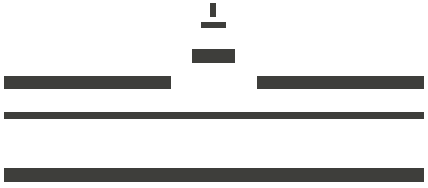

Westfälische
Wilhelms-Universität
Münster

Mathematical modelling of atherosclerotic plaque formation

living.knowledge
WWUMünster

Stefan Girke

September 25th, 2013

Atherosclerosis

Mathematical Modelling

Simulation

Summary

Atherosclerosis

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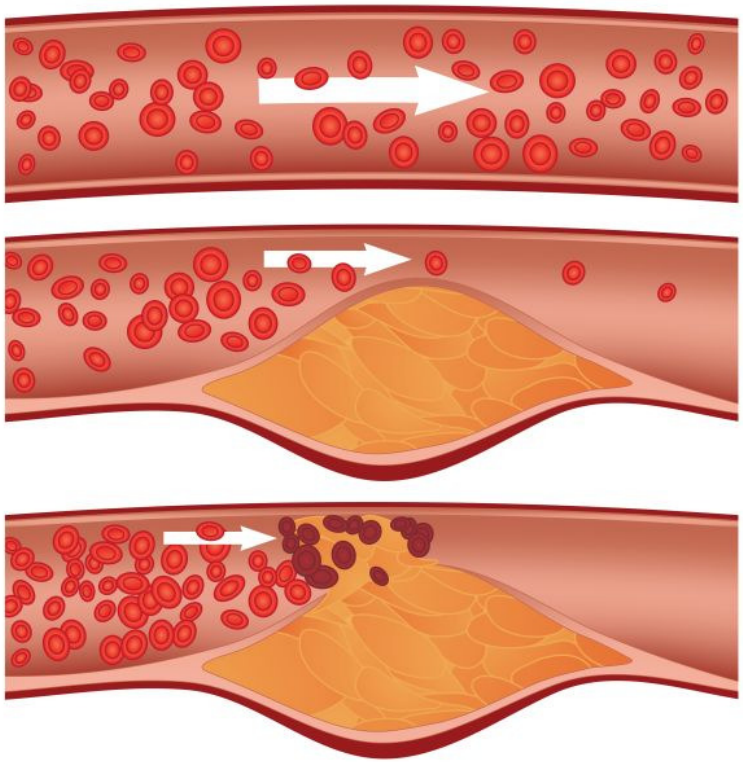
Simulation

Summary

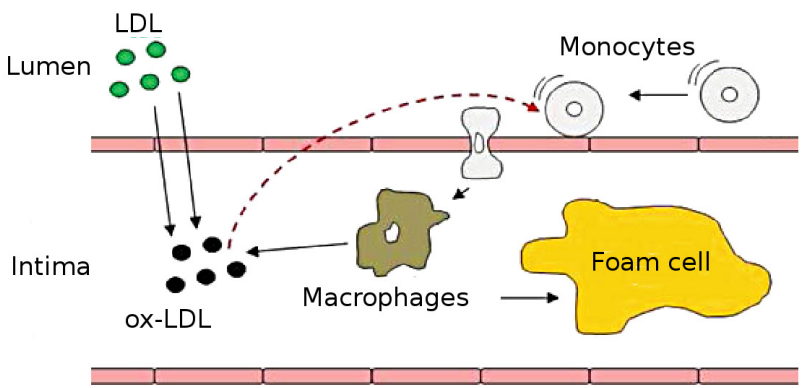
Atherosclerosis

- atherosclerosis is an inflammatory process mainly triggered by low-density lipoproteins (LDL)
- may lead to: occlusion of artery, rupture
  $\Rightarrow$ heart attack, stroke
- risk factors: blood pressure, age, gender, genetic endowment, smoking...



Atherosclerosis II

- LDL penetration/oxidation initiate inflammatory process
- intima LDL concentration depends on plasma LDL/wall permeability
- ox. LDL activates endothelial cells which trigger monocyte recruitment
- monocytes differentiate into active macrophages
- active macrophages absorb ox. LDL (mass action law)
- macrophages transform into foam cells
- foam cells are responsible for local volume increase
- smooth muscle cells migrate to form fibro-muscular cap

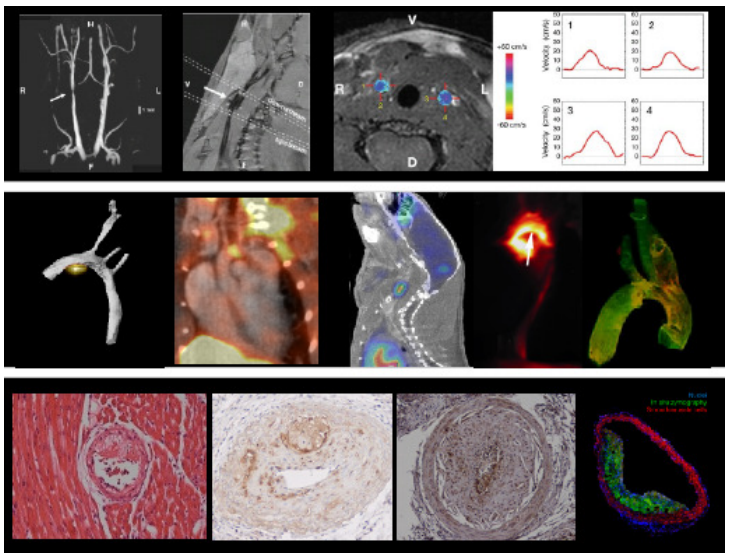


SFB 656 - Molecular Cardiovascular Imaging

SFB 656
MoBil

- last funding proposal:
  07/2013 – 06/2017

- broad investigations in molecular and inflammatory aspects of atherosclerosis through newly developed tracers and methods
- mouse models

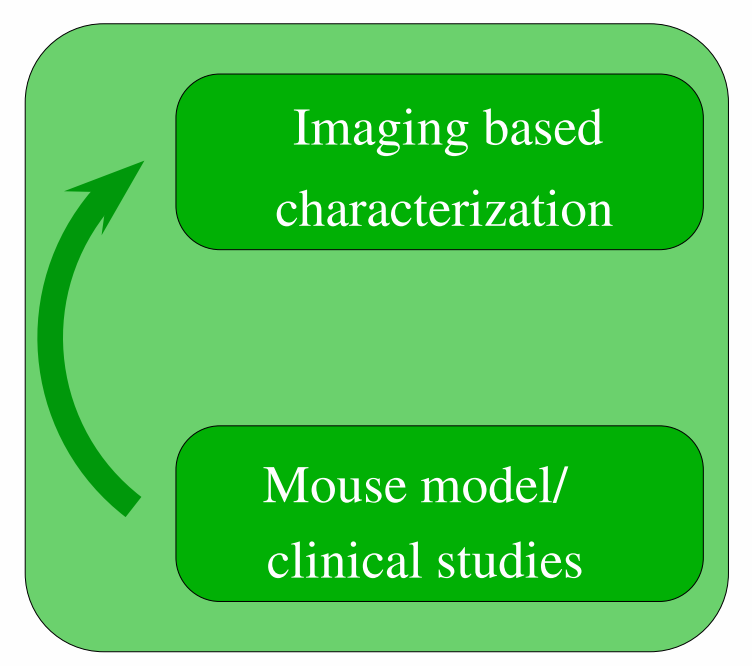


Project B07

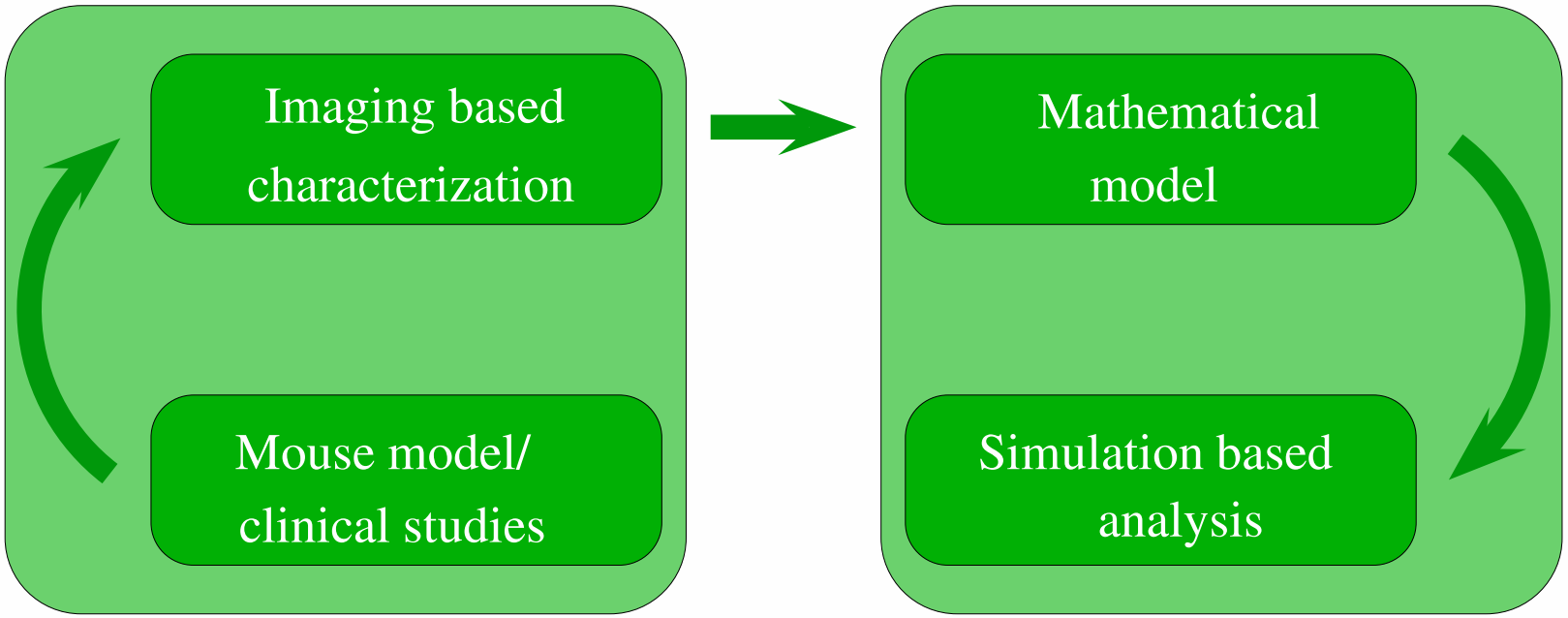
- Mathematical modelling of atherosclerotic plaque formation based on data from multiparametric imaging
- principal investigator: Prof. Mario Ohlberger
- scientific staff: Rene Milk, Stefan Girke
- co-operation partner: Prof. Christina Surulescu, Prof. Michael Schäfers





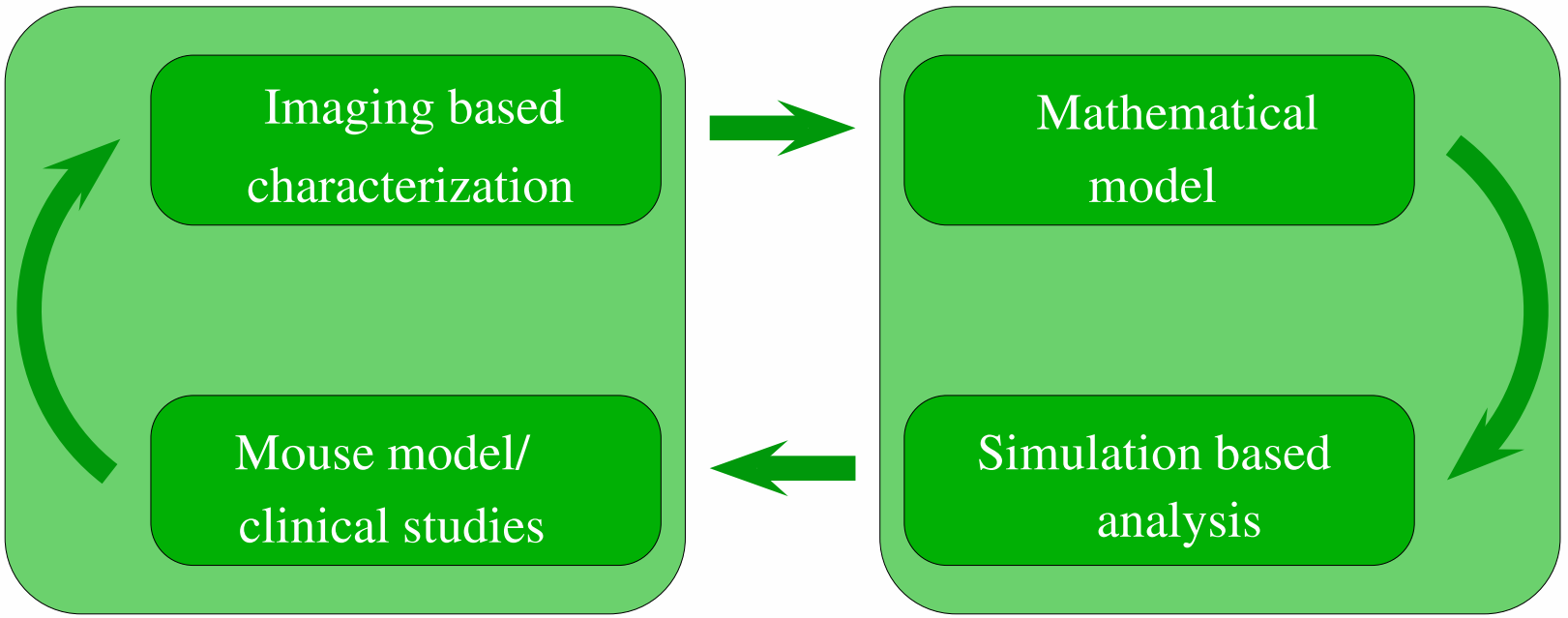


SFB 656
MoBil



SFB 656 MoBil

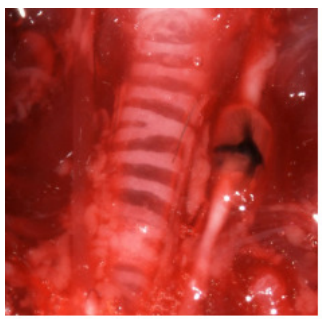
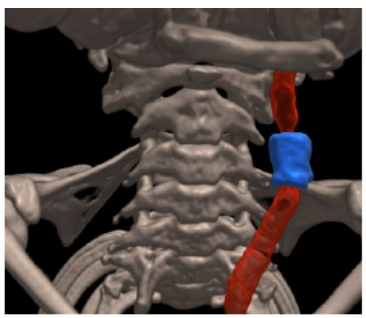
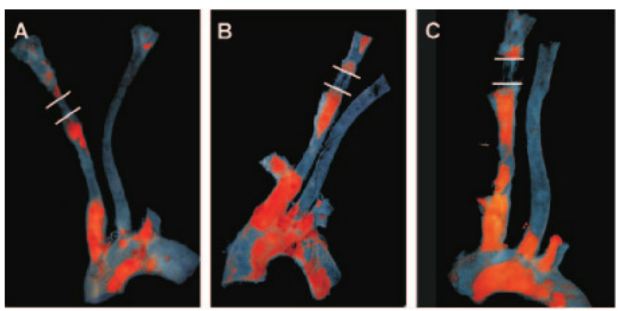
B07

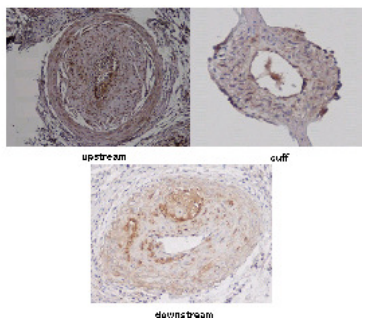


Provide deeper insight into
plaque progression and stability

New aspects - wall shear stress

- penetration of LDL through the endothelial layer is influenced by the blood flow through the wall shear stress



- all ApoE$^{-/-}$ mice with a cuff around right carotid suffered a heart attack after fed with a high cholesterol diet

New aspects - matrix metalloproteinase

- matrix metalloproteinase (MMP) helps degrading the extracellular matrix
  $\Rightarrow$ restructuring of the lesion
- it is believed that MMPs contribute to remodelling, by
  - enabling smooth muscle cells to migrate
    $\Rightarrow$ form a fibrous cap
  - degrading this encapsulation
    $\Rightarrow$ mechanical instability, vulnerability of the plaques

Atherosclerosis

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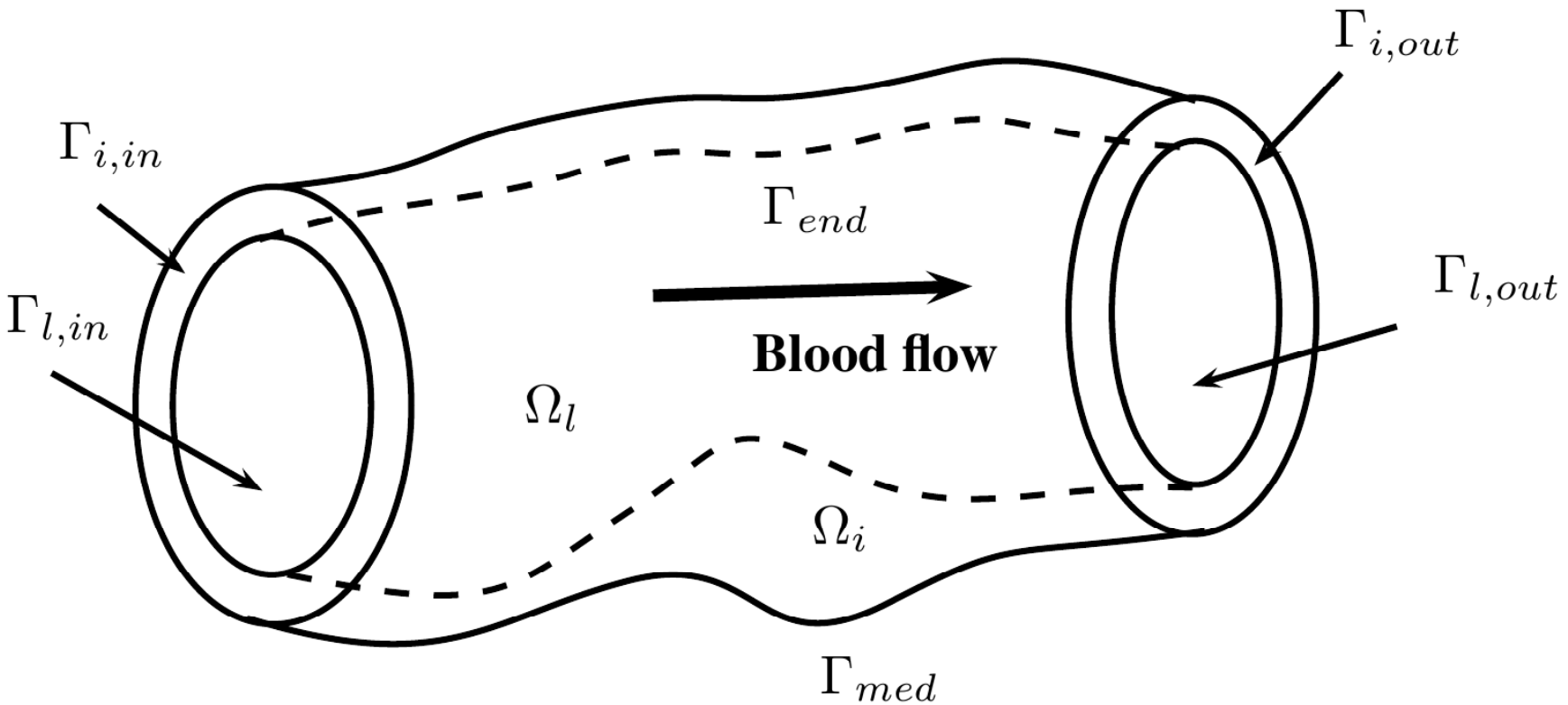
Summary

Domain



Overview mathematical model [Calvez2009]

- Navier-Stokes flow in the lumen
- Darcy perfusion in the intima
- reactive transport system for
  - LDL in the lumen
  - LDL in the intima
  - oxidized LDL in the intima
  - signal
  - macrophages
  - foam cells
  - smooth muscle cells
  - (matrix metalloproteinase)

Blood flow [Calvez2009]

lumen (Navier-Stokes)

$$
\begin{aligned}
\rho[\partial_t u_l + (u_l \cdot \nabla)u_l] - \nu\Delta u_l + \nabla p_l &= 0, && x \in \Omega_l, t \in [0,T],\\
\nabla \cdot u_l &= 0, && x \in \Omega_l, t \in [0,T],\\
u_l &= U_{l,in}, && x \text{ on } \Gamma_{l,in}, t \in [0,T],\\
T(u_l, p_l)n_l &= -p_{out} n_l, && x \text{ on } \Gamma_{l,out}, t \in [0,T],\\
u_l \cdot n_l &= J_v, && x \text{ on } \Gamma_{end}, t \in [0,T],\\
u_l - (u_l \cdot n_l)n_l &= 0, && x \text{ on } \Gamma_{end}, t \in [0,T].
\end{aligned}
$$

intima (Darcy)

$$
\begin{aligned}
u_i &= -\frac{K}{\mu}\nabla p_i, && x \in \Omega_i, t \in [0,T],\\
\nabla \cdot u_i &= 0, && x \in \Omega_i, t \in [0,T],\\
u_i \cdot n_i &= 0, && x \text{ on } \Gamma_{i,in} \cup \Gamma_{i,out}, t \in [0,T],\\
u_i \cdot n_i &= -J_v, && x \text{ on } \Gamma_{end}, t \in [0,T],\\
p_i &= p_{med}, && x \text{ on } \Gamma_{med}, t \in [0,T].
\end{aligned}
$$

LDL evolution

lumen

$$
\begin{aligned}
\partial_t c_l + \nabla \cdot (-D_l \nabla c_l + u_l c_l) &= 0, && x \in \Omega_l, t \in [0, T],\\
c_l &= C_{l,in}, && x \text{ on } \Gamma_{l,in}, t \in [0, T],\\
\nabla c_l \cdot n_l &= 0, && x \text{ on } \Gamma_{l,out}, t \in [0, T],\\
(-D_l \nabla c_l + u_l c_l) \cdot n_l &= J_s, && x \text{ on } \Gamma_{end}, t \in [0, T].
\end{aligned}
$$

intima

$$
\begin{aligned}
\partial_t c_i + \nabla \cdot (-D_i \nabla c_i + u_i c_i) &= -r_{ox} c_i, && x \in \Omega_i, t \in [0, T],\\
\nabla c_i \cdot n_i &= 0, && x \text{ on } \Gamma_{i,in} \cup \Gamma_{i,out} \cup \Gamma_{med}, t \in [0, T],\\
(-D_i \nabla c_i + u_i c_i) \cdot n_i &= -J_s, && x \text{ on } \Gamma_{end}, t \in [0, T].
\end{aligned}
$$

Coupling of blood flow and LDL evolution

Kedem-Katachalsky equations
(flux through semipermeable membrane)

$$J_v = L_p \left([p_l - p_i] - \alpha [c_l - c_i] \right),$$
$$J_s = \xi \left([c_l - c_i] - \beta J_v \right)$$

$\Rightarrow$ simplification

$$J_v = L_p \left(p_l - p_i \right),$$
$$J_s = \xi \left(c_l - c_i \right)$$

Inflammatory process

Plaque growth

$$
\begin{aligned}
-\nabla \cdot D(v) + \nabla q = 0, \nabla \cdot v = \frac{k_F}{A} c_{ox} \cdot M \qquad & x \in \Omega_i, t \in [0, T], \\
-D(v) n_i u - q n_i = 0, \qquad & x \text{ on } \Gamma_{end}, t \in [0, T], \\
v = 0, \qquad & x \text{ on } \partial\Omega_i \setminus \Gamma_{end}, t \in [0, T].
\end{aligned}
$$

oxidized LDL

$$
\begin{aligned}
\partial_t c_{ox} = d_{ox} \Delta c_{ox} - k_F c_{ox} \cdot M + r_{ox} c_i, \qquad & x \in \Omega_i, t \in [0, T], \\
\partial_{n_i} c_{ox} = 0, \qquad & x \text{ on } \partial\Omega_i, t \in [0, T].
\end{aligned}
$$

macrophage

$$
\begin{aligned}
\partial_t M = d_M \Delta M - k_F c_{ox} \cdot M, \qquad & x \in \Omega_i, t \in [0, T], \\
\partial_{n_i} M = -f(S), \qquad & x \text{ on } \Gamma_{end}, t \in [0, T], \\
\partial_{n_i} M = 0, \qquad & x \text{ on } \partial\Omega_i \setminus \Gamma_{end}, t \in [0, T].
\end{aligned}
$$

signal

$$
\begin{aligned}
\partial_t S = d_S \Delta S - \lambda S + \gamma (c_{ox} - c_{ox}^{th})_+ + k_F c_{ox} \cdot M, \qquad & x \in \Omega_i, t \in [0, T], \\
\partial_{n_i} S = 0, \qquad & x \text{ on } \partial\Omega_i, t \in [0, T].
\end{aligned}
$$

Atherosclerosis

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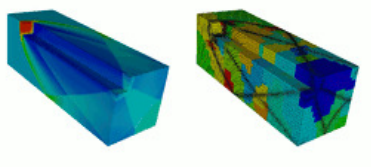
Implementation

- Dune 2.2.1-release and Dune-Fem 1.3-release
- implementation is based on code from fuel cell project

  [Steinkamp2008]



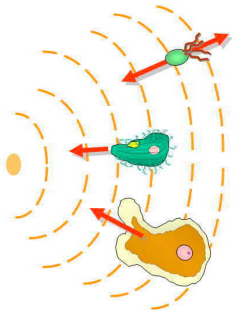
- using LDG passes [Burri2006]
  (example: $\mathcal{L} = \Delta = \nabla \cdot (\nabla) = \mathcal{L}_{\text{post}} \circ \mathcal{L}_2 \circ \mathcal{L}_1 \circ \mathcal{L}_{\text{pre}}$)

Inflammation, 3 species, intima [Ibragimov2005]

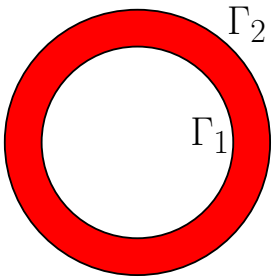
$$\partial_t n_1 = \mu_1 \Delta n_1 - \underbrace{\chi_{11}^0 \nabla \cdot \left(\frac{n_1}{c_1} \nabla c_1 \right)}_{\text{chemotaxis}},$$

$$\partial_t n_3 = \mu_3 \Delta n_3 + \underbrace{F_0 n_1 n_3}_{\text{dying immune cells increase debris}},$$

$$\partial_t c_1 = \nu_1 \Delta c_1 - \underbrace{\alpha_1 n_1 c_1}_{\text{immune cells dec. signal}} + \underbrace{\gamma n_3}_{\text{debris prod. signal}}$$



- n_1 = immune cells (i.e. macrophages...),
- n_3 = debris (i.e. foam cells...),
- c_1 = signal



Boundary data

no inflow, except:

- immune cells are triggered and enter intima through the inner boundary, if a threshold is reached

$$\partial_\eta n_1 = \begin{cases} \beta_1, & c_1(x) > c_1^*, \\ 0, & \text{else} \end{cases}, \qquad x \in \Gamma_1,$$

$$\partial_\eta n_1 = 0, \qquad x \in \Gamma_2,$$

$$\partial_\eta n_3 = 0, \qquad x \in \Gamma_i, i = 1, 2,$$

$$\partial_\eta c_1 = 0, \qquad x \in \Gamma_i, i = 1, 2$$

Initial data

- immune cells are more likely near the inner boundary
- debris is seeded at a point x_0
- signal with constant distribution

$$
\begin{aligned}
n_1^0(x) &= \varepsilon_1 \exp(-Q_1 |r_1^2 - \|x\|_2^2|), \\
n_3^0(x) &= \varepsilon_2 \exp(-Q_2 \|x_0 - x\|_2^2), \\
c_1^0(x) &= \varepsilon_3
\end{aligned}
$$

Discretization

- Local Discontinuous Galerkin
- polynomial order 1
- explicit euler scheme
- adaptivity

start movie cross section

Inflammation in a cuff model (3D)

start movie cuff 3D

Atherosclerosis

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Summary

Further implementation

- (semi) implicit solvers
- parallelization
- solving whole system
- different time scales
- more dofs
- real data

Project outline

- efficient numerical model for atherogenesis
- usage of imaging derived parameters
- analysis of the influence of local blood flow dynamics on plaque formation
- modelling of macrophages and the production of MMPs in the context of lesion restructuring
- simulation based analysis for a well defined mouse model

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Thank you for your attention!