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The effect of reversible binding sites on the drug release from drug eluting stent

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Abstract

A coupled non-Fickian model of a cardiovascular drug delivery system using a biodegradable drug eluting stent is proposed. The reversible reaction between the drug and the arterial tissue binding sites are taken into account. The proposed model accounts for the different nature of the therapeutic compounds used. The numerical results are obtained using an IMEX finite element method in the variational form.

Key words: Reversible binding, Non-Fickian coupled model, Cardiovascular drug delivery, Drug eluting stent, Numerical simulation.

1 Introduction

Drug eluting stent (DES) is a device to release anti-proliferative drug with programmed pharmacokinetics into the arterial wall. It 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.

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The arterial walls of the cardiovascular system are known to display complex mechanical response under physiological conditions. Experiments like *creep test* ([5]) have clearly demonstrated that the vascular tissue is viscoelastic.

During the last years, a number of studies have proposed mathematical models for coupled drug delivery in the cardiovascular tissues. We refer without being exhausive to [1, 7, 9, 12]. Most of these studies address the release of drug and its numerical behavior while the viscoelasticity of the arterial wall and the behaviour of the biodegradable materials are disregarded. In [2], we proposed a coupled reaction diffusion cardiovascular drug delivery system where biodegradation of polylactic acid was taken into account. In [3], viscoelasticity of the arterial wall was added to the previous work ([2]) and its effect in the presence of drug in the arterial wall was studied.

In this paper, we develop the model proposed in [2] and [3] to consider the reversible nature of the bindings between the drug and specific sites inside the arterial wall ([7]). This demand comes from the different nature of the therapeutic compounds used. We can distinguish between hydrophobic drugs, which are retained within the tissue and hydrophilic which are rapidly cleared and sometimes are ineffective.

The paper is organized as follows. Section 2 is devoted to the description of reversible binding reactions and setup the model and its initial, boundary and interface conditions. The effect of reversible binding sites in the presence of drug in the arterial wall as well as numerical simulations of different drugs with different reversible binding properties in the healthy and diseased arterial wall are discussed in Section 3. Finally in Section 4, some conclusions are presented.

2 Non-Fickian Reaction-Diffusion-Convection Model

When a DES is implanted in a vessel, the coated stent will be gradually covered by neo-intima. For a sake of simplicity, the presence of the atherosclerosis plaque is neglected and the drug eluting stent is embedded in the arterial wall (see Figure 1). This is a reasonable assumption for mathematical modeling of the problem because of the complex dynamics of tissue healing and regrowth which take place immediately after DES implantation in the arterial wall. However, since growing of neo-intima and endothelium cells around DES are

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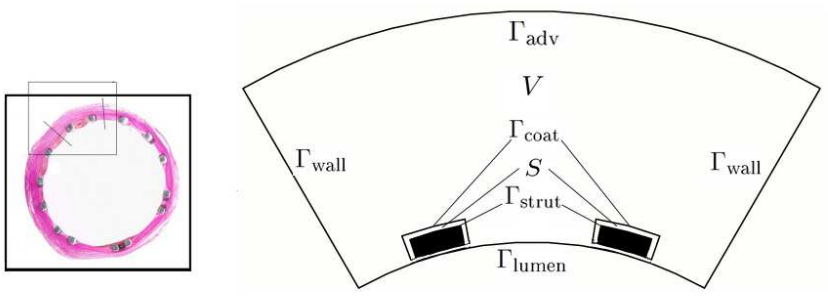

Figure 1: Drug eluting stent embedded in the arterial wall.

not well studied in the literature, the evolution of neo-intima around the stent is considered negligible [7].

The complex multi-layerd structure of the arterial wall is lumped into a homogeneous porous material whose physical properties are the ones corresponding to the intermediate layer, namely the *media*. We also neglect the dynamics of the drug into the blood flow. We assume that the drug that is conveyed by blood flow is immediately transported away without influencing the downstream region of the artery.

Let us consider DES coated with polylactic acid (PLA) where drug is distributed uniformly. PLA is a biodegradable polymer and three main reactions are responsible for the degradation of PLA into lactic acid and oligomers both in the coated stent and in the arterial wall. In the first reaction, the hydrolysis of the PLA occurs resulting in small molecules with smaller molecular weights i.e. oligomers (with molecular weight M_W such that $2 \times 10^4\ g/mol \leq M_W \leq 1.2 \times 10^5\ g/mol$) and lactic acid (with molecular weight $M_W \leq 2 \times 10^4\ g/mol$). The second and the third reactions are the hydrolysis of the oligomers resulting in lactic acid occurring in the coating and in the arterial wall respectively.

In what follows the subscript S stands for the coated stent while the subscript V stands for the arterial wall. Let $C_{1,S}$ and $C_{1,V}$ be the concentrations of plasma in the stent and in the arterial wall respectively. The concentrations of oligomers in the stent and in the arterial wall are denoted by $C_{3,S}$ and $C_{3,V}$ respectively. By $C_{4,S}$ and $C_{4,V}$ we denote the

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concentrations of lactic acid in the stent and in the arterial wall respectively. By $C_{2,S}$ we represent the concentration of PLA while concentration of drug in the stent is represented by $C_{5,S}$.

The reactions are represented schematically by

$$C_{1,S} + C_{2,S} \xrightarrow{\kappa_{1,S}} C_{3,S} + C_{4,S}, \quad C_{1,S} + C_{3,S} \xrightarrow{\kappa_{2,S}} C_{4,S}, \quad C_{1,V} + C_{3,V} \xrightarrow{\kappa_{1,V}} C_{4,V}, \tag{1}$$

where $\kappa_{1,S}$ and $\kappa_{2,S}$ denote the reaction rates of the hydrolysis of PLA and oligomers in the stent and $\kappa_{1,V}$ denotes the reaction rate of the hydrolysis of oligomers in the arterial wall.

Bindings occur when ligand (drug) and receptor (binding site) collide due to diffusion forces and when the collision has the correct orientation and enough energy ([7]). When binding has occurred, drug and binding site remain bound together for an amount of time depending on their affinity. After dissociation, the drug and the binding site are the same as they were before binding. The drug-binding site reaction is schematically represented by

$$\text{Drug} + \text{Binding sites} \underset{\text{dissociation}}{\overset{\text{association}}{\rightleftharpoons}} \text{Drug-binding complex.} \tag{2}$$

To define the mathematical kinetic model associated to (2), the following assumptions are made: all the binding sites are equally accessible to the drug; all the binding sites are either free or bound to the drug, there are not states of partial binding; neither drug nor binding site are altered by binding ([7]).

The concentration of free drug in the arterial wall is represented by $C_{5,V}$ with initial concentration $C^0_{5,V} = 0$, while $C_{6,V}$ represents the concentration of free binding sites in the arterial wall with initial concentration $C^0_{6,V} \neq 0$. The concentration of activated drug-binding sites is represented by $C_{7,V}$, and we assume that its initial concentration is null. The drug-binding reaction is schematically represented by

$$C_{5,V} + C_{6,V} \underset{\kappa_{u,V}}{\overset{\kappa_{b,V}}{\rightleftharpoons}} C_{7,V}, \tag{3}$$

where $\kappa_{b,V}$ is the association rate between the drug and the binding sites and $\kappa_{u,V}$ is the dissociation rate.

The drug assumes two different states: the dissolved state where drug moves by convection and non-Fickian diffusion and the bound state where drug attaches reversibly to specific sites inside the arterial wall and no longer diffuse or be transported by plasma.

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It should be noted that $K_b = \frac{C^0_{6,V}\kappa_{b,V}}{\kappa_{u,V}} \gg 1$ corresponds to the drugs that have high affinity for their target binding sites.

The coupled non-Fickian nonlinear reaction-diffusion-convection model that discribes the evolution of PLA and its compounds, the drug and free and activated drug-binding site, is defined by

$$\begin{cases} \frac{\partial C_{m,S}}{\partial t} &= -\nabla.J_{m,S}(\mathcal{C}_S) + F_{m,S}(\mathcal{C}_S) \quad \text{in } S\times\mathbb{R}^+,\ m=1,\dots,5,\\ \frac{\partial C_{m,V}}{\partial t} &= -\nabla.J_{m,V}(\mathcal{C}_V) + F_{m,V}(\mathcal{C}_V) \quad \text{in } V\times\mathbb{R}^+,\ m=1,\dots,5,\ m\neq 2,\\ \frac{\partial C_{6,V}}{\partial t} &= F_{6,V}(\mathcal{C}_V) \quad \text{in } V\times\mathbb{R}^+,\\ \frac{\partial C_{7,V}}{\partial t} &= F_{7,V}(\mathcal{C}_V) \quad \text{in } V\times\mathbb{R}^+, \end{cases} \tag{4}$$

where $\mathcal{C}_S = \big(C_{m,S}\big)_{m=1,\dots,5}$ and $\mathcal{C}_V = \big(C_{m,V}\big)_{\substack{m=1,\dots,7\\ m\neq 2}}$, and the mass fluxes in the stent and in the arterial wall are defined respectively by

$$\begin{aligned} &J_{m,S}(\mathcal{C}_S) = -D_{m,S}\nabla C_{m,S} + u_S C_{m,S},\ m=1,\dots,5,\\ &J_{m,V}(\mathcal{C}_V) = -D_{m,V}\nabla C_{m,V} + u_V C_{m,V} - D_{m,\sigma}\int_0^t e^{-\frac{t-s}{\tau_1}}\nabla C_{m,V}(s)ds,\ {\scriptstyle m=1,\dots,5,\ m\neq 2.} \end{aligned} \tag{5}$$

In [9], the expression

$$D_{m,S} = D^0_{m,S} e^{\alpha_{m,S}\frac{C^0_{2,S}-C_{2,S}}{C^0_{2,S}}} \quad \text{in } \bar{S}\times\mathbb{R}^+,\ m=1,\dots,5, \tag{6}$$

is used for diffusion coefficients of species in the stent where $D^0_{m,S},\ m=1,\dots,5$, are the diffusion coefficients of the respective species in the unhydrolyzed PLA and $C^0_{2,S}$ is the concentration of the unhydrolyzed PLA at $t=0$.

For a sake of simplicity, we assume that the diffusion coefficients in the vessel wall $D_{m,V},\ m=1,\dots,5,\ m\neq 2$, are constants.

In (4), $F_{m,S},\ m=1,\dots,5$, are reaction terms introduced in [9], and used in [2–4] are given by

$$F_{m,S}(\mathcal{C}_S) = \begin{cases} -\sum\limits_{i=1,2}\mathcal{F}_{i,S}(\mathcal{C}_S), & \text{m=1,}\\ -\mathcal{F}_{1,S}(\mathcal{C}_S), & \text{m=2,}\\ \sum\limits_{i=1,2}(-1)^{i-1}\mathcal{F}_{i,S}(\mathcal{C}_S), & \text{m=3,}\\ \sum\limits_{i=1,2}\mathcal{F}_{i,S}(\mathcal{C}_S), & \text{m=4,}\\ 0, & \text{m=5,} \end{cases} \tag{7}$$

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that define the degradation of PLA.

We assume that the degradation of oligomers and also binding and unbinding of the drug take place in the arterial wall and are defined by

$$F_{m,V}(\mathcal{C}_V) = \begin{cases} -\mathcal{F}_{1,V}(\mathcal{C}_V), & \text{m=1,} \\ -\mathcal{F}_{1,V}(\mathcal{C}_V), & \text{m=3,} \\ \mathcal{F}_{1,V}(\mathcal{C}_V), & \text{m=4,} \\ -\mathcal{F}_{2,V}(\mathcal{C}_V), & \text{m=5,} \\ -\mathcal{F}_{2,V}(\mathcal{C}_V), & \text{m=6,} \\ \mathcal{F}_{2,V}(\mathcal{C}_V), & \text{m=7,} \end{cases} \tag{8}$$

In (7) and (8) the following definitions are used

$$\begin{cases} \mathcal{F}_{1,S}(\mathcal{C}_S) = \kappa_{1,S} C_{1,S} C_{2,S}\big(1 + \alpha C_{4,S}\big), \\ \mathcal{F}_{2,S}(\mathcal{C}_S) = \kappa_{2,S} C_{1,S} C_{3,S}\big(1 + \beta C_{4,S}\big), \\ \mathcal{F}_{1,V}(\mathcal{C}_V) = \kappa_{1,V} C_{1,V} C_{3,V}\big(1 + \gamma C_{4,V}\big), \\ \mathcal{F}_{2,V}(\mathcal{C}_V) = \kappa_{b,V} C_{5,V} C_{6,V} - \kappa_{u,V} C_{7,V}, \end{cases} \tag{9}$$

where and α, β and γ are some positive constants.

The velocities $u_j,\ j = S, V$, in (4) are obtained by solving *Darcy*'s equations

$$\begin{cases} u_V = -\frac{k_V}{\mu_V} \nabla p_V & \text{in } V, \\ \nabla . u_V = 0 & \text{in } V, \\ p_V = p_{lumen} & \text{on } \Gamma_{\text{lumen}}, \\ p_V = p_{adv} & \text{on } \Gamma_{\text{adv}}, \\ u_V . \eta_V = 0 & \text{on } \Gamma_{\text{wall}}, \end{cases} \tag{10}$$

in the arterial wall and

$$\begin{cases} u_S = -\frac{k_S}{\mu_S} \nabla p_S & \text{in } S, \\ \nabla . u_S = 0 & \text{in } S, \\ u_S . \eta_S = 0 & \text{on } \Gamma_{\text{strut}}, \end{cases} \tag{11}$$

in the stent, where η_S and η_V represent exterior unit normals.

Equations (10) and (11) are completed with the interface condition

$$\begin{cases} p_S = p_V & \text{on } \Gamma_{\text{coat}}, \\ u_S . \eta_S = -u_V . \eta_V & \text{on } \Gamma_{\text{coat}}. \end{cases} \tag{12}$$

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In (10) and (11), we assume that the permeabilities $k_j,\ j = S, V$, and the viscosities $\mu_j,\ j = S, V$, are constants.

To complete the coupled problem (4)-(12), we define in what follows the initial, the boundary and the interface conditions. The initial conditions in the coating and in the arterial wall are given by

$$\begin{cases} C_{m,S}(0) = 0,\ m = 1, 3, 4,\ C_{m,S}(0) = C^0_{m_S},\ m = 2, 5, \\ C_{m,V}(0) = C^0_{m_V},\ m = 1, 6,\ C_{m,V}(0) = 0,\ m = 3, 4, 5, 7. \end{cases} \tag{13}$$

The boundary and interface conditions are defined by

$$\begin{cases} J_{m,S}.\eta_S = 0 & \text{on } \Gamma_{\text{strut}} \times \mathbb{R}^+,\ \ m = 1, \ldots, 5, \\ J_{2,S}.\eta_S = 0 & \text{on } \Gamma_{\text{coat}} \times \mathbb{R}^+, \\ C_{m,S} = C_{m,V} & \text{on } \Gamma_{\text{coat}} \times \mathbb{R}^+,\ \ m = 1, \ldots, 5,\ m \neq 2, \\ J_{m,S}.\eta_S = -J_{m,V}.\eta_V & \text{on } \Gamma_{\text{coat}} \times \mathbb{R}^+,\ \ m = 1, \ldots, 5,\ m \neq 2, \\ J_{1,V}.\eta_V = \gamma_{1,V}(C^{\text{out}}_{1,V} - C_{1,V}) & \text{on } \Gamma_{\text{lumen}} \times \mathbb{R}^+, \\ J_{m,V}.\eta_V = -\gamma_{m,V} C_{m,V} & \text{on } \Gamma_{\text{lumen}} \times \mathbb{R}^+,\ m = 3, 4, 5, \\ J_{m,V}.\eta_V = 0 & \text{on } (\Gamma_{\text{wall}} \cup \Gamma_{\text{adv}}) \times \mathbb{R}^+,\ m = 1, \ldots, 5,\ m \neq 2. \end{cases} \tag{14}$$

3 Numerical Experiments

For simulation of the problem (4), (13) and (14), we fix $h > 0$ and define in $\Omega = S \cup V$ (Figure 1) an admissible triangulation $\mathcal{T}_h$, depending on $h > 0$, such that the corresponding admissible triangulations in S and V, respectively $\mathcal{T}_{h_S}$ and $\mathcal{T}_{h_V}$, are compatible in Γ_{coat} (see the zoomed part of Figure 2). We represent by Δ_1 a typical element of $\mathcal{T}_{h_S}$ and by Δ_2 a typical element of $\mathcal{T}_{h_V}$.

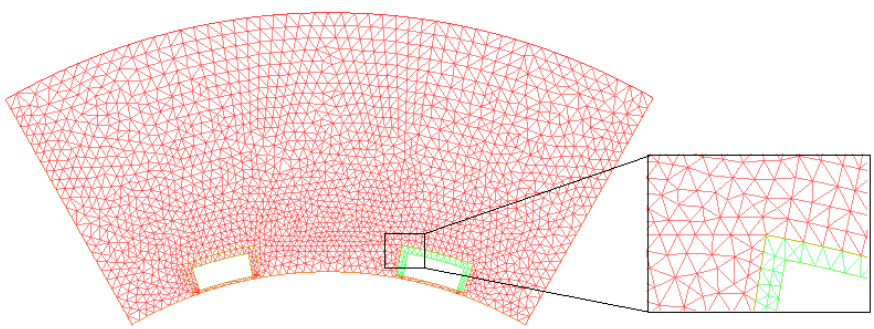

Figure 2: Triangulations in the stent and in the arterial wall.

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Several choices of finite element spaces can be made, but we use here the piecewise linear finite element space P_1 for concentrations of molecules.

All numerical experiments have been done with the open source PDE solver freeFEM++ considering the triangulation plotted in Figure 2 with 3688 elements (1968 vertices) for the arterial wall and 100 elements (83 vertices) for each stents and using an implicit-explicit backward integrator with time step size $\Delta t = 10^{-3}$.

We define the mass in the coated stent and in the arterial wall by

$$\begin{aligned} \mathcal{M}_{m,S,h}(t_n) &= \int_{S_h} C_{m,S,h}(t_n) dS,\ m = 1, \ldots, 5, \\ \mathcal{M}_{m,V,h}(t_n) &= \int_{V_h} C_{m,V,h}(t_n) dV,\ m = 1, \ldots, 7,\ m \neq 2, \end{aligned} \tag{15}$$

respectively, where $\mathcal{M}_{m,j,h}(t_n),\ j = S, V$, are the numerical approximation for $\mathcal{M}_{m,j}(t_n),\ j = S, V$, respectively at time interval.

The following values for the parameters, have been considered in the numerical experiments ([9],[12]).
$\kappa_{1,S} = \kappa_{2,V} = 1{\times}10^{-6}\, cm^2 g^{-1} s^{-1}$, $\kappa_{2,S} = 1{\times}10^{-7}\, cm^2 g^{-1} s^{-1}$, $\gamma_{m,V} = 1{\times}10^{10}\, cm.s^{-1}$, $D^0_{1,S} = 1 \times 10^{-8}\ cm^2 s^{-1}$, $D^0_{2,S} = 1 \times 10^{-15}\ cm^2 s^{-1}$, $D^0_{3,S} = 1 \times 10^{-10}\ cm^2 s^{-1}$, $D^0_{4,S} = 2 \times 10^{-10}\ cm^2 s^{-1}$, $D^0_{5,S} = 1 \times 10^{-8}\ cm^2 s^{-1}, k_S = 2 \times 10^{-14}\ cm^2$, $k_V = 1 \times 10^{-15}\ cm^2$, $\mu_S = 0.72 \times 10^{-2}\ g.cm^{-1} s^{-1}$, $\mu_V = 0.5 \times 10^{-2}\ g.cm^{-1} s^{-1}, D_{1,V} = 1 \times 10^{-8}\ cm^2 s^{-1}$, $D_{3,V} = 1{\times}10^{-10}\, cm^2 s^{-1}$, $D_{4,V} = 2{\times}10^{-10}\, cm^2 s^{-1}, \alpha = 1\ s.cm^{-2}$, $\beta = \gamma = 10\ s.cm^{-2}$, $p_{\text{lumen}} = 100$ mmHg and $p_{\text{adv}} = 0$ mmHg, $C^0_{6,V} = 1 \times 10^{-5}$ mol.

Parameters in Table 1 for a hydrophilic drug (heparin) and a hydrophobic drug (paclitaxal) have been considered in our experiments ([1, 10, 11]).

Drug	$D^0_{5,S}[cm^2 s^{-1}]$	$D_{5,V}[cm^2 s^{-1}]$	$k_{b,V}[Mol^{-1} s^{-1}]$	$k_{u,V}[s^{-1}]$	K_b
Heparin	1×10^{-10}	7.7×10^{-8}	9.2×10^4	15×10^{-3}	60
Paclitaxal	5.7×10^{-9}	2.6×10^{-8}	3.6×10^6	9×10^{-2}	400

Table 1: Properties of heparin and paclitaxal.

Figure 3 will illustrate the evolution of heparin with and without binding. We remark that when binding occurs the drug stays more in the arterial wall.

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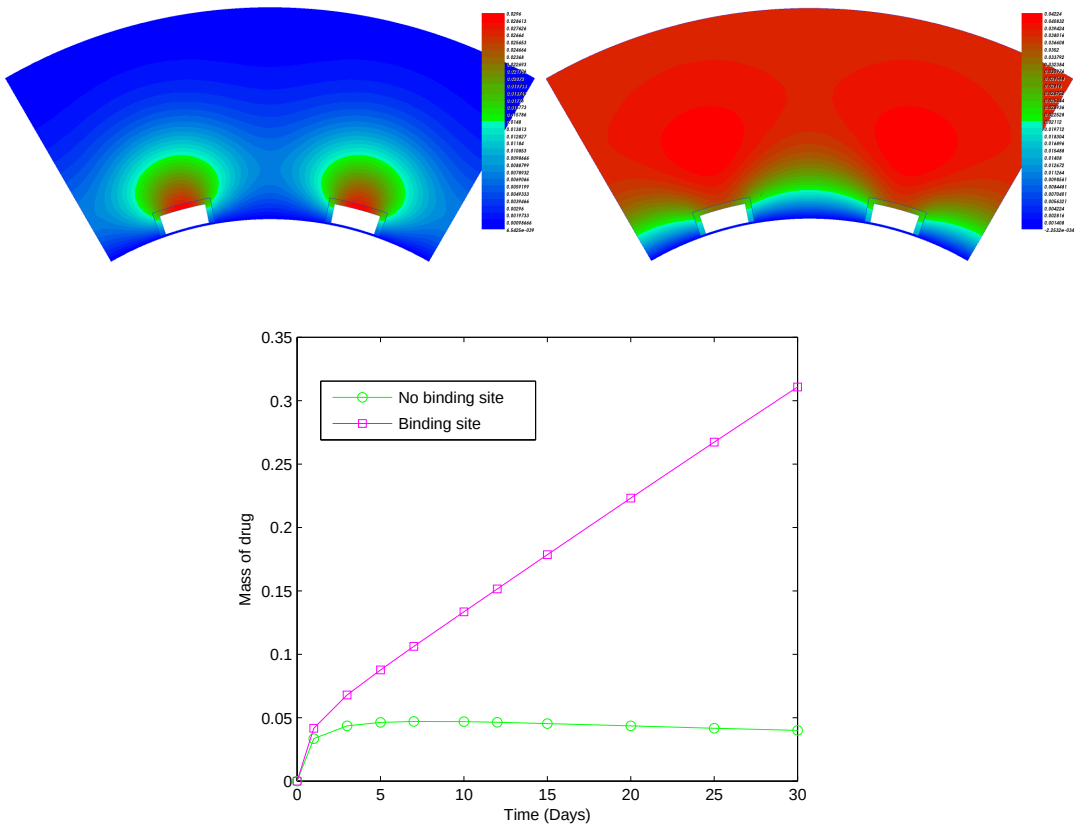

Figure 3: The Effect of binding sites in evolution of heparin in the healthy arterial wall.

Hydrophilic drugs like heparin are known to be rapidly cleared and ineffective. Nowadays they have been discarded from clinical use in favour of the more persistent hydrophobic drugs such as paclitaxel, sirolimus and everolimus ([1]). Comparing heparin and paclitaxal shows the role of reversible binding process in holding the drug in the arterial wall for a longer time. Taxus^{TM} paclitaxel eluting stent from Boston Scientific, Natick, MA, USA, applies paclitaxal, a fairly hyrophobic drug ($K_b = 400$), as therapeutic agent to control migration of smooth muscle cells from endothelium caused by in-stent restenosis. Heparin, a hydrophilic drug ($K_b = 60$), is used in Carmeda BioActive Surface (CBAS) heparin coating made by Carmeda, Upplands Vasby, Stockholm, Sweden.

Distribution of two different drugs, heparin and paclitaxal, released from correspond

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drug eluting stents in the arterial wall are compared in Figure 4. We observe that the heparin leaves the arterial wall faster than the paclitaxal.

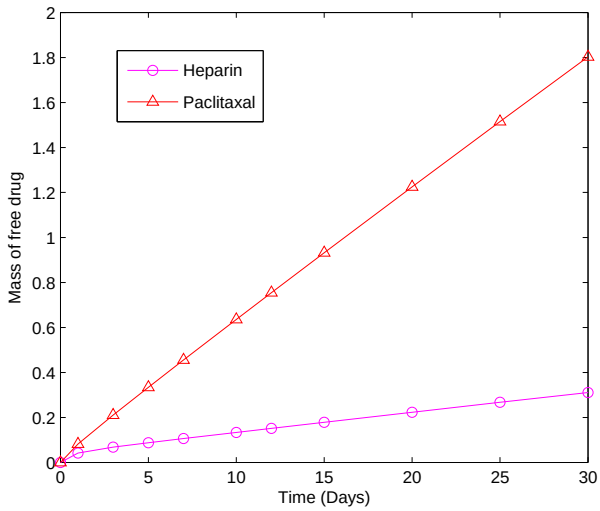

Figure 4: Distribution of heparin (left) and paclitaxal (right) in the arterial wall during 30 days.

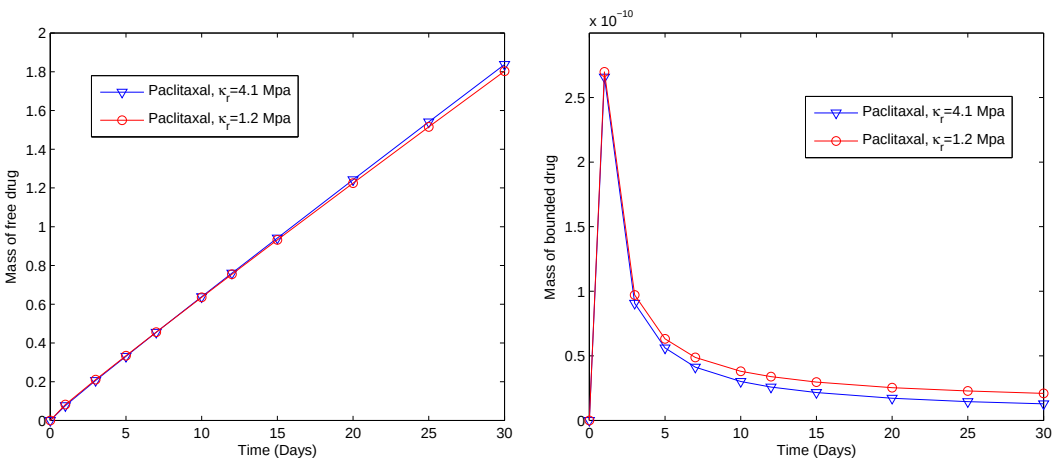

Figure 5: Concentration of bounded (left) and unbounded (right) paclitaxal in the healthy and diseased arterial wall during 30 days.

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Concentration of paclitaxal in a healthy coronary artery with Young modulus $\kappa_r = 1.2$ MPa ([6]) is compared with a highly diseased coronary artery with Young modulus $\kappa_r = 4.1$ MPa ([8]) in Figure 5 (left). When κ_r increases due to age or atherosclerosis, less drug penetrates to the coronary wall in the beginning of the process. A crossing occurs after the initial times around day 2. This finding is justified by the fact that the stiffness of the arterial wall imposes a resistance to the penetration of the drug in the beginning of the process and leads to a drug accumulation in the long time. Figure 5 (right) shows that after 2 days, the amount of bounded drug in the healthy artery is more than bounded drug in the diseased one.

4 Conclusions

In this paper, we updated models presented in [2–4] taking into consideration of some properties of drug in the arterial wall. From the numerical viewpoint two particular aspects of clinical importance are addressed in the paper: the effect of reversible binding sites in the evolution of different drugs and the influence of the viscoelasticity of the vessel wall.

Concerning the first aspect, we show that paclitaxal as a hydrophobic drug stays longer in the arterial wall than heparin (a hydrophilic drug). This observation can help construct effective drug eluting stents. The second aspect that we want to stress is the effect of stiffness of the arterial wall in the presence of drug in the wall. Our findings suggest that the initial concentration of drug in the stent should be tailored to the rheological properties of the arterial walls.

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