Personalized mathematical models of blood flows

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Working group for modeling of blood flows and vascular pathologies

RSF project (2014-2018): Multiscale modeling of blood flow in patient-specific treatment technologies of cardiology, vascular neurology, oncology

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- Automated segmentation of blood vessels (coronary, cerebral)
- Blood flow models (1D, 3D, 1D-3D)
- Personalized estimate of hemodynamic significance of stenoses (coronary, cerebral)
- Angiogensis and tumor growth, antiangiogenic therapy combined with chemical and radiological treatments
- Ultrasound vessel examination
- Non-invasive electrophisiological study of heart

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Co-authors

- Timur Gamilov
- Sergey Simakov
- Roman Pryamonosov
- Aleksander Danilov
- Aleksander Lozovskii
- Maxim Olshanskii

1D hemodynamic equations (flows in elastic tubes)

Mass and momentum balance

$$
\begin{aligned}
\partial S_k/\partial t + \partial\left(S_k u_k\right)/\partial x &= 0, \\
\partial u_k/\partial t + \partial\left(u_k^2/2 + p_k/\rho\right)/\partial x &= -\frac{8\pi\mu u_k}{S_k},
\end{aligned}
$$

k is index of the tube, t is the time, x is the distance along the tube, ρ is the blood density (constant), $S_k(t,x)$ is the cross-section area, $u_k(t,x)$ is the linear velocity averaged over the cross-section, $p_k(S_k)$ is the blood pressure

S.S.Simakov, A.S.Kholodov. Computational study of oxygen concentration in human blood under low frequency disturbances. *Mathematical Models and Computer Simulations*, 2009 **1** (2)

1D hemodynamic equations (flows in elastic tubes)

At the vessels junctions continuity of the total pressure and mass conservation

$$p_i\left(S_i\left(t,\tilde{x}_i\right)\right)+\frac{\rho u_i^2\left(t,\tilde{x}_i\right)}{2}=p_j\left(S_j\left(t,\tilde{x}_j\right)\right)+\frac{\rho u_j^2\left(t,\tilde{x}_j\right)}{2},$$

$$\sum_{k=k_1,k_2,\ldots,k_M}\varepsilon_k S_k\left(t,\tilde{x}_k\right)u_k\left(t,\tilde{x}_k\right)=0,$$

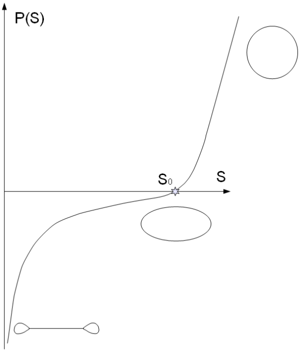
$\varepsilon=1, \tilde{x}_k=L_k$ for incoming tubes, $\varepsilon=-1$, and $\tilde{x}_k=0$ for outgoing tubes

S.S.Simakov, A.S.Kholodov. Computational study of oxygen concentration in human blood under low frequency disturbances. *Mathematical Models and Computer Simulations*, 2009 **1** (2)

1D hemodynamic equations (flows in elastic tubes)

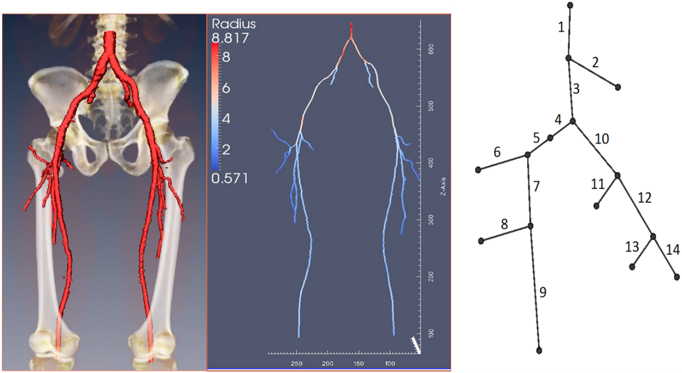
Elasticity of the tube wall:

$$p_k(S_k) - p_{*k} = \rho c_k^2 f(S_k)$$



Vassilevski Yu., Salamatova V., Simakov S. On the elastisity of blood vessels in one-dimensional problems of hemodynamics. J. Computational Mathematics and Mathematical Physics, V.55, No.9, p.1567-1578, 2015.

Personalized model of femoral artery stenosis



S. Simakov, T. Gamilov, Yu. Vassilevski et.al. Patient specific haemodynamics modeling after occlusion treatment in leg. *MMNP* 9(6), 2014.

Boundary conditions and parameter identification

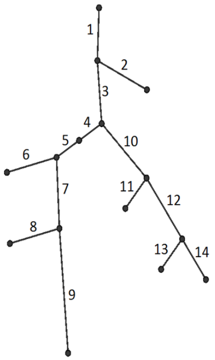
Boundary conditions:
inlet (arteries):

$$Q = \alpha Q_{heart}$$

outlet (veins):

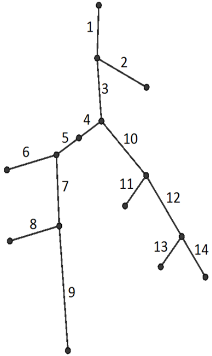
$$Q = \overline{\alpha Q_{heart}}$$

Parameter identification: Ultrasound measurements (before surgery), angles of bifurcations, vessel sizes...



Simulation result

Art.	Peak blood velocity (cm/s)			
	Presurgical		Postsurgical	
	Patient	Model	Patient	Model
3	148	149	150	155
4	48	54	65	70
12	103	93	69	83
5	> 300	340	-	71
7	-	67	98	86
9	52	56	72	72



3 - common femoral.,4 - superficial femoral, 12 - deep femoral,5 - occlusion, 7 - superficial femoral (dist), 9 - popliteal art.

MRI failed to connect branch of 12 to 9

Ischemic heart disease and presonalized models

Ischemic heart disease is caused by

- pathology of microvasculature (therapy)
- pathology of coronary arteries (revascularization)

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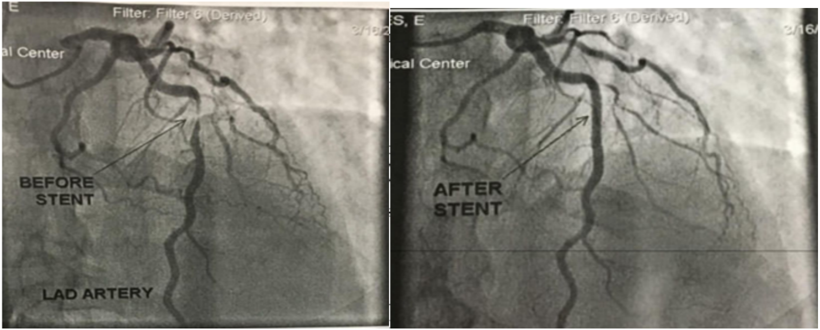

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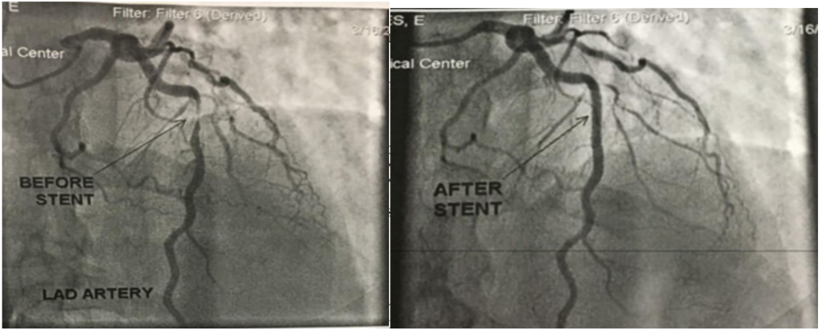
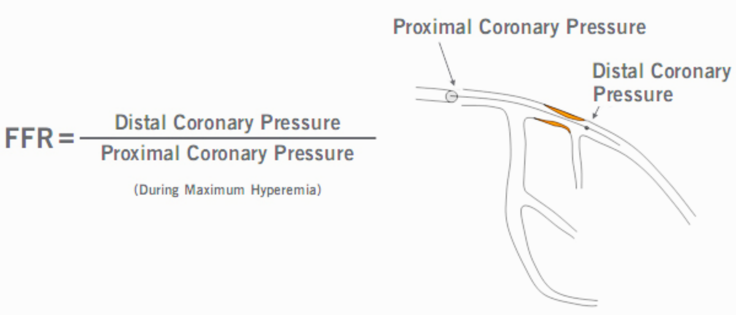


Indication for revascularization

- before 2014: Vascular occlusion factor (relative lesion cross-sectional area) $VOF > 0.7$
- after 2014: Fractional flow reserve $FFR < 0.75$

2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur.Heart J*, 2014 **35** (37)

Fractional flow reserve (FFR)



Clinical practice: endovascular intervention, expensive transducer

Pijls NH, Sels JW., Functional measurement of coronary stenosis. *J.Am. Coll. Cardiol.*, 2012 **59** (12)
Kopylov Ph., Bykova A., Vassilevski Yu., Simakov S. Role of measurement of fractional flow reserve (FFR) in coronary artery atherosclerosis. *Therapeutic archive*, 2015 **87** (9)

Virtual fractional flow reserve FFR_{CT}

- Hemodynamic simulation based on personalized data:
  - Computed Tomographic Coronary Angiography (DICOM)
- $FFR_{CT} = \frac{\overline{P}_{dist}}{\overline{P}_{aortic}}$

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- Hemodynamic simulation based on personalized data:
  - Computed Tomographic Coronary Angiography (DICOM)
- $FFR_{CT} = \frac{\overline{P}_{dist}}{\overline{P}_{aortic}}$
- Advantages of FFR_{CT}
  - non-invasivity
  - physiological significance of each of multiple lesions
  - virtual stenting
  - applicability to any segment of the coronary tree

Virtual fractional flow reserve from 3D simulations

3D Navier-Stokes equations

HeartFlow has gained U.S. Food and Drug Administration (FDA) approval for the use of FFR_{CT} as a class II Coronary Physiologic Simulation Software Device

Morris P. et al. “Virtual” (Computed) Fractional Flow Reserve: Current Challenges and Limitations. *J Am Coll Cardiol Intv.* 2015, **8** (8)

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Difficulties of FFR_{CT} evaluation by 3D simulations:

- boundary conditions for 3D problem
- simulation time
- frozen vascular walls (physics?) or FSI (expensive,coefficients?)

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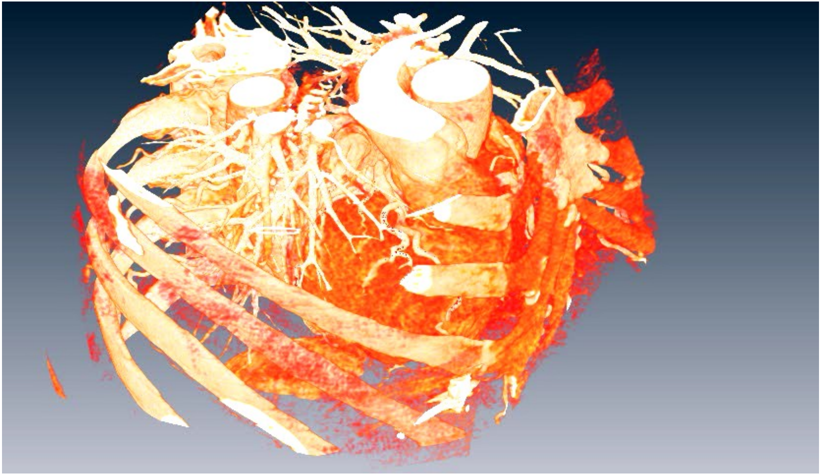
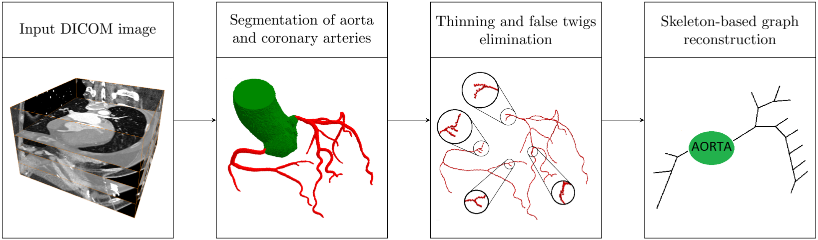
Alternative approach: 1D hemodynamics

Patient-specific segmentation of coronary arteries



Automatic segmentation and skeletonization



Overview of pipeline for automatic network reconstruction

A. Danilov, et al. Methods of graph network reconstruction in personalized medicine. IJNMBE, 2016

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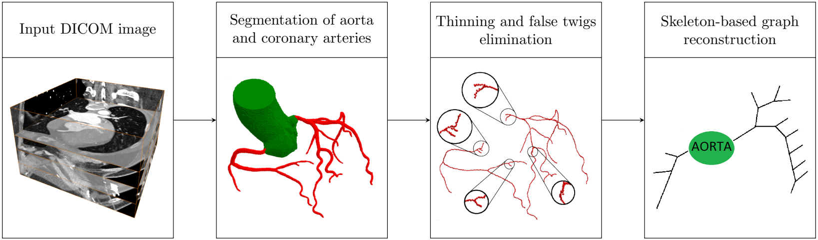

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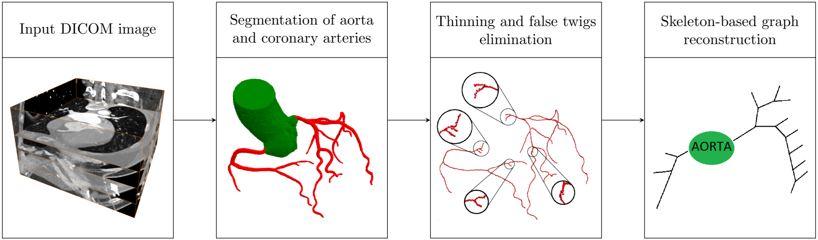
Aorta segmentation by isoperimetric distance trees

L. Grady. Fast, quality, segmentation of large volumes – Isoperimetric distance trees. ECCV, 2006.

Automatic segmentation and skeletonization



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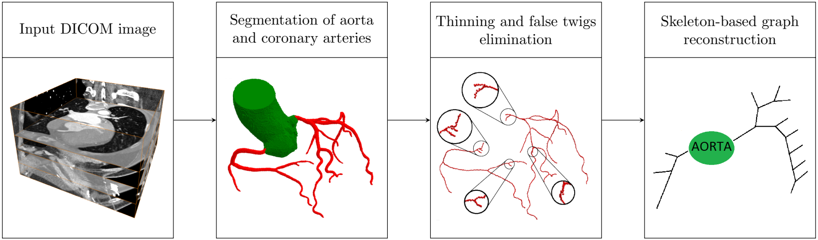
Frangi vesselness filter generates bigger values inside bright tubular structures

A. Frangi, W. Niessen, K. Vincken, and M. Viergever. Multiscale vessel enhancement filtering. MICCAI, 1998.

Automatic segmentation and skeletonization



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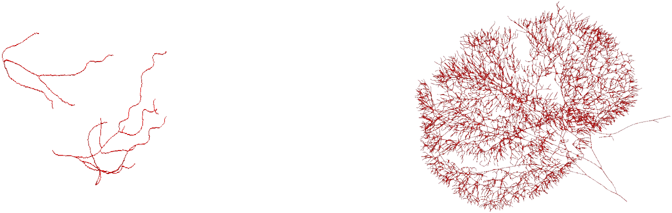
Skeletonization produces vascular 1D computational network

C. Pudney. Distance-ordered homotopic thinning: A skeletonization algorithm for 3D digital images.CVIU, 1998.

Skeletonization efficiency



Skeletons of a coronary tree and of a micro-CT of vascular corrosion cast of rabbit kidney provided by J. Alastruey,

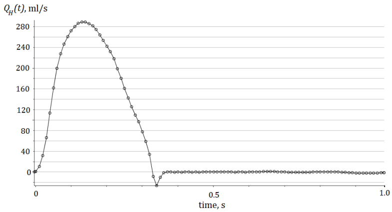
Department of Bioengineering, King's College London, UK

	Case 1	Rabbit kidney
Resolution	$512 \times 512 \times 248$	$2000 \times 1989 \times 910$
Distance map	0.20 sec	58.12 sec
Thinning	0.79 sec	526.98 sec
False twigs cleaning	0.15 sec	16.61 sec
Graph construction	0.13 sec	12.27 sec
Skeleton segments	22	4302

Coronary hemodynamics in silico

T.Gamilov, Ph.Kopylov, R.Pryamonosov, S.Simakov. Virtual Fractional Flow Reserve Assesment in Patient-Specific Coronary Networks by 1D Hemodynamic Model. *Russ. J. Numer. Anal. Math. Modelling*, 2015 **30** (5)

- On arterial entry unsteady flux (1Hz, 65ml) is scaled to HR and systolic/diastolic pressures, venous pressure (12 mmHg) is given



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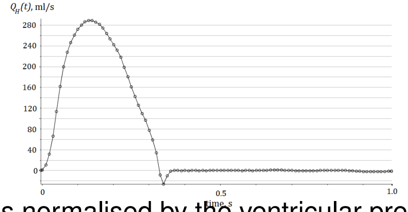
- Compression of arteries during systola by myocard: $p_{*k} = P_{ext}^{cor}(t)$, $R_k^{syst} = 3R_k^{diast}$



P_{ext}^{cor} is normalised by the ventricular pressure

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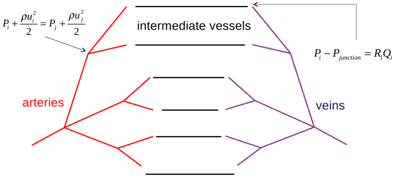
- Compression of arteries during systola by myocard: $p_{*k} = P^{cor}_{ext}(t)$, $R^{syst}_k = 3R^{diast}_k$
- Resistance of microcirculation $p_k\left(S_k\left(t, \tilde{x}_k\right)\right) - p_{veins} = R_k S_k\left(t, \tilde{x}_k\right) u_k\left(t, \tilde{x}_k\right)$



Systole: 1) $P^{ext}(t, x)$ to intermediate vessels

2) increased resistance of intermediate vessels

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- Compression of arteries during systola by myocard:
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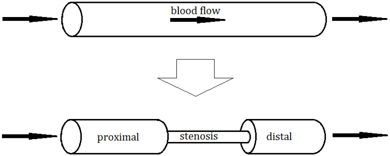
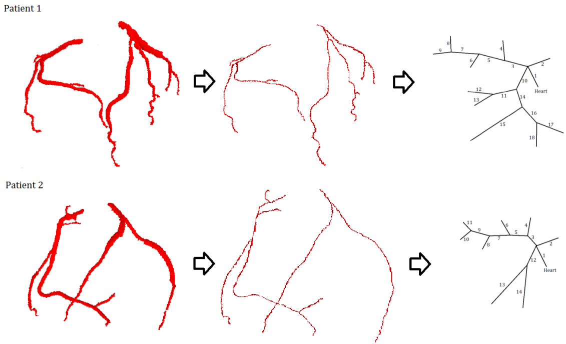
- Stenosis with fraction α: $S_0^{st} = (1-\alpha)S_0$



Computation of virtual fractional flow reserve



reconstructed arterial part based on two anonymous patient-specific data sets

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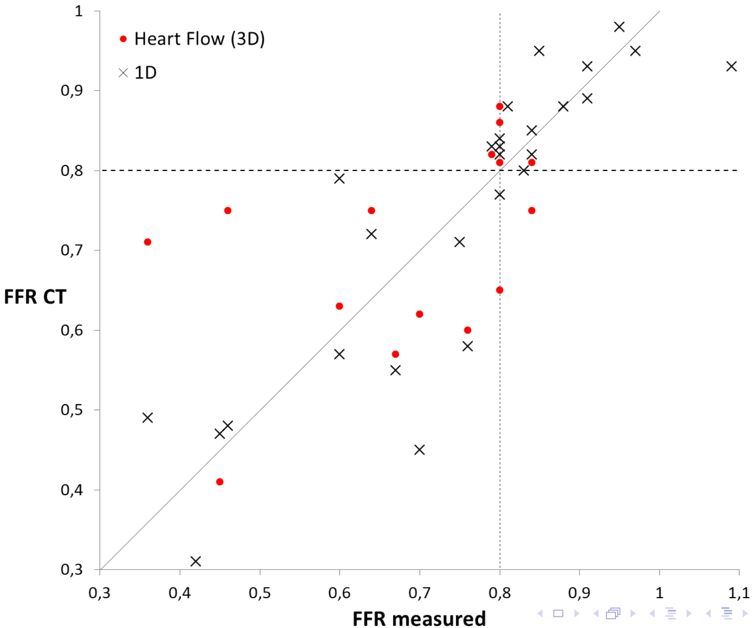
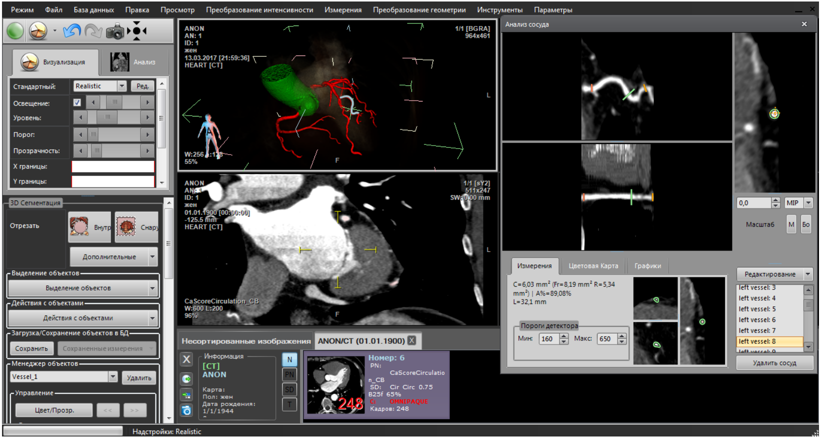
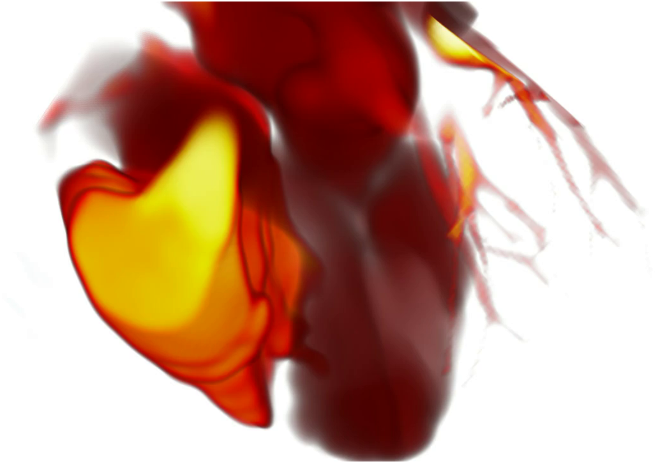
Computation of virtual fractional flow reserve



FFR_{CT} within Multivox toolbox

Medical computer systems, Lomonosov Moscow State Univ.





Personalized model of blood flow in left ventricle

- reference domain Ω_0
- transformation ξ mapping Ω_0 to $\Omega(t)$ is given
- $\mathbf{v}$ and $\mathbf{u}$ denote velocities and displacements in Ω_0
- $\xi(\mathbf{x}) := \mathbf{x} + \mathbf{u}(\mathbf{x})$, $\mathbf{F} := \nabla\xi = \mathbf{I} + \nabla\mathbf{u}$, $J := \det(\mathbf{F})$
- Cauchy stress tensor $\boldsymbol{\sigma}$
- pressure p
- density ρ is constant

Model of incompressible fluid flow in a moving domain

Navier-Stokes equations in reference domain Ω_0

Let ξ mapping Ω_0 to $\Omega(t)$, $\mathbf{F} = \nabla\xi = \mathbf{I} + \nabla\mathbf{u}$, $J = \det(\mathbf{F})$ be given

Model of incompressible fluid flow in a moving domain

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Dynamic equations

$$\frac{\partial \mathbf{v}}{\partial t} = (J\rho_f)^{-1}\mathrm{div}\left(J\boldsymbol{\sigma}_f\mathbf{F}^{-T}\right) - \nabla\mathbf{v}\left(\mathbf{F}^{-1}\left(\mathbf{v} - \frac{\partial \mathbf{u}}{\partial t}\right)\right) \quad \text{in } \Omega_0$$

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Fluid incompressibility

$$\mathrm{div}\,(J\mathbf{F}^{-1}\mathbf{v}) = 0 \quad \text{in } \Omega_0 \quad \text{or} \quad J\nabla\mathbf{v} : \mathbf{F}^{-T} = 0 \quad \text{in } \Omega_0$$

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Constitutive relation for the fluid stress tensor

$$\boldsymbol{\sigma}_f = -p_f\mathbf{I} + \mu_f((\nabla\mathbf{v})\mathbf{F}^{-1} + \mathbf{F}^{-T}(\nabla\mathbf{v})^T) \quad \text{in } \Omega_0$$

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Mapping ξ does not define material trajectories $\rightarrow$ quasi-Lagrangian formulation

Finite element scheme

Let $\mathbb{V}_h, \mathbb{Q}_h$ be Taylor-Hood P_2/P_1 finite element spaces.
Find $\{\mathbf{v}_h^k, p_h^k\} \in \mathbb{V}_h \times \mathbb{Q}_h$ satisfying b.c.
("do nothing" $\boldsymbol{\sigma}\mathbf{F}^{-T}\mathbf{n} = 0$ or no-penetration no-slip $\mathbf{v}^k = (\boldsymbol{\xi}^k - \boldsymbol{\xi}^{k-1})/\Delta t$)

$$\int_{\Omega_0} J_k \frac{\mathbf{v}_h^k - \mathbf{v}_h^{k-1}}{\Delta t} \cdot \psi \,\mathrm{d}\mathbf{x} + \int_{\Omega_0} J_k \nabla \mathbf{v}_h^k \mathbf{F}_k^{-1} \left(\mathbf{v}_h^{k-1} - \frac{\boldsymbol{\xi}^k - \boldsymbol{\xi}^{k-1}}{\Delta t} \right) \cdot \psi \,\mathrm{d}\mathbf{x} -$$
$$\int_{\Omega_0} J_k p_h^k \mathbf{F}_k^{-T} : \nabla \psi \,\mathrm{d}\mathbf{x} + \int_{\Omega_0} J_k q \mathbf{F}_k^{-T} : \nabla \mathbf{v}_h^k \,\mathrm{d}\mathbf{x} +$$
$$\int_{\Omega_0} \nu J_k (\nabla \mathbf{v}_h^k \mathbf{F}_k^{-1} \mathbf{F}_k^{-T} + \mathbf{F}_k^{-T} (\nabla \mathbf{v}_h^k)^T \mathbf{F}_k^{-T}) : \nabla \psi \,\mathrm{d}\mathbf{x} = 0$$

$$\int_{\Omega_0} J_k \nabla \mathbf{v}^k : \mathbf{F}_k^{-T} q \,\mathrm{d}\Omega = 0$$

for all ψ and q from the appropriate FE spaces

Finite element scheme

The scheme

- semi-implicit
- produces one linear system per time step
- first order in time (may be generalized to the second order)

Finite element scheme

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- semi-implicit
- produces one linear system per time step
- first order in time (may be generalized to the second order)
- unconditionally stable (no CFL restriction) and 2nd order accurate, proved with assumptions:
  - $\inf_Q J \geq c_J > 0, \quad \sup_Q(\|\mathbf{F}\|_F + \|\mathbf{F}^{-1}\|_F) \leq C_F$
  - LBB-stable pairs (e.g. P_2/P_1)
  - Δt is not large

A.Danilov, A.Lozovskiy, M.Olshanskii, Yu.Vassilevski. A finite element method for the Navier-Stokes equations in moving domain with application to hemodynamics of the left ventricle. *Russian J. Numer. Anal. Math. Modelling, 32, 2017*
A.Lozovskiy, M.Olshanskii, Yu.Vassilevski. A quasi-Lagrangian finite element method for the Navier-Stokes equations in a time-dependent domain. Comput. Methods Appl. Mech. Engrg. 333, 2018

3D: left ventricle of a human heart

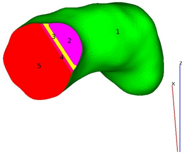


Figure: Left ventricle

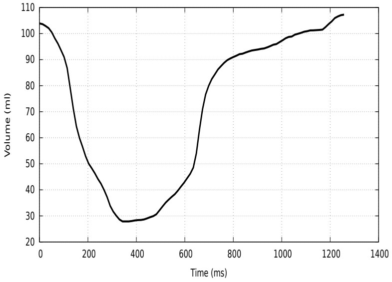
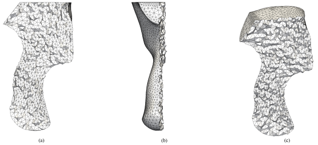


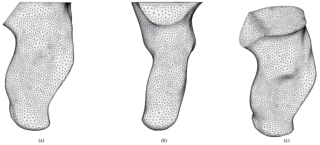
Figure: Ventricle volume

The law of motion for the ventricle walls is known thanks to ceCT scans $\rightarrow$ 100 mesh files with time gap 0.0127 s $\rightarrow$ $\mathbf{u}$ given as input $\rightarrow$ FSI reduced to NSE in a moving domain

- 2 - aortic valve (outflow)
- 5 - mitral valve (inflow)

3D: left ventricle of a human heart





- Quasi-uniform mesh: 14033 vertices, 69257 elements, 88150 edges.
- Boundary conditions: Dirichlet $\mathbf{v} = \frac{\partial \mathbf{u}}{\partial t}$ except:
  - Do-nothing on aortal valve during systole
  - Do-nothing on mitral valve during diastole
- Time step 0.0127 s is too large!
  $\Longrightarrow$ refined to $\Delta t = 0.0127/20$ s
  $\Longrightarrow$ Cubic-splined $\mathbf{u}$.
- Blood parameters: $\rho_f = 10^3$ kg/m^3, $\mu_f = 4 \cdot 10^{-3}$ Pa $\cdot$s.

Open source software

- ITK-SNAP - `www.itksnap.org`
- Ani3D - `sf.net/p/ani3d`

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Announcement of workshops, 7-11 October 2019

Far East Federal University, island Russky, Vladivostok, Russia

Week of Applied Mathematics & Mathematical Modelling

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- 11th Workshop on Numerical Methods and Mathematical Modelling in Biology and Medicine
- 3d Workshop on Multiscale Methods and Large-scale Scientific Computing
- 6th Russian-Chinese Workshop on Numerical Mathematics and Scientific Computing