Modeling and Simulation of Physiological Systems

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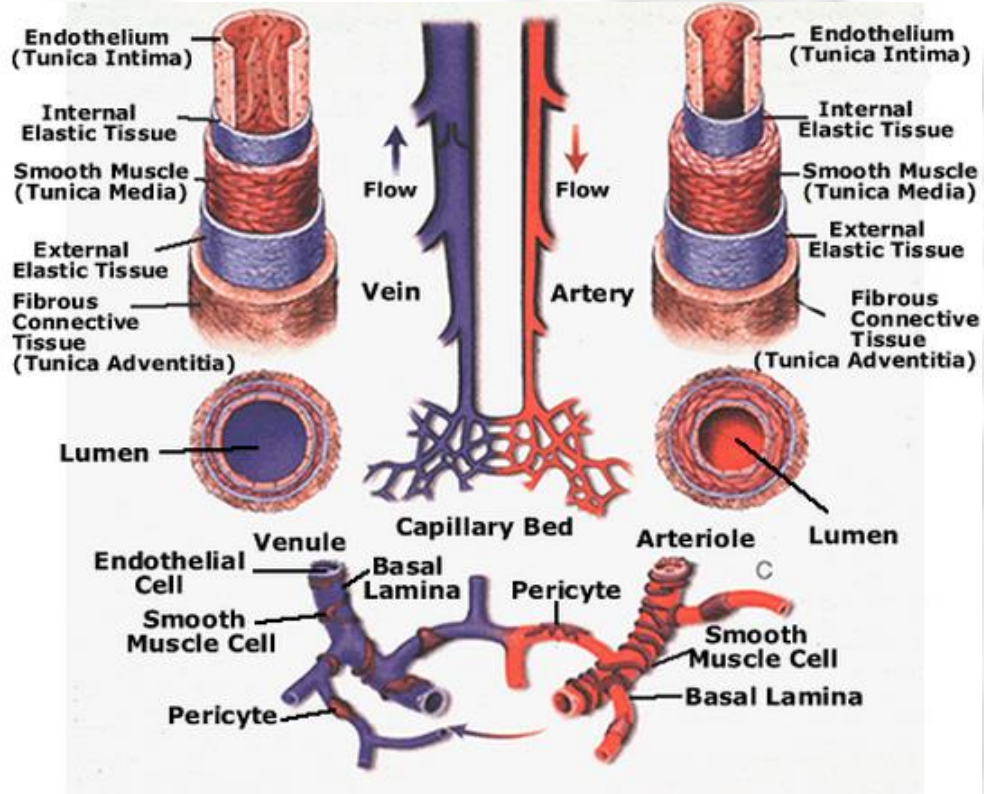
MEDICAL TECHNOLOGY Med & Lab INTELLIGENT INFORMATION SYSTEMS

Outline

- Modeling in circulatory system
  - Introduction in circulatory system and blood
  - Modeling blood flow
  - Modeling mass transport
  - Modeling plaque growth
  - Modeling stent deployment
- Modeling heart function
  - Introduction in heart physiology
  - Mechanics of heart
  - Electrophysiology of heart
  - Electro-mechanics of heart
  - Modeling heart failure

Introduction

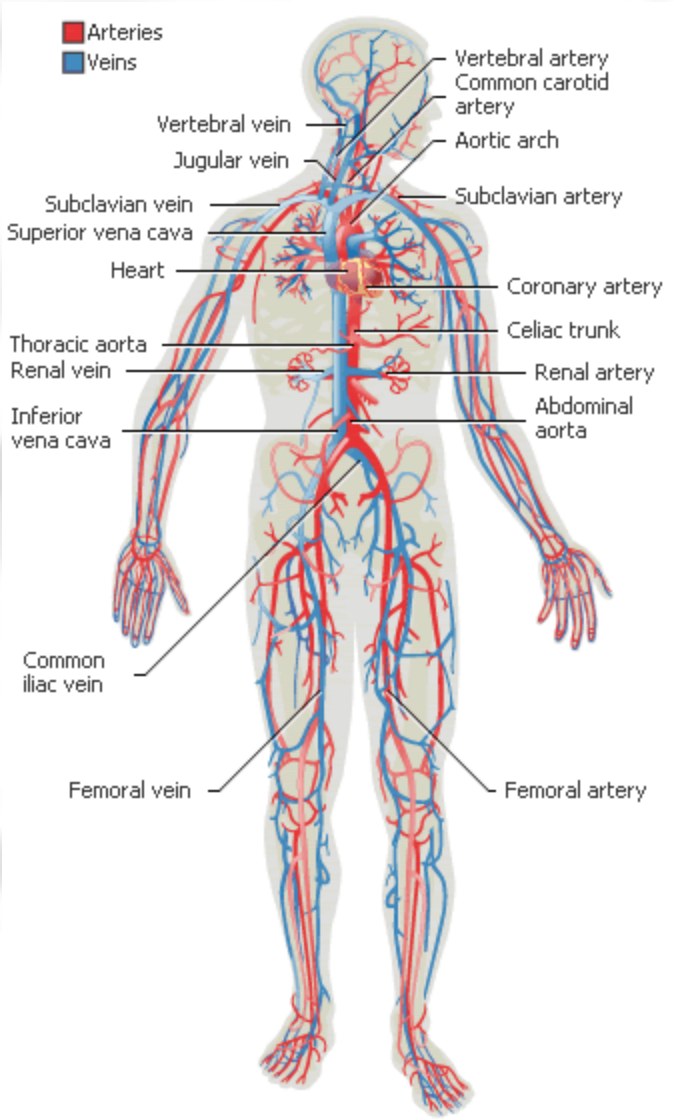
- Arteries are the vessels beginning from the heart and delivers blood to the whole body.
- The vessels that end to the heart are the veins.



http://bme240.eng.uci.edu/students/08s/sshreim/bvd.htm

Introduction

- Human arterial and vein system.



http://www.pelmasoft.com/article.php?id=225

Arterial wall structure

- The structure of the arterial wall depends on its size, which changes the elastic properties.
- Large arteries have high elastic behaviour because they must have the smallest resistance to heart motion.
- Small arteries have lower elasticity and almost no elasticity at the arterioles.
- Arterial wall consists of three layers:
  - The inner layer (intima),
  - The middle layer (media),
  - The outer layer(adventitia).

Arterial wall structure

- The intima layer is composed of an elastic membrane lining and smooth endothelium (special type of epithelial tissue) that is covered by elastic tissues.

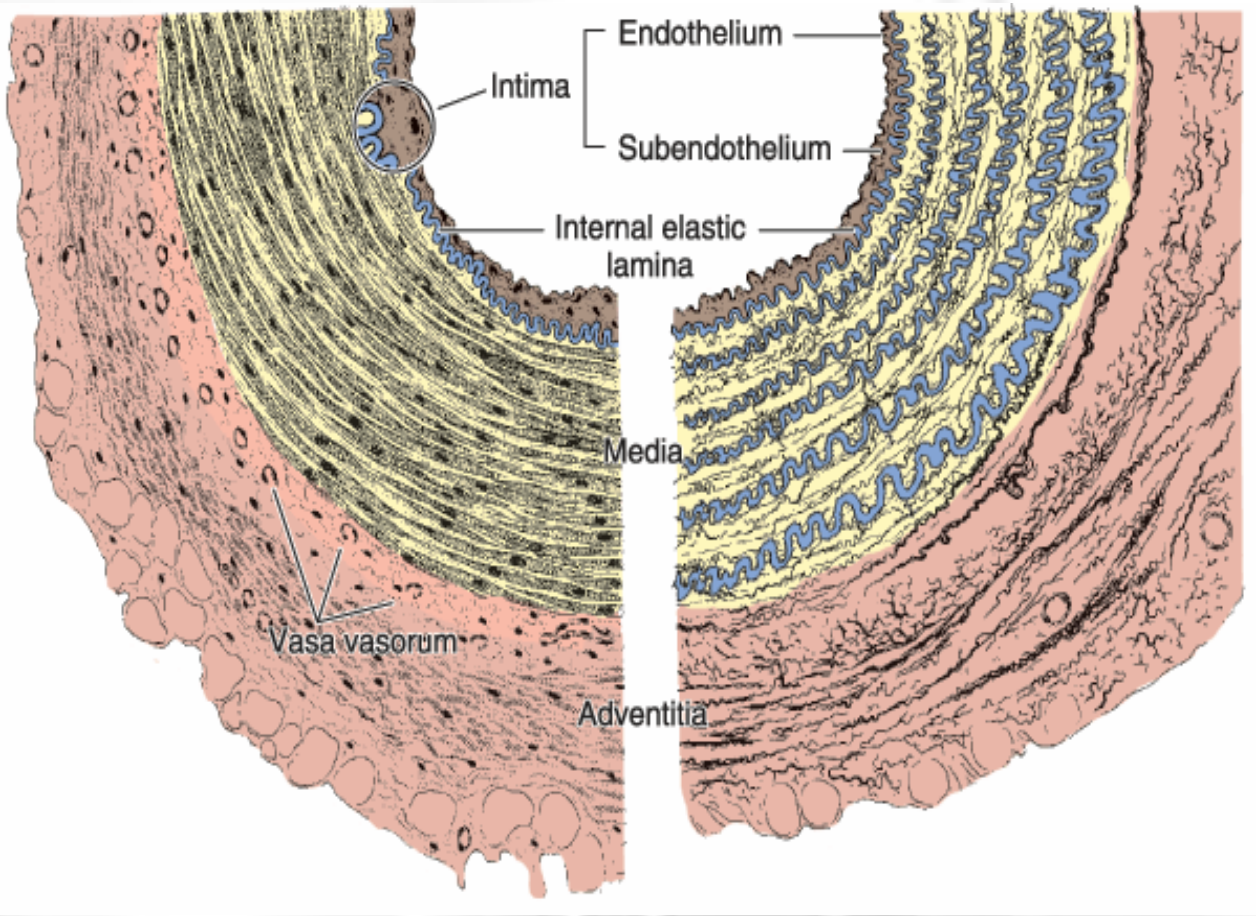
- The media is composed of smooth muscle cells, a network of elastic and collagen fibrils and elastic laminae. The media consists of a highly organized three-dimensional network of elastin, vascular smooth muscle cells and collagen with extracelluar matrix proteoglycans.

- The adventitia is the outer layer composed primarily of thick bundles of collagen fibrils arranged in helical structures and fibroblast cells.

Arterial wall structure

- The large arteries contain a large amount of elastic fibers and smooth muscle cells which provide the elastic properties of the wall.
- The outer layer is loose at the diastole, while it is activated later in the cardiac cycle in order to restrain the diameter increase of large arteries.
- The small arteries are restrained by smooth muscles and the arterioles are restrained by the endothelial cells.

Arterial wall structure



Junqueira *et. al.,* 2005

Arterial geometry

- Arterial geometry is characterized by three parameters:
  - the diameter,
  - The area of each cross-section,
  - The arterial thickness.
- An indicator of the general condition of the vessel is the monitoring of the cross-sectional area throughout the course of the cardiac cycle.
- The arterial thickness is also a significant parameter since it is related with several arterial diseases: atherosclerosis, aneurysm.

Arterial wall cells

Endothelial cells

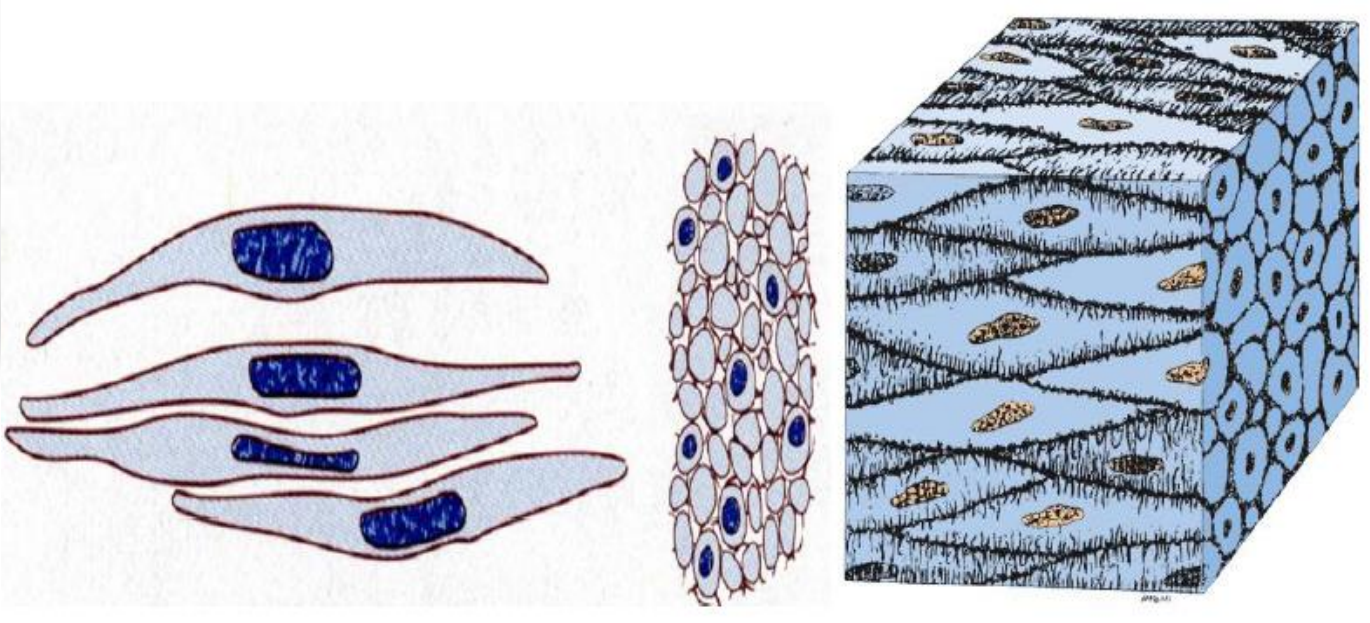
- Endothelial cells form a layer overlying the entire vascular system, thus creating the most important barrier permeability of blood vessels.
- They play an important role in mass transfer phenomena and directly subordinate to the forces of blood flow.
- Endothelial cells have a planar shape, consisting of a thin layer of cytoplasm and a single ellipsoidal core which protrudes in the intraluminal space.

Arterial wall cells

Smooth muscle cells

- The vascular smooth muscle cells (VSMCs) are structural units with main function the contraction.
- Their structure is such that serves their basic function.
- Dominant position in VSMCs holds the contractile apparatus, while the cytoskeleton and the connections with neighboring cells with the extracellular matrix are also important, as they are used for signaling message transport.

Arterial wall cells



- Schematic illustration of isolated smooth muscle cells

Junqueira *et. al.*, 2005

Arterial wall cells

- The most important mechanical stimulus, which is known to induce changes in the tone of VSMC, is a sudden increase of blood pressure.
- The increase in blood pressure may cause the contraction of the vessel wall area and thus increase the deformation of VSMCs, contained in the wall.
- The VSMCs react in this sudden deformation by direct constriction.
- The contraction is called myogenic reaction and is designed to protect the artery by destruction.

Arterial wall cells

- Contraction of VSMCs maintain constant blood flow to normal levels by restoring the vessel diameter in its homeostatic state, despite increased pressure.
- When VSMCs are not under agitation, they are in a light contraction condition, called basic VSMCs tone mode or normal VSMCs tuna.
- When the VSMCs are in light contraction state, they give the artery the ability both to relax and to contract without consuming an excessive amount of energy, which would be required to maintain a higher level of contraction.

Structure of the extracellular components of the vascular wall

- The extracellular components of blood vessels generally referred to as connective tissue components.
- Includes the collagen fibers and elastic fibers and contribute significantly to the maintenance of vascular homeostasis.
- The macromolecules of collagen and elastin perform multiple actions:
  - serve to transfer signals,
  - bind and retain lipoproteins,
  - constitute a reservoir of growth factors

Structure of the extracellular components of the vascular wall

- Collagen and elastin contribute to strength and structural integrity of the vascular wall.
- In normal tissues, expression and reorganization of the extracellular matrix is a well-regulated dynamic equilibrium.
- Contrary to pathological conditions such as rheumatoid arthritis, atherosclerosis and fibromuscular hyperplasia the above balance is disturbed favoring the development and the clinical manifestation of the above disorders.

Structure of the extracellular components of the vascular wall

Elastic fibers

- The elastic fibers are the main component of the extracellular matrix of large vessels and are required to address the mechanical loads in blood pressure.

- The elastic fiber system consists of two biochemical and ultrastructural components:
  - elastin, component responsible for the elasticity of the elastic fibers,
  - ingredients of mikro-fibers.

Structure of the extracellular components of the vascular wall

Collagen

- The macromolecule is normally synthesized by vascular smooth muscle cells of the medial layer of the vessel and ensure the integrity of the vessel against mechanical forces exerted by circulating blood.

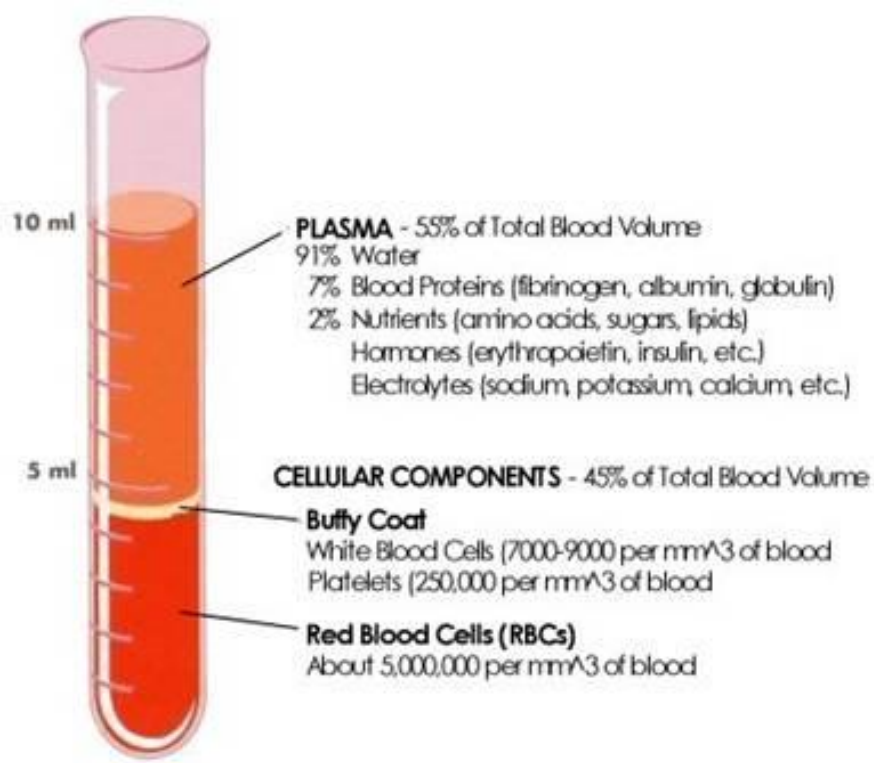
- The quantitative presence of collagen vascular tissue is the result of a dynamic equilibrium between the synthesis and its degradation and determine the structure of the vascular wall.

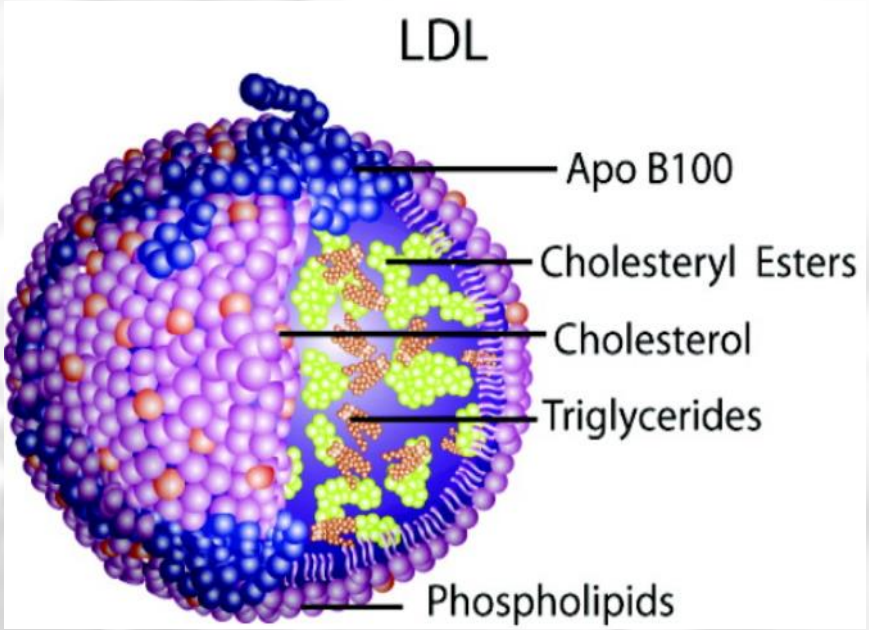
Structure of the extracellular components of the vascular wall

- The collagen fibrils are an essential structural component of blood vessels.
- During fibril formation, the three strands of the collagen wrapped in a clockwise superhelix.
- This helical configuration gives the molecule a very stable and solid form.

Blood

Blood and low density lipoprotein



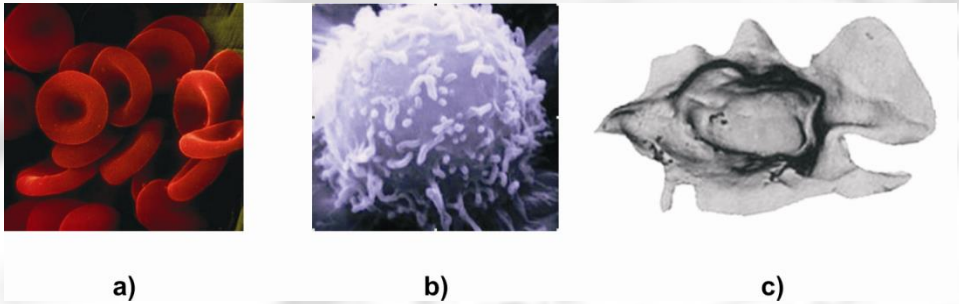


http://el.wikipedia.org/wiki/%CE%91%CE%AF%CE%BC%CE%B1

http://www.mpbio.com/product.php?pid=0859392&country=84

Blood

- Blood represents two component system which consists of cells (formed cellular elements) and plasma.
- There are several blood cells types which are present in blood in a form of functional mature cells such as erythrocytes, leucocytes and platelets.



a) Erythocytes **b)** Leukocytes **c)** Activated platelet

 Kojic M., Filipovic N., Stojanovic B., Kojic N. (2008), "**Computer Modeling in Bioengineering**", ch. 7, WILEY

Blood

- Red blood cells (RBCs) or erythrocytes are mature, highly differentiated cells which only consist of plasma membrane and citosol, inner fluid with dissociated protein hemoglobin.
- Leukocytes are the only fully morphologically complete cells, because they contain all cell elements (nucleus, cytosol and cell organelles). They represent the base of the immune system.
- Platelets are cell fragments produced from giant precursor cell called megakariocyte during differentiation. They are disc-shaped enabling adherention to vessel wall as well to each other when activated.
- Plasma is liquid constituent of blood. It contains water, various electrolytes, small organic molecules (glucoses and amino acids) and also large proteins and lipids.

Blood

Blood flow in large arteries

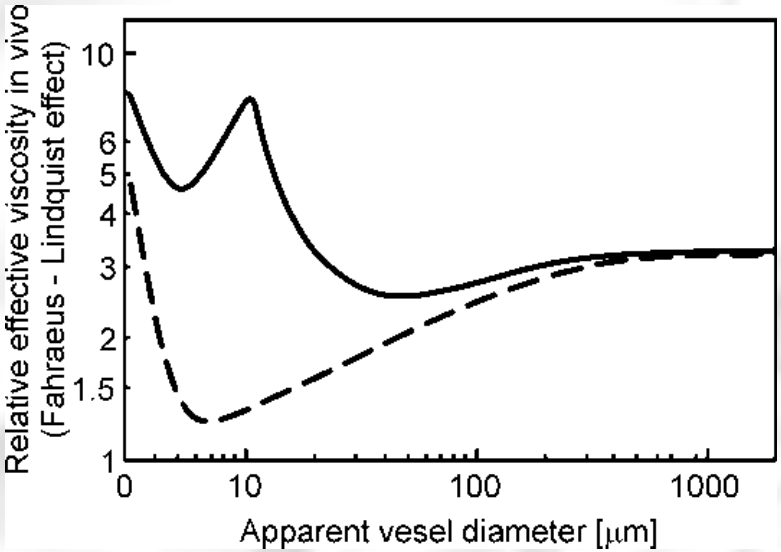
- In most arteries, blood behaves in a Newtonian fashion, and the viscosity can be taken as a constant.
- However, non-Newtonian mechanical behavior of blood is pronounced in smaller blood vessels.
- In the case when the shear strain rates of blood flow are not too low, as in medium size arteries and veins , the blood viscosity can be expressed as a function of the hematocrit H and shear strain rate. This functional relationship is called the Cason relation:

$$\mu = \frac{1}{2\sqrt{D_{II}}}\left(k_0(H) + k_1(H)\sqrt{2\sqrt{D_{II}}}\right)^2$$

where $k_0(H), k_1(H)$ are the functions determined experimentally (Perktold et al. 1998); and D_{II} is the second invariant of the strain rate

$$D_{II} = \frac{1}{2} D_{ij} D_{ij}$$

Blood



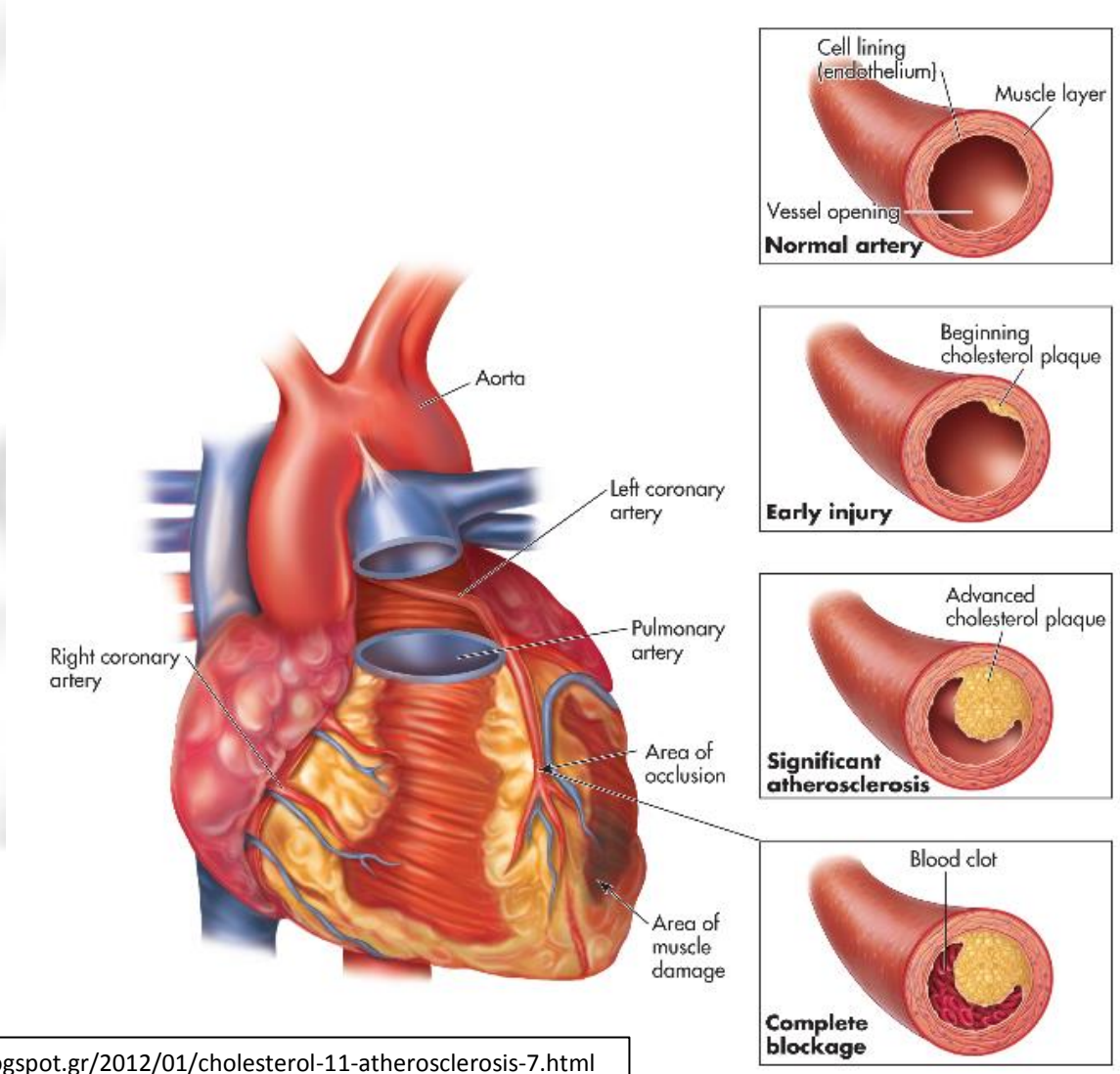
Dependence of the relative apparent viscosity of blood on the microvessel diameter (according to Pries and Secomb 2005): solid line is for blood vessels in vivo measurement on rat mesentery; dashed line is for glass tube. The hematocrit is 45. Large differences between the results for blood vessels and tube are due to effects of the endothelial surface layer present in blood vessels.

Atherosclerosis

- It is the formation of plaque in the arterial wall.
- Atherosclerosis is a disease of large arteries and regards the lipid accumulation, the formation of fibrous tissue and the proliferation of smooth muscle cells.
- Atherosclerosis is mainly found at curved regions of arteries or at bifurcations where flow is low and low wall shear stress exists.
- The main factors are the hyperlipidemia, hypertension, the male gender, smoking and diabetes.
- It is characterized by:
  - The increased accumulation of lipids into the arterial wall.
  - The fattening of the wall.
  - The blockage of the lumen to blood flow.
- It is widely accepted that regions of low wall shear stress are prone to atherosclerosis.

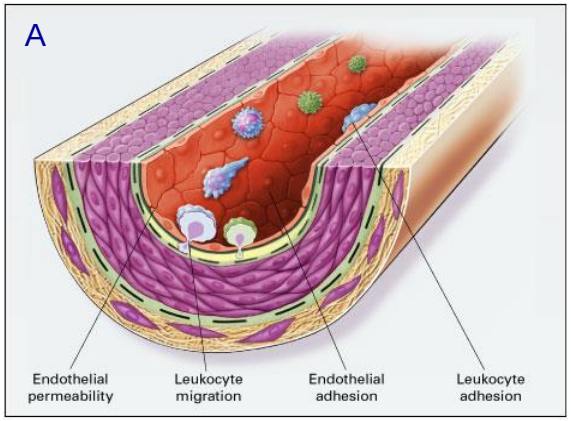
Atherosclerosis

Different stages of atherosclerosis

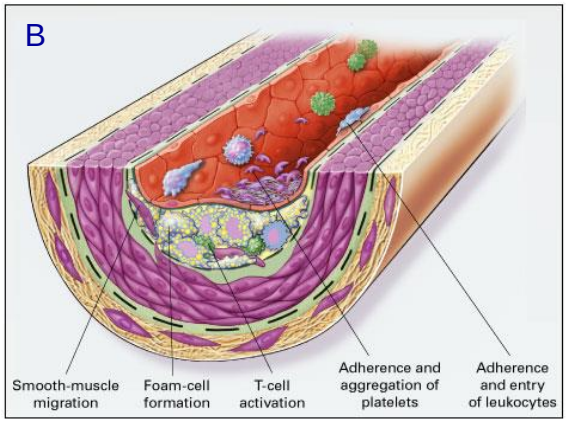


http://kendhilkencana.blogspot.gr/2012/01/cholesterol-11-atherosclerosis-7.html

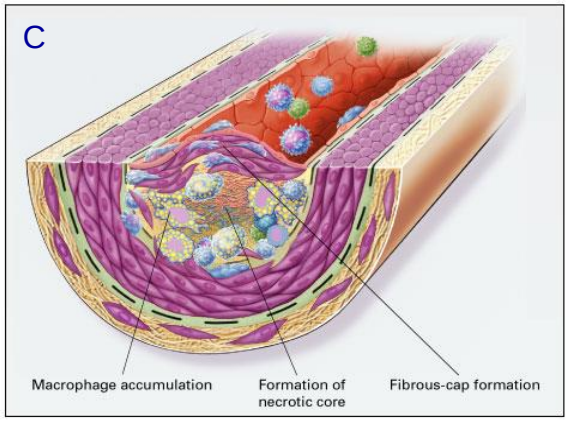
Atherosclerosis



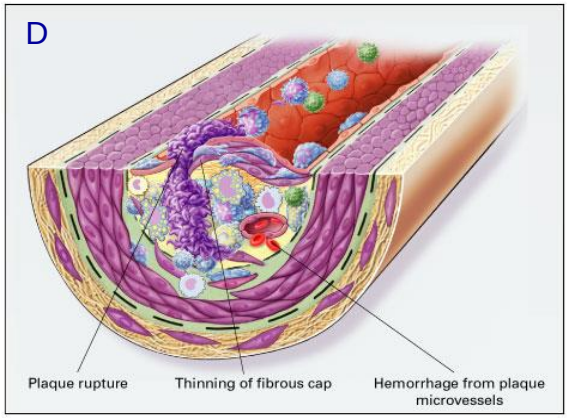
Endothelial dysfunction



Lipid accumulation



Formation of necrotic core and fibrous cap



Plaque rupture

Ross *et. al* 1999

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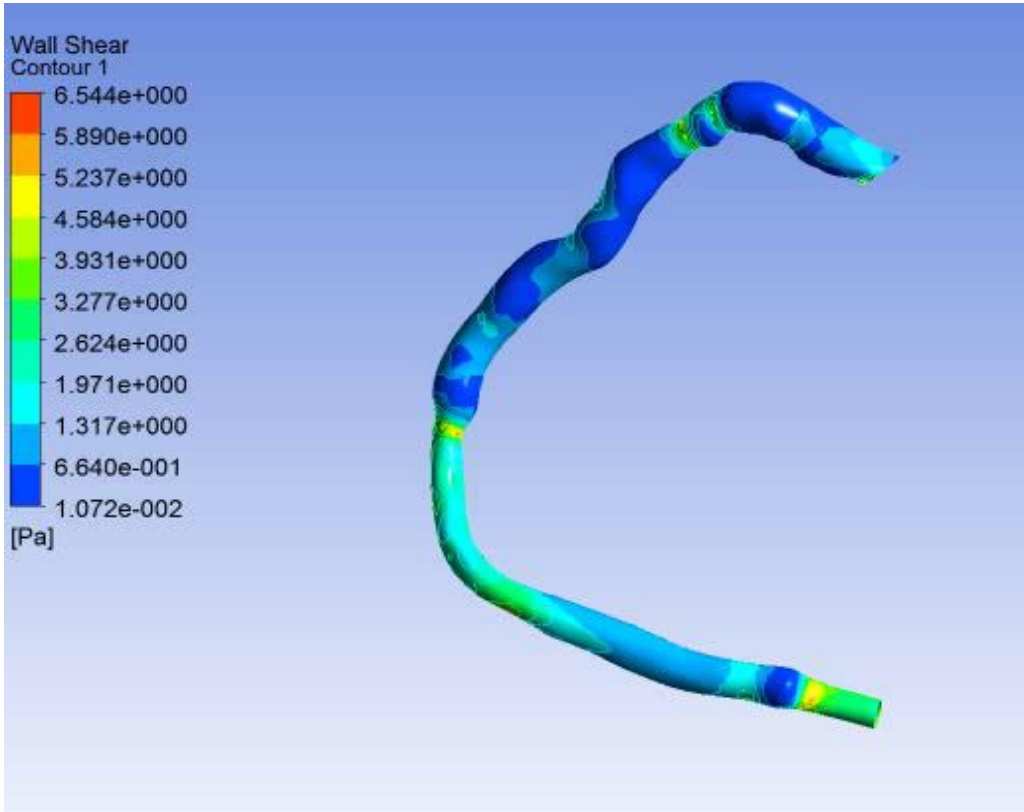
Blood Flow Modeling

- In large vessels the blood is considered as an incompressible homogenous viscous fluid
- It is assumed that the blood flow is laminar
- Blood flow is modeled using the Navier-Stokes equations and the continuity equations
- Endothelial shear stress (ESS) is crucial for plaque growth



$$\rho\left(\frac{\partial v_i}{\partial t}+\frac{\partial v_i}{\partial x_k}v_k\right)=-\frac{\partial p}{\partial x_i}+\mu\frac{\partial^2 v_i}{\partial x_k \partial x_k}+f_i^V$$

$$\frac{\partial \rho}{\partial t}+\nabla\cdot(\rho\mathbf{v})=0$$

Blood flow modeling

- Plasma and cells are main constituents of blood.
- Depending on the size of the vessel, blood acts as either a Newtonian (arteries, aorta) or a non-Newtonian fluid (arterioles, capillaries).
- In FSI simulations, due to the interaction of the blood with the arterial wall, the blood domain is deformable. Therefore, the following equations that govern momentum and mass conservation are used:

$$\rho\frac{\partial \mathbf{v}}{\partial t}+\rho\left(\left(\mathbf{v}-\mathbf{w}\right)\bullet\nabla\right)\mathbf{v}-\nabla\bullet\boldsymbol{\tau}=\mathbf{f}^{B}$$

$$\nabla\bullet\mathbf{v}=0$$

ρ : blood density

$\mathbf{v}$: velocity vector

$\mathbf{w}$: moving mesh velocity vector

$\boldsymbol{\tau}$: stress tensor

$\mathbf{f}^{B}$: body forces

$$\boldsymbol{\tau}=-p\delta_{ij}+2\mu\varepsilon_{ij}$$

$$\varepsilon_{ij}=\frac{1}{2}\left(\nabla\mathbf{v}+\nabla\mathbf{v}^{T}\right)$$

δ_{ij} : Kronecker delta

μ : blood dynamic viscosity

p : blood pressure

ε_{ij} : strain rate

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Blood flow modelling

- Regarding the solid domain (wall), the governing equation is the following momentum conservation equation:

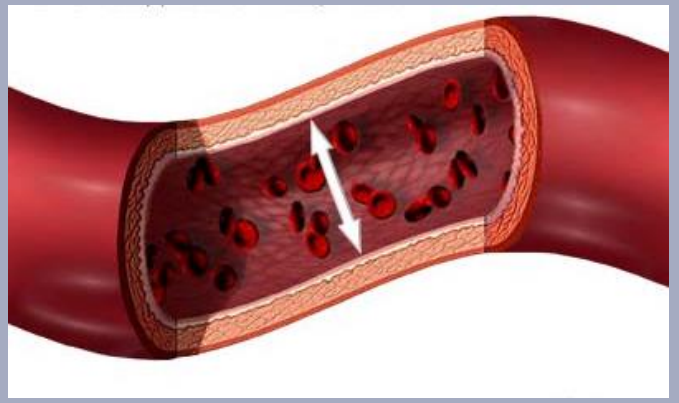
$$\nabla \boldsymbol{\tau}_s + \mathbf{f}_s^{\mathbf{B}} = \rho_s \ddot{\mathbf{d}}_s$$

$\boldsymbol{\tau}_s$: arterial wall tensor

$\mathbf{f}_s^{\mathbf{B}}$: body forces per unit volume

ρ_s : arterial wall density

$\ddot{\mathbf{d}}_s$: local acceleration of the solid



- The arterial wall was treated as hyperelastic material in our simulations.

Elastic properties of the arterial wall

- Arterial wall has complex mechanical properties and for this reason the use of a linear elastic model is very simplified.
- In the literature hyperelastic materials has been used to describe arterial wall.
- The energy-deformation function for a hyperelastic material is given by[2]:

$$W = c_{10}(\bar{I}_1 - 3) + c_{01}(\bar{I}_2 - 3) + c_{20}(\bar{I}_1 - 3)^2 + c_{11}(\bar{I}_1 - 3)(\bar{I}_2 - 3) + c_{02}(\bar{I}_2 - 3)^2 + c_{30}(\bar{I}_1 - 3)^3$$
$$+ c_{21}(\bar{I}_1 - 3)^2(\bar{I}_2 - 3) + c_{12}(\bar{I}_1 - 3)(\bar{I}_2 - 3)_2 + c_{03}(\bar{I}_2 - 3)^3 + \frac{1}{d}(J - 1)^2$$

$\bar{I}_1 =$ the first invariant of deformation

$\bar{I}_2 =$ the second invariant of deformation

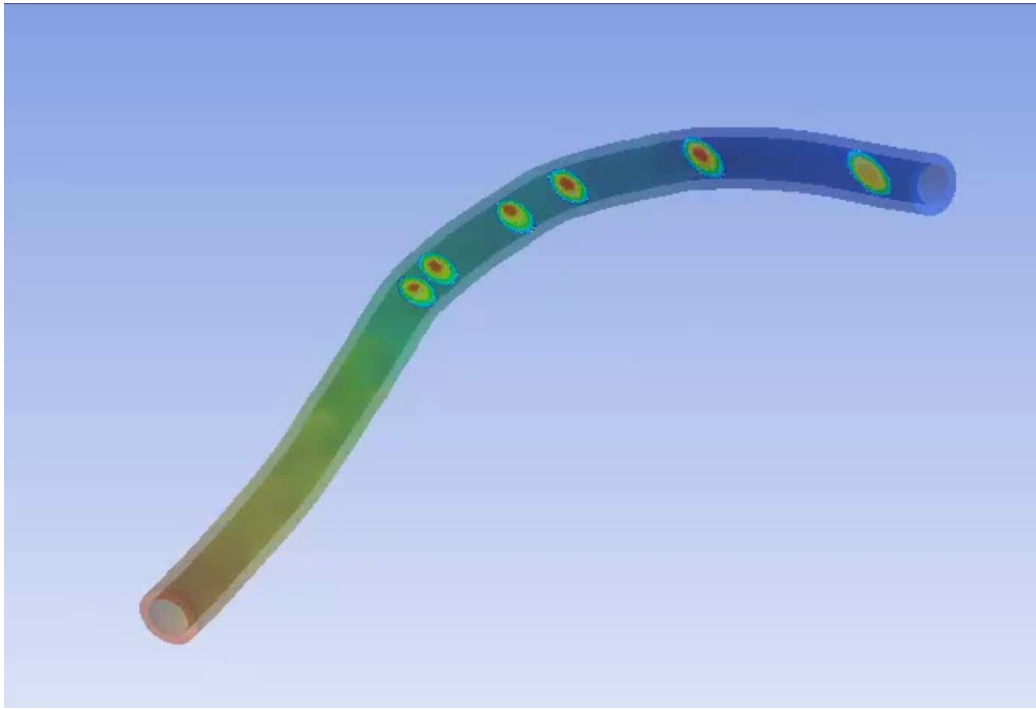
J is the Jacobian of the deformation gradient

d is α parameter of material compressibility

(2) Torii R., Wood N.B., Hadjiloizou N., Dowsey A.W., Wright A.R., Hughes A.D., Davies J., Xu X.Y., "**Fluid-structure interaction analysis of a patient-specific right coronary artery with physiological velocity and pressure waveforms**", Comm. in Num. Met. in Eng.., vol. 25, no. 5, pp. 565-580, 2009

Blood Flow Modeling
Arterial wall - deformation modeling

- Blood flow velocities and pressure are determined
- Loads which arrived from blood are calculated
- The deformation of the wall is determined based on the current loads
- The overall convergence is checked
- Update blood domain geometry for the new calculation of the blood flow



Biological Process Modeling
Mass transport modeling in the lumen

- LDL and HDL transport are modeled in the lumen using the convection-diffusion equation:

$$\nabla \cdot \left(-D_l \nabla c_l + c_l u_l \right) = 0$$

$$\nabla \cdot \left(-D_{l,HDL} \nabla c_{l,HDL} + c_l u_{l,HDL} \right) = 0$$

Diffusivity D_l
LDL concentration c_{LDL}
Diffusivity $D_{l,HDL}$
HDL concentration c_{HDL}

- Patient's concentrations are applied at the inflow boundary
- At the endothelial boundary appropriate conditions which describe the trans-membrane penetration are prescribed

A.I. Sakellarios et al. American Journal of Physiology - Heart and Circulatory Physiology 2013

Biological Process Modeling
Interaction between endothelial sides

- Endothelial permeability is modelled using the Kedem – Katchalsky equations

$$Jv = Lp(\Delta p - \sigma_d \Delta \pi)$$

$$Js = P\Delta c + (1-\sigma_f)Jv\bar{c}$$

Jv: velocity across endothelium (m s^{-1})

Lp: hydraulic conductivity (m s^{-1} Pa^{-1})

Δp: pressure drop across the endothelium

σ_d : endothelial reflection coefficient

$\Delta\pi$: osmotic pressure difference

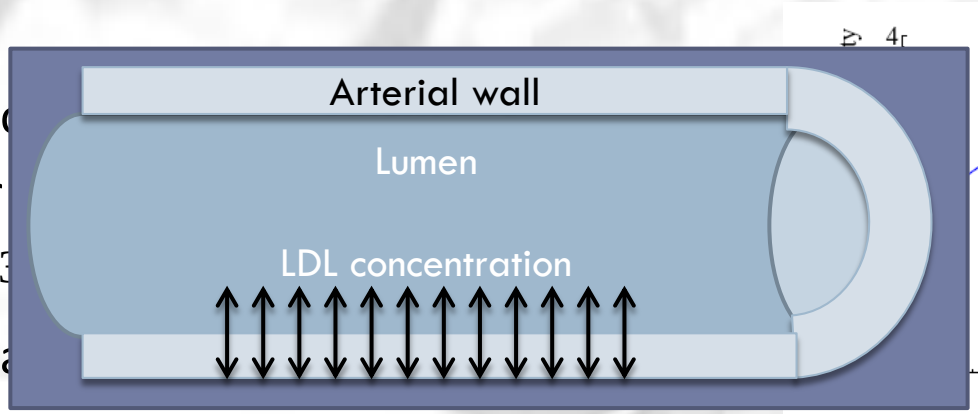
P: Endothelial permeability (m s^{-1})

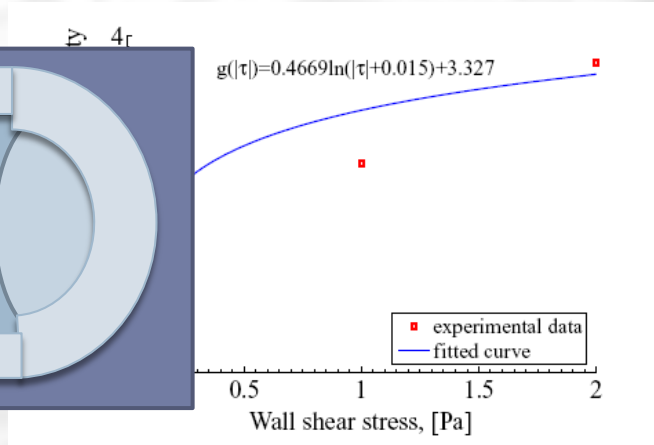
σ_f : solvent reflection coefficient

c: concentration (mol m^{-3})

Js: Solute flux

- Hydraulic c
  wall shear
  $L_p(|\tau_w|) = 0.3$
  τ_w: wall shea





O. Kedem and A. Katchalsky. Biochem. Biophys. Acta, 1958.

Biological Process Modeling
Mass transport modeling in the wall

- LDL transport in the wall is modeled using the convection-diffusion-reaction equation:

$$\nabla \cdot \left(-D_w \nabla c_w + k c_w u_w \right) = r_w c_w$$

Consumption rate r_w
Diffusivity D_w
Solute lag coefficient k

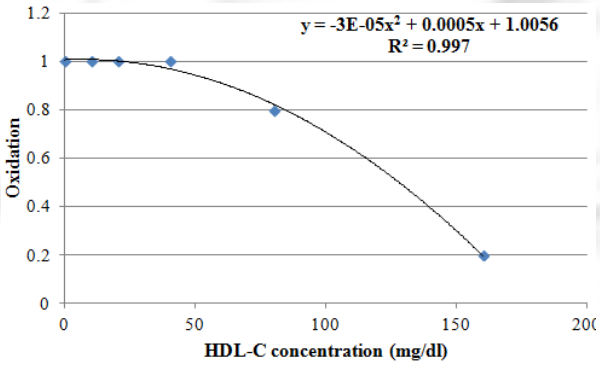
- We model LDL oxidation in the arterial wall taking into account the HDL concentration

$$\partial_t c_{ox} = d_{ox} \Delta c_{ox} - k_F c_{ox} \cdot M + \tau(wss) c_{ox} - k_{anti-ox} \cdot c_{HDL}$$

Oxidized LDL concentration c_{ox}
Shear stress wss
Coefficients k
Macrophages concentration M

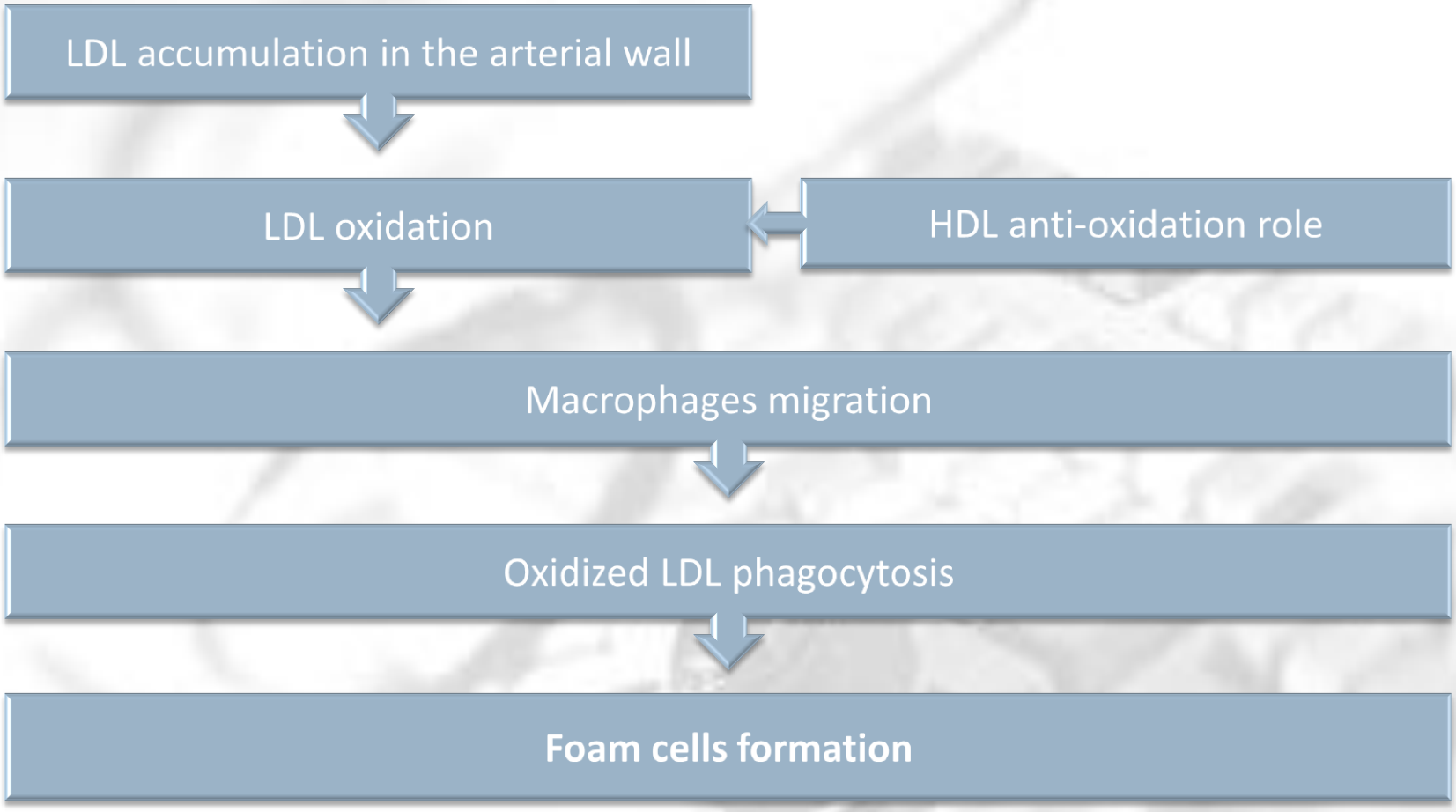
Oxidation rate of LDL depends on HDL concentration

BUT



A.I. Sakellarios et al., Conf Proc IEEE Eng Med Biol Soc. 2013

Plaque Growth Prediction



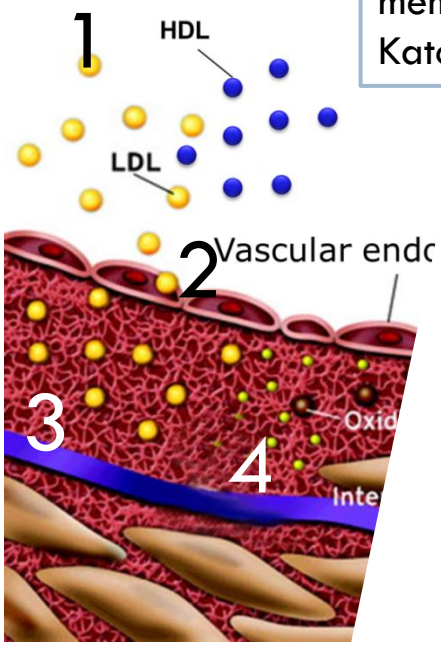
1 LDL and HDL transport are modeled in the lumen

6 Foam cells formation

Lumen

2 LDL penetrates endothelial membrane based on Kedem-Katchalsky equations

5 Monocytes migration



6

5

3 LDL transport is modeled in the wall

4 LDL oxidation based on HDL atheroprotection

D.P. Faxon et al., Circulation 2004

Plaque Growth Prediction

The migration of macrophages (*M*) is given by:

$$\partial_t M + div(v_w M) = d_2 \Delta M - k_1 Ox \cdot M + S/(1+S)$$

The effect of cytokines is modeled using:

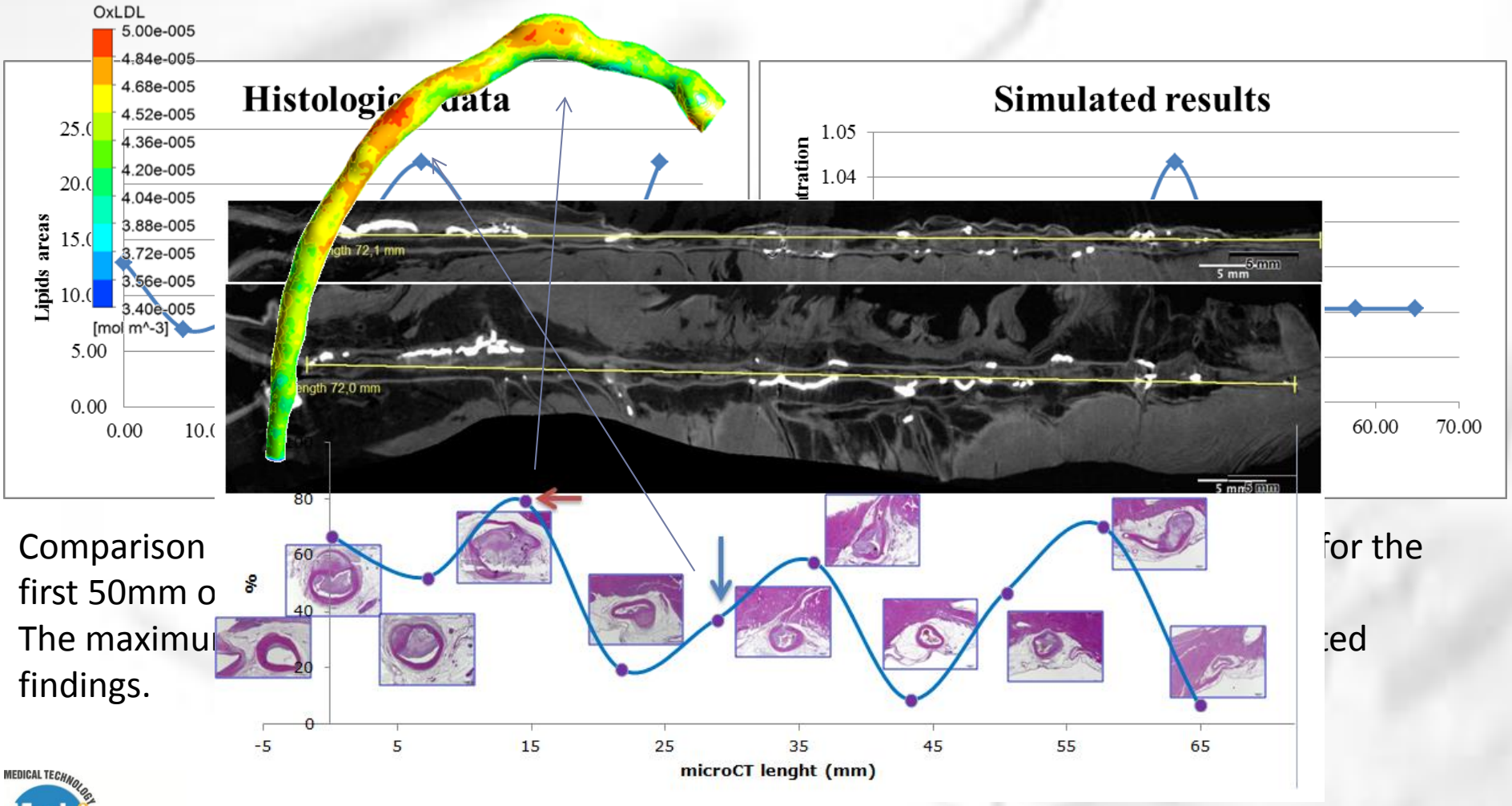
$$\partial_t S = d_3 \Delta S - \lambda S + k_1 Ox \cdot M + \gamma (Ox - O_x^{thr})$$

The growth caused by LDLox and macrophages is calculated by:

$$\nabla v_w = k_1 Ox \cdot M$$

N. Sun et al., Journal of Biomech Eng., 2009.
U. Olgac et al., American Journal of Physiology-Heart and Circulatory Physiology, 2009.
A.I. Sakellarios et al. American Journal of Physiology - Heart and Circulatory Physiology 2013
A.I. Sakellarios et al., Conf Proc IEEE Eng Med Biol Soc. 2013

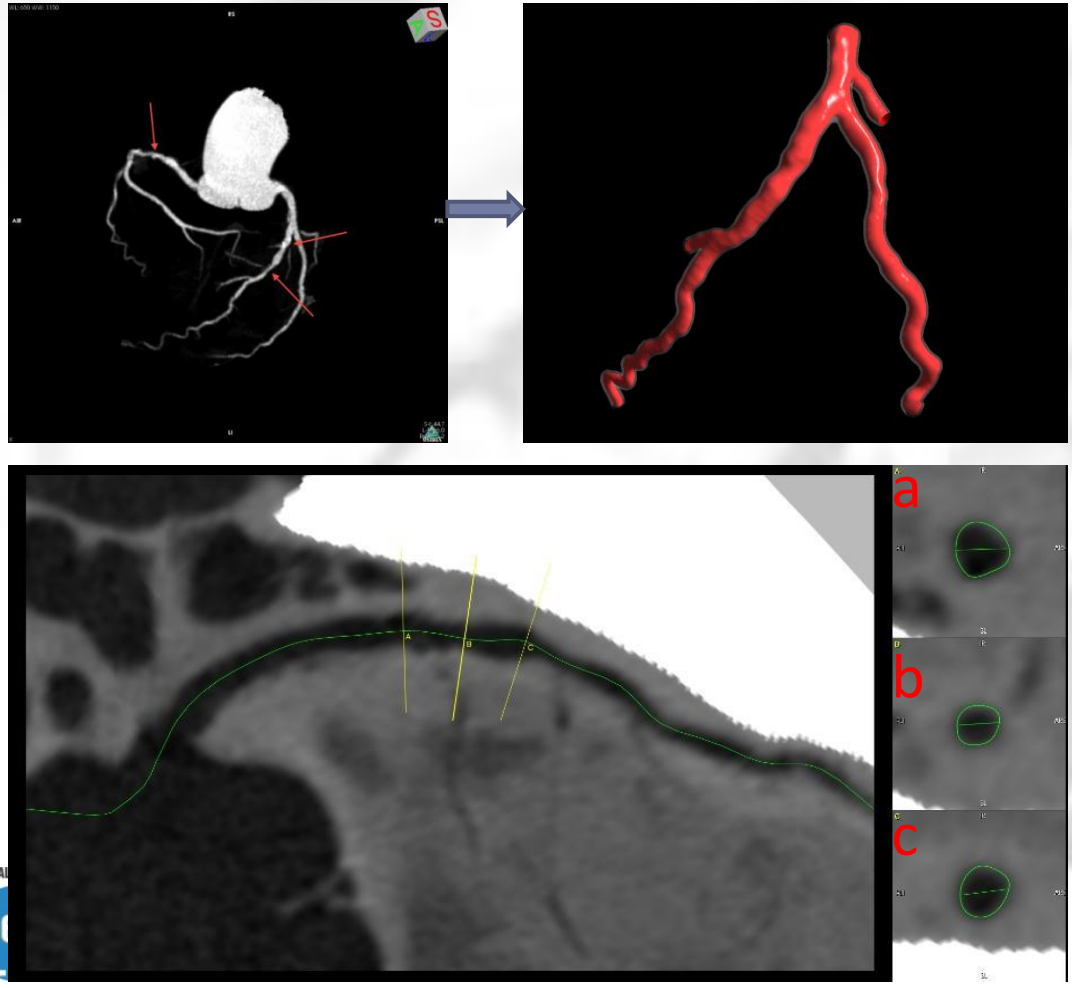
Plaque Growth Prediction



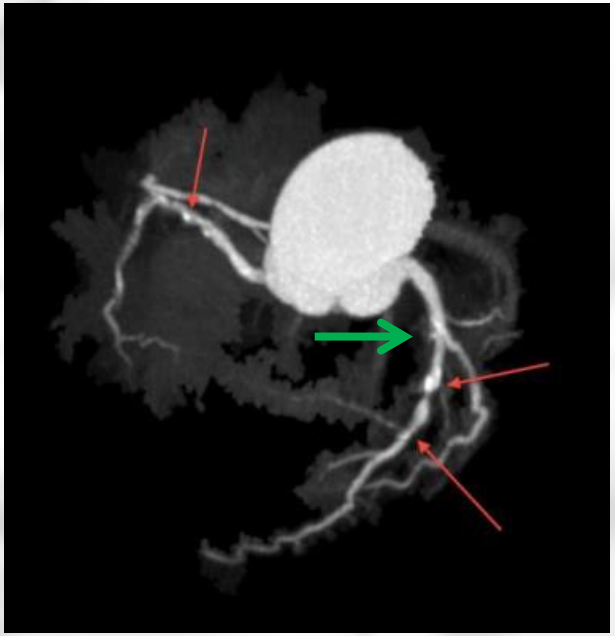
Comparison for the first 50mm o
The maximu ted findings.

Plaque Growth Prediction

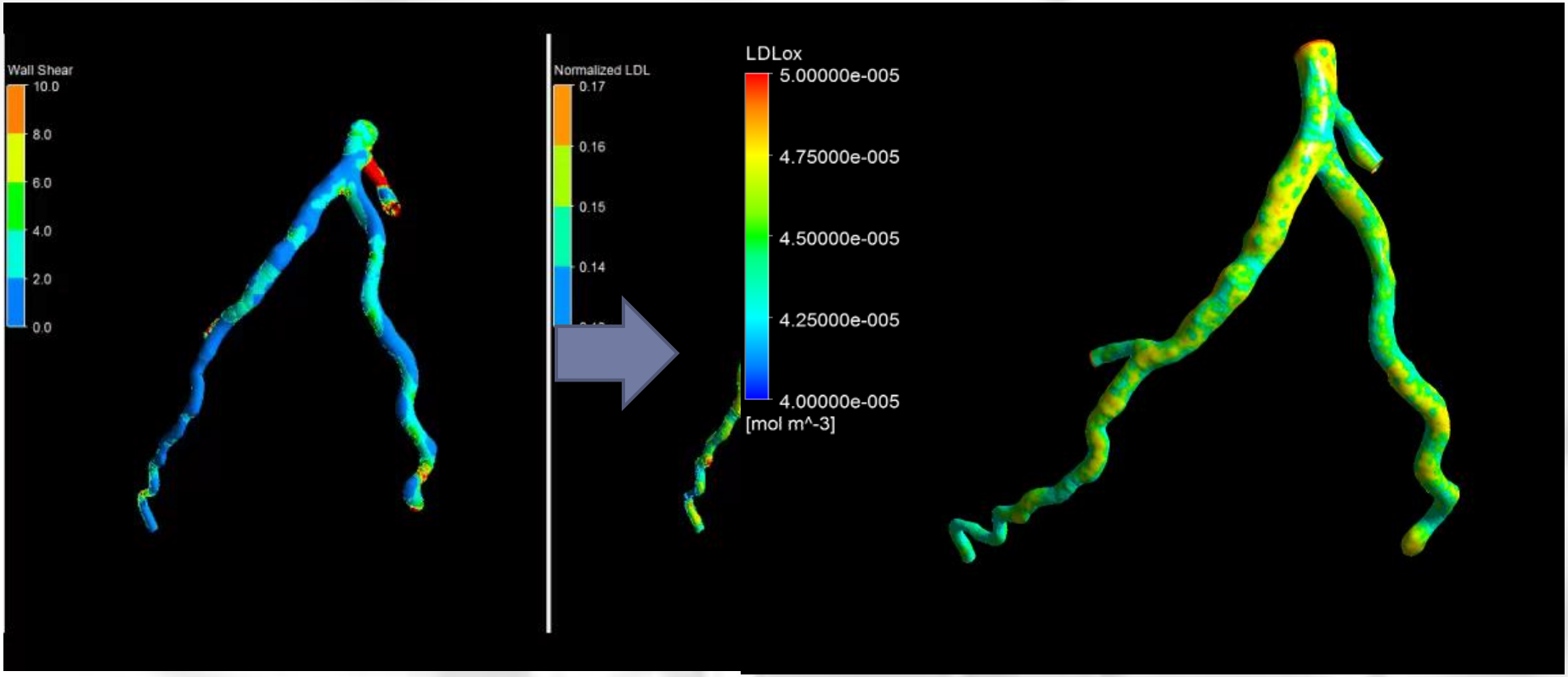
Baseline examination



Follow-up examination



Plaque Growth Prediction



Endothelial shear stress (left panel) and normalized LDL concentration (right panel)

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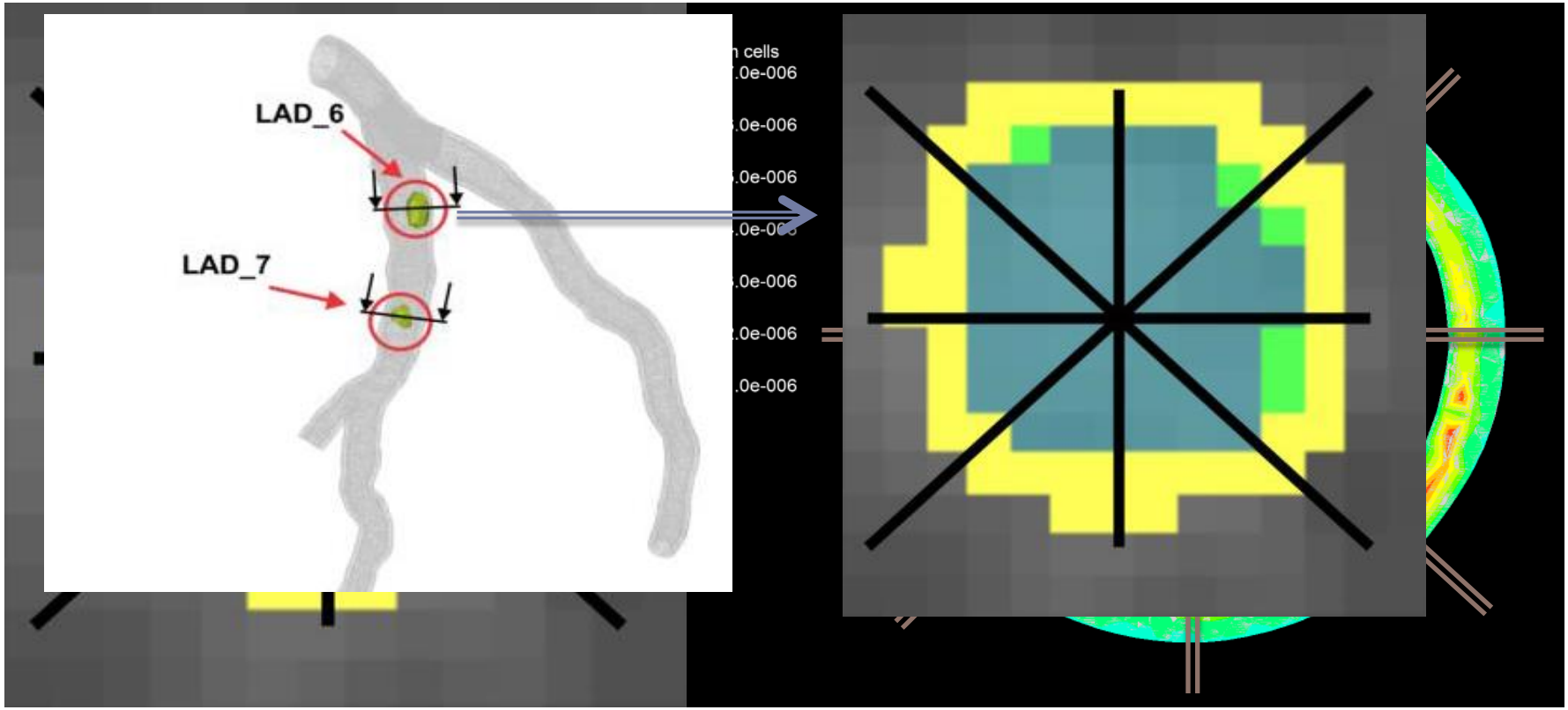
Plaque Growth Prediction



Annotated CT image

Calculated foam cell concentration

Stent modeling

Stent

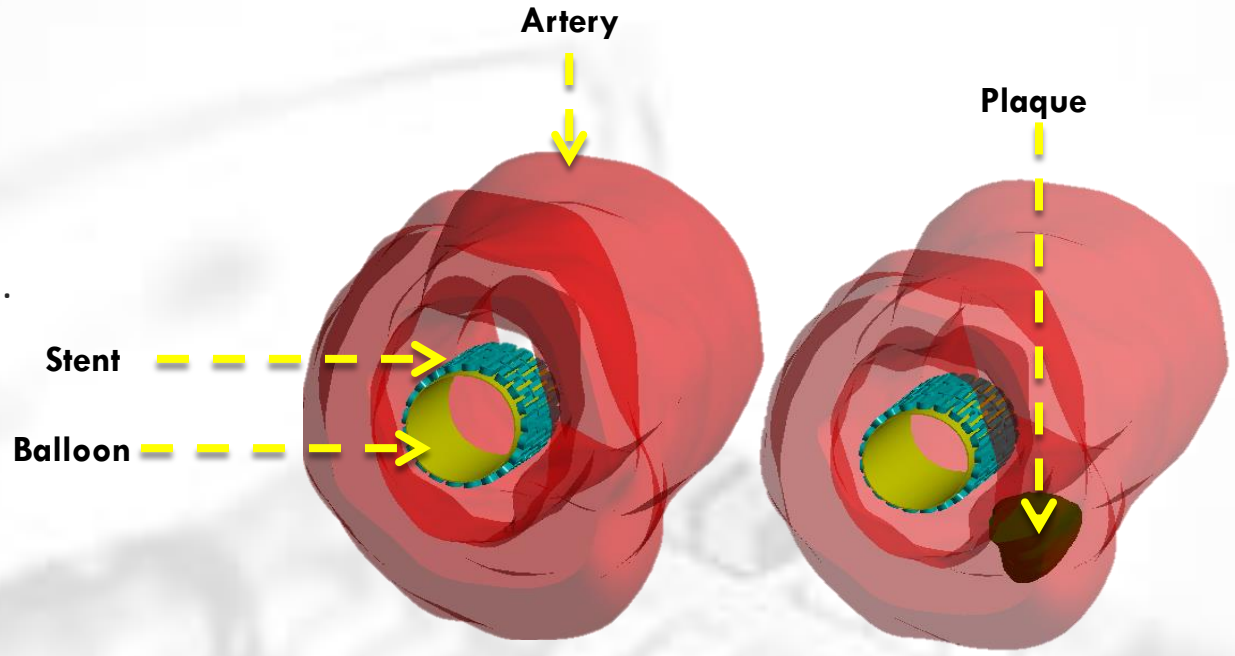
- based on the **Open Stent** design.
  - Open Stent is a generic realistic stent useful for scientific and designing purposes.

Balloon

- modeled as a plane cylinder.

Stent -Balloon

- ***Appropriately positioned***
  - in initial contact
  - In distance with the arterial lumen



First model | Second model

Comparison	First Model	Second Model
Artery	✓	✓
Plaque		✓
Stent	✓	✓
Balloon	✓	✓

Plaque thickness: 1.05mm - 1.40mm.
Plaque length: 3.27mm.
Arterial segment length: 17.54mm

❖ **Stenosis exists in both models**

Bonsignore C, Open Stent Design

Stent modeling

Material properties

Artery & Polyurethane Balloon

- Hyperelastic material
  - Five parameter Mooney Rivlin model

$$W = C_{10}(I_1 - 3) + C_{01}(I_2 - 3) + C_{20}(I_1 - 3)^2 + C_{11}(I_1 - 3)(I_2 - 3) + C_{30}(I_1 - 3)^3$$

$$I_1 = \lambda_1^2 + \lambda_2^2 + \lambda_3^2, \qquad I_2 = \lambda_1^2\lambda_2^2 + \lambda_1^2\lambda_3^2 + \lambda_2^2\lambda_3^2, \qquad I_3 = \lambda_1^2\lambda_2^2\lambda_3^2$$

Coefficients	C_{10}	C_{01}	C_{20}	C_{11}	C_{30}
Artery	0.0189	0.00275	0.08572	0.5904	0
Balloon	1.0318	3.6927	0	0	0

$\lambda_1, \lambda_2, \lambda_3$
principal stretches of material

I_1, I_2, I_3
strain invariants

Plaque

- Calcified plaque
  - Linear isotropic elastic material

E=2.7MPa

v=0.4913

Only for the Second model

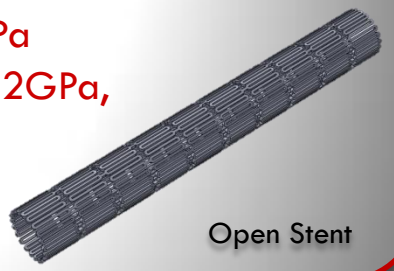
Stent

- Stainless Steel Stent
  - Bi-linear elasto-plastic material

E=193GPa

E_{tan}=0.692GPa,

v=0.27



Open Stent

E	Young modulus
E_{tan}	Tangent modulus
v	Poisson ratio

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Stent modeling

Boundary Conditions

Artery

Fixed at its ends

Stent

Tethered, only radial displacement allowed

Balloon

Initial contact with stent
Radial displacement (0.8mm) inner balloon surface

Balloon & Stent

Frictionless contact

Artery & Plaque

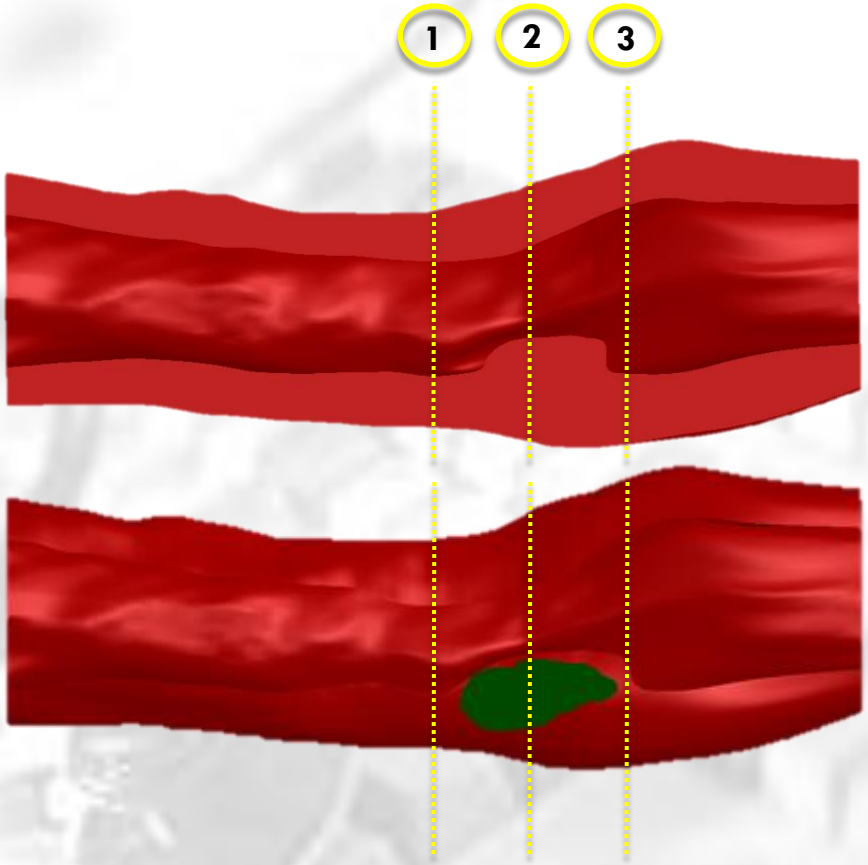
Bonded
Only for the Second model

Stent modeling

Three different cross sections along longitudinal axis

1. *before,*
2. *in,*
3. *after*

the stenotic region.



Stent modeling

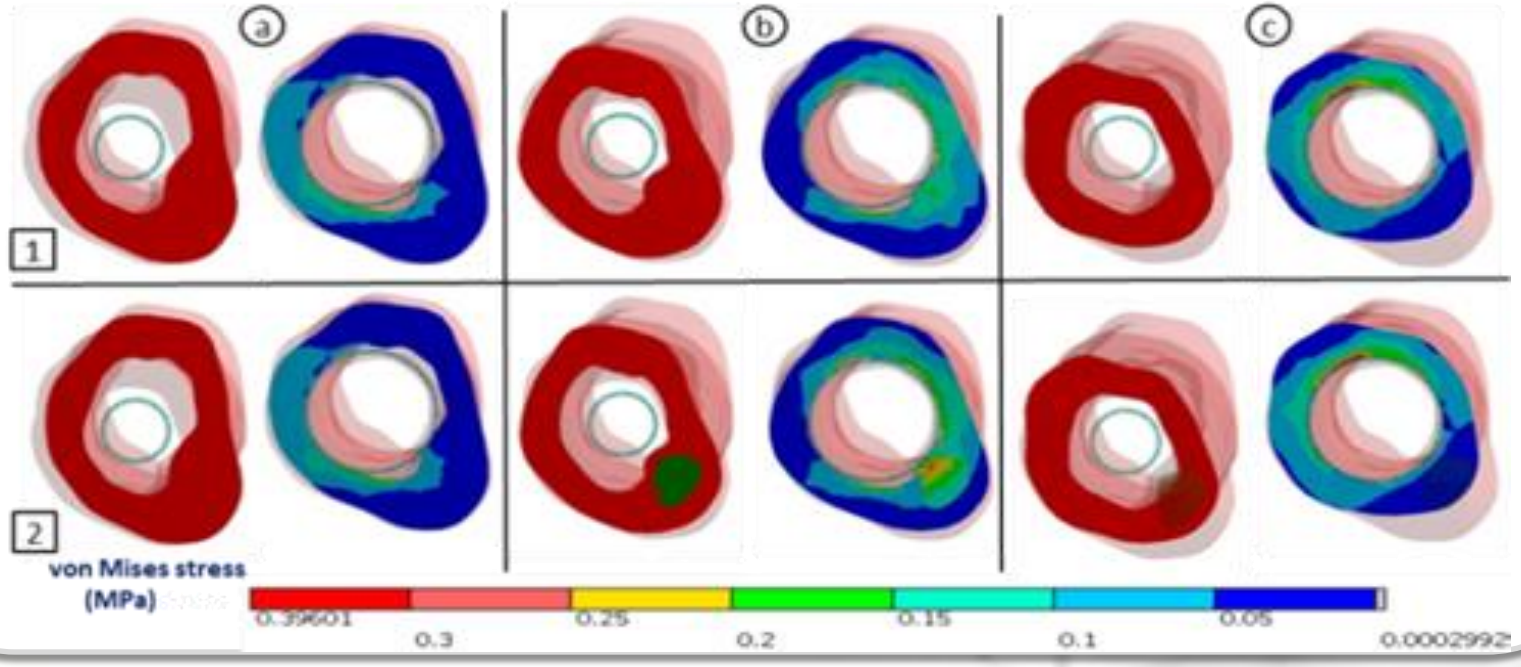
In both cases

Arterial wall stresses caused have a descending ratio when going from the artery's lumen interface to the outer wall surface.

Difference

Higher arterial wall stresses in the second model compared to the first one

- ❑ region of stenosis



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Stent modeling

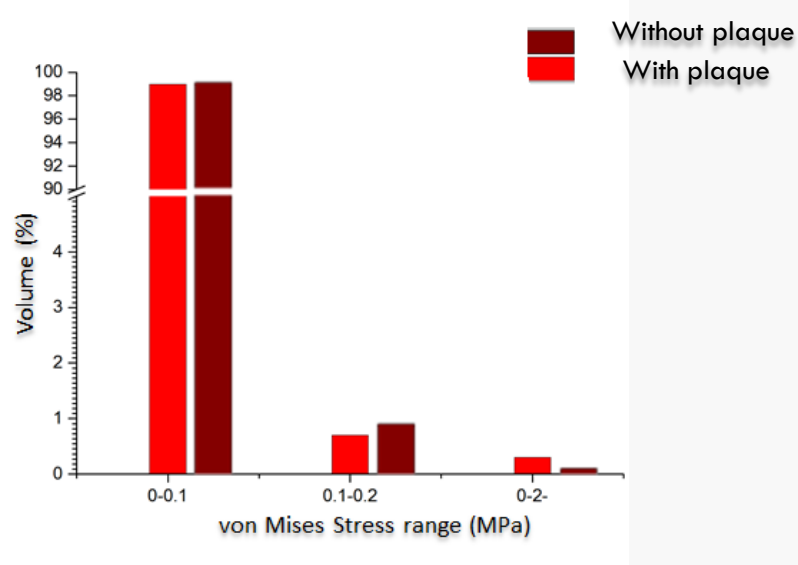
Similarity

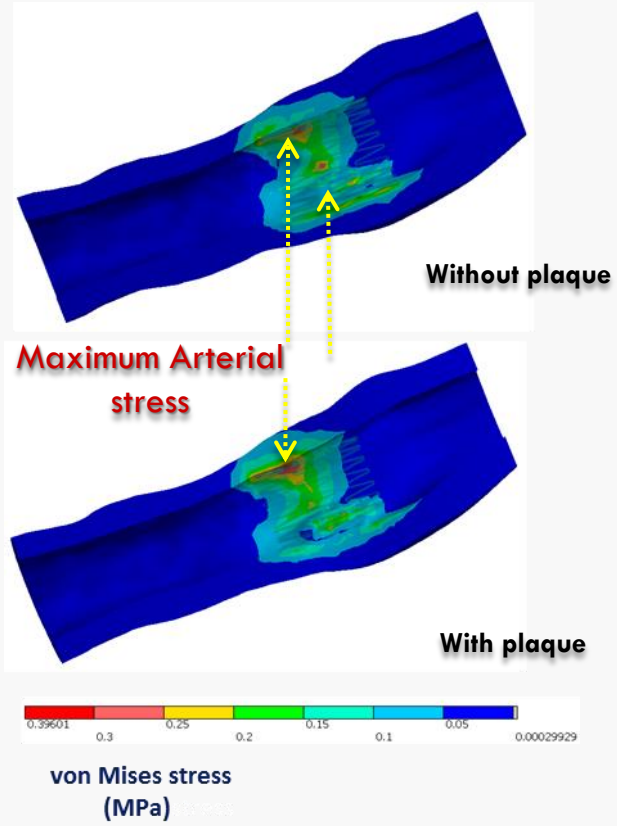
- Arterial wall stresses are high in the contact area of stent-arterial wall
- Percentage volume in specific stress range is the same

Difference

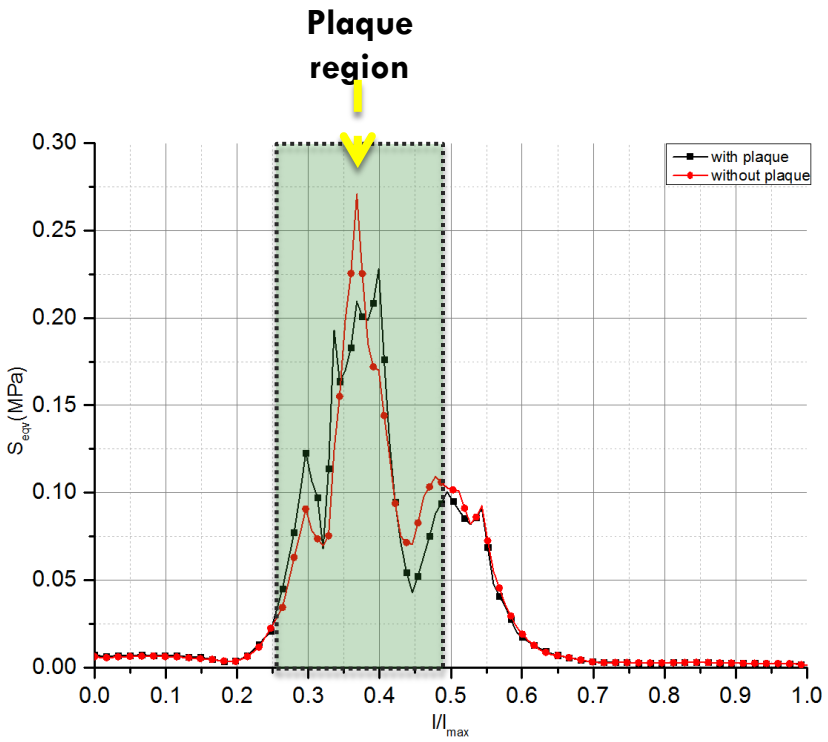
Maximum arterial stress

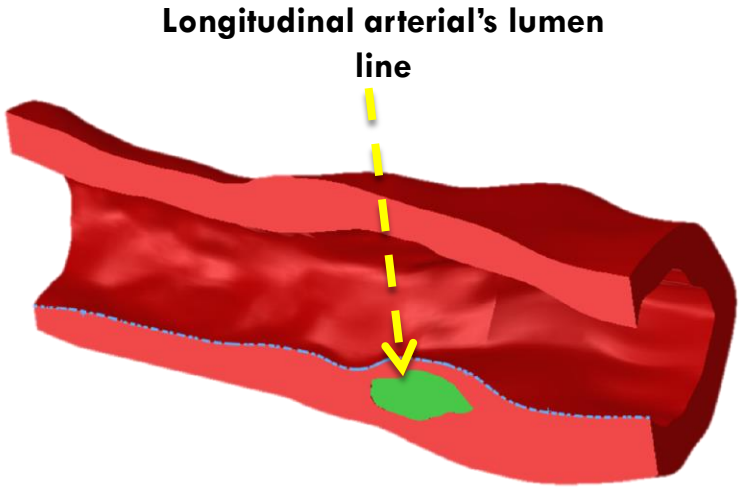
- first model, in two different regions
- second model, concentrated in one region





Stent modeling





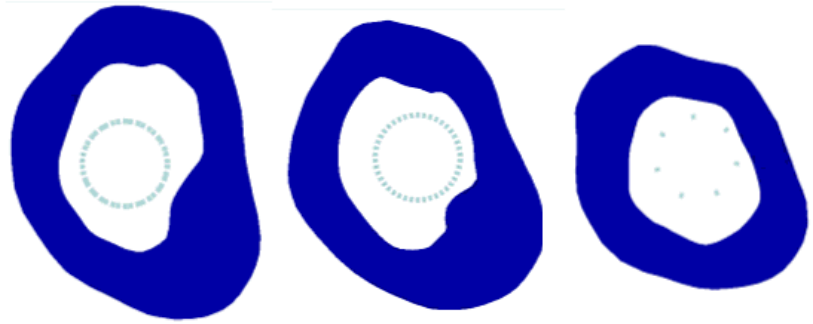
Plaque affects the induced arterial stresses

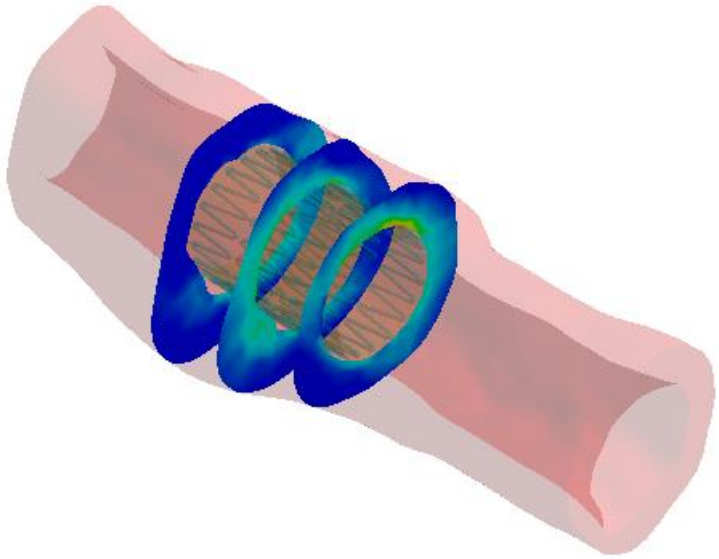
- Higher arterial stresses in the first model for this path

Stent modeling

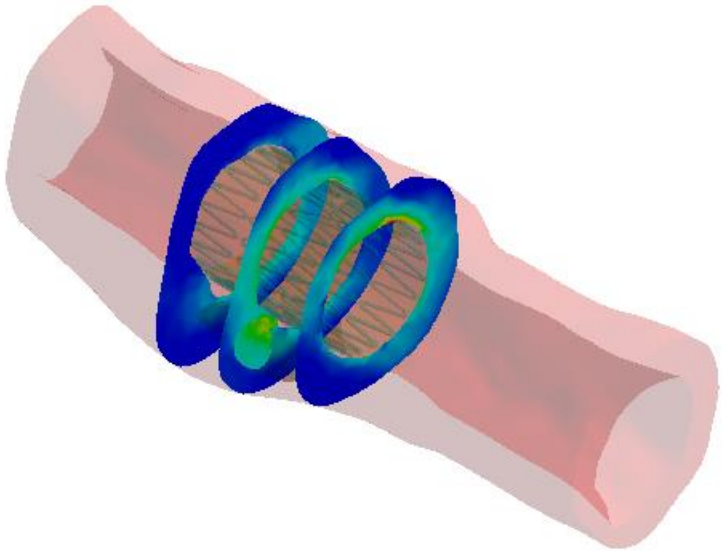
Von Mises arterial stress

Without plaque



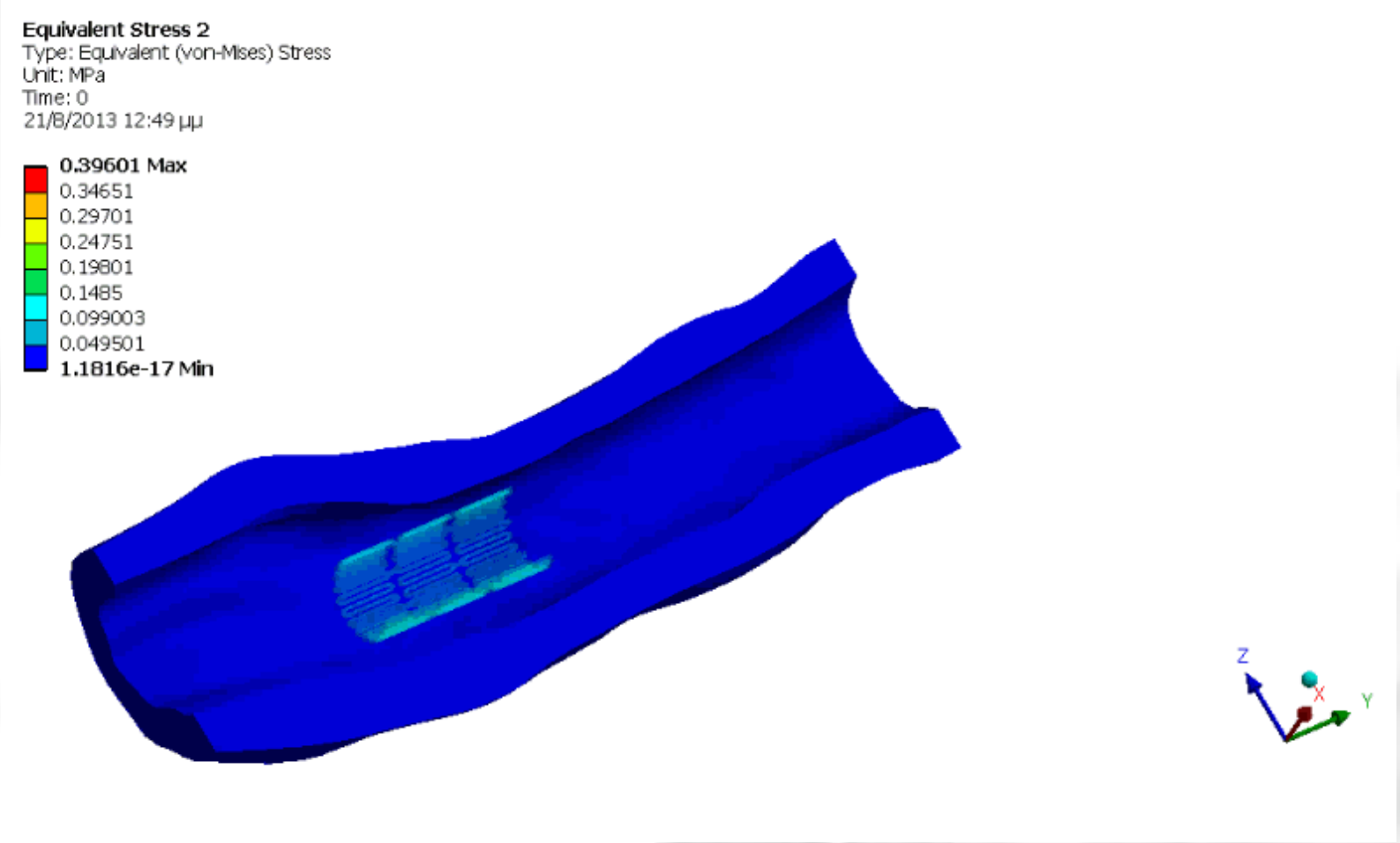


With plaque



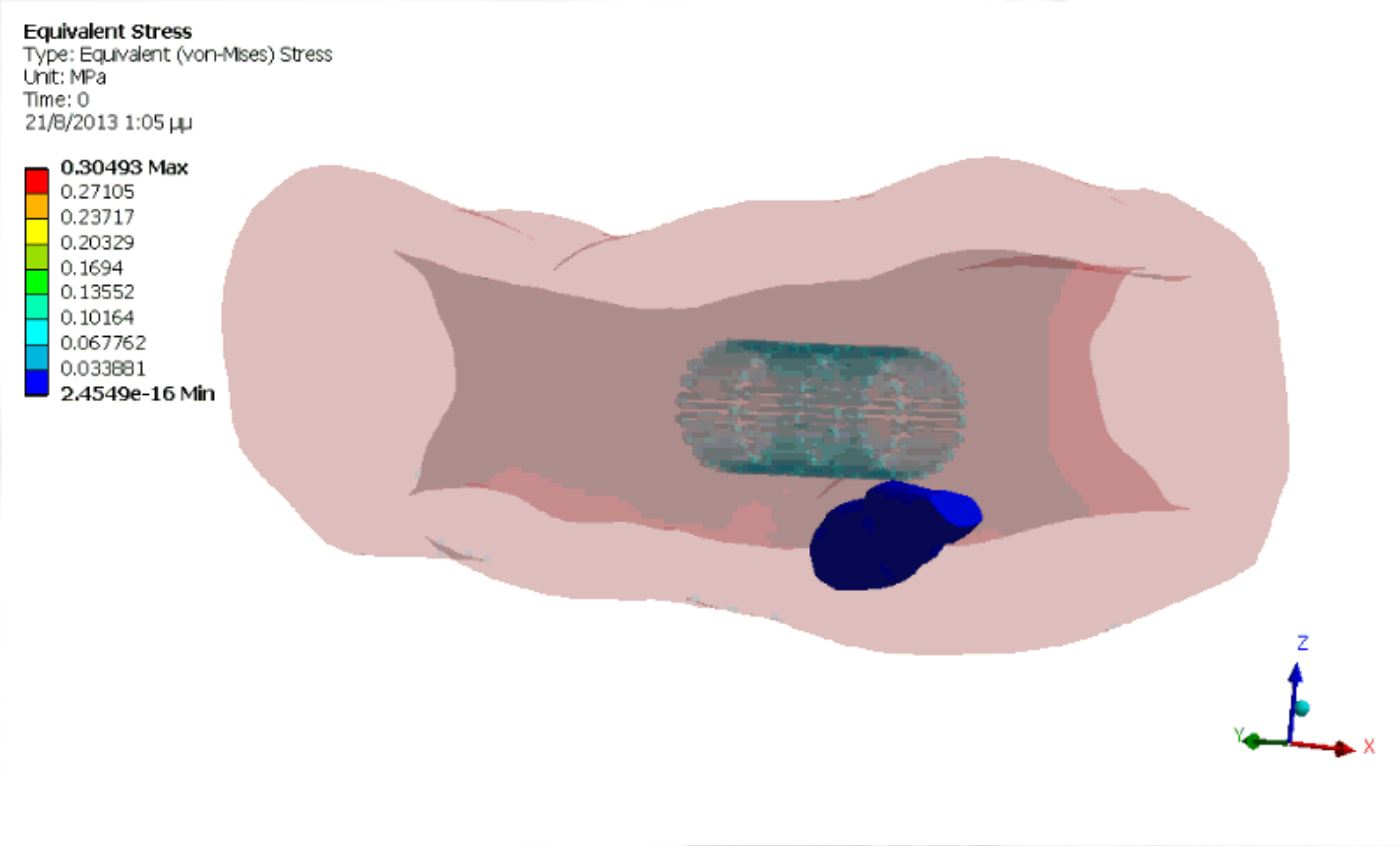
Stent modeling

Von Mises arterial stress

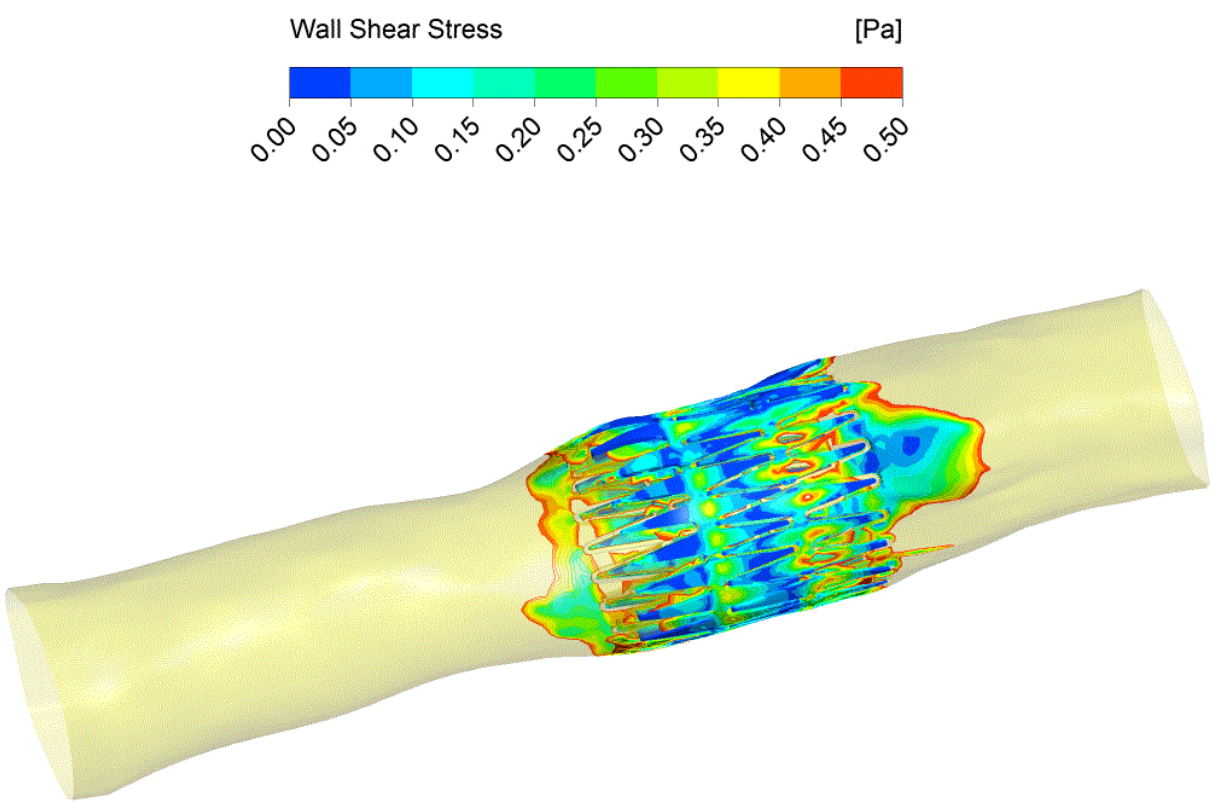


Stent modeling

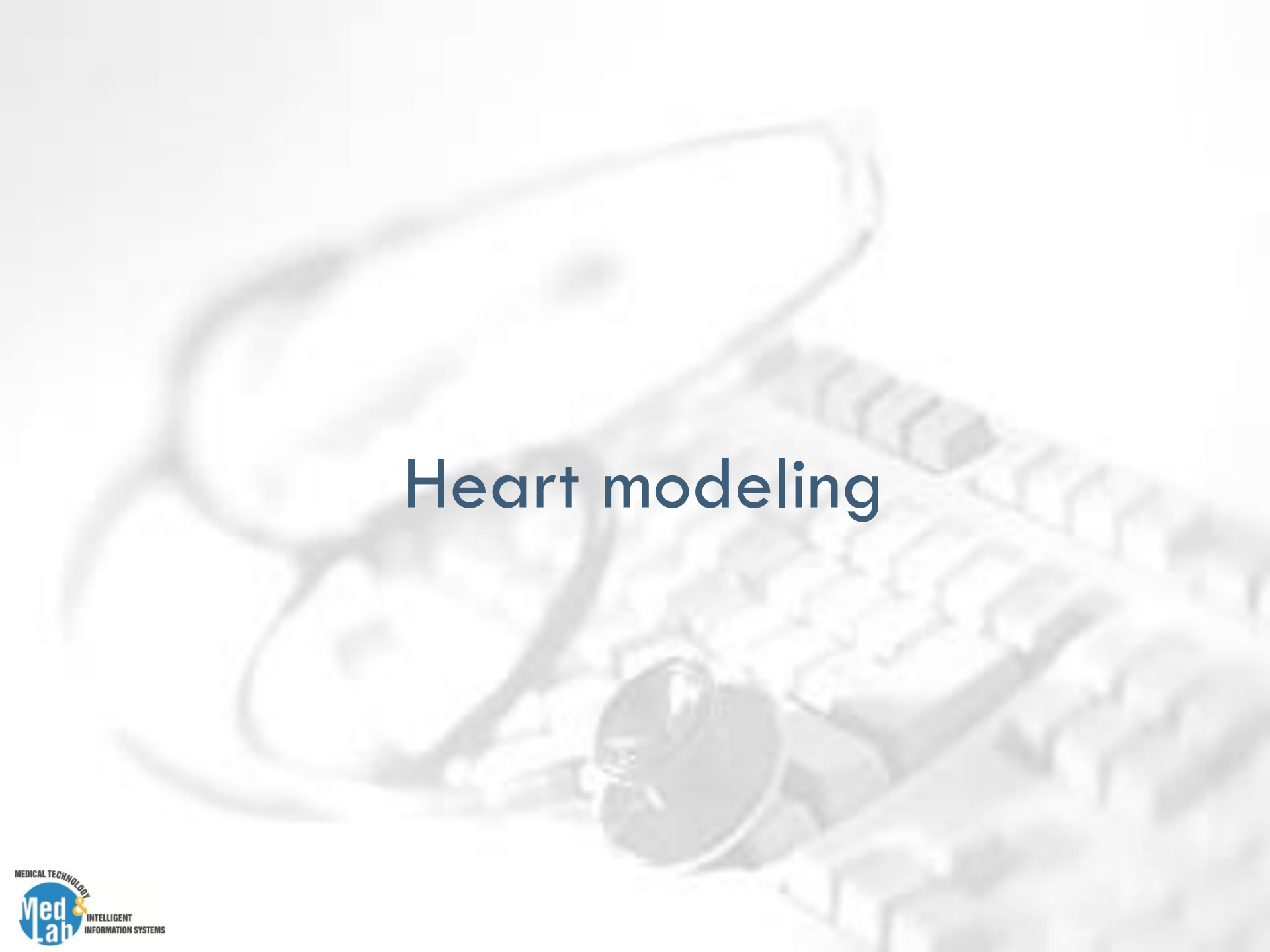
Von Mises plaque stress



Stent modeling

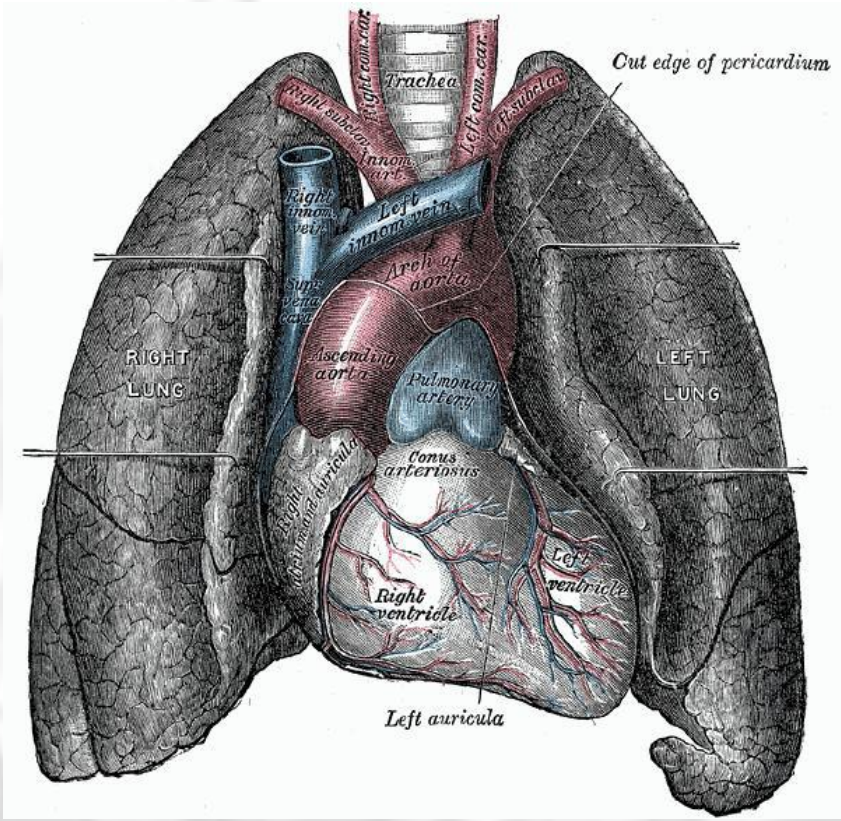


Heart modeling



Heart

- The heart is the central organ of circulation. It is a muscular organ that receives blood from the veins and pushes the arteries.
- The heart is located within the thoracic cavity between both lungs.
- It is surrounded by a film of two sheets, the pericardium, while the interior of the cavities is covered by a thin membrane, the endocardium.
- Among the pericardium and endocardium is the thicker wall of the heart called myocardium and consists of strong muscle fibers.

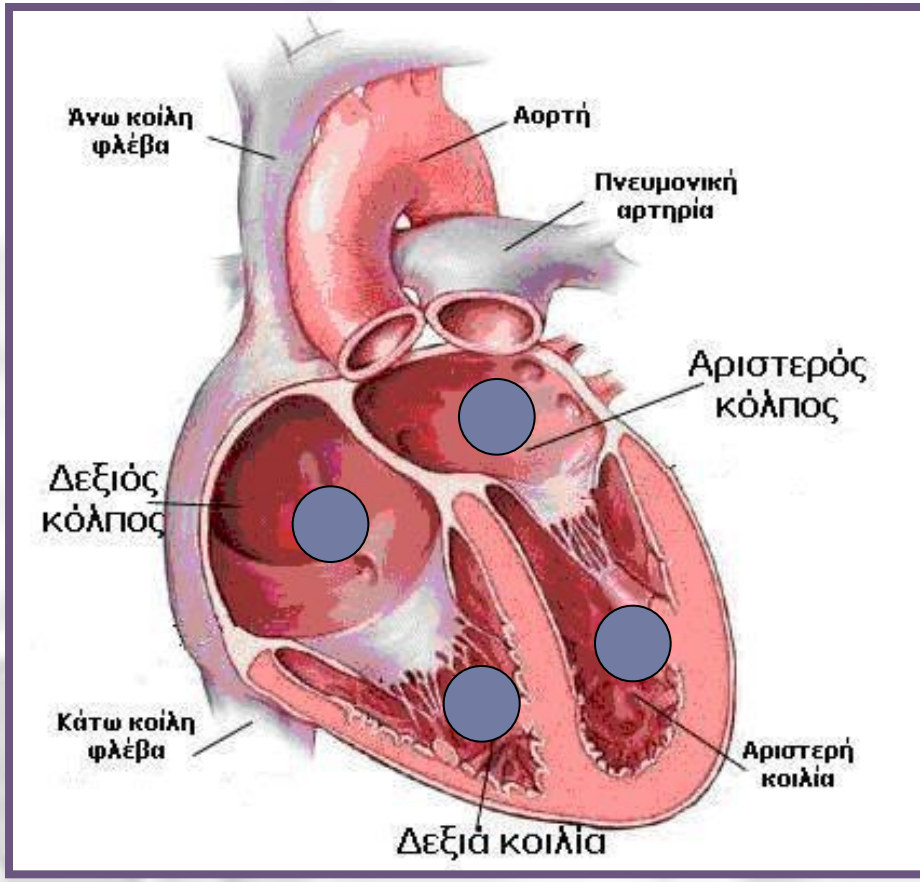


Heart anatomy[1]

[1] H. Gray and W. H. Lewis, *Anatomy of the human body, Lea & Febiger, Philadelphia,* 20 edition, http://www.bartleby.com/107/ 1918.

Heart

The heart has four separate compartments or **chambers**.
The upper chamber on each side of the heart, which is called an **atrium**, receives and collects the blood coming to the heart. T
he atrium then delivers blood to the powerful lower chamber, called a **ventricle**, which pumps blood away from the heart through powerful, rhythmic contractions.
The human heart is actually two pumps in one. The right side receives oxygen-poor blood from the various regions of the body and delivers it to the lungs. In the lungs, oxygen is absorbed in the blood. The left side of the heart receives the oxygen-rich blood from the lungs and delivers it to the rest of the body.



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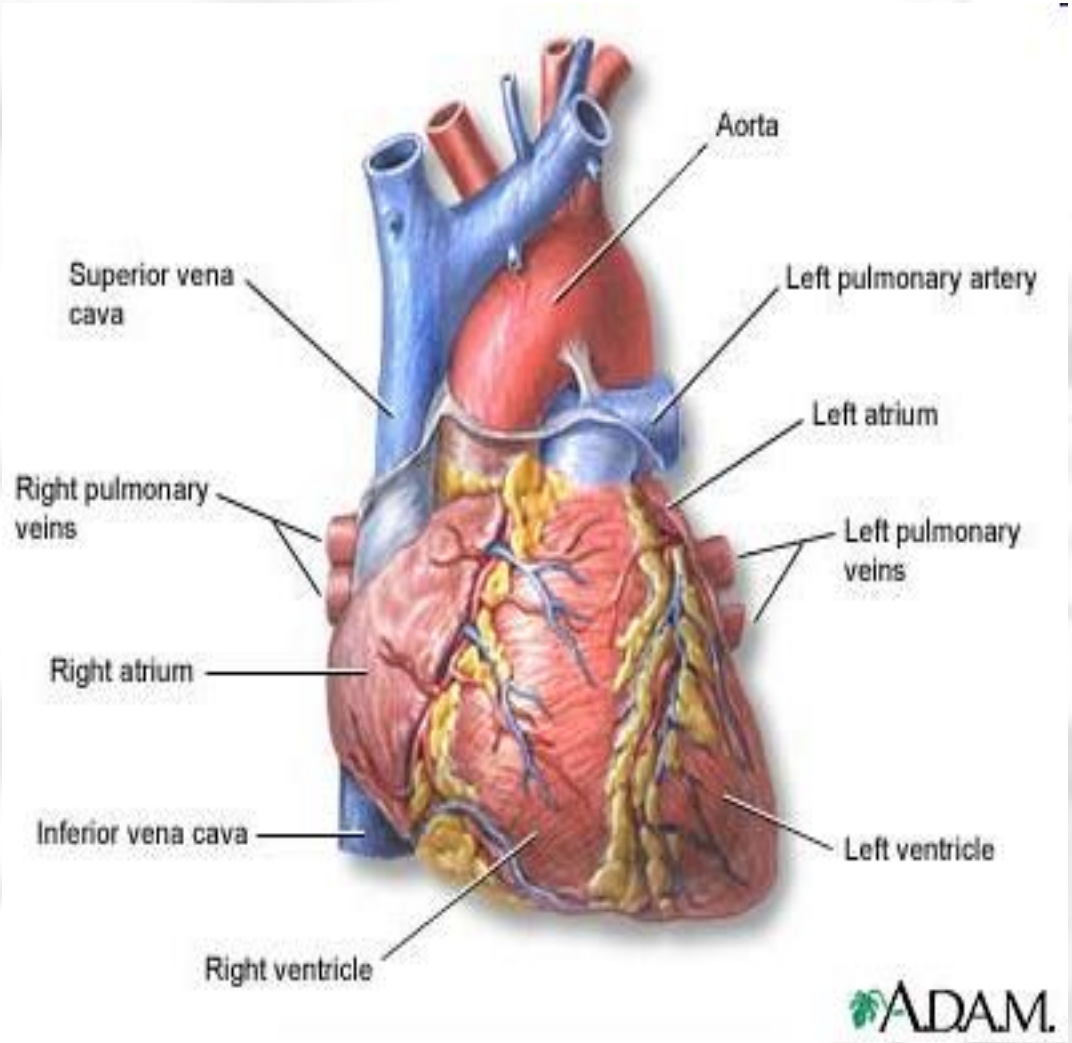
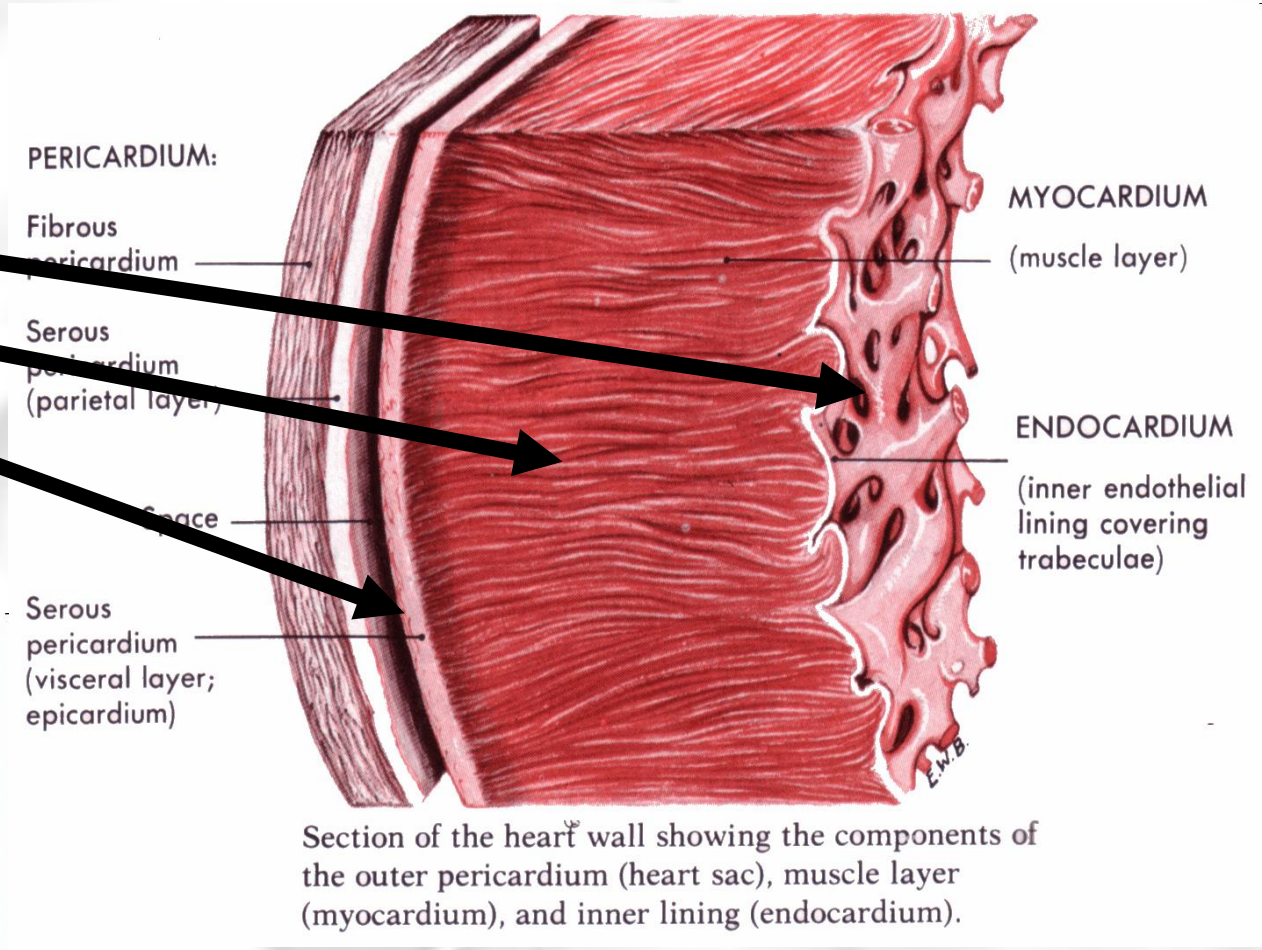
Heart



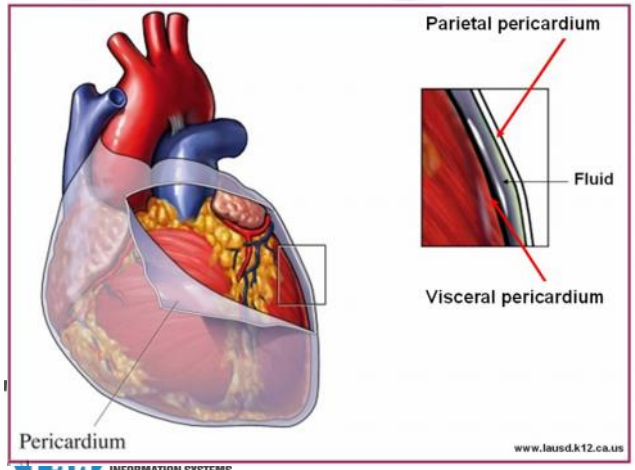
1 Adamimages.com: Your online Source of Medical Images. http://www.adamimages.com/

The heart's wall

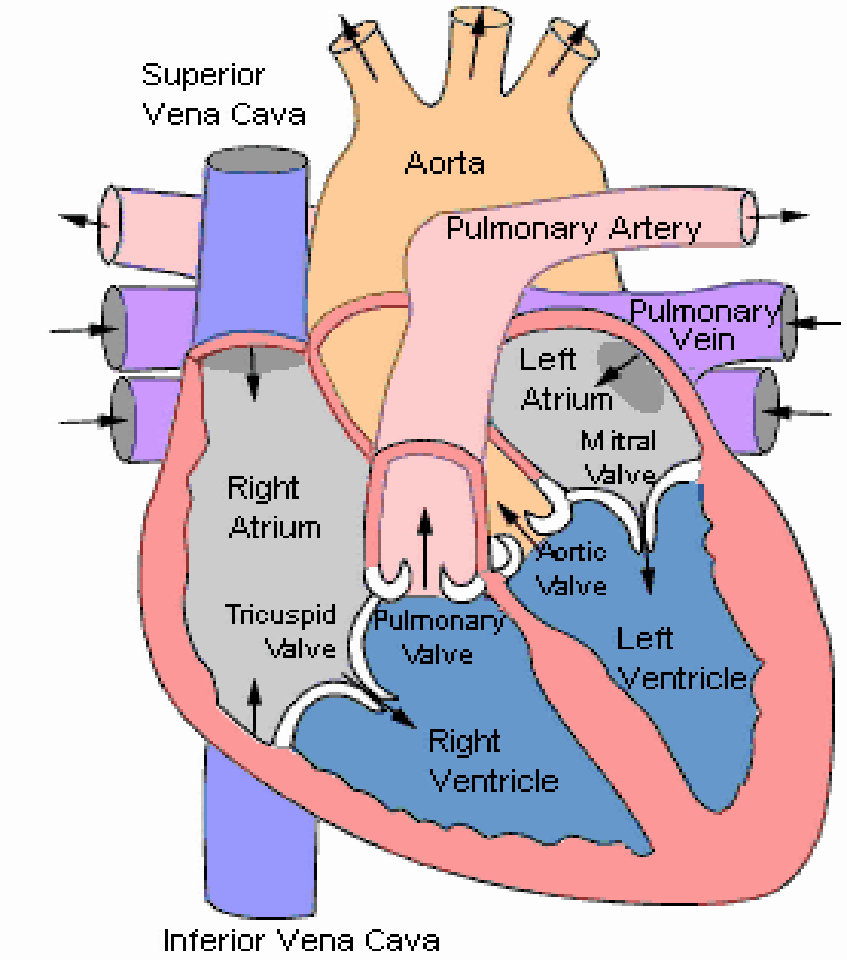
- Heart wall consists of:
  - Endocardium
  - Myocardium
  - Pericardium



Section of the heart wall showing the components of the outer pericardium (heart sac), muscle layer (myocardium), and inner lining (endocardium).



The main circulatory system of the heart

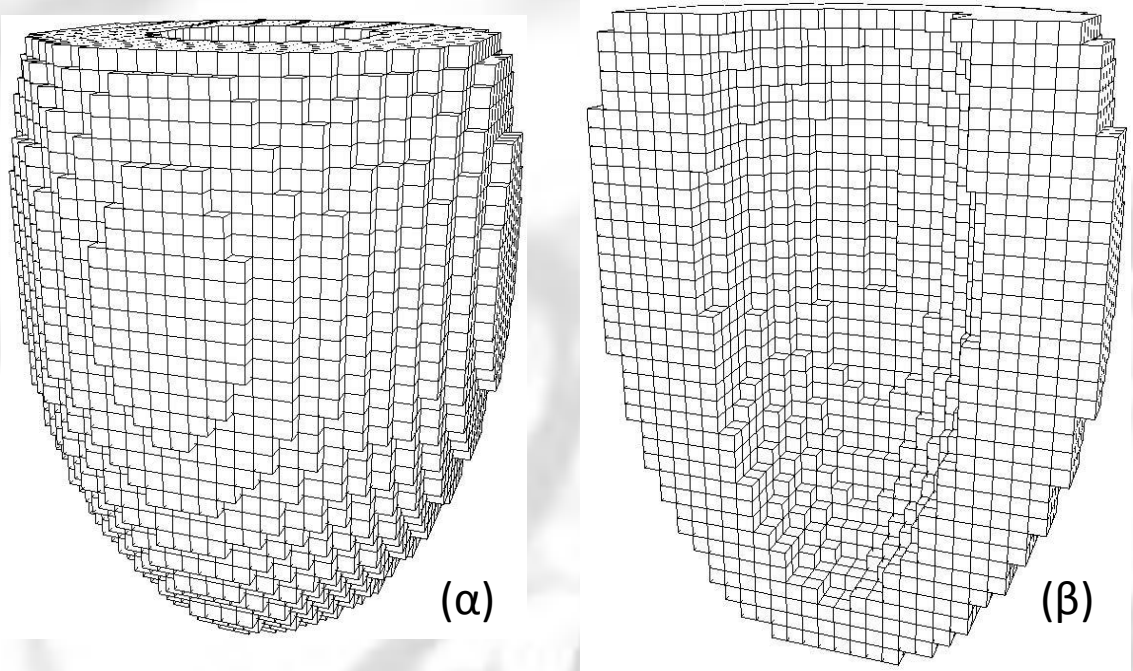


Modeling heart anatomy

- In recent years modeling of the anatomy of the heart is achieved based on medical images.
- Mainly ultrasound, magnetic resonance imaging and computed tomography are used for visualization of the heart
- Pre-processing of images with image processing techniques produce the model of the anatomy.
- The quality depends on the type of processing and the number of elements that represent the model.

Modeling heart anatomy

- Analytical left ventricular model



A model of left ventricular anatomy cut through two confocal truncated ellipsoids. The (a) the full and (b) the split model. The model consists of 30 x 30 x 38 cubic elements[1]

[1] Frank B. Sachse, Computational Cardiology: Modeling of Anatomy, Electrophysiology, and Mechanics. 2004, Springer-Verlag Berlin Heidelberg NewYork, Germany

Modeling heart anatomy

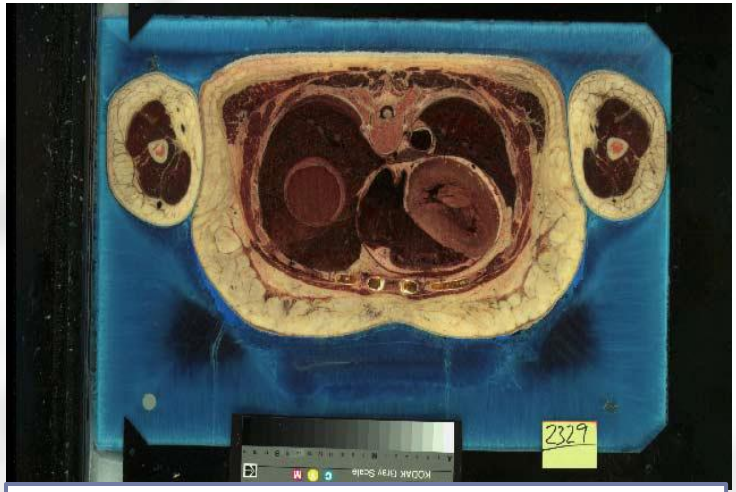
Modeling orientation of cardiac myocytes

- The method is based on using measurement characteristics of histological observations and imaging (diffusion weighted magnetic resonance tomography - enables measurement of orientation)
- It can be based on rules that were derived from anatomical studies. Originally a specialist indicates the orientation, and then algorithms based on existing information identifying the orientation in other areas

Modeling heart anatomy

Models from Visible Human Project[1]

- Corpses of a man and woman, 38 years and 59 years, respectively, are used for three-dimensional reconstruction
- A 3D data set is generated after pre-processing of 2D images
- Combination of CT images and frozen images with image processing methods produces four data sets corresponding to red, green and blue range of the frozen image in Hounsfield values of CT
- The 3D set is classified in different types of tissues



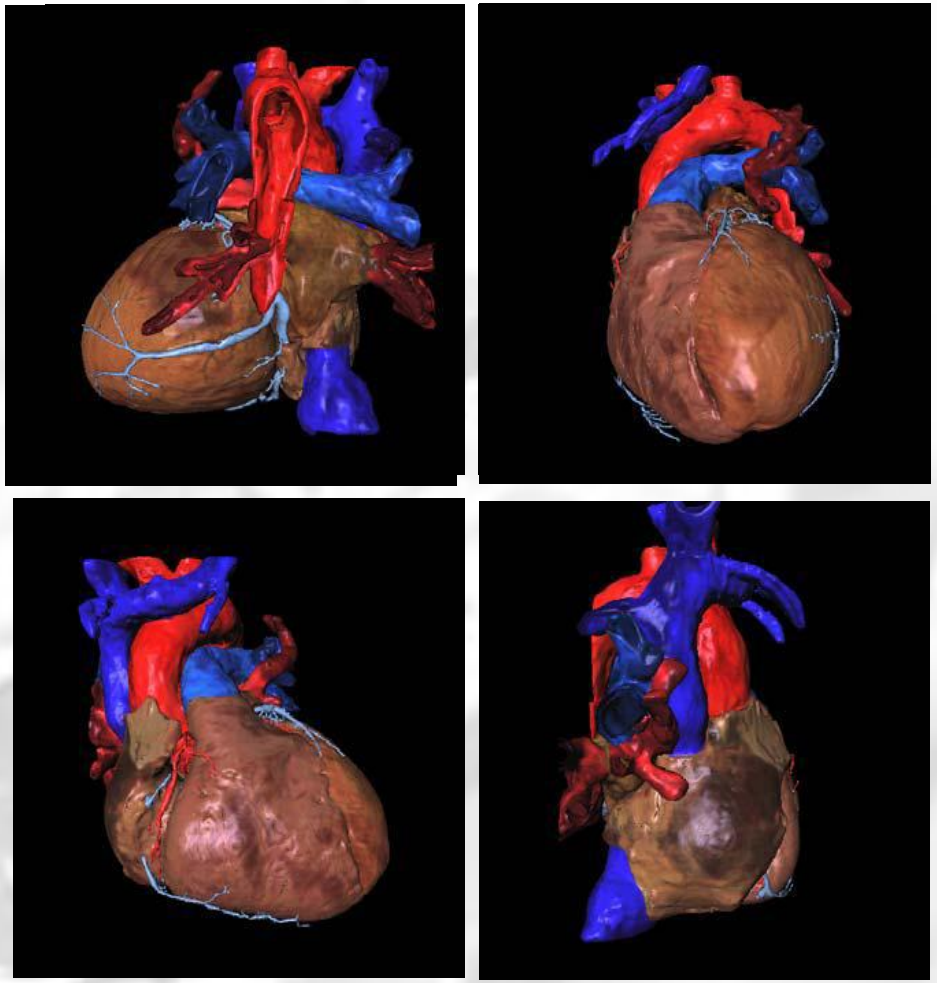
Vertical plane at the region of the heart

[1] M. J. Ackerman, "Viewpoint: The Visible Human Project," J. Biocommunication, vol. 18, no. 2, pp. 14, 1991.

Modeling heart anatomy

Tissue classification

- Interactively deformable meshes, thresholding, region growing, and morphological operators are the main techniques for tissue classification[1]
- The ventricles, the atria and aorta are reconstructed using 2D splines
- Region growing techniques are used for vessel reconstruction

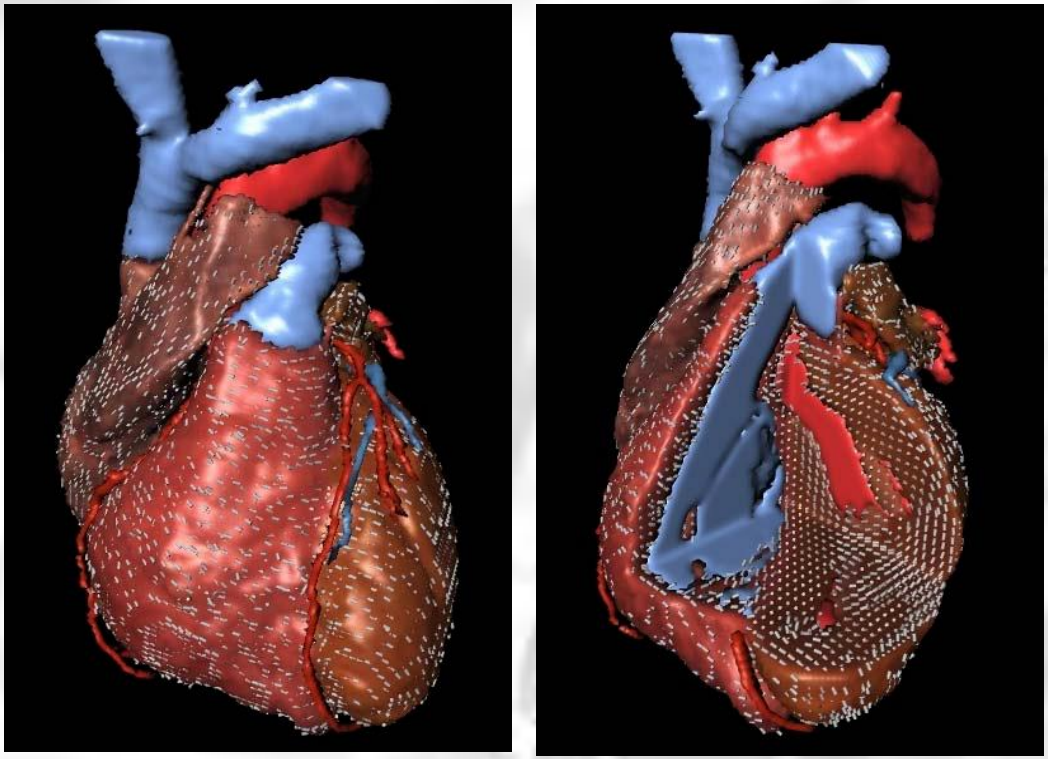


Model of human heart

[1] C. D. Werner, Simulation der elektrischen Erregungsausbreitung in anatomischen Herzmodellen mit adaptiven zellul¨aren Automaten, Ph.D. thesis, Universit¨at Karlsruhe (TH), Institut f¨ur Biomedizinische Technik, Berlin, 2001.

Modeling heart anatomy

Modeling orientation of cardiac myocytes[1]

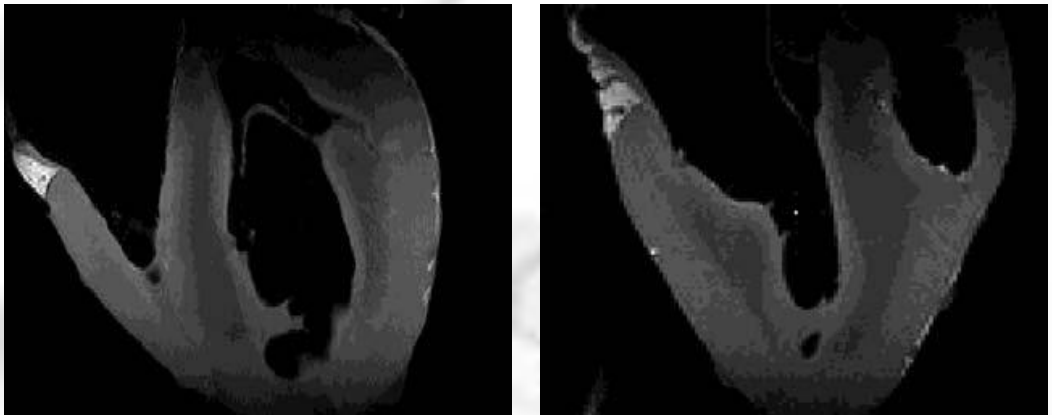


[1]F. B. Sachse, M. Wolf, C. D. Werner, and K. Meyer-Waarden, “Extension of anatomical models of the human body: Three dimensional interpolation of muscle fiber orientation based on restrictions,” Journal of Computing and Information Technology, vol. 6, no. 1, pp. 95–101, 1998.
[2]R. Schulte, F. B. Sachse, C. D. Werner, and O. Dossel, “Rule based assignment of myocardial sheet orientation,” in Biomedizinische Technik, 2000, Vol. 45-2, pp. 97–102.

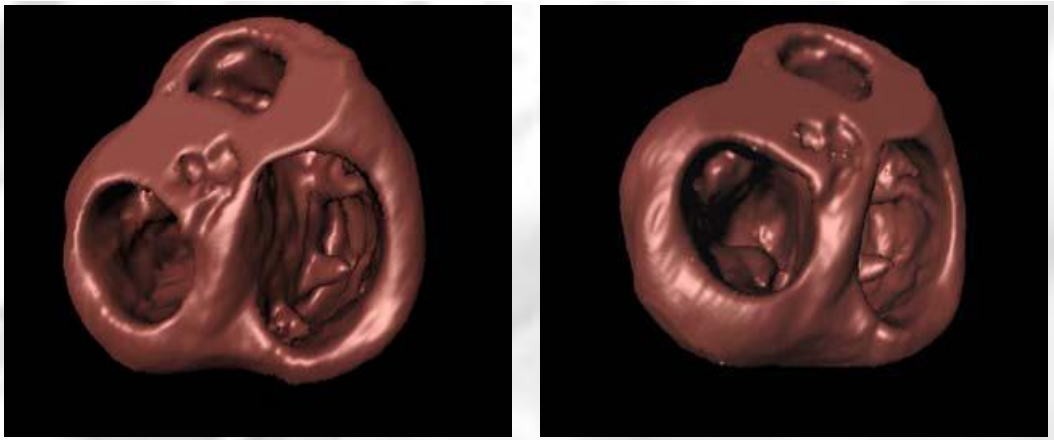
Modeling heart anatomy

3D reconstruction of the heart

- MRI images are used for the reconstruction
- interactively deformable meshes, thresholding, region growing, and morphological operators are utilized for the segmentation



MRI images from dog's heart

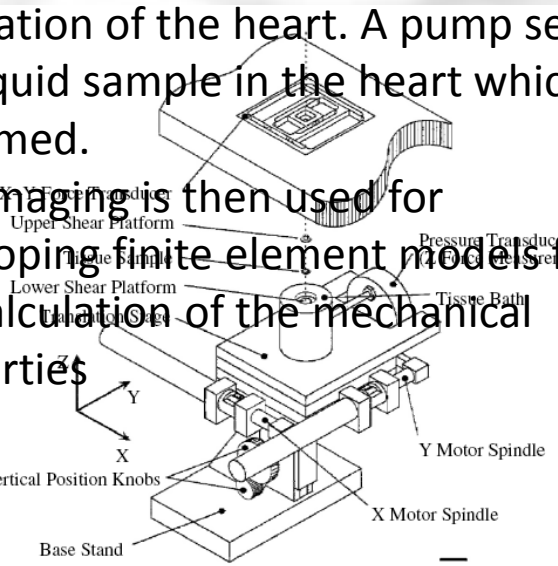


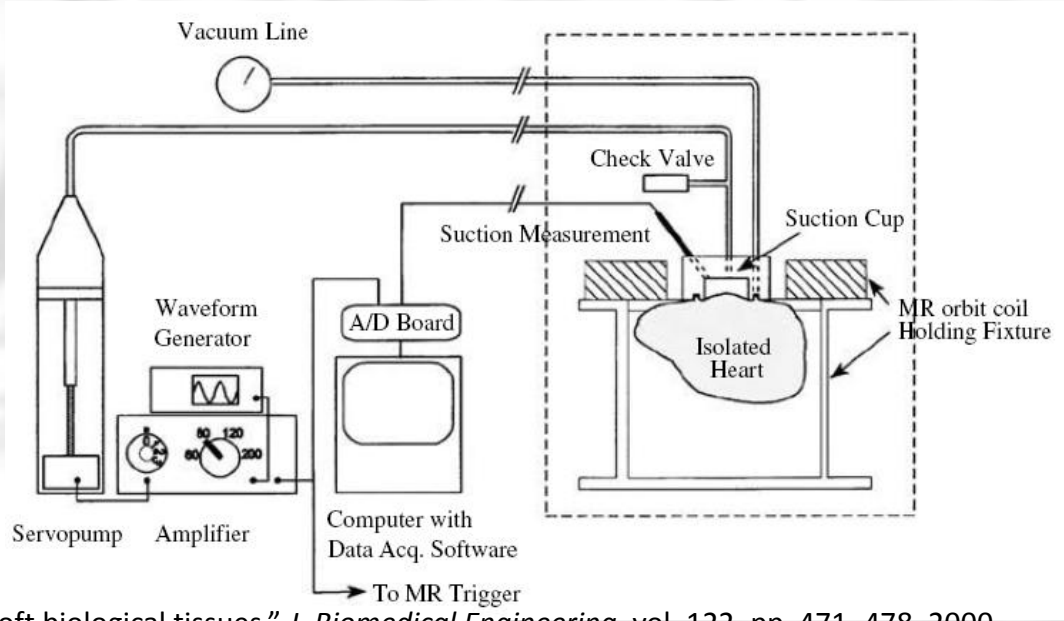
[1]P. Zerfass, F. B. Sachse, C. D. Werner, and O. D¨ossel, "Deformation of surface nets for interactive segmentation of tomographic data," in Biomedizinische Technik, Sep. 2000, vol. 45-1, pp. 483–484.

Heart mechanics

- The first data on the mechanical properties of the heart came from laboratory experiments
- Various provisions are designed for this purpose
- The mechanical properties were found to be non-linear, anisotropic and viscoelastic
- The finite element method is mainly used for modeling the mechanical heart

Simulation of the heart. A pump sends the liquid sample in the heart which is deformed.
MRI imaging is then used for developing finite element models for the calculation of the mechanical properties

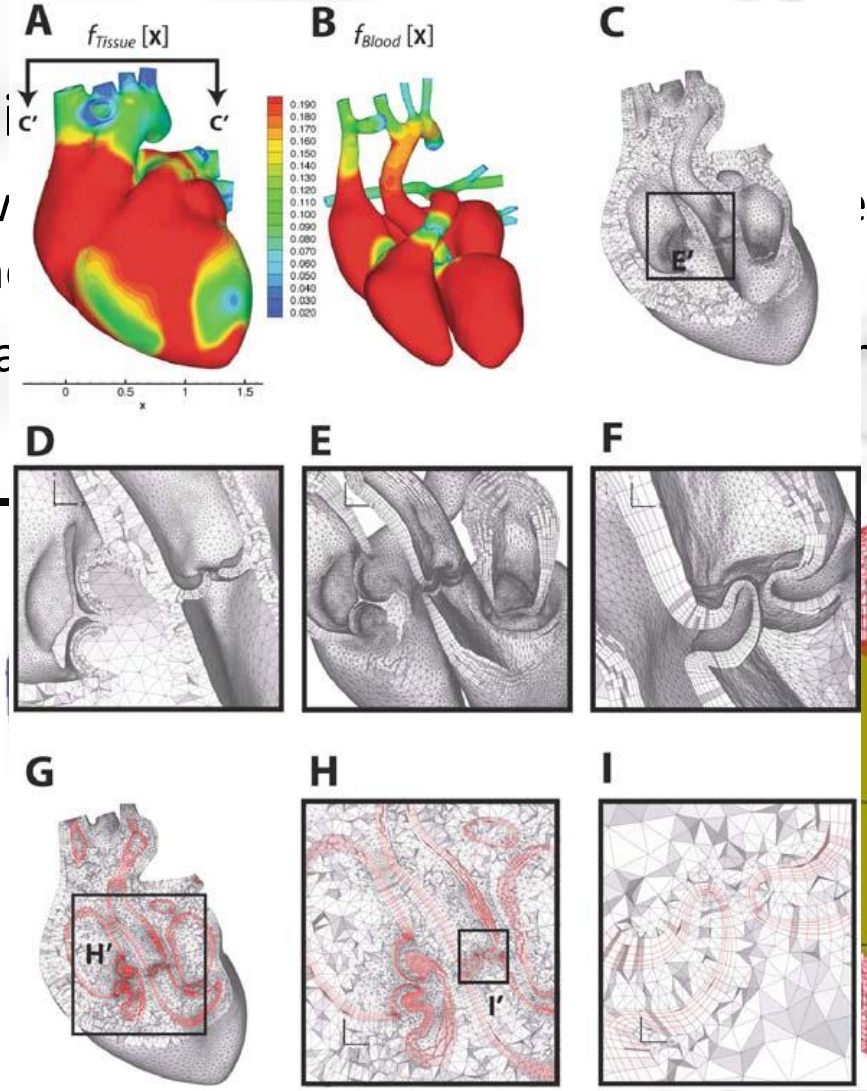


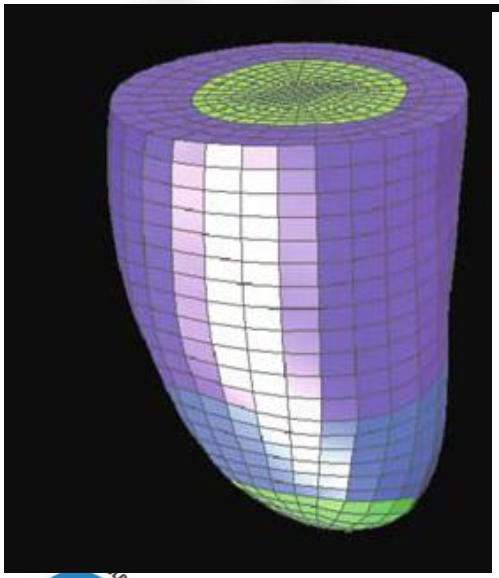


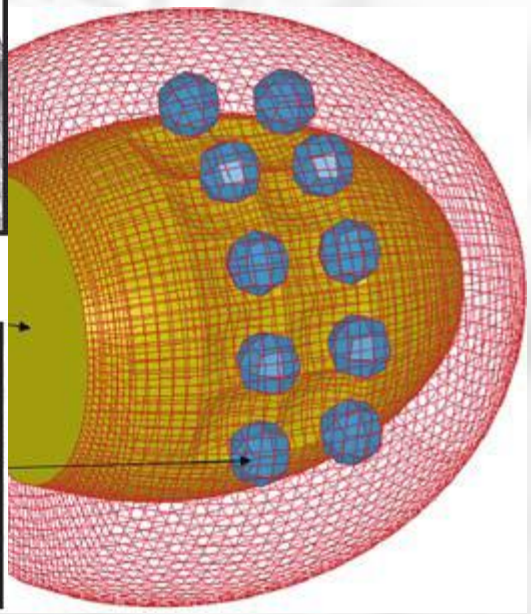
[1]S. Dokos et al, "A triaxialmeasurement shear-test device for soft biological tissues," *J. Biomedical Engineering,* vol. 122, pp. 471–478, 2000.
[2]R. J. Okamoto et al "Epicardial suction: A new approach to mechanical testing of the passive ventricular wall," *J. Biom. Eng, 122, 479–487,* 2000.

Heart mechanics

- Modeling usi
  - Initially it w ecause of non-linearity an
  - The first ma neration







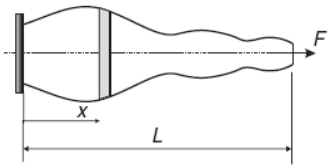
[1] Dyedov V, Einstein DR, Jiao X, Kuprat AP, Carson JP, del Pin F. Variational generation of prismatic boundary-layer meshes for biomedical computing. *Int J Numer Methods Eng. 2009*

Heart mechanics

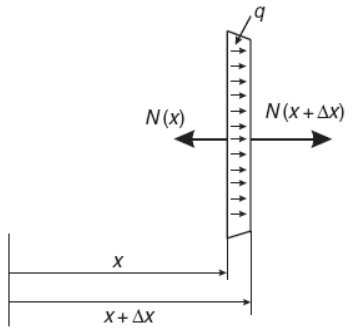
Elasticity equations

For a fixed load the produced force is given by:

$$N(x) = N(x + \Delta x) + q\Delta x.$$



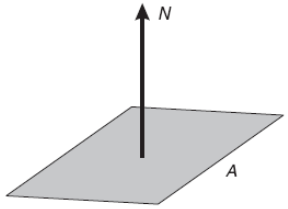
(a) Representation of a bar



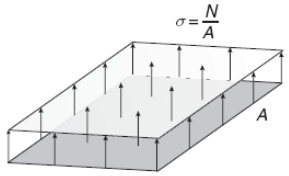
(b) Free body diagram of a slice at position x

The stress at the area is:

$$\sigma = \lim_{\Delta A \to 0} \frac{\Delta N}{\Delta A}.$$



(a) Force acting on a surface having area A



(b) Stress σ if N is homogeneously distributed over the area A

The linear deformation related to the displacement is given by:

$$\varepsilon = \frac{du}{dx}.$$

The relation of stress – defomration is:

$$\sigma = E\varepsilon, \quad \Rightarrow \quad \sigma = E\frac{du}{dx}.$$

Where E is the Young's Modulus

Heart mechanics

The main equations used for heart modeling

- The function distortion-energy is used:

$$W = 0.5\alpha_{ijkl}E_{ij}E_{kl} + (\beta_0 + \beta_{mnpq}E_{mn}E_{pq}) \exp(\gamma_{ij}E_{ij} + \kappa_{mnpq}E_{mn}E_{pq} + \cdots)$$

  - The parameters α_{ijkl}, β_0, β_{mnpq}, γ_{ij}, and κ_{mnpq} are calculated experimentally and E_{ij} is the 3D Green deformation tensor

- The parameters are calculated using a cylindrical model. The final equations has the form:

$$W = 0.5C \exp[b_f E_{11}E_{11} + b_t(E_{22}E_{22} + E_{33}E_{33} + E_{23}E_{23} + E_{32}E_{32}) + b_{fs}(E_{12}E_{12} + E_{21}E_{21} + E_{13}E_{13} + E_{31}E_{31})]$$

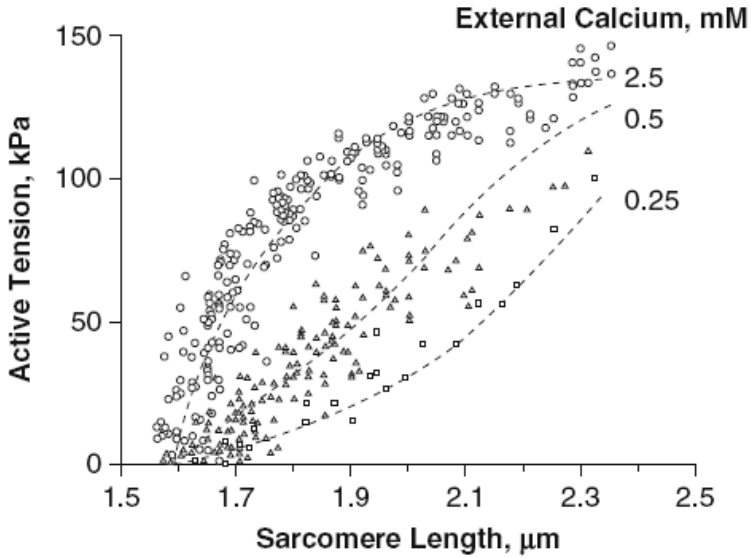
  - C, b_f, b_t, and b_{fs} are constants, 1 means the direction of the muscle fibers, the 2 direction of crossed fibers, the 3 the radial - transmural direction.

$C = 0.88$ kPa, $b_f = 18.5$, $b_t = 3.56$, και $b_{fs} = 1.63$.

Heart mechanics

Modeling of myocardial move

- we need to calculate the overall tension of the myocardium as the sum of:
  - Passive 3D myocardial stress and
  - Active stress that is a function of the length of the sarcomere, calcium and time

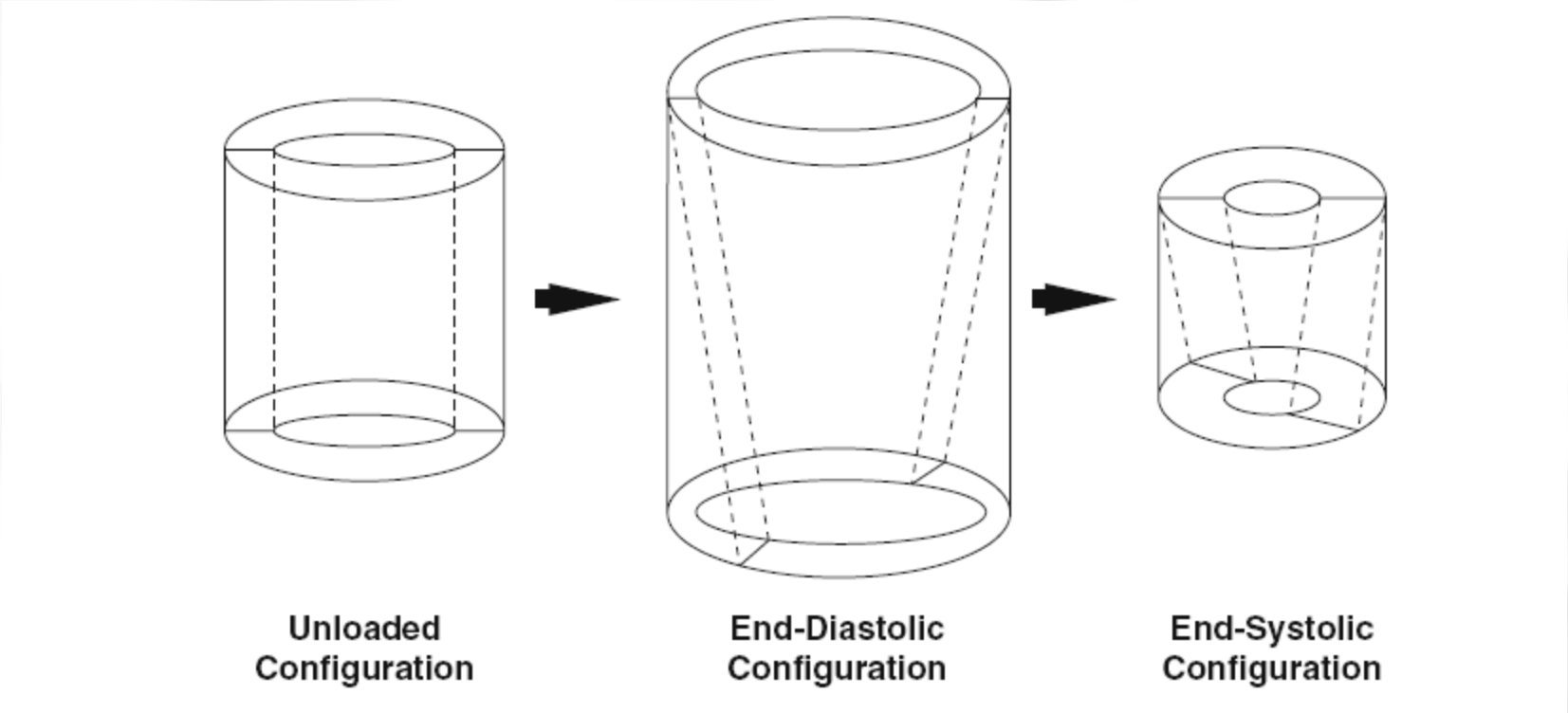


Effect of outer calcium[1]

Guccione JM, McCulloch AD. Mechanics of active contraction in cardiac muscle: Part I – Constitutive relations for fiber stress that describe deactivation. *J Biomech Eng. 1993;115:*72–81.

Heart mechanics

Modeling of myocardial movement simulated using a cylinder



[1] Guccione JM, Waldman LK, McCulloch AD. Mechanics of active contraction in cardiac muscle: Part II – Cylindrical models of the systolic left ventricle. J Biomech Eng. 1993;115:82–90.

Heart mechanics

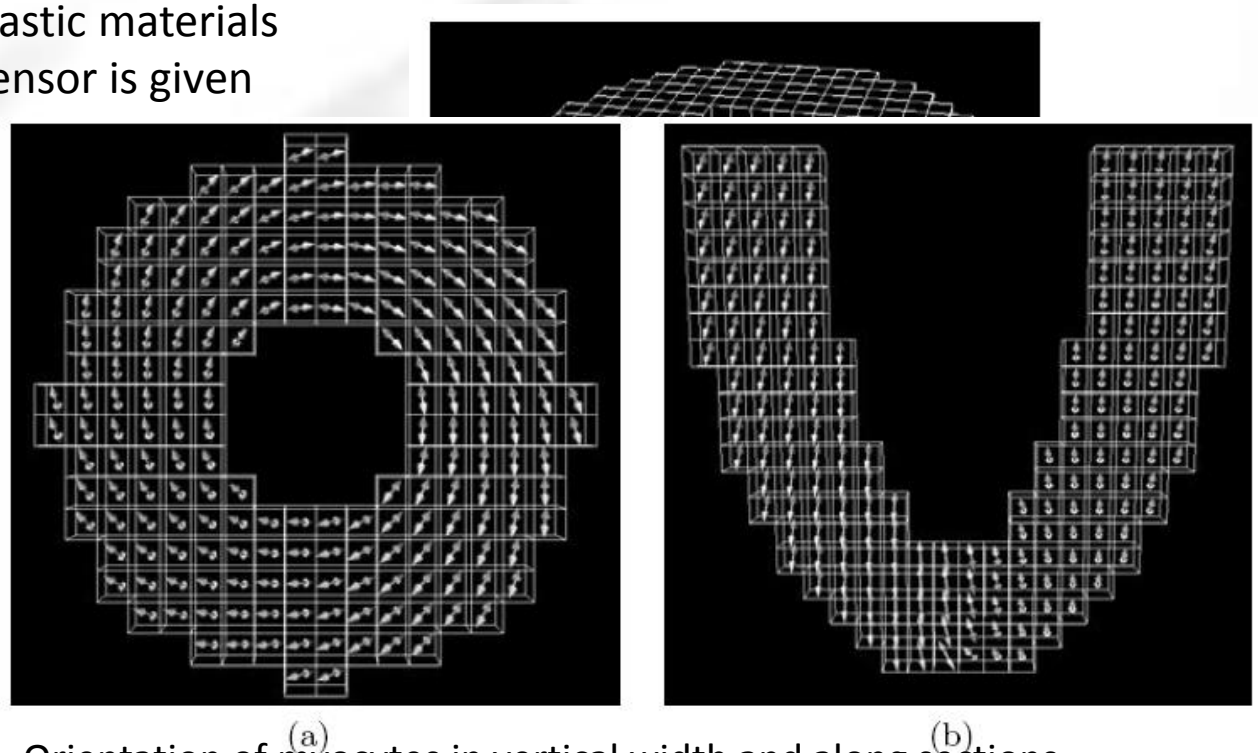
Coupling passive mechanics and strength development

For uncompressed, hyperelastic materials
The Piola-Kirchhoff stress tensor is given by:

$$S_{ij} = \frac{\partial W}{\partial E_{ij}} - p\delta_{ij} + S_{ac}$$

W: deformation energy functio
E: deformation tensor Green-L
δ: delta Kronecker
p: hydrostatic pressure

$$S_{local,active} = \begin{pmatrix} s_{fiber,active} \\ 0 \\ 0 \end{pmatrix}$$



Orientation of myocytes in vertical width and along sections

J. M. Guccione, A. D. McCulloch, and L. K.Waldman, "Passive material properties of intact ventricular myocardium determined from a cylindrical model," *J. Biomechanical Engineering, vol. 113, pp. 42–55, Feb. 1991.*

Heart mechanics

- The orientation of muscle is responsible for movement
- The orientation is proportional to the depth at which the myocytes are located
- The deformation is more pronounced outwardly

The orthotropic properties defined by the relationship (Law Guccione):

$$W = \frac{C}{2}\left(e^{Q} - 1\right)$$

$$Q = 2b_1(E_{RR} + E_{FF} + E_{CC}) + b_2 E_{FF}^2 + b_3(E_{CC}^2 + E_{RR}^2 + E_{CR}^2 + E_{RC}^2) + b_4(E_{RF}^2 + E_{FR}^2 + E_{FC}^2 + E_{CF}^2)$$

C and Q depend on the deformation tensor Green-Lagrange ***E***

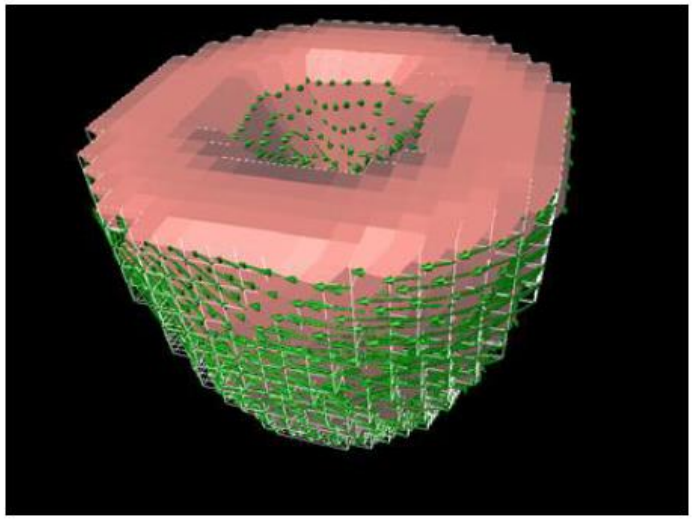
Necessary boundary conditions are defined

The resulting linear system of equations is solved by the conjugate gradient method

Heart mechanics

Ventricle deformation

1. The orientation of endocardial through and epicardial myocytes are -45, -45, -45 degree, respectively
2. The orientation of endocardial through and epicardial myocytes is -45, 0, 45 degrees respectively
3. The orientation of endocardial through and epicardial myocytes are 0, 0 0 degree respectively



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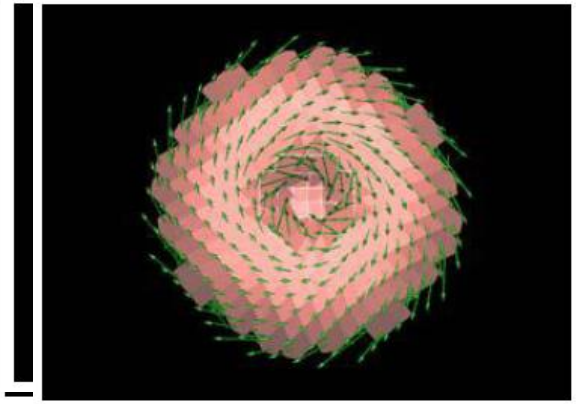
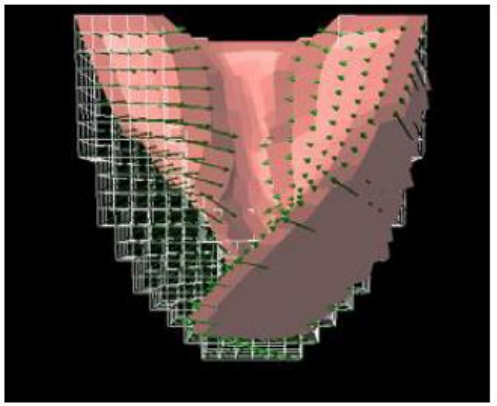


(b)

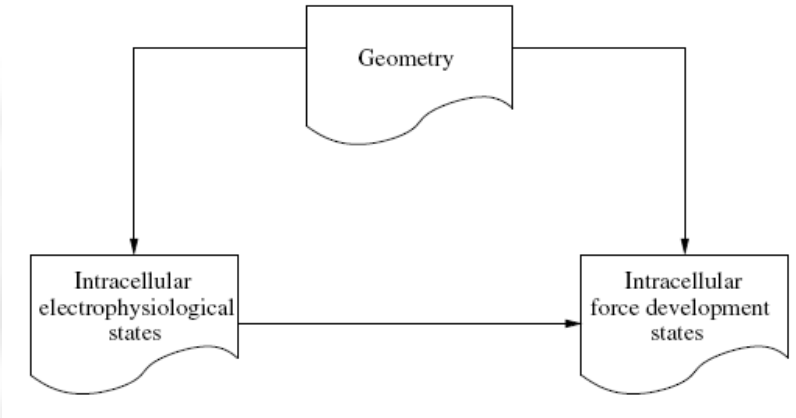


(c)

F. B. Sachse, G. Seemann, M. B. Mohr, and Arun V. Holden, "Mathematical modeling of cardiac electro-mechanics: From protein to organ," *Int. J. Bifurc. Chaos, vol. 13, no. 12, pp. 3747–3755, 2003.*

Electro-mechanics of the heart

- The electromechanical models can be developed at the cellular, macroscopic but also in heart level
- The function of the heart requires continuous adjustment
- This is achieved by interaction of cell electrophysiology, intracellular excitation and cell force development
- Mechano-elektro-physiologic control the adjustment of the heart



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Electro-mechanics of the heart

Electrophysiology and developing power at the cellular level

- Control of the power in the muscle cells is made by the intracellular calcium concentration
- Initially cytoplasmic calcium binds to troponin C, and then it is released again in the cytoplasm
- This interaction has been successfully modeled by several models:

1. Luo-Rudy phase-2
2. Noble-Varghese-Kohl-Noble
3. 3rd Rice-Winslow-Hunter

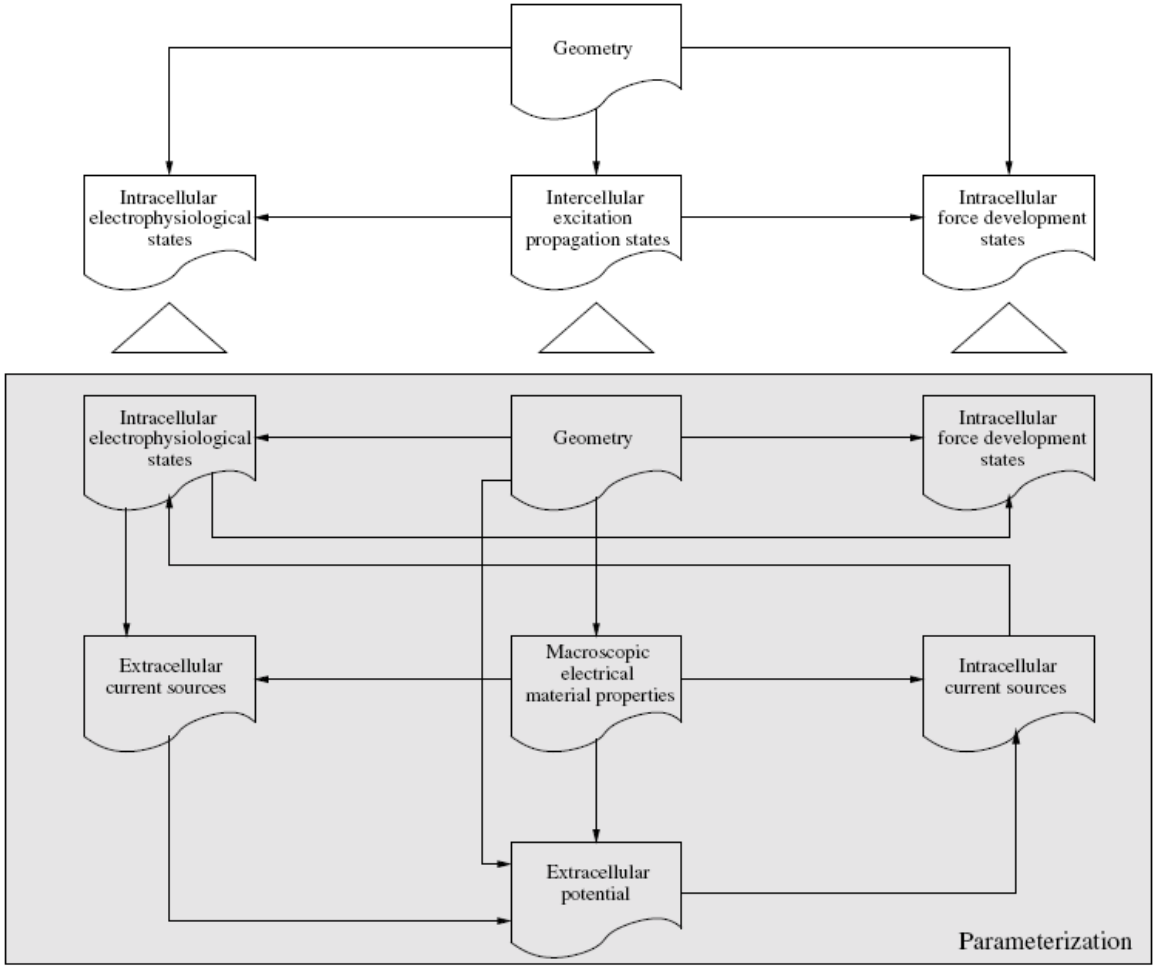
- Models of Glanzel-Sachse-Seemann and Priebe-Beuckelmann aimed at rebuilding many phenomena of electromechanical ventricular myocytes

Electro-mechanics of the heart

The cellular automata can model the development of strength in areas of the myocardium and the heart

It can calculate the forces deployed due to electrical stimulation

Modeling based on cellular automate



F. B. Sachse, G. Seemann, M. B. Mohr, L. G. Bl¨umcke, and C. D. Werner, “Models of the human heart for simulation of clinical interventions,” in *Proc. CARS 2002, 2002, pp. 43–48.*

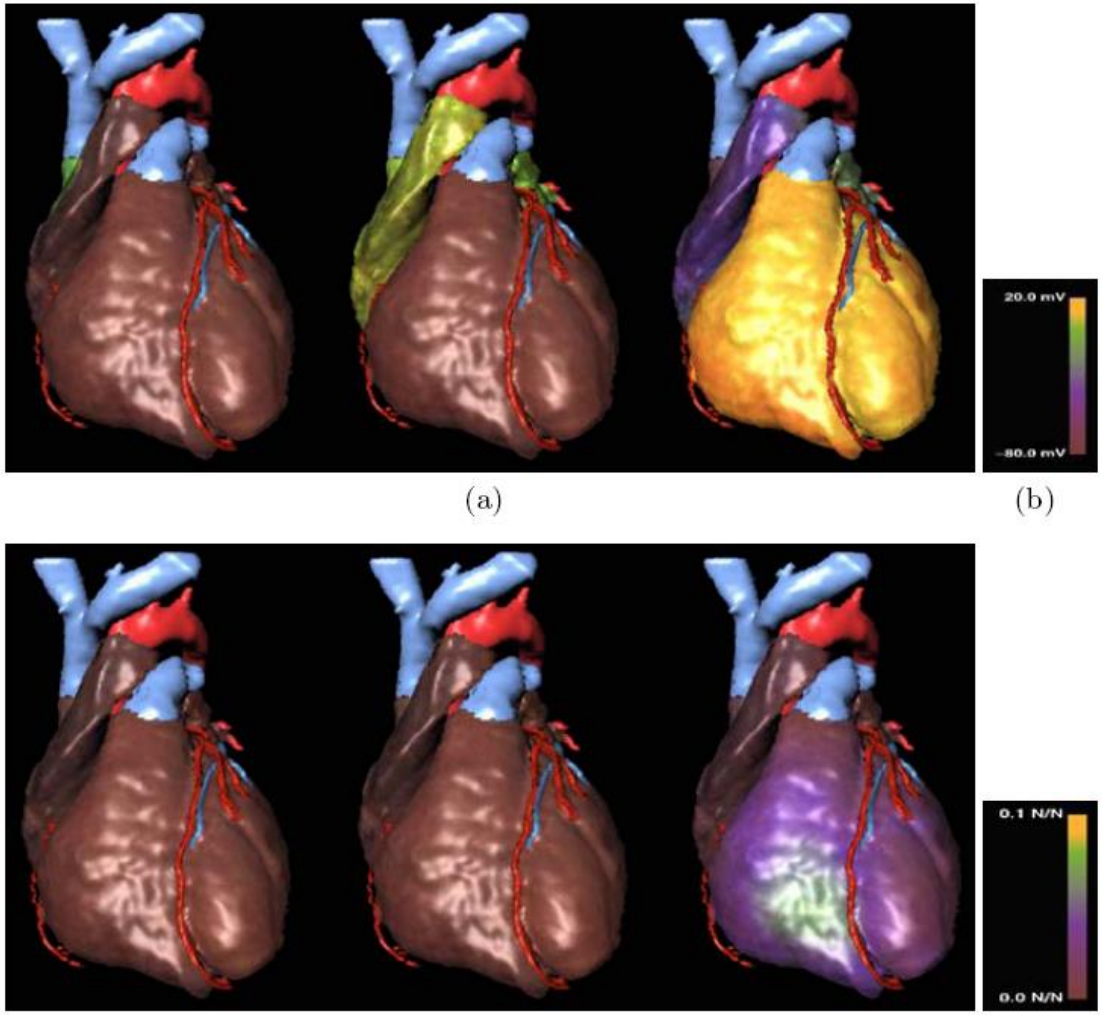
Electro-mechanics of the heart

- Cellular automata

Capacity building on heart's surface

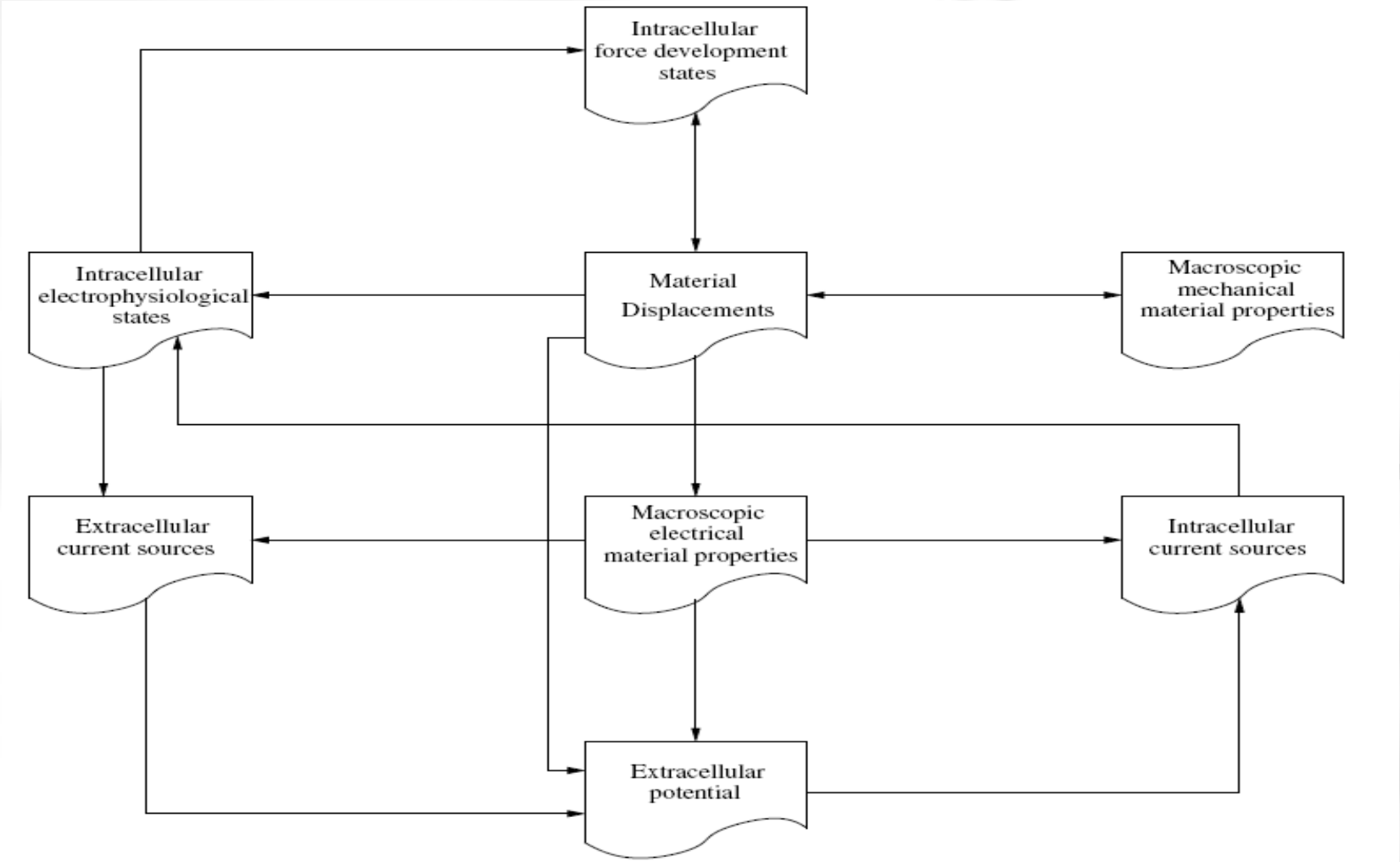
Leads to

Force development at the myocardium cells



F. B. Sachse, G. Seemann, M. B. Mohr, L. G. Bl¨umcke, and C. D. Werner, "Models of the human heart for simulation of clinical interventions," in *Proc. CARS 2002, 2002, pp. 43–48.*

Electro-mechanics of the heart

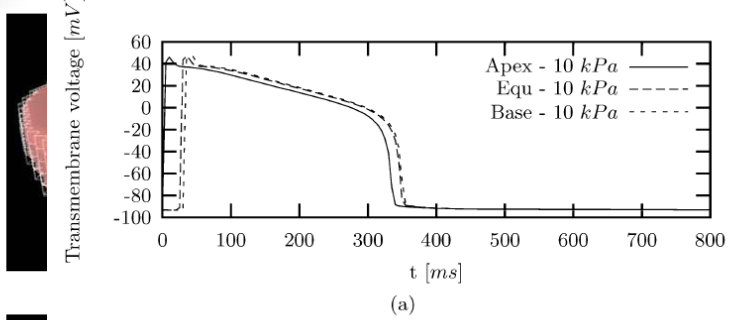


[1]Frank B. Sachse, Computational Cardiology: Modeling of Anatomy, Electrophysiology, and Mechanics. 2004, Springer-Verlag Berlin Heidelberg NewYork, Germany.

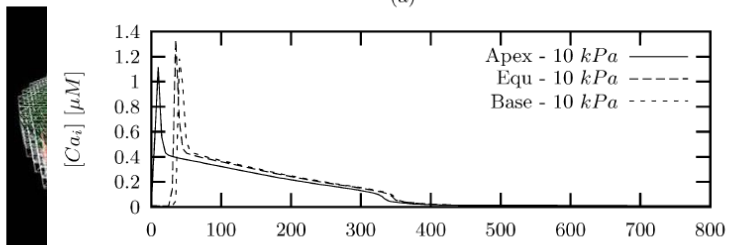
Electro-mechanics of the heart

Electromechanical left ventricular model

- The simulations show the electric polarization and excitation-decay for a cardiac cycle
- The orientation of the myocytes is -70, 0, -70 degrees
- Boundary conditions simulating the actual set
  - The displacements are radial
  - They are not allowed along the abdomen



(a)



The deformation causes significant reduction in tumor infarction and increased wall thickness

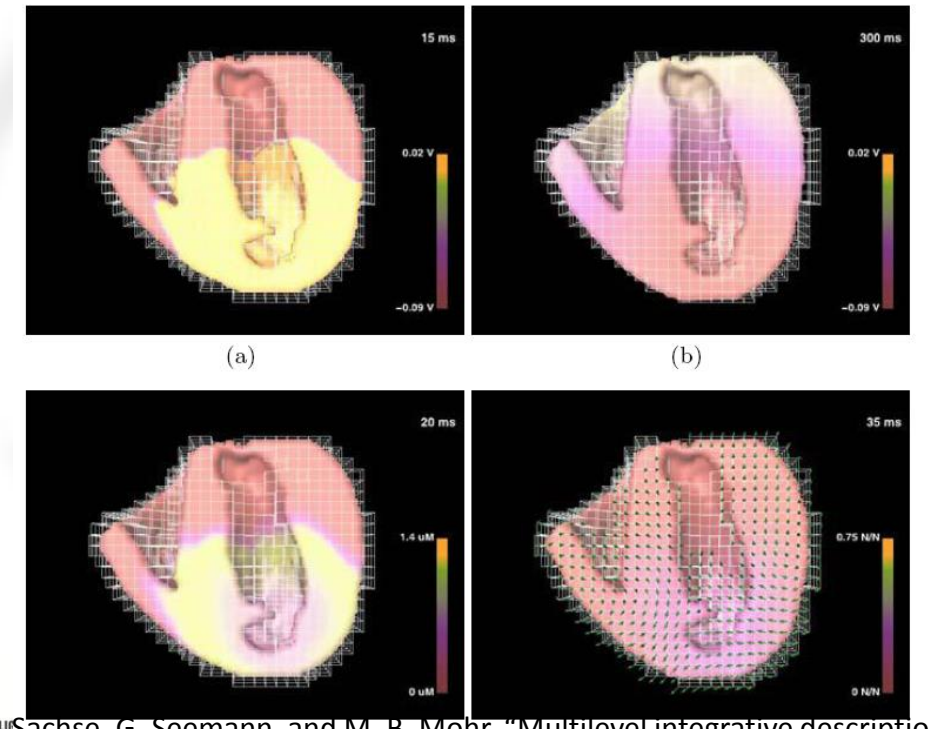
The transmembrane potential and intracellular calcium is not significantly affected by the different strain rates

[1] Frank B. Sachse, Computational Cardiology: Modeling of Anatomy, Electrophysiology, and Mechanics. 2004, Springer-Verlag Berlin Heidelberg NewYork, Germany.

Electro-mechanics of the heart

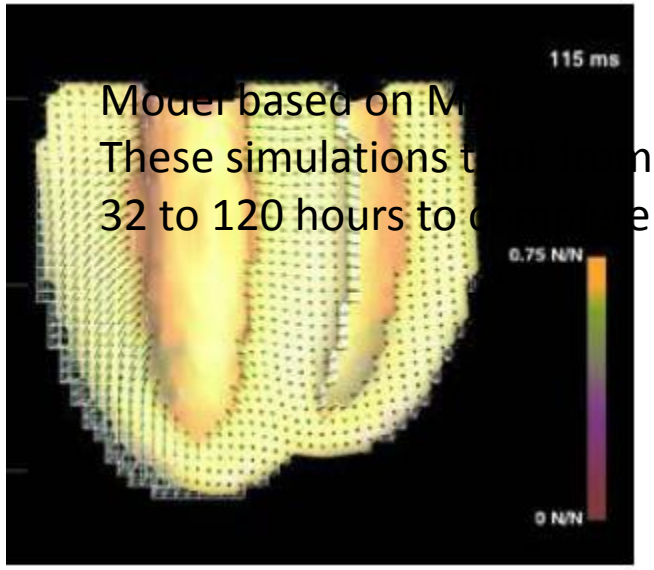
Electromechanical model of two ventricles

- Mechanical boundary conditions were defined only in the left ventricle
- Electrical boundary conditions defined in the right ventricle



stimulation

Model based on M
These simulations t n
32 to 120 hours to e



F. B. Sachse, G. Seemann, and M. B. Mohr, "Multilevel integrative description of cardiac electro-mechanics," *Medical Image Analysis, 2004*

Heart failure

- The restructuring of the left ventricle after heart attack is very important in the progression of the heart failure
- Therefore, the modeling can result in correct decision for treatment or intervention planning

Parameter	3 weeks	1 year
End-diastolic volume	302 ml	377 ml
End-systolic volume	186 ml	271 ml
Circumference	59.5 cm	62.8 cm
Contractile segment	30.5 cm	33.8 cm
Non-contractile segment	23.7 cm	23.5 cm
Diastolic sphericity index	0.71	0.74
Systolic sphericity index	0.60	0.77

- the left ventricle

Zhong L, Ghista DN, Ng EY, Lim ST. Passive and active ventricular elastances of the left ventricle. *Biomed Eng Online. 2005; 4(1):14.*

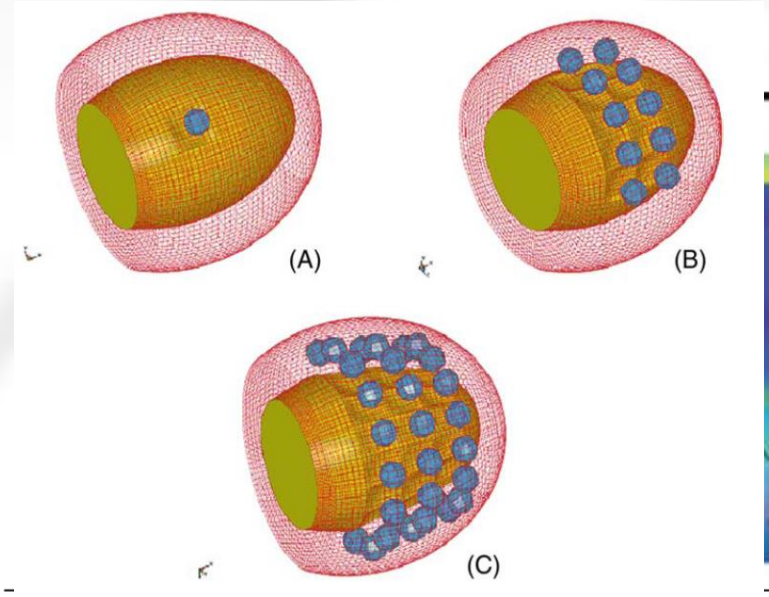
Heart failure

Implantation of biomaterials in the myocardium

- In recent years stem cells are implanted to prevent heart failure
- The stem cells are contained within a pouch biomaterial
- There was found (accidentally) that biomaterials are those that improve the function and not the stem cells
- For this reason finite element modeling is performed for accurate implant position of the biomaterials
- Increased tension in the left ventricle is a sign of heart failure
- The aim of the implantation is to drop the voltage

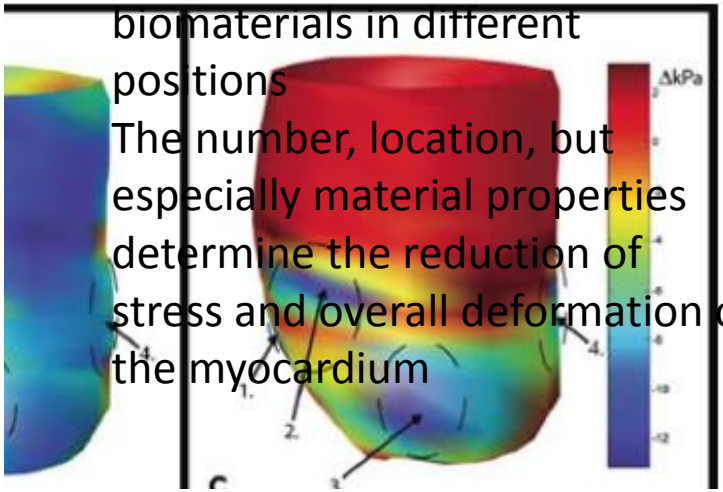
Heart failure

- Biomaterial implantation



Cases of implantation of biomaterials in different positions

The number, location, but especially material properties determine the reduction of stress and overall deformation of the myocardium



Design point	Number of longitudinal	Number of circumferential	Mean end-diastolic stress (kPa)	Mean end-systolic stress (kPa)
A	1	1	3.275	22.481
B	2	5	3.117	22.088
C	**3**	**10**	**2.785**	**21.380**

Wall ST, Walker JC, Healy KE, Ratcliffe MB, Guccione JM. Theoretical impact of the injection of material into the myocardium: a finite element model simulation. *Circulation. 2006 ;*114(24):2627–35. 2006

Heart failure

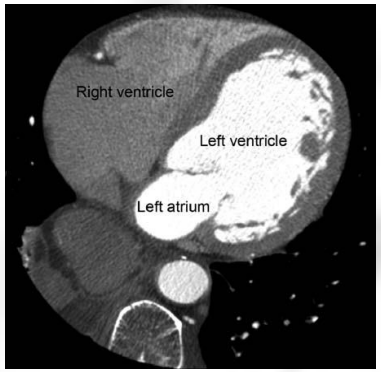
Cardiac resynchronization therapy (CRT)

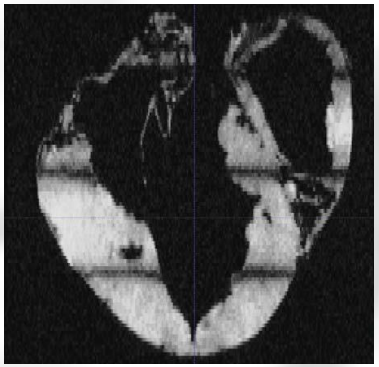
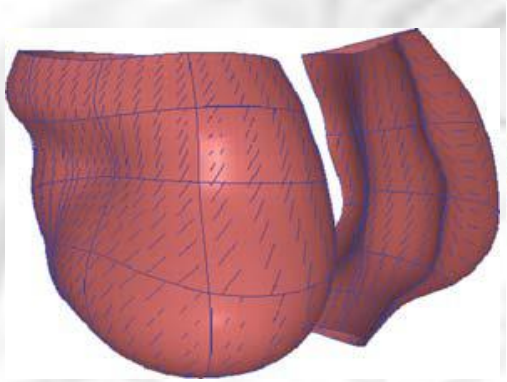
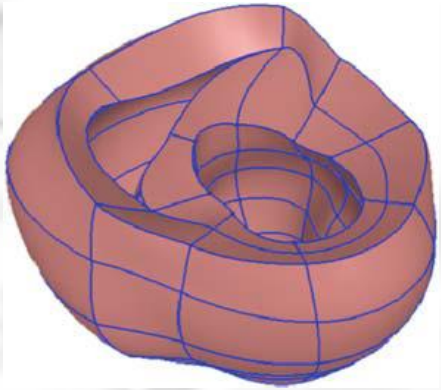
- In recent years the problem of heart failure due to a disturbance of conductivity can be cured
- However 30% of patients do not respond positively to the treatment
- Computers and imaging methods have led to the development of models of patients for successful CRT
- Many pathological conditions (stroke, atherosclerosis) can result in detuning of the heart
- A pacemaker is placed near the vein of the left ventricle that leads to the right ventricle
- The model must contain the anatomy, the orientation of the fibers and a conductivity impulse model. Also accurate material properties are required and finally the modeling of flow in the near circulatory system

Heart failure

Modeling resynchronization of the heart

1. The anatomy and the orientation of the heart and the fibers can be achieved using CT and MRI, respectively



2. The modeling of the conductivity can be made with the electrocardiogram (not accurate). Best approaches include clinical tools of electroanatomical mapping

Vetter FJ, McCulloch AD. Three-dimensional analysis of regional cardiac function: a model of rabbit ventricular anatomy. *Prog Biophys Mol Biol. 1998;69:157–83.*

Helm PA, Younes L, Beg MF, Ennis DB, Leclercq C, Faris OP, McVeigh ER, Kass DA,Miller MI,Winslow RL. Evidence of structural remodeling in the dyssynchronous failing heart. *Circ Res. 2006;98:125–132.*

Heart failure

Modeling resynchronization of the heart

3. Modeling of cardiac mechanics and materials properties

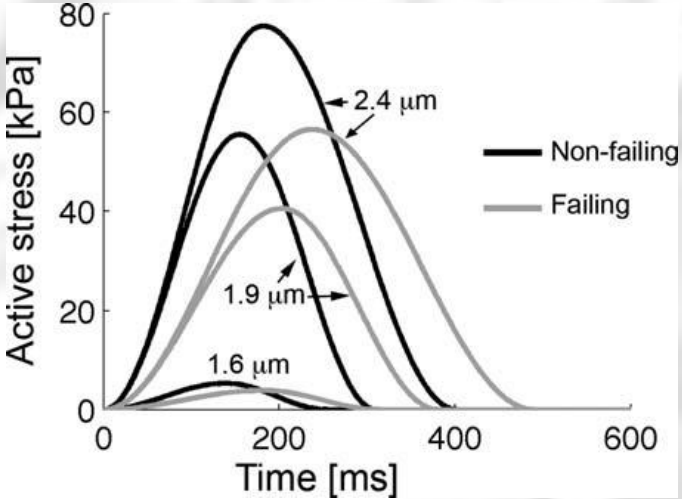
Exponentially anisotropic displacement-energy function for the mechanical model

MRI and CT can be used for the material properties, but also the volume of the ventricle (measured in diastolic and systolic time intervals)

4. Modeling of fluid dynamics

Blood flow can be in aggregated in a parametrical system.

Rules adjusting vessels are used to estimate the resistance and compliance parameter values in extended circulatory heart



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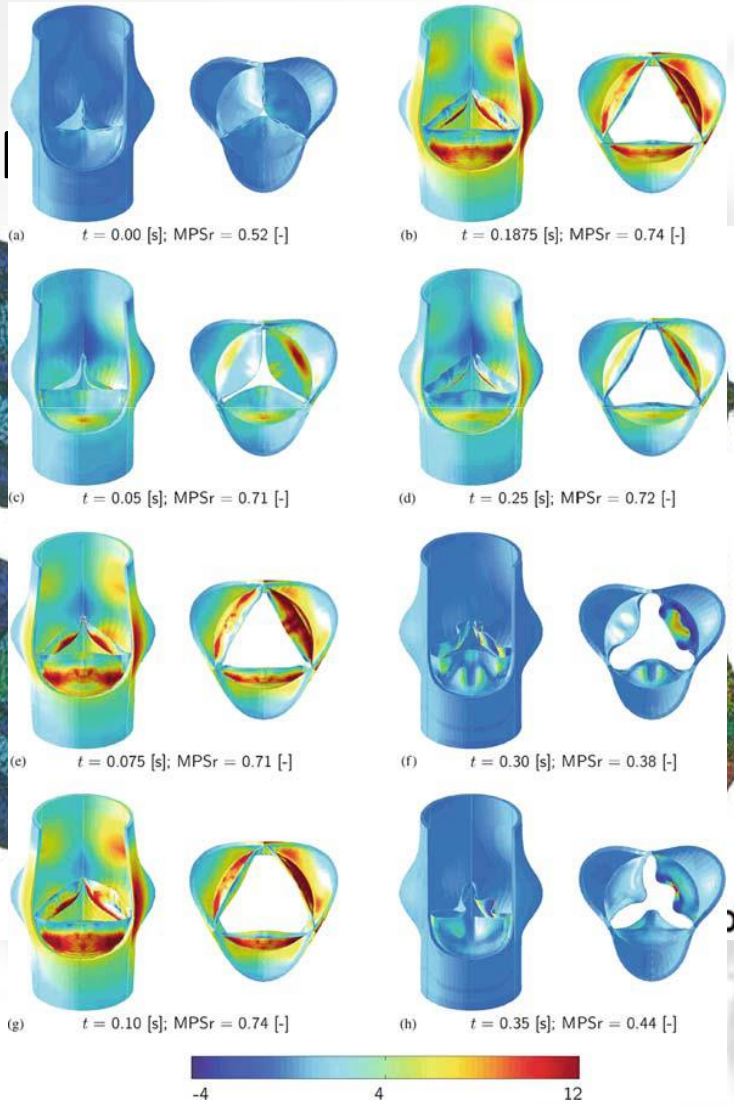
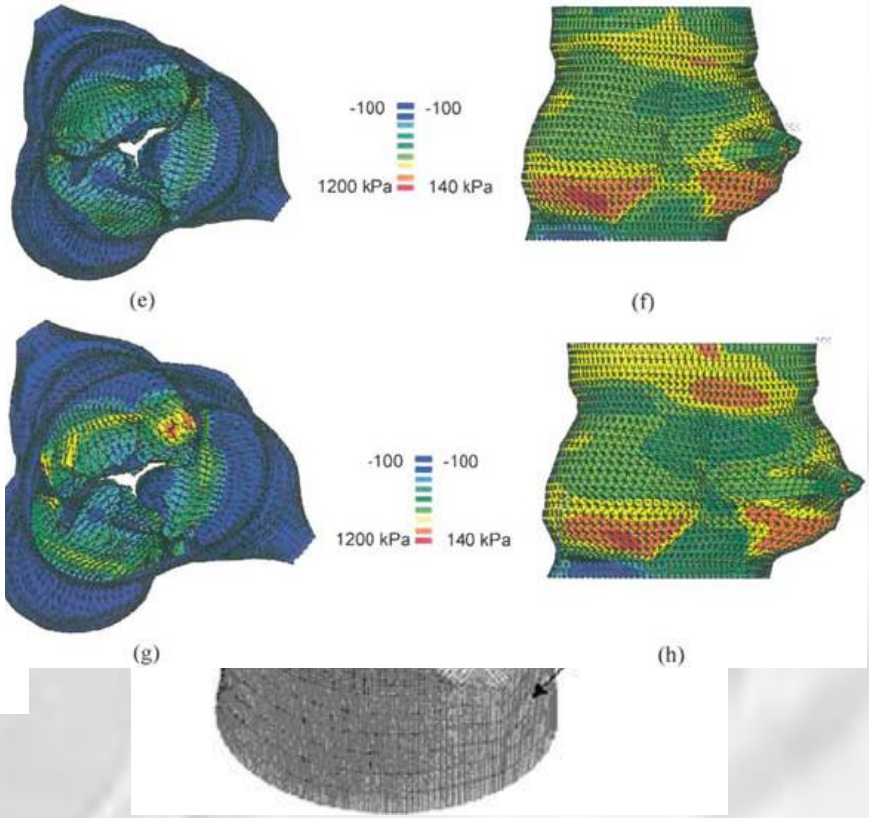
Heart failure



Cauchy stresses during systole



Grande-Allen KJ, Cochran RP, Reinhall PG, Kunzelman KS. *J Thorac Cardiovasc Surg.* 2001;122:946–54.

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