Modeling Arterial Wall Transport For Drug-Eluting Stents

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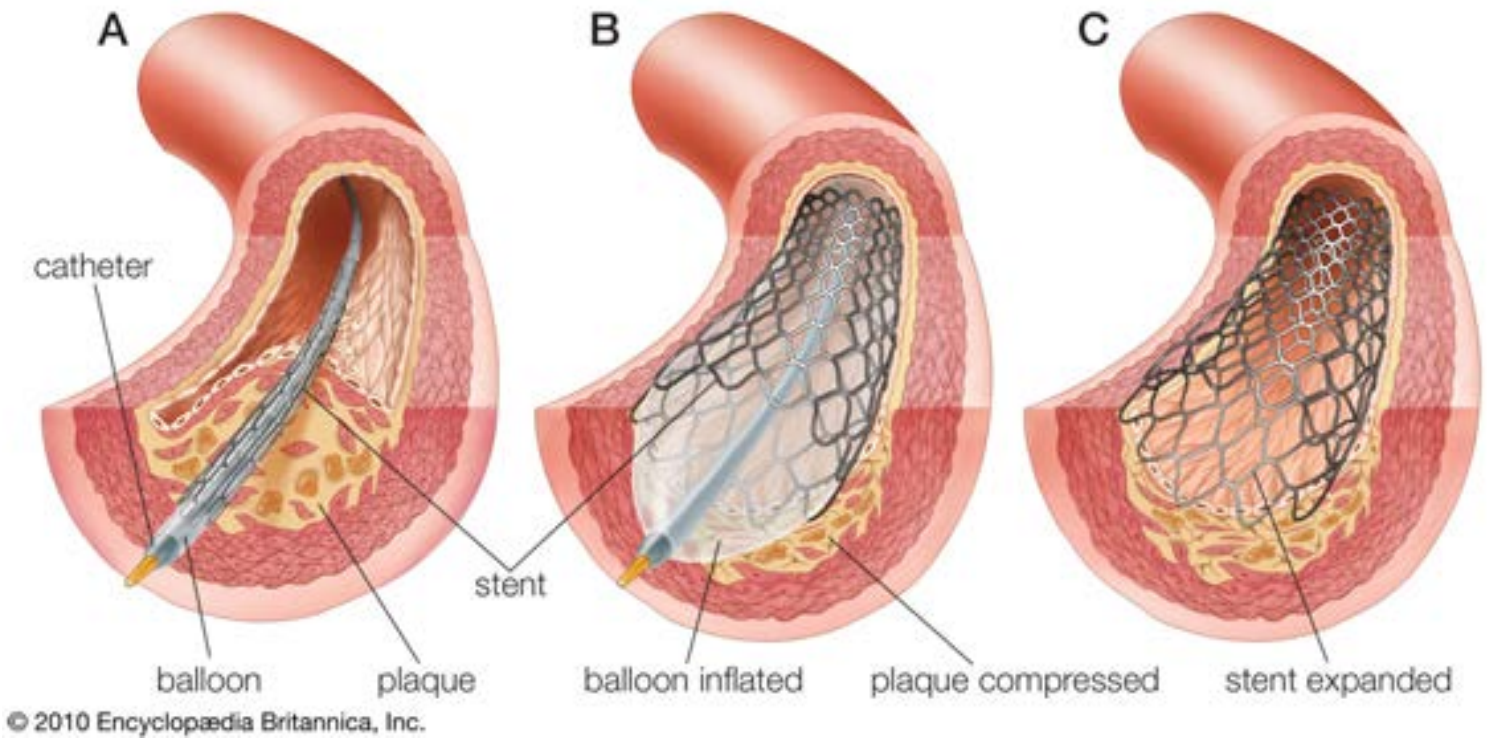
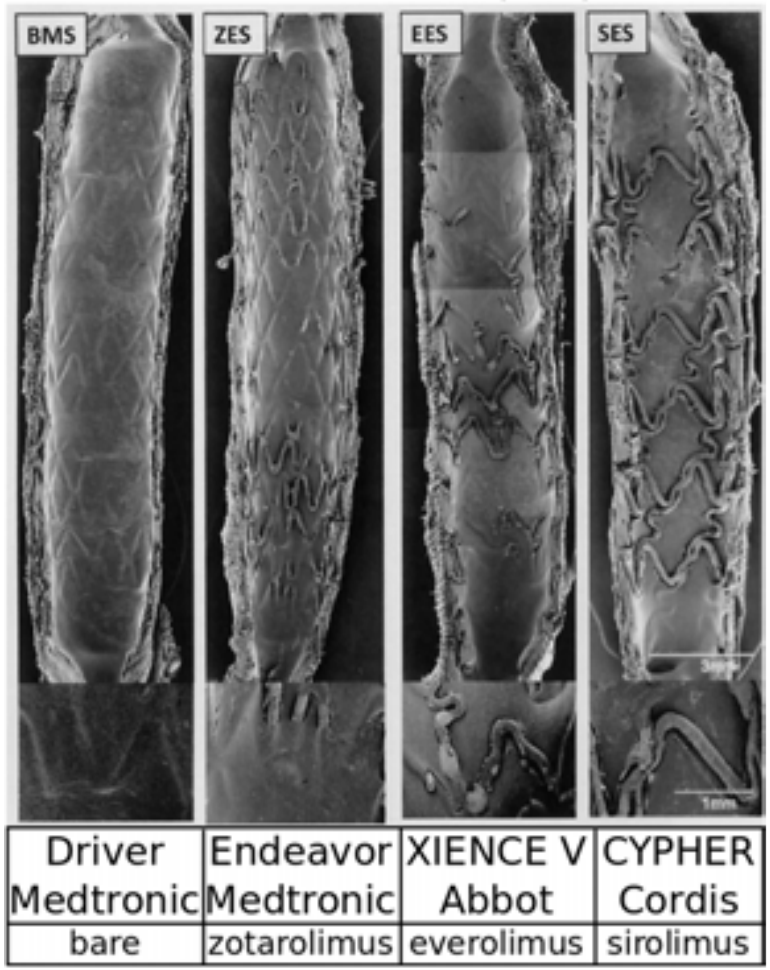
Why Drug-Eluting Stents?



- Initial problem: re-occlusion of Bare-metal stents quickly after implantation
- Today's common solution: Drug-eluting stents (DES) for treating coronary atherosclerosis

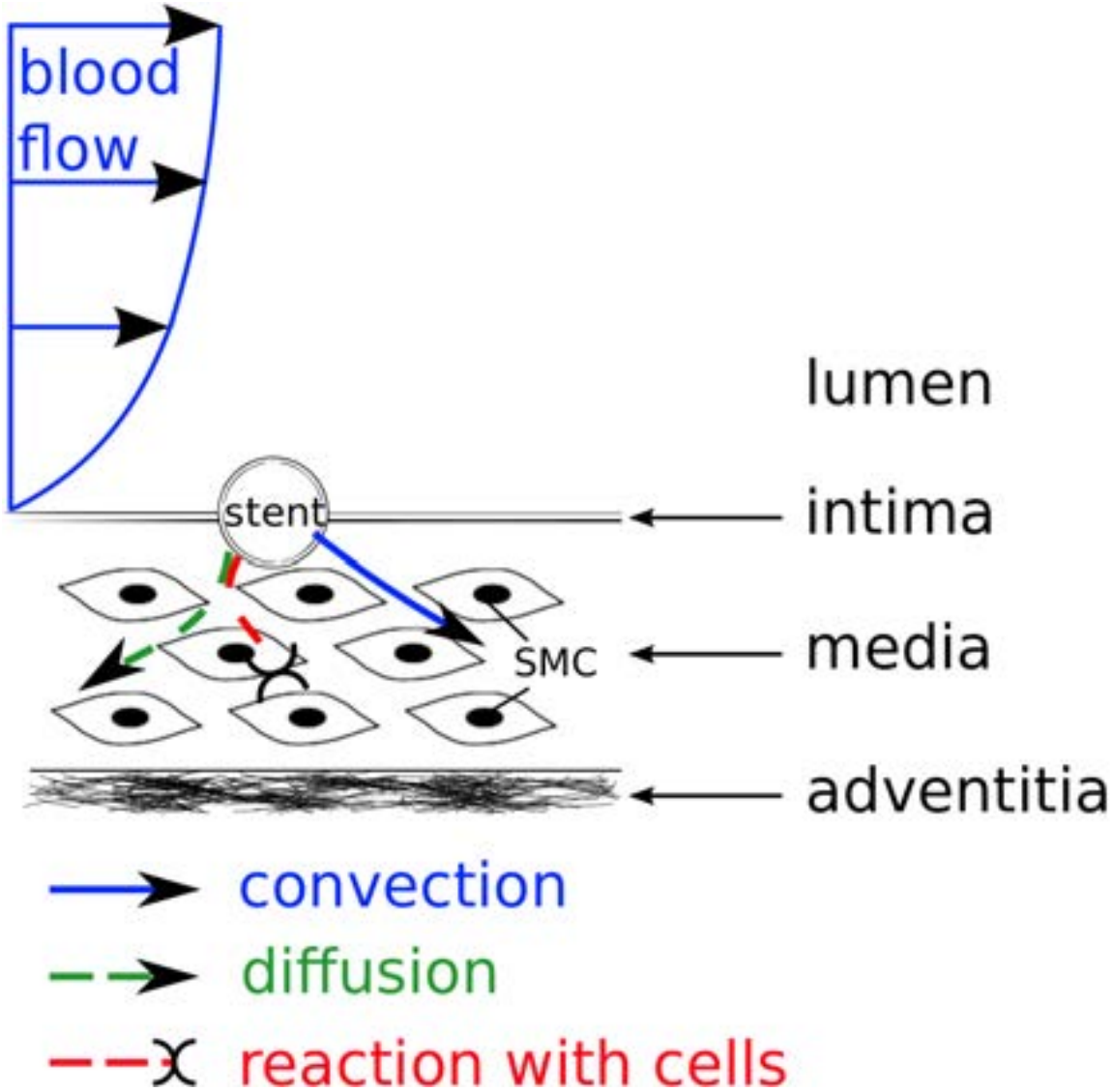
Atherosclerosis and Drug-Eluting Stents

Endothelial Stent Coverage @ 28 days,
Nakazawa *et al.* (2011)



- *Many different* DES *designs* have been proposed.
- Clinical trials and animal studies of different stents show *diverse responses* of the target vessel.
- The underlying *causes are not well understood*.

Modeling the Arterial Wall and Drug Transport



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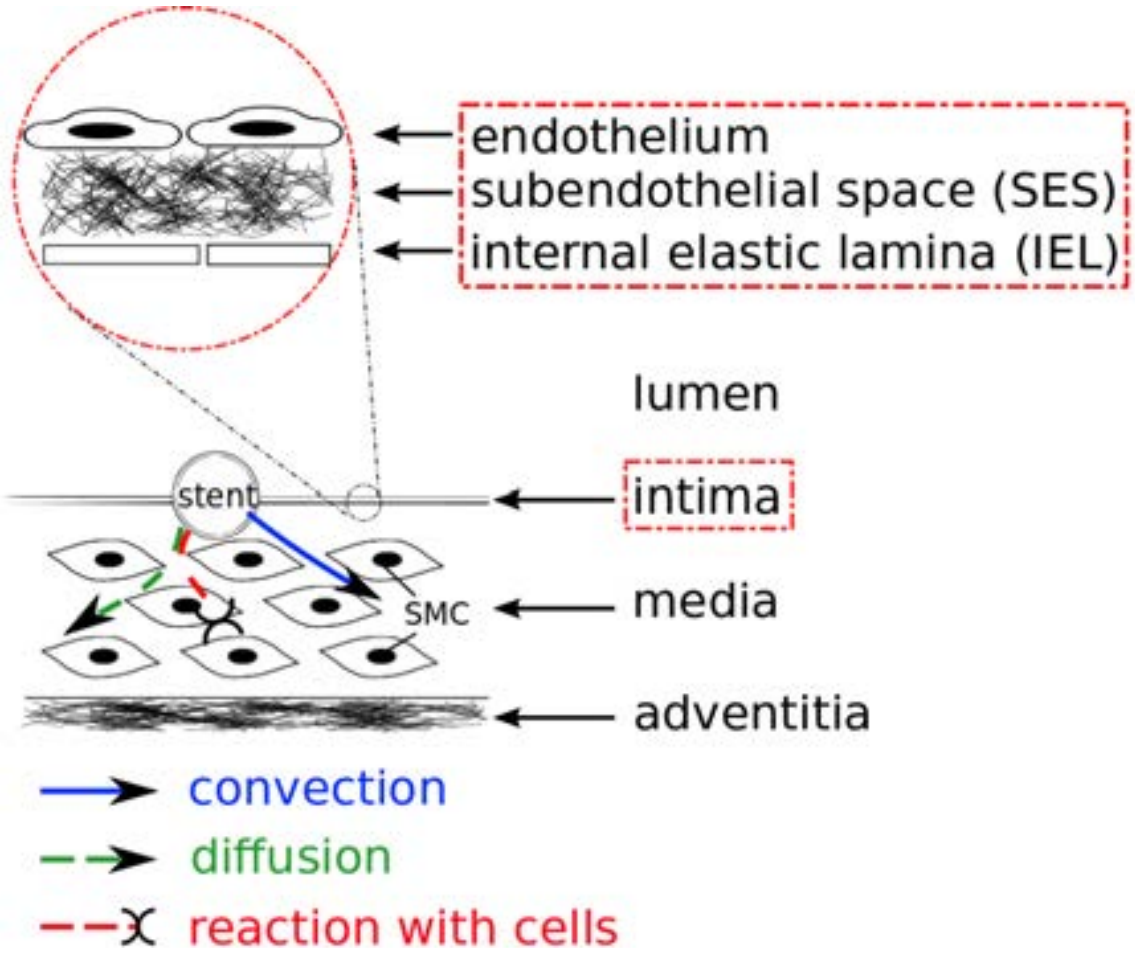
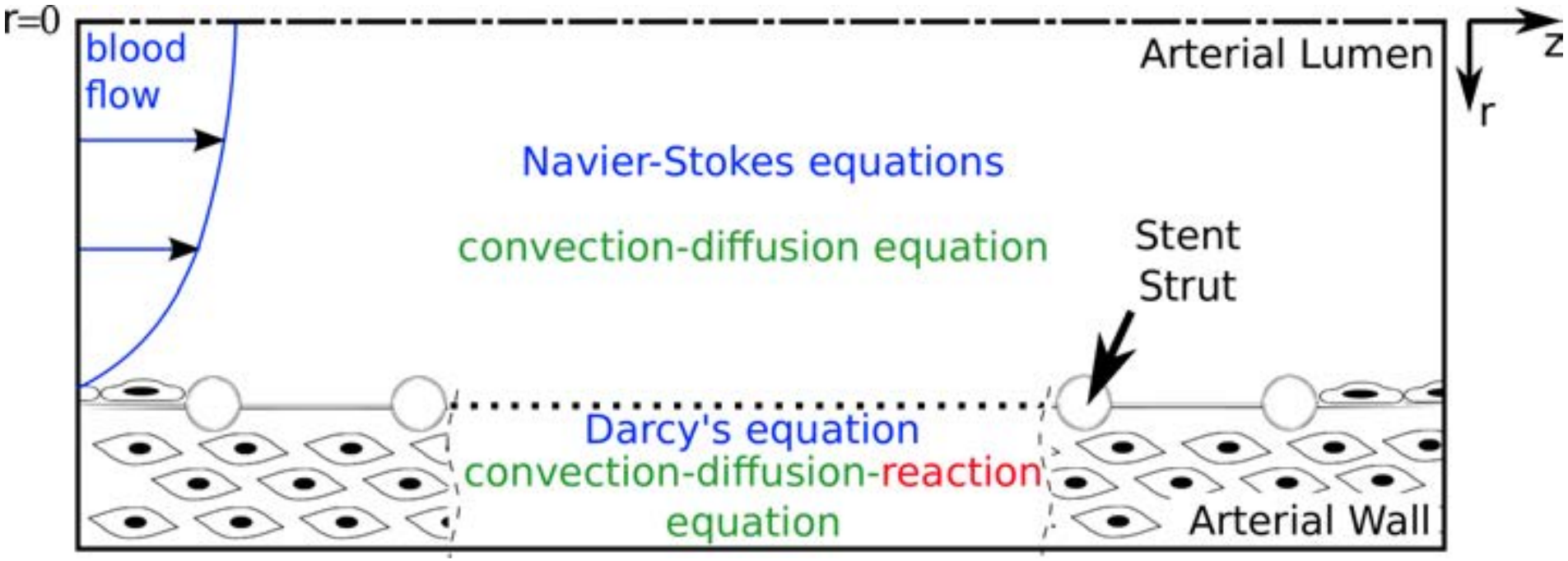


Model of the Arterial Wall

Multi-Layer

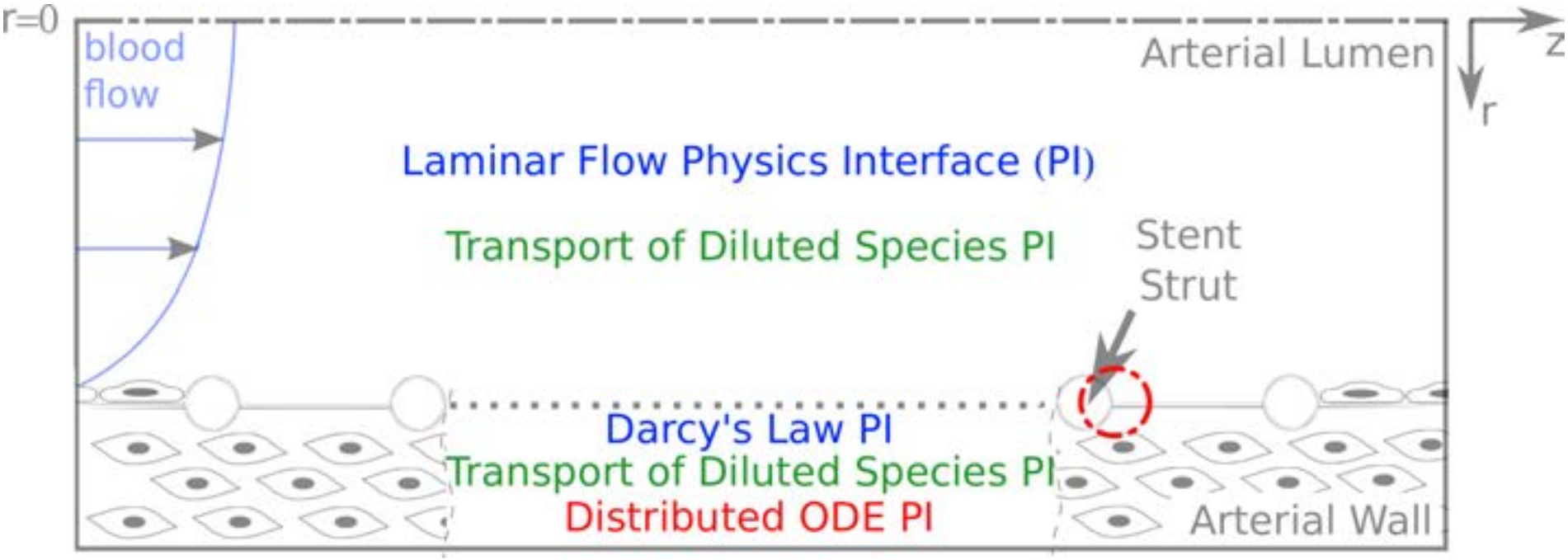
- SES and media described as porous layers
- ET and IEL expressed as Kedem-Katchalsky membranes (Prosi *et al.* (2005))
- Commonly used for macromolecular transport simulations

Baseline Model of the Stented Artery



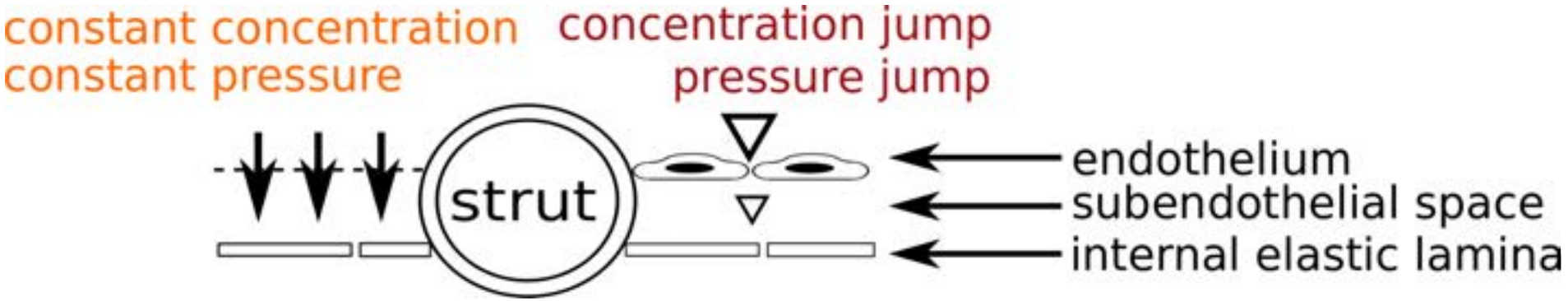
Layers:	multi-layer model	+
Reaction:	reversible binding model	+
Drug:	paclitaxel	

Baseline Model of the Stented Artery



Implemented in COMSOL Multiphysics 4.2

Baseline Model of the Stented Artery: Intima



Solute Dynamics Model: Reaction Model

Reaction Model of Specific Binding and Differential Equation Representation

$$L + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B \quad \Rightarrow \quad \frac{db}{dt} = \mathrm{Da}_2 \Big(\underbrace{c\,(1-b)}_{\text{forward}} - \underbrace{\frac{b_M}{c_0 B_p} b}_{\text{reverse}} \Big)$$

b : Concentration of Bound Drug c : Concentration of Free Drug

(Tzafriri *et al.* (2009))

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b : Concentration of Bound Drug $\quad$ c : Concentration of Free Drug

Da_2: 2nd Damköhler number $= \frac{\text{reaction}}{\text{diffusion}}$ $\quad$ B_p: Binding Potential: hydrophilic drugs: small B_p; hydrophobic drugs: large B_p

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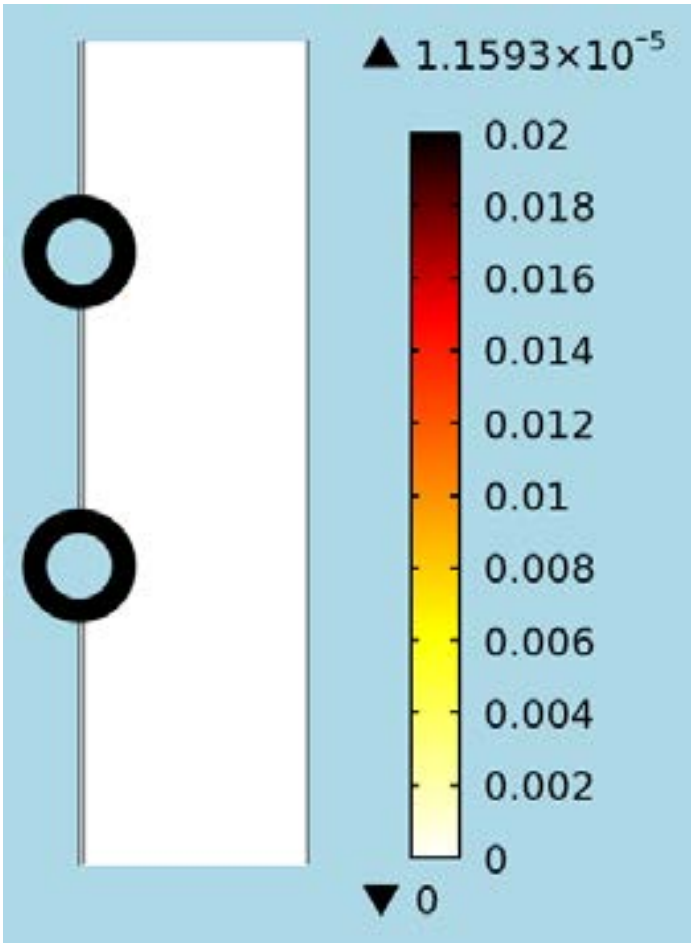
Drug Properties: Paclitaxel vs. Sirolimus

Drug	Pe	$\mathrm{Da}_1 = \frac{\text{reaction}}{\text{convection}}$	Da_2	$B_p = \frac{b_m}{\varepsilon K_d}$	$K_d = \frac{k_r}{k_f}\left[\frac{\text{mol}}{\text{m}^3}\right]$	$b_M\left[\frac{\text{mol}}{\text{m}^3}\right]$
Paclitaxel	13.0	0.5	6.8	41	$3.1 \cdot 10^{-3}$	0.127
Sirolimus	3.7	33.8	125.0	139	$2.6 \cdot 10^{-3}$	0.366

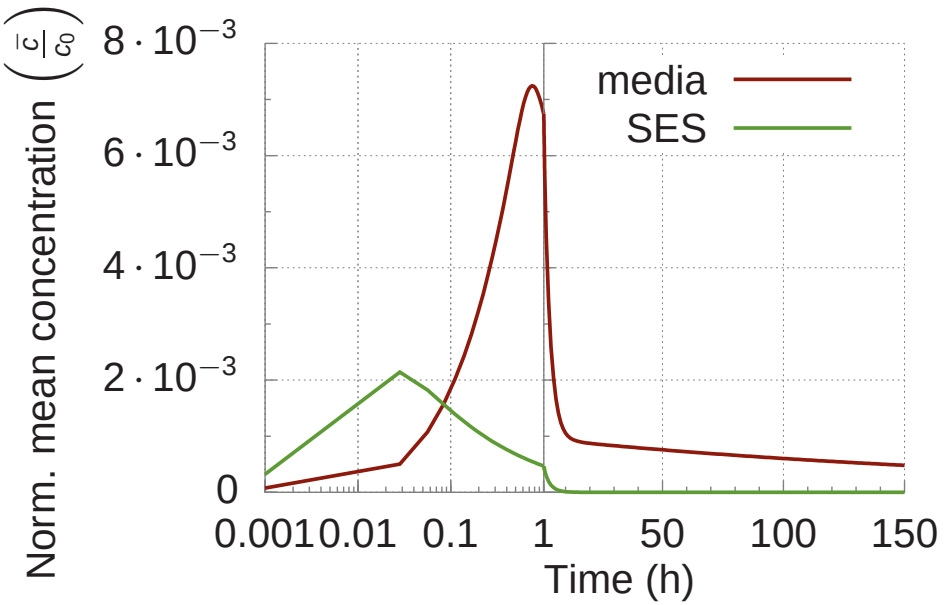
Study Objectives

- Assess the advantages of a multi-layer model
- Investigate the transport dynamics of the two commonly applied hydrophobic drugs paclitaxel and sirolimus.

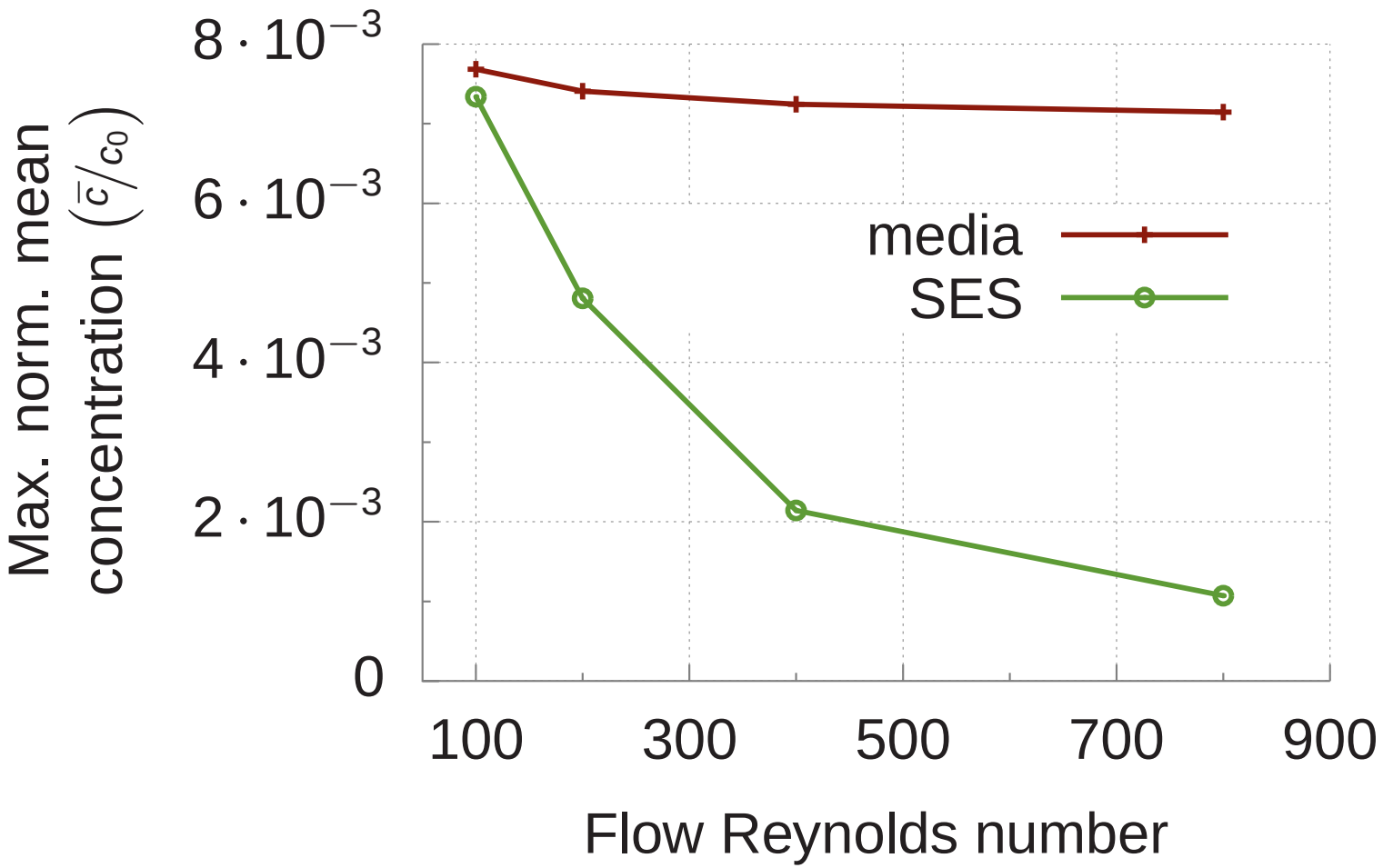
Arterial Wall Dynamics: Drug Transport



Total Drug Concentration

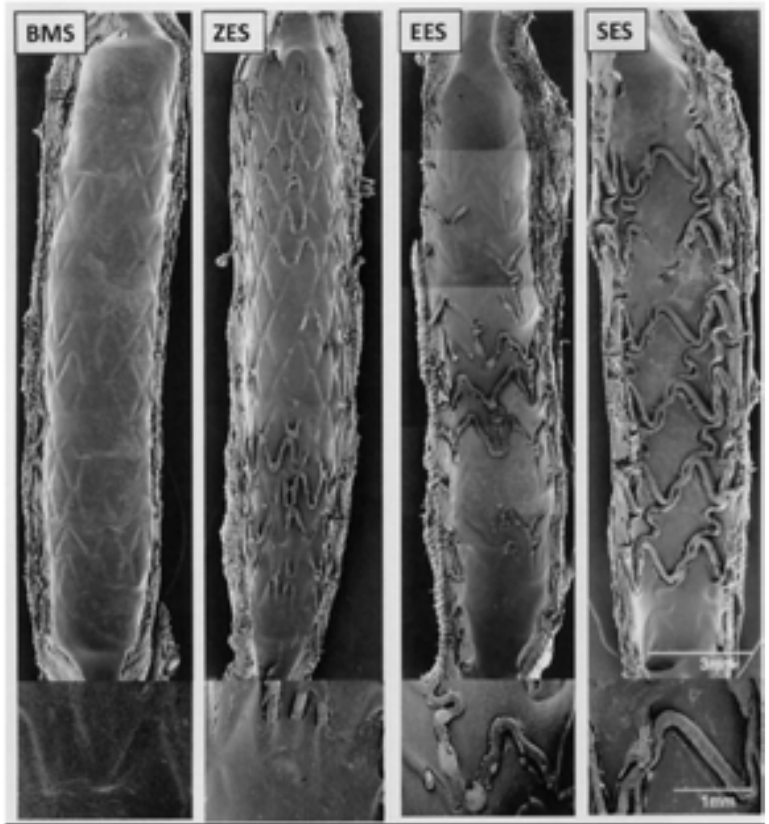


Effect of Flow Reynolds Number



Effect of the Choice of Drug

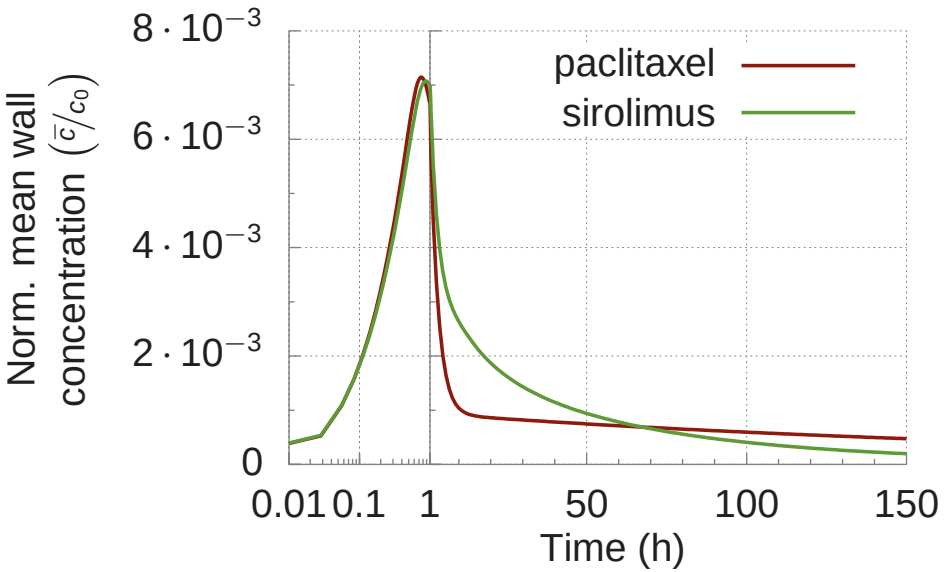
Endothelial Stent Coverage @ 28 days,
Nakazawa *et al.* (2011)



Driver	Endeavor	XIENCE V	CYPHER
Medtronic	Medtronic	Abbot	Cordis
bare	zotarolimus	everolimus	sirolimus

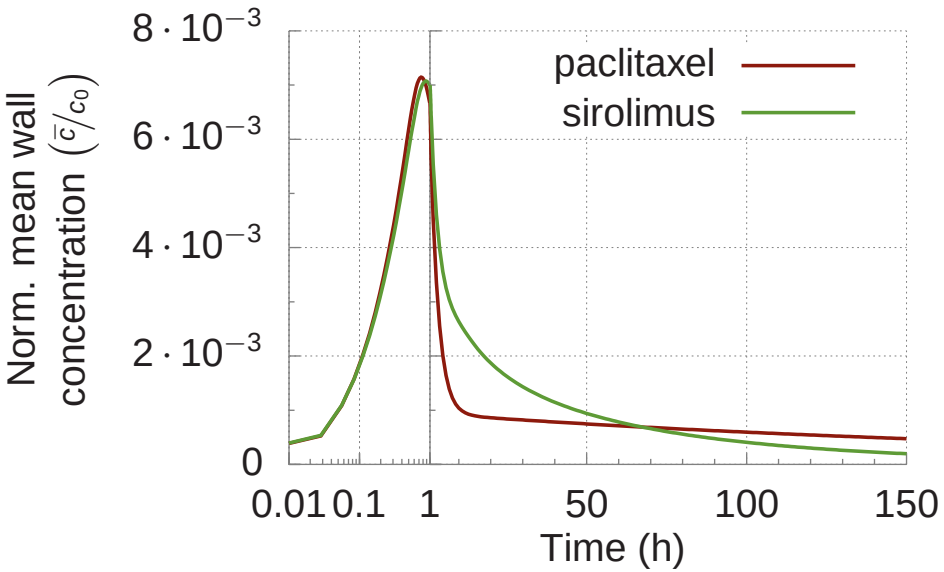
Arterial Wall Dynamics: Fast- vs. Slow-Release

Fast-release

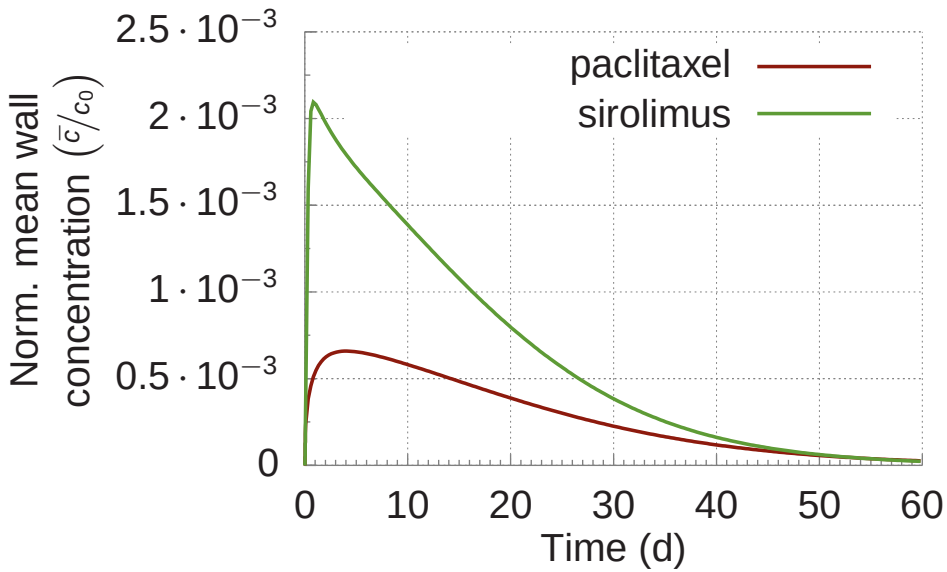


Arterial Wall Dynamics: Fast- vs. Slow-Release

Fast-release

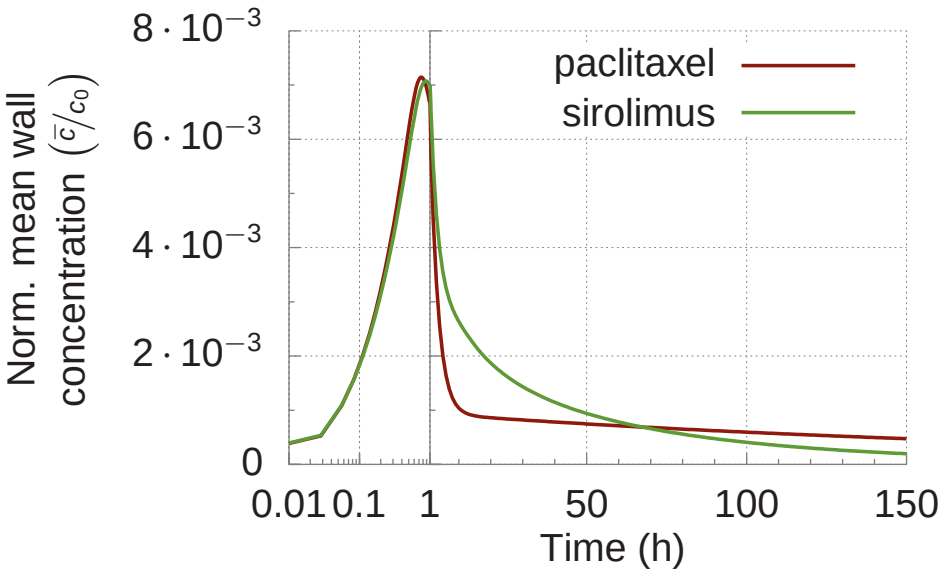


Slow-release



Arterial Wall Dynamics: Fast- vs. Slow-Release

Fast-release



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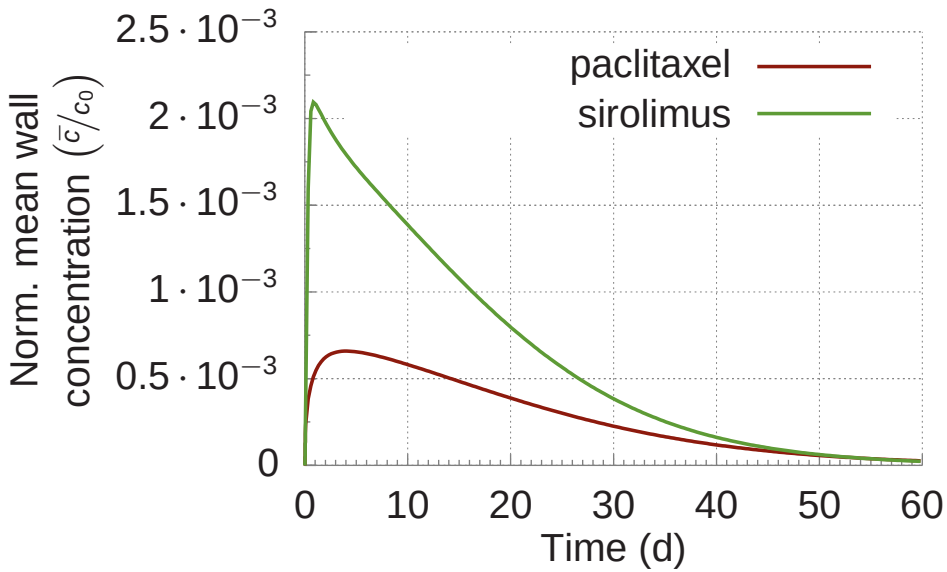

Drug	Pe	1st Da	2nd Da	$B_p = \frac{b_m}{\varepsilon K_d}$	$K_d = \frac{k_r}{k_f}$ $\left[\frac{\text{mol}}{\text{m}^3}\right]$	b_M $\left[\frac{\text{mol}}{\text{m}^3}\right]$
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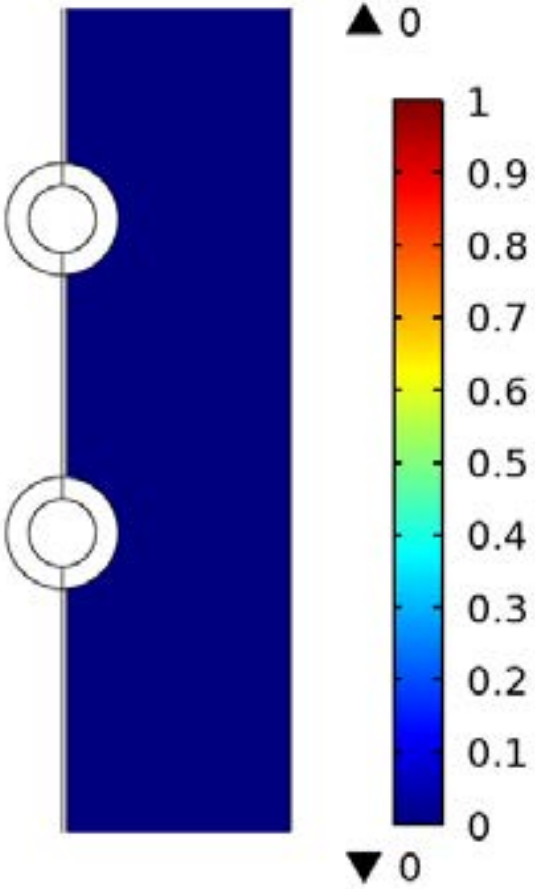
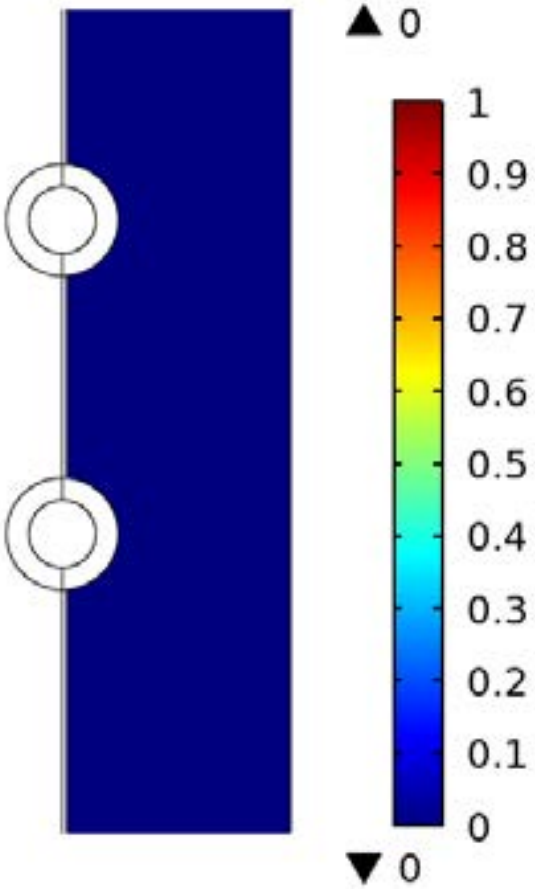
Arterial Wall Dynamics: Drug Binding

Paclitaxel



Sirolimus



Occupied Binding Site Fraction

Arterial Wall Dynamics: Transport Modes

Paclitaxel

- Mode I: Transport-dominated
- Mode II: Competition of transport and reaction (binding)
- Mode III: Reaction-dominated (unbinding)

Sirolimus

- Mode I: Reaction-dominated (binding)
- Mode II: Competition of transport and reaction (binding)
- Mode III: Reaction-dominated (unbinding)

Drug	Pe	Da_1	Da_2
Paclitaxel	13.0	0.5	6.8
Sirolimus	3.7	33.8	125.0

Conclusions

- MULTI-LAYER MODEL INCREASES SPATIAL RESOLUTION
  - Different properties of intima and media have to be taken into account.
- TRANSPORT DYNAMICS DIVIDED IN THREE DISTINCT MODES
  - Modes I+II: set distribution pattern and toxicity/efficacy levels.
  - Mode III: determine the efficiency of the stent design.
- OPTIMIZATION POTENTIAL
  - Adjusting drug properties and release kinetics as part of the stent design with the goal of improving drug retention and distribution within the arterial wall.

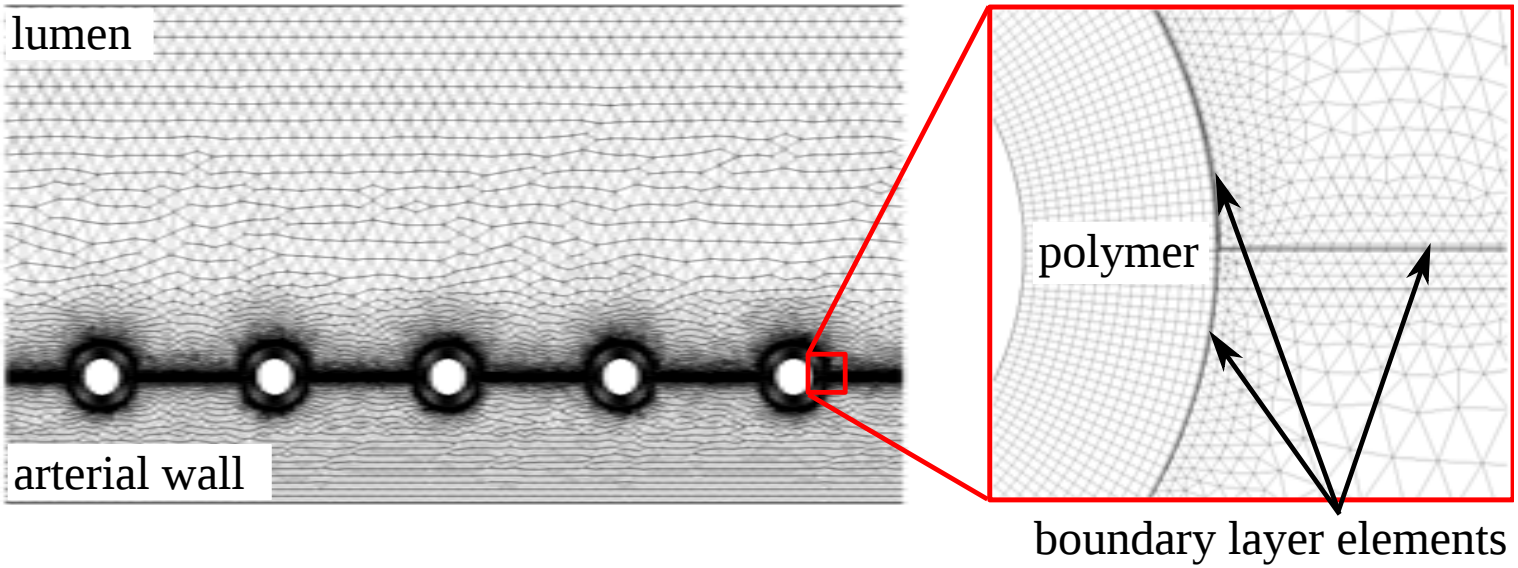
Acknowledgments

PhD Fellowship: Ecole Polytechnique

Sponsor: AXA Research Fund

Thank you for your Attention!

Numerical Model: Mesh



- $\approx 300,000$ elements