TÉCNICO LISBOA

A mathematical model for blood flow and mass transport by a drug eluting stent

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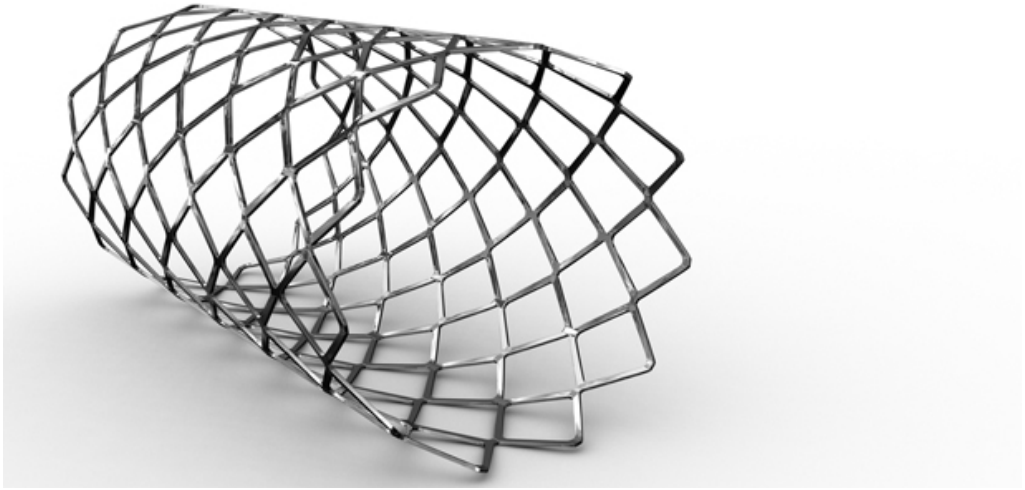
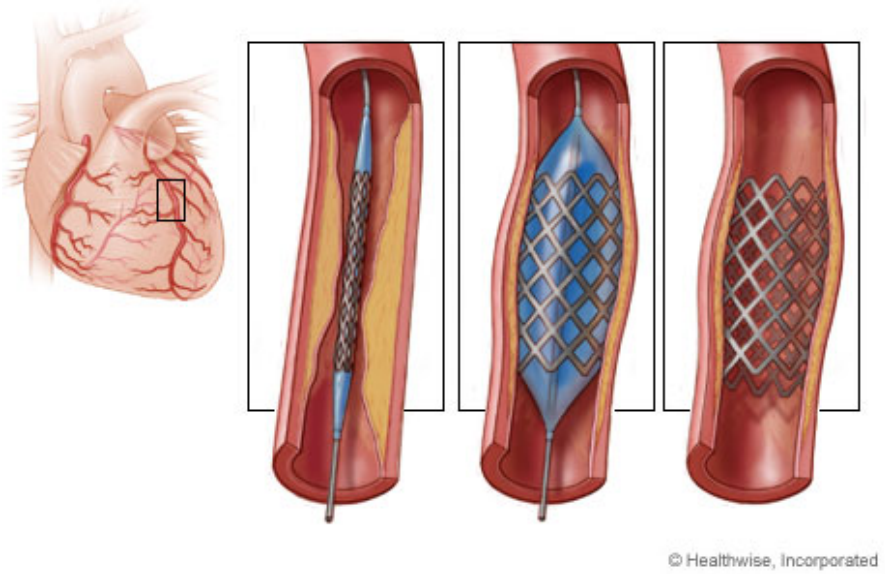
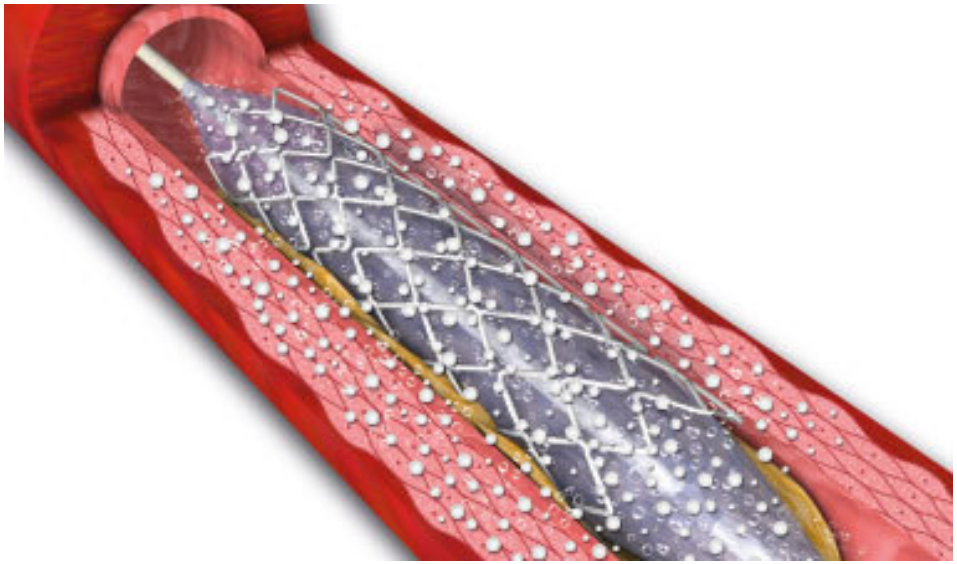


A stent is an expandable metallic tube used to open a narrowed or clogged artery.



During a procedure called angioplasty, the stent is inserted into a coronary artery and expanded using a small balloon.



Drug eluting stents: polymeric coating loaded with drugs that inhibit smooth muscle cells proliferation.

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2 Modeling blood flow

Assumptions

- The stented vessel region is a straight cylinder with axis Γ_l.

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- Flow is stable and laminar in the lumen (characteristic Reynolds number is low).
- The wall is a single homogeneous layer (the fluid-wall model).

Domain

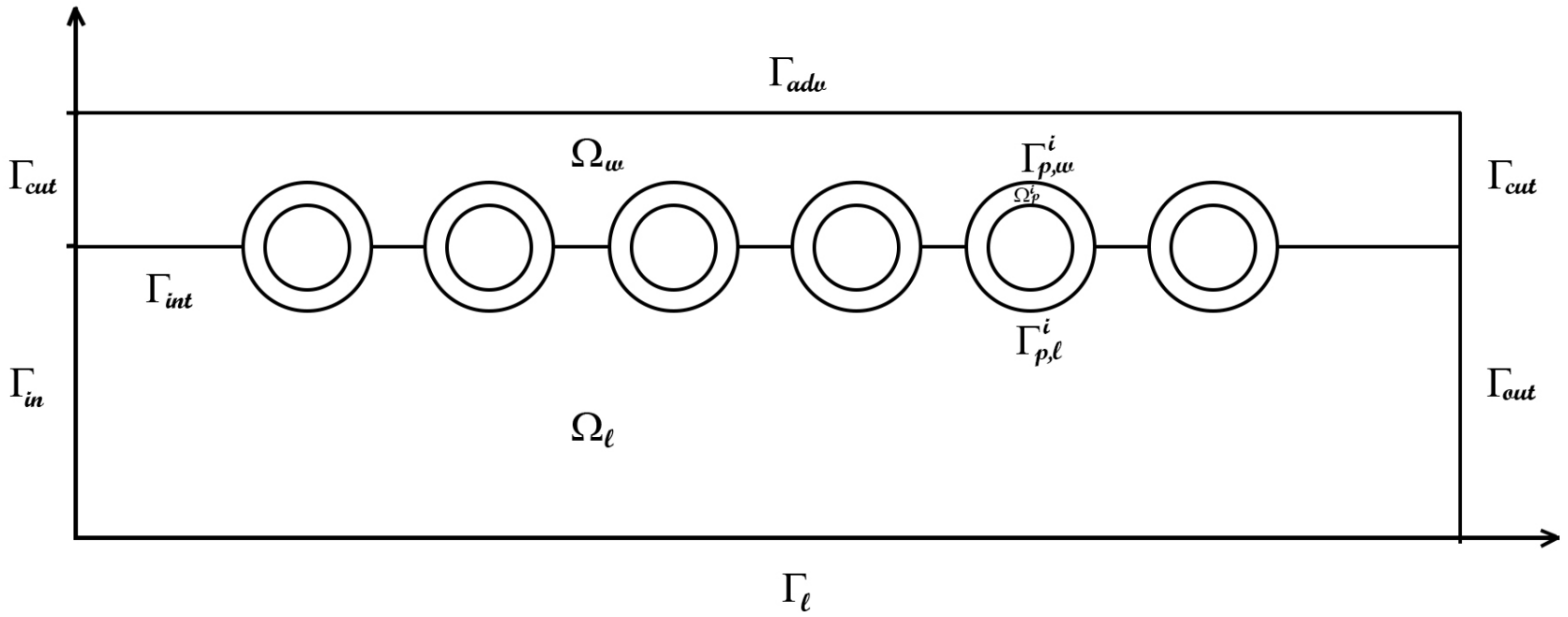

Figure : Physical domain

System of equations

The model is defined by the following system of equations,

$$\begin{aligned} \mu\Delta u_l - (u_l \cdot \nabla)u_l - \nabla p_l &= 0 \quad \text{in } \Omega_l \times (0,T), \\ \nabla \cdot u_l &= 0 \quad \text{in } \Omega_l \times (0,T), \end{aligned}$$

System of equations

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$$\begin{aligned}
\mu\Delta u_l - (u_l \cdot \nabla)u_l - \nabla p_l &= 0 \quad \text{in } \Omega_l \times (0,T),\\
\nabla \cdot u_l &= 0 \quad \text{in } \Omega_l \times (0,T),\\
\kappa_1 u_w + \nabla p_w &= 0 \quad \text{in } \Omega_w \times (0,T),\\
\nabla \cdot u_w &= 0 \quad \text{in } \Omega_w \times (0,T),
\end{aligned}$$

where μ is the blood dynamic viscosity and κ_1 is the inverse permeability of the arterial wall.

System of equations

We denote by $\Omega_p = \bigcup_{i=1}^{k} \Omega_{p,}^{(i)}$ the polymeric coating of the stent, then,

$$\begin{aligned} \kappa_1 u_p + \nabla p_p &= 0 \quad \text{in } \Omega_p \times (0,T), \\ \nabla \cdot u_p &= 0 \quad \text{in } \Omega_p \times (0,T), \end{aligned}$$

where κ_2 is the inverse permeability of polymeric coating.

Boundary conditions

Coupled with boundary conditions,

$$\begin{aligned} u_l &= u_{in} \quad \text{on } \Gamma_{in}, \\ p_l &= p_0 \quad \text{on } \Gamma_{out}, \\ u_l \cdot \eta_l &= 0 \quad \text{on } \Gamma_l, \\ u_w \cdot \eta_w &= 0 \quad \text{on } \Gamma_{cut}, \\ p_w &= p_0 - 100 \quad \text{on } \Gamma_{adv}, \end{aligned}$$

where $u_{in} : \mathbb{R}^2 \to \mathbb{R}^2$ is a given function and $p_0 \in \mathbb{R}$ is a constant.

Interface conditions

We consider the continuity of the pressure and the continuity of the normal component of the velocity,

$$\begin{aligned} p_w &= p_l, \quad u_l \cdot \eta_l = -u_w \cdot \eta_w \quad \text{on } \Gamma_{int}, \\ p_p &= p_w, \quad u_p \cdot \eta_p = -u_w \cdot \eta_w \quad \text{on } \Gamma_{p,w}, \\ p_l &= p_p, \quad u_l \cdot \eta_l = -u_p \cdot \eta_p \quad \text{on } \Gamma_{p,l}. \end{aligned}$$

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3 Modeling drug release

Assumptions

- The coating of the drug eluting stent is made of a porous polymeric matrix that encapsulates a therapeutic drug in solid phase.

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- The coating of the drug eluting stent is made of a porous polymeric matrix that encapsulates a therapeutic drug in solid phase.
- Drug transfer does not affect blood and plasma flow.
- The drug is present in two states (dissolved and undissolved).
- Drug release is controlled by non-Fickian diffusion of plasma into the polymeric matrix, by advection activated by trans-mural pressure gradients and dissolution.

Non-Fickian diffusion

- Fick's classic law:

$$\frac{\partial C}{\partial t} = -\nabla \cdot \ J_F(C)$$

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$$J = J_F(C) + J_{NF}(\sigma) \quad \rightarrow \quad J_{NF}(C) = -D_v(C)\nabla\sigma$$

- Non-Fickian diffusion equation:

$$\frac{\partial C}{\partial t} = -\nabla \cdot (J_F(C) + J_{NF}(\sigma))$$

Non-Fickian behavior

We consider a generalized Maxwell-Wiechert model with $m+1$ arms in parallel. The stress associated to solvent uptake and exerted by the polymer is defined as

$$\sigma(c_p) = -\left(\sum_{k=0}^{m} E_k\right) \nabla f(c_p) + \int_0^t \left(\sum_{k=1}^{m} \frac{E_k}{\tau_k} e^{-\frac{t-s}{\tau_k}}\right) \nabla f(c_p)(s) ds \ ,$$

where $\tau_k = \frac{\mu_k}{E_k}$ are the relaxation times associated to each of the m Maxwell fluid arms

System of equations

The evolution of solvent penetration, drug diffusion and dissolution in the polymeric matrix are described by the following equations on the domain Ω_p and for $t > 0$,

$$\begin{aligned}
\frac{\partial c_p}{\partial t} &= \nabla \cdot (D_p(c_p)\nabla c_p + D_v(c_p)\nabla \sigma(c_p) - \gamma_p u_p c_p) \ , \\
\frac{\partial c_d}{\partial t} &= \nabla \cdot (D_d(c_p)\nabla c_d + (\upsilon(c_p) - \gamma_d u_p)c_d) + K_p \left(\frac{ds - c_p}{ds}\right) c_p H(s) \ , \\
\frac{\partial s}{\partial t} &= -K_p \left(\frac{ds - c_p}{ds}\right) c_p H(s) \ ,
\end{aligned}$$

where $\upsilon(c_p) = D_v(c_p)\frac{\nabla \sigma(c_p)}{c_p}$ and H is the heaviside step function.

System of equations

The concentration of dissolved drug in the lumen and in the wall can be tracked with the following equations

$$\begin{aligned} \frac{\partial c_w}{\partial t} &= \nabla \cdot (D_w(c_w)\nabla c_w - \gamma_w u_w c_w)\,, \\ \frac{\partial c_l}{\partial t} &= \nabla \cdot (D_l(c_l)\nabla c_l - u_l c_l)\,, \end{aligned}$$

where D_w and D_l denote the diffusion coefficients of the drug in the lumen and in the wall respectively. The constant $0 < \gamma_i \leq 1$ denotes the hindrance coefficient accounting for penetrant-media frictional effects.

The fluxes

They are defined as,

$$
\begin{aligned}
J_p &= -\left(D_p(c_p)\nabla c_p + D_v(c_p)\nabla\sigma(c_p) - \gamma_p u_p c_p\right), \\
J_d &= -\left(D_d(c_p)\nabla c_d + (\upsilon(c_p) - \gamma_d u_p)c_d\right), \\
J_w &= -\left(D_w(c_w)\nabla c_w - \gamma_w u_w c_w\right), \\
J_l &= -\left(D_l(c_l)\nabla c_l - u_l c_l\right).
\end{aligned}
$$

Initial conditions

We have,

$$\begin{aligned} c_p(0) &= 0 \quad \text{in } \Omega_p, \\ c_d(0) &= 0 \quad \text{in } \Omega_p, \\ s(0) &= s_0 \quad \text{in } \Omega_p, \\ c_w(0) &= 0 \quad \text{in } \Omega_w, \\ c_l(0) &= 0 \quad \text{in } \Omega_l. \end{aligned}$$

Boundary conditions

Coupled with,

$$
\begin{aligned}
c_p &= 1 && \text{on } \Gamma_{p,l} \cup \Gamma_{p,w}, \\
J_w \cdot \eta_w &= 0 && \text{on } \Gamma_{adv} \cup \Gamma_{cut}, \\
J_l \cdot \eta_l &= 0 && \text{on } \Gamma_{in} \cup \Gamma_{out}, \\
J_d \cdot \eta_p &= 0 && \text{on } \Gamma_{str}, \\
J_p \cdot \eta_p &= 0 && \text{on } \Gamma_{str}.
\end{aligned}
$$

Interface conditions

We consider the continuity of the drug concentrations and the continuity of the normal component of the fluxes,

$$\begin{aligned} c_w &= c_l, \quad J_w \cdot \eta_w = -J_l \cdot \eta_l \quad \text{on } \Gamma_{int}, \\ c_d &= c_w, \quad J_d \cdot \eta_p = -J_w \cdot \eta_w \quad \text{on } \Gamma_{p,w}, \\ c_l &= c_d, \quad J_l \cdot \eta_l = -J_d \cdot \eta_p \quad \text{on } \Gamma_{p,l}. \end{aligned}$$

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4 Finite element discretization for blood flow

Preliminaries

We use the edge stabilization technique introduced by Badia and Codina [1], further explored by D'Angelo and Zunino [2, 3] based on a H^1-conforming approximation for velocities on each subdomain together with Nitsche's type penalty method for the coupling between different subproblems. This combination leads to a continuous-discontinuous Galerkin type penalty method.

Preliminaries

We will assume that each Ω_i is a convex polygonal domain, equipped with a family of quasi-uniform triangulations $\mathcal{T}_{h,i}$ made of affine triangles that are conforming on each interface.

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On each subregion we consider the spaces,

$$\begin{aligned} \mathbf{V}_{h,i} &= \{v_h \in C(\Omega_i) \ : \ v_h|_K \in \mathbb{P}^k(K), \ \forall K \in \mathcal{T}_{h,i}\}, \quad V_{h,i} = [\mathbf{V}_{h,i}]^2, \\ Q_{h,i} &= \{q_h \in L^2(\Omega_i) \ : \ q_h|_K \in \mathbb{P}^{k-1}(K), \ \forall K \in \mathcal{T}_{h,i}\}, \end{aligned}$$

where $k \geq 1$.

Preliminaries

As global approximation spaces, we define

$$V_h = \bigoplus_{i=1}^{N} V_{h,i}, \qquad Q_h = \bigoplus_{i=1}^{N} Q_{h,i}.$$

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For the treatment of the nonlinear advective term of the steady Navier-Stokes equation, we consider Picard's iteration, thus we have that

$$\mu \Delta u_l - (w_l \cdot \nabla) u_l - \nabla p_l = 0 \quad \text{in } \Omega_l \times (0, T).$$

Preliminaries

We denote with

- $\Gamma_{ij} = \partial\Omega_i \cap \partial\Omega_j$, for all $j = 1, .., N$.

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- $\mathcal{B}_{h,i}$ the trace meshes at the boundary subdomains.
- $\mathcal{F}_{h,i}$ the set of all interior edges of $\mathcal{T}_{h,i}$.
- h_E a piecewise constant function taking the value $diam(E)$ on each edge E.

Preliminaries

Let ϕ_h represent a finite element function, we define the jump and the average across any (internal) face F of the computational domain in the usual ways,

$$\begin{aligned} [\![\phi_h]\!](x) &= \lim_{\delta \to 0} \left[\phi_h(x - \delta\eta_F) - \phi_h(x + \delta\eta_F)\right], \quad x \in F, \\ \{\phi_h\}(x) &= \lim_{\delta \to 0} \frac{1}{2}\left[\phi_h(x - \delta\eta_F) + \phi_h(x + \delta\eta_F)\right], \quad x \in F. \end{aligned}$$

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We also define the weighted average on Γ_{ij},

$$\{\phi_h\}_w = \alpha_l \phi_{h,i} + \alpha_w \phi_{h,j}, \tag{1}$$

where $\alpha = (\alpha_l, \alpha_w)$ are suitable weights such that $\alpha_l + \alpha_w = 1$.

Bilinear forms

For any $u_h, v_h \in V_v$ and $p_h, q_h \in Q_h$, we define,

$$\begin{aligned} a(u_h, v_h; w_l) \quad = \quad & \int_\Omega (\mu \nabla u_h : \nabla v_h + (w_l \cdot \nabla u_h) \cdot v_h + \kappa u_h \cdot v_h) \\ & - \int_{\partial\Omega} \mu \left(\nabla u_h \eta \cdot v_h + \nabla v_h \eta \cdot u_h \right) \\ & + \int_{\mathcal{B}_h} \left(\frac{1}{2} \left(|w_l \cdot \eta| - w_l \cdot \eta \right) + \frac{\tau_u}{h_E} \mu \right) u_h \cdot v_h \end{aligned}$$

Bilinear forms

For any $u_h, v_h \in V_v$ and $p_h, q_h \in Q_h$, we define,

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\begin{aligned}
a(u_h, v_h; w_l) &= \int_\Omega (\mu \nabla u_h : \nabla v_h + (w_l \cdot \nabla u_h) \cdot v_h + \kappa u_h \cdot v_h) \\
&\quad - \int_{\partial\Omega} \mu \left(\nabla u_h \eta \cdot v_h + \nabla v_h \eta \cdot u_h\right) \\
&\quad + \int_{\mathcal{B}_h} \left(\frac{1}{2}\left(|w_l \cdot \eta| - w_l \cdot \eta\right) + \frac{\tau_u}{h_E}\mu\right) u_h \cdot v_h \\
b(p_h, v_h) &= -\int_\Omega p_h \nabla \cdot v_h + \int_{\partial\Omega} p_h v_h \cdot \eta,
\end{aligned}
$$

Bilinear forms

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a(u_h, v_h; w_l) &= \int_\Omega (\mu \nabla u_h : \nabla v_h + (w_l \cdot \nabla u_h) \cdot v_h + \kappa u_h \cdot v_h) \\
&\quad - \int_{\partial\Omega} \mu \left(\nabla u_h \eta \cdot v_h + \nabla v_h \eta \cdot u_h\right) \\
&\quad + \int_{\mathcal{B}_h} \left(\frac{1}{2}\left(|w_l \cdot \eta| - w_l \cdot \eta\right) + \frac{\tau_u}{h_E}\mu\right) u_h \cdot v_h \\
b(p_h, v_h) &= -\int_\Omega p_h \nabla \cdot v_h + \int_{\partial\Omega} p_h v_h \cdot \eta, \\
d(p_h, v_h) &= \int_\Gamma \{p_h\}_w [\![v_h \cdot \eta_\Gamma]\!],
\end{aligned}
$$

Bilinear forms

$$
\begin{aligned}
c(u_h, v_h) &= \int_{\mathcal{G}_h} \frac{\tau_u}{h_E} \{\mu\}_w [\![u_h]\!] \cdot [\![v_h]\!] \\
&- \int_{\Gamma} \left(\{\mu \nabla u_h \eta_\Gamma\}_w \cdot [\![v_h]\!] + \{\mu \nabla v_h \eta_\Gamma\} \cdot [\![u_h]\!] \right),
\end{aligned}
$$

Bilinear forms

$$
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c(u_h, v_h) &= \int_{\mathcal{G}_h} \frac{\tau_u}{h_E} \{\mu\}_w [\![u_h]\!] \cdot [\![v_h]\!] \\
&- \int_{\Gamma} \left(\{\mu \nabla u_h \eta_\Gamma\}_w \cdot [\![v_h]\!] + \{\mu \nabla v_h \eta_\Gamma\} \cdot [\![u_h]\!] \right), \\
j_u(u_h, v_h) &= \int_{\mathcal{G}_h} \frac{\tau_u}{h_E} [\![u_h \cdot \eta_\Gamma]\!] [\![v_h \cdot \eta_\Gamma]\!] \\
&+ \int_{\mathcal{B}_h} \frac{\tau_u}{h_E} \mu (u_h \cdot \eta)(v_h \cdot \eta),
\end{aligned}
$$

Bilinear forms

$$
\begin{aligned}
c(u_h, v_h) &= \int_{\mathcal{G}_h} \frac{\tau_u}{h_E} \{\mu\}_w [\![u_h]\!] \cdot [\![v_h]\!] \\
&- \int_{\Gamma} \left(\{\mu \nabla u_h \eta_\Gamma\}_w \cdot [\![v_h]\!] + \{\mu \nabla v_h \eta_\Gamma\} \cdot [\![u_h]\!] \right), \\
j_u(u_h, v_h) &= \int_{\mathcal{G}_h} \frac{\tau_u}{h_E} [\![u_h \cdot \eta_\Gamma]\!] [\![v_h \cdot \eta_\Gamma]\!] \\
&+ \int_{\mathcal{B}_h} \frac{\tau_u}{h_E} \mu (u_h \cdot \eta)(v_h \cdot \eta), \\
j_p(p_h, q_h) &= \int_{\mathcal{F}_h} \tau_p h_E [\![p_h]\!] [\![q_h]\!].
\end{aligned}
$$

Mixed formulation

Find $(u_h, p_h) \in V_h \times Q_h$ such that

$$
\begin{aligned}
& a(u_h, v_h; w_l) + c(u_h, v_h) + j_u(u_h, v_h) + b(p_h, v_h) \\
& + d(p_h, v_h) = \mathcal{F}(v_h), \qquad \forall v_h \in V_h, \\
& b(q_h, u_h) + d(q_h, u_h) - j_p(p_h, q_h) = 0, \quad \forall q_h \in Q_h,
\end{aligned}
$$

where

$$
\begin{aligned}
\mathcal{F}(v_h) \quad = \quad & \int_{\Gamma_{in}} \left(\frac{1}{2} \left(|w_l \cdot \eta| - w_l \cdot \eta \right) + \frac{\tau_u}{h_E} \mu \right) u_{in} \cdot v_{h,l} \\
& + \int_{\Gamma_{in}} \frac{\tau_u}{h_E} \mu (u_{in} \cdot \eta)(v_{h,l} \cdot \eta) \\
& - \int_{\Gamma_{out}} p_0 v_{h,l} \cdot \eta_l - \int_{\Gamma_{adv}} (p_0 - 100) v_{h,w} \cdot \eta_w .
\end{aligned}
$$

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5 Finite element discretization for drug delivery

Preliminaries

We use the Implicit-Explicit (IMEX) finite element method introduced by Ferreira, Gudiño and de Oliveira [6, 7], in combination with the domain decomposition method for advection-diffusion equations introduced by Burman and Zunino [4] on each subdomain.

Preliminaries

On each subregion we consider the space,

$$V_{h,i} \quad = \quad \{v_h \in C(\Omega_i) \ : \ v_h|_K \in \mathbb{P}^k(K), \ \forall K \in \mathcal{T}_{h,i}\},$$

where $k \geq 1$.

As global approximation space, we define

$$V_h = \bigoplus_{i=1}^{N} V_{h,i}.$$

Bilinear form

For any $c_h, v_h \in V_h$ we define,

$$
\begin{aligned}
e(c_h, v_h) \quad = \quad & \int_\Gamma \left(\frac{\tau_c}{h_E} \{D\}_w [\![\nabla c_h]\!][\![\nabla d_h]\!] + \{u_h \cdot \eta\}\{c_h\}_w [\![d_h]\!] \right. \\
& \left. - \{D\nabla c_h \cdot \eta\}_w [\![d_h]\!] - \{D\nabla d_h \cdot \eta\}_w [\![c_h]\!] \right).
\end{aligned}
$$

Plasma diffusion

Find $c_{h,p} \in V_{h,p}$ such that

$$a_p(c_{h,p}, v_h) + e(c_{h,p}, v_h) = (\frac{c_{h,p}^{n-1}}{\Delta t}, v_h), \quad \forall v_h \in V_{h,p},$$

where,

$$\begin{aligned} a_p(c_{h,p}, v_h) \quad = \quad & \int_\Omega \Big(\frac{c_{h,p}}{\Delta t} v_h + \Big(D_p(c_{h,p}^{n-1}) \nabla c_{h,p} \\ & + D_v(c_{h,p}^{n-1}) \nabla \sigma(c_{h,p}^{n-1}) - \gamma_p u_{h,p} c_{h,p} \Big) \cdot \nabla v_h \Big) \\ & + \int_{\mathcal{F}_{h,p}} \tau_u h_E^2 \|u_{h,p} \cdot \eta\|_{L^\infty(E)} [\![\nabla c_{h,p} \cdot \eta]\!] [\![\nabla d_h \cdot \eta]\!]. \end{aligned}$$

Drug diffusion in the polymer

Find $c_{h,d} \in V_{h,p}$ such that

$$a_d(c_{h,d}, v_h) + e(c_{h,d}, v_h) = (\frac{c_{h,d}^{n-1}}{\Delta t}, v_h), \quad \forall v_h \in V_{h,p},$$

where,

$$\begin{aligned} a_d(c_{h,d}, v_h) \quad = \quad & \int_\Omega \Big(\frac{c_{h,d}}{\Delta t} v_h + (D_d(c_{h,p}) \nabla c_{h,d} \\ & + (\upsilon(c_{h,p}) - \gamma_d u_h) c_{h,d}) \cdot \nabla v_h \\ & + K_d \left(\frac{ds - c_{h,d}^{n-1}}{ds} \right) c_{h,p} H(s_h^{n-1}) v_h \Big) \\ & + \int_{\mathcal{F}_{h,p}} \tau_u h_E^2 \|u_{h,p} \cdot \eta\|_{L^\infty(E)} [\![\nabla c_{h,d} \cdot \eta]\!] [\![\nabla d_h \cdot \eta]\!]. \end{aligned}$$

Drug diffusion in the lumen and wall

Find $c_{h,i} \in V_{h,i}$ such that

$$a_i(c_{h,i}, v_h) + e(c_{h,i}, v_h) = (\frac{c_{h,i}^{n-1}}{\Delta t}, v_h), \quad \forall v_h \in V_{h,i},$$

where ,

$$\begin{aligned} a_i(c_{h,i}, v_h) &= \int_{\Omega_i} \left(\frac{c_{h,i}}{\Delta t} v_h + \left(D_i(c_{h,i}^{n-1}) \nabla c_{h,i} - \gamma_i u_i c_{h,i} \right) \cdot \nabla v_h \right) \\ &\quad + \int_{\mathcal{F}_{h,i}} \tau_u h_E^2 \| u_{h,i} \cdot \eta \|_{L^\infty(E)} [\![\nabla c_{h,i} \cdot \eta]\!] [\![\nabla d_h \cdot \eta]\!]. \end{aligned}$$

for $i = l, w$.

Contents

6 Numerical experiments

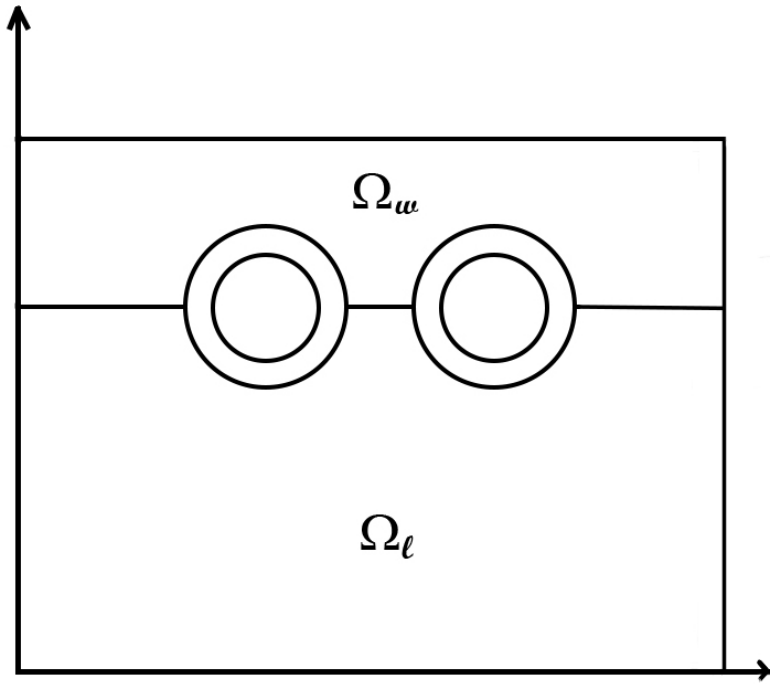

Figure : Simplified domain

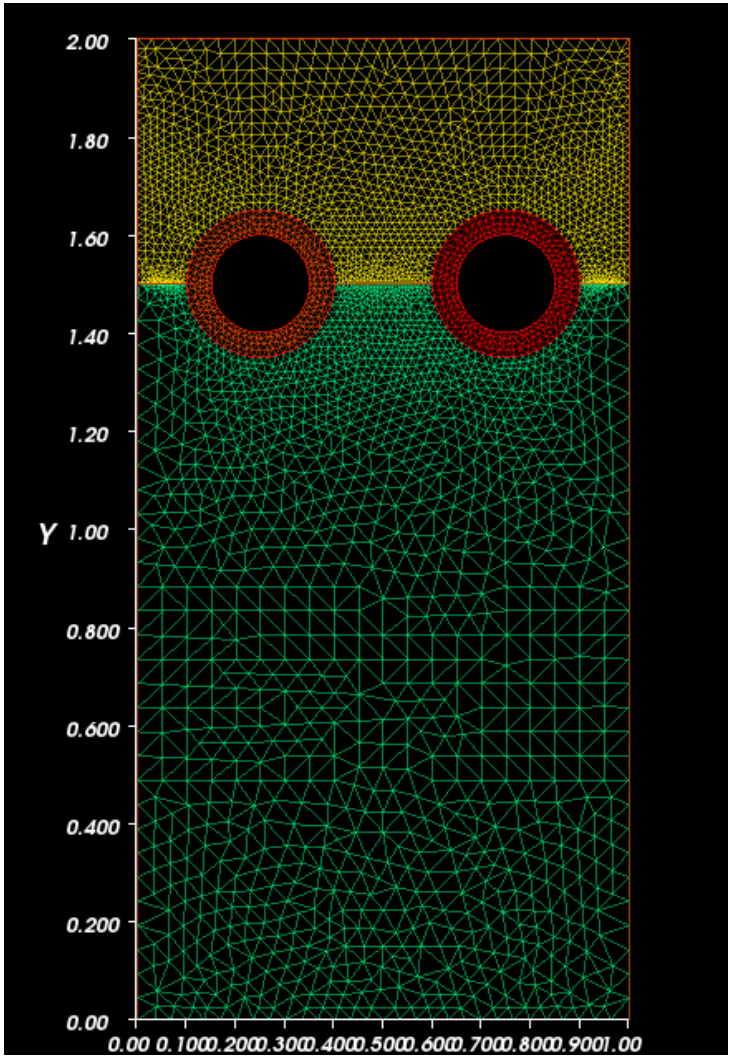

Figure : Computational domain, $N_T = 10314$ and $N_V = 5306$

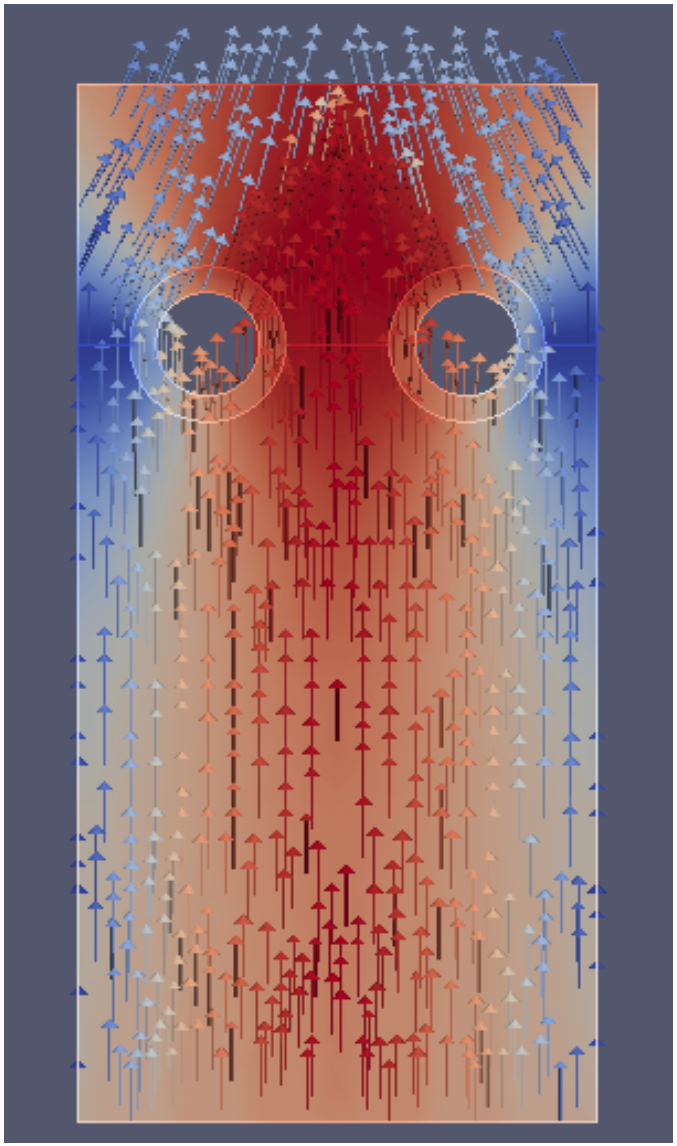

Figure : Velocity field

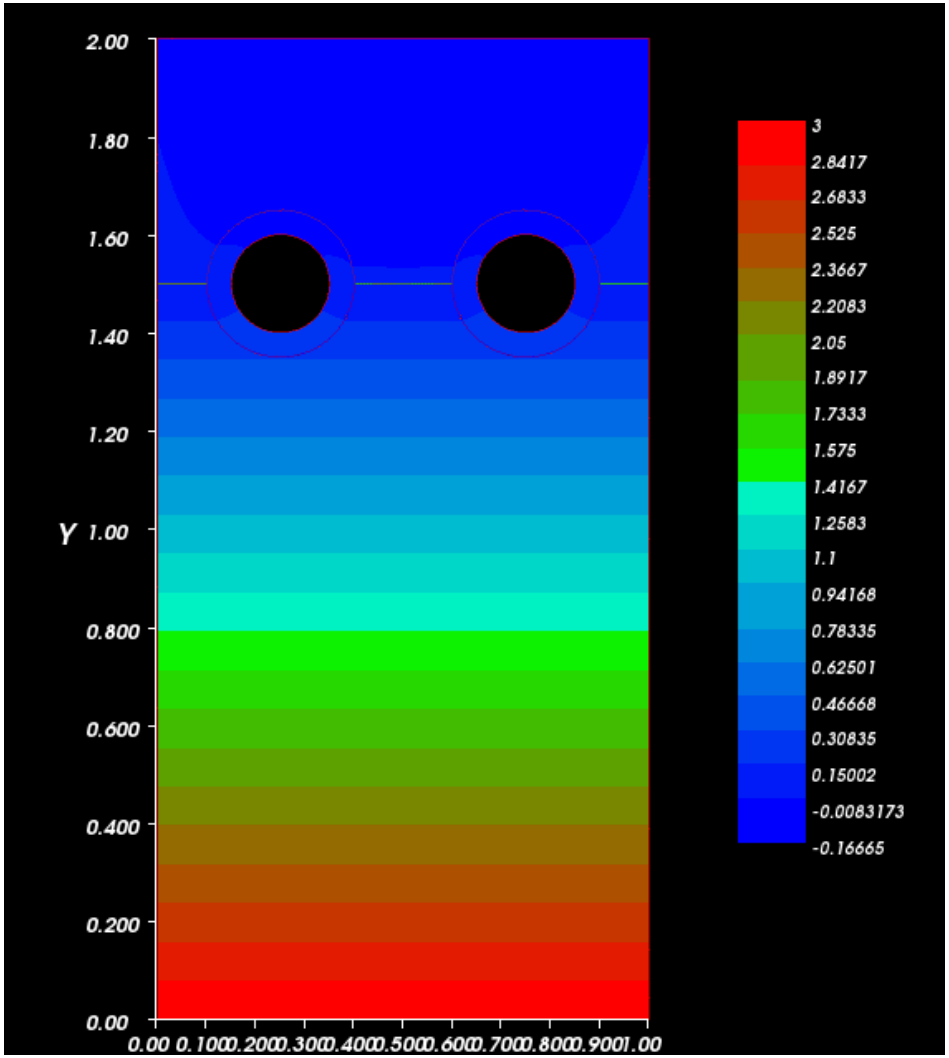

Figure : Pressure

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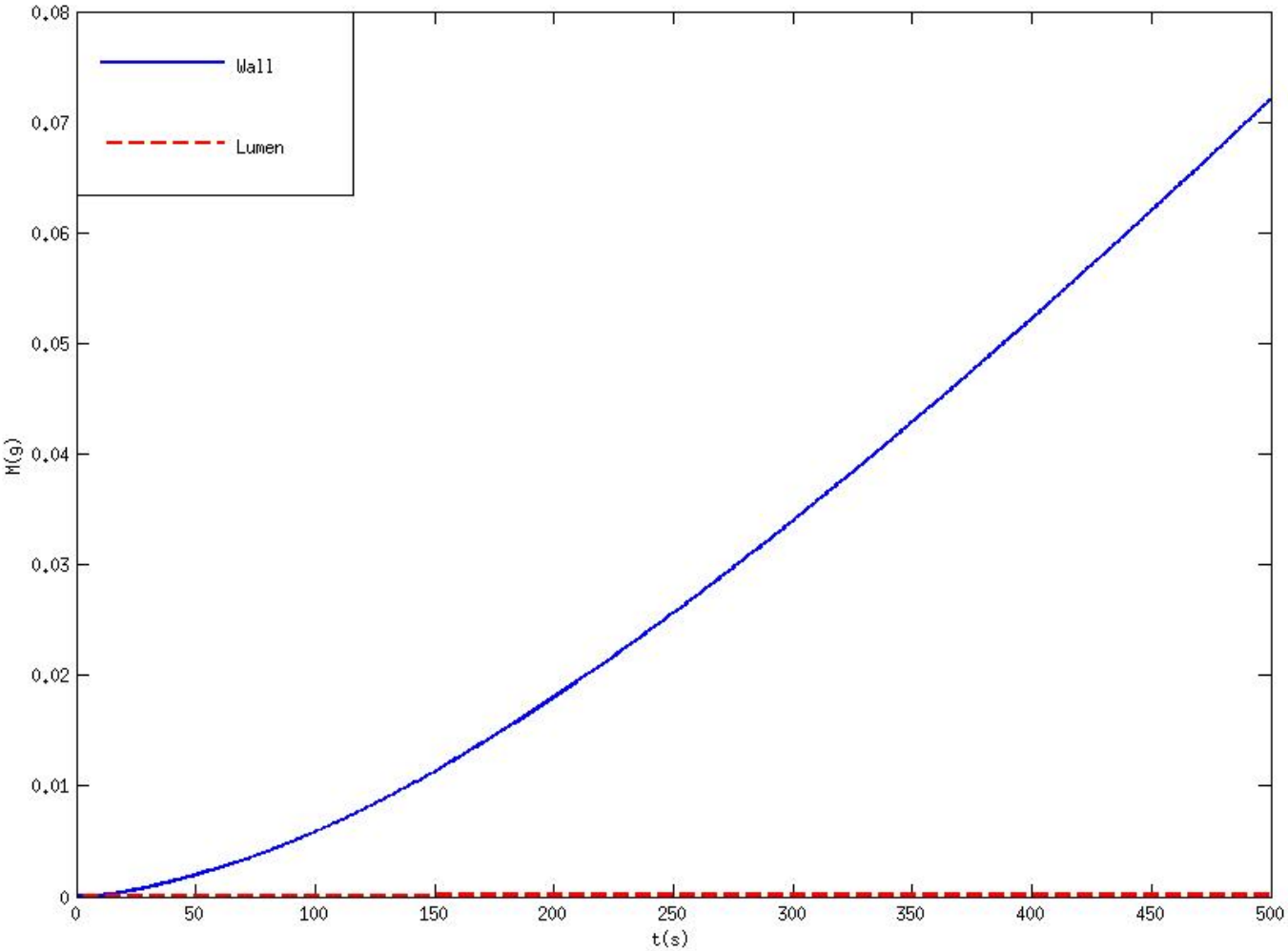

Figure : Mass of drug in the wall vs the lumen

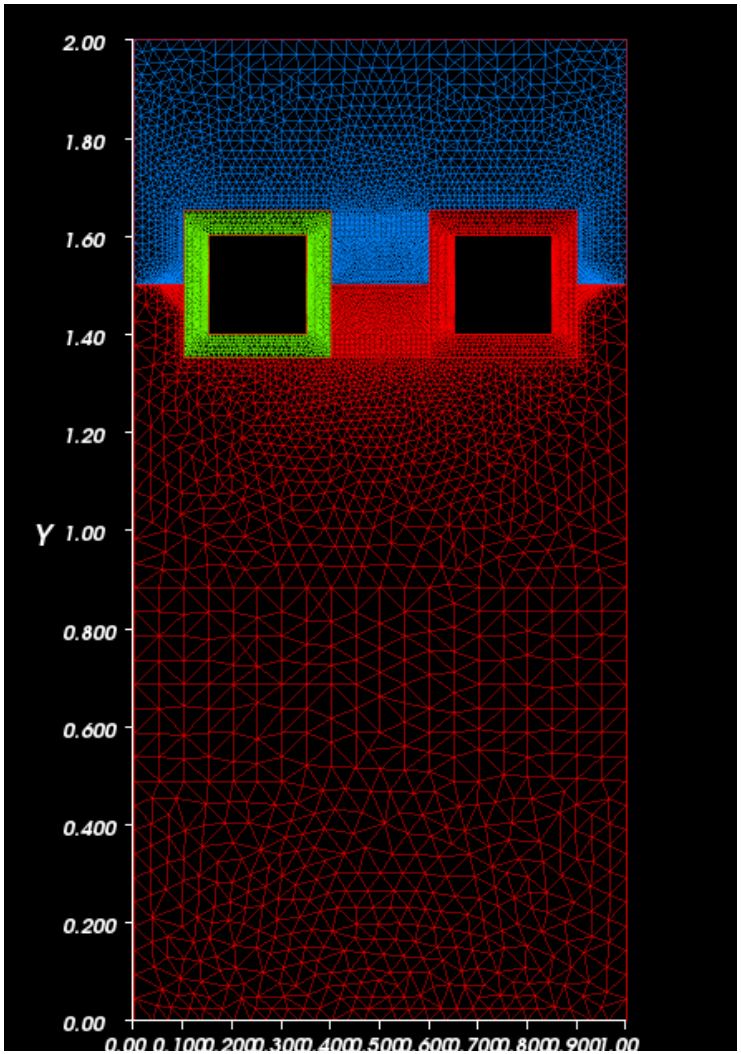

Figure : Computational domain, $N_T = 10314$ and $N_V = 5306$

Loading video

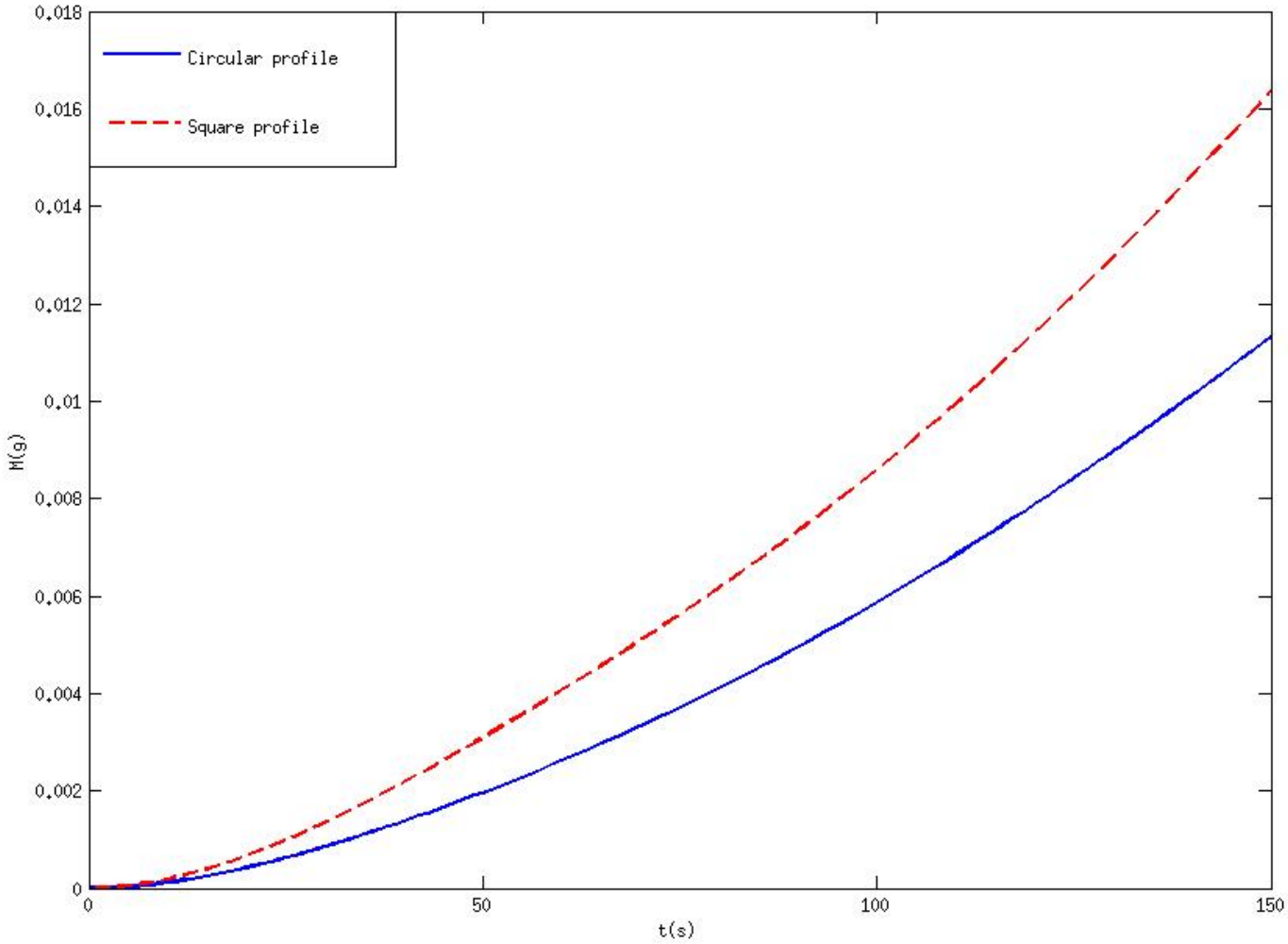

Figure : Mass of drug different stent profiles

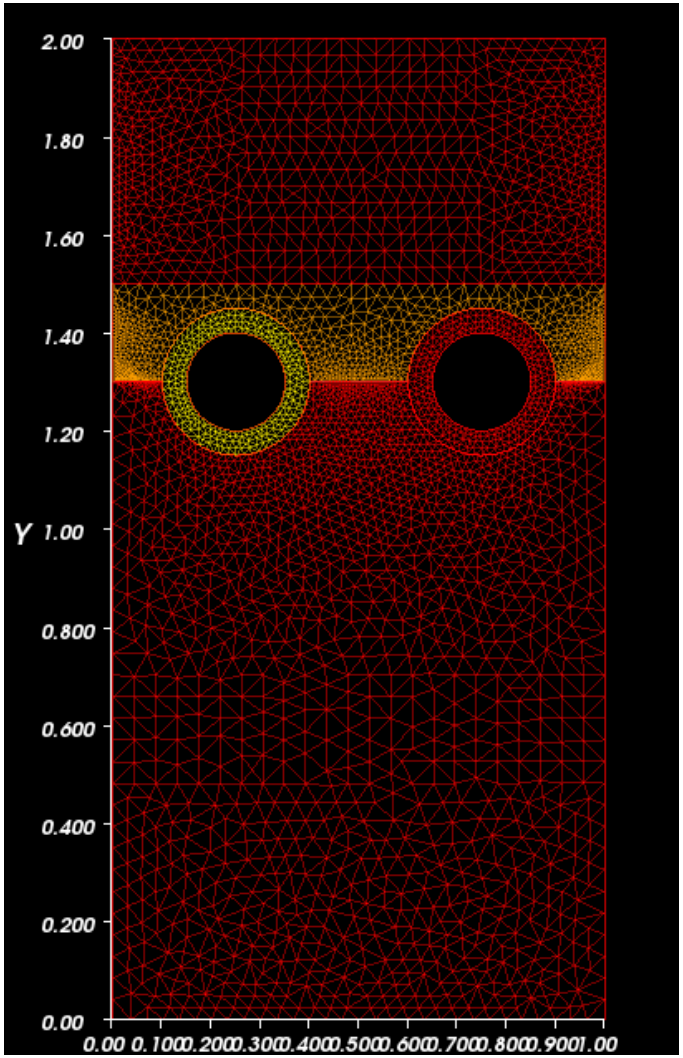

Figure : Computational domain, $N_T = 10314$ and $N_V = 5306$

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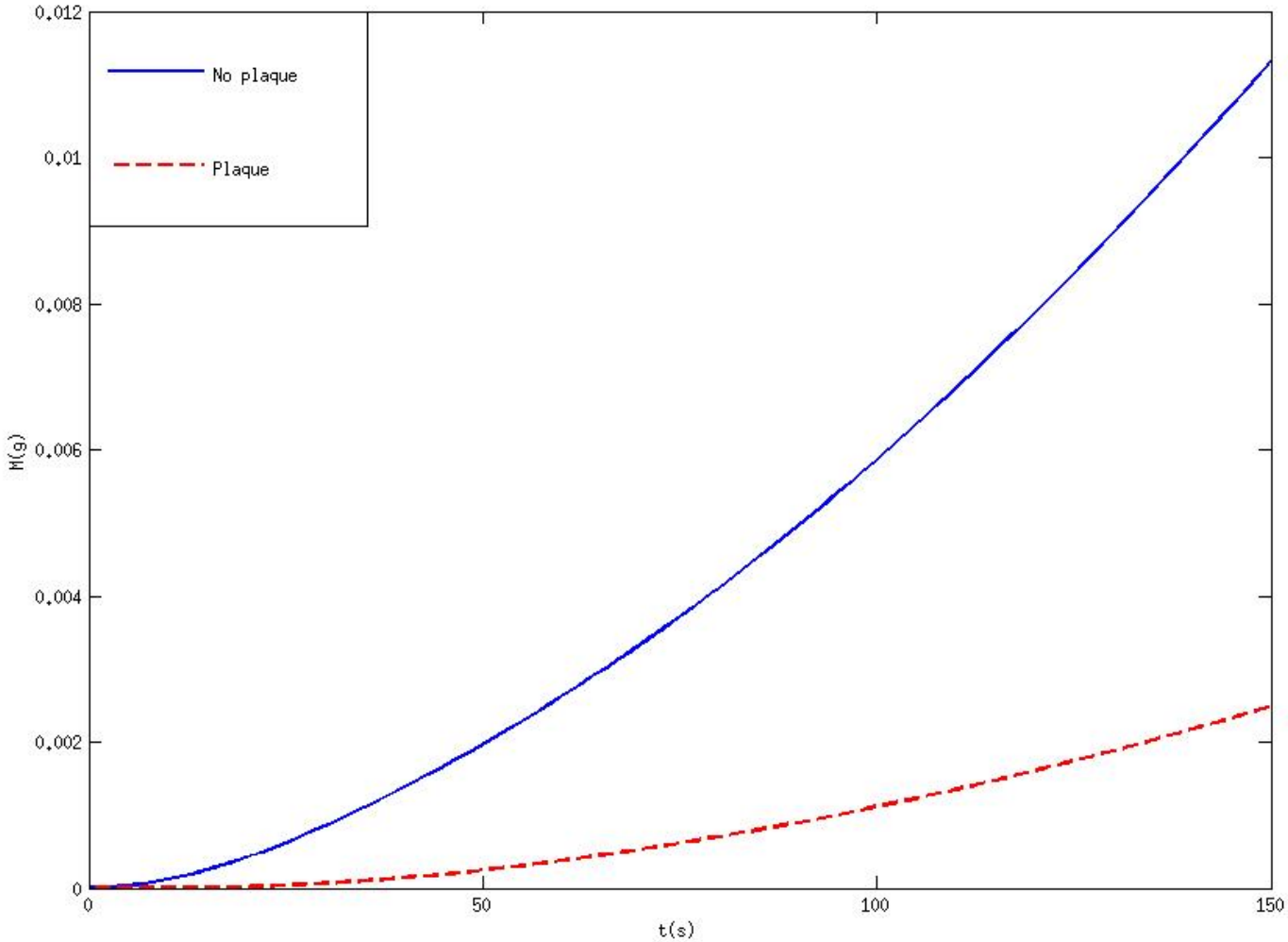

Figure : Mass of drug in the wall plaque vs no plaque

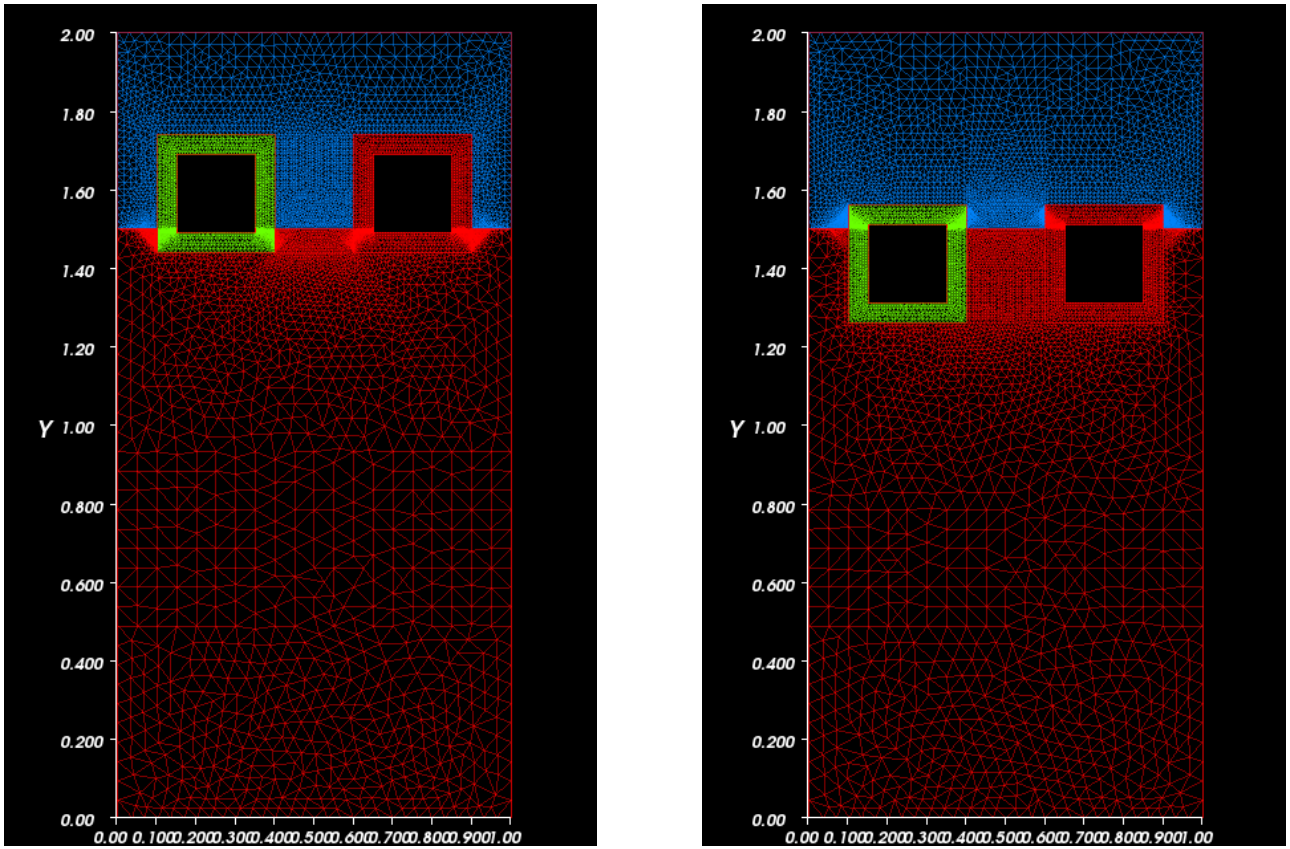

Figure : Computational domains, $N_T = 10314$ and $N_V = 5306$

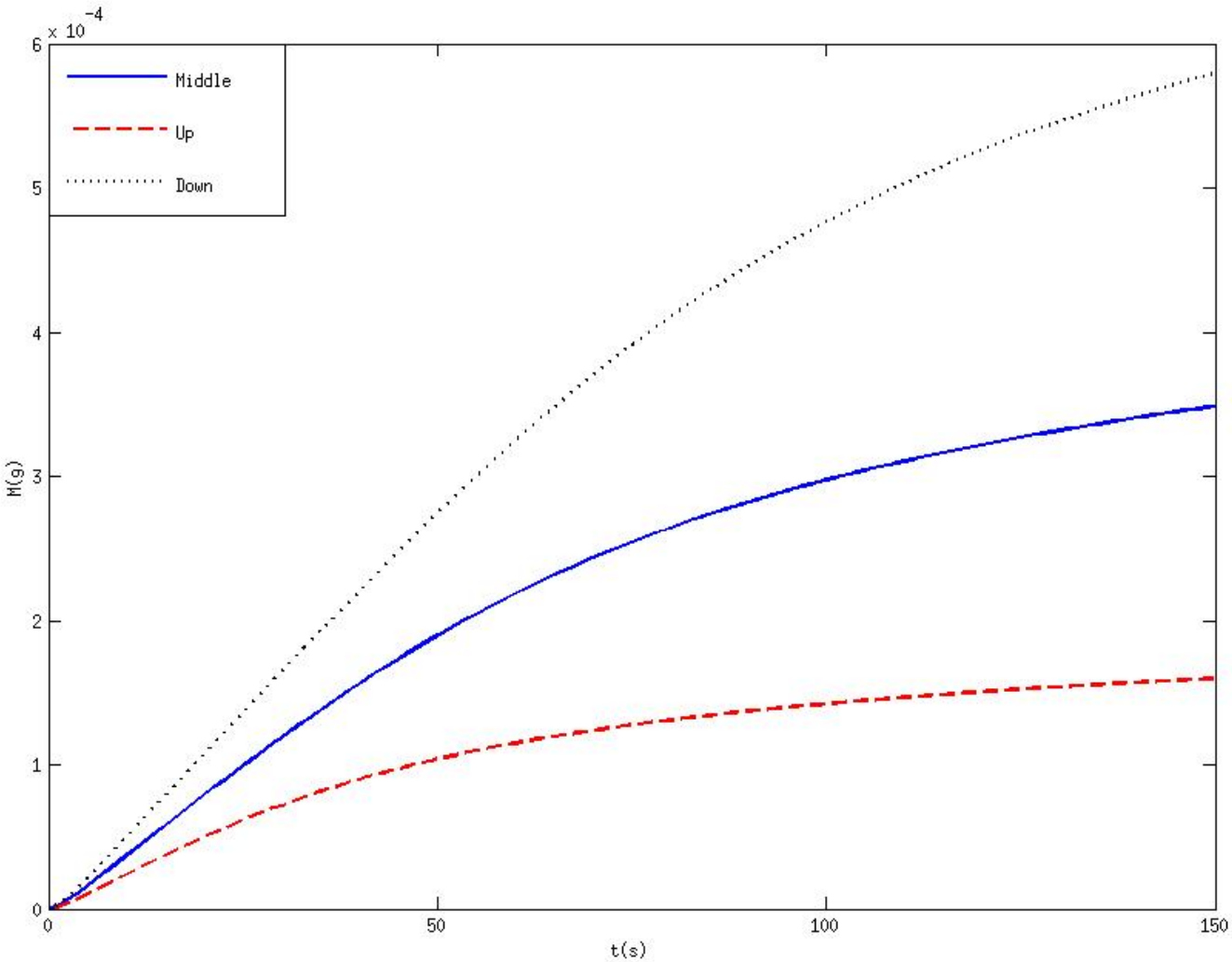

Figure : Mass of drug in the wall different positions

Acknowledgments

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