ENCIT 2018

ABCM Associação Brasileira de Engenharia e Ciências Mecânicas

17th Brazilian Congress of Thermal Sciences and Engineering
November 25th-28th, 2018, Águas de Lindóia, SP, Brazil

ENCIT-2018-0509
ANISOTROPIC TRANSPORT THROUGH POLYMER LAYER AND POROUS ARTERIAL WALL WITH BINDING IN DRUG-ELUTING STENTS USING THE FEM

Fabiane Frazzoli
Rachel Lucena
Norberto Mangiavacchi
José Pontes
Gustavo Rabello dos Anjos
State University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
fabiane_frazzoli@hotmail.com, rachel.lucena@gmail.com, norberto.mangiavacchi@gmail.com, jose.pontes@uerj.br, gustavo.anjos@uerj.br
Sean McGinty
Division of Biomedical Engineering, University of Glasgow, Glasgow, UK
sean.mcginty@glasgow.ac.uk

Abstract. *The safety and efficacy of Drug-eluting stents is strongly influenced by the anisotropic transport of the antiproliferative/anti-inflammatory drugs in the arterial wall. Dissolution in the polymer coating and specific binding in the artery wall play an important role in the process. We consider the model of dissolution, transport and binding of sirolimus on an axisymmetric domain representing the polymer coating layer and the porous artery wall in the vicinity of a stent strut. We employ the FEM on an unstructured mesh to discretise the governing equations. We employ a non-linear dissolution model for the dynamics in the coating, and a non-linear saturable binding model that includes both specific and non-specific binding in the arterial wall as separate phases, as proposed by McGinty-2016. The arterial wall is considered an anisotropic porous media and the flow is considered to be governed by Darcy flow. The principal directions of the diffusion tensor are considered to be, in general, non aligned with the Cartesian coordinates and are determined by the gradient of signed distance function computed from the inner arterial wall. The permeability in the polymer coating is considered to be very small, but finite. The endothelium lamina, where present, is modelled as a no-flow boundary. The effect of slow and fast release polymers is considered, showing that the time evolution of the process can be efficiently controlled by the polymer diffusion coefficient. However, the spatial distribution of the sirolimus is greatly influenced by the flow and the arterial wall properties, being therefore susceptible to patient health conditions. The effect of the anisotropic diffusion tensor is seen in the sirolimus concentration distribution around the polymer layer, that becomes considerably higher and more uniform around the stent than in the orthotropic model, and in the enhanced mass flux, resulting form the realignment of the principal directions of the tensor with the direction of the interface.*

Keywords: *drug-eluting stents, Darcy's law, convection-diffusion-reaction equations, anisotropic diffusion, finite element method*

1. INTRODUCTION

Drug-eluting stents (DES) marked a technology breakthrough in the field of percutaneous coronary intervention (PCI) due to a profound reduction in neointimal hyperplasia and the need for repeat revascularization as compared with bare-metal stents (BMS). However several concerns related to a higher risk of late thrombotic events and catch-up in efficacy during long-term follow-up hampered their widespread adoption in clinical practice, according toChisari *et al.* (2016).

In DES, safety and efficacy are strongly influenced by the anisotropic transport of the antiproliferative/anti-inflammatory drugs in the arterial wall. Dissolution in the polymer coating and specific binding in the artery wall play an important role in the process.

We developed a computational model employing the FEM on an unstructured mesh to discretise the governing equations. We consider the model of dissolution, transport and binding of sirolimus on an axisymmetric domain representing the polymer coating layer and the porous artery wall in the vicinity of a stent strut. We employ a nonlinear dissolution model for the dynamics of sirolimus in the polymer coating, and a nonlinear saturable binding model that includes both specific and non-specific binding in the arterial wall as separate phases, as proposed by McGinty and Pontrelli (2016). The arterial wall is considered an anisotropic porous media, and the flow is considered to be governed by Darcy flow.

We consider the effect of the variation of the polymer properties, to show that the time evolution of the process can be efficiently controlled by the polymer diffusion coefficient. However, the spatial distribution of the sirolimus is greatly influenced by the flow and the arterial wall properties, being therefore susceptible to patient health conditions.

The anisotropy in drug transport parameters, and in particular the diffusion tensor, is related to tissue fibres orientation. In a previous work (Lucena *et al.* (2017)) the diffusion tensor in the artery wall was considered orthotropic, with principal directions aligned with longitudinal (larger diffusion eigenvalue) and radial (smaller diffusion eigenvalue) directions, due to the orientation of tissue fibers in the artery wall, particularly plain muscle fibers in fine bundles, arranged in lamellæ and disposed circularly around the vessel. However, the presence of the stent causes the compression and realignment of tissue fibers, such that they are parallel to the stent surface in its proximity. Hence, the principal directions of the diffusion tensor must be re-oriented in the vicinity of the stent to properly account for this stent-artery interaction.

In this work, the diffusion tensor is considered to be a general symmetric positive definite tensor, obtained by similarity transformation, considering the realignment of the principal directions obtained by an algebraic approach.

2. THE MATHEMATICAL MODEL

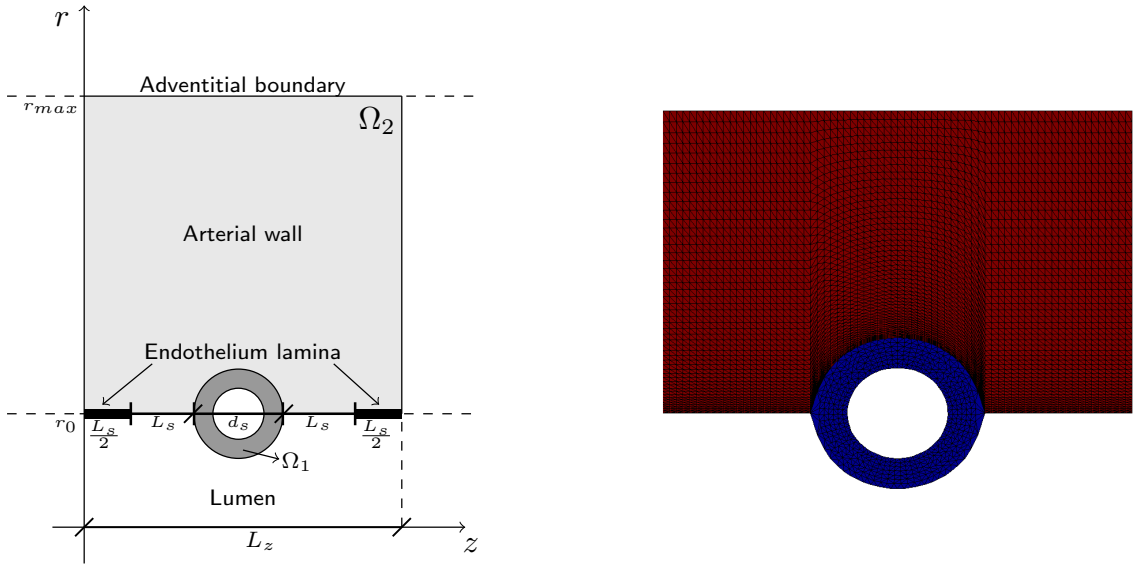


Figure 1. Left: Model 2D axisymmetric geometry. Note that the endothelium is assumed to be denuded in the vicinity of the stent strut. Right: Computational domain and unstructured triangular mesh employed in the simulations. Blue: polymer layer Ω_1. Red: arterial wall Ω_2.

In this work we assume a geometric symmetry about a reference axis, and therefore we employ an axisymmetric formulation. Figure 1 shows the model geometry where z direction is the axis of symmetry and r is the radial direction. The region Ω_1 represents the polymer layer and Ω_2 represents the arterial wall.

We adopt the modeling framework of McGinty and Pontrelli (2016) and Bozsak *et al.* (2014). The arterial wall and the polymer layer are considered as porous media, and flow within these layers is assumed to be governed by Darcy's law, thus

$$\mathbf{u} = -\kappa_i \nabla p, \tag{1}$$

where $\mathbf{u} = (u, v)$ is the velocity field, p is the pressure in the arterial wall, $\kappa_i = P_{Di}/\mu$, P_{Di} is the Darcy permeability of the media and μ is the fluid viscosity. Assuming the continuity equation $\nabla \cdot \mathbf{u} = 0$, we can rewrite the Eq. 1:

$$\nabla \cdot (-\kappa_i \nabla p) = 0. \tag{2}$$

The drug dynamics in the coating is modeled in terms of b_0 (solid) and c_0 (dissolved) concentrations by the equations:

$$\frac{\partial b_0}{\partial t} = -\beta_0 b_0^{2/3}(S_0 - c_0) \tag{3}$$

$$\frac{Dc_0}{Dt} = \nabla \cdot (\mathcal{D}_0 \nabla c_0) + \beta_0 b_0^{2/3}(S_0 - c_0), \tag{4}$$

where the operator D/Dt is the material derivative:

$$\frac{D}{Dt} = \frac{\partial}{\partial t} + \mathbf{u}_s \cdot \nabla \tag{5}$$

where $\mathbf{u}_s = \mathbf{u}/\phi_i$ is the seepage velocity, and ϕ_i is the effective porosity of the media, $\mathcal{D}_0$ is the effective scalar diffusion coefficient of the solute, β_0 the dissolution rate and S_0 is the solubility limit.

Drug elution in the arterial wall is governed by the convection-diffusion-reaction equations:

$$\frac{Dc_1}{Dt} = \nabla \cdot (\mathcal{D}_1 \nabla c_1) - k_1^f c_1 (b_1^{max} - b_1) + k_1^r b_1 - k_2^f c_1 (b_2^{max} - b_2) + k_2^r b_2 \tag{6}$$

$$\frac{\partial b_1}{\partial t} = k_1^f c_1 (b_1^{max} - b_1) - k_1^r b_1 \tag{7}$$

$$\frac{\partial b_2}{\partial t} = k_2^f c_1 (b_2^{max} - b_2) - k_2^r b_2 \tag{8}$$

where c_1 is the concentration of a drug transported in the arterial wall b_1 and b_2 denote non-specifically and specifically bound drug, respectively, k_i^f, k_i^r, b_i^{max} are constant parameters related to the binding kinetics, $\mathcal{D}_1$ is diffusion coefficient, given, in the previous work (Lucena *et al.* (2017)), by the orthotropic tensor:

$$\mathcal{D}_1 = \begin{bmatrix} \mathcal{D}_{1r} & 0 \\ 0 & \mathcal{D}_{1z} \end{bmatrix}. \tag{9}$$

And in this work, is given by an anisotropic tensor:

$$\mathcal{D}_1 = \begin{bmatrix} \mathcal{D}_{1rr} & \mathcal{D}_{1rz} \\ \mathcal{D}_{1zr} & \mathcal{D}_{1zz} \end{bmatrix}, \tag{10}$$

with r the radial direction and z the axial direction.

The tensor $\mathcal{D}_1$ is constructed from the principal directions α_i and the principal values λ_i, as:

$$\mathcal{D}_1 = P \Lambda P^{-1} \tag{11}$$

where Λ is the diagonal matrix of the principal values:

$$\Lambda = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix}, \tag{12}$$

and P is the block matrix of column vectors α_i, given by:

$$P = (\alpha_1 \alpha_2) \tag{13}$$

The direction α_1 is perpendicular to the direction of the fibers of the arterial tissue and therefore it is associated to a smaller diffusion principal value λ_1, while the direction α_2 is tangent to the direction of the arterial fibers, hence associated to a large diffusion principal value λ_2. Values of λ_1 and λ_2 are taken from the radial and axial diffusion coefficients reported in the literature (see Table 1).

To obtain an approximation of the direction perpendicular to the fibers (α_1) we employ the gradient of the distance d from the wall.

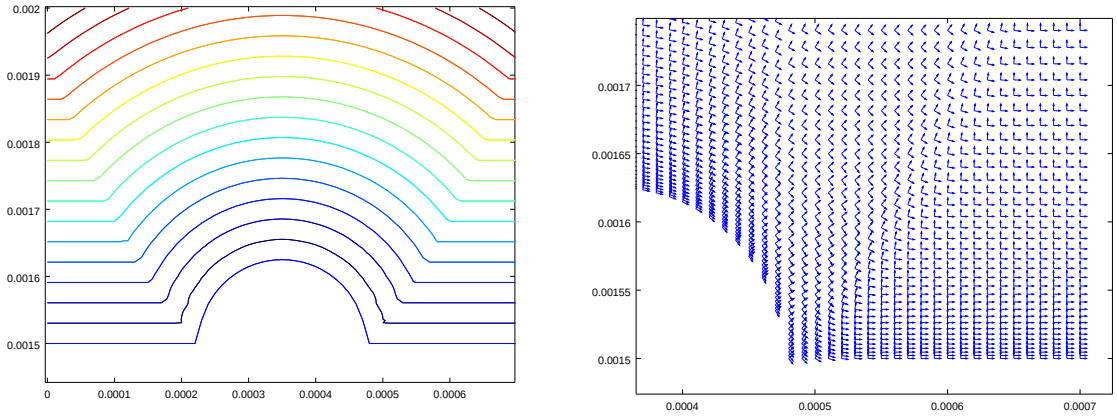
$$\alpha_1 = \nabla d, \tag{14}$$

d is computed for every mesh point as the shortest euclidean distance between the point and all the discrete points on the artery internal surface. Subsequently, the direction α_2 is constructed employing orthogonality:

$$\alpha_{21} = \alpha_{12} \tag{15}$$

$$\alpha_{22} = -\alpha_{11} \tag{16}$$

The computed distance d field is shown in Fig. 2(a), and the computed principal directions field is shown in Fig. 2(b).



(a) (b)

Figure 2. (a) Distance field d. (b) Principal directions field.

The permeability in the polymer coating, P_{D0}, is considered to be very small, but finite. The endothelium lamina, where present, is modeled as a no-flow boundary. The boundary conditions on drug in the denuded endothelium is $c_1 = 0$, between polymer and blood, i.e., on interface Γ_1 is $c_0 = 0$ (see Fig. 3), and in the interior surface of Ω_1 we impose zero flux (see Fig. 1, left). We assume periodic conditions at the side boundaries.

The mass flux is established across the interface and the drug starts to be transferred to the adjacent release medium. The instantaneous flux is given by:

$$\varphi_i(t) = \int_{\Gamma_i} \mathbf{n} \cdot \mathcal{D}_0 \nabla c_0(t) d\Gamma, \quad \text{with} \quad i = 1, 2, \tag{17}$$

where $i = 1$ refers to the lumen interface, and $i = 2$ refers to the arterial wall (see Fig. 3), and $\mathbf{n}$ is the surface normal. $d\Gamma = 2\pi r ds$ and the mass flux (integral) is given by:

$$\Phi_i = \int_0^t \varphi_i(t) dt, \tag{18}$$

where t is the time.

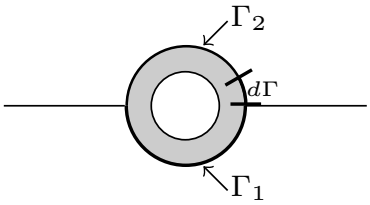


Figure 3. Sketch of interface polymer-lumen and polymer-arterial wall.

The volume averaged total solid and bound sirolimus concentration is defined as:

$$\bar{B}(t) = \frac{1}{V} \int_V (b_0 + b_1 + b_2)(t) dV, \tag{19}$$

where V is the volume of the polymer. Similarly, the volume averaged total free sirolimus concentration is:

$$\bar{C}(t) = \frac{1}{V} \int_V (c_0 + c_1)(t) dV, \tag{20}$$

in both Eqs.(19) and (20) the unit is mol·m^{-3}.

When the flux tends asymptotically at lumen and artery wall boundaries, it is possible to measure the relationship between them, so we have:

$$R_1 = \frac{\Phi_1(t \to \infty)}{\Phi_1(t \to \infty) + \Phi_2(t \to \infty)} \tag{21}$$

and

$$R_2 = \frac{\Phi_2(t \to \infty)}{\Phi_1(t \to \infty) + \Phi_2(t \to \infty)}, \tag{22}$$

where R_1 and R_2 denote the relationship between integral flux in the boundary Γ_1 and Γ_2.

3. NUMERICAL METHOD

The governing equations in 2D axisymmetric coordinates are solved on an unstructured triangular mesh, using linear base functions and the Galerkin Finite Element Method (see Lucena, 2016). The convective terms are discretised using a semi-Lagrangian approach. The Darcy flow is considered to be steady, and driven by the average pressure difference between the lumen and the adventitial boundary (outer boundary of the arterial wall). A semi-implicit fractional step method is employed for the convection-diffusion-reaction equations. The dimensional parameters employed in the simulations are shown in Tab. 1.

Table 1. Dimensional parameters used in the simulations

Parameter		Simulated value	Reference
r_0	lumen radius	1.5×10^{-3}m	Bozsak *et al.* (2014)
$r_{max} - r_0$	arterial wall thickness	5.0×10^{-4}m	Bozsak *et al.* (2014)
d_s	stent strut diameter	2.5×10^{-4}m	Bozsak *et al.* (2014)
L_s	denuded endothelium	1.5×10^{-4}m	Bozsak *et al.* (2014)
L_p	polymer thickness	5.0×10^{-5}m	Bozsak *et al.* (2014)
L_z	domain length	7.0×10^{-4}m	Bozsak *et al.* (2014)
p_{wall}	lumen overpressure	9.31×10^3 Pa	Bozsak *et al.* (2014)
μ	fluid viscosity	7.2×10^{-4} Pa s	Bozsak *et al.* (2014)
dt	simulation time step	100s	
t_{end}	time of simulation	20 and 200 days	
	Polymer layer		
P_{D0}	permeability	2.78×10^{-21}m^2	
ϕ_0	porosity	0.29	
β_0	dissolution rate	1.0×10^{-4}(mol m^{-3})$^{-2/3}$ s^{-1}	McGinty and Pontrelli (2016)
B_0	initial drug eluting	100 mol m^{-3}	McGinty and Pontrelli (2016)
S_0	drug solubility	$B_0/10$ mol m^{-3}	McGinty and Pontrelli (2016)
$\mathcal{D}_0$	fast diffusion coefficient	1.0×10^{-14}m^2 s^{-1}	Bozsak *et al.* (2014)
$\mathcal{D}_0$	slow diffusion coefficient	1.0×10^{-15}m^2 s^{-1}	
	Arterial wall		
P_{D1}	permeability	2.0×10^{-18}m^2	Bozsak *et al.* (2014)
ϕ_1	porosity	0.29	Bozsak *et al.* (2014)
$\mathcal{D}_{1r} = \lambda_1$	radial diffusion coefficient	7×10^{-12}m^2 s^{-1}	Bozsak *et al.* (2014)
$\mathcal{D}_{1z} = \lambda_2$	axial diffusion coefficient	4×10^{-11}m^2 s^{-1}	Bozsak *et al.* (2014)
k_1^f		2 (mol m^{-3} s)$^{-1}$	McGinty and Pontrelli (2016)
k_1^r		5.2×10^{-3} s^{-1}	McGinty and Pontrelli (2016)
b_1^{max}		3.63×10^{-1} mol m^{-3}	McGinty and Pontrelli (2016)
k_2^f		800 (mol m^{-3} s)$^{-1}$	McGinty and Pontrelli (2016)
k_2^r		$1.6 \times 10^{-4} s^{-1}$	McGinty and Pontrelli (2016)
b_2^{max}		3.3×10^{-3} mol m^{-3}	McGinty and Pontrelli (2016)

4. COMPUTATIONAL RESULTS AND DISCUSSION

The pressure and velocity distributions are shown in Figs. 4 and 5. These distributions are assumed constant along the simulation of the sirolimus transport.

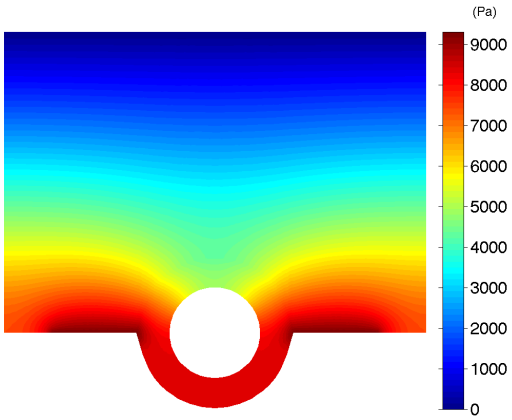
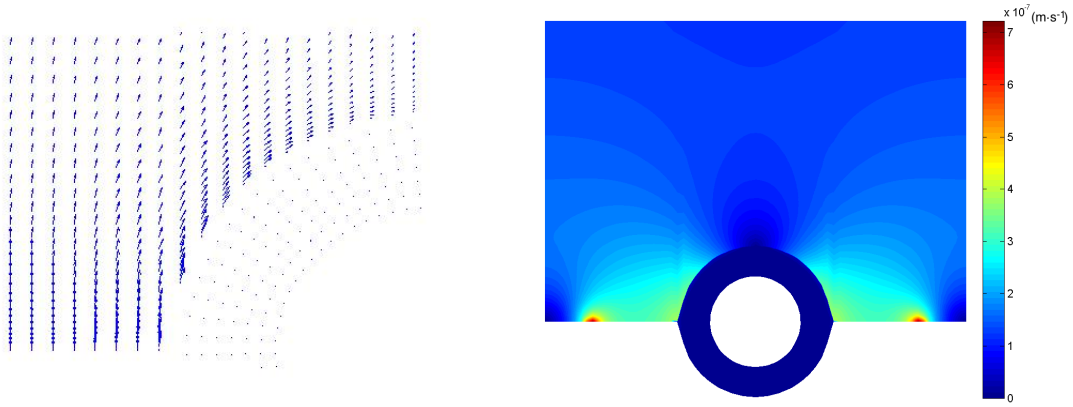


Figure 4. Pressure distribution obtained by the solution of Darcy Eq. (2).



(a) (b)

Figure 5. (a) Velocity field showing relatively large flow velocity close to the junction of the denuded endothelium and the polymer layer, with $\mathbf{u}_{\max} = 7.229 \times 10^{-7}$ m·s^{-1}; (b) Magnitude of velocity computed from Eq. (1).

The simulation starts with all the sirolimus in solid form in the polymer layer, with concentration B_0, and null concentration elsewhere. The solid sirolimus gradually dissolves in the polymer layer and diffuses to the porous artery wall, where it is convected-diffused-bound (see Figs. 6 and 7).

However, even being quite stable during a long time interval, sirolimus concentration is very uneven along the artery wall, showing relatively large concentrations on the top of the struts, and low concentrations on the regions of denuded endothelium, due to the convection and the velocity patterns of the Darcy flow (Fig. 5). A sensitivity analysis is performed (not shown) demonstrating that changes in permeability and diffusivity in the arterial wall, that could be associated to patient conditions, greatly affect the spatial distribution of the sirolimus concentration.

4.1 Fast release polymer

Figures 6 and 7 show the concentration of dissolved and bound sirolimus in the case of a fast release polymer.

Figure 6 shows that the sirolimus distribution at $t = 2$ days and Fig. 7 shows that the sirolimus distribution at $t = 20$, where the differences in concentration due to orthotropic and anisotropic orientation can be observed.

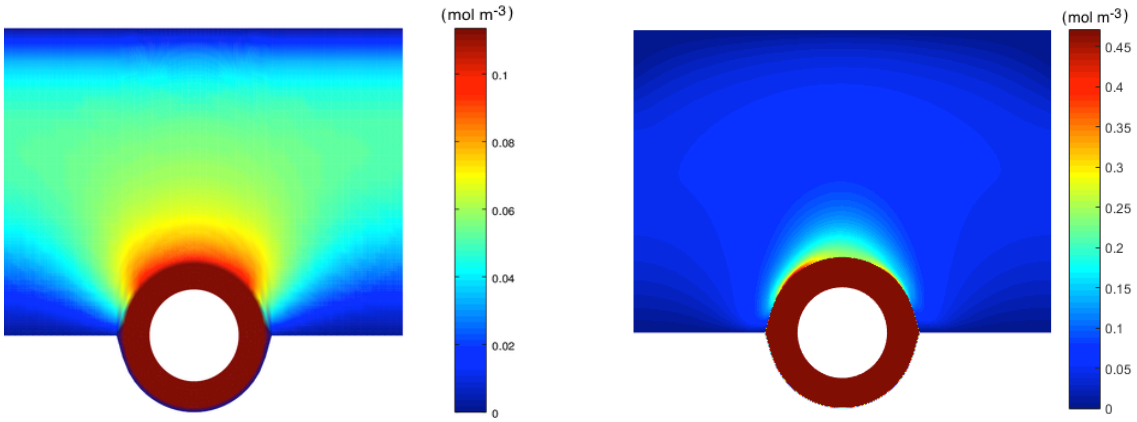


Figure 6. Results of sirolimus concentration for fast release polymer at $t = 2$ days for orthotropic and anisotropic orientation, respectively. Concentration of free sirolimus at the artery wall and polymer layer.

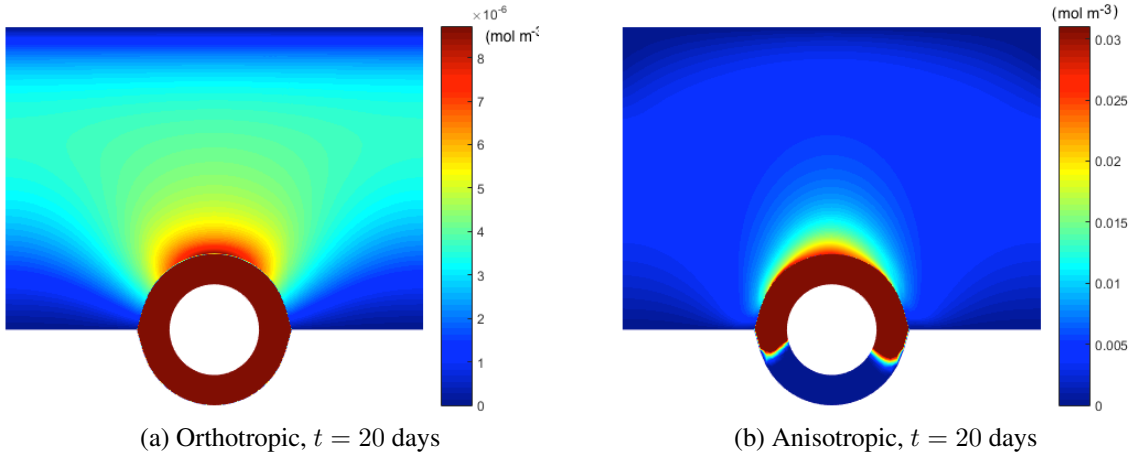


Figure 7. Results of sirolimus concentration for fast release polymer at $t = 20$ days for orthotropic and anisotropic orientation respectively. Concentration of free sirolimus at the artery wall and polymer layer.

4.2 Slow release polymer

Figures 8 and 9 show the concentration of dissolved and bound sirolimus in the case of a slow release polymer.

Figure 8 shows that the sirolimus distribution at $t = 2$ days and 7 shows that the sirolimus distribution at $t = 20$, where the differences in concentration due to orthotropic and anisotropic orientation can be observed.

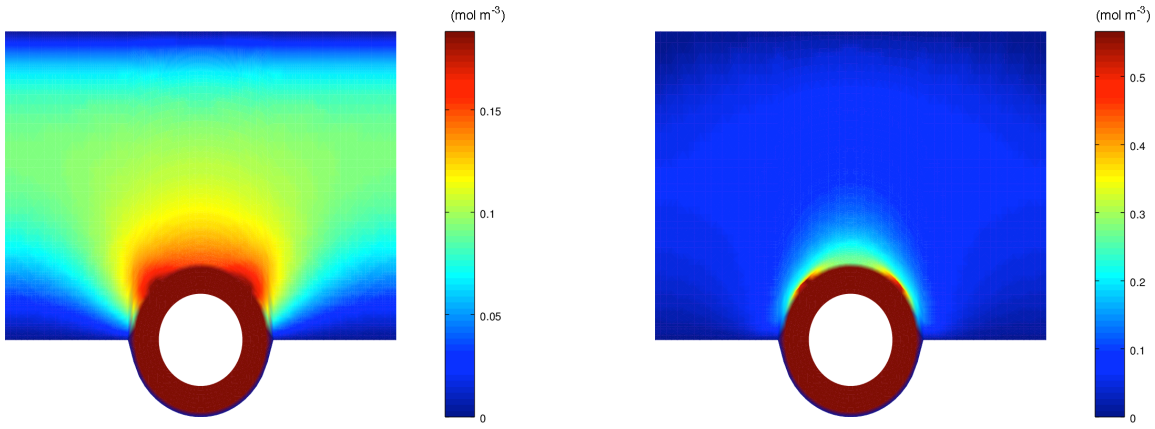
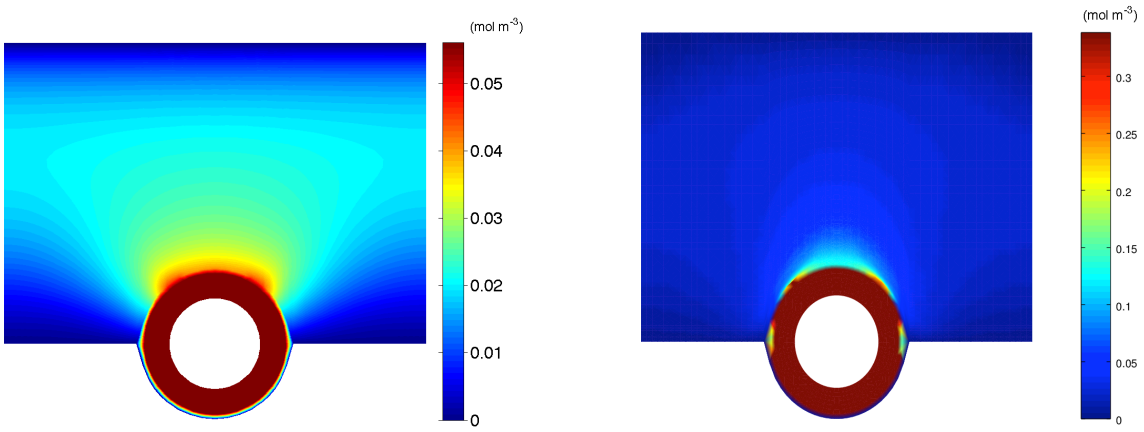


Figure 8. Results of sirolimus concentration for slow release polymer at $t = 2$ days for orthotropic and anisotropic orientation, respectively. Concentration of free sirolimus at the artery wall and polymer layer.



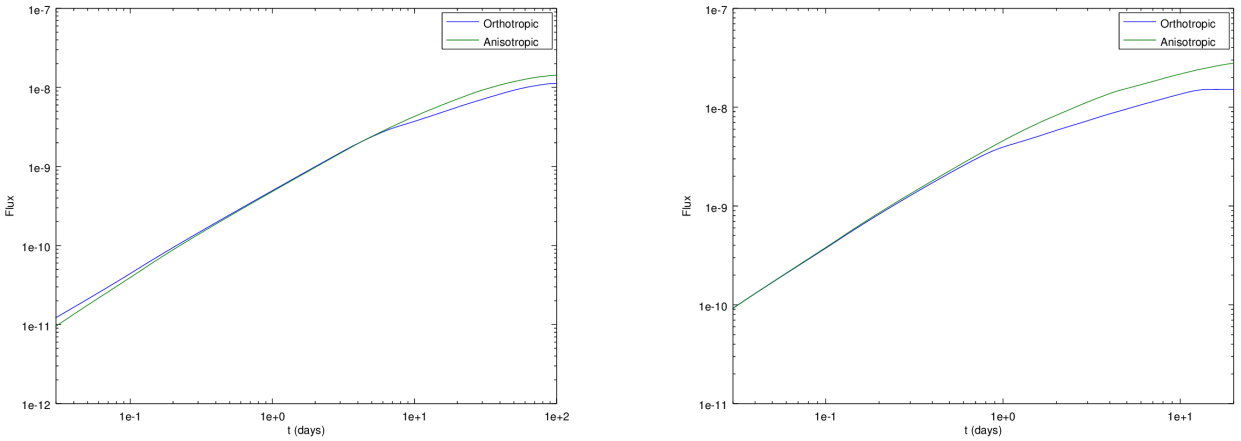
(a) Orthotropic, $t = 20$ days (b) Anisotropic, $t = 20$ days

Figure 9. Results of sirolimus concentration for slow release polymer at $t = 20$ days for orthotropic and anisotropic orientation, respectively. Concentration of free sirolimus at the artery wall and polymer layer.

4.3 Average mass flux

The effect of the anisotropic diffusion tensor can be observed by the analysing the average integral sirolimus mass flux to the arterial wall, Φ_2, and comparing with results of the case employing the orthotropic tensor model, Fig. 10.

For slow release polymer, Fig. 10 (a), the anisotropic model predicts a reduced average mass flux at initial time, and an enhanced average mass flux at later times, when compared to the previous orthotropic model. The results indicate that the use of the orthotropic model could lead to severe underestimates of the concentration of sirolimus occurring at later times in layers of the artery wall in the proximity of the polymer layer, that, if not properly accounted for, may increase the risk of vascular thrombosis.



(a) (b)

Figure 10. Sirolimus flux (integral) Φ_i. (a) Slow release polymer. (b) Fast release polymer.

5. CONCLUSIONS

The simulation of the transport through a polymer layer and a porous arterial wall with binding in drug-eluting stent is performed. We consider the model of dissolution, transport and binding of sirolimus on an axisymmetric domain representing the polymer coating layer and the porous artery wall in the vicinity of a stent strut. We employ the FEM on an unstructured mesh to discretise the governing equations. On one hand, the nonlinear dissolution and diffusion in the polymer coating play a key role in determining the limiting time scale of the process. On the other hand, the nonlinear saturable binding model that includes both specific and non-specific binding in the arterial wall as separate phases plays an important role in determining the temporal-spatial distribution of the drug.

In a previous work (Lucena *et al.* (2017)), using the sirolimus gradient at the interfaces, it was estimated that $46-48\%$ of the sirolimus is diffused to the lumen and it was lost to the flowing blood, while $52-54\%$ actually gets into the arterial wall. However, the spatial distribution of the sirolimus is greatly influenced by the flow and the arterial wall properties, being therefore susceptible to patient health conditions.

In this work, a new anisotropic model for the diffusion tensor in the artery wall that takes into account the realignment of the principal directions of the diffusion tensor due to the introduction of the stent, employing an algebraic model to define the principal directions, is presented. Results of simulations with the new model are compared to results obtained with a previous orthotropic model (Bozsak *et al.* (2014)). The comparison of the two models shows that the realignment of the principal directions of the diffusion tensor, due to the presence of the stent, greatly interferes in the sirolimus transport. The effect of the anisotropic diffusion tensor is particularly seen in the sirolimus concentration distribution around the polymer layer, that becomes considerably more uniform along the polymer interface, but showing a reduced diffusion in the interface normal direction and an enhanced diffusion in the surface tangent direction. For slow release polymer, the anisotropic model predicts a reduced average mass flux at initial time, and an enhanced average mass flux at later times, producing higher concentration of sirolimus for longer times in a narrow region around the polymer layer, when compared to the previous orthotropic model. The results indicate that the use of the orthotropic model could lead to severe underestimates of the concentration of sirolimus occurring at later times in layers of the artery wall in the proximity of the polymer layer, that, if not properly accounted for, may increase the risk of vascular thrombosis.

6. ACKNOWLEDGEMENTS

The authors would like to acknowledge financial support from FAPERJ, CNPq, and the University of Glasgow EPSRC GCF ISF fund.

7. REFERENCES

Bozsak, F., Chomaz, J. and Barakat, A., 2014. "Modelling the transport drugs of eluted from stents: physical phenomena driving drug distribution in the arterial wall". *Biomech Model Mechanobiol*, Vol. 13, pp. 327–347.

Chisari, A., Pistritto, A., Piccolo, R., Manna, A.L. and Danzi, G., 2016. "The ultimaster biodegradable-polymer sirolimus-eluting stent: An updated review of clinical evidence". *Int. J. Mol. Sci.*, Vol. 17(9), p. 1490.

Lucena, R.M., 2016. *Numerical study of CO2 dissolution in saline aquifers with deformed interface*. Ph.D. thesis, State University of Rio de Janeiro.

Lucena, R.M., Mangiavacchi, N., Pontes, J., Anjos, G. and McGinty, S., 2017. "Transport through polymer layer and porous arterial wall with binding in drugeluting stents using the fem". In *Proceedings of the 24th ABCM International Congress of Mechanical Engineering - COBEM*. ABCM, Rio de Janeiro, Brazil, Vol. 1.

McGinty, S. and Pontrelli, G., 2016. "On the role of specific drug binding in modelling arterial eluting stents". *J Math Chem*, Vol. 54, pp. 967–976.

8. RESPONSIBILITY NOTICE

The authors are the only responsible for the printed material included in this paper.