Mathematical modelling of atherosclerotic plaque formation
Atherosclerosis

Mathematical Modelling

Simulation

Summary
Atherosclerosis

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Atherosclerosis

- Atherosclerosis is an inflammatory process mainly triggered by low-density lipoproteins (LDL)
- May lead to: occlusion of artery, rupture ⇒ 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

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

- last funding proposal: 07/2013 – 06/2017
Project B07

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

Imaging based Mouse model/ characterization clinical studies

SFB 656 MoBiL
Mathematical modelling of atherosclerotic plaque formation

Imaging based Mathematical Mouse model/ Simulation based characterization model
clinical studies analysis

SFB 656 MoBil

B07
Mathematical modelling of atherosclerotic plaque formation

Imaging based Mathematical Mouse model/ Simulation based characterization model

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
  ⇒ restructuring of the lesion
- it is believed that MMPs contribute to remodelling, by
  - enabling smooth muscle cells to migrate
    ⇒ form a fibrous cap
  - degrading this encapsulation
    ⇒ mechanical instability, vulnerability of the plaques
Atherosclerosis

Mathematical Modelling

Simulation

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)

\[
\begin{align*}
\rho[\partial_t u_l + (u_l \cdot \nabla)u_l] - \nu \Delta u_l + \nabla p_l &= 0, \\
\nabla \cdot u_l &= 0, \\
u l &= U_{l,in}, \\
T(u_l, p_l)n_l &= -p_{\text{out}} n_l, \\
u_l \cdot n_l &= J_v, \\
u_l - (u_l \cdot n_l)n_l &= 0,
\end{align*}
\]

\(x \in \Omega_1, t \in [0, T],\)

\(x \in \Omega_1, t \in [0, T],\)

\(x \text{ on } \Gamma_{l,in}, t \in [0, T],\)

\(x \text{ on } \Gamma_{l,out}, t \in [0, T],\)

\(x \text{ on } \Gamma_{\text{end}}, t \in [0, T],\)

\(x \text{ on } \Gamma_{\text{end}}, t \in [0, T].\)

intima (Darcy)

\[
\begin{align*}
u_i &= -\frac{K}{\mu} \nabla p_i, \\
\nabla \cdot u_i &= 0, \\
\nu_i \cdot n_i &= 0, \\
u_i \cdot n_i &= -J_v, \\
P_i &= P_{\text{med}},
\end{align*}
\]

\(x \in \Omega_i, t \in [0, T],\)

\(x \in \Omega_i, t \in [0, T],\)

\(x \text{ on } \Gamma_{i,in} \cup \Gamma_{i,out}, t \in [0, T],\)

\(x \text{ on } \Gamma_{\text{end}}, t \in [0, T],\)

\(x \text{ on } \Gamma_{\text{med}}, t \in [0, T].\)
LDL evolution

lumen

\[ \partial_t c_1 + \nabla \cdot (-D_l \nabla c_1 + u_1 c_1) = 0, \quad x \in \Omega_l, t \in [0, T], \]
\[ c_1 = C_{1, \text{in}}, \quad x \text{ on } \Gamma_{l, \text{in}}, t \in [0, T], \]
\[ \nabla c_1 \cdot n_1 = 0, \quad x \text{ on } \Gamma_{l, \text{out}}, t \in [0, T], \]
\[ (-D_l \nabla c_1 + u_1 c_1) \cdot n_1 = J_s, \quad x \text{ on } \Gamma_{\text{end}}, t \in [0, T]. \]

intima

\[ \partial_t c_i + \nabla \cdot (-D_i \nabla c_i + u_i c_i) = -r_{ox} c_i, \quad x \in \Omega_i, t \in [0, T], \]
\[ \nabla c_i \cdot n_i = 0, \quad x \text{ on } \Gamma_{i, \text{in}} \cup \Gamma_{i, \text{out}} \cup \Gamma_{\text{med}}, t \in [0, T], \]
\[ (-D_i \nabla c_i + u_i c_i) \cdot n_i = -J_s, \quad x \text{ on } \Gamma_{\text{end}}, t \in [0, T]. \]
Coupling of blood flow and LDL evolution

Kedem-Katchalsky equations
(flux through semipermeable membrane)

\[ \mathbf{J}_V = L_p \left( [p_l - p_i] - \alpha [c_l - c_i] \right), \]
\[ \mathbf{J}_S = \xi \left( [c_l - c_i] - \beta \mathbf{J}_V \right) \]

⇒ simplification

\[ \mathbf{J}_V = L_p \left( p_l - p_i \right), \]
\[ \mathbf{J}_S = \xi \left( c_l - c_i \right) \]
Inflammatory process

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

oxidized LDL
\[\partial_t c_{ox} = d_{ox} \Delta c_{ox} - k_F c_{ox} \cdot M + r_{ox} c_i, \quad x \in \Omega_i, t \in [0, T], \]
\[\partial_n c_{ox} = 0, \quad x \text{ on } \partial \Omega_i, t \in [0, T]. \]

macrophage
\[\partial_t M = d_M \Delta M - k_F c_{ox} \cdot M, \quad x \in \Omega_i, t \in [0, T], \]
\[\partial_n M = -f(S), \quad x \text{ on } \Gamma_{end}, t \in [0, T], \]
\[\partial_n M = 0, \quad x \text{ on } \partial \Omega_i \setminus \Gamma_{end}, t \in [0, T]. \]

signal
\[\partial_t S = d_S \Delta S - \lambda S + \gamma(c_{ox} - c_{ox}^{th})_+ + k_F c_{ox} \cdot M, \quad x \in \Omega_i, t \in [0, T], \]
\[\partial_n S = 0, \quad x \text{ on } \partial \Omega_i, t \in [0, T]. \]
Implementation

- Dune 2.2.1-release and Dune-Fem 1.3-release
- implementation is based on code from fuel cell project
  \[[\text{Steinkamp2008}]\]
- using LDG passes \[[\text{Burri2006}]\]
  (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]

\[ \partial_t n_1 = \mu_1 \Delta n_1 - \chi_1^{0} \nabla \cdot \left( \frac{n_1}{c_1} \nabla c_1 \right), \]

\[ \partial_t n_3 = \mu_3 \Delta n_3 + F_0 n_1 n_3, \]

\[ \partial_t c_1 = \nu_1 \Delta c_1 - \alpha_1 n_1 c_1 + \gamma n_3, \]

\( n_1 = \) 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

\[
\partial_n \eta_1 = \begin{cases} 
\beta_1, & c_1(x) > c_1^*, \\
0, & \text{else}
\end{cases}, \quad x \in \Gamma_1, \\
\partial_n \eta_1 = 0, \quad x \in \Gamma_2, \\
\partial_n \eta_3 = 0, \quad x \in \Gamma_i, i = 1, 2, \\
\partial_n c_1 = 0, \quad x \in \Gamma_i, i = 1, 2
\]
Initial data

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

\[
n_1^0(x) = \varepsilon_1 \exp(-Q_1 r_1^2 - \|x\|_2^2),
\]
\[
n_3^0(x) = \varepsilon_2 \exp(-Q_2 \|x_0 - x\|_2^2),
\]
\[
c_1^0(x) = \varepsilon_3
\]
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
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
References

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A non-isothermal PEM fuel cell model including two water transport mechanisms in the membrane

A general object oriented framework for discretizing non-linear evolution equations
Thank you for your attention!