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## **Numerical Simulation 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. The qualitative behaviour of the model is analyzed. 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, Drug eluting stent, Coupled model*  
*MSC 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 tool 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, 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 [1, 7]. 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 [1 – 6, 8] and also [7] 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 [3 – 5], 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 [3] and an heterogenous multi-layered wall [5] 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 [6] 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 [6] 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 [6], we have completed the model with the dynamics of the drug in the arterial vessel.

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 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.

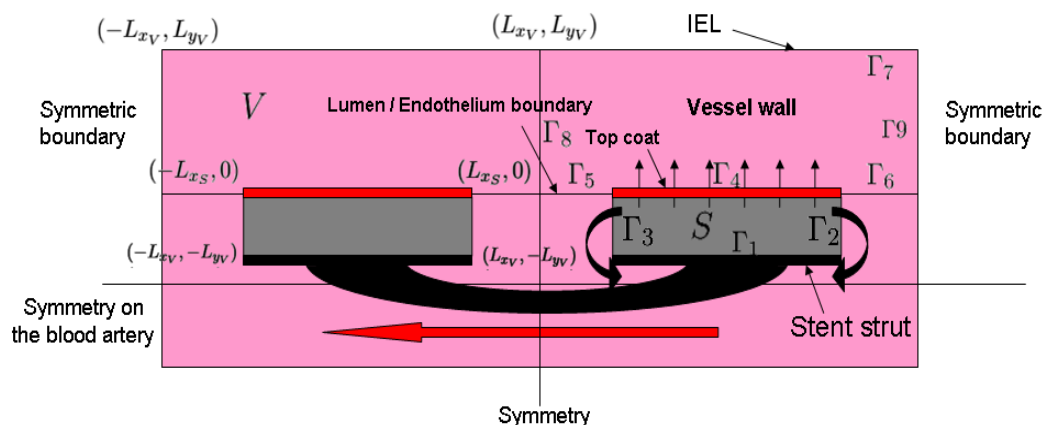
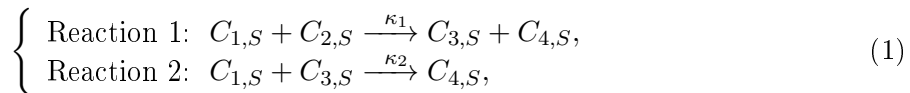


Figure 1:  $xy$ -cross section of the physical model

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,  $20K \leq M_W \leq 120K$  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



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  $\kappa_1$  and  $\kappa_2$  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

$$\frac{\partial C_{m,S}}{\partial t} = \nabla \cdot (D_{m,S} \nabla C_{m,S}) + F_m(C_{1,S}, \dots, C_{4,S}), \quad m = 1, \dots, 5 \quad (2)$$

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

$$F_m(C_{1,S}, \dots, C_{4,S}) = \begin{cases} -\sum_{i=1,2} \mathcal{F}_i(C_{1,S}, \dots, C_{4,S}) & m=1 \\ -\mathcal{F}_1(C_{1,S}, \dots, C_{4,S}) & m=2 \\ \sum_{i=1,2} (-1)^{i-1} \mathcal{F}_i(C_{1,S}, \dots, C_{4,S}) & m=3 \\ \sum_{i=1,2} \mathcal{F}_i(C_{1,S}, \dots, C_{4,S}) & m=4 \\ 0 & m=5. \end{cases} \quad (3)$$

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

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

We will simulate the model in two dimensions. Accordingly the concentration  $C_{m,S}$ ,  $m = 1, \dots, 5$  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

$$D_{m,S} = D_{m,S}^0 e^{\alpha_{m,S} \frac{C_{2,S}^0 - C_{2,S}}{C_{2,S}^0}}, \quad m = 1, \dots, 5, \quad (5)$$

where  $D_{m,S}^0$  ( $cm^2/s$ ) is the diffusivity of the respective species in the unhydrolyzed PLA and  $C_{2,S}^0$  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

$$\frac{\partial C_d}{\partial t} = \nabla \cdot (D_d \nabla C_d), \quad (6)$$

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

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

We also assume that the boundary  $\Gamma_1$  is impermeable to the materials which means no mass flux crosses it, that is

$$D_{m,S}\nabla C_{m,S}\eta_S = 0, \quad m = 1, \dots, 5 \quad \text{on } \Gamma_1. \quad (8)$$

where  $\eta_S$  is the unit exterior normal to  $\Gamma_1$ .

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  $\Gamma_2$  and  $\Gamma_3$ , the boundary conditions are defined by

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

where  $\gamma_{m,S}$ ,  $m = 1, \dots, 5$  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

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

Concentration jumps may occur at the interface  $\Gamma_4$  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  $\Gamma_4$  are represented by

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

where  $P_c$  is the permeability of the topcoat,  $\varepsilon_1$  and  $\varepsilon_2$  are the porosity of the coating and the vessel wall respectively. We have also assumed that  $\Gamma_4$  is impermeable to all other elements. In what concerns  $\Gamma_7$ , the interface layer between intima and media named IEL a *Robin* condition of type

$$D_d\nabla C_d\eta_V = -\gamma_d C_d \quad \text{on } \Gamma_7. \quad (12)$$

is considered.

In the symmetric boundary layers of the vessel wall,  $\Gamma_8$  and  $\Gamma_9$ , 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

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

where  $\gamma_b$  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  $\Gamma_5$  and  $\Gamma_6$ . 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

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

### 3 Qualitative behaviour of the total mass of the system

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

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

where  $S$  and  $V$  stand for the stent and the vessel wall domains.

As we have

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

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

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

The coupling conditions (10) lead to

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

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

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

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

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

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  $\Omega$  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  $(\cdot, \cdot)$ ,  $(\cdot, \cdot)_1$ , and  $(\cdot, \cdot)_{\partial\Omega}$ , respectively, and norms  $\|\cdot\|_{L^2(\Omega)}$  and  $\|\cdot\|_{H^1(\Omega)}$ ,  $\|\cdot\|_{L^2(\partial\Omega)}$ , respectively.

The space of functions  $v : (0, T) \rightarrow H^1(\Omega)$  such that

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

will be denoted by  $L^2(0, T; H^1(\Omega))$ .

The Hilbert space

$$\mathcal{W}_{\Omega}(0, T) = \left\{ g \in L^2(0, T; H^1(\Omega)) \text{ such that } \frac{\partial g}{\partial t} \in L^2(0, T; H^{-1}(\Omega)) \right\} \quad (15)$$

where  $H^{-1}(\Omega)$  denotes the dual of  $H^1(\Omega)$ , will be used to define the weak solution of (2) – (6) and (14).

Let  $C$ ,  $\gamma$  and  $D$  be defined by

$$C = \begin{cases} C_{5,S} & \text{in } S, \\ C_d & \text{in } V, \end{cases} \quad (16)$$

$$\gamma = \begin{cases} \gamma_{5,S} & \text{on } \Gamma_2 \cup \Gamma_3, \\ \gamma_b & \text{on } \Gamma_5 \cup \Gamma_5, \\ \gamma_d & \text{on } \Gamma_7, \end{cases} \quad (17)$$

and

$$D = \begin{cases} D_{5,S}^0 e^{\alpha_{5,S} \frac{c_{2,S}^0 - C_{2,S}}{c_{2,S}^0}} & \text{in } S, \\ D_d & \text{in } V. \end{cases} \quad (18)$$

and let  $C^* = (C_{1,S}, C_{2,S}, C_{3,S}, C_{4,S})$ .

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  $(C^*, C) \in \left( \mathcal{W}_S(0, T) \right)^4 \times \mathcal{W}_{S \cup V}(0, T)$  such that for any  $T > 0$

$$\left\{ \begin{array}{l} \sum_{m=1}^4 \left( \frac{\partial C_{m,S}}{\partial t}(t), v_m \right)_S + \left( \frac{\partial C}{\partial t}(t), w \right)_{S \cup V} = - \sum_{m=1}^4 \left( D_{m,S} \nabla C_{m,S}(t), \nabla v_m \right)_S \\ \quad - \left( D \nabla C(t), \nabla w \right)_{S \cup V} + \sum_{m=1}^4 \left( F_m(C^*(t)), v_m \right)_S + \gamma_{1,S} \left( 1 - C_{1,S}(t), v_1 \right)_{\Gamma_2 \cup \Gamma_3} \\ \quad - \sum_{m=2}^4 \gamma_{m,S} \left( C_{m,S}(t), v_m \right)_{\Gamma_2 \cup \Gamma_3} - \gamma \left( C(t), w \right)_\Gamma \\ \text{a.e. in } (0, T), \text{ for all } (v_1, \dots, v_4) \in \prod_{m=1}^4 H^1(S), w \in H^1(S \cup V), \\ C_{i,S}(0) = 0, i = 1, 3, 4 \\ C_{i,S}(0) = 1, i = 2, 5, \\ C_d(0) = 0. \end{array} \right. \quad (19)$$

## 5 Finite dimensional approximation

To define a finite dimensional approximation for the solution of (19) we fix  $h > 0$  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  $\Gamma_4$ .

To compute the semi-discrete Ritz-Galerkin counterpart  $(C_h^*, C_h)$  for the weak solution  $(C^*, C)$  defined by (19), we introduce the finite dimensional spaces

$$\mathcal{P}_Q^m = \left\{ u \in C^0(\bar{Q}) \cap H^1(\bar{Q}) : u|_\Delta = P_m, \Delta \in \mathcal{T}_{h_Q}, u \text{ satisfies (14)} \right\},$$



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

We assume that  $C_h^* = (C_{h_1,S}, C_{h_2,S}, C_{h_3,S}, C_{h_4,S})$  and  $C_h = \begin{cases} C_{h_5,S} & \text{in } S, \\ C_{h_d} & \text{in } V, \end{cases}$

Find  $(C_h^*, C_h) \in \left( \mathcal{W}_S(0, T) \right)^4 \times \mathcal{W}_{S \cup V}(0, T)$  such that for any  $T > 0$

$$\left\{ \begin{array}{l} \sum_{m=1}^4 \left( \frac{\partial C_{h_m,S}}{\partial t}(t), v_{h_m} \right)_S + \left( \frac{\partial C_h}{\partial t}(t), w_h \right)_{S \cup V} = - \sum_{m=1}^4 \left( D_{h_m,S} \nabla C_{h_m,S}(t), \nabla v_{h_m} \right)_S \\ \quad - \left( D \nabla C_h(t), \nabla w_h \right)_{S \cup V} + \sum_{m=1}^4 \left( F_m(C_h^*(t)), v_{h_m} \right)_S + \gamma_{1,S} \left( 1 - C_{h_1,S}(t), v_{h_1} \right)_{\Gamma_2 \cup \Gamma_3} \\ \quad - \sum_{m=2}^4 \gamma_{m,S} \left( C_{h_m,S}(t), v_{h_m} \right)_{\Gamma_2 \cup \Gamma_3} - \gamma \left( C_h(t), w_h \right)_\Gamma \\ \quad \text{a.e. in } [0, T], \text{ for all } (v_{h_1}, \dots, v_{h_4}) \in \prod_{m=1}^4 \mathcal{P}_S^m, \text{ and } w_h \in \mathcal{P}_{S \cup V}^m \\ C_{h_{i,S}}(0) = 0, i = 1, 3, 4 \\ C_{h_{i,S}}(0) = 1, i = 2, 5, \\ C_{h_d}(0) = 0. \end{array} \right. \quad (20)$$

In (20), the inner products are the same as before and  $D_{h_m,S} = D_{m,S}^0 e^{\alpha_{m,S} \frac{C_{2,S}^0 - C_{h_2,S}(t)}{C_{2,S}^0}}$  for  $m = 1, \dots, 4$ ,  $\gamma$  is defined by (17) and  $D = \begin{cases} D_{5,S}^0 e^{\alpha_{5,S} \frac{C_{2,S}^0 - C_{h_2,S}(t)}{C_{2,S}^0}} & \text{in } S, \\ D_d & \text{in } V. \end{cases}$

Parameter	Value	Parameter	Value
$L_{x_S}$	$7 \times 10^{-4}$	$L_{x_V}$	$9 \times 10^{-4}$
$L_{y_S}$	$1 \times 10^{-4}$	$L_{y_V}$	$2 \times 10^{-4}$
$\gamma_{m,S}, \gamma_d$	$10^5$	$\gamma_b$	$10^{10}$
$\kappa_1$	$1 \times 10^{-6}$	$\alpha$	1
$\kappa_2$	$1 \times 10^{-7}$	$\beta$	10
$D_{1,S}^0$	$5 \times 10^{-7}$	$D_{2,S}^0$	$1 \times 10^{-15}$
$D_{3,S}^0$	$5 \times 10^{-12}$	$D_{4,S}^0$	$3 \times 10^{-12}$
$D_{5,S}^0$	$1 \times 10^{-8}$	$D_d$	$2 \times 10^{-7}$

Table 1: Parameters of the model in the drug eluting stent and vessel wall

## 6 Numerical Experiments

All experiments have been done with open source partial differential equation solver freeFEM++ with a maximum number of mesh elements  $n=150$ , 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.

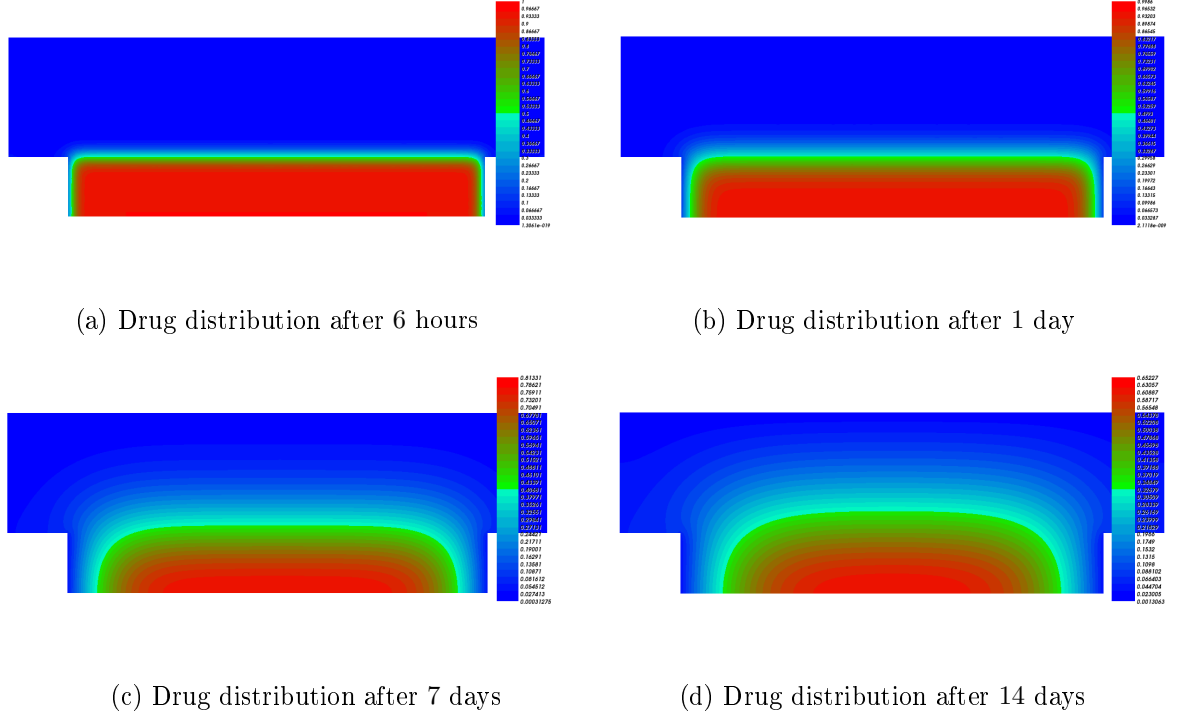


Figure 2: Drug distribution in the coating and the vessel wall after 6 hours, 1, 7 and 14 days

We compute the fraction of the masses retained in the coating and also drug in the vessel wall by

$$\begin{aligned} \rho_{m,S}(t) &= \frac{1}{|S|} \int_{-L_{yS}}^{L_{yS}} \int_0^{L_{xS}} C_{m,S}(t) dx dy, \quad m = 1, \dots, 5 \\ \rho_d(t) &= \frac{1}{|V|} \int_{-L_{yV}}^{L_{yV}} \int_0^{L_{xV}} C_d(t) dx dy. \end{aligned} \quad (21)$$

where  $|S|$  and  $|V|$  represent the measure of  $S$  and  $V$  respectively.

The numerical results obtained are in agreement with the kinetics of the problem: the drug is eluting from coating to the vessel wall, with wall concentration increasing and finally decaying in time at large time scales.

In Figure 2, the process of drug diffusion into the vessel wall and the blood artery after 6 hours, 1 day, 7 and 14 days using parameters of Table 1 is shown. When the drug reaches  $\Gamma_7$  it crosses to another layer as described by Robin boundary conditions.

Time Day:Hour	Drug (Coating)	Drug (Vessel wall)	Fluid	PLA
$t = 0s$	100	0	0	100
$t = 1h$	97.3338	1.2074	4.3221	99.9969
$t = 6h$	93.4958	2.4634	10.5708	99.9541
$t = 12h$	91.1188	3.1586	14.9292	99.8702
$t = 1d$	87.8848	4.0584	21.0495	99.6336
$t = 3d$	80.0537	6.0798	35.9577	98.1062
$t = 7d$	70.4715	7.7552	52.6751	93.3128
$t = 14d$	58.8958	8.1546	65.7553	81.7219

Table 2: Mass of the drug in the coating and vessel wall, fluid and PLA in the coating  $D_{1,S}^0 = 5 \times 10^{-7}$

Time Day:Hour	Drug (Coating)	Drug (Vessel wall)	Fluid	PLA
$t = 0s$	100	0	0	100
$t = 1h$	99.3180	0.3657	0.4376	99.9997
$t = 6h$	97.8165	0.9573	1.0605	99.9954
$t = 12h$	96.7201	1.3212	1.4963	99.9871
$t = 1d$	95.2351	1.7864	2.1091	99.9633
$t = 3d$	91.7390	2.7999	3.6138	99.8108
$t = 7d$	87.5380	3.9391	5.4055	99.3356
$t = 14d$	82.5605	5.2212	7.3438	98.1696

Table 3: Mass of the drug in the coating and vessel wall, fluid and PLA in the coating  $D_{1,S}^0 = 5 \times 10^{-8}$

In Tables 2 and 3 we exhibit the mass concentration of drug both in the coating and in the vessel wall as well as the mass concentration of the fluid and PLA in the coating computed using parameters of Table 1. In Table 2, due to a large diffusion coefficient  $C_{1,S}$ , all components diffuse very fast when compared with the results in Table 3. In Table 3, a smaller diffusion coefficient of the fluid is considered and consequently all material's concentration exhibit a slower change, leading to a delayed whole transport process. We observe that after 2 weeks, around 18 percent of the drug is released to the blood and the vessel wall whereas in Table 2 more that 41 percent is already released at the same time, which shows that the fluid diffusion coefficient has a strong impact in the penetration of the materials, specially on the release of the drug into the vessel wall. As it is expected the penetration of the fluid is also much slower than in Table 2.

## 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 in both biodegradable polymer and artery.

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 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 from eluting stents can be obtained.

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