t)C_{2,S}(t)\tilde{C}_{4,S}(t), \\ \mathcal{F}_{J,2}(\mathcal{C}(t))\tilde{\mathcal{C}}(t) & = \kappa_2 C_{3,S}(t)(1+\beta C_{4,S}(t))\tilde{C}_{1,S}(t) + \kappa_2 C_{1,S}(t)(1+\beta C_{4,S}(t))\tilde{C}_{3,S}(t) \\ & \quad +\kappa_2\beta C_{1,S}(t)C_{3,S}(t)\tilde{C}_{4,S}(t). \end{cases} \tag{28}$$

Let $\tilde{\mathcal{C}}$ and $\tilde{\tilde{\mathcal{C}}}$ in $\left(L^2(0,T;H^1(S))\right)^4 \times L^2(0,T;H^1(S\cup V))$ in which $\frac{\partial C^*}{\partial t} \in \left(L^2(0,T;L^2(S))\right)^4$ and $\frac{\partial C}{\partial t} \in L^2(0,T;L^2(S\cup V))$, be solutions of the variational problem associated with the initial value problem (26) corresponding to (18), with initial conditions $\tilde{\mathcal{C}}(0)$ and $\tilde{\tilde{\mathcal{C}}}(0)$.
We establish in what follows an upper bound for $\mathcal{E}_W(t)$ defined by

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

where $W = \tilde{\mathcal{C}} - \tilde{\tilde{\mathcal{C}}}$.
It can be shown that

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

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

$$\frac{d}{dt}\mathcal{E}_W(t) \leq \mathcal{K}(\|C^*\|_{L^\infty(L^\infty)})\mathcal{E}_W(t),\ t>0.$$

This inequality leads to

$$\mathcal{E}_W(t) \leq e^{\mathcal{K}(\|C^*\|_{L^\infty(L^\infty)})t}\mathcal{E}_W(0), \tag{29}$$

which allow us to conclude the stability of the linearization of (18).

5. Finite dimensional approximation

To define a finite dimensional approximation for the solution of (18) we fixe $h > 0$ and we introduce in $S \cup V$ an admissible triangulation $\mathcal{T}_h$, depending on $h > 0$, such that the correspondent admissible triangulations induced in S and V, respectively $\mathcal{T}_{h_S}$ and $\mathcal{T}_{h_V}$, are compatible on Γ_4.

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 (18), we introduce the finite dimensional spaces

$$\mathcal{P}_Q^m = \left\{ u \in C^0(\bar{Q}) \cap H^1(\bar{Q}) : u\big|_\Delta = P_m,\ \Delta \in \mathcal{T}_{h_Q}, u \text{ satisfies boundary conditions } \right\},$$

where $Q = S, S \cup V$ and P_m denotes a polynomial in the space variables with degree at most m.

Let $C_h^* = (C_{h_{1,S}}, C_{h_{2,S}}, C_{h_{3,S}}, C_{h_{4,S}})$ and

$$C_h = \begin{cases} C_{h_{5,S}} & \text{in } S, \\ C_{h_d} & \text{in } V, \end{cases} \tag{30}$$

The Ritz-Galerkin approximation $\mathcal{C}_h = (C_h^*, C_h)$ for the weak solution $\mathcal{C} = (C^*, C)$ defined by (18), is computed solving the following variational problem:

Find $(C_h^*, C_h) \in \left(L^2(0,T; H^1(S)) \right)^4 \times L^2(0,T; H^1(S \cup V))$ such that $\frac{\partial C_h^*}{\partial t} \in$

$\left(L^2(0,T;L^2(S))\right)^4$ and $\frac{\partial C_h}{\partial t} \in L^2(0,T;L^2(S\cup V))$ and

$$
\begin{cases}
\displaystyle\sum_{m=1}^{4}\left(\frac{\partial C_{h_{m,S}}}{\partial t}(t), v_{h_m}\right)_S + \left(\frac{\partial C_h}{\partial t}(t), w_h\right)_{S\cup V} = -\sum_{m=1}^{4}\left(D_{h_{m,S}}\nabla C_{h_{m,S}}(t), \nabla v_{h_m}\right)_S \\
\qquad -\left(D\nabla C_h(t), \nabla w_h\right)_{S\cup V} + \displaystyle\sum_{m=1}^{4}\left(F_m(C_h^*(t)), v_{h_m}\right)_S \\
\qquad +\gamma_{1,s}\left(1 - C_{h_{1,S}}(t), v_{h_1}\right)_{\Gamma_2\cup\Gamma_3} - \displaystyle\sum_{m=2}^{4}\gamma_{m,S}\left(C_{h_{m,S}}(t), v_{h_m}\right)_{\Gamma_2\cup\Gamma_3} \\
\qquad -\left(\gamma C_h(t), w_h\right)_{\Gamma} \\
\qquad \text{in } (0,T], \text{ for all } (v_{h_1},\ldots,v_{h_4}) \in \displaystyle\prod_{m=1}^{4}\mathcal{P}_S^m, \text{ and } w_h \in \mathcal{P}_{S\cup V}^m \\
C_{h_{i,S}}(0) = 0,\ i = 1,3,4, \\
C_{h_{i,S}}(0) = 1,\ i = 2,5, \\
C_{h_d}(0) = 0.
\end{cases}
\tag{31}
$$

In (31), we consider $D_{h_{m,s}} = D^0_{m,s} e^{\alpha_{m,S}\frac{C^0_{2,S} - C_{h_{2,S}}(t)}{C^0_{2,S}}}$ for $m = 1,\ldots,4$, and

$$
D_h = \begin{cases} D^0_{5,S} e^{\alpha_{5,S}\frac{C^0_{2,S} - C_{h_{2,S}}(t)}{C^0_{2,S}}} & \text{in } S, \\ D_d & \text{in } V. \end{cases}
$$

Following the proof of Theorem 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 (20). Moreover, for the linearization of (31) in its solution of $\mathcal{C}_h = (C_h^*, C_h)$ it can be shown an inequality analogous to (29).

6. Numerical Experiments

In this section, we analyse the material behavior and influence of parameters of the model in the release rate.
All experiments have been done with open source partial differential equation solver freeFEM++ with a maximum number of mesh elements n=150 and using IMEX backward integrator with $\Delta t = 10^{-3}$. Several choices of finite element spaces can be made, but we consider here the piecewise linear finite element space $P1$. In Figure 3, we plot the drug distribution in the stent and vessel wall after 6 hours, 1 day, 7 and 14 days using parameters of Table 1. When the drug reaches Γ_7 it crosses to another layer as described by Robin boundary conditions (12). We compute the fraction of the masses retained

Parameter	Value	Parameter	Value
L_{x_S}	7×10^{-4}	L_{x_V}	9×10^{-4}
L_{y_S}	1×10^{-4}	L_{y_V}	2×10^{-4}
$\gamma_{m,S}$,γ_d	10^5	γ_b	10^{10}
κ_1	1×10^{-6}	α	1
κ_2	1×10^{-8}	β	10
$D^0_{1,S}$	5×10^{-7}	$D^0_{2,S}$	1×10^{-15}
$D^0_{3,S}$	5×10^{-12}	$D^0_{4,S}$	3×10^{-12}
$D^0_{5,S}$	2×10^{-8}	D_d	5×10^{-8}

TABLE 1. Parameters of the model in the drug eluting stent and vessel wall

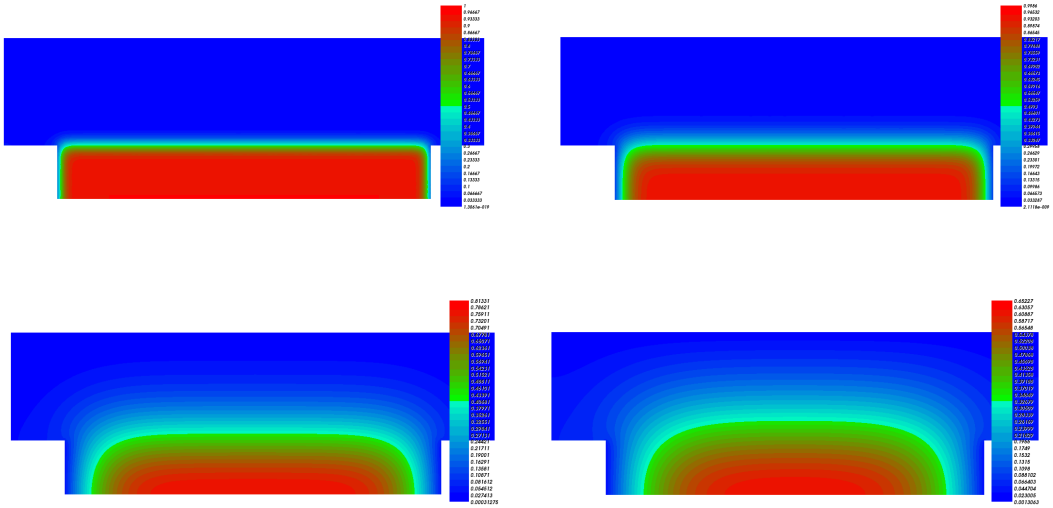

FIGURE 3. Drug distribution in the coating and the vessel wall after 6 hours (up-left), 1 day (up-right),7 (down-left) and 14 days (down-right)

in the coating and also drug in the vessel wall by

$$\begin{aligned} \rho_{m,S}(t) &= \frac{1}{|S|}\int_{-L_{y_S}}^{L_{y_S}}\int_{0}^{L_{x_S}} C_{m,S}(t)dxdy, \ m = 1,\dots,5, \\ \rho_d(t) &= \frac{1}{|V|}\int_{-L_{y_V}}^{L_{y_V}}\int_{0}^{L_{x_V}} C_d(t)dxdy, \end{aligned} \tag{32}$$

where $|S|$ and $|V|$ represent the measure of S and V respectively. In Figure 4, 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. It is observed in Figure 4 (a) that small diffusion coefficient will increase accumulation of the drug in

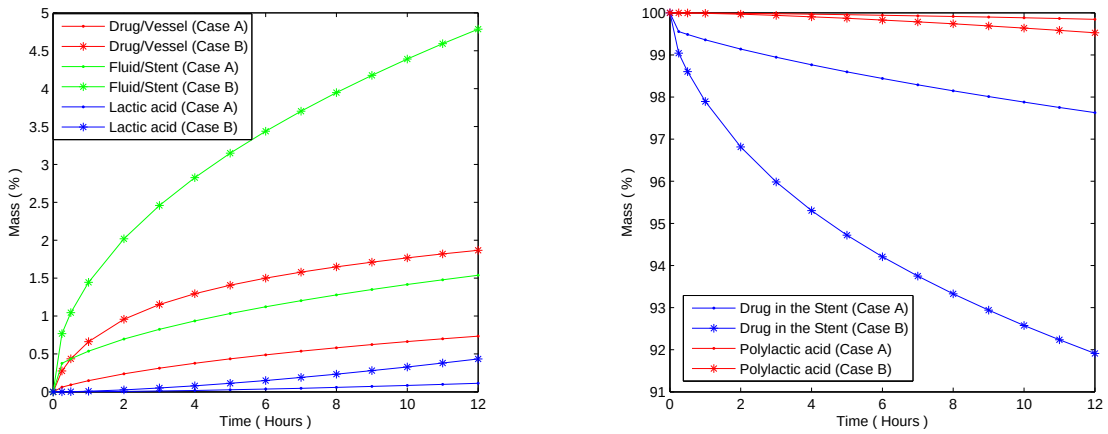

FIGURE 4. (a), left: Mass of Drug in the Vessel wall, Fluid and lactic acid in the stent, (b), right: Mass of Drug and PLA in the stent, $D_{1,S} = 5\times10^{-8}, D_{5,S} = 2\times10^{-9}, D_d = 5\times10^{-9}$ (Case A) and $D_{1,S} = 5\times10^{-7}, D_{5,S} = 2\times10^{-8}, D_d = 5\times10^{-8}$ (Case B)

α and β	Fluid	PLA	Oligomer	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 2. Mass of the fliud, PLA, oligomers and lactic acid in the coating using data of Table 1 by manipulating α and β at the first day

the vessel wall resulting in higher drug resistance time and also will increase the value of fluid and lactic acid in the stent. In Figure 4 (b), an increment in the PLA degradation and also drug release are observed by decaying the diffusion coefficients of drug and fluid. In Figure 5 (left), we exhibit the fluid penetration into the coated stent. we observe that the fluid is penetrating into the PLA increasingly during the time till it reaches a steady state level. In Figure 5 (right), the degradation of PLA into smaller particles, released into the blood artery is shown. It is assumed that the penetration of the PLA and also its products, oligomer and lactic acid, into the vessel wall are negligible. There is a good agreement between fluid's penetration into the polymer and surface errosion of PLA in the stent.

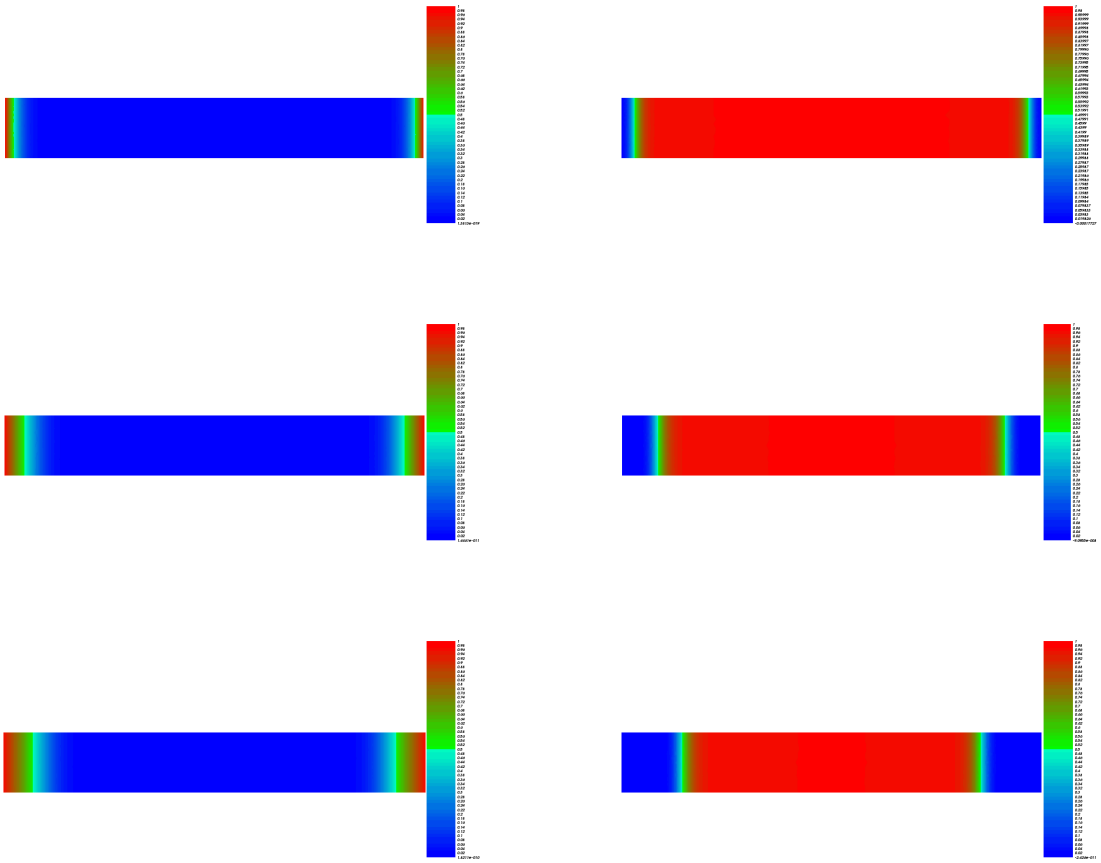

FIGURE 5. Fluid penetration (left) and PLA degradation (right) after 1 day, 7 and 14 days

Table 2 shows the effect of the autocatalysis coefficients on the degradation of the polymer. As it can be observed, the polymer degrades a bit faster at higher values of the autocatalysis coefficients α and the amount of oligomer and lactic acid are also influenced by α. The mass does not seems very sensitive to changes in β.

Figure 6 shows the influence of reaction rates on the release process. In Figure 6 (a) we observe that when the reaction rate κ_1 is decreased, more accumulated fluid in the stent will be obtained. A little increment will also happen when we decrease κ_2. As it is seen in Figure 6 (b), when we decrease the value of reaction rates κ_1 and κ_2, we will have some reduction in lactic acid production.

Figures 6 $(c) - (e)$ indicate that the changes in κ_2 does not have any effect on

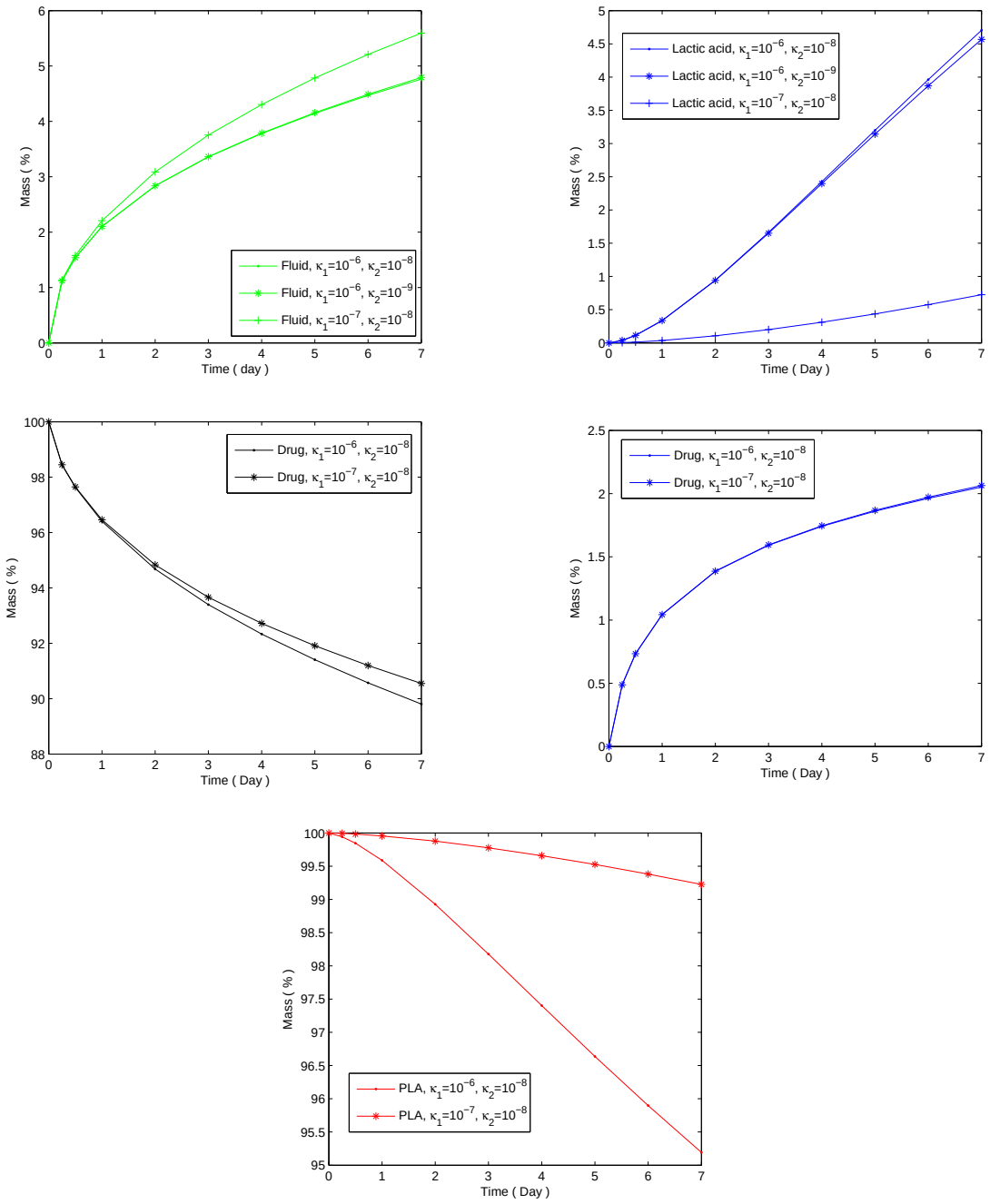

FIGURE 6. Mass of particles during 7 days with different reaction rates, (a), up-left: Mass of fluid in the stent, (b), up-right: Mass of lactic acid in the stent, (c), down-left: Mass of Drug in the stent, (d), down-right: Mass of Drug in the vessel wall, (e), down: Mass of PLA in the stent

the value of drug in the stent and vessel wall and also on the degradation of PLA, whereas decrement of κ_1 will decelerate the speed of drug release and

PLA degradation in the stent and will accelerate a bit the speed of drug in the vessel wall.

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 polymer and in the artery. Even though the cardiovascular drug delivery process is not completely understood and is under influence of different biochemical and physical factors and also the complete study needs a coupling with the blood flow and the mechanics of the stent, but a simplified release model can help to figure out the phenomena in a macroscopic viewpoint.
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 smaller particles such as oligomer and lactic acid has been taken into account. The process of penetration of the liquid into biodegradable polymer as well as the process of drug diffusion into the blood and the vessel wall has been analyzed from a numerical viewpoint. The sensitivity of the model to the perturbation of the effective parameters such as diffusion coefficients, reaction rates and autocatalytic parameters are 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 from eluting stents can be obtained.

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