Validation of Finite-Volume Methods for Clot Formation Modelling

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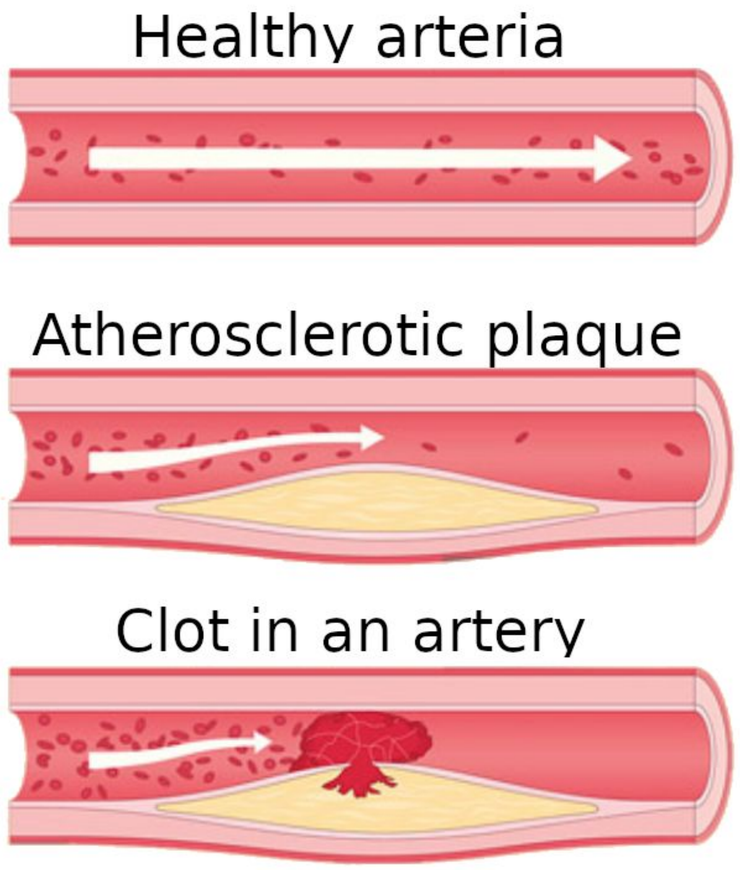
BIOMATH, 2 November 2020

Problem

actuality and complexity

Problem:

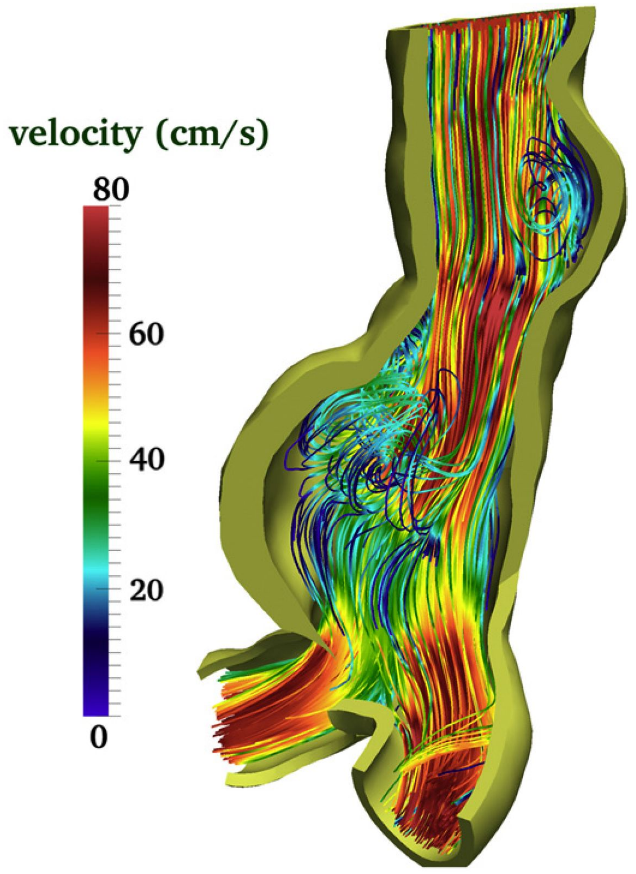
- Construction of **three-dimensional** model of blood flow and coagulation, clot formation after damage of blood vessel



Clot formulation
(illustration from internet)

What for?

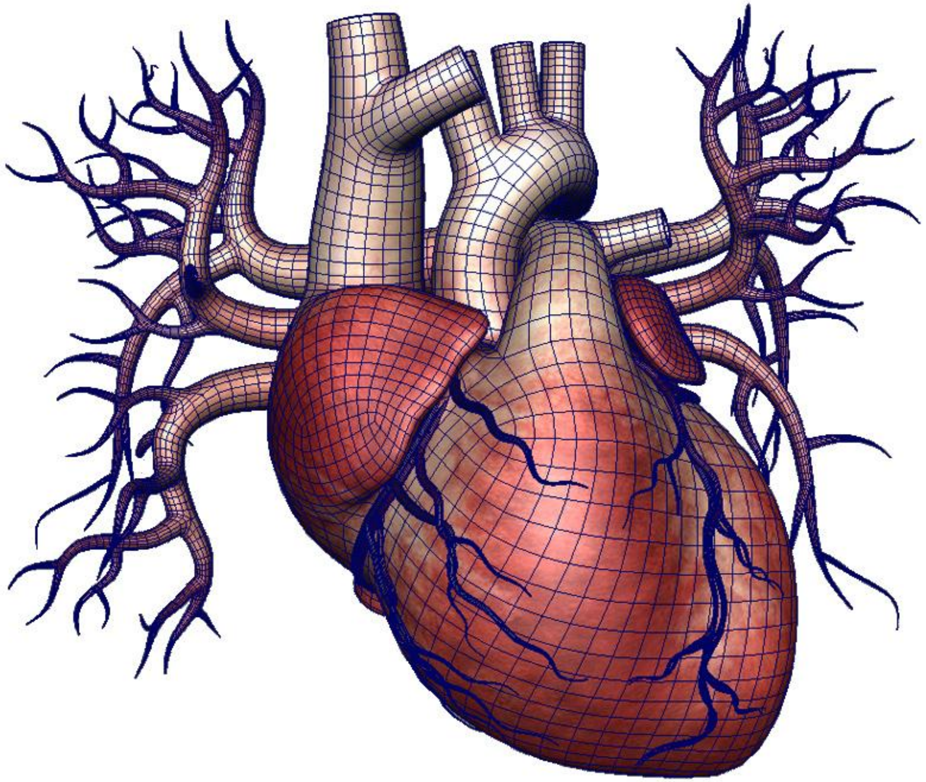
- **Three-dimensional** model is needed for decision making in case of complex patient-oriented geometry of blood vessel or arteria.



Modeling of aneurysm
(from Quarteroni)

What for?

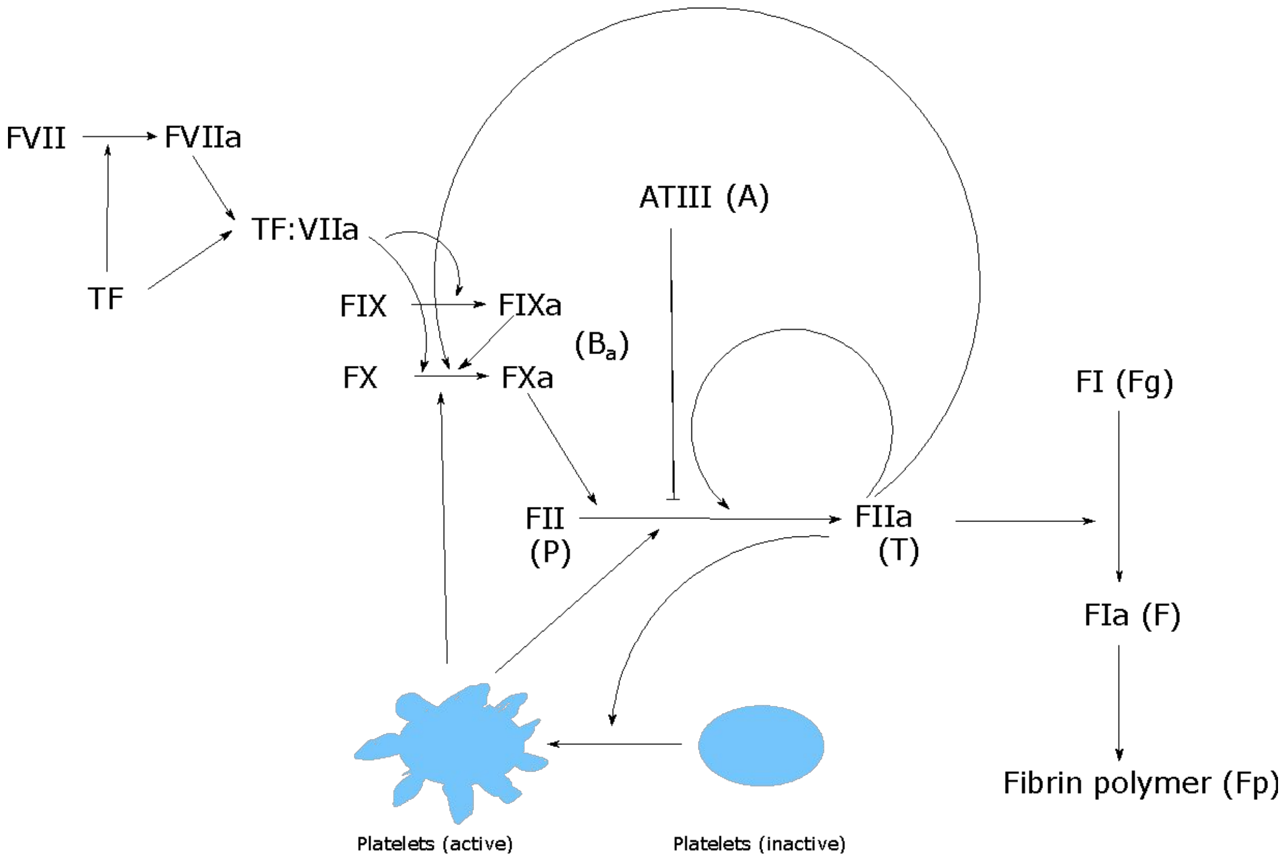
- Diseases of the heart and blood vessels is the **primary** cause o death
  - thromboembolic complications
- **Three-dimensional** model allows to assess the risk of
  - vessel occlusion
  - myocardial infarction



Heart model

Complexity

- Model coupling:
  - **Hemodynamics** model with account for fibrin-polymer permeability
  - Model of **biochemical reactions** for blood plasma coagulation
  - Model of **platelets**
- **Reaction cascade** and model for **platelets** are **stiff**: very small time step
- Fully implicit model



Каскад реакций

Assumptions

- Blood is considered as an **incompressible Newton's** fluid: no account for **complex nonlinear rheology** of blood

- Blood vessels/arteria are **rigid**: no account for **wall motion**

- Fibrin-polymer is **immoble**: no account for clot **detachment**

System of Equations

- Conservation of momentum:

$$\frac{\partial \rho \boldsymbol{u}}{\partial t} + \mathrm{div}(\rho \boldsymbol{u}\boldsymbol{u}^T - \mu \nabla \boldsymbol{u} + pI) = \frac{1}{k(F_p, \phi_c)} \boldsymbol{u}$$

- Incompressibility:

$$\mathrm{div}(\boldsymbol{u}) = 0$$

- Prothrombin:

$$\frac{\partial P}{\partial t} + \mathrm{div}(P\boldsymbol{u} - D\nabla P) = -(k_1\phi_c + k_2 B_a + k_3 T + k_4 T^2 + k_5 T^3)P$$

- Thrombin:

$$\frac{\partial T}{\partial t} + \mathrm{div}(T\boldsymbol{u} - D\nabla T) = (k_1\phi_c + k_2 B_a + k_3 T + k_4 T^2 + k_5 T^3)P - k_6 A T$$

- Clot formation factors FIXa, Fxa:

$$\frac{\partial B_a}{\partial t} + \mathrm{div}(B_a\boldsymbol{u} - D\nabla B_a) = (k_7\phi_c + k_8 T)(B^0 - B_a) - k_9 A B_a$$

- Antithrombin:

$$\frac{\partial A}{\partial t} + \mathrm{div}(A\boldsymbol{u} - D\nabla A) = -k_6 A - k_9 A B_a$$

- Fibrinogen:

$$\frac{\partial F_g}{\partial t} + \mathrm{div}\left(F_g\boldsymbol{u} - D\nabla F_g\right) = -\frac{k_{10} T F_g}{K_{10} + F_g}$$

System of Equations

- Fibrin: $$\frac{\partial F}{\partial t} + \mathrm{div}(F\boldsymbol{u} - D\nabla F) = \frac{k_{10} T F_g}{K_{10} + F_g} - k_{11} F$$
- Fibrin-polymer: $$\frac{\partial F_p}{\partial t} = k_{11} F$$
- Inactivated platelets: $$\frac{\partial \phi_c}{\partial t} + \mathrm{div}\left(\tanh\left(\pi\left(1 - \frac{\phi_c + \phi_f}{\phi_{max}}\right)\right)(\phi_c \boldsymbol{u} - D_p \nabla \phi_c) \right) = -(k_{12} T - k_{13} \phi_c)\phi_f$$
- Activated platelets: $$\frac{\partial \phi_f}{\partial t} + \mathrm{div}\left(\tanh\left(\pi\left(1 - \frac{\phi_c + \phi_f}{\phi_{\max}}\right)\right)(\phi_f \boldsymbol{u} - D_p \nabla \phi_f) \right) = (k_{12} T - k_{13} \phi_c)\phi_f$$
- Media permeability: $$\frac{1}{k(F_p, \phi_c)} = \frac{16}{a^2} \tilde{F}_p^{\frac{3}{2}} (1 + 56 \tilde{F}_p) \frac{\phi_{\max} + \phi_c}{\phi_{\max} - \phi_c}$$ with $$\tilde{F}_p = \min\left(\frac{7}{10}, \frac{F_p}{7000}\right)$$

Bouchnita, A., Terekhov, K., Nony, P., Vassilevski, Y., & Volpert, V.: ***A mathematical model to quantify the effects of platelet count, shear rate, and injury size on the initiation of blood coagulation under venous flow conditions***. **PloS one,** 15(7), e0235392, 2020

Boundary Conditions

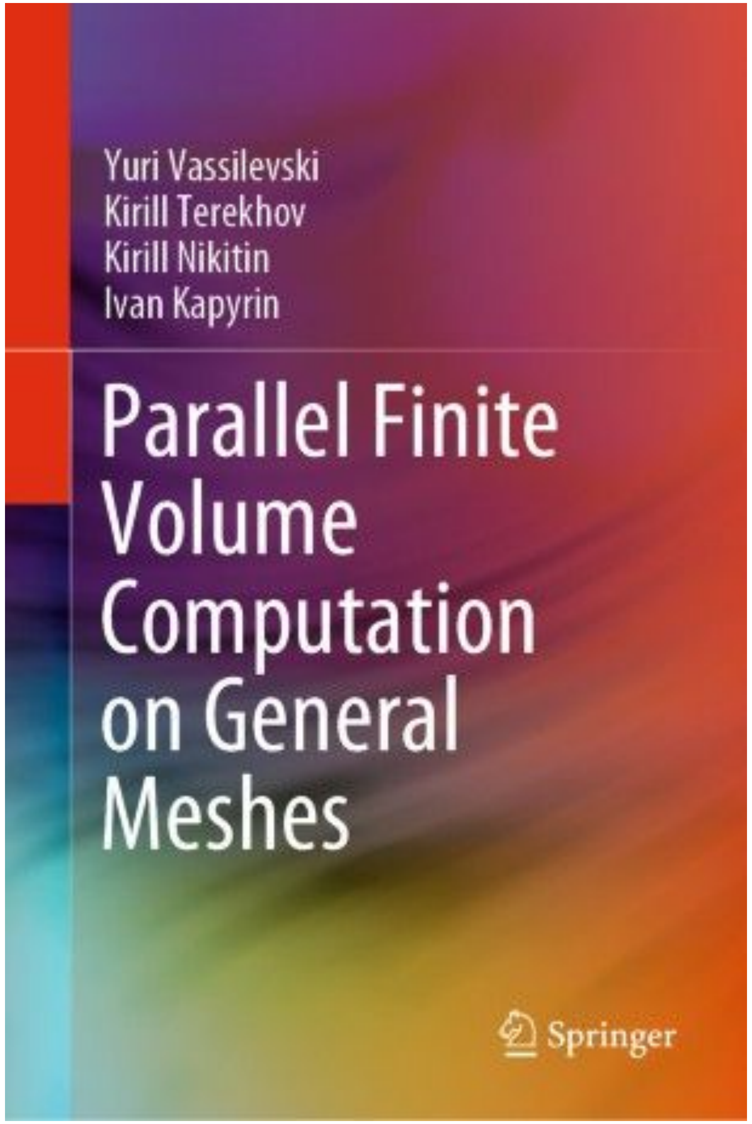
- BC on blood vessel damage:

$$\frac{\partial B_a}{\partial \boldsymbol{n}} = \frac{\alpha(B^0 - B_a)}{1 + \beta(B^0 - B_a)}$$

- BC for Navier-Stokes:
  - no-slip condition on walls
  - pressure drop between inflow and outflow
- BC of Dirichlet/Neumann type for blood components
- Model parameters:
  - from literature,
  - from 0D thrombin generation model,
  - tuned.

Numerical Methods

for model construction



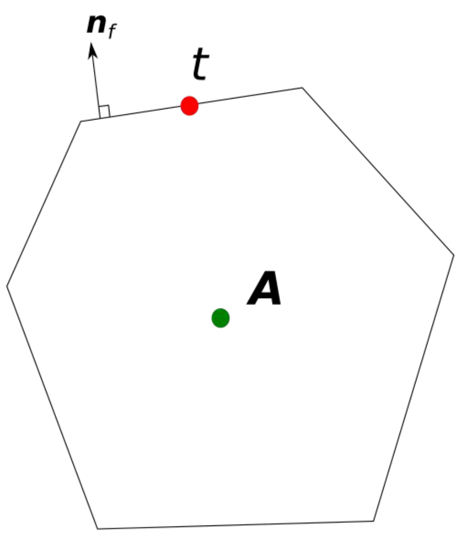
- Vassilevski, Y., Terekhov, K., Nikitin, K., & Kapyrin, I. (2020). **Parallel Finite Volume Computation on General Meshes.** Springer Nature.
- Terekhov, K. (2020). **Collocated Finite-Volume Method for the Incompressible Navier-Stokes Problem.** Journal of Numerical Mathematics

Finite-Volume Method

- Ostrogradsky-Gauss theorem:

$$-\mathrm{div}(\boldsymbol{A}) = \boldsymbol{g} \implies -\oint_{\partial V} \boldsymbol{A}\mathrm{d}\boldsymbol{S} = \int_{V} \boldsymbol{g}\mathrm{d}\boldsymbol{V}$$

$$\implies -\sum_{f\in\mathcal{F}(\boldsymbol{V})} |f|\, \boldsymbol{An}|_{\mathbf{x}_f} = |V|\, \boldsymbol{g}|_{\mathbf{x}_V}$$



- Requires the **flux approximation**:

$$\boldsymbol{t} = \boldsymbol{An}|_{\mathbf{x}_f}$$

FVM for Navier-Stokes

- Full flux expression:

$$t = \left\{ \begin{array}{c} \rho u u^T n - \mu \nabla u n + p n \\ n^T u \end{array} \right|_{\mathbf{x}_f}$$

- **Second-order** Taylor Series approximation:

$$\rho u u^T n\big|_{\mathbf{x}_f} \approx \rho u u^T n\big|_{\mathbf{x}_1} + \rho \left.\frac{\partial u u^T n}{\partial u}\right|_{\mathbf{x}_1} \nabla u \left(\mathbf{x}_f - \mathbf{x}_1\right)$$

- **Upstream** approximation:

3x3 matrix $Q(u_1)$, eigenvalues $n^T u_1, 2n^T u_1, 0$

$$\rho u u^T n\big|_{\mathbf{x}_f} \approx \frac{\rho}{2} \left(u_1 n^T + n^T u_1 \mathbb{I}\right) \times \left\{ \begin{array}{ll} 3u_1 - 2u_f + 4\nabla u(\mathbf{x}_f - \mathbf{x}_1), & n^T u_1 > 0, \\ 2u_f - u_1, & n^T u_1 < 0. \end{array} \right.$$

FVM for Navier-Stokes

- Full flux expression:

$$\boldsymbol{t} = \left\{ \begin{array}{c} \rho \boldsymbol{u}\boldsymbol{u}^T\boldsymbol{n} - \mu \nabla \boldsymbol{u}\boldsymbol{n} + p\boldsymbol{n} \\ \boldsymbol{n}^T\boldsymbol{u} \end{array} \right|_{\mathbf{x}_f}$$

- **Second-order** splitting:

Distance to interface

$$-\mu \nabla \boldsymbol{u}\boldsymbol{n}\big|_{\mathbf{x}_f} \approx \mu \left(\boldsymbol{u}_1 - \boldsymbol{u}_f\right)/r_1 - \mu \nabla \boldsymbol{u}\left(\boldsymbol{n} - (\mathbf{x}_f - \mathbf{x}_1)/r_1\right)$$

Two-point part

Transversal correction

- Two-point yields positive matrix coefficients.
- Transversal correction is zero on orthogonal grids.

FVM for Navier-Stokes

- Full flux expression:

$$\mathbf{t} = \left\{ \begin{array}{c} \rho \mathbf{u}\mathbf{u}^T\mathbf{n} - \mu \nabla \mathbf{u}\mathbf{n} + p\mathbf{n} \\ \mathbf{n}^T\mathbf{u} \end{array} \right|_{\mathbf{x}_f}$$

- **Stable** approximation:

Positive and negative eigenvalues

$$\left\{ \begin{array}{c} p\mathbf{n} \\ \mathbf{n}^T\mathbf{u} \end{array} \right. = \begin{bmatrix} & \mathbf{n} \\ \mathbf{n}^T & \end{bmatrix} \begin{bmatrix} \mathbf{u} \\ p \end{bmatrix}$$

Positive eigenvalues

$$\approx \begin{bmatrix} \xi \mathbf{n}\mathbf{n}^T & \mathbf{n} \\ \mathbf{0}^T & \end{bmatrix} \begin{bmatrix} \mathbf{u}_1 \\ p_1 \end{bmatrix} + \begin{bmatrix} -\xi \mathbf{n}\mathbf{n}^T & \mathbf{0} \\ \mathbf{n}^T & \end{bmatrix} \begin{bmatrix} \mathbf{u}_f \\ p_f \end{bmatrix}$$

$$+ \begin{bmatrix} \xi \mathbf{n}\mathbf{n}^T & \mathbf{0} \\ \mathbf{0}^T & \end{bmatrix} \begin{bmatrix} \nabla \mathbf{u} \left(\mathbf{x}_f - \mathbf{x}_1 \right) \\ \\ \end{bmatrix}$$

Negative eigenvalues

Compensation term

FVM for Navier-Stokes

- Full flux expression:

$$\boldsymbol{t} = \left\{ \begin{array}{c} \rho \boldsymbol{u}\boldsymbol{u}^T\boldsymbol{n} - \mu\nabla\boldsymbol{u}\boldsymbol{n} + p\boldsymbol{n} \\ \boldsymbol{n}^T\boldsymbol{u} \end{array} \right|_{\mathbf{x}_f}$$

- Combination of approximations:

$$\begin{aligned} \boldsymbol{t} \approx & \left(\frac{3}{2}Q(\boldsymbol{u}_1)^+ - \frac{1}{2}Q(\boldsymbol{u}_1)^- + \frac{\mu}{r_1}\mathbb{I} + \xi\boldsymbol{n}\boldsymbol{n}^T\right)\boldsymbol{u}_1 \\ & - \left(Q(\boldsymbol{u}_1)^+ - Q(\boldsymbol{u}_1)^- + \frac{\mu}{r_1}\mathbb{I} + \xi\boldsymbol{n}\boldsymbol{n}^T\right)\boldsymbol{u}_f \\ & - \nabla\boldsymbol{u}\left(\mu\boldsymbol{n} - \left(\frac{\mu}{r_1}\mathbb{I} + \xi\boldsymbol{n}\boldsymbol{n}^T + 2Q(\boldsymbol{u}_1)^+\right)(\mathbf{x}_f - \mathbf{x}_1) + p_1\boldsymbol{n}\right. \end{aligned}$$

- Interface unknown elimination is based on the flux continuity.
- Computation of gradients is based on Green's formula

FVM for Blood Components

- Flux expression: $\boldsymbol{n}^T(C\boldsymbol{u} - D\nabla C)$
- Advection: **first-order** upstream:

$$C\boldsymbol{n}^T\boldsymbol{u} \approx \frac{1}{2}\left(C_1(\boldsymbol{n}^T\boldsymbol{u} + |\boldsymbol{n}^T\boldsymbol{u}|) + C_2(\boldsymbol{n}^T\boldsymbol{u} - |\boldsymbol{n}^T\boldsymbol{u}|)\right)$$

- Diffusion: **second-order** nonlinear two-point approximation:
-

$$D\boldsymbol{n}^T\nabla C \approx D\frac{(C_1 - C_2)}{|\boldsymbol{x}_1 - \boldsymbol{x}_2|} - D(\mu_1\nabla C_1 + \mu_2\nabla C_2)\cdot\left(\boldsymbol{n} - \frac{(\boldsymbol{x}_1 - \boldsymbol{x}_2)}{|\boldsymbol{x}_1 - \boldsymbol{x}_2|}\right) = D(T_1C_1 - T_2C_2)$$

- Solution is **nonnegative** – very important for reactions!

FVM for Traffic Flow

- Flux expression: $\lambda(C)\boldsymbol{n}^T\boldsymbol{u}$
  - advection: $\lambda(C) = C$
  - traffic: $\lambda(C) = C(1 - C)$
  - our case: $\lambda(C) = C\tanh(1 - C)$
- **First-order** upstream approximation:

$\lambda'(C_1)\boldsymbol{n}^T\boldsymbol{u}$	$\lambda'(C_1)\boldsymbol{n}^T\boldsymbol{u}$	$\boldsymbol{t}$
+	+	$\lambda(C_1)\boldsymbol{n}^T\boldsymbol{u}$
-	-	$\lambda(C_2)\boldsymbol{n}^T\boldsymbol{u}$
+	-	$\mathrm{minmod}(\lambda(C_1), \lambda(C_2))\boldsymbol{n}^T\boldsymbol{u}$
-	+	$\lambda(C)\boldsymbol{n}^T\boldsymbol{u},\ \lambda'(C) = 0$

Moscow traffic
(image from internet)

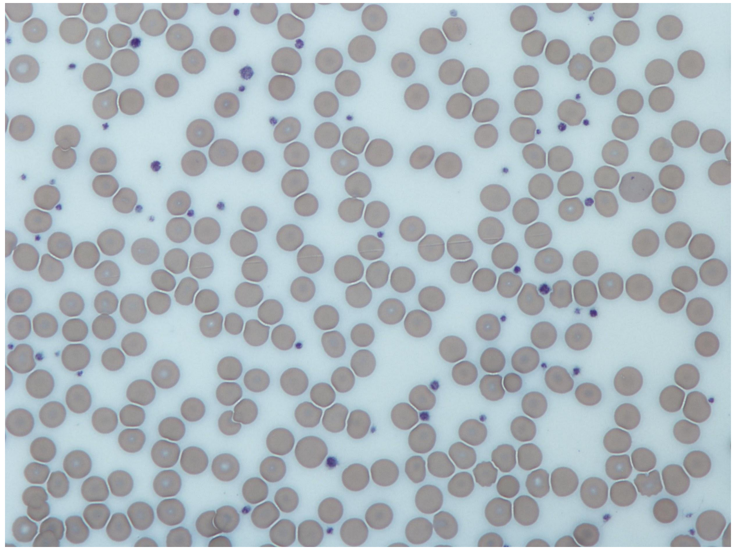
FVM for Platelets

- Flux expression: $\boldsymbol{t}(\phi_c, \phi_f) = \tanh\left(\pi\left(1 - \frac{\phi_c + \phi_f}{\phi_{max}}\right)\right)\boldsymbol{n}^T(\boldsymbol{u} - D_p\nabla)\begin{pmatrix}\phi_c \\ \phi_f\end{pmatrix}$
- Jacobian contribution:

$$J(\phi_c, \phi_f) = \begin{pmatrix} \frac{\partial \boldsymbol{t}_1(\phi_c, \phi_f)}{\partial \phi_c} & \frac{\partial \boldsymbol{t}_1(\phi_c, \phi_f)}{\partial \phi_f} \\ \frac{\partial \boldsymbol{t}_2(\phi_c, \phi_f)}{\partial \phi_c} & \frac{\partial \boldsymbol{t}_2(\phi_c, \phi_f)}{\partial \phi_f} \end{pmatrix} \begin{pmatrix} d\phi_c \\ d\phi_f \end{pmatrix} = Q(\phi_c, \phi_f)\begin{pmatrix} d\phi_c \\ d\phi_f \end{pmatrix}$$

- Matrix-weighted combination for two cells:

$$\Phi = M_1\begin{pmatrix}\phi_{c,1} \\ \phi_{f,1}\end{pmatrix} + M_2\begin{pmatrix}\phi_{c,2} \\ \phi_{f,2}\end{pmatrix}$$



Platelets
(image from internet)

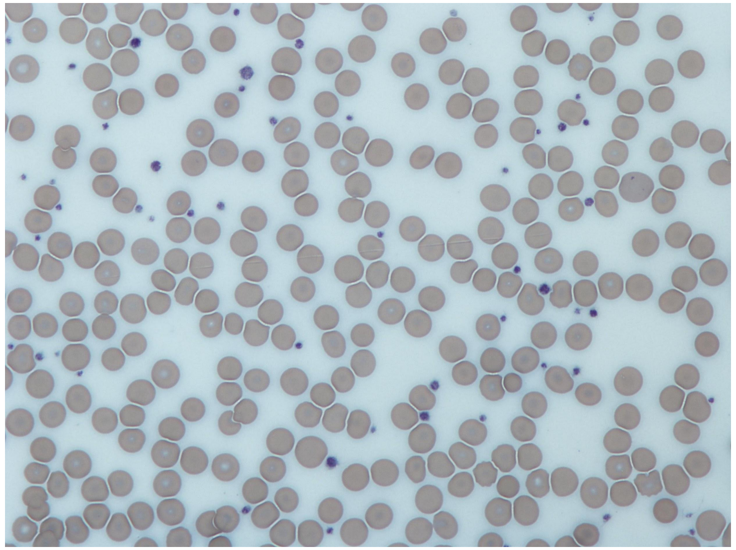
FVM for Platelets

- Flux expression: $\boldsymbol{t}(\phi_c, \phi_f) = \tanh\left(\pi\left(1 - \frac{\phi_c + \phi_f}{\phi_{max}}\right)\right)\boldsymbol{n}^T(\boldsymbol{u} - D_p\nabla)\begin{pmatrix}\phi_c \\ \phi_f\end{pmatrix}$
- Iterative search:

$$J(\Phi) = Q(\Phi)M_1\begin{pmatrix}d\phi_{c,1} \\ d\phi_{f,1}\end{pmatrix} + Q(\Phi)M_2\begin{pmatrix}d\phi_{c,2} \\ d\phi_{f,2}\end{pmatrix}$$

- Matrices are obtained using eigendecomposition:

$$Q(\Phi) = L\Lambda L^T,$$
$$M_1 = \frac{1}{2}L(\mathrm{sgn}(\Lambda) + |\mathrm{sgn}(\Lambda)|)L^T$$
$$M_2 = \frac{1}{2}L(\mathrm{sgn}(\Lambda) - |\mathrm{sgn}(\Lambda)|)L^T$$



Platelets
(image from internet)

Approximation for Reactions

- Reactions lead to very **small time step** even with fully implicit integration.
- Problem – **bad contribution** to off-diagonal terms of Jacobian matrix.
- Approach for terms leading to bad contribution:
  - time extrapolation, physics-based limiter for extrapolation
  - space interpolation

Approximation for Reactions

- Red terms are extrapolated from previous time steps:

$$R(\Theta^{n+1}) \approx \begin{pmatrix} -\left(k_1\hat{\phi}_c + k_2 B_\alpha^{n+1} + k_3\hat{T} + k_4\hat{T}^2 + k_5\hat{T}^3\right) P^{n+1} \\ \left(k_1\hat{\phi}_c + k_2 B_\alpha^{n+1} + k_3\hat{T} + k_4\hat{T}^2 + k_5\hat{T}^3\right) P - k_6 A^{n+1} T^{n+1} \\ \left(k_7\phi_c^{n+1} + k_8 T^{n+1}\right)\left(B^0 - B_\alpha^{n+1}\right) - k_9 A^{n+1} B_\alpha^{n+1} \\ -\left(k_6 T^{n+1} + k_9 B_\alpha^{n+1}\right) A^{n+1} \\ -\frac{k_{10}\hat{T} F_g^{n+1}}{K_{10}+F_g^{n+1}} \\ \frac{k_{10}\hat{T} F_g^{n+1}}{K_{10}+F_g^{n+1}} - k_{11} F^{n+1} \\ k_{11} F^{n+1} \\ -\left(k_{12}\hat{T} - k_{13}\phi_c^{n+1}\right)\phi_f^{n+1} \\ \left(k_{12}\hat{T} - k_{13}\phi_c^{n+1}\right)\phi_f^{n+1} \end{pmatrix}$$

P T B_α A F_g F ϕ_f ϕ_c

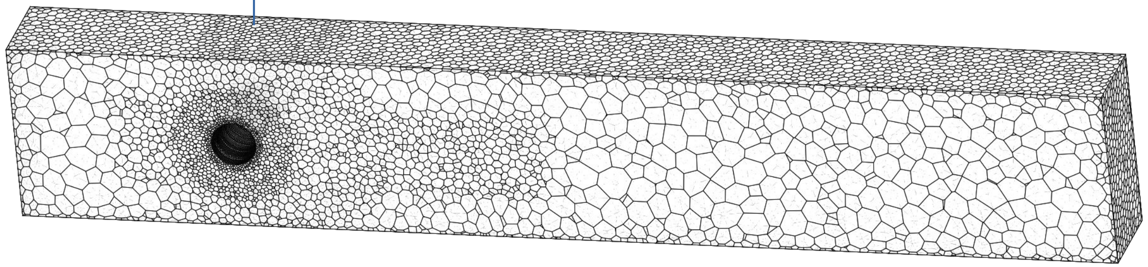
- Fully implicit model with 13 unknowns.

Verification

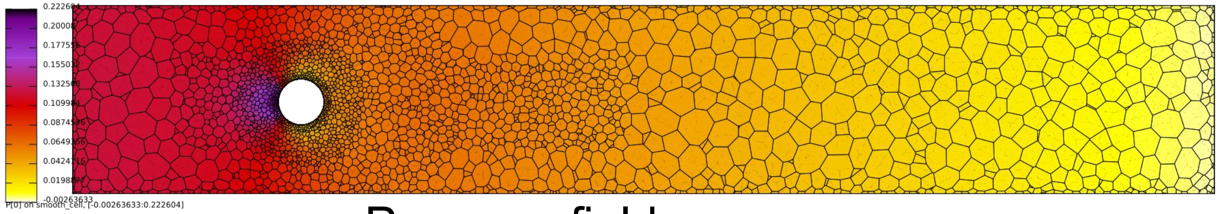
of the model

Viscous Flow Past a Cylinder

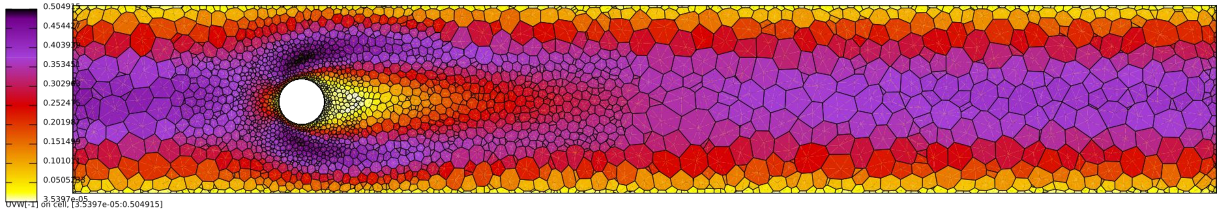
Refinement	Cells	Drag	Lift	Pressure drop
1	910	3.862	-0.08556	0.1481
2	4328	4.964	-0.02525	0.1854
3	24687	5.515	0.07256	0.1672
4	164806	5.876	0.00803	0.1890
$3^{\dagger}$	53211	6.064	0.01015	0.1801
$3^{\ddagger}$	98517	6.155	0.01006	0.1792
Schäfer & Turek [23]	-	6.05-6.25	0.008-0.01	0.165-0.175
Braack & Richter [7]	-	6.185331	0.00940	0.1713



Locally refined polyhedral mesh



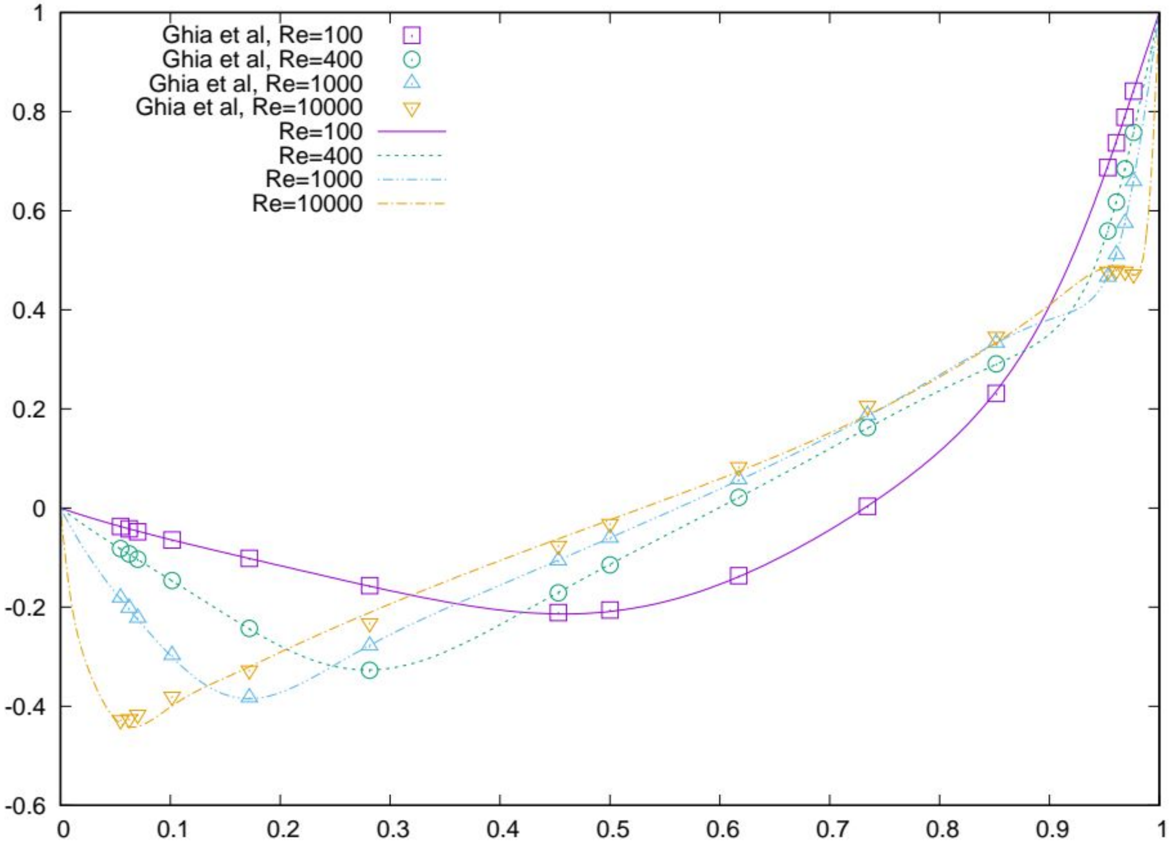
Pressure field

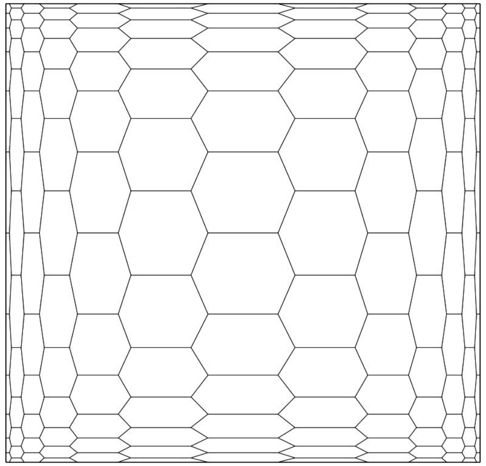


Velocity magnetude

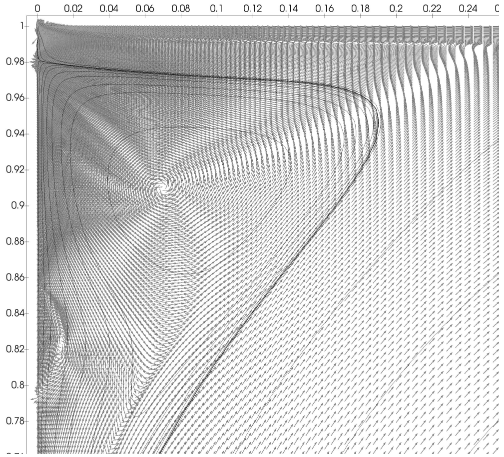
Cavity Flow at High Reynolds Numbers

- Comparison to reference data of Ghia et al.

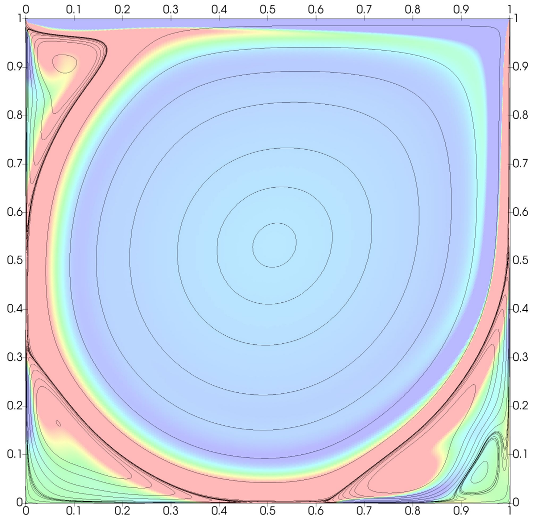




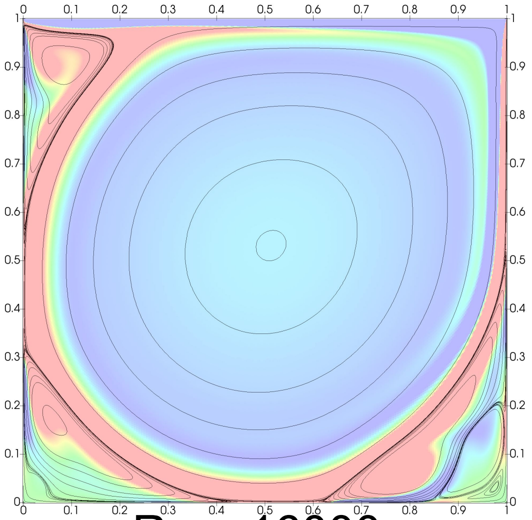
Hexagonal mesh



Tertiary vortex, Re = 16000



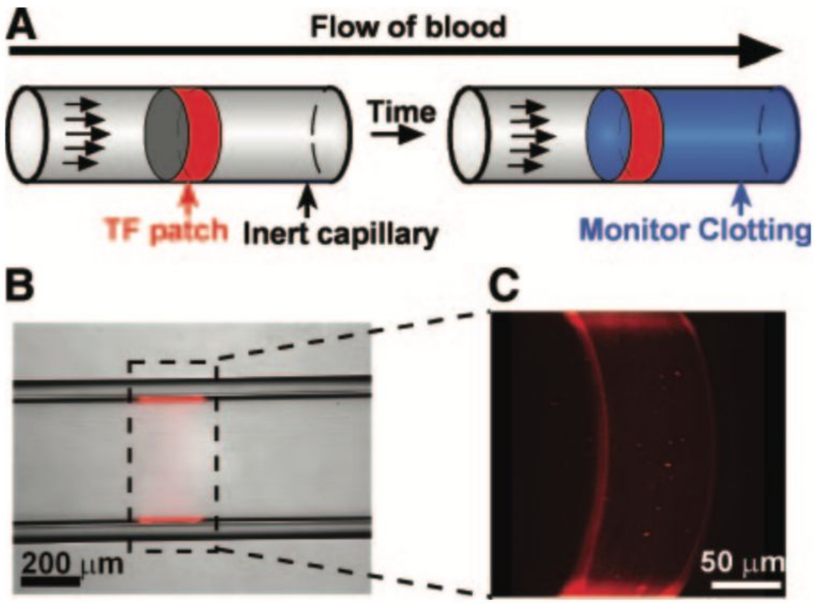
Re = 10000



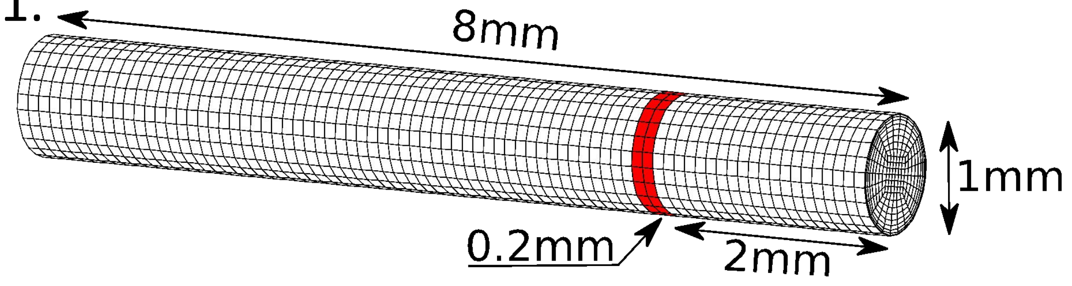
Re = 16000

Comparison to the Experimental Data

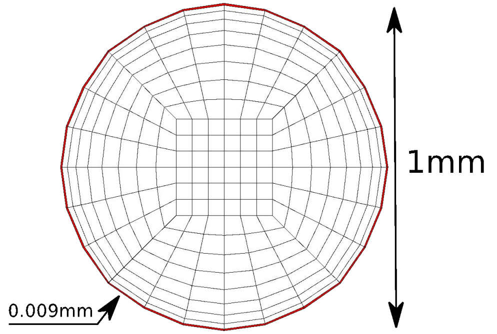
- Based on the **experimental research**: Shen F., Kastrup C.J., Liu Y., Ismagilov R.F.: ***Threshold response of initiation of blood coagulation by tissue factor in patterned microfluidic capillaries is controlled by shear rate.*** **Arteriosclerosis, thrombosis, and vascular biology.** 2008, 28(11): 2035–2041.



Experiment illustration



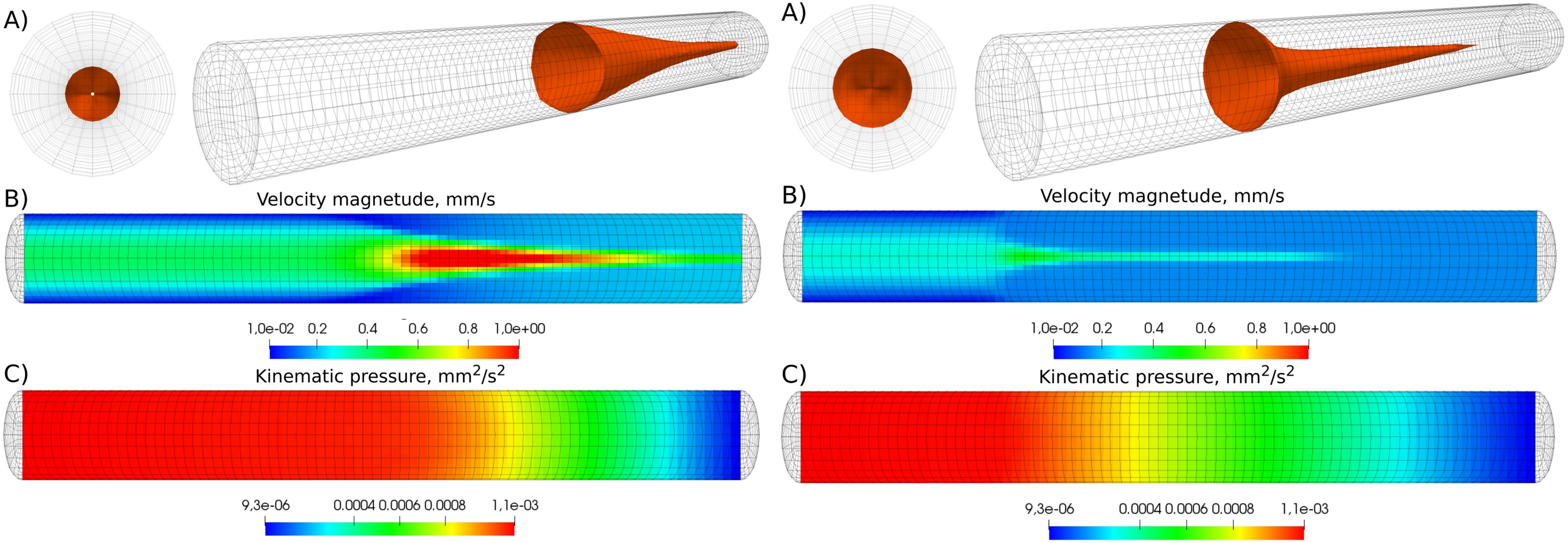
Computational domain



Section of the cylinder

Comparison to the Experimental Data

T=60s T=70s



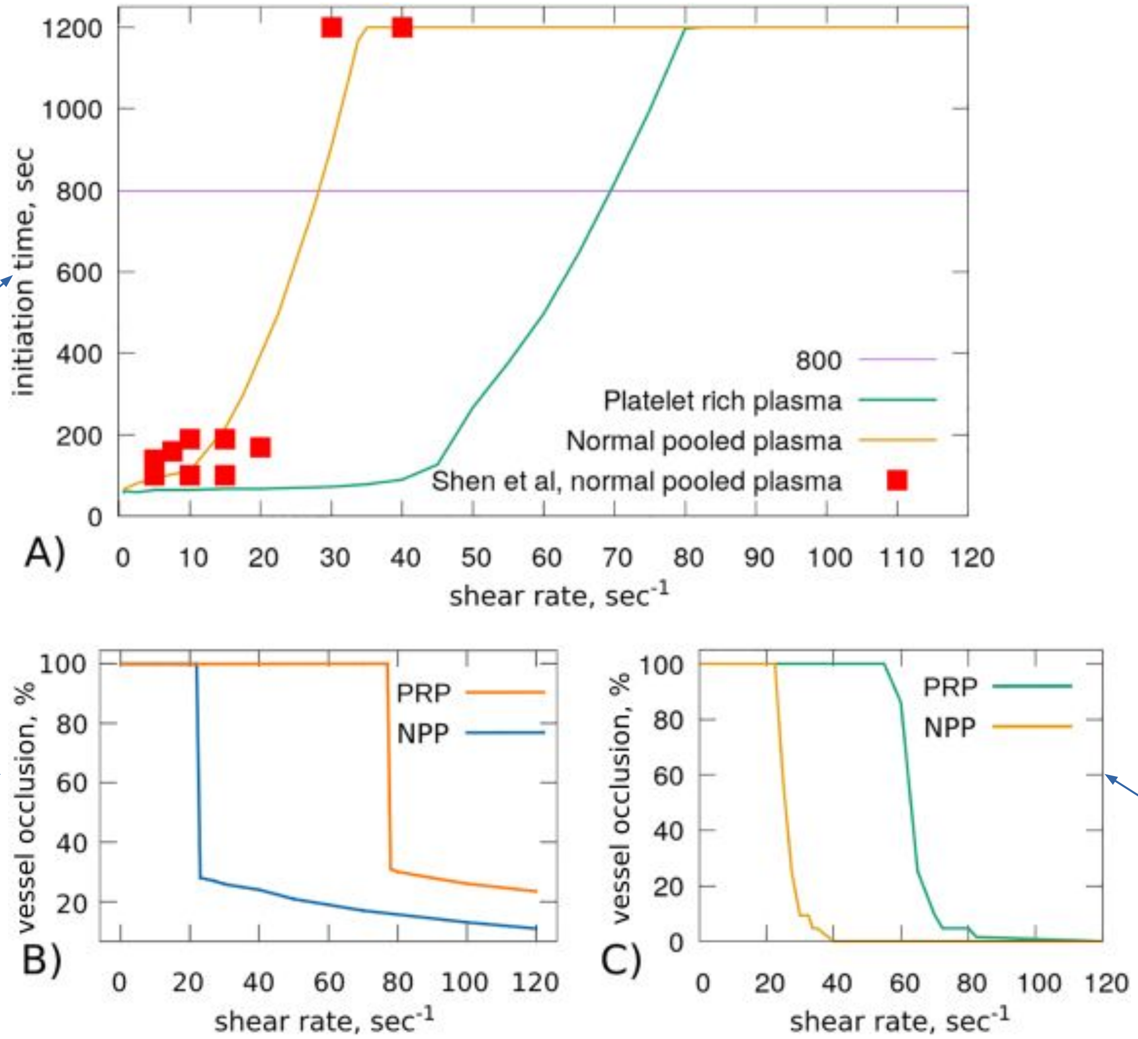
Reproduction of qualitative characteristics of the experiment

Comparison to the Experimental Data

A) Validation of 3D model on experimental data

B) Simplified 1D clot formation model

C) Full 3D simulation of clot flormation



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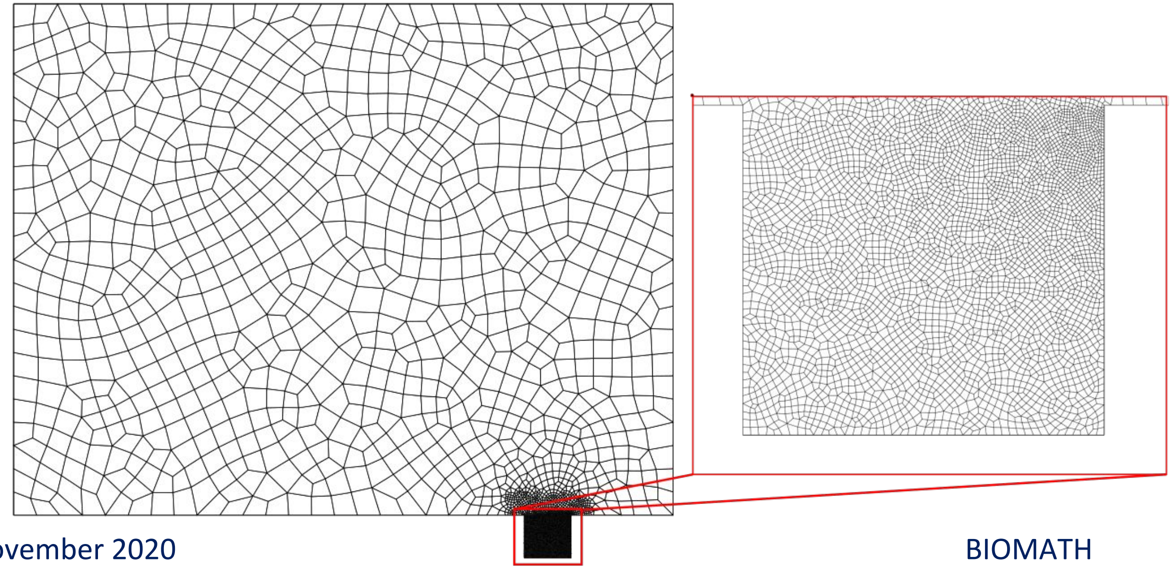
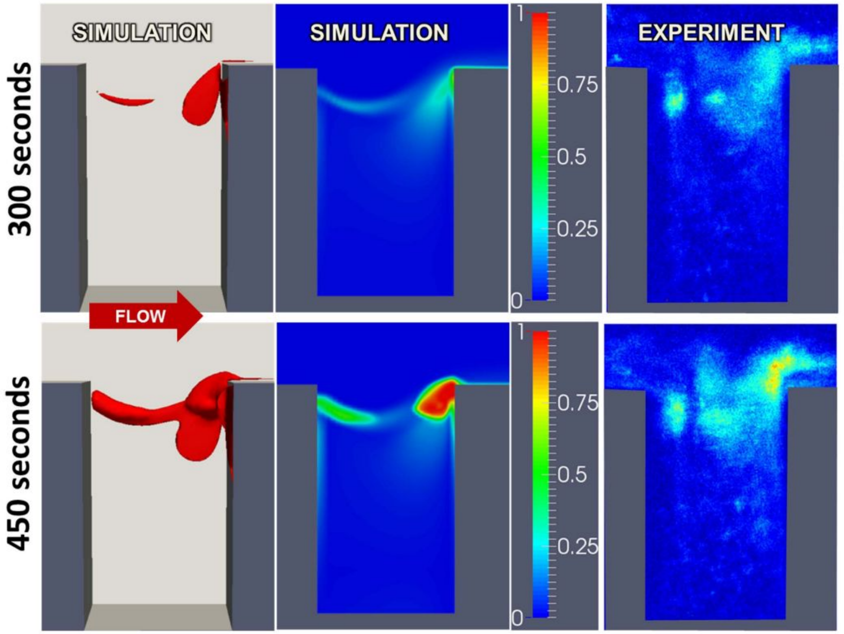
Future Directions

- Clot formation due to von Willebrand factor in the flow with high share rate (Nadezhda Suslova)
- Automatic stabilization of chemical reactions (Ivan Butakov)





from Wei-Tai Wu et al, Multi-Constituent Simulation Of Thrombus Deposition

Thank you for your attention!

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Links

- [WWW.INMOST.ORG]