Mathematical models and numerical simulation of drug release in the vascular system

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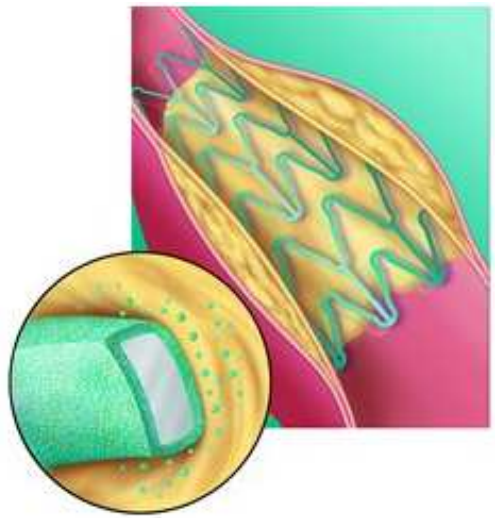
Workshop IV:
Optimal Transport in the Human Body – Lungs and Blood
UCLA-IPAM 19-23 May 2008

A collaboration with LaBS
Laboratory of Biological Structure Mechanics - Polimi

Overview

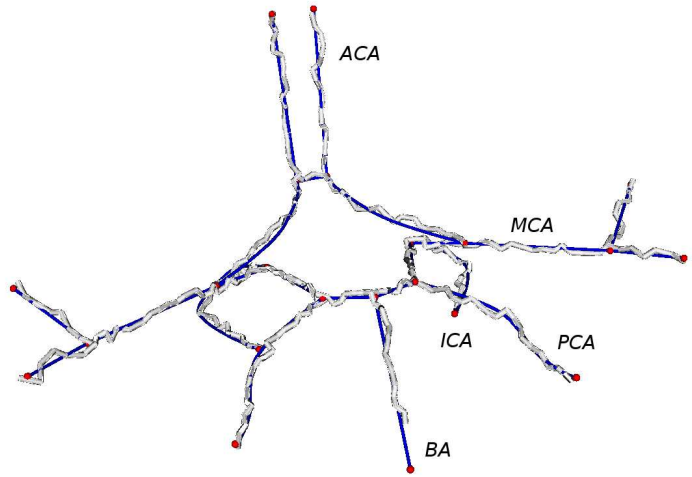
Drug release in the vascular system

Local analysis:
drug eluting stents.



- Mechanics
- Drug release
- Interaction with arteries

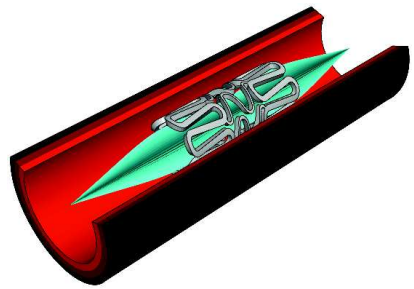
Global analysis:
the vascular network.



- Blood flow
- Perfusion
- Mass transfer

Local analysis: drug eluting stents

Motivations: atherosclerosis induces a reduction of the blood flow because of the narrowing of the affected arteries



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stents enlarge the arterial lumen and restore blood perfusion

Drawbacks: re-narrowing of an artery at the same site where the stent was placed

⇓

DES release anti-proliferative drugs that prevent restenosis.

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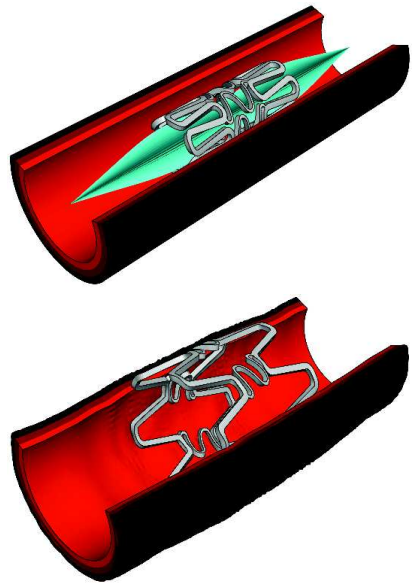

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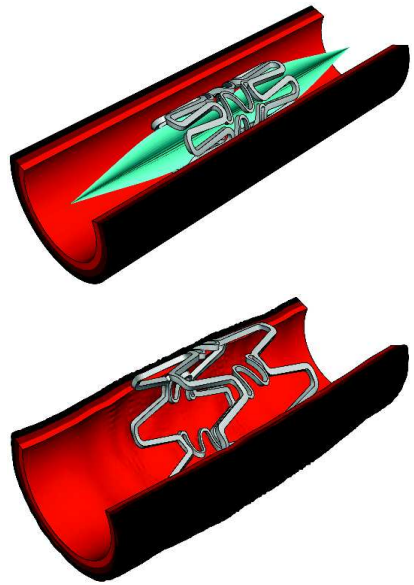

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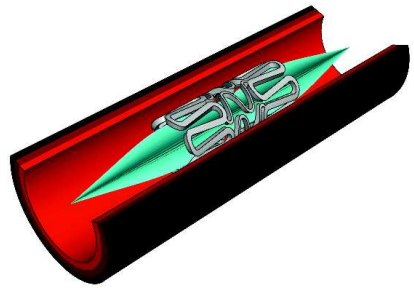

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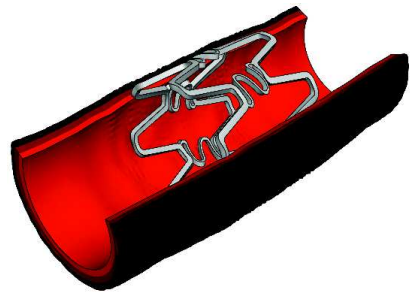

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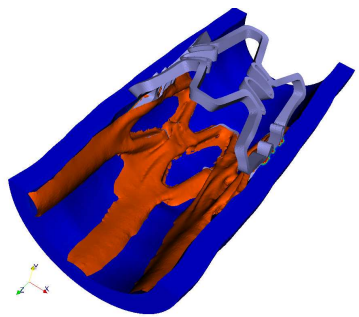

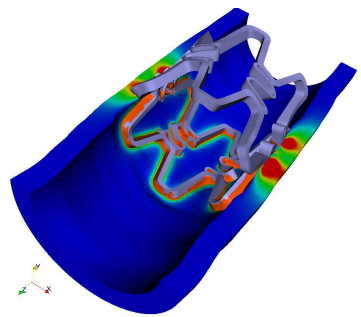

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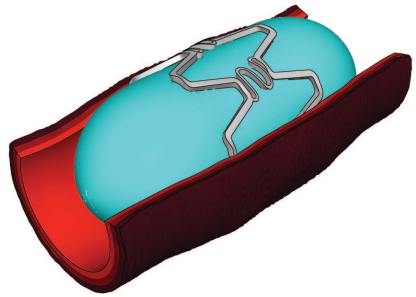
DES release anti-proliferative drugs that prevent restenosis.

Problem overview

Mechanics:

- analysis of balloon/stent expansion;



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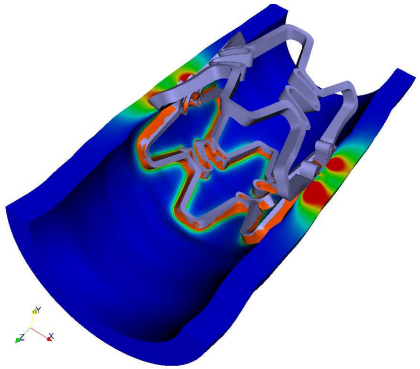
Mass Transfer:

- drug release from a substrate;
- drug release in the arterial walls;



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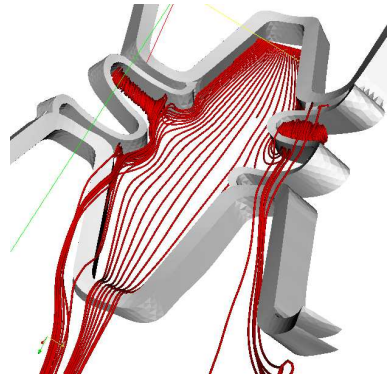
Fluid Dynamics:

- blood flow;
- filtration through arteries;



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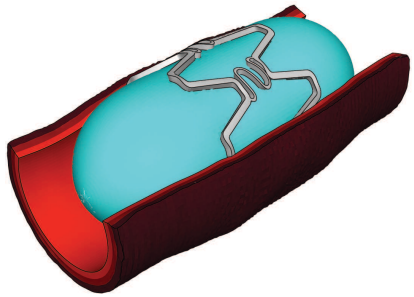
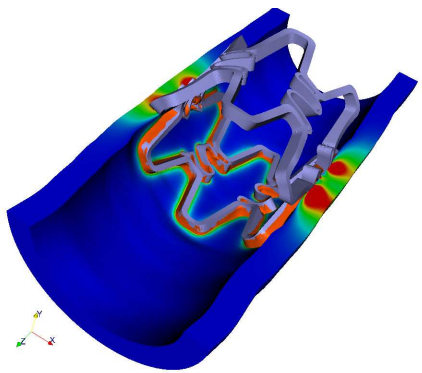


Global analysis:

- drug release in the vascular network;
- what if the stent pattern is too complex?

Mass Transfer:

- drug release from a substrate;
- drug release in the arterial walls;



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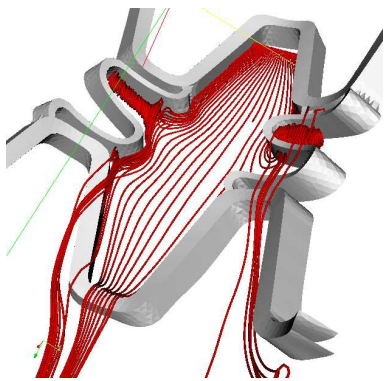
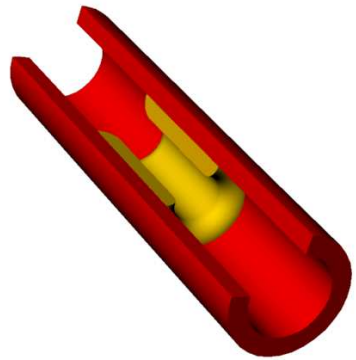


Mechanical analysis

Simulation of the stent expansion inside an atherosclerotic coronary artery:

Migliavacca F., Gervaso F., Prosi M., Zunino P., Minisini S., Formaggia L., Dubini G., Expansion and drug elution model of a coronary stent, *Comput. Methods. Biomech. Biomed. Engin.*, 10, 63-73, 2007.



Geometry: two hollow co-axial cylinders
artery internal diam.=2.15 mm, thickness=0.5 mm
plaque internal diam.=1.25 mm, thickness=0.45 mm

Material model: incompressible, isotropic and hyperelastic material for each arterial layer.

Mechanical analysis: the deformed geometry is the input on which the drug release simulation is carried out.

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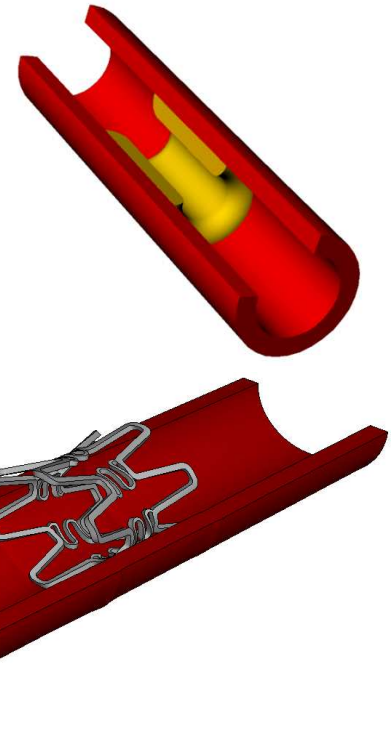

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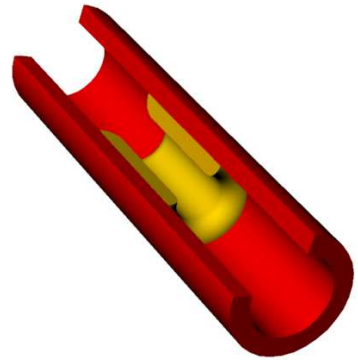

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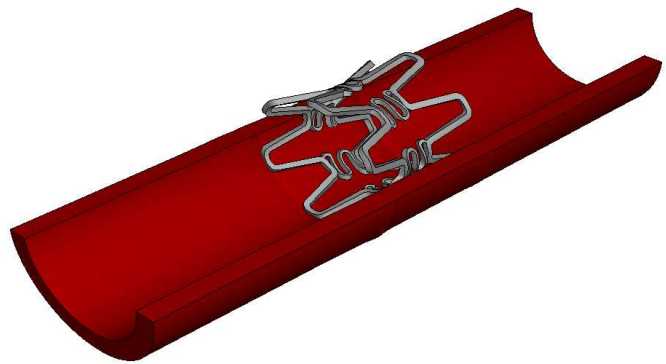

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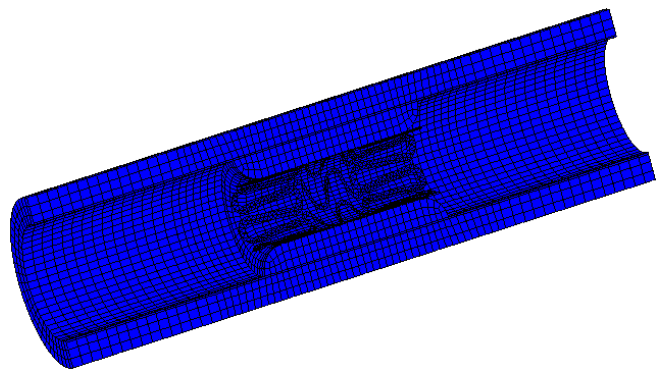
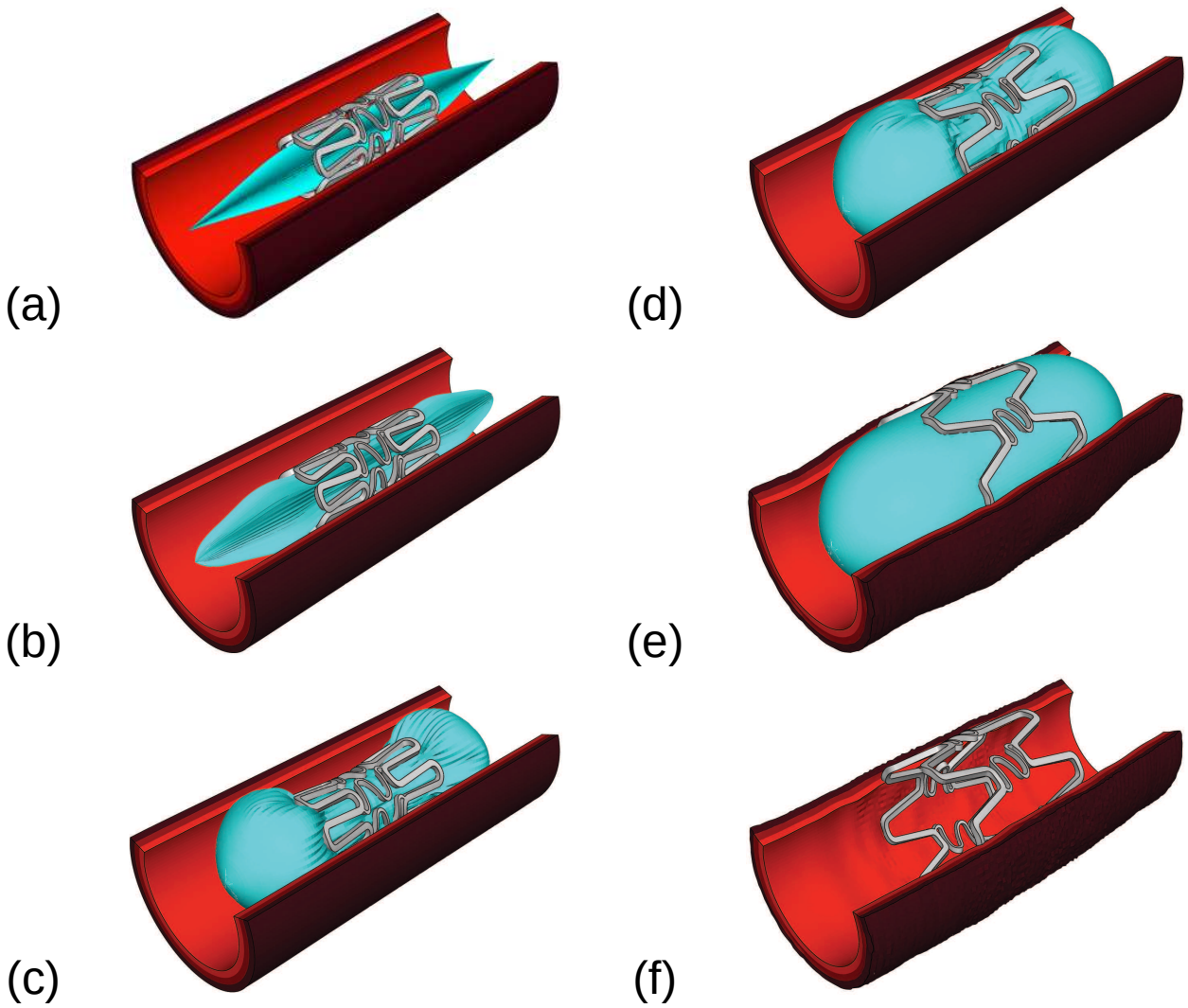


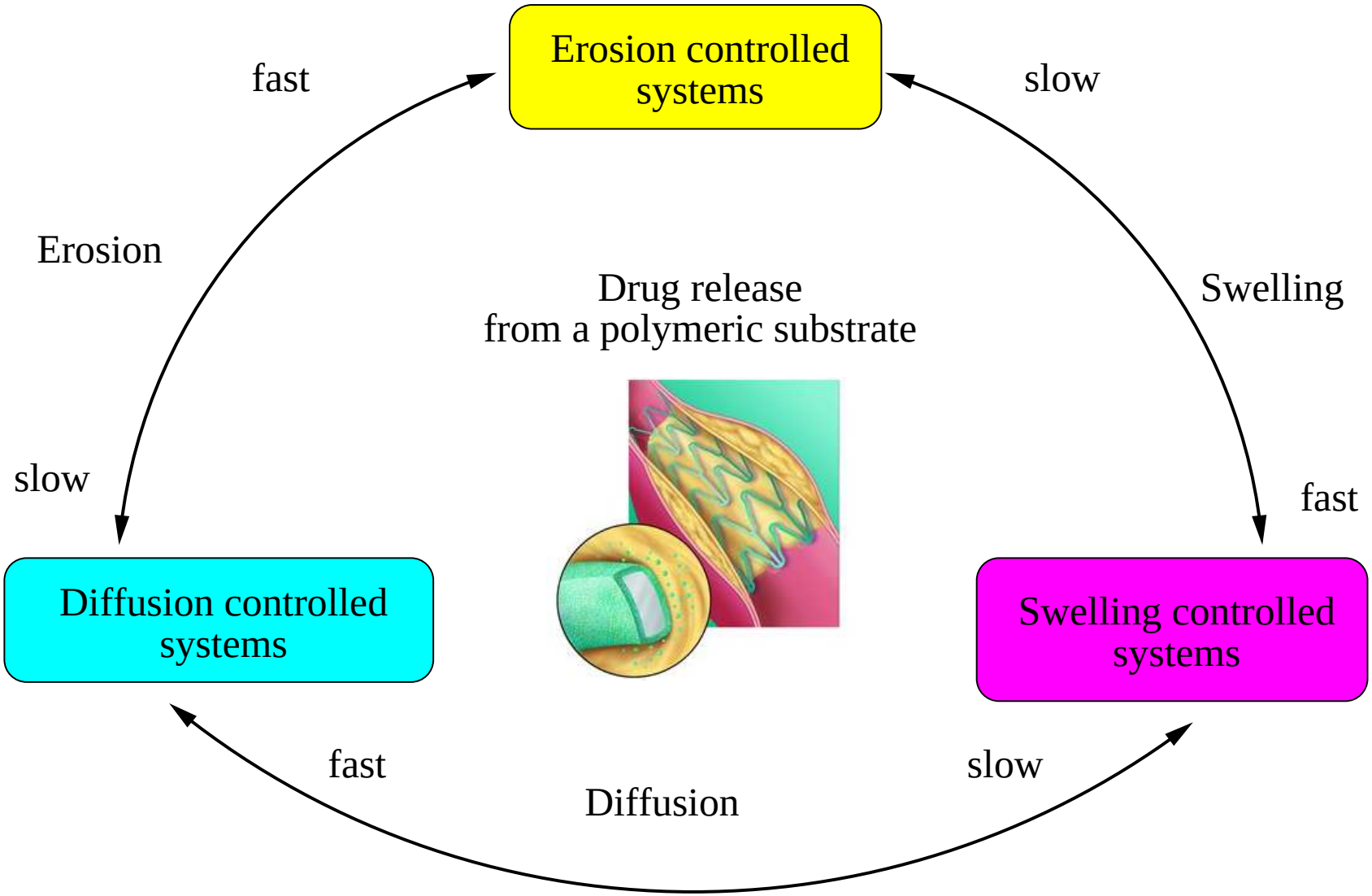
Coupled balloon/stent expansion

performed by LaBS - Laboratory of Biological Structure Mechanics - Polimi

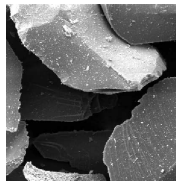
P. Zunino, C. D'Angelo, L. Petrini, C. Vergara, C. Capelli, F. Migliavacca, *Numerical simulation of drug eluting coronary stents: mechanics, fluid dynamics and drug release*, MOX Report 3/2008, submitted.



Governing principles for drug release



Drug dissolution models



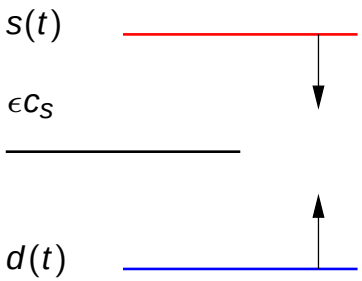
drug in solid phase $\Rightarrow$ drug dissolved in water permeating the substrate

Physical unknowns:

- d drug concentration in the dissolved phase
- s drug concentration in the solid pahse
- c_s saturation

Parameters:

- D drug diffusivity
- k_d dissolution rate
- ϵ porosity



$$\partial_t d = D\Delta d - \partial_t s, \text{ in } (0,T] \times \Omega,$$

$$\partial_t s = -k_d s^{\frac{2}{3}}(\epsilon c_s - d), \text{ in } (0,T] \times \Omega,$$

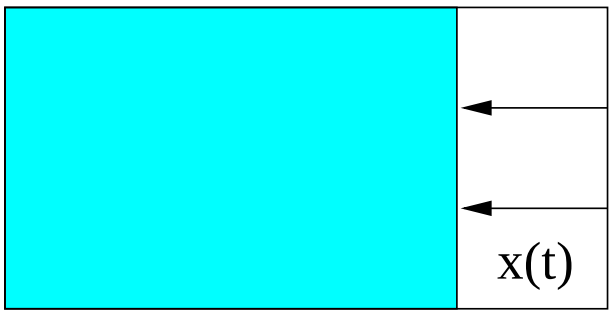
References:

T. Higuchi, *Rate of release of medicaments from ointment bases containing drugs in suspension*, J. Pharmac. Sci., 50 (1961), 874–875.

G. Fremming, U. Brohede, M. Stromme, *Finite element analysis of the release of slowly dissolving drugs from cilyndrical matrix systems*, J. of Controlled Release, 107 (2005), 320–329.

Substrate erosion models

Surface erosion model:



$$\partial_t d = D\Delta d - \partial_t s,$$

$$\partial_t s = -k_d s^{\frac{2}{3}}(\epsilon c_s - d),$$

$$x(t) = L - Bt,$$

the erosion velocity B

is determined experimentally.

Bulk erosion model:

$$\partial_t d = D\Delta d - \partial_t s,$$

$$\partial_t s = -k_d m(\epsilon c_s - d),$$

$$\partial_t m = k_e m_0 \exp(-k_e t),$$

m: monomer concentration

clevage of polymer chains

monomer formation $\Leftrightarrow$ drug dissolution

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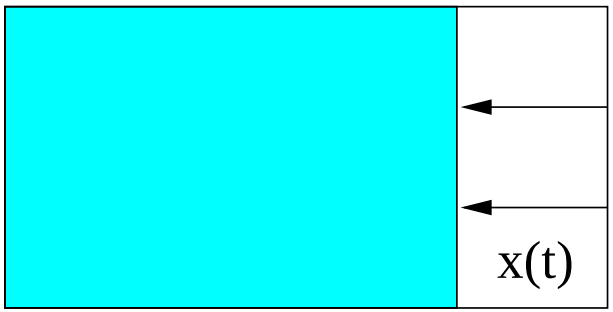

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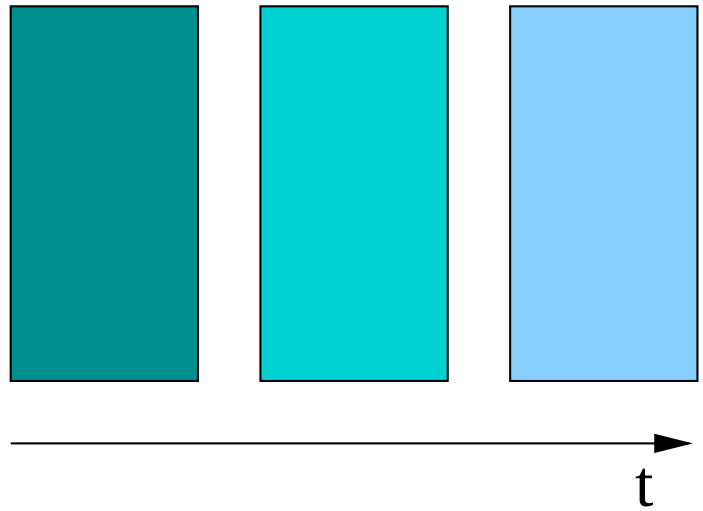

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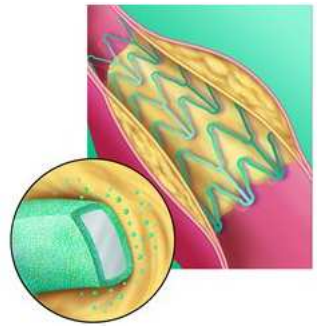
Drug release in the arterial wall

Ω_c: stent coating releasing the drug

Concentration $d(t, \boldsymbol{x})$

Two subregions:



Ω_w: arterial wall absorbing the drug

Concentrations $\overbrace{a(t, \boldsymbol{x})}^{\text{free drug}}$, $\underbrace{b(t, \boldsymbol{x})}_{\text{free binding sites}}$ and $\underbrace{c(t, \boldsymbol{x})}_{=b_0 - b}$

Governing operators:

diffusion (with $\epsilon c_s \simeq d_0$)

$$\mathfrak{L}_c d := -D_c \Delta d$$
$$\mathfrak{B}_c d := \nabla d \cdot \boldsymbol{n}_c$$

Interface conditions:

mass balance

$$\mathfrak{B}(a, d) := \begin{cases} a - d \\ D_w \nabla a \cdot \boldsymbol{n} - D_c \nabla d \cdot \boldsymbol{n} \end{cases}$$

Governing operators:

diffusion and transport

$$\mathfrak{L}_w a := -D_w \Delta a + \boldsymbol{u} \cdot \nabla a,$$
$$\mathfrak{B}_{fw} a := -D_w \nabla a \cdot \boldsymbol{n}_w + P_w a$$

Reaction

$$a + b \xrightarrow{k_1} c, \; c \xrightarrow{k_2} a + b$$
$$\mathfrak{R}_w(a, b) := k_1 ab + k_2 (b - b_0)$$

Sakharov D.V., Kalachev L.V., Rijken D.C., Numerical simulation of local pharmacokinetics of a drug after intravascular delivery with an eluting stent, *J. Drug Targ.*, 10(6), 507–513, 2002.

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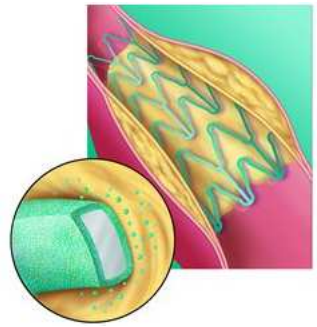

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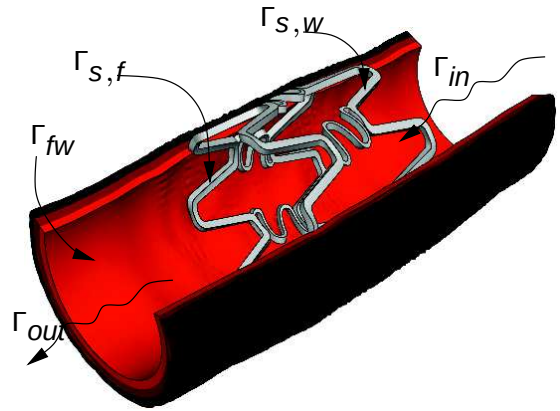
A mathematical model for drug release in arteries

Governing equations
for the stent and the arterial wall:



$$
\begin{cases}
\partial_t a + \mathfrak{L}_w a + \mathfrak{N}_w(a,b) = 0, & \text{in } (0,T] \times \Omega_w, \\
\partial_t d + \mathfrak{L}_c d = 0, & \text{in } (0,T] \times \Omega_c, \\
\partial_t b + \mathfrak{N}_w(a,b) = 0, & \text{in } (0,T] \times \Omega_w, \\
\mathfrak{B}_{fw} a = 0, & \text{on } (0,T] \times \Gamma_{fw}, \\
\mathfrak{B}_c d = 0, & \text{on } (0,T] \times \partial\Omega_c \setminus \Gamma_{s,w}, \\
\mathfrak{B}(a,d) = 0, & \text{on } (0,T] \times \Gamma_{s,w},
\end{cases}
$$

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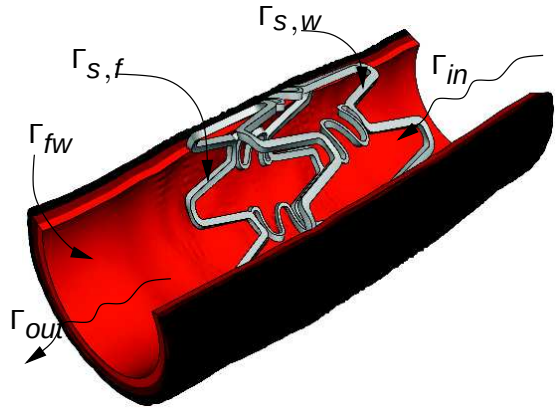

Coupling between the free drug (a) and the receptors in the arterial wall (b):

$$
\begin{cases}
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A mathematical model for drug release in arteries

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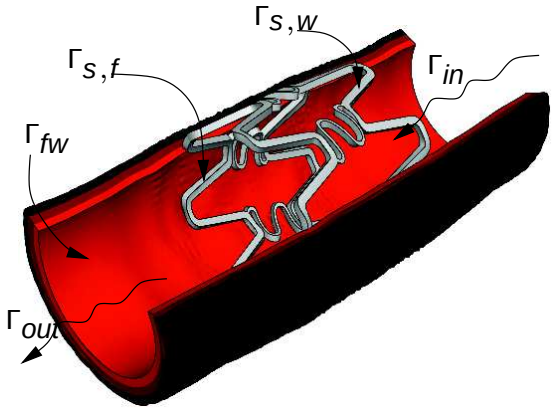

Coupling between the stent coating (d) and the arterial wall (a, b):

$$
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\end{cases}
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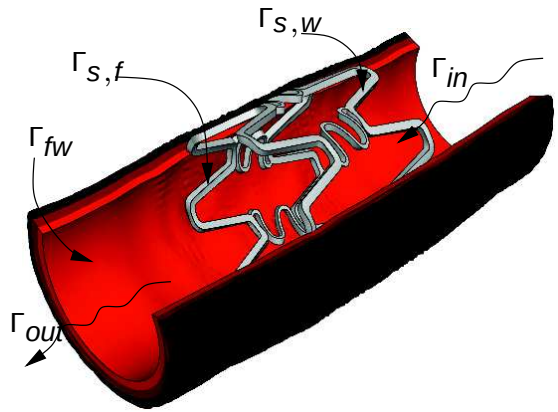
A mathematical model for drug release in arteries

Governing equations for the stent, the arterial wall and the lumen:



$$
\begin{cases}
\partial_t a_w + \mathfrak{L}_w a_w + \mathfrak{N}_w(a_w, b) = 0, & \text{in } (0,T] \times \Omega_w, \\
\partial_t a_f + \mathfrak{L}_f a_f = 0, & \text{in } (0,T] \times \Omega_f, \\
\partial_t d + \mathfrak{L}_c d = 0, & \text{in } (0,T] \times \Omega_c, \\
\partial_t b + \mathfrak{N}_w(a, b) = 0, & \text{in } (0,T] \times \Omega_w, \\
\mathfrak{B}_{fw}(a_f, a_w) = 0, & \text{on } (0,T] \times \Gamma_{fw}, \\
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\mathfrak{B}(a_w, d) = 0, & \text{on } (0,T] \times \Gamma_{s,w}, \\
\mathfrak{B}(a_f, d) = 0, & \text{on } (0,T] \times \Gamma_{s,f},
\end{cases}
$$

$$
\text{with } \mathfrak{B}_{fw}(a_f, a_w) := \begin{cases} -D_w \nabla a_w \cdot \boldsymbol{n}_w - P_w(a_w - a_f) \\ -D_w \nabla a_w \cdot \boldsymbol{n}_w - D_f \nabla a_f \cdot \boldsymbol{n}_f \end{cases}
$$

Fluid dynamics

Drug can be transported by blood flow and plasma filtration inside the tissue.

Incompressible Navier-Stokes equations on a rigid domain are applied for blood flow:

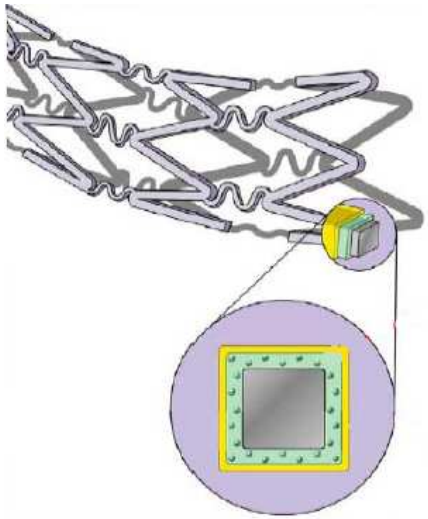
$$\begin{cases} \partial_t \mathbf{u}_f - \mu \Delta \mathbf{u}_f + (\mathbf{u}_f \cdot \nabla)\mathbf{u}_f + \nabla p_f = \mathbf{0} \quad \text{and} \quad \nabla \cdot \mathbf{u}_f = 0, \quad \text{in } (0,T] \times \Omega_f, \\ \mathbf{u}_f = \mathbf{u}_{in}(t) \text{ on } (0,T] \times \Gamma_{in}, \\ p_f \mathbf{n}_f - \mu \nabla \mathbf{u}_f \mathbf{n}_f = 0 \text{ on } (0,T] \times \Gamma_{out}, \\ \mathbf{u}_f = 0 \text{ on } (0,T] \times \Gamma_{fw}, \end{cases}$$

Filtration of plasma is described by Darcy's law of filtration:

$$\begin{cases} \mathbf{u}_w + \frac{k_w}{\mu_w} \nabla p_w = 0 \text{in } (0,T] \times \Omega_w, \quad \text{and} \quad \nabla \cdot \mathbf{u}_w = 0 \quad \text{in } (0,T] \times \Omega_w, \\ p_w - \delta p_f(t) = 0 \text{on } \Gamma_{fw}, \end{cases}$$

Time dependent data may account for blood pulsatility.

Computational limitations - multiple space scales



length $\simeq$ 10 mm
diameter $\simeq$ 3 mm
thickness $\simeq$ 5 μm

the set up of a conforming and regular computational mesh is extremely demanding

a multiscale approach is required to treat realistic geometries

Assumption: in Ω_c the derivatives in the normal direction w.r.t Γ are much larger than the tangential ones.
$\Rightarrow$ reduced model for the unknown $d(t, z)$, for any $\boldsymbol{x} \in \Gamma$.

Γ

z

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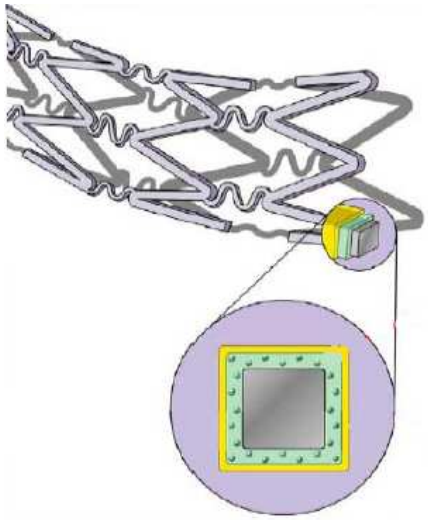

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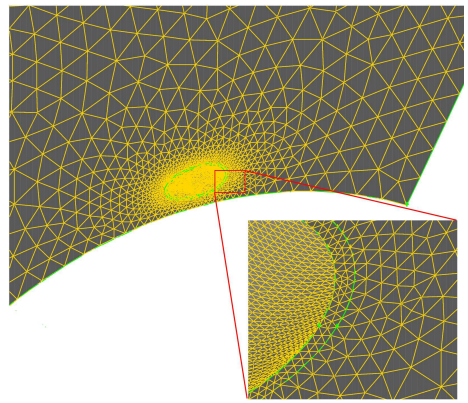

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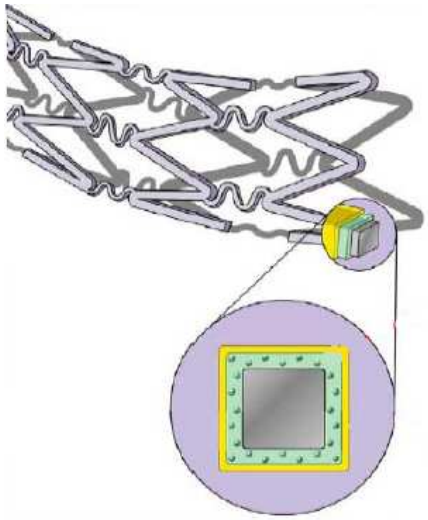

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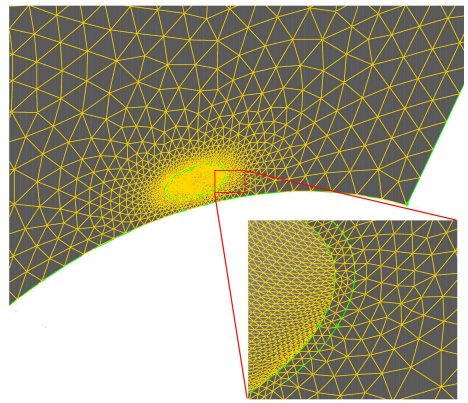

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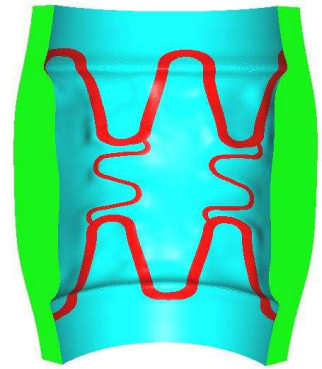

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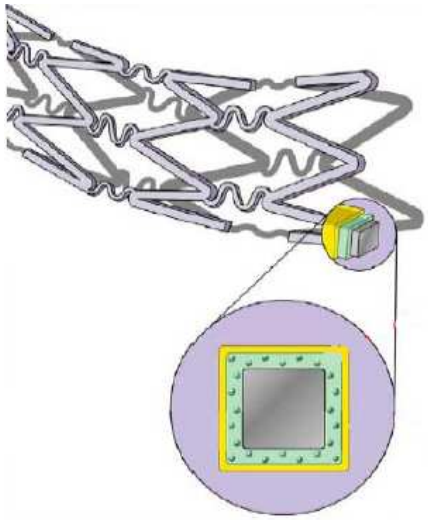

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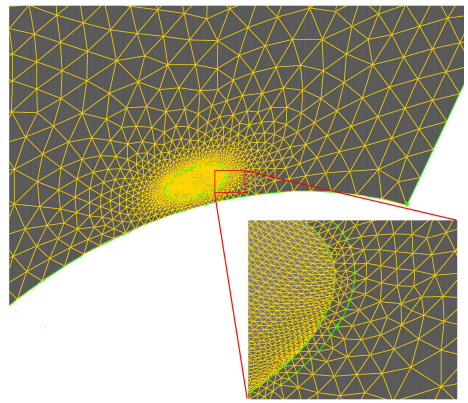

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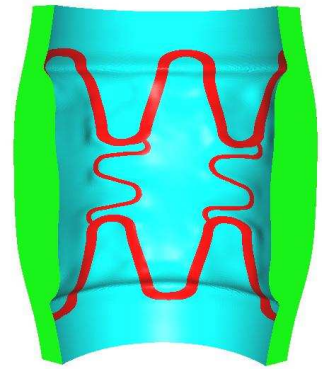

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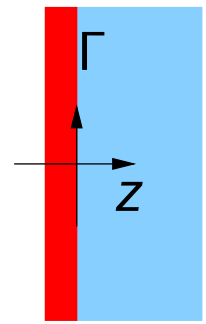
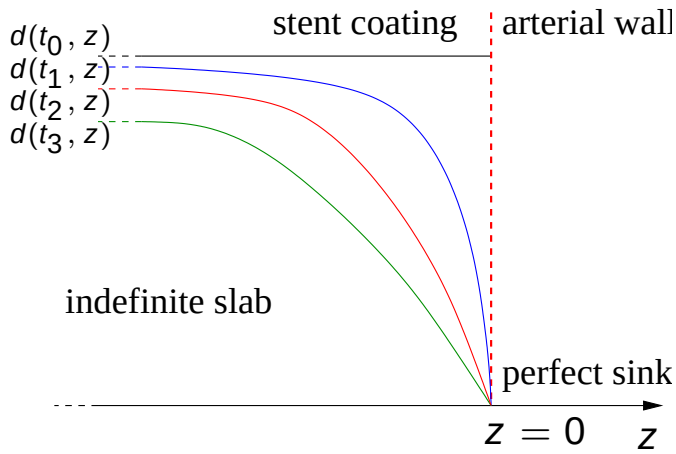


Model reduction for the stent coating (I)

A review of the Higuchi model

$$\begin{cases} \partial_t d - D_c\, \partial_z^2 d = 0 \text{ in } (0,T] \times (-\infty, 0), \\ \partial_z d = 0 \text{ on } (0,T] \times \{z = -\infty\}, \\ d = 0 \text{ on } (0,T] \times \{z = 0\}, \\ d = d_0 \text{ on } \{t = 0\} \times (-\infty, 0), \end{cases}$$



Exact solution of the model:

$$\frac{d(t,z;\boldsymbol{x})}{d_0} = 1 - \operatorname{erf}\left(\frac{z}{\sqrt{4D_c t}}\right),\ z \in (-\infty, 0),\ t \in (0,T],\ \boldsymbol{x} \in \Gamma,$$

Explicit expression of the drug release rate (flux):

$$J(t;\boldsymbol{x}) = -D_c \partial_z d(t, z = 0; \boldsymbol{x}) = \sqrt{\frac{D_c d_0^2}{\pi t}},\ t \in (0,T],\ \boldsymbol{x} \in \Gamma.$$

This model is reliable for short time scales.

The total amount of drug that is released is unbounded!

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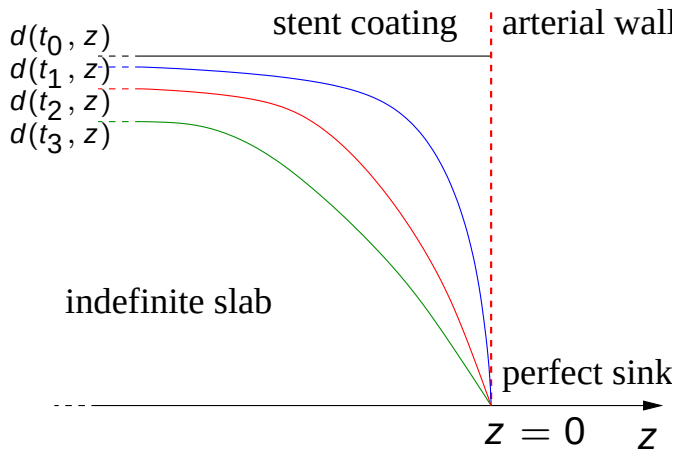

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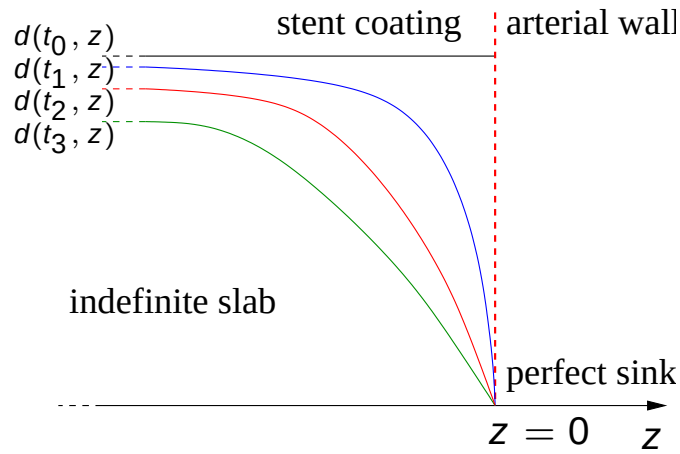

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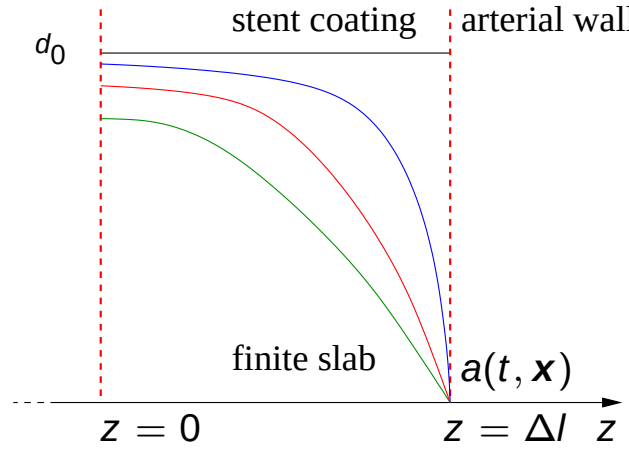
An improved model

$$\begin{cases} \partial_t d - D_c\, \partial_z^2 d = 0 \text{ in } (0,T] \times (0,\Delta l), \\ \partial_z d = 0 \text{ on } (0,T] \times \{z=0\}, \\ d = a(t,\boldsymbol{x}) \text{ on } (0,T] \times \{z=\Delta l\}, \\ d = d_0 \text{ on } \{t=0\} \times (0,\Delta l), \end{cases}$$



If $a(t,\boldsymbol{x})$ is quasi-steady:

$$\frac{d(t,z)-a(t,\boldsymbol{x})}{d_0-a(t,\boldsymbol{x})} = \sum_{n=0}^{\infty} \frac{2(-1)^n}{(n+1/2)\pi} e^{-(n+1/2)^2 kt} \cos\left(\left(n+\frac{1}{2}\right)\pi \frac{z}{\Delta l}\right),$$

Explicit expression of the Dirichlet to Neumann map:

$$\underbrace{-D_c \partial_z d(t,\Delta l;\boldsymbol{x})}_{\text{Neumann}} = \varphi_1(t)(d_0 - \underbrace{a(t,\boldsymbol{x})}_{\text{Dirichlet}}), \quad \varphi_1(t) := \frac{2D_c}{\Delta l} \sum_{n=0}^{\infty} e^{-(n+1/2)^2 kt}$$

$$-D_c \partial_z d(t,\Delta l;\boldsymbol{x}) = D_w \nabla a \cdot \boldsymbol{n}_w$$

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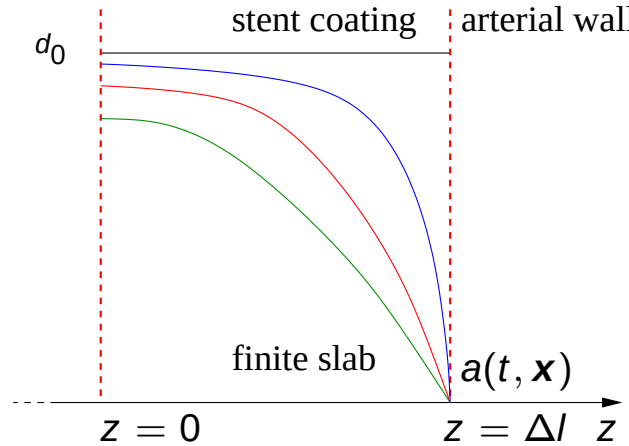

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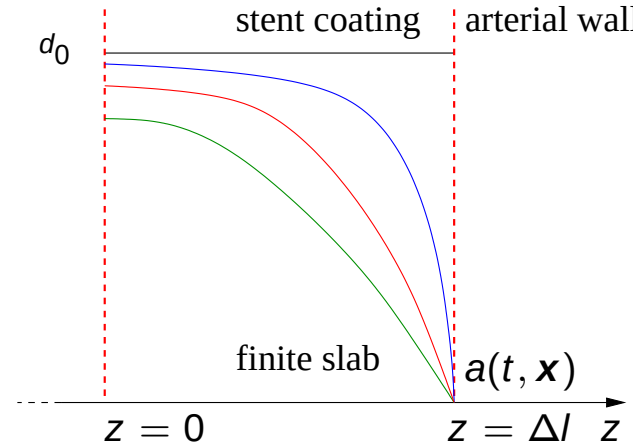

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A multiscale boundary conditions for drug release

The original model for drug release in the arterial wall:

$$\begin{cases} \partial_t a + \mathfrak{L}_w a + \mathfrak{R}_w(a,b) = 0, & \text{in } (0,T] \times \Omega_w, \\ \partial_t d + \mathfrak{L}_c d = 0, & \text{in } (0,T] \times \Omega_c, \\ \partial_t b + \mathfrak{R}_w(a,b) = 0, & \text{in } (0,T] \times \Omega_w, \\ \mathfrak{B}_{fw} a = 0, & \text{on } (0,T] \times \Gamma_{fw}, \\ \mathfrak{B}_c d = 0, & \text{on } (0,T] \times \partial\Omega_c \setminus \Gamma_{s,w}, \\ \mathfrak{B}(a,d) = 0, & \text{on } (0,T] \times \Gamma_{s,w}, \end{cases}$$

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C. Vergara, P. Zunino, *Multiscale boundary conditions for drug release from cardiovascular stents*, MOX Report 15/2007, to appear on Multiscale. Model. & Simul.

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Linear finite elements for the space discretization of $a(t, \boldsymbol{x})$ and $b(t, \boldsymbol{x})$.

Fixed point **iterative method** for the treatment of the nonlinear term $\mathfrak{N}_w(a, b)$.

Implicit Euler scheme for the time discretization.

$$J(t) \simeq \sqrt{\frac{D_c d_s^2}{\pi t}}$$

$\Rightarrow$ The release rate is fast but it progressively slows down.

$\Rightarrow$ **Adaptive time stepping.**

Control the fraction of released drug $f(t)$ $\Rightarrow$ a-priori adaptivity:

$$\text{Higuchi model} \Rightarrow f(t) := \frac{q(t)}{q(\infty)} = \sqrt{\frac{4D_c t}{\pi \Delta l^2}}, \quad t = \frac{\pi \Delta l^2}{4D_c} f^2$$

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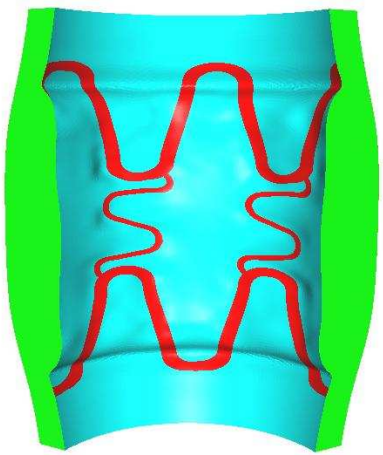
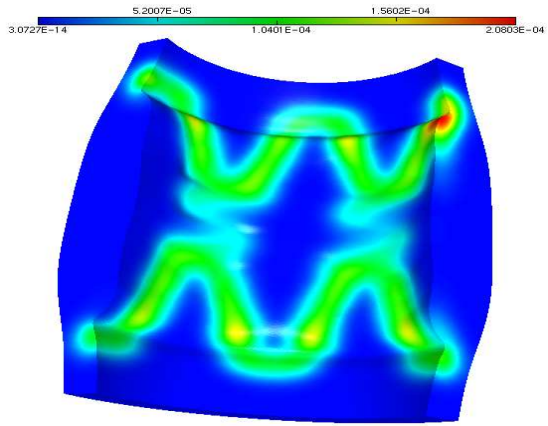
Numerical Results - Drug release in the arterial wall

Geometrical model:
the stent and
the artery

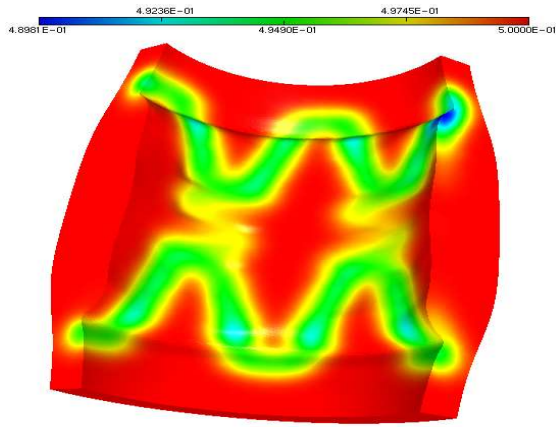


Dissolved drug inside
the arterial walls
$a(t, \boldsymbol{x})$:



Time scale: 3 days.

Extracelluar sites
filled with drug
$b(t, \boldsymbol{x})$:



Time scale: 3 days.

Life V C++ finite element library (PoliMi-EPFL-Inria) `www.lifeV.org`

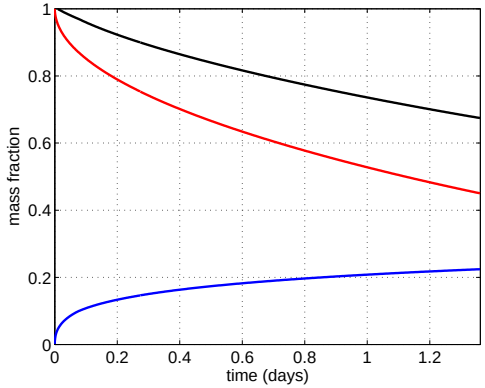
- the distribution of the drug inside the wall is substantially influenced by the geometrical design of the stent.
- drug in the vessel wall is mainly present in the state attached to the specific sites of the extra-cellular matrix.

Postprocessing - Quantitative analysis

Drug release dynamics:

$$M_w(t) = \int_{\Omega_w} \left(a(t,\boldsymbol{x}) + c(t,\boldsymbol{x})\right) dV$$

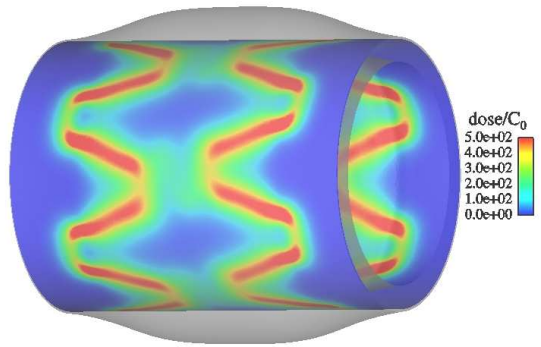
$$M_c(t) = \Delta l \int_{\Gamma} \rho(t,\boldsymbol{x}) d\sigma$$



Drug dose:

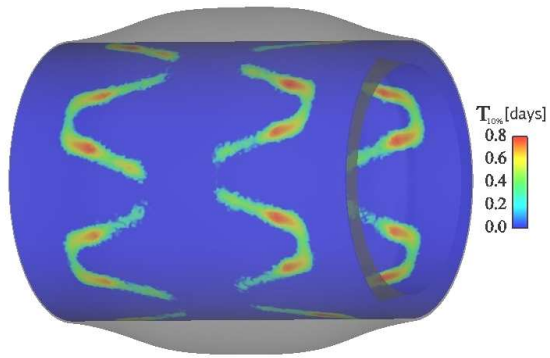
accumulative concentration

$$z(\boldsymbol{x}) = \int_0^T \left(a(t,\boldsymbol{x}) + c(t,\boldsymbol{x})\right) dt$$



Residence times:

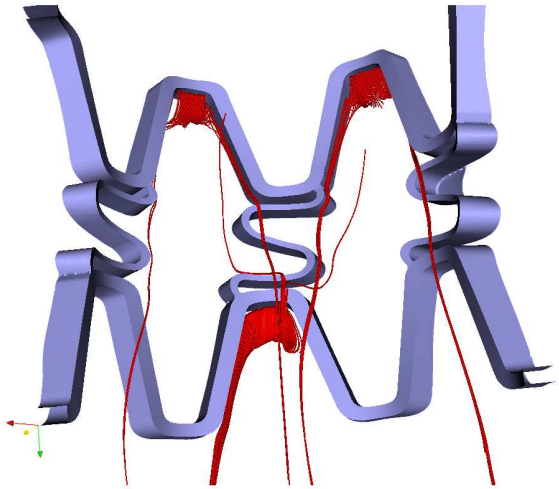
$$\tau(\boldsymbol{x}) = |\mathrm{supp}\{a(t,\boldsymbol{x}) + c(t,\boldsymbol{x}) > \epsilon\}|$$



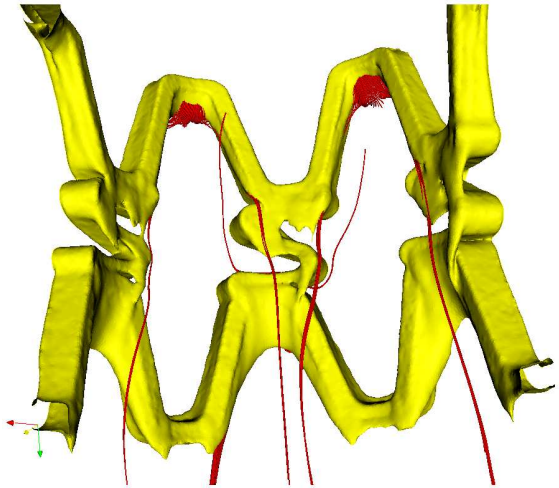
Numerical Results - Fluid dynamics

The stent induces blood recirculation and 3D secondary flow patterns

blood streamlines



drug isosurface



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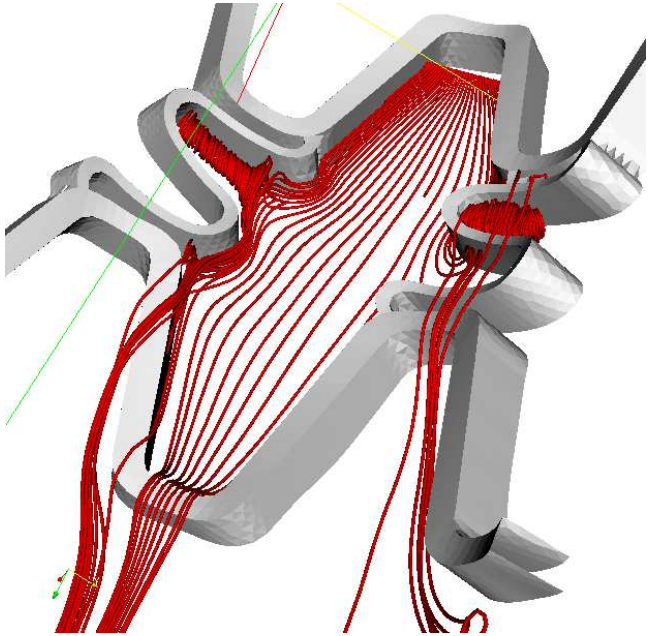
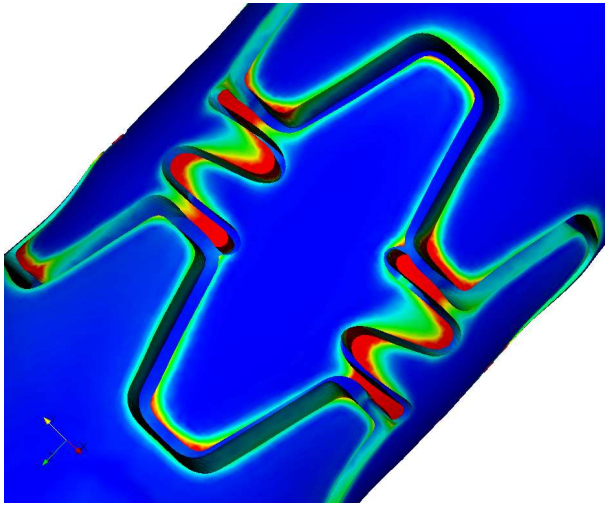


Secondary flows strongly influence drug release in blood.

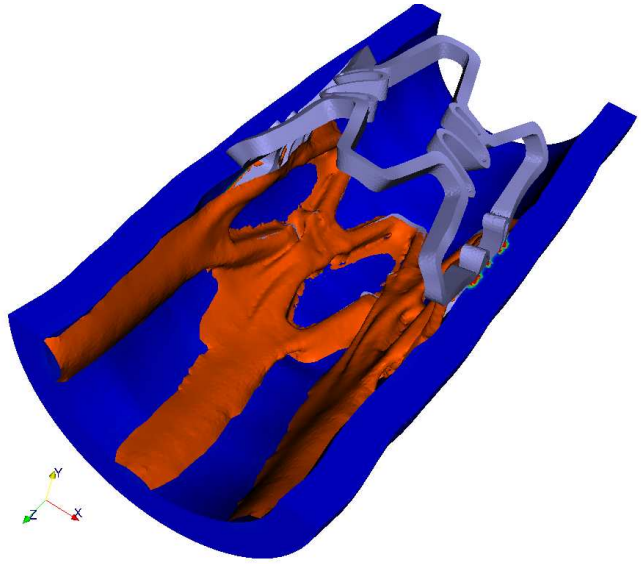
C. D'Angelo, P. Zunino, *Numerical simulation of the interaction between blood flow and drug release from stents* accepted on Numerical Mathematics and Advanced Applications, Springer, Proceedings of ENUMATH 2007, Graz, Austria, September 2007.

Coupled drug release in blood and arterial wall

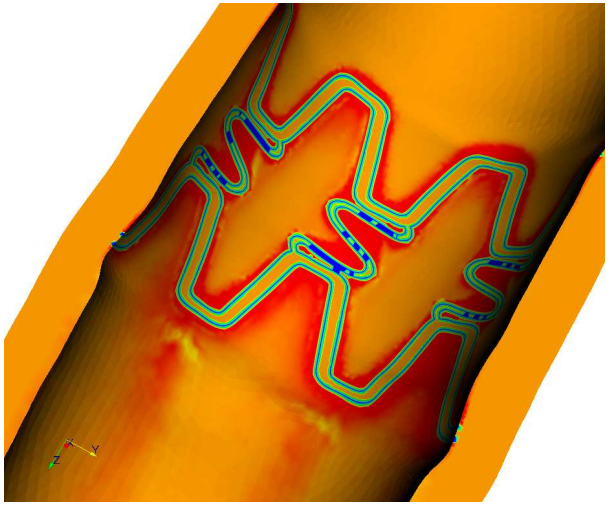
drug on the lumenal surface Γ_{fw}, $t = 40$ s



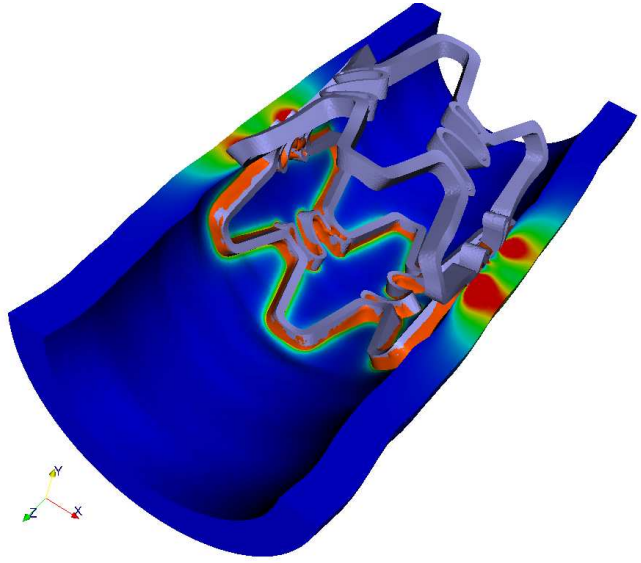
drug concentration lumen and wall, $t = 40$ s



drug flux on the lumenal surface Γ_{fw}, $t = 40$ s



drug concentration lumen and wall, $t = 1$ h



Global analysis: blood flow, perfusion, mass transfer

References:

Carlo D'Angelo *Mathematical modelling of the interaction between hemodynamics and metabolism* Ph.D. Thesis. Lausanne, EPFL. 2007

Carlo D'Andelo and Alfio Quarteroni, *On the coupling of 1D and 3D diffusion-reaction equations. Application to tissue perfusion problems.* To appear on Mathematical Models and Methods in Applied Sciences (M3AS), 2008.

Aim: blood flow and mass transport through arteries and tissues
Issue: manage the complexity of the vascular network

Idea: to separate the scales

- Capillary matrix $\Rightarrow$ homogeneization $\Rightarrow$ 3D models (Ω)
- Small vessels $\Rightarrow$ model reduction $\Rightarrow$ 1D models (λ)

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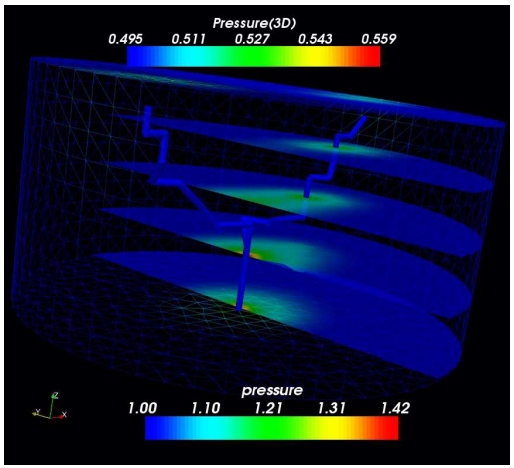
Problem setting

Blood flow and tissue perfusion:

$p_v : \Lambda \to \mathbb{R}$ blood pressure in the vessels (1D)
$p_t : \Omega \to \mathbb{R}$ blood pressure in the tissue (3D)



Mass transfer:

$u_v : \Lambda \to \mathbb{R}$ vessel concentration of chemicals (1D)
$u_t : \Omega \to \mathbb{R}$ tissue concentration of chemicals (3D)

Coupling terms:

$\phi(p_t, p_v)$ flow rate from the vessel to the tissue
$\theta(u_t, u_v)$ mass transfer from the vessel to the tissue

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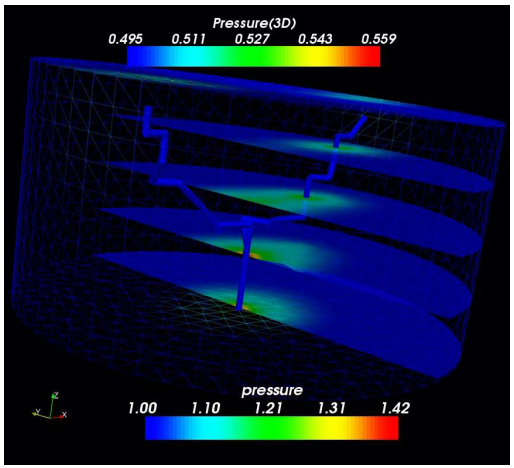

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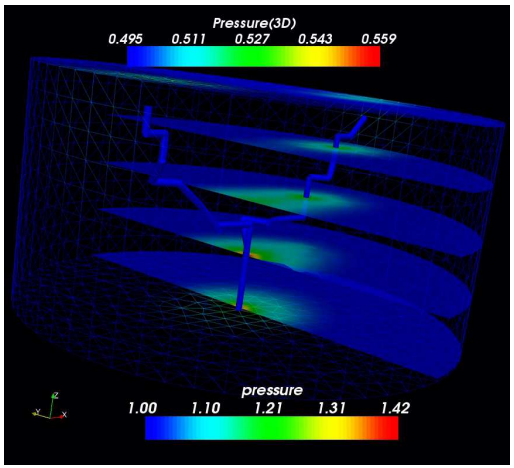

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3D-1D coupling for blood flow

- 1D hyperbolic model for blood flow into small vessels
- 3D Darcy model for the flow into the capillary matrix

Find p_t, p_v (pressures) and q_v (flow rate) such that

$$\begin{cases} \dfrac{\partial}{\partial t}\begin{bmatrix} p_v \\ q_v \end{bmatrix} + H\dfrac{\partial}{\partial s}\begin{bmatrix} p_v \\ q_v \end{bmatrix} + \mathbf{r}(p_v, q_v) = \mathbf{0}, & t > 0, s \in \Lambda, \\ C_t\dfrac{\partial}{\partial t}p_t + \nabla\cdot(K_t\nabla p_t) + \alpha p_t - \phi(p_t, p_v)\delta_\Lambda = f_p, & t > 0, \in \Omega, \end{cases}$$

with suitable BC/IC, and where $\phi(p_t, p_v)$, H and $\mathbf{r}(p_t, p_v)$ are defined by

$$H = \begin{bmatrix} 0 & c^{-1} \\ l^{-1} & 0 \end{bmatrix}, \qquad \mathbf{r}(p_v, q_v) = \begin{bmatrix} c^{-1}\phi \\ rq_v \end{bmatrix},$$

$$\phi(p_t, p_v) = \beta(p_v - \bar{p}_t), \quad \bar{p}_t \text{ is the mean value of } p_t \text{ on the vessel surface}$$

A. Quarteroni, L. Formaggia, *Mathematical modelling and numerical simulation of the cardiovascular system.* Handbook of numerical analysis. Vol. XII, 3–127, Handb. Numer. Anal., XII, North-Holland, Amsterdam, 2004.

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with suitable BC/IC, where

$$\omega_t = \alpha(p_t - p_{bed}), \quad \mathbf{v} = \frac{1}{n_b} K_t \nabla p_t, \quad \theta(u_t, u_v) = \gamma(u_v - \bar{u}_t).$$

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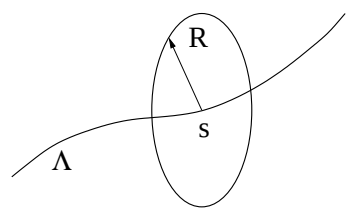

Analysis of a model problem for mass transfer

A simplified problem featuring 3D-1D coupling:

$$\begin{cases} -\nabla \cdot (k \nabla u) + \beta(\bar{u} - u_0)\delta_\Lambda = 0 & \text{in } \Omega, \\ -k \dfrac{\partial u}{\partial \mathbf{n}} = 0 & \text{on } \partial\Omega, \end{cases}$$

Weighted spaces: let $H^1_\alpha(\Omega)$ be the completion of $C^\infty(\Omega)$ w.r.t. the norm

$$\|f\|^2_{H^1_\alpha(\Omega)} := \int_\Omega f(\boldsymbol{x})^2 \mathrm{dist}(\boldsymbol{x}, \Lambda)^{2\alpha} \, \mathrm{d}\boldsymbol{x} + \int_\Omega |\nabla f(\boldsymbol{x})|^2 \mathrm{dist}(\boldsymbol{x}, \Lambda)^{2\alpha} \, \mathrm{d}\boldsymbol{x}, \text{ with } |\alpha| < 1$$

Let $k \in L^\infty(\Omega)$, $\beta \in L^\infty(\Lambda)$, $u_0 \in L^2(\Lambda)$, with $k \geq k_0 > 0$ in Ω, and

$$a(u, v) = \int_\Omega k \nabla u \cdot \nabla v \, \mathrm{d} + \beta \int_\Lambda \bar{u}(s) v(s) \, \mathrm{d}s, \quad F(v) = \beta \int_\Lambda u_0(s) v(s) \, \mathrm{d}s.$$

Theorem: there is $\delta \in (0, 1)$ and a positive function $\beta_{\max}(\alpha)$ such that if $\alpha \in (0, \delta)$ and $\|\beta\|_\infty \leq \beta_{\max}(\alpha)$, problem $a(u, v) = F(v) \qquad \forall v \in H^1_{-\alpha}(\Omega)$, admits a unique solution $u \in H^1_\alpha(\Omega)$. (from the *Banach-Babuska-Necas Th.*)

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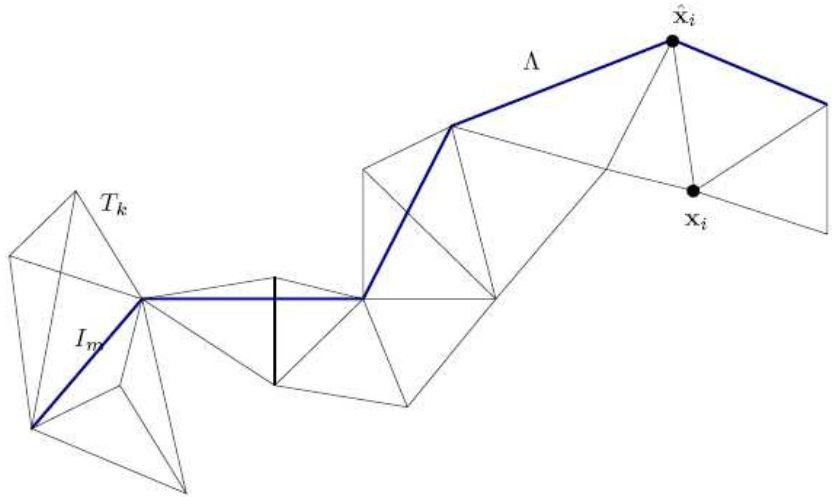
Numerical approximation

FE semi-discretization Implicit Euler for time.

Geometrical model: given a 3D mesh the 1D model lies on its edges:



Finite elements:

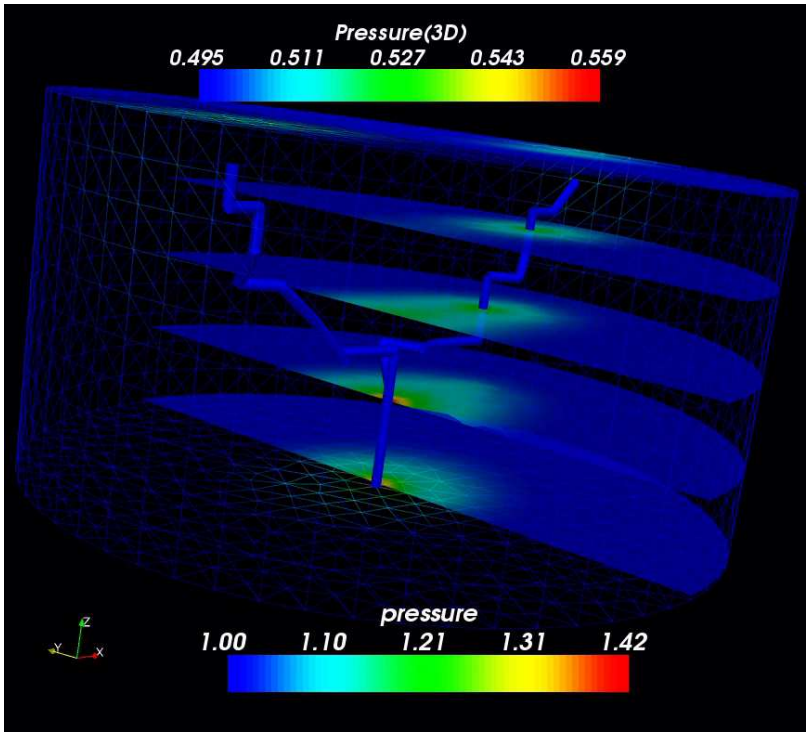
test space $\neq$ search space $\Rightarrow$ The convergence of the FE scheme lays on an *inf* $-$ *sup* condition for $a(\cdot,\cdot)$.

Time stepping:

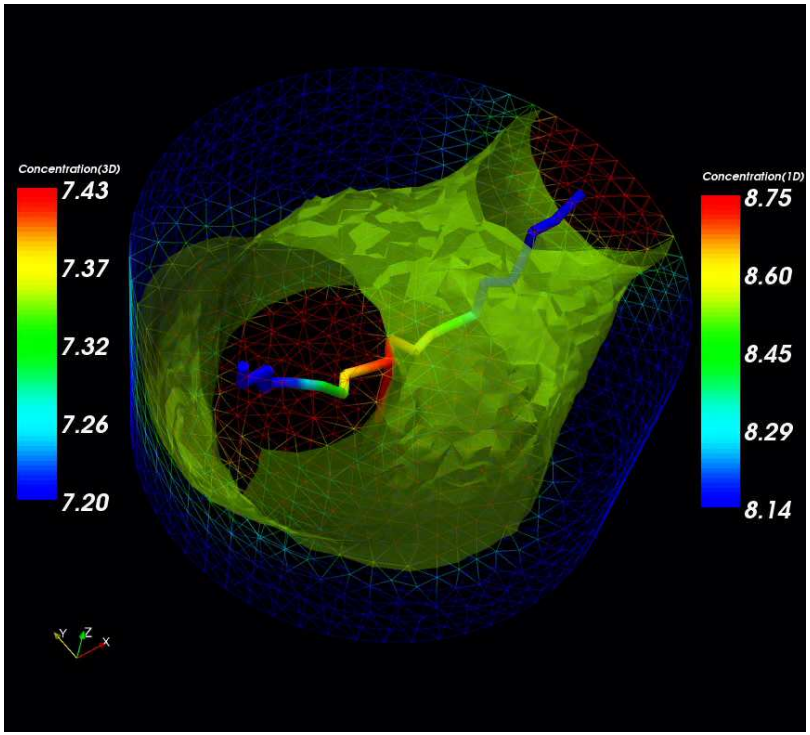
fast flow in the 1D vessels and slow flow in the 3D matrix $\Rightarrow$ multirate scheme, different time steps for the two sub-problems.

Application: blood flow and oxygen transport

Numerical simulation of a branching artery and the surrounding tissue.



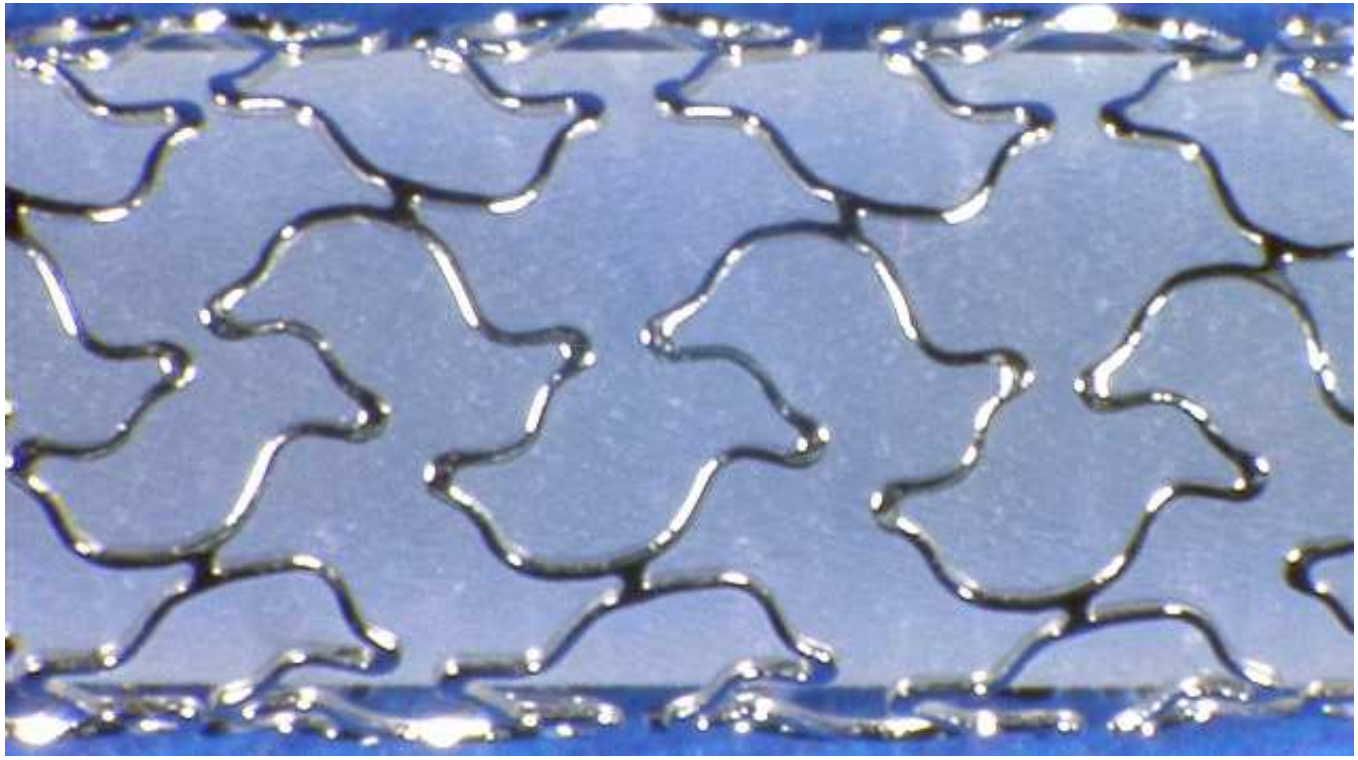
Blood perfusion.



Oxygen transport.

New perspective: 1D models for stents

what to do if the stent pattern is too complex?



Approximate the stent structure with 1D segments.

Conclusions

Local-to-global model interaction is at the basis of the study of mass transfer in the vascular system.

Scales	**Problem**	**Model**	
Micro	Capillary matrix, cells etc.	local models	
			⇓
Meso	small vessels, micro-devices etc.	PDEs(1D)	model reduction homogeneization
			⇓
Macro	vascularized tissues, organs etc.	PDEs(3D)	

Pharmacokineitc models play a fundamental role in medical applications:

- stents
- bone implants
- etc.

References

- A. Quarteroni, L. Formaggia, A. Veneziani (Eds)., *Cardiovascular Mathematics*, to appear on Interdisciplinary Applied Mathematics (IAM), Springer.
- C. Vergara, P. Zunino, *Multiscale boundary conditions for drug release from cardiovascular stents*, MOX Report 15/2007, to appear on SIAM Multiscale Model. Simul.
- F.Migliavacca, F.Gervaso, M.Prosi, P.Zunino, S.Minisini, L.Formaggia and G.Dubini, *Expansion and drug elution model of a coronary stent*, Comput. Methods. Biomech. Biomed. Engin. Vol. 10, No. 1 (2007), pp. 63-73.
- C. D'Angelo, P. Zunino, *Numerical simulation of the interaction between blood flow and drug release from stents* accepted on Numerical Mathematics and Advanced Applications, Springer, Proceedings of ENUMATH 2007, Graz, Austria, September 2007.
- P. Zunino, C. D'Angelo, L. Petrini, C. Vergara, C. Capelli, F. Migliavacca, *Numerical simulation of drug eluting coronary stents: mechanics, fluid dynamics and drug release*, MOX Report 3/2008, accepted on Comput. Meth. Appl. Mech. Eng. (CMAME).