Modeling Arterial Wall Transport For Drug-Eluting Stents

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COMSOL Conference Stuttgart 2011 October 26, 2011

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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

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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.

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Modeling the Arterial Wall and Drug Transport



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Modeling the Arterial Wall and Drug Transport



--x reaction with cells

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



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Baseline Model of the Stented Artery



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



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Baseline Model of the Stented Artery



Implemented in COMSOL Multiphysics 4.2

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Baseline Model of the Stented Artery: Intima



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Solute Dynamics Model: Reaction Model

Reaction Model of Specific Binding and Differential Equation Representation

$$L + S \rightleftharpoons_{k_r} B \Rightarrow \frac{db}{dt} = \text{Da}_2(\underbrace{c(1-b)}_{\text{forward}} - \underbrace{\frac{b_M}{c_0 B_p}}_{\text{reverse}} b)$$

b: Concentration of Bound Drug c: 0

c : Concentration of Free Drug

(Tzafriri *et al.* (2009)) Bozsak (LadHyX)

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Solute Dynamics Model: Reaction Model

Reaction Model of Specific Binding and Differential Equation Representation

$$L + S \rightleftharpoons_{k_r} B \Rightarrow \frac{db}{dt} = \underbrace{\mathsf{Da}_2}_{\text{forward}} \underbrace{(c(1-b) - \frac{b_M}{c_0 B_p} b)}_{\text{reverse}}$$

$$b : \text{Concentration of Bound Drug} \quad c : \text{Concentration of Free Drug}$$

$$\mathsf{Da}_2 : 2^{\text{nd}} \text{ Damköhler number} = \frac{\text{reaction}}{\text{diffusion}} \quad B_p : \text{Binding Potential:} \quad \begin{array}{c} \text{hydrophilic drugs: small } B_p \\ \text{hydrophobic drugs: large } B_p \end{array}$$

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Solute Dynamics Model: Reaction Model

Reaction Model of Specific Binding and Differential Equation Representation

$$L + S \rightleftharpoons_{k_r} B \Rightarrow \frac{db}{dt} = \underbrace{\mathsf{Da}_2}_{\text{forward}} \underbrace{(c(1-b))}_{c_0} - \underbrace{\frac{b_M}{c_0}}_{\text{reverse}} b)$$

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

Da₂: 2nd Damköhler number = $\frac{\text{reaction}}{\text{diffusion}}$

Bp: Binding Potential:

hydrophilic drugs: small B_p hydrophobic drugs: large B_p

Drug Properties: Paclitaxel vs. Sirolimus							
	Drug	Pe	$Da_1 = \frac{reaction}{convection}$	Da ₂	$B_{\mathcal{P}} = rac{b_m}{arepsilon K_d}$	$K_d = \frac{k_r}{k_f} \left[\frac{\text{mol}}{\text{m}^3} \right]$	$b_M \left[\frac{\text{mol}}{\text{m}^3}\right]$
	Paclitaxel Sirolimus	13.0 3.7	0.5 33.8	6.8 125.0	41 139	$\begin{array}{c} 3.1 \cdot 10^{-3} \\ 2.6 \cdot 10^{-3} \end{array}$	0.127 0.366

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Study Objectives

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



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Arterial Wall Dynamics: Drug Transport



Total Drug Concentration

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Effect of Flow Reynolds Number



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Effect of the Choice of Drug

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



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Arterial Wall Dynamics: Fast- vs. Slow-Release

Fast-release



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Arterial Wall Dynamics: Fast- vs. Slow-Release

Fast-release



Slow-release

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Slow-release

Arterial Wall Dynamics: Fast- vs. Slow-Release

Fast-release

$8\cdot 10^{-3}$ $2.5 \cdot 10^{-3}$ paclitaxel paclitaxel Norm. mean wall oncentration (\overline{c}/c_0) sirolimus Norm. mean wall oncentration $(ar{c}/lpha_{lpha})$ $2\cdot 10^{-3}$ sirolimus $6 \cdot 10^{-3}$ concentration concentration $1.5\cdot10^{-3}$ $4\cdot 10^{-3}$ $1 \cdot 10^{-3}$ $2\cdot 10^{-3}$ $0.5 \cdot 10^{-3}$ 0 0.010.1 100 1 50 150 10 20 30 40 50 60 0 Time (d) Time (h) $K_d = \frac{k_f}{k_f} \left| \frac{\text{mol}}{\text{m}^3} \right|$ 2nd Da 1st Da $B_p = \frac{b_m}{\varepsilon K_d}$ mol m³ Drug Pe Ь_М $3.1 \cdot 10^{-3}$ Paclitaxel 13.0 0.5 6.8 41 0.127 $2.6 \cdot 10^{-3}$ Sirolimus 3.7 33.8 125.0 139 0.366

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Arterial Wall Dynamics: Drug Binding

Paclitaxel



Occupied Binding Site Fraction

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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.

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Acknowledgments

PhD Fellowship: Ecole Polytechnique



Sponsor: AXA Research Fund



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Thank you for your Attention!



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Numerical Model: Mesh



boundary layer elements

$\bullet \approx 300,000$ elements