Universidad Zaragoza
1542

Mathematical and numerical modelling of the mechanobiology of the atheroma plaque

E. Peña

Mechanical Engineering Dept. School of Engineering and Architecture.
Bioengineering Division. Aragón Institute of Engineering Research (I3A). University of Zaragoza.
CIBER-BBN. Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina.
***fany@unizar.es**

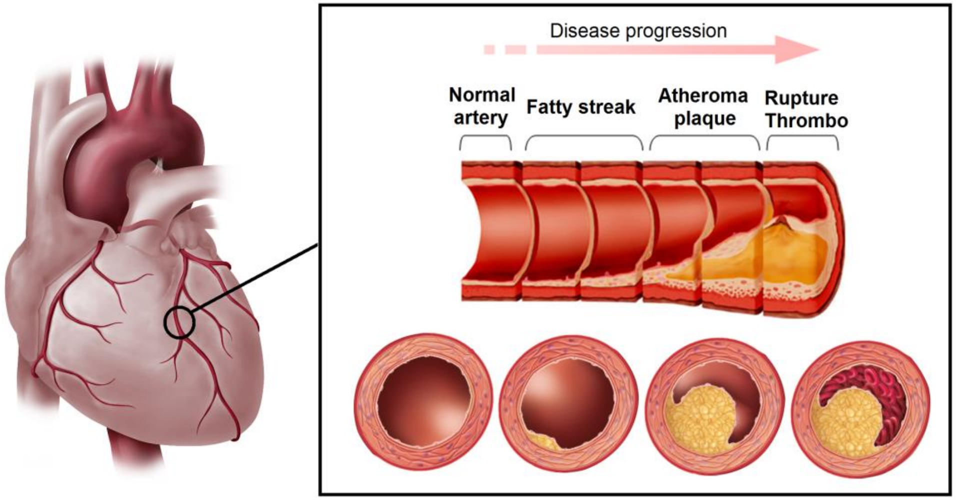
instituto de investigación en ingeniería de Aragón
Universidad de Zaragoza

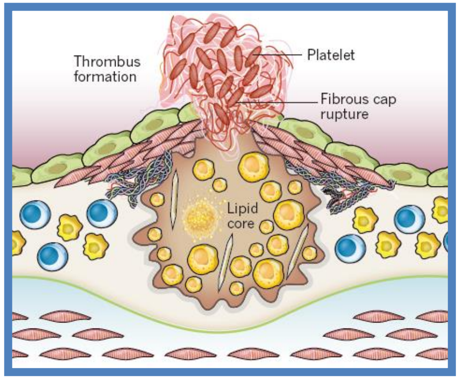
ciber-bbn
Centro Investigación Biomédica en Red
Bioingeniería, Biomateriales y Nanomedicina

Atherosclerosis

Process in which plaques, consisting of deposits of cholesterol and other lipids, macrophages and calcium, are built up in the arterial walls causing:

- Narrowing (stenosis)
- Hardening of the arteries
- Loss of elasticity
- Reduction of the blood flow





Plaque rupture provokes blood clots, which travel around cardiovascular system producing:

- Heart attacks
- Strokes
- Ischemia
- ….

Atherosclerosis

Spontaneous plaque rupture

Means to detect unstable plaques and predict rupture location would then be valuable for clinical diagnosis.

Ref.: P. Libby . Pour la Science, juillet 2003

A cascade of events leads to plaque rupture

ELSEVIER

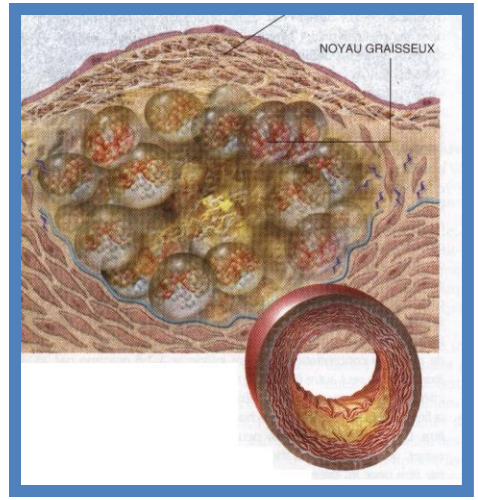
Cardiovascular Research 41 (1999) 369–375

Cardiovascular Research

Review

Mechanisms of plaque rupture: mechanical and biologic interactions

Luis H. Arroyo, Richard T. Lee*



Lipid Accumulation *(decades)* ↔ Inflammation *(Probably years)*

Lipid Accumulation → Increased Fibrous Stress

Inflammation → Increased Matrix Degradation

Inflammation → Decreased Matrix Synthesis

Increased Fibrous Stress, Increased Matrix Degradation, Decreased Matrix Synthesis → **Plaque Rupture**

Factors of development:

Journal of Surgical Research 142, 202–217 (2007)
doi:10.1016/j.jss.2006.11.001

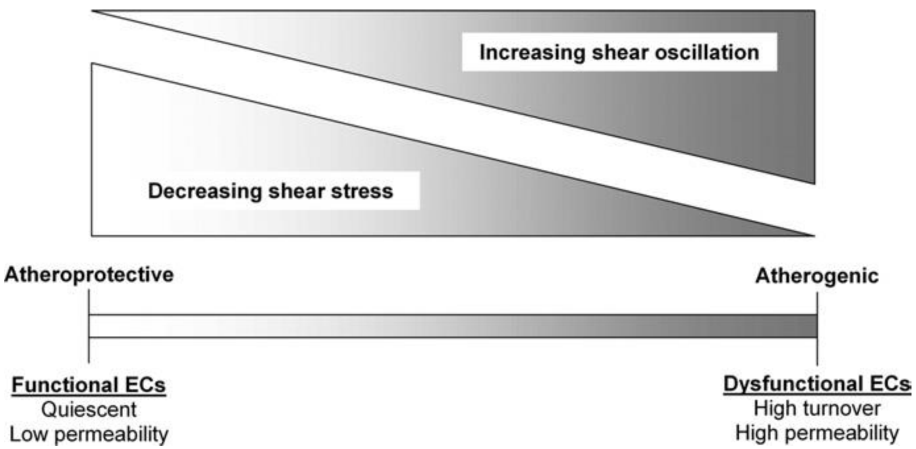
RESEARCH REVIEW

Mechanopathobiology of Atherogenesis: A Review

J. Scott VanEpps, B.S., and David A. Vorp, Ph.D.[1]

- ✓ Biological factors: genetic, LDL, diabetes, Endothelial Dysfunction
- ✓ Environmental factors: smoke, diet …
- ✓ Biomechanical factors:
  - Atherosclerotic plaques, are located at predilection sites, such as side branches, curved segments and bifurcations, which are known to disturb several properties in the blood flow velocity field.
  - Several lines of research indicate that biomechanical factors play an essential role in progression of plaques (e.g. plaque size) and plaque composition .
  - vessel compliance, curvature, pulsatile blood flow or cardiac motion

Biomechanical factors:

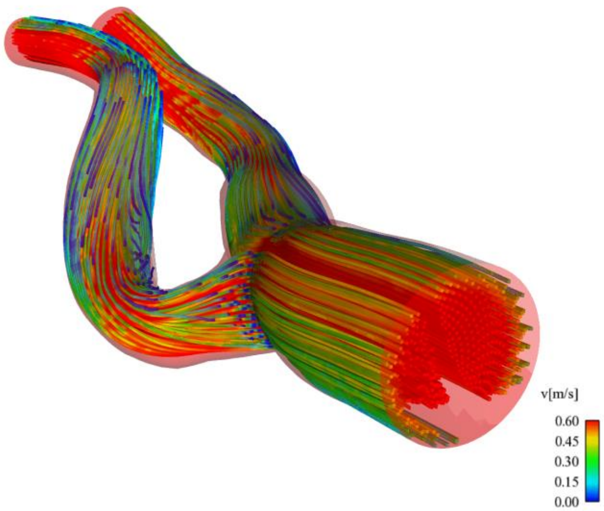


Journal of Surgical Research 142, 202–217 (2007)
doi:10.1016/j.jss.2006.11.001

RESEARCH REVIEW

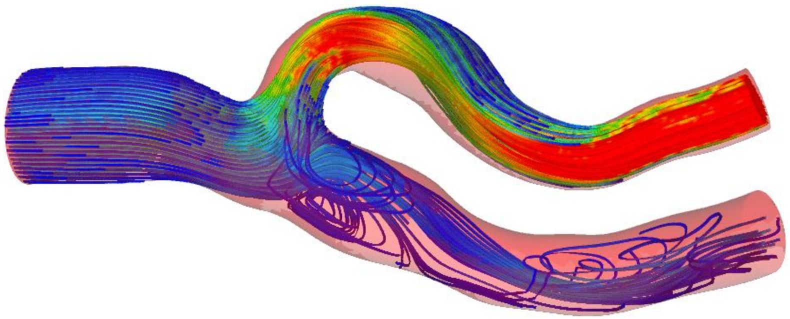
Mechanopathobiology of Atherogenesis: A Review

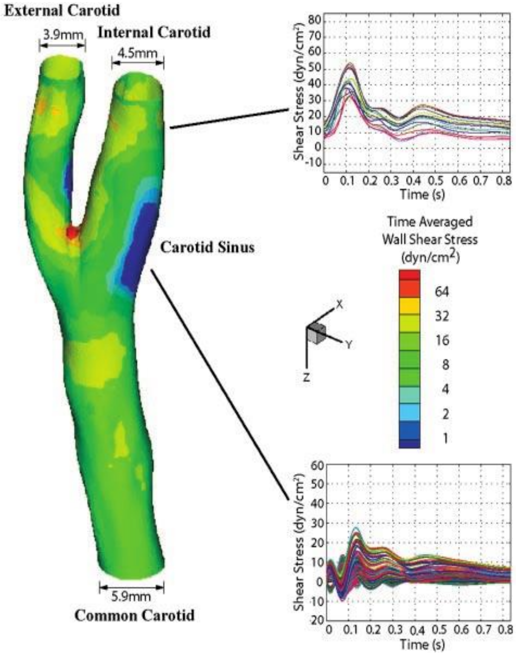
J. Scott VanEpps, B.S., and David A. Vorp, Ph.D.[1]

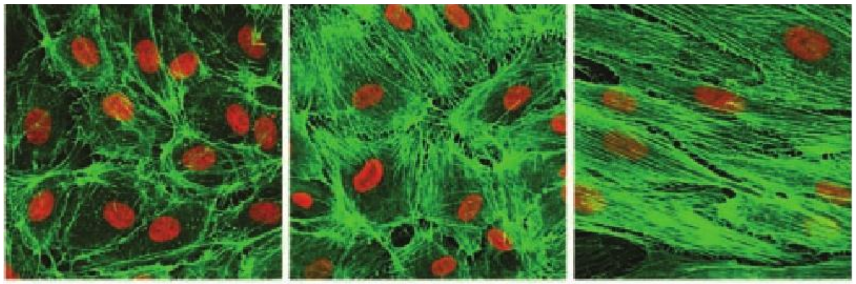


Side branches, curved segments and bifurcations are known to disturb several properties in the blood flow velocity field

Biomechanical factors:

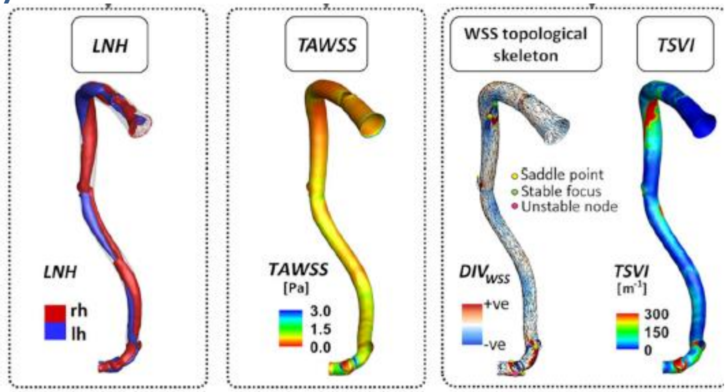


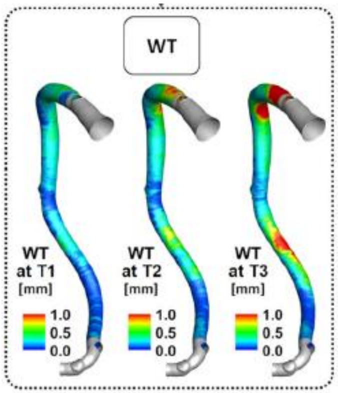




Dai et al. 2004. PNAS 101(41),
14871-14876

Plaque location





$$OSI = 0.5 \cdot \left(1 - \frac{\left|\frac{1}{T}\int_o^T \tau(t)\cdot dt\right|}{TAWSS}\right)$$

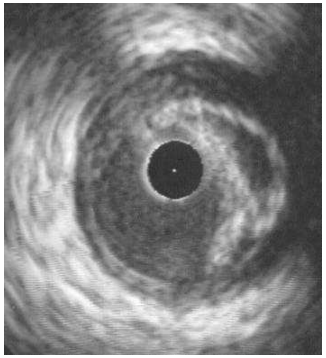
$$TAWSS = \frac{1}{T}\int_o |\tau(t)| \cdot dt$$

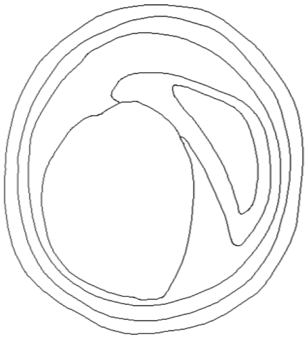
Plaque evolution

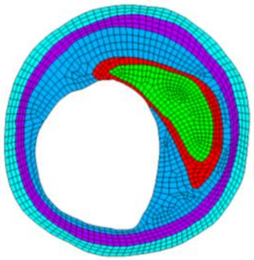
?

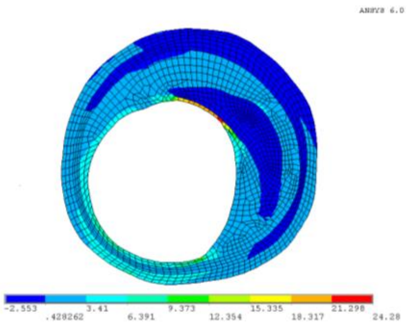
Plaque rupture

IVUS

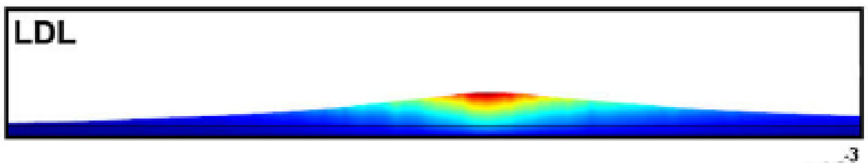








Continumm models



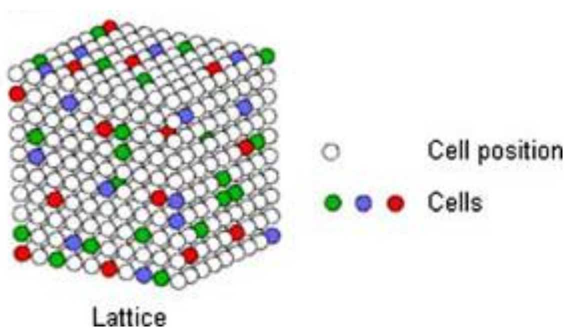
JOURNAL OF THE ROYAL SOCIETY Interface

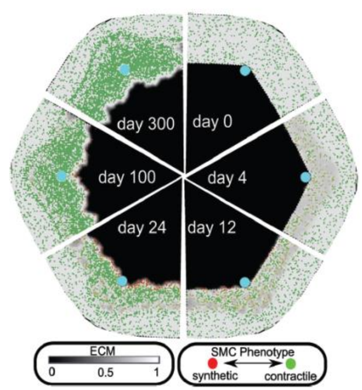
rsif.royalsocietypublishing.org

Mathematical modelling of atheroma plaque formation and development in coronary arteries

Myriam Cilla[1,2,†], Estefanía Peña[1,2] and Miguel A. Martínez[1,2]

Agent Based Models (ABM)





Annals of Biomedical Engineering, Vol. 37, No. 1, January 2009 (© 2008) pp. 129–145
DOI: 10.1007/s10439-008-9594-9

A Mechanobiological Model for Tissue Differentiation that Includes Angiogenesis: A Lattice-Based Modeling Approach

SARA CHECA and PATRICK J. PRENDERGAST

Contents lists available at SciVerse ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech www.JBiomech.com

Application of a mechanobiological simulation technique to stents used clinically

Colin J. Boyle[a], Alex B. Lennon[a,b], Patrick J. Prendergast[a,*]

Continuum Models:

- ✓ Based on reaction–convention– diffusion equations.
- ✓ Consider the wall as a continua
- ✓ Model Transport Phenomena
- ✓ Easy couple with mechanics
- ✓ Phenomenological models
- ✓ Determinist, no statistics.
- ✓ Difficult to validate
- ✓ Numerical problems - growth

Journal of Theoretical Biology 297 (2012) 1–10
Contents lists available at SciVerse ScienceDirect
Journal of Theoretical Biology
journal homepage: www.elsevier.com/locate/yjtbi
ELSEVIER

Long time evolution of atherosclerotic plaques
M.A.K. Bulelzai, Johan L.A. Dubbeldam*

Med Biol Eng Comput (2013) 51:607–616
DOI 10.1007/s11517-012-1031-4
ORIGINAL ARTICLE

Computer simulation of three-dimensional plaque formation and progression in the carotid artery

Nenad Filipovic · Zhongzhao Teng · Milos Radovic · Igor Saveljic · Dimitris Fotiadis · Oberdan Parodi

JOURNAL OF THE ROYAL SOCIETY Interface
rsif.royalsocietypublishing.org

Mathematical modelling of atheroma plaque formation and development in coronary arteries

Myriam Cilla[1,2,†], Estefanía Peña[1,2] and Miguel A. Martínez[1,2]

Agent Based Models:

- ✓ Based on statistical roles.
- ✓ Consider the wall as a laticce
- ✓ Based on cell populations behavior
- ✓ Probabilistic solutions.
- ✓ No numerical problems
- ✓ Difficulty to couple with mechanics
- ✓ No Model Transport Phenomena
- ✓ Difficult to validate

ELSEVIER
Journal of Biomechanics 40 (2007) 2244–2253
JOURNAL OF BIOMECHANICS
www.elsevier.com/locate/jbiomech
www.JBiomech.com

Random-walk models of cell dispersal included in mechanobiological simulations of tissue differentiation

M.A. Pérez[a,b], P.J. Prendergast[a,*]

Journal of Biomechanics ▮ (▮▮▮) ▮▮–▮▮▮
Contents lists available at SciVerse ScienceDirect
Journal of Biomechanics
journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com
ELSEVIER

Application of a mechanobiological simulation technique to stents used clinically

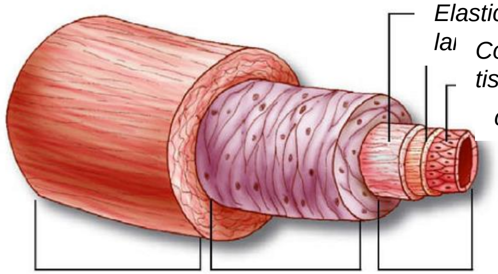
Colin J. Boyle[a], Alex B. Lennon[a,b], Patrick J. Prendergast[a,*]

Biomech Model Mechanobiol
DOI 10.1007/s10237-011-0316-0
ORIGINAL PAPER

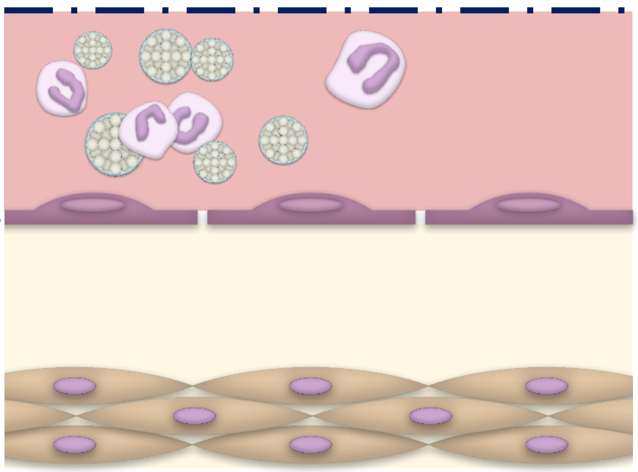
A multiscale mechanobiological modelling framework using agent-based models and finite element analysis: application to vascular tissue engineering

Houman Zahedmanesh · Caitríona Lally

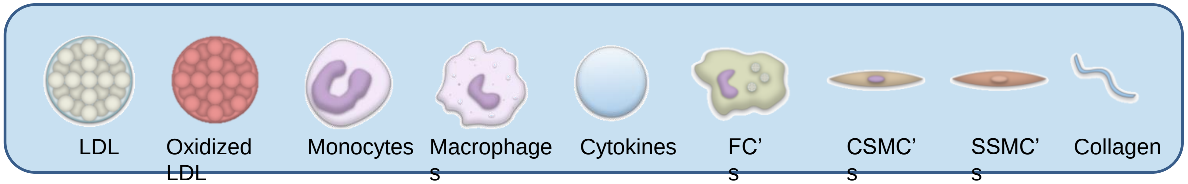
Formation process



https://yomedicoblasto.com/aterosclerosis-formacion-evolucion-y-riesgos/

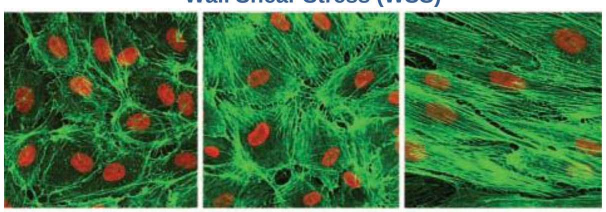


Formation process

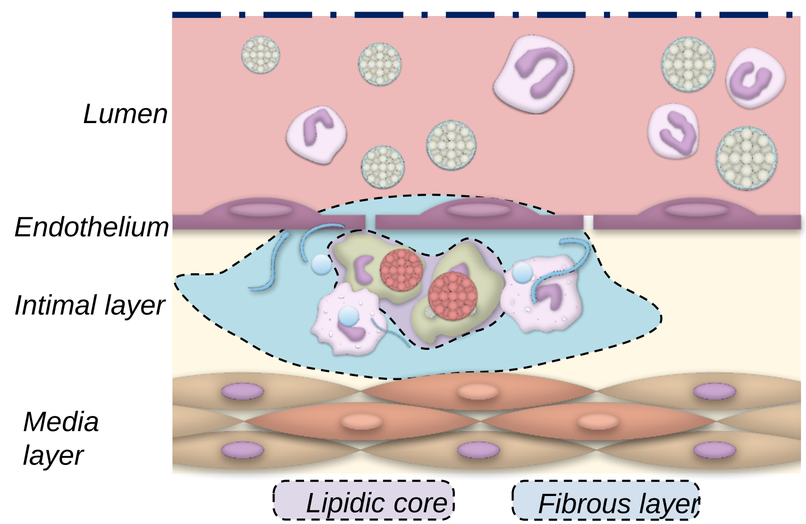


Mechanical stimulus

Wall Shear Stress (WSS)

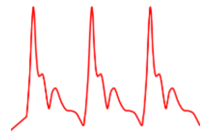


Dai et al. 2004



Blood flow

- ✓ Stationary or pulsatile flow
- ✓ Newtonian fluid
- ✓ Homogeneus fluid



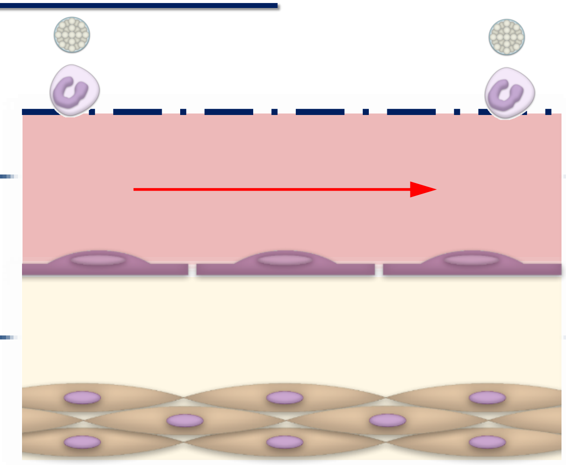
$$u = 2u_0\left(1-\left(\frac{r}{R}\right)^2\right)$$

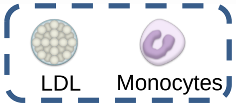
$$P_{sal}$$

Navier-Stokes and continuity equations

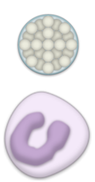
$$\rho_s(\boldsymbol{u_s}\cdot\nabla)\boldsymbol{u_s} = \nabla\cdot[-p_s I + \mu_s(\nabla\boldsymbol{u_s} + (\nabla\boldsymbol{u_s})^T)] + \boldsymbol{F_s}$$

$$\rho_s\nabla\cdot\boldsymbol{u_s} = 0$$





Solute flux along lumen



Difusión | Convección

$$\nabla\cdot\left(-D_{LDL,l}\nabla C_{LDL,l}\right) + u\cdot\nabla C_{LDL,l} = 0$$

$$\nabla\cdot\left(-D_{m,l}\nabla C_{m,l}\right) + u\cdot\nabla C_{m,l} = 0$$

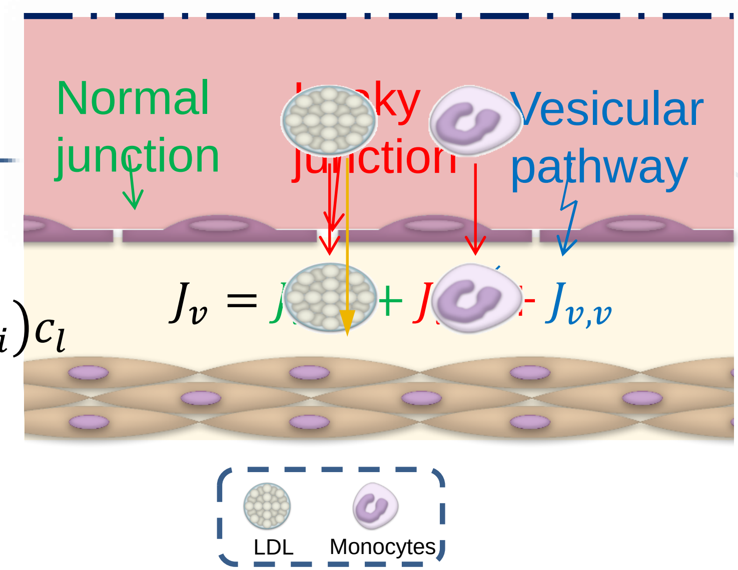
Plasma flow

Ley de Darcy and continuity equation

$$\boldsymbol{u_w} = \frac{k_w}{\mu_p} \nabla p_w; \qquad \frac{\partial(\rho_p \epsilon_w)}{\delta t} + \rho_p \nabla \cdot \boldsymbol{u_w} = J_v$$

3 pore model

Olgac et al. (2008)



Solute flux along lumen

$$J_{s,LDL} = P_i(c_l - c_w)\frac{Pe_i}{e^{Pe_i} - 1} + J_v(1 - \sigma_{f,i})c_l$$

$$J_{s,m} = \frac{m_r}{1 + \frac{WSS}{WSS_0}} C_{LDL_{ox,W}} C_{m,l}$$

TIME DEPENDENT: Convection-diffusion-reaction equations along the arterial wall

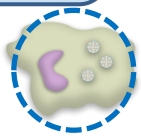
Inflammatory process

Temporal		Diffusion		Convection		Reaction
$\frac{\partial C_{LDL,w}}{\partial t}$	+	$\nabla\cdot(-D_{LDL,w}\nabla C_{LDL,w})$	+	$u_w\cdot\nabla C_{LDL,w}$	=	$-d_{LDL}C_{LDL,w}$
$\frac{\partial C_{LDLox,w}}{\partial t}$	+	$\nabla\cdot(-D_{LDLox,w}\nabla C_{LDLox,w})$	+	$\cancel{u_w\cdot\nabla C_{LDLox,w}}$	=	$d_{LDL}C_{LDL,w} - LDL_{ox,r}C_{LDLox,w}C_{M,w}$
$\frac{\partial C_{m,w}}{\partial t}$	+	$\nabla\cdot(-D_{m,w}\nabla C_{m,w})$	+	$\cancel{u_w\cdot\nabla C_{m,w}}$	=	$-d_m C_{m,w} - m_d C_{m,w}$
$\frac{\partial C_{M,w}}{\partial t}$	+	$\nabla\cdot(-D_{M,w}\nabla C_{M,w})$	+	$\cancel{u_w\cdot\nabla C_{M,w}}$	=	$d_m C_{m,w} - \frac{LDL_{ox,r}}{n_{FC}}C_{LDLox,w}\cdot C_{M,w}$
$\frac{\partial C_{cw}}{\partial t}$	+	$\cancel{\nabla\cdot(-D_{c,w}\nabla C_{c,w})}$	+	$\cancel{u_w\cdot\nabla C_{c,w}}$	=	$C_r\cdot C_{LDLox,w}\cdot C_{M,w} - d_c C_{c,w}$
$\frac{\partial C_{CSMC,w}}{\partial t}$	+	$\cancel{\nabla\cdot(-D_{CSMC,w}\nabla C_{CSMC,w})}$	+	$\cancel{u_w\cdot\nabla C_{CSMC,w}}$	=	$-C_{CSMC,w}\cdot S_r\left(\frac{C_{c,w}}{k_c\cdot C^{th}_{c,w}+C_{c,w}}\right)$
$\frac{\partial C_{SSMC,w}}{\partial t}$	+	$\cancel{\nabla\cdot(-D_{SSMC,w}\nabla C_{SSMC,w})}$	+	$\cancel{u_w\cdot\nabla C_{SSMC,w}}$	=	$C_{CSMC,w}\cdot S_r\left(\frac{C_{c,w}}{k_c\cdot C^{th}_{c,w}+C_{c,w}}\right)+\left(\frac{p_{ss}C_{c,w}}{\frac{C^{th}_{c,w}}{2}+C_{c,w}}\right)C_{SSMC,w}\left(1-\frac{C_{SSMC,w}}{C^{th}_{SSMC,w}}\right)-r_{Apop}\cdot C_{SSMC}$
$\frac{\partial C_{FC,w}}{\partial t}$	+	$\cancel{\nabla\cdot(-D_{FC,w}\nabla C_{FC,w})}$	+	$\cancel{u_w\cdot\nabla C_{FC,w}}$	=	$\frac{LDL_{ox,r}}{n_{FC}}C_{LDLox,w}\cdot C_{M,w}$
$\frac{\partial C_{G,w}}{\partial t}$	+	$\cancel{\nabla\cdot(-D_{G,w}\nabla C_{G,w})}$	+	$\cancel{u_w\cdot\nabla C_{G,w}}$	=	$G_r C_{SSMC,w} - d_G C_{G,w}$

Plaque growth

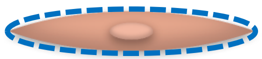
$$\nabla \cdot v = \frac{\partial \Delta C_{F,w}}{\partial t} \cdot \boxed{Vol_{foam\ cell}} + \frac{\partial \Delta C_{SSMC,w}}{\partial t} \cdot \boxed{Vol_{SSMC}} + \frac{\partial \Delta C_{G,w}}{\partial t} \cdot \frac{1}{\boxed{\rho_G}}$$

Spheres



$$Vol_{foam\ cell} = \frac{4}{3}\pi R^3_{Foamcell}$$

Ellipses



$$Vol_{SSMC} = \frac{4}{3}\pi R^3_{SSMC} l_{SSMC}$$

$$\rho_G = 1\ g/mL$$

Saez et al. 2012b

Hyperelastic material

- **Yeoh model:**

$$\Psi = \sum_{i=1}^{3} C_i \cdot [I_1 - 3]^i$$

$$C_1 = 17{,}005\ \mathrm{k}Pa$$

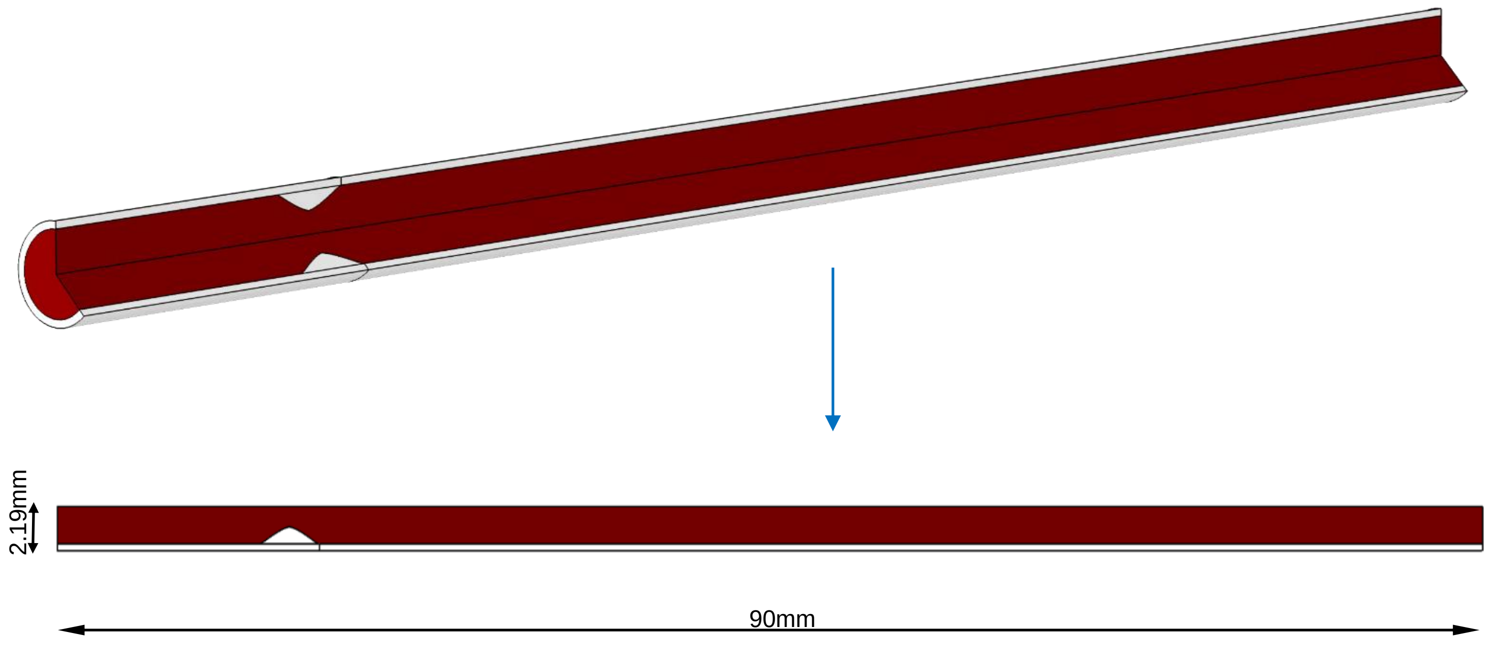
$$C_2 = -73{,}424\ \mathrm{k}Pa$$

$$C_3 = 414{,}952\ \mathrm{k}Pa$$

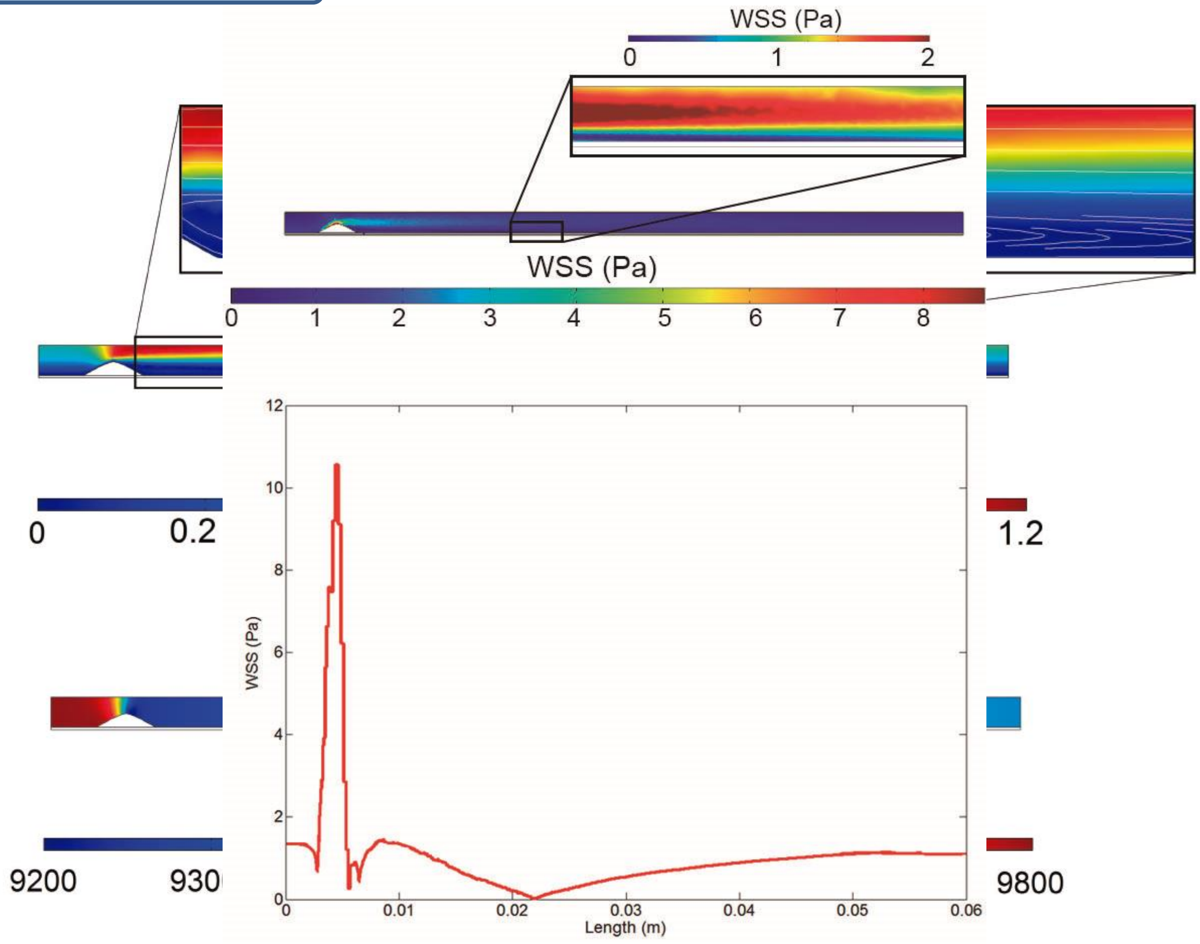
Cebollero Burgués, M.
Trabajo Fin de Master 2017

GEOMETRY

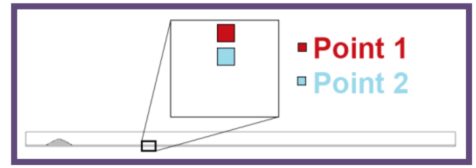
2D axysimmetric model

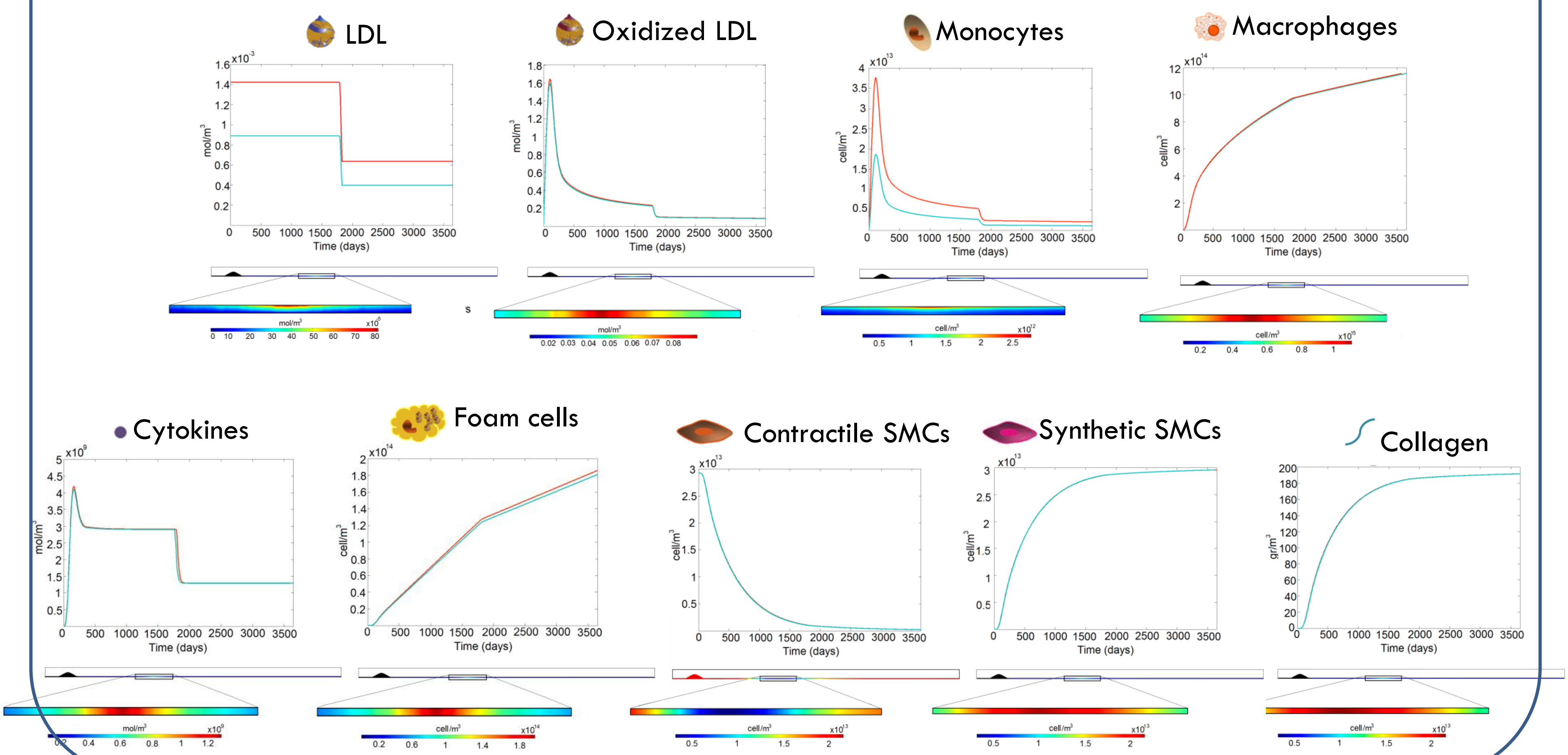


Hemodynamic results

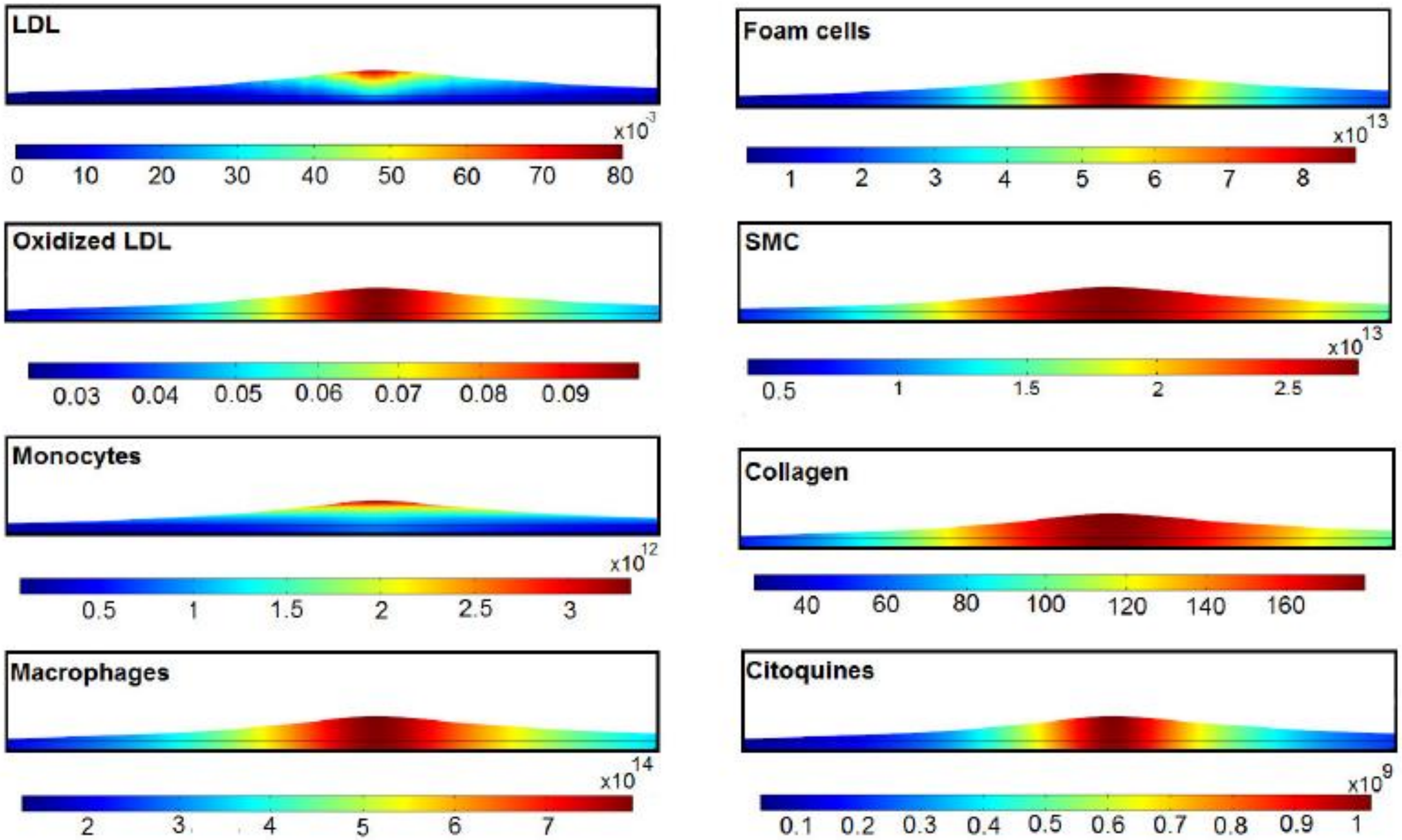


Artery wall concentration evolution





Artery wall concentration evolution

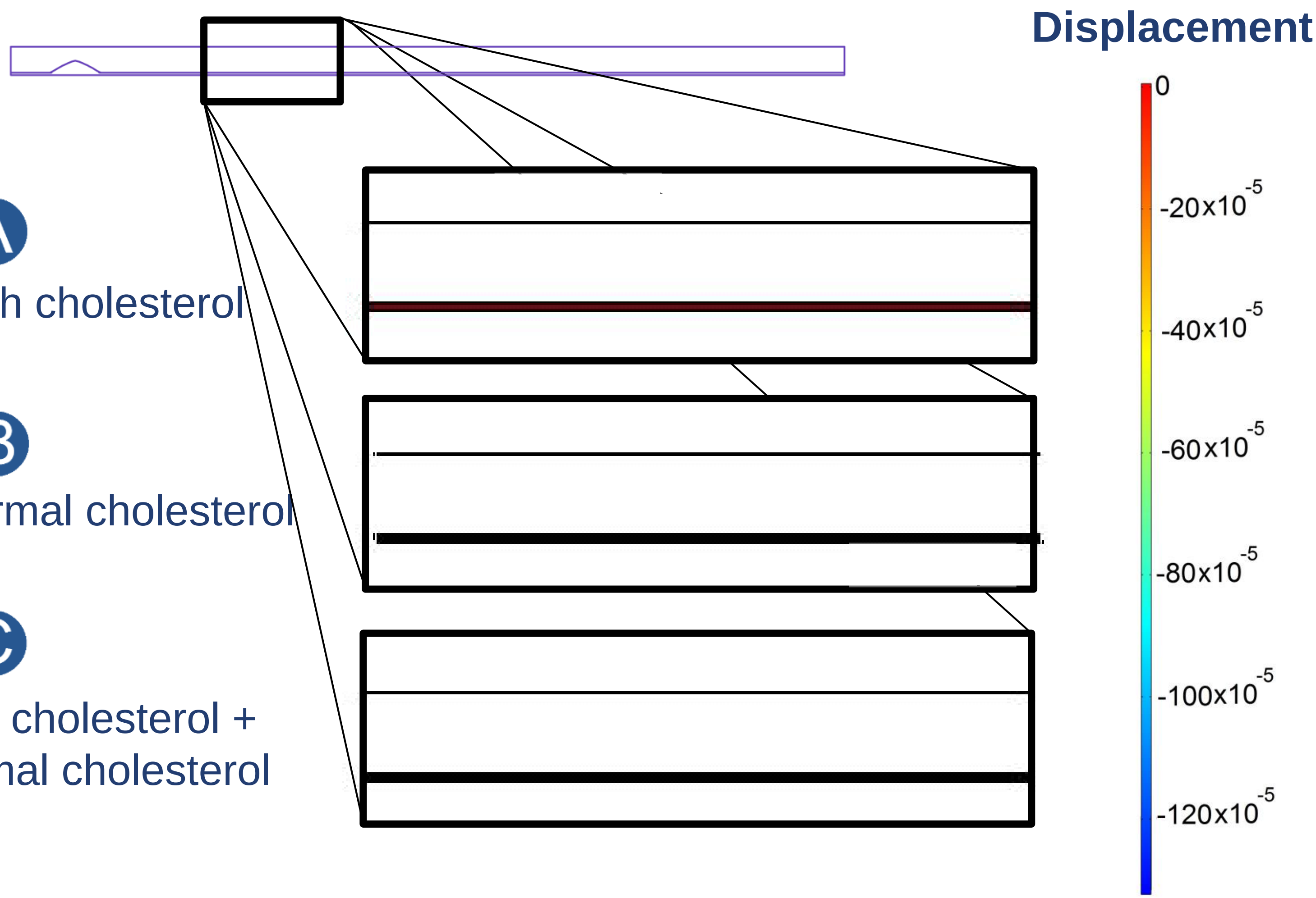


Growth after treatments

Ⓐ 10 years high cholesterol

Ⓑ 10 years normal cholesterol

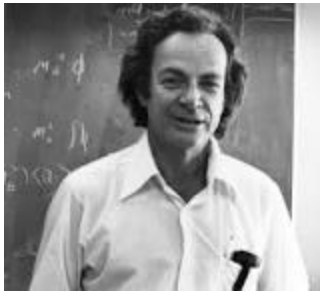
Ⓒ 5 years high cholesterol +
5 years normal cholesterol



Validation

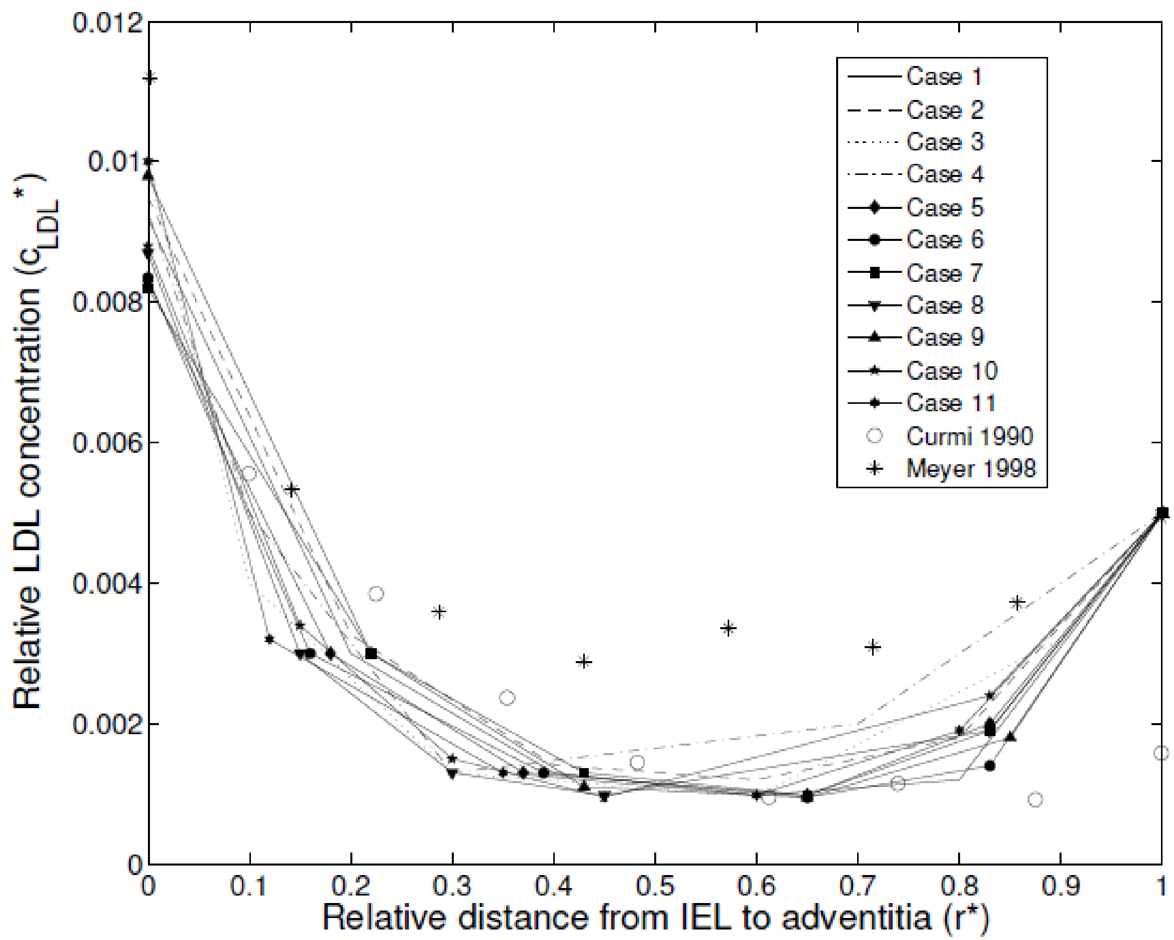
Mechanobiological models:

If it disagrees with experiment, it is wrong. And that simple statement is the key to science. It does not make a difference how beautiful your guess is, it does not matter how smart you are, who made the guess, or what his name is. If it disagrees with experiment, it is wrong. That is all there is to it



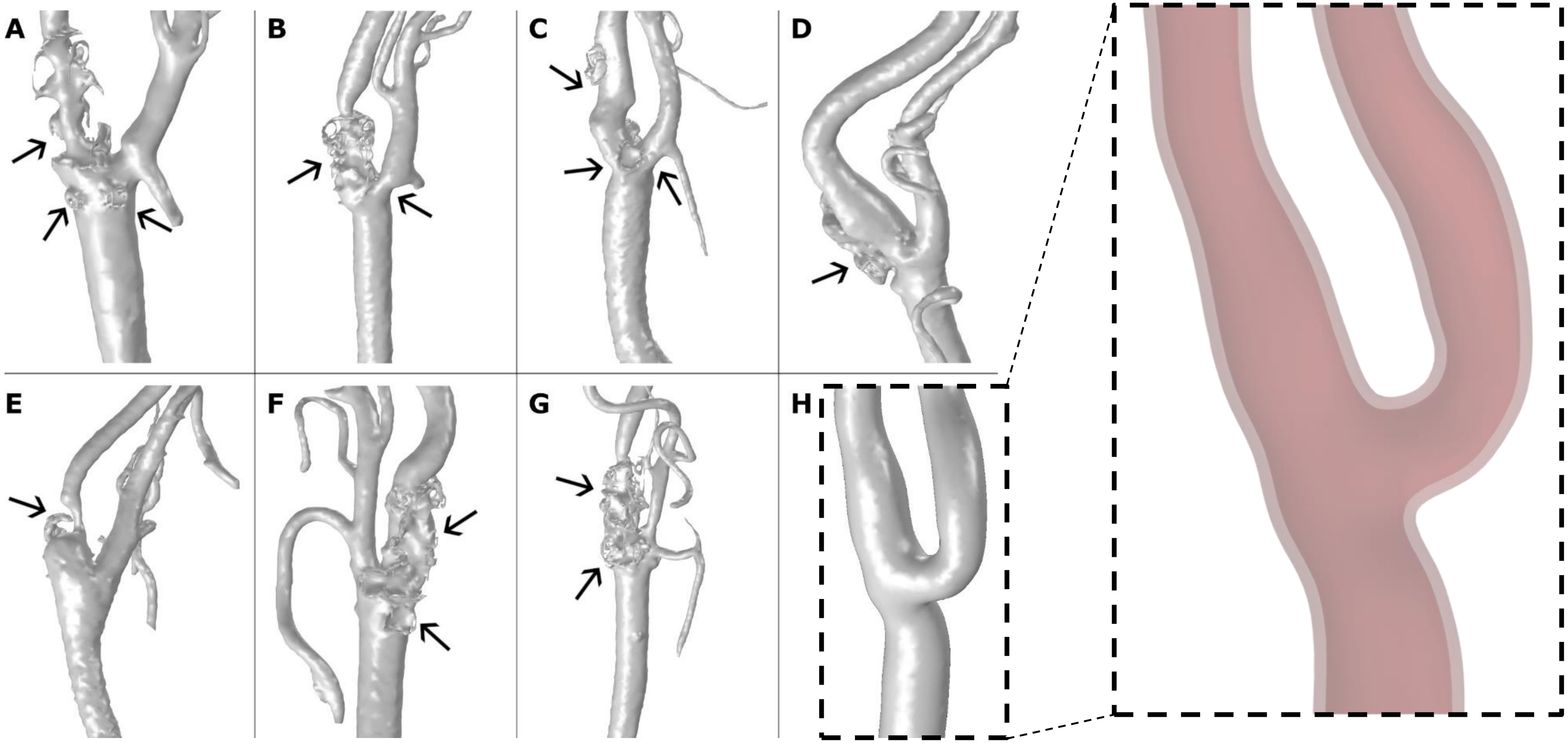
Richard Feynman

Validation

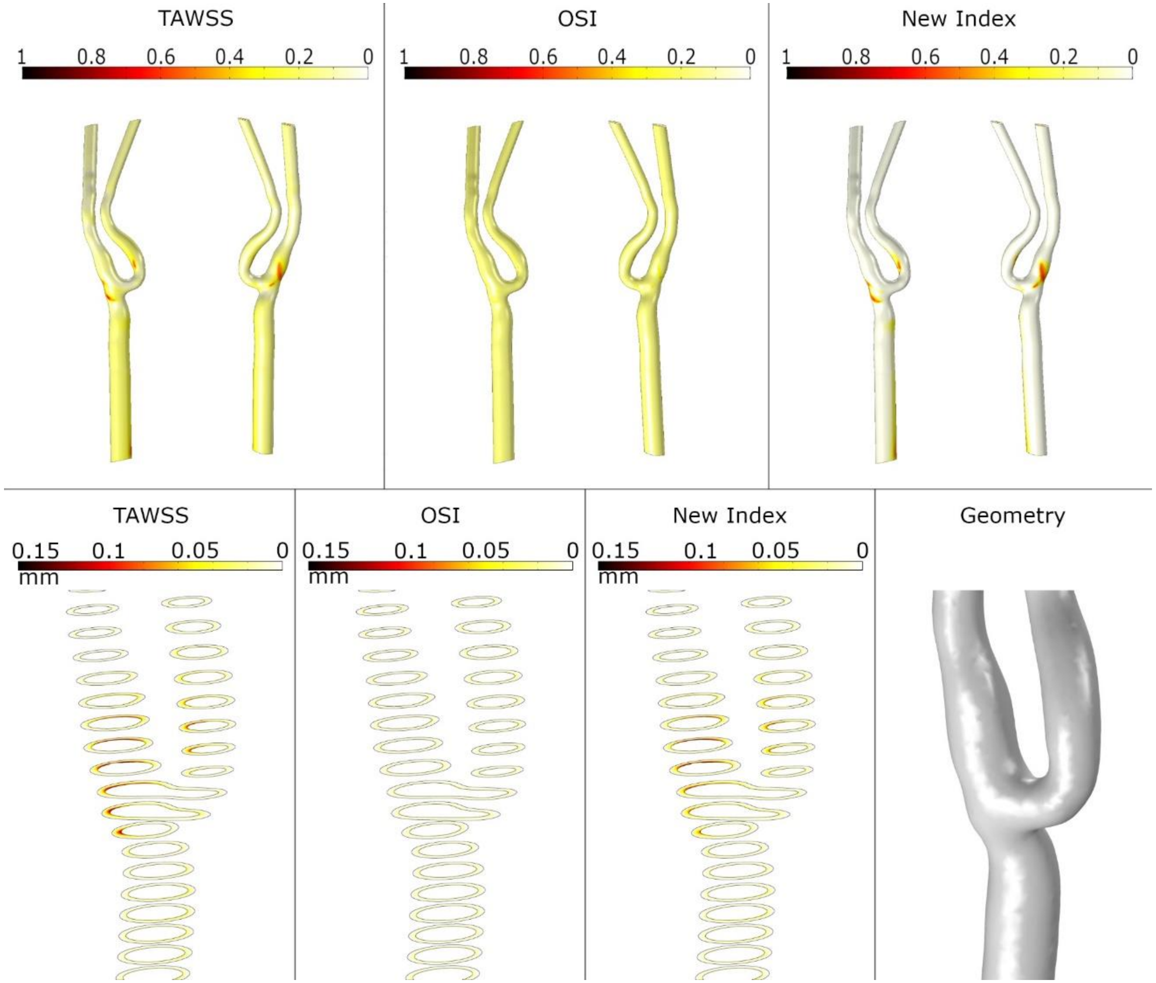


Cilla et al. 2015

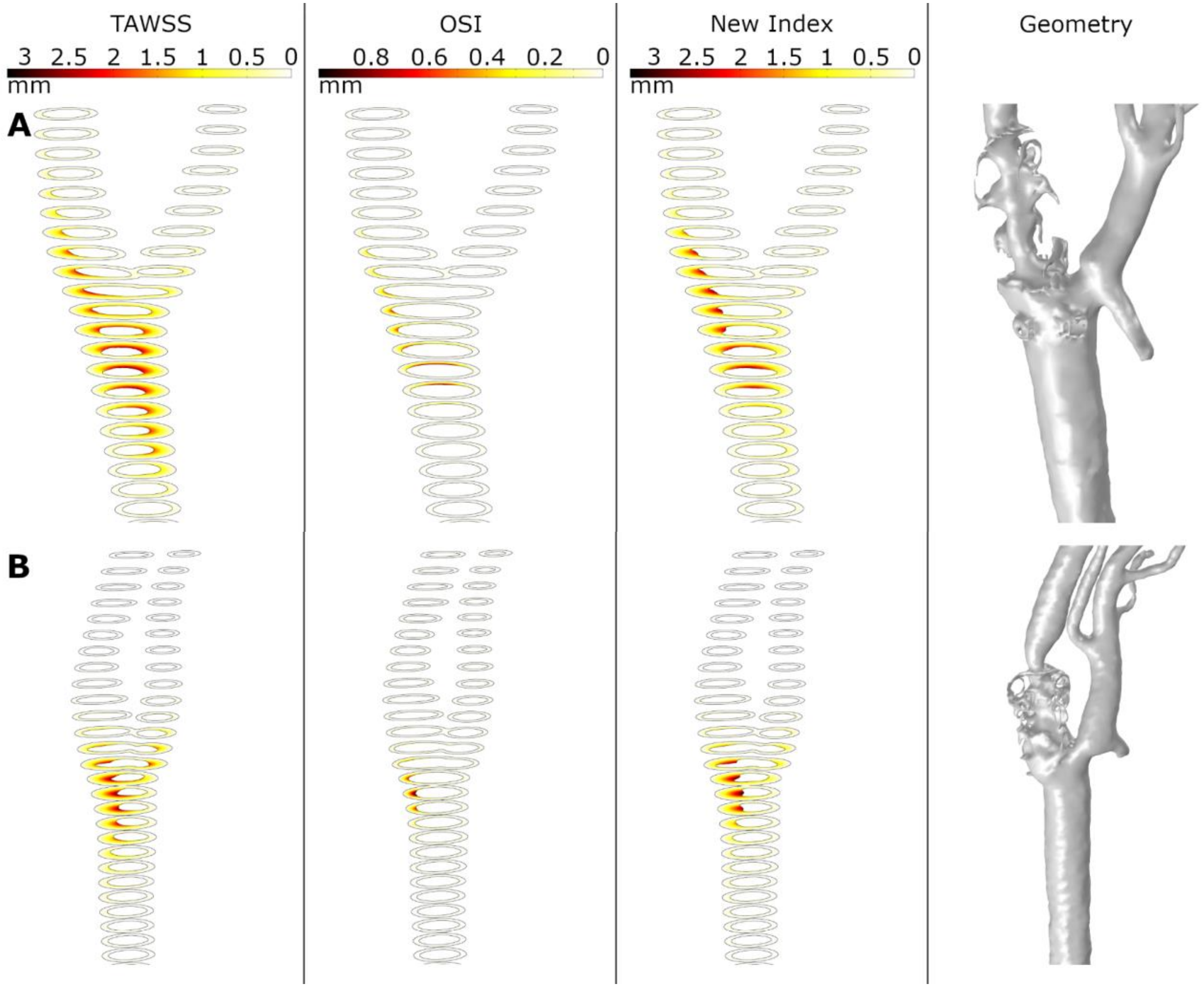
Validation



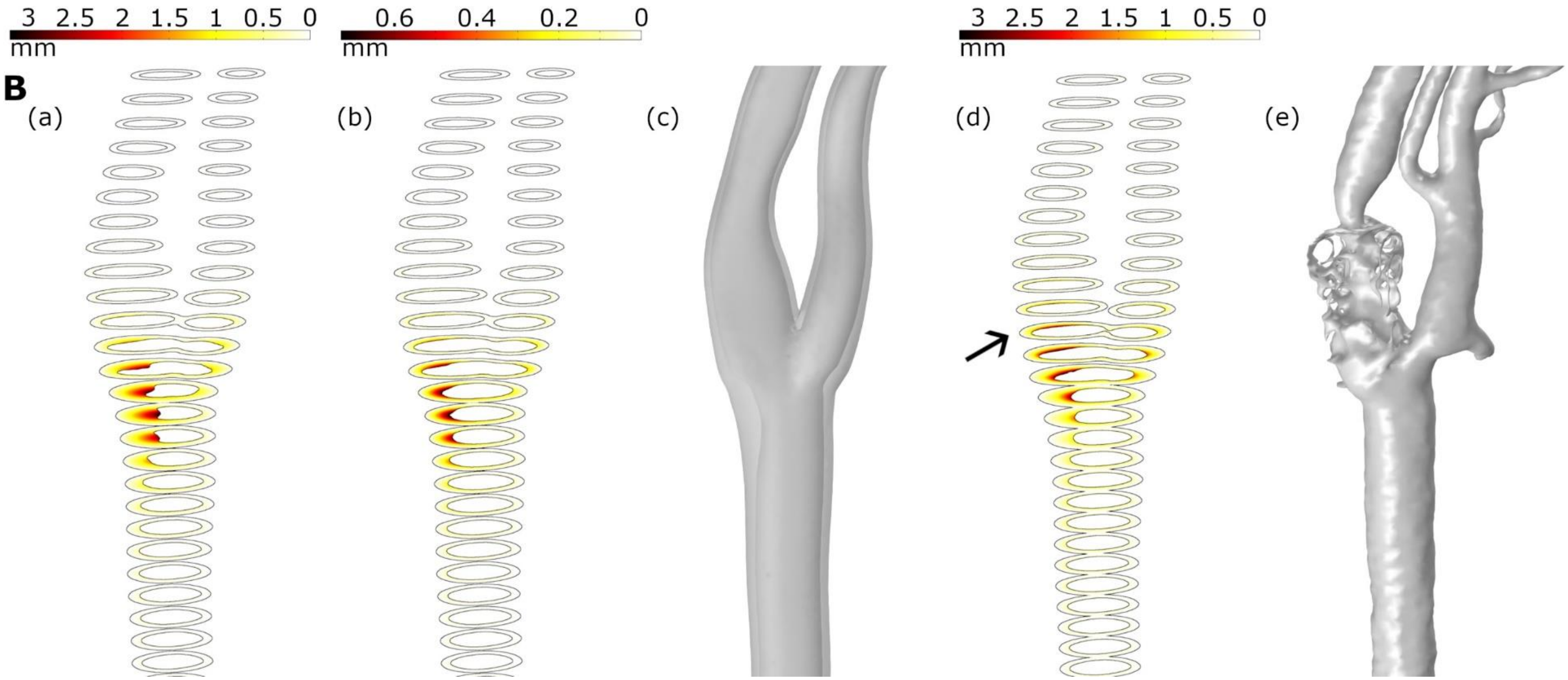
Validation


TAWSS
OSI
New Index
1 0.8 0.6 0.4 0.2 0
TAWSS
OSI
New Index
Geometry
0.15 0.1 0.05 0
mm

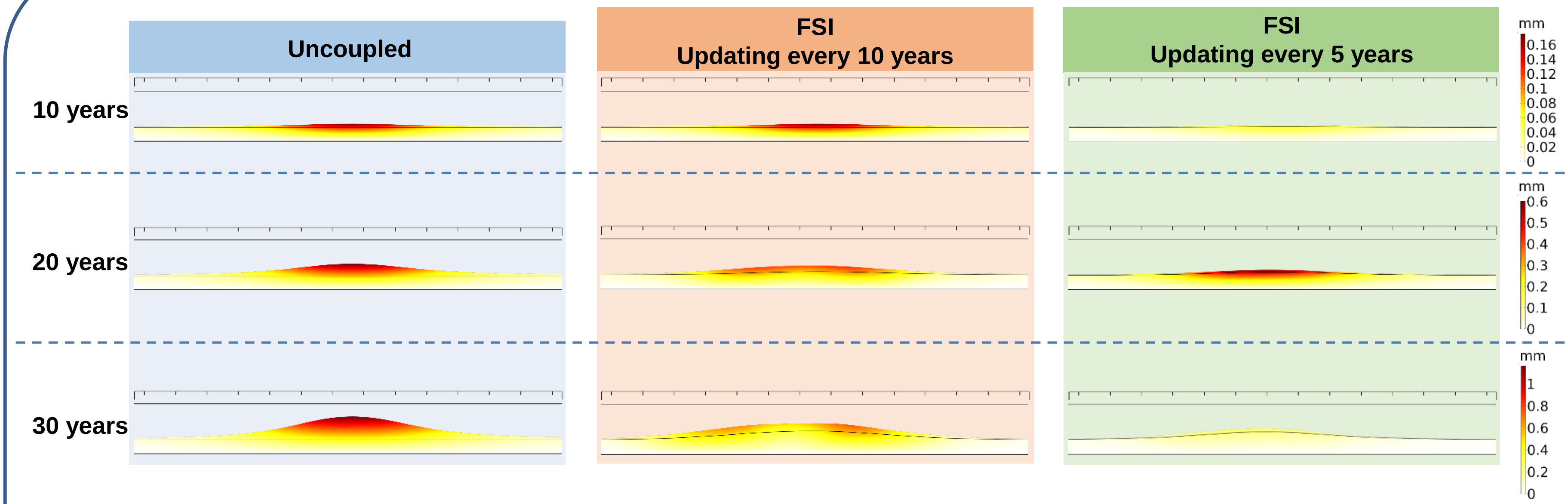
Validation


TAWSS
3 2.5 2 1.5 1 0.5 0
mm
OSI
0.8 0.6 0.4 0.2 0
mm
New Index
3 2.5 2 1.5 1 0.5 0
mm
Geometry
A
B

Validation

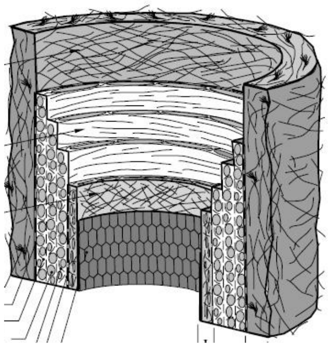


Plaque growth



	Uncoupled		FSI – Updating every 10 years		FSI – Updating every 5 years	
	Plaque Area (mm²)	Stenosis Ratio (%)	Plaque Area (mm²)	Stenosis Ratio (%)	Plaque Area (mm²)	Stenosis Ratio (%)
10 years	2.098	9.61	2.177	9.97	1.29	5.61
20 years	6.536	33.04	5.675	26.00	3.407	16.08
30 years	13.075	64.14	10.928	46.97	6.64	32.61

Effect of the anisotropy of mass transport properties



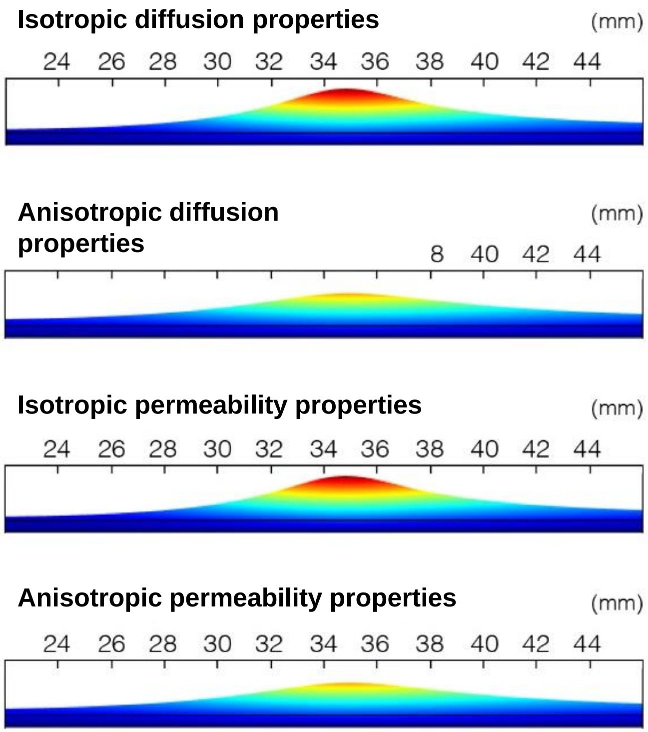
(Holzapfel et al 2000)

$$D = \begin{pmatrix} D_i & 0 \\ 0 & 10D_i \end{pmatrix} \qquad Di = 8 \cdot 10^{-13}\ m^2/s$$

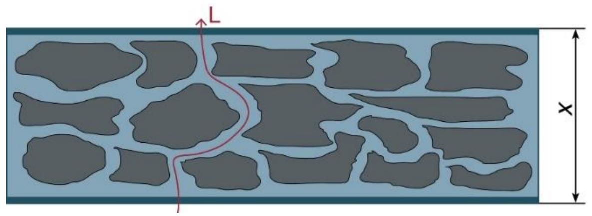
Tarbell et al. 2003

$$\kappa_w = \begin{pmatrix} 1.2 & 0 \\ 0 & 1.8359 \end{pmatrix} \cdot 10^{-18}$$

Chooi et al. 2016

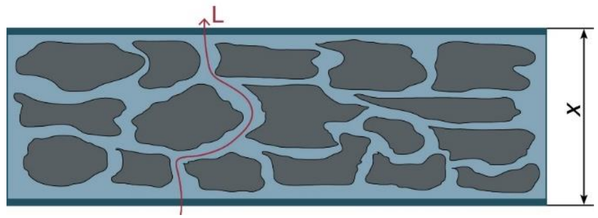


Effect of strain on difussion



$$\tau_0 = \frac{L}{x}$$

$$D_{eff} = \frac{\epsilon}{\tau} D_{free}$$

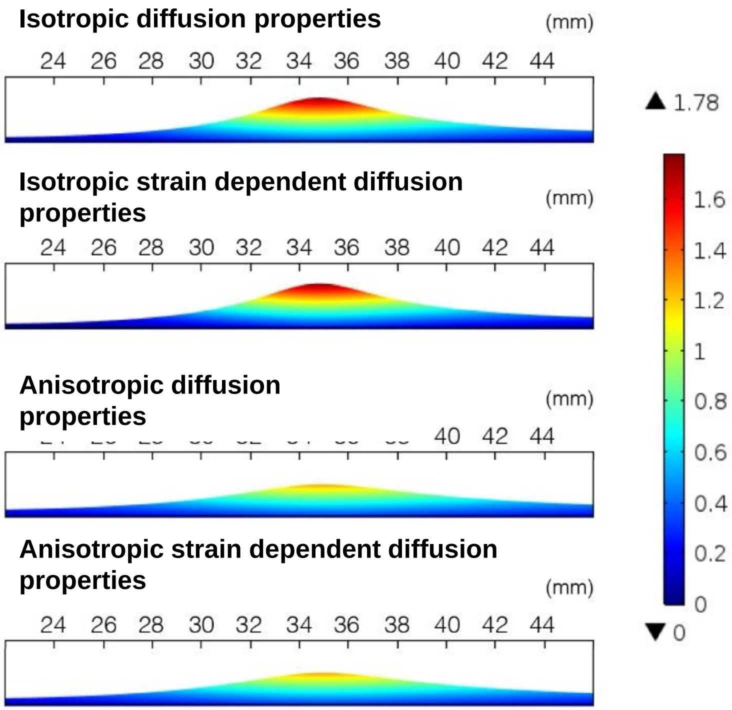


$$\tau = \frac{L}{x - \Delta x}$$

$$\tau = \frac{\tau_0}{1 + \varepsilon_r}$$

$$D_{eff} = \frac{\epsilon \cdot (1 + \varepsilon_r)}{\tau_0} D_{free}$$

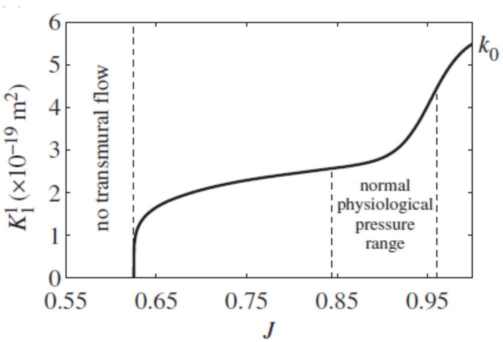
$$D_{eff} = \begin{pmatrix} (1 + \varepsilon_r) \cdot D_i & 0 \\ 0 & (1 + \varepsilon_z) \cdot D_i \end{pmatrix}$$

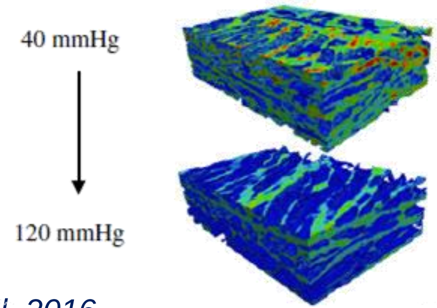


Denny et al. 2014

Effect of strain on permeability

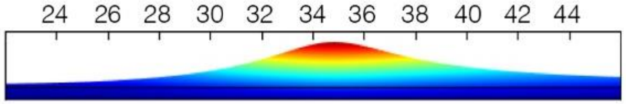
$$K_{w,i} = K_{w,i}^{0} \cdot \left(\frac{1-\phi^{S}}{1-\phi_{R}^{S}}\right)^{m} \cdot \left[p_1 + \frac{p_2}{1+e^{(J-p_3)\cdot p_4}}\right]$$



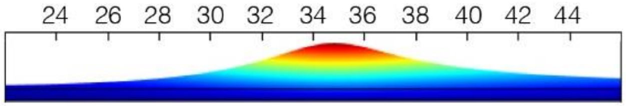


Chooi et al. 2016

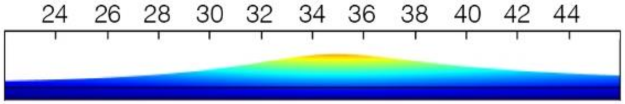
Isotropic permeability properties



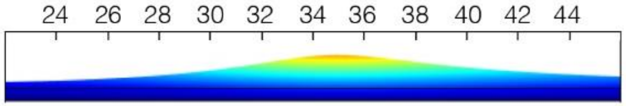
Isotropic strain dependent permeability properties



Anisotropic permeability properties



Anisotropic strain dependent permeability properties

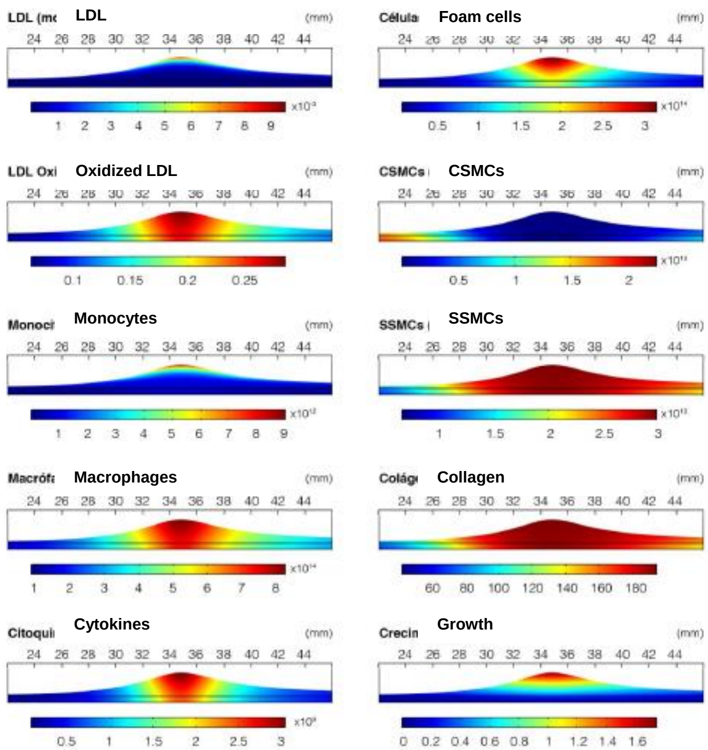


$\Delta V = 9{,}31\% \rightarrow J = 0{,}9069 \rightarrow \kappa = 4{,}46 \cdot 10^{4}$

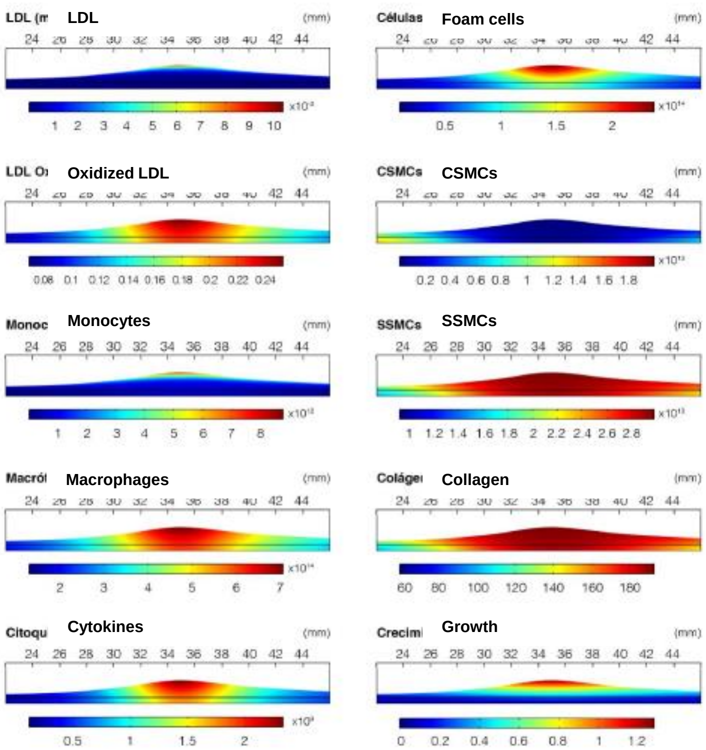
Nolan et al. 2016

$$K_w = \begin{pmatrix} K_{w,r}(J) & 0 \\ 0 & K_{w,z}(J) \end{pmatrix}$$

Isotropic and strain-independent



Anisotropic and strain-dependent



- A mathematical and computational model of atheromatous plaque emergence has been presented that allows the lesion to growth in particular areas in relation to the hemodynamics of the blood flow.

- Due to the fact that foam cells concentration is associated to the necrotic core formation, the final distribution of foam cells is critical to evolve into a vulnerable or fibrotic plaque

- A computational model based on real patient geometries has been developed.

- The disturbance of the fluid flow during growth process affects to LDL distribution and plaque geometry.

- There is a great influence of the anisotropic transmural properties on LDL distribution, Foam cell and collagen.

- There is no a great influence of the strain wall on growth and stenosis.

Universidad Zaragoza 1542

Acknowledgments :
- State Research Agency: PID2019-107517RB-I00
- Department of Industry and Innovation (Regional government of Aragón): T24-20R

THANK YOU FOR YOUR ATTENTION

instituto de investigación en ingeniería de Aragón
Universidad de Zaragoza

fany@unizar.es

ciber-bbn
Centro Investigación Biomédica en Red
Bioingeniería, Biomateriales y Nanomedicina