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Modeling erosion controlled drug release and transport phenomena in the arterial tissue*

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Abstract

We introduce and analyze a model for simulating the release of a drug from a polymeric matrix into the arterial tissue, with the aim to describe the processes which occur after the implantation of a cardiovascular drug eluting stent (DES). The main processes occurring in the polymeric matrix are drug dissolution and diffusion. Moreover, surface erosion, which consists in mass loss due to the degradation of the polymeric network, is considered as well. The drug eluted from the matrix is released in the arterial wall, modelled as an homogeneous porous medium. By consequence, we assume that drug molecules are transported by diffusion and convection. Moreover, inside the tissue the reversible reaction of the drug with specific binding sites is taken into account and the coupled problem of mass transfer between matrix and tissue is formulated. It is shown that the mass conservation

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principle leads to non standard boundary coupling conditions to describe the transfer of the drug both in the solid and dissolved phases. Then, the problem at hand is solved numerically, highlighting the importance of enforcing mass conservation and focusing on the influence of the polymer erosion on the drug release profile and drug distribution in the tissue.

1 Introduction and motivations

Drug eluting stents have been a major breakthrough in the cure of vascular occlusions. Their effectiveness depends on the correct dosage of the drug, typically an anti-inflammatory and anti-proliferation agent. The first devices developed were characterized by immediate and uncontrolled drug release. As a consequence, it may happen that drug concentration approaches toxic levels for the body tissues or it falls down below the therapeutic level needed. Thus, the purpose of controlled release systems is to maintain drug concentration in the target tissue at a given value for the desired time.
The treatment of arteriosclerotic arterial diseases by DES is a widespread technique. These devices are tube-like structures which are placed into narrowed, diseased coronary arteries and expanded by balloon angioplasty [20]. They are used to restore physiological hemodynamic conditions and they release a drug to slow down cell proliferation. This prevents the abnormal growth of the arterial wall, which could block the stented artery again, a process called restenosis. The structure of a DES is covered by a polymeric layer (coating) or it contains honeycombed elements with an inlaid polymer whose role is to release the drug with a prescribed kinetics.
The drug elution from pharmaceutical polymeric systems involves multiple steps due to different physical and chemical phenomena. The porous network that contains the drug is called "matrix". Matrices can be classified according to their chemical properties, as hydrophilic or hydrophobic, and may have different physical characteristics. During the preparation, the drug is embedded in the polymeric matrix in form of solid microcrystals, nanocrystals or amorphus phase and, after dissolution it diffuses through the matrix. The polymeric matrix itself can erode. With erosion we identify the mass loss that follows the degradation of the polymeric chains. The erosion process can be classified as surface erosion or bulk erosion. In the former, only the outer parts of the matrix are affected by erosion while in the latter the phenomenon takes place also inside the matrix. The bulk or surface eroding properties of the matrix depend on the diffusion rate of the solution (water or physiological solution in a laboratory, blood plasma with an in-vivo situation) and on the relative polymeric chain distribution of the matrix system [32]. The erosion phenomena are usually investigated by empirical models [28] or by simulations employing Monte Carlo techniques [11]. In this work we consider only the surface erosion, which is desirable since it allows a better control of the release process manipulating the degradation rate by changing the surface area, while water labile drugs are

protected within the inner parts of the device [30]. We will however consider the erosion rate to be known a priori, as this quantity can be easily inferred from experiments.
The surrounding medium also plays an important role in the definition of the pattern of drug release. We consider a general model for mass transfer through the arterial tissue, modeled as an homogenous media, consisting of an advection, diffusion reaction system of equations. Such model, proposed in [27], has already been applied to computational studies about drug release from stents [2, 31]. The purpose of this work is to generalize previous works by describing the release into the tissue from an eroding matrix in which solid drug dissolution is considered.

To fulfill these tasks in section 2, we present the general setting of our mathematical model. At first, we introduce the drug diffusion and dissolution model in an eroding matrix. This requires the reformulation on a moving boundary domain of a classical dissolution problem. Then, the tissue model and the formulation of the complete drug mass transfer problem is outlined. In section 3, we derive the coupling conditions between tissue and matrix. The drug transfer conditions between the two domains are obtained by imposing the principle of mass conservation for a closed system. In the following section the particular case of a non eroding coupled problem is analyzed in order to highlight the behavior of the solution of the problem. In section 4 we provide some numerical results focusing on the specific application of drug eluting stents. Finally, in section 5, we discuss the relevance of the proposed models and the possible extension to some more realistic settings.

2 The mathematical model

The aim of our mathematical model is to describe drug release from a drug eluting stent into the arterial wall. We focus on devices where the drug eluting agent is a polymeric matrix filled with drug. Thus, we need a suitable model for the dynamics of the drug transport both in the polymeric matrix and in the tissue. Even if our target application are DES, great part of this work can be extended to other medical devices, such as coated bone implants [15].
Let us describe the geometry of the deployed stent inside the wall. The presence of the plaque is neglected and the device is embedded in the tissue Fig.1-left. This is a simplification with respect to the complex dynamics of tissue healing and regrowth that takes place after the implantation of the stent. Even if the problem can be analyzed in a three dimensional setting [31], for the sake of simplicity, we restrict the present analysis to a two dimensional geometry. In particular we consider a transversal cross section of the artery containing a fixed number of struts, as shown in Fig.1-right. We also neglect the metallic part of the struts. In practice, this corresponds to consider a completely degradable

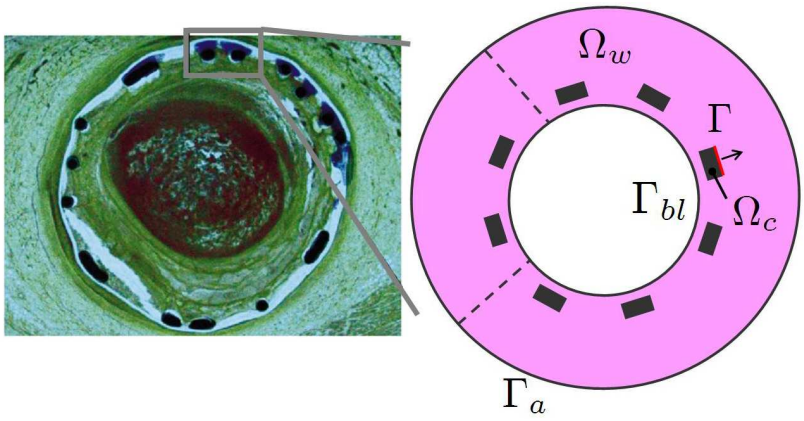


Figure 1: *Section of the artery with the implanted stent on the left. Schematic representation of the two dimensional computational domain on the right. The dark areas represent stent elements, the* Ω_c *domains. The mass transport takes place through the boundary* Γ. *The remaining colored region represents the tissue,* Ω_w.

device [8] or one of reservoir type [3]. Yet, the analysis can be readily extended to different stent designs.
We denote by Ω_w the tissue domain and with Ω_c the polymeric elements and we assume that Ω_c is embedded into Ω_w, that is $\Omega_c \subset\subset \Omega_w$ and each subregion features a regular boundary, precisely $\partial\Omega_c$ and $\partial\Omega_w$ are of class $C^{1+\epsilon}$ with $\epsilon \in (0,1)$, such that linear parabolic equations on $\Omega_c \times [0,T)$, $\Omega_w \times [0,T)$ feature strong solutions. In particular we denote with Γ_a the outer layer of the arterial wall and with Γ_{bl} the luminal surface, see Fig.1-right. The polymer erosion takes place through Γ which consists on a measurable non empty subset of the entire boundary of Ω_c.

We start focusing on the coating side. Diffusion controlled drug release is significantly dependent on the structure of the delivery system. The main phenomena we consider are the dissolution, which is the process where the drug dissolves from its solid phase, and the diffusion of the dissolved drug molecules. In particular, the basic step of the dissolution is the reaction at the liquid-solid interface and depends mainly on the uptake of dissolution medium inside the material, and on the kinetic rate of drug dissolution. We add to this model the description of surface erosion. Since the erosion process is confined to the boundary of Ω_c, the dimension of the slab gradually decreases whereas the average polymer molecular weight does not change appreciably. Of course this is an idealization, since in reality some solvent penetrates into the matrix network and a more realistic approach would require to define the dependence on some factors such as pH, the hydrophobicity and composition of the polymer, and even the hydrophobicity of the drug that sometimes affects the rate of water uptake [7].

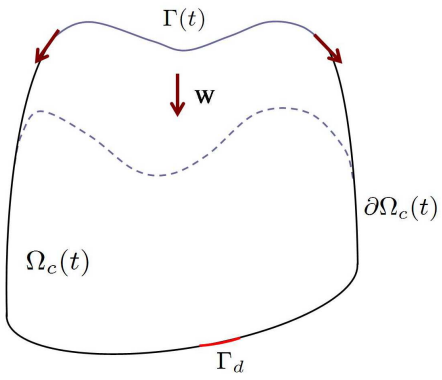


Figure 2: *Schematization of the surface erosion problem. The moving boundary* $\Gamma(t)$ *slides on* $\partial\Omega_c\backslash\Gamma(t)$ *with velocity* $\mathbf{w}$*.*

However, if the rate of water absorption is low compared to the polymeric chains degradation kinetics the hypothesis of a pure surface erosion is reasonable.
In our model, the rate of movement of the release boundary of the polymeric material is prescribed. More precisely, the model we present is applicable to any convex domain $\Omega_c(t)$ under suitable hypothesis on the vector field describing the erosion rate. This velocity field denoted by $\mathbf{w}$ has to be a Hölder continuous function in $\Omega_c(t)$, $\mathbf{w} \in C^\epsilon(\Omega_c(t))$ with $\epsilon \in (0,1)$. This ensures that the boundary $\partial\Omega_c(t)$ is maintained regular when it flows along the field $\mathbf{w}$, provided that $\partial\Omega_c(t)$ is regular i.e. $\partial\Omega_c(0)$ is of class $C^{1+\epsilon}$. Moreover, in order to describe a regressing/eroding solid domain we require $\mathrm{w}_n(t) \equiv \mathbf{w}\cdot\mathbf{n}_c(t) \leq 0$, $\mathbf{n}_c(t)$ being the outward normal vector on the boundary of $\Omega_c(t)$. In our particular case the domain can be partitioned in two parts. Referring to Fig.2, $\Gamma(t)$ is the moving boundary, while on $\partial\Omega_c(t) \setminus \Gamma(t)$, we require $\mathrm{w}_n(t) = 0$. The tangential component is defined as $\mathrm{w}_\tau(t) = \mathbf{w}\cdot\boldsymbol{\tau}(t)$, where $\boldsymbol{\tau}(t)$ is the tangential vector on the boundary. We require,

$$\mathrm{w}_\tau(t) \in C^\epsilon(\partial\Omega_c(t) \setminus \Gamma_d), \quad \text{and} \quad \mathrm{w}_\tau \mid_{\Gamma_d} = 0,$$

Γ_d being part of the boundary or at least a point (set of zero measure), $\Gamma_d \subseteq \partial\Omega_c(t) \setminus \Gamma$.
The simplest way to describe the drug release from this type of system is the second Fick's law with additional terms to account for dissolution [12]. The Higuchi model [13, 14] is frequently used to describe the drug release. It considers the dissolution as an instantaneous process for matrices of different shape (slabs, spheres) when the initial drug concentration stored in the device, c_0, is considerably higher than the drug solubility, c_s. An analytical solution can be obtained, see [5], under the hypothesis of perfect sink condition, $c = 0$ on the release boundary, meaning that the external resistance to mass transfer is negligible. The Higuchi's model is appropriate to describe the release at early time and for non-degrading matrices as verified by experimental results.

In our work we use a more general model that extends Higuchi's results to more complex situations. It accounts for the kinetic of the dissolution as a distinct process with respect to diffusion [9]. It is obtained by imposing a conservation law for the dissolved phase c,

$$\frac{\partial c}{\partial t} + \nabla \cdot \mathrm{j} = R,$$

where $\mathrm{j}(\mathbf{x}, t)$ is the diffusive flux and $R(\mathbf{x}, t)$ is a source term accounting for the solid phase dissolution. The latter is modeled using a reformulation of the empirical Noyes-Whitney equation [21]. Thus, we find a system of two equations which describes the evolution of both the solid and dissolved drug, s and c respectively, as proposed in [9]. The model reads,

$$\begin{aligned} &\frac{\partial c}{\partial t} - \nabla \cdot (D_c \nabla c) = k_d s^{2/3}(c_s - c), && \text{in } \ \Omega_c(t) \times (0, T], \\ &\frac{\partial s}{\partial t} = -k_d s^{2/3}(c_s - c), && \text{in } \ \Omega_c(t) \times (0, T], \\ &s = s_0, \ c = c_0, && \text{in } \ \Omega_c(0), \end{aligned} \tag{1}$$

where s_0 and c_0 are the initial values of the solid and dissolved drug concentrations respectively. The first is a diffusion reaction equation, D_c being the diffusivity of the dissolved drug in the matrix. The second equation, an ordinary differential equation, describes the reaction of dissolution as being dependent on the solubility, c_s, and on the reaction kinetics through the dissolution rate constant k_d. We assume that the mass transfer takes place on Γ, while on the other boundary we impose no flux so that:

$$D_c \nabla c \cdot \mathbf{n}_c = 0, \qquad \text{on } \ \partial\Omega_c(t) \setminus \Gamma(t). \tag{2}$$

We focus now on the tissue surrounding the slab. We assume that the tissue follows the movement of the matrix and remains in contact with the eroding material. Thus, to formulate the complete model we make the following assumptions:

- During the erosion process the tissue boundary $\Gamma(t)$ remains in contact with the matrix eroding front. So that, we have

  $$\Omega = \Omega_c(t) \cup \Omega_w(t), \ \forall \ t \ \in (0, T].$$

  Considering that the motion of $\Omega_c(t)$ is imposed, $\Omega_w(t)$ can be recovered at each instant as $\Omega \backslash \Omega_c(t)$.

- Both the solid $s(\mathbf{x}, t)$ and dissolved $c(\mathbf{x}, t)$ concentrations are released during the erosion process. We assume that the dissolution of $s(\mathbf{x}, t)$ in the tissue is instantaneous. This assumption is confirmed for hydrophilic drugs, such as heparin [18], and can be equivalently stated saying that the solubility of the drug in the tissue is much greater than c_s.

- The degradation products of a biodegradable material are polymeric chains of lower molecular weight, called monomers or oligomers. These products are metabolized by complex enzymatic processes that depend on the nature of the polymer and on the dimensions and molecular weight of the fragments [26]. We neglect the chemical phenomena involved in the fragments digestion by the cells within the tissue, assuming they dissolve without interfering with the drug transport process.

We introduce now the tissue model defined on $\Omega_w(t)$. The complex multi-layerd structure of the arterial wall is lumped into a homogeneous porus material with averaged properties, as in [24]. We adopt the model proposed in [27] to consider the reversible nature of the bindings between the drug and specific sites inside the arterial wall. This model accounts for the different nature of the therapeutic compounds used. We can distinguish between hydrophobic drugs, which are retained within the tissue and hydrophilic ones, which are rapidly cleared compared to the former case. The reversible reaction we have considered is based on the mass action law, synthesized in (3). Bindings occur when ligand (L) and receptor (R) collide. The rate of association is k_1. When binding has occurred, ligand and receptor remain bound together for an amount of time which depends on the affinity of the receptor and ligand, thus the rate of dissociation is k_2. After dissociation, the ligand and the receptor are the same as they were before binding,

$$L \; + \; R \; \underset{k_2}{\overset{k_1}{\rightleftarrows}} \; LR. \tag{3}$$

In our particular case we identify the concentration of the ligand as that of the dissolved drug, a. The concentration of the receptors is equivalent to that of the specific free binding sites, r, where the drug attaches. The mathematical model describes the transport of the drug in the tissue with a system of advection, diffusion reaction equations. The drug assumes two different states: the dissolved and the bound state. In the former the drug moves by convection and diffusion. In the latter the drug attaches reversibly to specific sites inside the tissue, and we indicate by $b(\mathbf{x}, t)$ its concentration. We denote with $r_0(\mathbf{x})$ the initial concentration of the free binding sites in the tissue thus $r(\mathbf{x}, t)$ and $b(\mathbf{x}, t)$ are related by $b(\mathbf{x}, t) = r_0(\mathbf{x}) - r(\mathbf{x}, t)$.
The system of equations in $\Omega_w(t)$ reads,

$$\begin{aligned} &\frac{\partial a}{\partial t} + \nabla \cdot (-D_w \nabla a + \mathbf{u}_w \, a) = -k_1 a(r_0 - b) + k_2 b, \quad \text{in } \Omega_w(t), \\ &\frac{\partial b}{\partial t} = k_1 a(r_0 - b) - k_2 b, \qquad\qquad\qquad\qquad\qquad\quad \text{in } \Omega_w(t), \end{aligned} \tag{4}$$

D_w being the diffusivity of the drug in the tissue. The filtration velocity $\mathbf{u}_w$ is computed assuming that the tissue is a homogeneous porous medium [19]. Under

this hypothesis the velocity field can be computed by means of the Darcy's law of filtration reformulated on the moving domain $\Omega_w(t)$,

$$\begin{aligned} \mathbf{u}_w &= K_{fil}\nabla p, \quad \text{in } (0,T]\times\Omega_w(t), \\ \nabla\cdot\mathbf{u}_w &= 0, \qquad \text{in } (0,T]\times\Omega_w(t), \end{aligned} \tag{5}$$

$p(x,t)$ being the pressure field and K_{fil} a constant coefficient that takes into account for the permeability of the arterial tissue and the viscosity of the plasma. The equation is solved using the following set of boundary conditions:

$$\begin{aligned} &\mathbf{u}_w\cdot\mathbf{n}_w = 0, \quad \text{on } (0,T]\times\partial\Omega_w(t)\setminus\{\Gamma_{bl}\cup\Gamma_a\}, \\ &p = p_{blood}, \qquad \text{on } (0,T]\times\Gamma_{bl}, \\ &p = p_{adv}, \qquad \text{on } (0,T]\times\Gamma_a. \end{aligned} \tag{6}$$

In particular, p_{adv} and p_{blood} are the pressure at the outer layer of the tissue and at the lumen side, respectively. This pressure drop promotes the filtration of the plasma. The blood flow is pulsatile and the pressure is a function of time and position along the vessel. However, we assume p_{blood} to be the average value of pressure during a cycle of the beating heart. As it will be underlined in the section of the numerical results the filtration velocity is slow and $Pe < 1$, thus the mass transport is dominated by diffusion.
The system of equations (4) needs a set of boundary conditions on $\partial\Omega_w$, and we impose,

$$\mathbb{B}_w \begin{cases} -D_w\nabla a\cdot\mathbf{n}_w + (\mathbf{u}_w\cdot\mathbf{n}_w)a - P_w a = 0, & \text{on } (0,T]\times\Gamma_a, \\ -D_w\nabla a\cdot\mathbf{n}_w + (\mathbf{u}_w\cdot\mathbf{n}_w)a = 0, & \text{on } (0,T]\times\partial\Omega_w\setminus\{\Gamma_a\cup\Gamma_{bl}\cup\Gamma\}, \\ a = 0, & \text{on } (0,T]\times\Gamma_b, \end{cases} \tag{7}$$

$\mathbf{n}_w$ being the outward oriented normal vector on the selected arterial boundary. At the interface between the wall and the lumen we simplify the physical problem assuming that the concentration of the drug in the blood is negligible. On the adventitia layer, Γ_a, a slow outgoing flux of drug is prescribed, P_w being the permeability of the wall. Finally, we summarize our complete model as follows:

$$\begin{aligned} &\frac{\partial c}{\partial t} + \mathbb{L}_c c = f_c(c,s), \qquad \text{in } \Omega_c(t), \\ &\frac{\partial s}{\partial t} = -f_c(c,s), \qquad \text{in } \Omega_c(t), \\ &\frac{\partial a}{\partial t} + \mathbb{L}_w a = f_w(a,b), \quad \text{in } \Omega_w(t), \\ &\frac{\partial b}{\partial t} = -f_w(a,b), \qquad \text{in } \Omega_w(t), \end{aligned} \tag{8}$$

where for the sake of clarity, we have defined the non linear reaction terms as:

$$\begin{aligned} f_c(c,s) &= k_d s^{2/3}(c_s - c), && \text{in } \Omega_c(t), \\ f_w(a,b) &= -k_1 a(r_0 - b) + k_2 b, && \text{in } \Omega_w(t), \end{aligned} \tag{9}$$

and the elliptic operators as:

$$\mathbb{L}_c c := \nabla \cdot (-D_c \nabla c), \qquad \text{in } \Omega_c(t),$$

$$\mathbb{L}_w a := \nabla \cdot (-D_w \nabla a + \mathbf{u}_w\, a), \qquad \text{in } \Omega_w(t).$$

The system is completed with the set of boundary conditions (2) and (7).

3 Boundary coupling conditions

To close problem (8), we still have to add proper mass transfer interface conditions on $\Gamma(t)$. We derive the coupling conditions imposing the mass balance on a closed system to external mass transfer. Thus, for the following analysis we reformulate the boundary conditions (7) imposing no flux on Γ_a and Γ_{bl}, that reads:

$$-D_w \nabla a \cdot \mathbf{n}_w + (\mathbf{u}_w \cdot \mathbf{n}_w) a = 0, \quad \text{on } \partial\Omega_w \setminus \Gamma(t). \tag{10}$$

The total mass, $M(t)$ of our system is:

$$\int_{\Omega_c(t)} (c+s)\; d\Omega + \int_{\Omega_w(t)} (b+a)\; d\Omega = M(t). \tag{11}$$

We introduce the supplementary functions,

$$\sigma(\mathbf{x},t) = \begin{cases} s & \text{in } \Omega_c(t) \\ 0 & \text{in } \Omega \setminus\, \Omega_c(t) \end{cases}, \gamma(\mathbf{x},t) = \begin{cases} c & \text{in } \Omega_c(t) \\ 0 & \text{in } \Omega \setminus\, \Omega_c(t) \end{cases} \tag{12}$$

and

$$\alpha(\mathbf{x},t) = \begin{cases} a & \text{in } \Omega_w(t) \\ 0 & \text{in } \Omega \setminus\, \Omega_w(t) \end{cases}, \beta(\mathbf{x},t) = \begin{cases} b & \text{in } \Omega_w(t) \\ 0 & \text{in } \Omega \setminus\, \Omega_w(t) \end{cases} \tag{13}$$

Thus, the mass of the system on Ω can be rewritten as:

$$M(t) = \int_{\Omega} (\alpha + \beta + \gamma + \sigma)\; d\Omega, \tag{14}$$

and to ensure the mass conservation, we impose:

$$\frac{d}{dt} M(t) = 0. \tag{15}$$

In order to obtain the coupling condition, as a first step we sum and integrate in space equations (8):

$$\int_{\Omega_c(t)} \frac{\partial c}{\partial t}\, d\Omega + \int_{\Omega_c(t)} \frac{\partial s}{\partial t}\, d\Omega + \int_{\Omega_w(t)} \frac{\partial a}{\partial t}\, d\Omega + \int_{\Omega_w(t)} \frac{\partial b}{\partial t}\, d\Omega + \int_{\Omega_c(t)} \mathbb{L}_c c\, d\Omega + \int_{\Omega_w(t)} \mathbb{L}_w a\, d\Omega = 0. \tag{16}$$

We recall some integral relations to relate the moving domain to its representation in a moving frame of reference (Arbitrary Lagrangian Eulerian (ALE) methods, [10, 29]). Let us focus on the moving domain $\Omega_c(t)$, even though these relations are valid also for $\Omega_w(t)$. Let $\mathcal{M}_t$ be the map such that for each $t \in (0, T]$:

$$\mathcal{M}_t : \hat{\Omega}_c \subset \mathbb{R}^2 \to \Omega_c(t); \quad \mathbf{x} = \mathcal{M}_t(\mathbf{Y}). \tag{17}$$

We have denoted with $\mathbf{Y}$ a point in the reference domain $\hat{\Omega}_c$ that could be taken equal to the domain configuration at time $t = t_0$, and with $\mathbf{x}$ one in current domain $\Omega_c(t)$. With the symbol $\hat{\cdot}$ we indicate the variables defined on the reference frame. It follows from the map definition (17) that the Eulerian coordinate $\mathbf{x}$ can be defined using the coordinate $\mathbf{Y}$, i.e.:

$$\mathbf{x} = \mathbf{x}(\mathbf{Y}, t) = \mathcal{M}_t(\mathbf{Y}).$$

We assume the map to be invertible and, $\mathcal{M}_t \in C^0(\overline{\hat{\Omega}}_c)$, $\mathcal{M}_t^{-1} \in C^0(\overline{\Omega}_c(t)),\ \forall\, t > 0$. We define the domain velocity field $\mathbf{w}$ as:

$$\mathbf{w}(\mathbf{x}, t) = \left.\frac{\partial \mathbf{x}}{\partial t}\right|_{\mathbf{Y}},$$

where $\cdot|_{\mathbf{Y}}$ represents the derivative on the ALE frame. We introduce the chain rule for the derivative of a function $u :\ \Omega(t) \times (0, T] \to \mathbb{R}$:

$$\left.\frac{\partial u}{\partial t}\right|_{\mathbf{Y}} = \left.\frac{\partial u}{\partial t}\right|_{\mathbf{x}} + \left.\frac{\partial \mathbf{x}}{\partial t}\right|_{\mathbf{Y}} \cdot \nabla_{\mathbf{x}} u = \frac{\partial u}{\partial t} + \mathbf{w} \cdot \nabla_{\mathbf{x}} u. \tag{18}$$

Let $\mathcal{M}_t$ be the function to map each point into the moving domain $\Omega_c(t)$ to the reference domain $\hat{\Omega}_c$ and $\mathbf{J}_{\mathcal{M}_t}$ be the Jacobian of the transformation with $det\,(\mathbf{J}_{\mathcal{M}_t}) = J_{\mathcal{M}_t}$. We wish to find an expression for the term:

$$\frac{d}{dt} \int_{\Omega_c(t)} c\, d\Omega,$$

that appears in the mass balance equation. The following integral relation states:

$$\int_{\Omega_c(t)} \left.\frac{\partial c}{\partial t}\right|_{\mathbf{Y}} d\Omega = \int_{\hat{\Omega}_c} \frac{\partial \hat{c}}{\partial t}\, J_{\mathcal{M}_t}\, d\hat{\Omega} = \frac{d}{dt} \int_{\hat{\Omega}_c} (J_{\mathcal{M}_t} \hat{c}) d\hat{\Omega} - \int_{\hat{\Omega}_c} \frac{\partial J_{\mathcal{M}_t}}{\partial t}\, \hat{c}\, d\hat{\Omega}. \tag{19}$$

We go back to the moving domain with the inverse map $\mathcal{M}_t^{-1}$, and the following formula [1] to relate the evolution of $J_{\mathcal{M}_t}$ with the divergence of the domain velocity $\mathbf{w}$:

$$\left.\frac{\partial J_{\mathcal{M}_t}}{\partial t}\right|_{\mathbf{Y}} = J_{\mathcal{M}_t} \nabla \cdot \mathbf{w}. \tag{20}$$

We obtain,

$$\int_{\Omega_c(t)} \left.\frac{\partial c}{\partial t}\right|_{\mathbf{Y}} d\Omega = \frac{d}{dt}\int_{\Omega_c(t)} c \; d\Omega - \int_{\Omega_c(t)} c(\nabla \cdot \mathbf{w}) \; d\Omega.$$

Using relation (18) we have,

$$\int_{\Omega_c(t)} \left(\left.\frac{\partial c}{\partial t}\right|_{\mathbf{Y}} - \mathbf{w} \cdot \nabla c \right) d\Omega = \int_{\Omega_c(t)} \frac{\partial c}{\partial t} d\Omega. \tag{21}$$

Using (19), and the Gauss theorem we can write the following chain of integral relations:

$$\begin{aligned} &\int_{\Omega_c(t)} \frac{\partial c}{\partial t} d\Omega = \frac{d}{dt}\int_{\Omega_c(t)} c \; d\Omega - \int_{\Omega_c(t)} c(\nabla \cdot \mathbf{w}) \; d\Omega - \int_{\Omega_c(t)} \mathbf{w} \cdot \nabla c \; d\Omega = \\ &= \frac{d}{dt}\int_{\Omega_c(t)} c \; d\Omega - \int_{\partial\Omega_c(t)} c \; (\mathbf{w} \cdot \mathbf{n}_c) \; d\Gamma. \end{aligned} \tag{22}$$

We apply the same relation for each time derivative in (16), obtaining

$$\begin{aligned} \int_{\Omega_c(t)} \frac{\partial s}{\partial t} \; d\Omega &= \frac{d}{dt}\int_{\Omega_c(t)} s \; d\Omega - \int_{\partial\Omega_c(t)} s \; (\mathbf{w} \cdot \mathbf{n}_c) \; d\Gamma, \\ \int_{\Omega_w(t)} \frac{\partial a}{\partial t} \; d\Omega &= \frac{d}{dt}\int_{\Omega_w(t)} a \; d\Omega - \int_{\partial\Omega_w(t)} a \; (\mathbf{w} \cdot \mathbf{n}_w) \; d\Gamma, \\ \int_{\Omega_w(t)} \frac{\partial b}{\partial t} \; d\Omega &= \frac{d}{dt}\int_{\Omega_w(t)} b \; d\Omega - \int_{\partial\Omega_w(t)} b \; (\mathbf{w} \cdot \mathbf{n}_w) \; d\Gamma. \end{aligned} \tag{23}$$

Owing relations (22) and (23) equation (16) becomes:

$$\begin{aligned} &\frac{d}{dt}\int_{\Omega_c(t)} (c+s) \; d\Omega + \frac{d}{dt}\int_{\Omega_w(t)} (a+b) \; d\Omega + \int_{\Omega_c(t)} \mathbb{L}_c c \; d\Omega + \int_{\Omega_w(t)} \mathbb{L}_w a \; d\Omega = \\ &\int_{\Gamma(t)} \left(c \, (\mathbf{w} \cdot \mathbf{n}_c) + s \, (\mathbf{w} \cdot \mathbf{n}_c)\right) \; d\Gamma + \int_{\Gamma(t)} \left(a \, (\mathbf{w} \cdot \mathbf{n}_w) + b \, (\mathbf{w} \cdot \mathbf{n}_w)\right) \; d\Gamma, \end{aligned} \tag{24}$$

where the boundary integral on $\partial\Omega_c(t)$, $\partial\Omega_w(t)$ are restricted to $\Gamma(t)$, because of the definition of the field velocity $\mathbf{w}$. Imposing the continuity of the dissolved concentration on $\Gamma(t)$, we have

$$\int_{\Gamma(t)} c \; (\mathbf{w} \cdot \mathbf{n}_c) \; d\Gamma + \int_{\Gamma(t)} a \; (\mathbf{w} \cdot \mathbf{n}_w) \; d\Gamma = 0$$

as $\mathbf{n}_c = -\mathbf{n}_w$.
We proceed integrating by parts the terms containing the elliptic operators defined on $\Omega_w(t), \Omega_c(t)$. Consider the integral on $\Omega_c(t)$ and the boundary conditions (2), thus

$$\int_{\Omega_c(t)} \mathbb{L}_c c \; d\Omega = -\int_{\partial\Omega_c(t)} D_c(\nabla c \cdot \mathbf{n}_c) \; d\Omega = -\int_{\Gamma(t)} D_c(\nabla c \cdot \mathbf{n}_c) \; d\Gamma. \tag{25}$$

Under the assumption $\nabla \cdot \mathbf{u}_w = 0$ in (5), for the integral on Ω_w we have,

$$\int_{\Omega_w(t)} \mathbb{L}_w a \; d\Omega = \int_{\partial\Omega_w(t)} \left(-D_w \, \nabla a \cdot \mathbf{n}_w + a \; (\mathbf{u}_w \cdot \mathbf{n}_w)\right) \; d\Gamma,$$

and with the boundary conditions (10), the integral reduces to,

$$\int_{\Omega_w(t)} \mathbb{L}_w a d\Omega = -\int_{\Gamma(t)} D_w \; (\nabla a \cdot \mathbf{n}_w) \; d\Gamma.$$

Thus, equation (24) becomes,

$$\frac{d}{dt}\int_{\Omega_c(t)} (c+s) \; d\Omega + \frac{d}{dt}\int_{\Omega_w(t)} (a+b) \; d\Omega = \int_{\Gamma(t)} s \; (\mathbf{w} \cdot \mathbf{n}_c) \; d\Gamma$$
$$+ \int_{\Gamma(t)} b \; (\mathbf{w} \cdot \mathbf{n}_w) \; d\Gamma + \int_{\Gamma(t)} D_w(\nabla a \cdot \mathbf{n}_w) \; d\Gamma \; + \int_{\Gamma(t)} D_c(\nabla c \cdot \mathbf{n}_c) \; d\Gamma$$

In conclusion, imposing the mass conservation, (15) the coupling conditions on $\Gamma(t)$ read :

$$\begin{cases} c = a, & \text{on } (0,T] \times \Gamma(t) \\ \\ D_w(\nabla a \cdot \mathbf{n}_w) + b\,(\mathbf{w} \cdot \mathbf{n}_w) = -D_c(\nabla c \cdot \mathbf{n}_c) - s\,(\mathbf{w} \cdot \mathbf{n}_c), & \text{on } (0,T] \times \Gamma(t). \end{cases} \tag{26}$$

The first condition of (26) describes the continuity at the interface of the dissolved concentrations. The second, a Robin type condition, involves not only the dissolved drug concentrations but also the solid and bound one. The presence of the solid contribution is a clear consequence of the erosion process. Furthermore, the contribution of b is a consequence of the hypothesis we have made on the movement of the domain. In view of our applications this hypothesis is justifiable. In fact, during stent deposition, the arterial tissue is compressed by the device expansion, [19]. Thus, is reasonable to expect the tissue to decompress and fill the space made by the polymeric material reducing dimensions.

3.1 Analysis of the coupled non eroding system

The purpose of this section is to investigate the existence and uniqueness time dependent solutions of system of equations (8) when the erosion velocity is set

to zero and the equations are defined on $\Omega = \Omega_c \cup \Omega_w$. In this case the boundary conditions (26) on the interface Γ prescribes the continuity of the dissolved concentration and of its fluxes with $\mathbf{w} = 0$. The approach we follow is based on the upper and lower solutions method [22] and depends on the monotone properties of the reaction functions f_c, f_w. In order to use the results presented in [22, 23] we introduce a regularization for the non linear term f_c such that, f_c^* is a Lipschitz continuous function with respect to c and s. A possible regularization is:

$$f_c^* = \begin{cases} f_c, & \text{for } s > \epsilon, \\ -\dfrac{1}{3}\epsilon^{-4/3}s^2 + \dfrac{4}{3}\epsilon^{-1/3}s, & \text{for } s \leq \epsilon, \end{cases} \tag{27}$$

with $\epsilon \in \mathbb{R}^+, \epsilon << 1$.
We focus on the monotone property of the non linear terms $f_c^*,\ f_w$. We have,

$$\partial f_c^*/\partial c = -k_d s^{2/3}(s > \epsilon) + 0(s \leq \epsilon) \leq 0,$$
$$\partial f_c^*/\partial s = (2/3)k_d s^{-1/3}(c_s - c)(s > \epsilon) + (2/3)\epsilon^{-4/3}(2\epsilon - s)(s \leq \epsilon) \geq 0,$$

thus, the function f_c^* is monotone nondecreasing and nonincreasing to s and c respectively. Considering the non linear term defined on the tissue we have,

$$\partial f_w/\partial a = -k_1(r_0 - b) \leq 0,$$
$$\partial f_w/\partial b = k_1 a + k_2 \geq 0,$$

i.e. f_w is monotone nondecreasing in b and nonincreasing in a.
We deal with the following system of quasilinear parabolic and ordinary differential equations:

$$\begin{aligned} &\frac{\partial c}{\partial t} + \mathbb{L}_c c = f_c^*(c,s), && \text{in } \Omega_c, \\ &\frac{\partial s}{\partial t} = -f_c^*(c,s), && \text{in } \Omega_c, \\ &\frac{\partial a}{\partial t} + \mathbb{L}_w a = f_w(a,b), && \text{in } \Omega_w, \\ &\frac{\partial b}{\partial t} = -f_w(a,b), && \text{in } \Omega_w. \end{aligned} \tag{28}$$

We require that the domain Ω is open and connected, with regular boundaries. In this setting we introduce the space W defined as:

$$\begin{aligned} W(\Omega_i, T) := \quad & \{w \in C^0((0,T] \times \overline{\Omega}_i) :\ w(\cdot,t) \in C^1((0,T])\ \ \forall \mathbf{x} \in \Omega_i, \\ & w(x,\cdot) \in C^2(\Omega_i)\ \ \forall t \in (0,T]\} \end{aligned}$$

where $i = c, w$, such that the global solution $\mathbf{u} = (c, s, a, b)$ belongs to the space $\mathbf{W} = W(\Omega_c, T) \times W(\Omega_c, T) \times W(\Omega_w, T) \times W(\Omega_w, T)$.

We show the existence of a solution of the regularized problem by means of the method of upper and lower solutions which are defined as follows:

Definition 3.1 *A pair of functions* $\tilde{\boldsymbol{u}} = (\tilde{c}, \tilde{s}, \tilde{a}, \tilde{b})$, $\hat{\boldsymbol{u}} = (\hat{c}, \hat{s}, \hat{a}, \hat{b})$ *are called upper and lower solutions of (28) if* $\tilde{\boldsymbol{u}} \geq \hat{\boldsymbol{u}}$ *and if*

$$\begin{aligned}
&\frac{\partial \tilde{c}}{\partial t} + \mathbb{L}_c \tilde{c} - f_c^*(\tilde{c}, \hat{s}) \geq 0 \geq \frac{\partial \hat{c}}{\partial t} + \mathbb{L}_c \hat{c} - f_c^*(\hat{c}, \tilde{s}), && \text{in } (0,T] \times \Omega_c, \\
&\frac{\partial \tilde{s}}{\partial t} + f_c^*(\hat{c}, \tilde{s}) \geq 0 \geq \frac{\partial \hat{s}}{\partial t} + f_c^*(\tilde{c}, \hat{s}), && \text{in } (0,T] \times \Omega_c, \\
&\frac{\partial \tilde{a}}{\partial t} + \mathbb{L}_w \tilde{a} - f_w(\tilde{a}, \hat{b}) \geq 0 \geq \frac{\partial \hat{a}}{\partial t} + \mathbb{L}_w \hat{a} - f_w(\hat{a}, \tilde{b}), && \text{in } (0,T] \times \Omega_w, \\
&\frac{\partial \tilde{b}}{\partial t} + f_w(\hat{a}, \tilde{b}) \geq 0 \geq \frac{\partial \hat{b}}{\partial t} + f_w(\tilde{a}, \hat{b}), && \text{in } (0,T] \times \Omega_w,
\end{aligned} \tag{29}$$

with the boundary and initial conditions:

$$\begin{aligned}
&\tilde{c} - \tilde{a} = 0 = \hat{c} - \hat{a}, && \text{on } (0,T] \times \Gamma, \\
&D_w \nabla \tilde{a} \cdot \boldsymbol{n} - D_c \nabla \tilde{c} \cdot \boldsymbol{n} = 0 = D_w \nabla \hat{a} \cdot \boldsymbol{n} - D_c \nabla \hat{c} \cdot \boldsymbol{n}, && \text{on } (0,T] \times \Gamma, \\
&\mathbb{B}_w(\tilde{a}) \geq 0 \geq \mathbb{B}_w(\hat{a}), && \text{on } (0,T] \times \partial\Omega_w \backslash \Gamma, \\
&D_c \nabla \tilde{c} \cdot \boldsymbol{n} = 0 \geq 0 \geq D_c \nabla \hat{c} \cdot \boldsymbol{n} = 0, && \text{on } (0,T] \times \partial\Omega_c \backslash \Gamma, \\
&\tilde{a} \geq a_0 \geq \hat{a}, \;\; \tilde{b} \geq b_0 \geq \hat{b}, && \text{on } \{0\} \times \Omega_w, \\
&\tilde{c} \geq c_0 \geq \hat{c}, \;\; \tilde{s} \geq s_0 \geq \hat{s}, && \text{on } \{0\} \times \Omega_c,
\end{aligned}$$

where $\mathbf{n}$ represents the normal unit vector relative to the interface Γ, for instance we choose $\mathbf{n} = \mathbf{n}_c$. We remind that f_c^* is nondecreasing in s and nonincreasing in c. This explains the combined evaluation with the upper and lower solutions, i.e. $f_c^*(\tilde{c}, \hat{s})$. A similar observation applies to $f_w(\cdot, \cdot)$. We refer to the following pair of functions:

$$\tilde{\mathbf{u}} = (\tilde{c}, \tilde{s}, \tilde{a}, \tilde{b}), \;\; \hat{\mathbf{u}} = (\hat{c}, \hat{s}, \hat{a}, \hat{b})$$

as upper and lower solutions respectively. In particular to satisfy system (29) $\tilde{\mathbf{u}}$ and $\hat{\mathbf{u}}$ assume the following expressions:

$$(\tilde{c}, \tilde{s}, \tilde{a}, \tilde{b}) = (c_s, s_0, c_s, r_0), \qquad (\hat{c}, \hat{s}, \hat{a}, \hat{b}) = (0, 0, 0, 0),$$

and we define the subset $\mathbf{R}$ as:

$$\begin{aligned}
\mathbf{R} := \{(c, s, a, b) \in \mathbf{W} \;\; s.t. \quad & 0 \leq c(t, \mathbf{x}) \leq c_s, \;\; 0 \leq s(t, \mathbf{x}) \leq s_0 \\
& 0 \leq a(t, \mathbf{x}) \leq c_s, \;\; 0 \leq b(t, \mathbf{x}) \leq r_0\}.
\end{aligned} \tag{30}$$

It is important to notice that in order to build up a global solution for the problem we need the continuity of the solution at the interface, see [31]. Thus, the

upper solution in the tissue is set to c_s. Then, following [22], we build an iterative process which, starting from a suitable initial guess, defines a sequence of functions which converges to the unique solution of the problem. More precisely, using either $\tilde{\mathbf{u}}$, or $\hat{\mathbf{u}}$ as the initial iteration we build up a sequence $\mathbf{u}^{(m)}$ where $\mathbf{u}^{(m)} = \{c^{(m)}, s^{(m)}, a^{(m)}, b^{(m)}\}$ with the following iterative process:

$$
\begin{aligned}
&\frac{\partial c^{(m)}}{\partial t} + \mathbb{L}_c c^{(m)} = f_c^*(c^{(m-1)}, s^{(m-1)}), && \text{in } (0,T] \times \Omega_c,\\
&\frac{\partial s^{(m)}}{\partial t} = -f_c^*(c^{(m-1)}, s^{(m-1)}), && \text{in } (0,T] \times \Omega_c,\\
&\frac{\partial a^{(m)}}{\partial t} + \mathbb{L}_w a^{(m)} = f_w(a^{(m-1)}, b^{(m-1)}), && \text{in } (0,T] \times \Omega_w,\\
&\frac{\partial b^{(m)}}{\partial t} = -f_w(a^{(m-1)}, b^{(m-1)}), && \text{in } (0,T] \times \Omega_w,\\
&c^{(m)} = a^{(m)}, && \text{on } (0,T] \times \Gamma,\\
&D_w \nabla a^{(m)} \cdot \mathbf{n} = D_c \nabla c^{(m)} \cdot \mathbf{n}, && \text{on } (0,T] \times \Gamma,\\
&\mathbb{B}_w(a^{(m)}) = 0, && \text{on } (0,T] \times \partial\Omega_w \backslash \Gamma,\\
&D_c \nabla c^{(m)} \cdot \mathbf{n} = 0, && \text{on } (0,T] \times \partial\Omega_c \backslash \Gamma.
\end{aligned}
\tag{31}
$$

We now recall the following result, see Theorem 3.2, Chapter 8 in [22], that assures the existence and uniqueness of the solution.

Theorem 3.1

1. *The sequences $\{\overline{\boldsymbol{u}}^m\}$, $\{\underline{\boldsymbol{u}}^m\}$, obtained by (31), converge monotonically to a maximal, $\overline{\boldsymbol{u}}$, and minimal, $\underline{\boldsymbol{u}}$, solution and satisfy the relation:*

$$\hat{\boldsymbol{u}} \leq \underline{\boldsymbol{u}}^{(m)} \leq \underline{\boldsymbol{u}}^{(m+1)} \leq \underline{\boldsymbol{u}} \leq \overline{\boldsymbol{u}} \leq \overline{\boldsymbol{u}}^{(m+1)} \leq \overline{\boldsymbol{u}}^{(m)} \leq \tilde{\boldsymbol{u}}.$$

2. *$\overline{\boldsymbol{u}}$ and $\underline{\boldsymbol{u}}$ are solutions of problem (28) in $\boldsymbol{R}$.*

3. *Problem (28) admits a unique solution, $\boldsymbol{u}^*$, that is $\overline{\boldsymbol{u}} = \underline{\boldsymbol{u}} = \boldsymbol{u}^*$.*

To prepare the proof of the theorem we assume that the operators, $\mathbb{L}_c$ and $\mathbb{L}_w$ are characterized by constant diffusion coefficients in each domain and we assume that the corresponding initial and boundary conditions are compatible.
A key point for the proof of theorem (3.1) consists of looking at problem (31) as a coupled system of linear parabolic equations for the unknown $d^{(m)}$ on $(\Omega_w \cup \Omega_c) \times (0,T]$ such that $d^{(m)} = a^{(m)}$ on Ω_w and $d^{(m)} = c^{(m)}$ on Ω_c. The resulting equivalent problem for $d^{(m)}$ is still a linear parabolic problem. Moreover, it

features non smooth but bounded coefficients, belonging to $L^\infty(\Omega_w \cup \Omega_c)$ rather than being Hölder continuous. Referring to [16] we remind that such problem still allows for an integral representation of the solution as well as it satisfies a positivity property that is reminded below.

Lemma 3.1 *Let $a \in W(\Omega_w, T)$ and $c \in W(\Omega_c, T)$ be such that:*

$$\begin{aligned}
&\frac{\partial a}{\partial t} + \mathbb{L}_w a \geq 0, && \text{in } (0,T] \times \Omega_w,\\
&\frac{\partial c}{\partial t} + \mathbb{L}_c c \geq 0, && \text{in } (0,T] \times \Omega_c,\\
&c - a = 0, && \text{on } (0,T] \times \Gamma,\\
&D_w \nabla a \cdot \boldsymbol{n} - D_c \nabla c \cdot \boldsymbol{n} = 0, && \text{on } (0,T] \times \Gamma,\\
&D_w \nabla a \cdot \boldsymbol{n} \geq 0, && \text{on } (0,T] \times \partial\Omega_w \backslash \Gamma,\\
&D_c \nabla c \cdot \boldsymbol{n} \geq 0, && \text{on } (0,T] \times \partial\Omega_c \backslash \Gamma,\\
&a \geq 0, && \text{on } t = \{0\} \times \Omega_w,\\
&c \geq 0, && \text{on } t = \{0\} \times \Omega_c.
\end{aligned} \tag{32}$$

Then, $a \geq 0 \in (0,T] \times \Omega_w$ and $c \geq 0 \in (0,T] \times \Omega_c$.

Proof. *of Theorem 3.1 - Part one*

We focus on the monotone properties of the two sequences $(\overline{c}^{(m)}, \underline{s}^{(m)}, \overline{a}^{(m)}, \underline{b}^{(m)})$ and $(\underline{c}^{(m)}, \overline{s}^{(m)}, \underline{a}^{(m)}, \overline{b}^{(m)})$ that satisfy:

$$\underline{\hat{w}} \leq \underline{w}^{(m)} \leq \underline{w}^{(m+1)} \leq \overline{w}^{(m+1)} \leq \overline{w}^{(m)} \leq \underline{\tilde{w}} \text{ for } w = a, b, c, s \tag{33}$$

with m=0, 1, 2..... . We prove this statement using different initial values for the iterative scheme (31). At first, we consider the initial values:

$$\overline{a}^{(0)} = \tilde{a}, \quad \underline{b}^{(0)} = \hat{b}, \quad \overline{c}^{(0)} = \tilde{c}, \quad \underline{s}^{(0)} = \hat{s}.$$

To simplify the notation we define the auxiliary functions:
$\alpha^{(0)} = \overline{a}^{(0)} - \overline{a}^{(1)} = \tilde{a} - \overline{a}^{(1)}$, $\beta^{(0)} = \underline{b}^{(1)} - \underline{b}^{(0)} = \underline{b}^{(1)} - \hat{b}$ and $\gamma^{(0)} = \overline{c}^{(0)} - \overline{c}^{(1)} = \tilde{c} - \overline{c}^{(1)}$, $\sigma^{(0)} = \underline{s}^{(1)} - \underline{s}^{(0)} = \underline{s}^{(1)} - \hat{s}$.
We consider for instance the auxiliary variable γ and the equality $\bar{c}^{(0)} = \tilde{c}$. Using the iterative scheme for the first iteration,

$$\frac{\partial \bar{c}^{(1)}}{\partial t} + \mathbb{L}_c \bar{c}^{(1)} = f_c^*(\overline{c}^{(0)}, \underline{s}^{(0)}),$$

and exploiting the fact that $\tilde{c}$ is a supersolution,

$$\frac{\partial \tilde{c}}{\partial t} + \mathbb{L}_c \tilde{c} - f_c^*(\tilde{c}, \hat{s}) \geq 0,$$

and $\overline{c}^{(1)} = \tilde{c} - \gamma^{(0)}$, we prove that

$$\frac{\partial \gamma^{(0)}}{\partial t} + \mathbb{L}_c\, \gamma^{(0)} = \frac{\partial \tilde{c}}{\partial t} + \mathbb{L}_c \tilde{c} - f_c^*(\tilde{c}, \hat{s}) \geq 0, \quad \text{in } \Omega_c \times (0, T].$$

Using the same procedure we have,

$$\begin{aligned}
&\frac{\partial \sigma^{(0)}}{\partial t} = -\frac{\partial \tilde{s}}{\partial t} - f_c^*(\tilde{c}, \hat{s}) \geq 0, && \text{in } \Omega_c \times (0, T],\\
&\frac{\partial \alpha^{(0)}}{\partial t} + \mathbb{L}_w\, \alpha^{(0)} = \frac{\partial \tilde{a}}{\partial t} + \mathbb{L}_w \tilde{a} - f_w(\tilde{a}, \hat{b}) \geq 0, && \text{in } \Omega_w \times (0, T],\\
&\frac{\partial \beta^{(0)}}{\partial t} = -\frac{\partial \hat{b}}{\partial t} - f_w(\tilde{a}, \hat{b}) \geq 0, && \text{in } \Omega_w \times (0, T],
\end{aligned}$$

and the boundary conditions satisfy:

$$\begin{aligned}
&\gamma^{(0)} = \alpha^{(0)}, && \text{on } (0, T] \times \Gamma,\\
&D_w \nabla \alpha^{(0)} \cdot \mathbf{n} - D_c \nabla \gamma^{(0)} \cdot \mathbf{n} = 0, && \text{on } (0, T] \times \Gamma,\\
&\mathbb{B}_w(\alpha^{(0)}) \geq 0, && \text{on } (0, T] \times \partial\Omega_w \backslash \Gamma,\\
&D_c \nabla \gamma^{(0)} \cdot \mathbf{n} \geq 0, && \text{on } (0, T] \times \partial\Omega_c \backslash \Gamma.
\end{aligned}$$

By using the positivity Lemma (32) we assert that $\alpha^{(0)}, \beta^{(0)}, \gamma^{(0)}$ and $\sigma^{(0)}$ are positive functions so that:

$$\overline{a}^{(0)} \geq \overline{a}^{(1)},\ \underline{b}^{(1)} \geq \underline{b}^{(0)},\ \overline{c}^{(0)} \geq \overline{c}^{(1)},\ \underline{s}^{(1)} \geq \underline{s}^{(0)}.$$

In the same way we proceed using the set of initial values:

$$\underline{a}^{(0)} = \hat{a},\ \ \overline{b}^{(0)} = \tilde{b},\ \ \underline{c}^{(0)} = \hat{c},\ \ \overline{s}^{(0)} = \tilde{s},$$

and the functions: $\alpha^{(0)} = \underline{a}^{(1)} - \underline{a}^{(0)}$, $\beta^{(0)} = \overline{b}^{(0)} - \overline{b}^{(1)}$ and $\gamma^{(0)} = \underline{c}^{(1)} - \underline{c}^{(0)}$, $\sigma^{(0)} = \overline{s}^{(0)} - \overline{s}^{(1)}$. Following the same approach as above we have:

$$\begin{aligned}
&\frac{\partial \gamma^{(0)}}{\partial t} + \mathbb{L}_c\, \gamma^{(0)} = -\frac{\partial \hat{c}}{\partial t} - \mathbb{L}_c \hat{c} + f_c^*(\hat{c}, \tilde{s}) \geq 0, && \text{in } \Omega_c \times (0, T],\\
&\frac{\partial \sigma^{(0)}}{\partial t} = \frac{\partial \tilde{s}}{\partial t} + f_c^*(\hat{c}, \tilde{s}) \geq 0, && \text{in } \Omega_c \times (0, T],\\
&\frac{\partial \alpha^{(0)}}{\partial t} + \mathbb{L}_w\, \alpha^{(0)} = -\frac{\partial \hat{a}}{\partial t} - \mathbb{L}_w \hat{a} + f_w(\hat{a}, \tilde{b}) \geq 0, && \text{in } \Omega_w \times (0, T]\\
&\frac{\partial \beta^{(0)}}{\partial t} = \frac{\partial \tilde{b}}{\partial t} + f_w(\hat{a}, \tilde{b}) \geq 0, && \text{in } \Omega_w \times (0, T],
\end{aligned}$$

and the boundary conditions satisfy:

$$\begin{aligned}
&\gamma^{(0)} = \alpha^{(0)}, && \text{on } (0, T] \times \Gamma,\\
&D_w \nabla \alpha^{(0)} \cdot \mathbf{n} - D_c \nabla \gamma^{(0)} \cdot \mathbf{n} = 0, && \text{on } (0, T] \times \Gamma,\\
&\mathbb{B}_w(\alpha^{(0)}) \geq 0, && \text{on } (0, T] \times \partial\Omega_w \backslash \Gamma,\\
&D_c \nabla \gamma^{(0)} \cdot \mathbf{n} \geq 0, && \text{on } (0, T] \times \partial\Omega_c \backslash \Gamma.
\end{aligned}$$

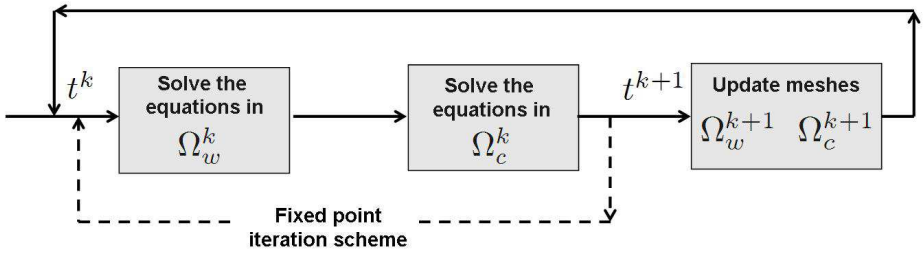


Figure 3: *Schematic representation of the numerical algorithm used.*

Using again the positivity Lemma (32) we prove that:

$$\underline{a}^{(1)} \geq \underline{a}^{(0)},\ \overline{b}^{(0)} \geq \overline{b}^{(1)},\ \underline{c}^{(1)} \geq \underline{c}^{(0)},\ \underline{s}^{(1)} \geq \underline{s}^{(0)}.$$

Finally, we consider $\alpha^{(1)} = \overline{a}^{(1)} - \underline{a}^{(1)}$, $\beta^{(0)} = \overline{b}^{(1)} - \underline{b}^{(1)}$ and $\gamma = \overline{c}^{(1)} - \underline{c}^{(1)}$,$\sigma = \overline{s}^{(1)} - \underline{s}^{(1)}$. Thus, exploiting the iterative process (31) and the monotone property of the non linear terms we obtain $\alpha^{(1)}, \beta^{(1)}, \gamma^{(1)}, \delta^{(1)} \geq 0$ which is equivalent to $\overline{\mathbf{u}}^{(1)} \geq \underline{\mathbf{u}}^{(1)}$. We have shown that,

$$\begin{aligned} \underline{a}^0 \leq \underline{a}^{(1)} \leq \overline{a}^{(1)} \leq \overline{a}^{(0)}, \quad \underline{b}^0 \leq \underline{b}^{(1)} \leq \overline{b}^{(1)} \leq \overline{b}^{(0)}, \\ \underline{c}^0 \leq \underline{c}^{(1)} \leq \overline{c}^{(1)} \leq \overline{c}^{(0)}, \quad \underline{s}^0 \leq \underline{s}^{(1)} \leq \overline{s}^{(1)} \leq \overline{s}^{(0)}, \end{aligned}$$

which proves property (33) for the case $m = 1$. Using induction, the property holds for every $m > 1$. To conclude the first part of Theorem (3.1) we note that the sequences $\underline{\mathbf{u}}^{(m)}, \overline{\mathbf{u}}^{(m)}$, are monotonically increasing functions and bounded from above/below, respectively. By consequence they are convergent and we denote with $\underline{\mathbf{u}}, \overline{\mathbf{u}}$ their limits.

We focus now on the *second part of Theorem 3.1.* The fact that $\underline{\mathbf{u}}, \overline{\mathbf{u}}$ are solutions of problem (28) is a consequence of the integral representation of $c^{(m)}, s^{(m)}, a^{(m)}, b^{(m)}$, solutions of (31), together with the dominated convergence theorem. For further details of this proof we refer to Theorem 3.1, Chapter 8, [22].

Finally, the proof of the *third part of Theorem 3.1* is a consequence of the fact that, owing to Theorem 9.1, Chapter 8, [22], problem (28) admits an unique solution. By consequence $\underline{\mathbf{u}}$ and $\overline{\mathbf{u}}$ coincide. □

4 Numerical approximations and results

In this section the numerical approximation of equations (1), (8) with boundary conditions (2), (7) and interface condition, (26) is presented. We briefly describe the numerical algorithm used to solve the coupled system with erosion (8). The system of equations is rewritten in the moving frame and discretized in time

with a third order BDF scheme, as follows:

$$\begin{aligned}
&\frac{\alpha}{\Delta t}c^k - D_c\Delta c^k - \mathbf{w}\cdot\nabla c^k - f_c(c^k,s^k) = \frac{1}{\Delta t}\sum_{n=1}^{3}\beta_n c^{k-n}, && \text{in } \Omega_c^k,\\
&\frac{\alpha}{\Delta t}s^k - \mathbf{w}\cdot\nabla s^k + f_c(c^k,s^k) = \frac{1}{\Delta t}\sum_{n=1}^{3}\beta_n s^{k-n}, && \text{in } \Omega_c^k,\\
&\frac{\alpha}{\Delta t}a^k - D_w\Delta a^k + (\mathbf{u}_w^k - \mathbf{w})\nabla a^k - f_w(a^k,b^k) = \frac{1}{\Delta t}\sum_{n=1}^{3}\beta_n a^{k-n}, && \text{in } \Omega_w^k,\\
&\frac{\alpha}{\Delta t}b^k - \mathbf{w}\cdot\nabla b^k + f_w(a^k,b^k) = \frac{1}{\Delta t}\sum_{n=1}^{3}\beta_n b^{k-n}, && \text{in } \Omega_w^k,
\end{aligned} \tag{34}$$

where $\mathbf{w}$ is the domain velocity, which is assumed to be Hölder continuous together with the other physical parameters in order to ensure the existence of the strong solutions of (28). The fourth equation in (34) belongs to the family of hyperbolic equations and is supplemented with a homogeneous Neumann condition on $\Gamma(t^k)$. No boundary conditions are required for the second equation. The filtration velocity $\mathbf{u}_w^k$ is computed by means of equation (5) and boundary conditions (6) conveniently discretized (details are omitted).
The BDF coefficients are set to $\alpha = 11/6$ and $\boldsymbol{\beta} = [3, -3/2, 1/3]$. The discrete problem is solved using a two-dimensional finite element method with linear elements. For each time step, Δt, we solve a non-linear coupled problem. First, the system in the coating is solved for $c^{k,i+1}, s^{k,i+1}$ by explicitly evaluating the non linear term, $f_c(c^{k,i}, s^{k,i})$, and the coupling conditions (26) with $a^{k,i}, b^{k,i}$ at the iteration i. Then, the system on the tissue is solved for $a^{k,i+1}, b^{k,i+1}$ by evaluating the non linear term, $f_w(c^{k,i+1}, s^{k,i+1})$, and the coupling conditions (26) $a^{k,i+1}, b^{k,i+1}$ at the iteration $i+1$. The iteration process is stopped when the following convergence condition is satisfied: $\sum_q \|q^{k,i+1} - q^{k,i}\|/\|q^{k,i}\| \leq \epsilon$, where $q = a,\, b,\, c,\, s$. In particular for the non linear term inside the coating we introduce a regularization similar to that introduced in (27) to preserve the convergence of the fixed point algorithm. Moreover to better control the positivity of the solution at the numerical level we apply the positive part of the f_c, i.e. $\langle f_c\rangle$=1/2 $(f_c + |f_c|)$.
Then, we update the domains and compute the velocity field. We need to know the ALE mapping only at some discrete time step $t^{k+1} = t^0 + k\Delta t$. The evolution of Ω_c is imposed and we can define the function $\boldsymbol{\eta}_0 := \partial\Omega_c(t^{k+1}) - \partial\Omega(t^k)$. We use a harmonic extension approach [10] to compute the movement of Ω_w. It consists in solving the following problem:

Problem 4.1 Given $\Omega(t^k)$ and a function $\boldsymbol{\eta}_0$ on $\partial\Omega(t^k) \to \mathbb{R}^d$, find $\boldsymbol{\eta} : \Omega(t^k) \to \mathbb{R}^d$ such that:

$$\begin{cases} \Delta\boldsymbol{\eta} = 0, & in\ \Omega(t^k),\\ \boldsymbol{\eta} = \boldsymbol{\eta}_0, & on\ \partial\Omega(t^k). \end{cases} \tag{35}$$

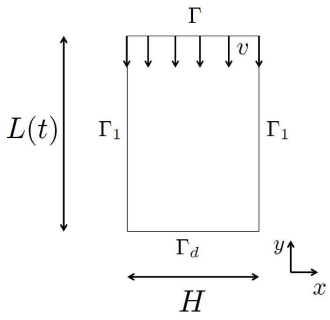


Figure 4: *Movement of domain Ω_c. The velocity of the boundary is $\mathbf{w} = -v\boldsymbol{j}$, $\boldsymbol{j}$ being the unit vector of the y axis. Thus, the length of the slab is $L(t) = L_c - vt$, while the width, H, is fixed.*

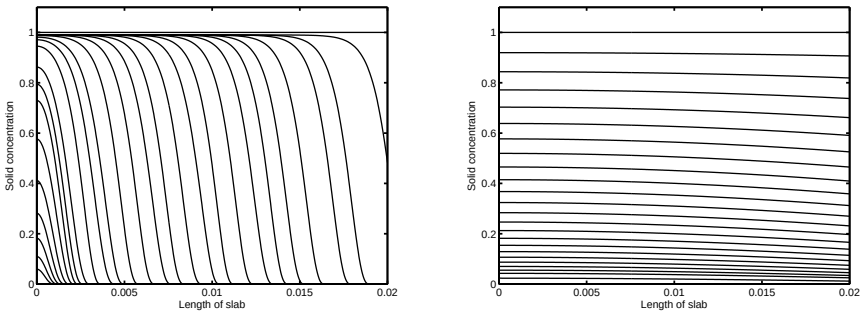
Thus Ω_w^{k+1} is reconstructed moving each point using $\mathbf{x}^{(k+1)} = \mathbf{x}^{(k)} + \boldsymbol{\eta}$. The algorithm is sketched in Fig.3.
For the following set of simulations we assume the slab to have a rectangular shape, and we define $\Omega_c(t) = (0, L(t)) \times (0, H)$, as shown in Fig.4. In particular, $\mathbf{w} = -v\mathbf{j}$, $\mathbf{j}$ being the unit vector of the y axis, see Fig. 4. Thus, we set $L(t) = L_c - vt$, where L_c is the initial length of the slab and v, an empirical velocity possibly estimated through experiments. The assumption that the slab dimensions decrease linearly in time are supported by experimental observations for typical surface-eroding polymers, [4, 17]. In particular when solving problem (35) on Ω_c^k, we impose the following boundary conditions, see Fig.4,

$$\begin{cases} \boldsymbol{\eta} = 0, & \text{on } \Gamma_d, \\ \dfrac{\partial \boldsymbol{\eta}}{\partial n} = 0, & \text{on } \Gamma_1, \\ \boldsymbol{\eta} = -\mathbf{w}\Delta t, & \text{on } \Gamma, \end{cases} \tag{36}$$

$\boldsymbol{\eta}$ being the displacement and $\Gamma_1 = \partial\Omega \setminus \{\Gamma \cup \Gamma_d\}$. The movement of the tissue is computed similarly. We study the problem in the time interval $(0, T = \bar{T} - \delta t)$, where $\bar{T} = L_c/v$ is the time taken by the slab to completely erode and δt is and infinitesimal quantity used to prevent the coefficients of the elliptic operators to degenerate and become singular matrices in the algebraic counterpart of problem (34).

4.1 Sensitivity analysis with respect to the transport parameters

In this section we perform a sensitivity analysis for model (1) when then erosion velocity is zero. The aim is to study the capability of the model to describe



(a) (b)

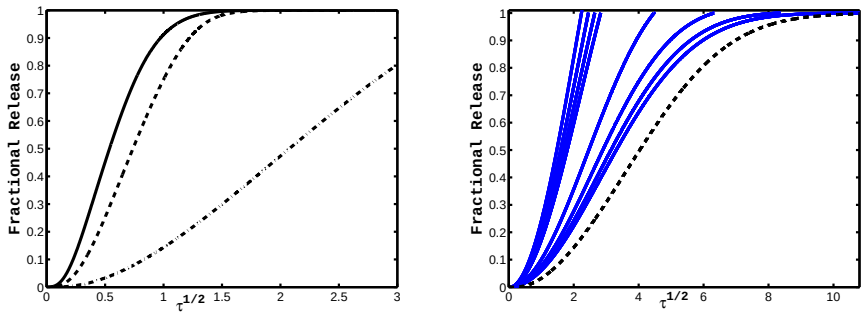
Figure 5: *Solid drug profiles in $x = H/2$ at different values. The initial concentrations is $s_0 = s(\mathbf{x}, 0) = 1$. In (a) the case of $\delta >> 1$. The matrix divided in two distinct regions and the dissolution front progressively moves inside the matrix. In (b) the case of $\delta < 1$. The solid concentration decreases uniformly in time.*

the limits of a diffusion domainated phenomenon as well as dissolution. For this analysis we adimensionalize the system (1) dividing each unknown by the initial load of the matrix ($m_0 = s_0 + c_0$). Moreover, we introduce the dimensionless parameter $\delta = k_d\, L^2/D_c$, and sink conditions on the release boundary:

$$\begin{aligned} c &= 0, && \text{on } \Gamma, \\ \nabla c \cdot \mathbf{n} &= 0, && \text{on } \partial\Omega_c \backslash \Gamma. \end{aligned}$$

First, we fix the solubility and change the dissolution rate δ. We assume the solubility to be smaller that 1, and we fix $c_s = 0.05$. The profiles of the solid and liquid concentration inside the matrix are different depending on the dominant effect between dissolution and diffusion. We can summarize the physical phenomenon as follows:

- When $\delta >> 1$, the matrix is divided into two zones, as shown in Fig.5.a. We have a depleted zone, where all the solid drug has been dissolved and s approaches zero, and a complementary region where the solid concentration has the value of its initial loading, s_0. We explain this behavior considering the pattern of dissolution that takes place inside the matrix. At the beginning of the process the drug concentration in the liquid phase increases due to the dissolution of the solid phase. The dissolution process continues until c reaches the value of the solubility, c_s. Due to the rapid dissolution the amount of solid drug is reduced or even depleted, while the effect of the diffusion is to decrease the drug concentration in the liquid phase. The dissolved drug flows out from the matrix regulated by the sink condition ($c = 0$), thus in the region near the release boundary



(a) (b)

Figure 6: *Fractional release profiles. In (a) the dependence of the release pattern on the solubility. The solid, dashed and dotted-dashed correspond to* $c_s/m_0 =$ 1.5, 0.5, 0.05 *respectively. In (b) the effect of erosion on dissolution is shown. The dashed line correspond to dissolution only. The dark solid lines from left to right are release profiles with increasing value of erosion velocity.*

$c_s - c$, namely the dissolution driving force, is greater that in any other points of the matrix. In fact the dissolution only happens when the liquid concentration is lower than the saturation concentration. Thus, the solid concentration is reduced essentially near the boundary. The consequence is that the profile of the solid concentration, namely $s(\mathbf{x}, t)$ is a progressive wave that moves from the boundary to the inner part of the slab.

- When δ is small, the solid phase decreases almost uniformly throughout the matrix, as shown in Fig.5.b. The filling due to the dissolved solid drug is very slow, while the effect of the diffusion is to uniformly distribute the liquid concentration inside the matrix. Thus, c never reaches its upper limit, c_s. The maximum values assumed by the liquid concentrations depend on the dissolution kinetics, defined by k_d.

The effect of a different value of the solubility c_s on the release rate against the dimensionless time $\tau = D_c t/L^2$ is shown in Fig.6.a. Increasing the solubility, the release rate is increased and that is in agreement with the fact that the solubility is the limiting step in the dissolution model. The kinetics of the dissolution is defined by k_d, but also by the value of the solubility that stops the dissolution process when c approaches c_s. Moreover we can notice and initial delay in the release profile due to the dissolution kinetics. This delay disappears gradually with increasing c_s. This is confirmed by the fact that as the initial drug loading does not exceed the solubility,($c_s > 1$) and the dissolution is rapid enough, the problem reduce to a standard diffusion problem, [6]. This behavior can be recovered when erosion is considered but the velocity is low. As we expect, the effect

of the erosion is to enhance the release rate, because both phases are released together. In Fig.6.b the release profiles are plotted against the square root of τ. The solid curves correspond to different values of the dimensionless parameter, $B = vL_c/D_c$, where v is the erosion velocity measured experimentally, while δ is set to 1. The solid lines from left to right have decreasing values of B, and the dashed line corresponds to dissolution only, $B = 0$. For high values of B, the release tends to be linear in τ while decreasing the value of the velocity, the drug is mainly released by dissolution and diffusion and the effect of the erosion is less evident.

4.2 Numerical results for the coupled problem

We here consider only a part of the the computational domain in Fig.1 right, representing a portion of a truncated coronary vessel in which a drug eluting stent is implanted. The complete section of the artery can be reconstructed using periodic and symmetry conditions. Thus, on the artificial boundaries, indicated by dashed lines in Fig.1 we impose homogeneous Neumann boundary conditions. The initial dimensions of the slab are $H = 0.02mm$ and $L_c = 0.08mm$, while the arterial wall thickness is set to $0.35mm$. We normalize the equations with the initial total mass of the system, m_0. To perform the numerical simulations we use the following values for the parameters that correspond to the release of an hydrophilic drug and are necessary to set up our model, $D_w = 1.0e-5\, mm^2\, s^{-1}$, $r_0/m_0 = 0.05$, $k_1 = 1.0e5\, mol^{-1}s^{-1}$, $k_2 = 1.0e-2\, s^{-1}$, $P_w = 1.0e-9\, mms^{-1}$, We refer to [27] for the transport and kinetic parameters in the tissue. To compute the velocity field we set a pressure drop of $60mmHg$, and $K_{fil} = 2.8e-9mm^3\, sg^{-1}$. In particular referring to the coating side, the velocity of erosion is set to $v = 1.2e-7\, mms^{-1}$, the diffusivity of the drug is $D_c = 1.0e-7mm^2s^{-1}$, $k_d = 0.015\ s^{-1}$ and $c_s/m_0 = 0.1$, [33, 9] .
Concerning the interpretation of the results, we show in Fig. 7 the concentration of the free drug and the percentage of free binding sites at different times. The drug is progressively transferred from the stent to the neighboring arterial wall, and after a relatively long time, i.e. 60hours, the polymeric matrix is completely eroded. Moreover, we notice that the concentration of the drug in the vessel wall is mainly present in the state bound to the tissue rather than the dissolved state, as shown in Fig.8. This is a consequence of the set of parameters used in the binding reaction described with relation (3) assuming an hydrophilic drug. In particular the association between the drug and the free binding sites described by k_1 is faster than the dissociation reaction. The kinetic parameter, $K_{eq} = k_2/k_1$ known as equilibrium dissociation constant is used to express the affinity between the components of the reaction. A small value of K_{eq} means high affinity between the drug and the binding sites. In our case, $K_{eq} = 1.0e-7\ mol$ thus most of the drug is permanently attached to the specific sites of the extra-cellular matrix of the tissue. The ability of the drug to bind to the arterial wall has on

the one hand a positive effect in increasing the residence time of the drug in the target tissue. On the other hand, it can increase the dose near the stent with the risk of reaching toxic levels. In Fig.8 we show the drug release profile in terms of the mass stored in the coating normalized with the total mass,

$$M_c = \frac{\int_{\Omega_c(t)} (c(t) + s(t)) \ d\Omega}{M_{tot}}.$$

Moreover, the drug released in the tissue in the bound an free states, M_b and M_d respectively, are shown. The release is dominated by the linear erosion. Thus, in order to underline also the contribution of the dissolution, we plot the fractional release against $\tau^{1/2}$, introduced in section 4.1. In particular, an initial delay can be seen in the profile of the bound drug. This is a consequence of the magnitude of the dissolution. The slow erosion velocity combined with a quite slow dissolution ($\delta = 60$) prevents the immediate release of the drug, and plays an important role in the beginning of the release process.

5 Discussion and conclusions

In this manuscript we derived a model to study the drug release into the tissue from a surface eroding material where the elution is due to drug dissolution and diffusion. A classical dissolution model was rewritten on a moving domain, where we assumed an imposed movement of the release boundary. This simple assumption was driven by experimental evidences that show a linear mass loss for a large class of surface eroding polymers. For the tissue model we considered an advection-diffusion equation complemented with a reaction term to account of the ability of the drug to bind reversibly with specific sites. The main novelty in this work is the derivation of suitable boundary conditions to describe the transfer of the drug from the polymeric material into the tissue. The coupling conditions were obtained imposing the mass conservation principle on the systems of equations.

For the coupled problem with no erosion, we investigated the existence and uniqueness of the solution and we proved the existence of a global solution for the coupled problem under suitable regularity assumptions.

The aim of the improved coupled model is to qualitatively describe the release process, especially describing the dissolution/erosion phenomena in the polymeric coating and its integration with reversible reaction model in the arterial tissue. This model improves the simple models where the drug is assumed to be completely dissolved in the matrix and the release governed by pure diffusion, but a quantitative analysis and an extension of the work to different drugs will require to focus on a specific set of materials and a deep knowledge of the physical and transport parameters involved. A sensitivity analysis highlighted the parameters that play an important role in the definition of the release rate, precisely the dissolution coefficient and the drug solubility. However, the model

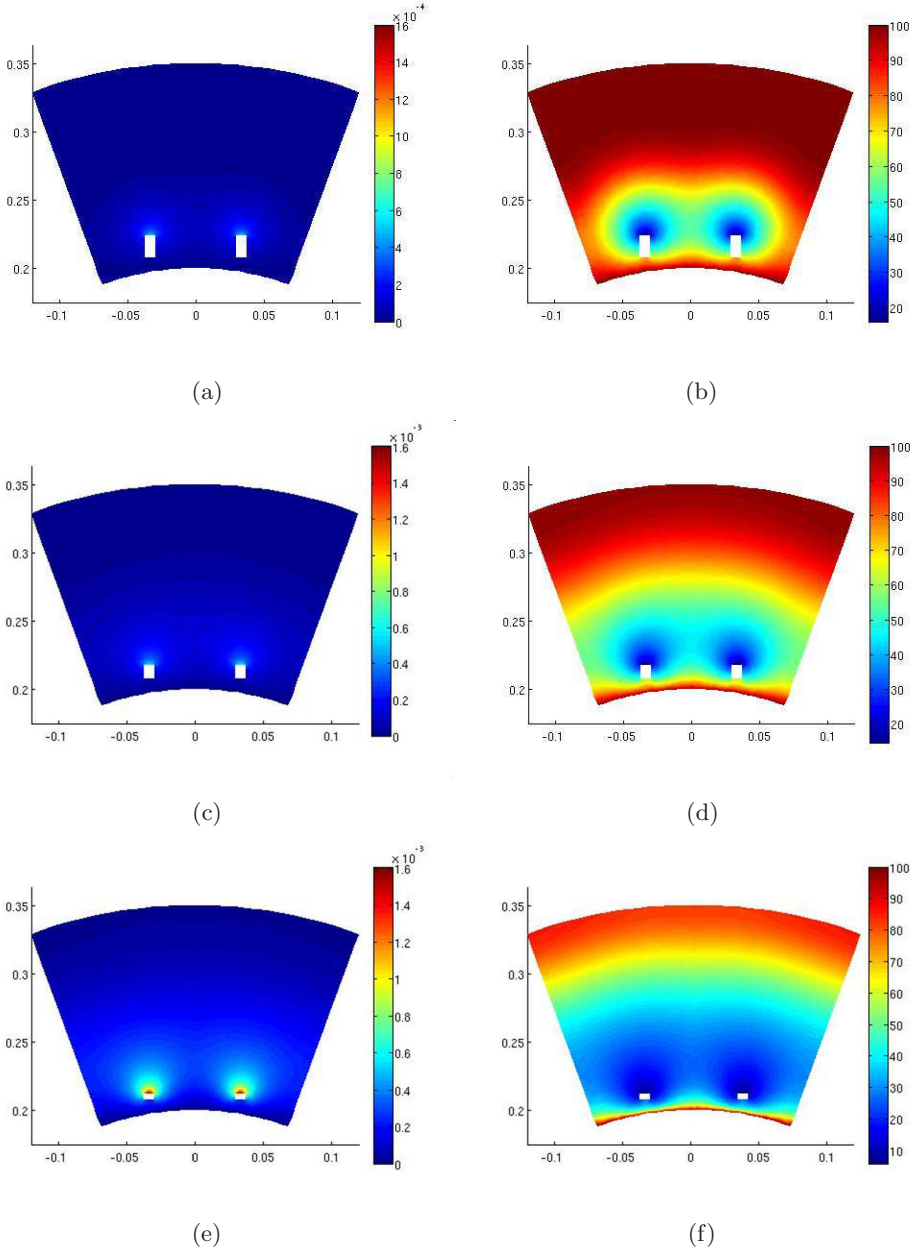


Figure 7: *The concentration of drug inside the tissue after 5, 13 and 44 hours is reported from top to bottom. On the left the concentration of the dissolved drug, on the right the percentage of the free binding* $(r(\boldsymbol{x},t)/r_0)100$.

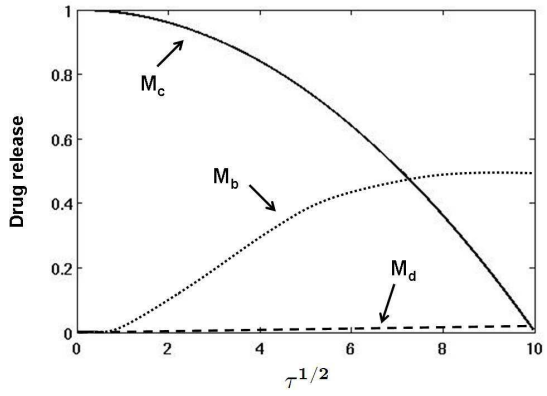


Figure 8: *Dynamics of the drug release against the dimensionless time* $\tau^{1/2}$.

and the numerical results were subject to some simplifications, as we assumed the linear degradation of the matrix and the hypothesis that the eroding front remains planar during the erosion process. To improve the model we should relate the erosion to the dissolution and diffusion. In fact as the dissolution is promoted by the penetration of the water inside the polymeric matrix, the degradation and consequently superficial erosion or mass loss are due to the hydrolysis of the polymeric chains. Indeed, an improved law to describe the eroding matrix could allow to describe a wider class of situations.
Finally, we underline that this model is not restricted to stents but could also be useful for other applications where a drug or other chemical substance is slowly released from an eroding device.

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