AMMA
A Multiscale Model of Atherosclerosis

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1 Background

Atherosclerosis plays a central role in the pathogenesis of cardiovascular diseases and is commonly found in the population of developed countries. It is characterized by an accumulation of inflammatory cells and lipids in the intima and media of the arterial wall resulting in arterial wall thickening and narrowing of the vessel lumen. Atherosclerosis causes sequelae such as angina, heart attack and stroke. So far the processes of disease progression, especially mechanically relevant aspects that promote arterial wall thickening, are not fully understood. Within the AMMA-Project we develop a mathematical multiscale model of atherosclerosis to establish a better understanding of its pathogenesis and especially its mechanobiology. Therefore, three disciplines join forces: **Vascular Biology, Medical Imaging and Computational Mechanics.**

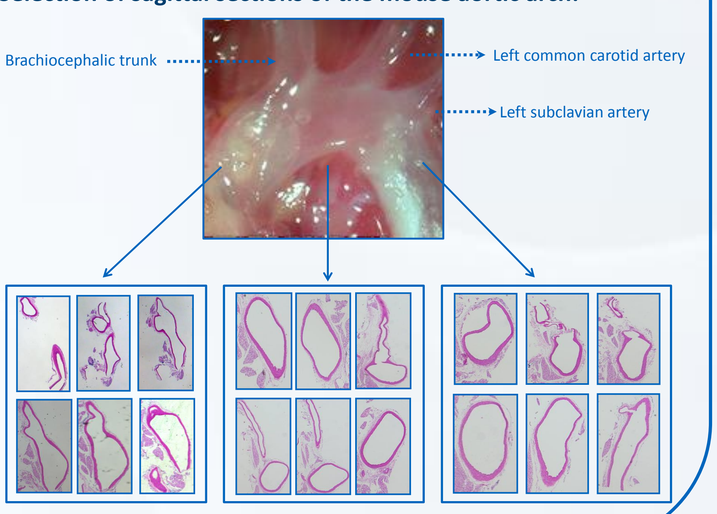
3 Vascular Biology

We combine the use of immunohistochemical and flow cytometric techniques to visualize and quantify basic pathomechanisms of lesion formation.

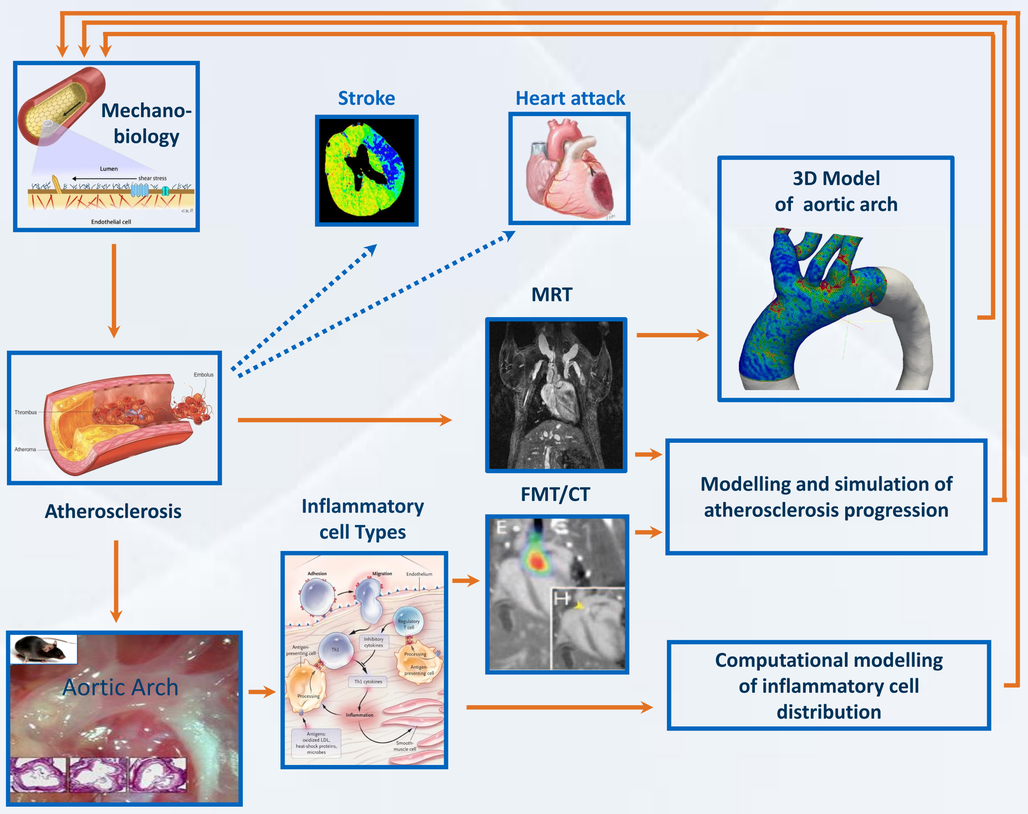
Workflow:

1. LDLr$^{-/-}$ - Mouse Model: Knockout of low density lipoprotein receptor, dissecting of aortic arch and proceeding for histological analysis
2. Embedding of aortic arch in paraffin
3. Sectioning of aortic arch in the sagittal plane (400-500 sections per arch), Hematoxylin and Eosin staining

Selection of sagittal sections of the mouse aortic arch:



2 Project Overview



5 Computational Mechanics

Modelling and simulation of atherosclerosis progression:

Fluid-porous-structure interaction for realistic flow fields:

$$\varrho^f \frac{\partial}{\partial t}\underline{\boldsymbol{u}}_f + \varrho^f \left(\underline{\boldsymbol{c}} \cdot \nabla\right)\underline{\boldsymbol{u}}_f - \mu^f \Delta \underline{\boldsymbol{u}}_f + \nabla p_f = 0 \quad \text{in } \Omega_f$$

$$\frac{\partial}{\partial t}\phi + \phi \nabla \cdot \underline{\boldsymbol{u}}_{pm} + \nabla \phi \left(\underline{\boldsymbol{u}}_{pm} - \underline{\boldsymbol{v}}^s\right) = 0 \qquad \text{in } \Omega_{pm}$$

$$\varrho^f \frac{\partial}{\partial t}\underline{\boldsymbol{u}}_{pm} + \frac{\mu^f}{K}\phi \left(\underline{\boldsymbol{u}}_{pm} - \underline{\boldsymbol{v}}^s\right) + \nabla p_{pm} = 0 \qquad \text{in } \Omega_{pm}$$

Scalar transport of low density lipoproteins and transport through arterial wall:

$$\frac{\partial}{\partial t}c_f^{LDL} + \nabla \cdot \left(-D_f^{LDL}\nabla c_f^{LDL} + \underline{\boldsymbol{u}}_f c_f^{LDL}\right) = 0 \quad \text{in } \Omega_f$$

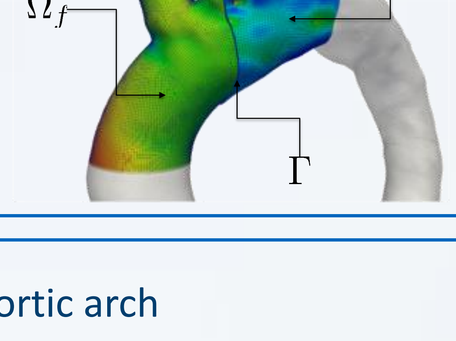
$$\left(-D_f^{LDL}\nabla c_f^{LDL} + \underline{\boldsymbol{u}}_f c_f^{LDL}\right) \cdot \underline{\boldsymbol{n}}_f = -J_s\left(\underline{\underline{\boldsymbol{\sigma}}}, \delta c^{LDL}, \delta p\right) \quad \text{on } \Gamma$$

Bio-chemical processes in arterial wall:

$$\frac{\partial}{\partial t}c_{pm}^{LDL} + \nabla \cdot \left(-D_{pm}^{LDL}\nabla c_{pm}^{LDL} + \underline{\boldsymbol{u}}_{pm} c_{pm}^{LDL}\right) = -r^{ox} c_{pm}^{LDL} \quad \text{in } \Omega_{pm}$$

Scalar depended volumetric growth:

$$\underline{\underline{\boldsymbol{F}}} = \underline{\underline{\boldsymbol{F}}}_e \underline{\underline{\boldsymbol{F}}}_g = \underline{\underline{\boldsymbol{F}}}_e \vartheta \, \underline{\underline{\boldsymbol{I}}}, \quad \frac{\partial}{\partial t}\vartheta = f_g(\vartheta, \underline{\underline{\boldsymbol{F}}}_e, c_{pm}^{LDL}, \ldots) \quad \text{in } \Omega_{pm}$$



4 Medical Imaging

Medical imaging techniques can be used to illustrate anatomical informations as well as monotoring of disease-associated biological processes. Within the AMMA-Project the following techniques are used:

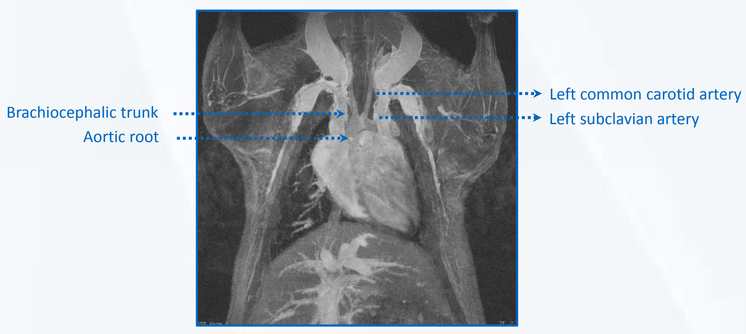
- Fluorescence-Molecular Tomography combined with x-ray Computed Tomography (FMT/CT), in collaboration with the group of Vasilis Ntziachristos, Chair for Biological Imaging, Technische Universität München
- Magnetic resonance tomography (MRT)

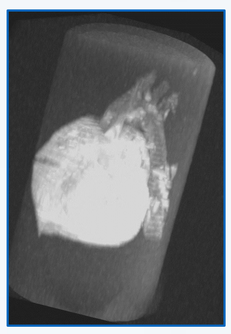
1 In-vivo FMT/CT Imaging of inflammtory atherogenic process:

Neutrophil granulocytes are short-lived inflammatory cell types which contribute to the pathophysiology of atherosclerosis. A new enzyme-activatable fluoregenic probe for in-vivo imaging of neutrophil elastase activity in LDLr$^{-/-}$ mice will be tested.

2 In-vivo and ex-vivo MRT imaging to develop a 3D model of the aortic arch:

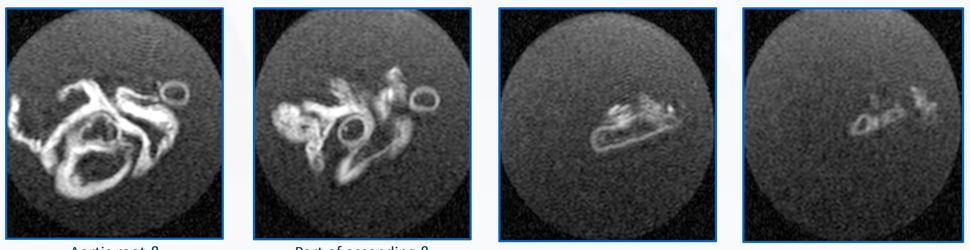
In- vivo MRT with contrast agent:





Reconstruction of ex-vivo agarose gel MRT images

Ex-vivo MRT of aortic arch in agarose gel:

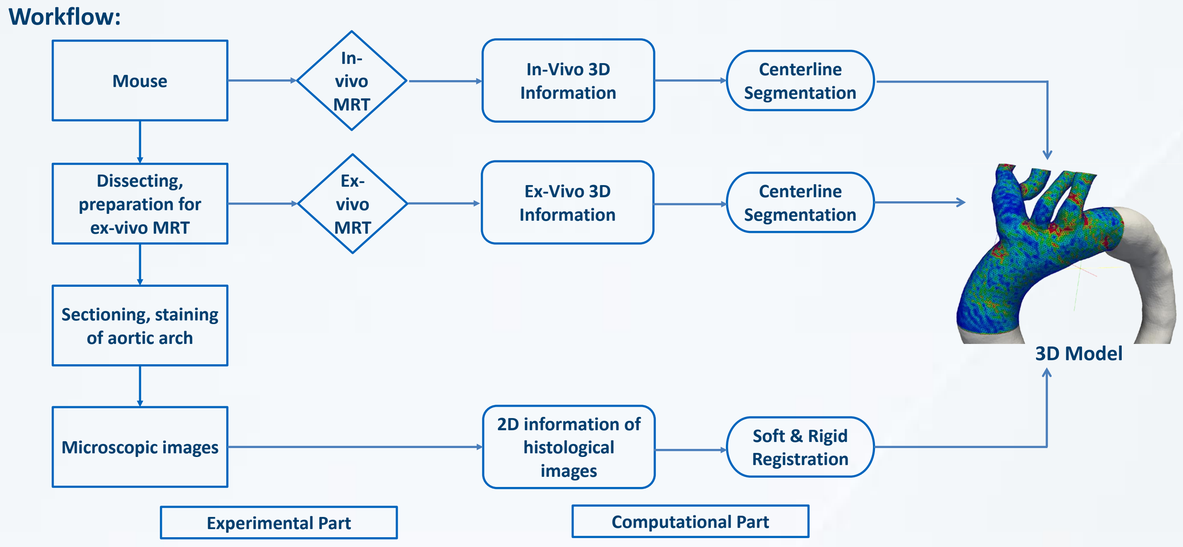


Aortic root & part of descending aorta | Part of ascending & descending aorta | Aortic arch | Bifurcations of aortic arch

6 Three dimensional model of aortic arch

The acquired data will be used to formulate a 3D model of the aortic arch. At later stages the 3D model can be used to simulate mechanical interactions of blood flow on the arterial wall.

Workflow:



Computational Part:

Soft Registration | Rigid Registration

Centerline-Computation

„Banana-Problem“

Segmentation

7 Outlook

Based on immunohistochemistry and flow cytometry in a mouse model of atherosclerosis, we combine the use of cell biology techniques together with medical imaging to visualize and quantify basic pathomechanisms of lesion formation. The acquired data is used to formulate mathematical equations establishing a 3D mechanobiological model of the mouse aortic arch. Simulation of mechanical interactions of blood flow and arterial wall biology and its impact on the pathogenesis of atherosclerosis will be verified at site specific localizations of plaque development and the accumulation of certain immune cells. With this interdisciplinary collaboration it will be possible to gain more knowledge on mechanical and biological interactions involved in atherogenesis.