Clot growth regimes for blood coagulation in flow

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Working group on mathematical models and numerical methods in biomathematics

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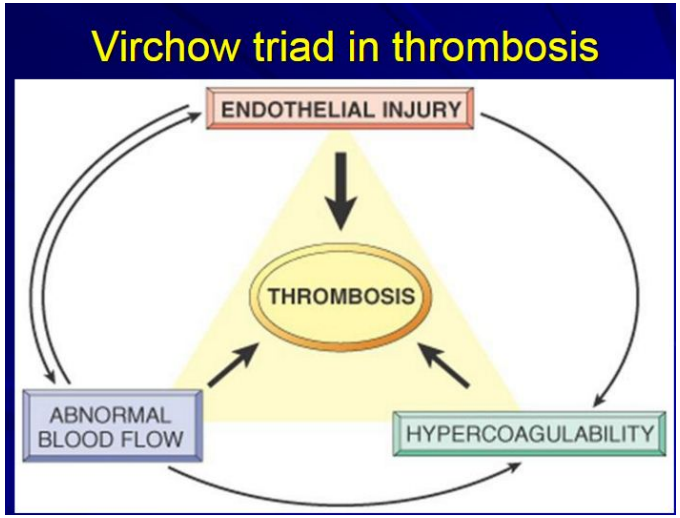
The potential role of blood flow in thrombosis development

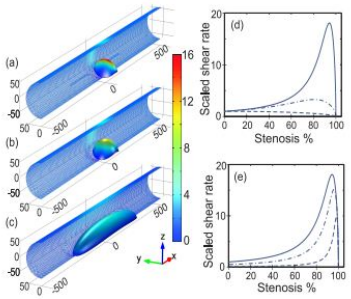


(V. Kumar et al. Robbins Basic Pathology. 8th edition. Elsevier)

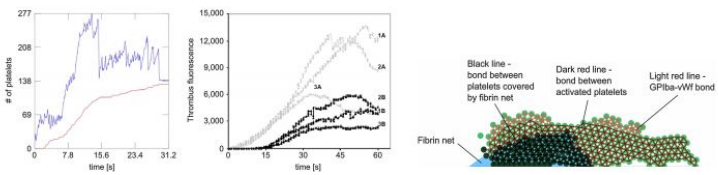
- Abnormal flow is one of the three components of Virchow's triad of thrombosis,
- it changes the distribution of clotting factor resulting in hypercoagulability,
- laminar fast flow washes away thrombin and clotting factor from the thrombus.

Recent models of thrombus growth in flow

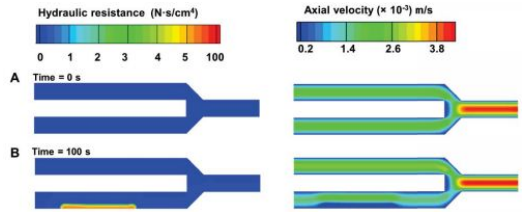
Belyaev, A. V., Panteleev, M. A., & Ataullakhanov, F. I. (2015). Threshold of microvascular occlusion: injury size defines the thrombosis scenario. Biophysical journal, 109(2), 450-456.



Tosenberger, A., Ataullakhanov, F., Bessonov, N., Panteleev, M., Tokarev, A., & Volpert, V. (2016). Modelling of platelet–fibrin clot formation in flow with a DPD–PDE method. Journal of mathematical biology, 72(3), 649-681.

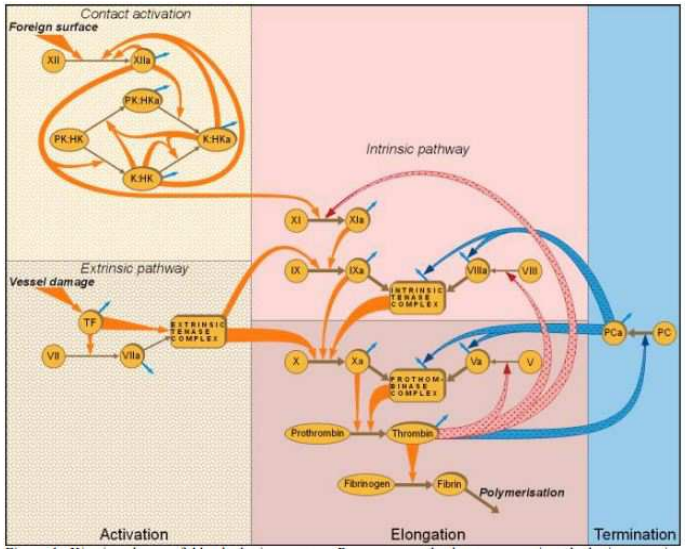


Govindarajan, V., Rakesh, V., Reifman, J., & Mitrophanov, A. Y. (2016). Computational Study of Thrombus Formation and Clotting Factor Effects under Venous Flow Conditions. Biophysical journal, 110(8), 1869-1885.

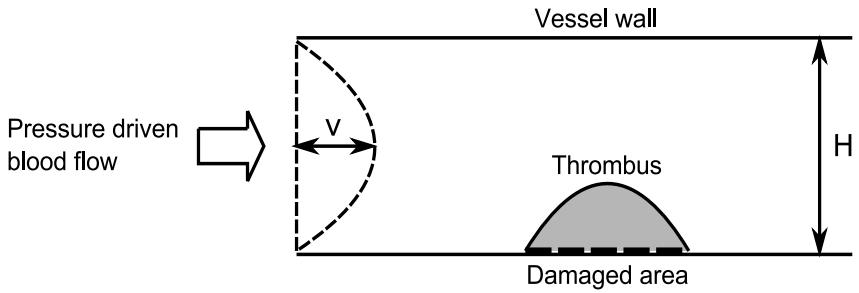


The interplay between thrombus growth and hemodynamics

a)



b)



Blood clotting cascade biochemistry

Bouchnita, A., Tosenberger, A., & Volpert, V. (2016). On the regimes of blood coagulation. Applied Mathematics Letters, 51, 74-79.

Reaction-diffusion-diffusion equations:

1 - Prothrombin and antithrombin are abundantly present in blood plasma. Initial conditions and left boundary conditions are set to $P = P_0$ and $A = A_0$:

$$\frac{\partial P}{\partial t}+\nabla.(vP) = D\Delta P-\Phi(T, B_a, C_a)P, \quad \frac{\partial A}{\partial t}+\nabla.(vA) = D\Delta A-k_a AT, \tag{1}$$

2 - Thrombin is the key enzyme responsible of blood clotting:

$$\frac{\partial T}{\partial t} + \nabla.(vT) = D\Delta T + \Phi(T, B_a, C_a)P - k_a AT, \tag{2}$$

In equations (1) and (2), we have:

$$\Phi(T, B_a, C_a) = \underbrace{k_3 B_a}_{\text{Initiation phase}} + \underbrace{k_4 T^m}_{\text{Amplification phase}} / (\underbrace{1 + k_5 C_a}_{\text{Inhibition by APC}})$$

Blood clotting cascade biochemistry

Reaction-diffusion-diffusion equations:

3 - The sum of factors IXa and Xa concentrations (B_a):

$$\frac{\partial B_a}{\partial t} + \nabla.(vB_a) = D\Delta B_a, \tag{3}$$

with B.C:

$$\frac{\partial B_a}{\partial n}\Big|_{\Gamma_d} = \frac{k_6(B^0 - B_a)}{1 + k_7(B^0 - B_a)}, \tag{4}$$

4 - Activated protein C concentration (C_a):

$$\frac{\partial C_a}{\partial t} + \nabla.(vC_a) = D\Delta C_a, \tag{5}$$

with B.C:

$$\frac{\partial C_a}{\partial n}\Big|_{\Gamma_u} = \frac{k_8(C^0 - C)T}{1 + k_9(C^0 - C_a)}, \tag{6}$$

Blood clotting cascade biochemistry

Reaction-diffusion-advection equations:

5 - Fibrinogen concentration (F_g) (Abundantly present in blood plasma $F_g = F_{g0}$):

$$\frac{\partial F_g}{\partial t} + \nabla.(vF_g) = D\Delta F_g - k_1 T F_g, \tag{7}$$

6 - Fibrin (F):

$$\frac{\partial F}{\partial t} + \nabla.(vF) = D\Delta F + k_1 T F_g - k_2 F, \tag{8}$$

7 - Fibrin polymer (F_p):

$$\frac{\partial F_p}{\partial t} = k_2 F. \tag{9}$$

Haemodynamics of clot growth

Navier-Stokes equations with the clot as a porous medium:

$$\rho\left(\frac{\partial\vec{v}}{\partial t}+\vec{v}.\nabla\vec{v}\right)=-\nabla p+\mu\Delta\vec{v}-\frac{\mu}{K_f(\vec{x})}\vec{v}; \tag{10}$$

$$\nabla\vec{v}=0.$$

In (10), the permeability $K_f(\vec{x})$ depends on the concentrations of fibrin polymer[1]:

$$\frac{1}{K_f(\vec{x})}=\alpha 16F_p(\vec{x})^{1.5}(1+56F_p(\vec{x})^3); \tag{11}$$

The factor α should express viscosity and fiber radius. In this simulation, we consider that $\alpha=0.02$.

[1] Wufsus, A. R., N. E. Macera, and K. B. Neeves. "The hydraulic permeability of blood clots as a function of fibrin and platelet density." Biophysical journal 104.8 (2013): 1812-1823.

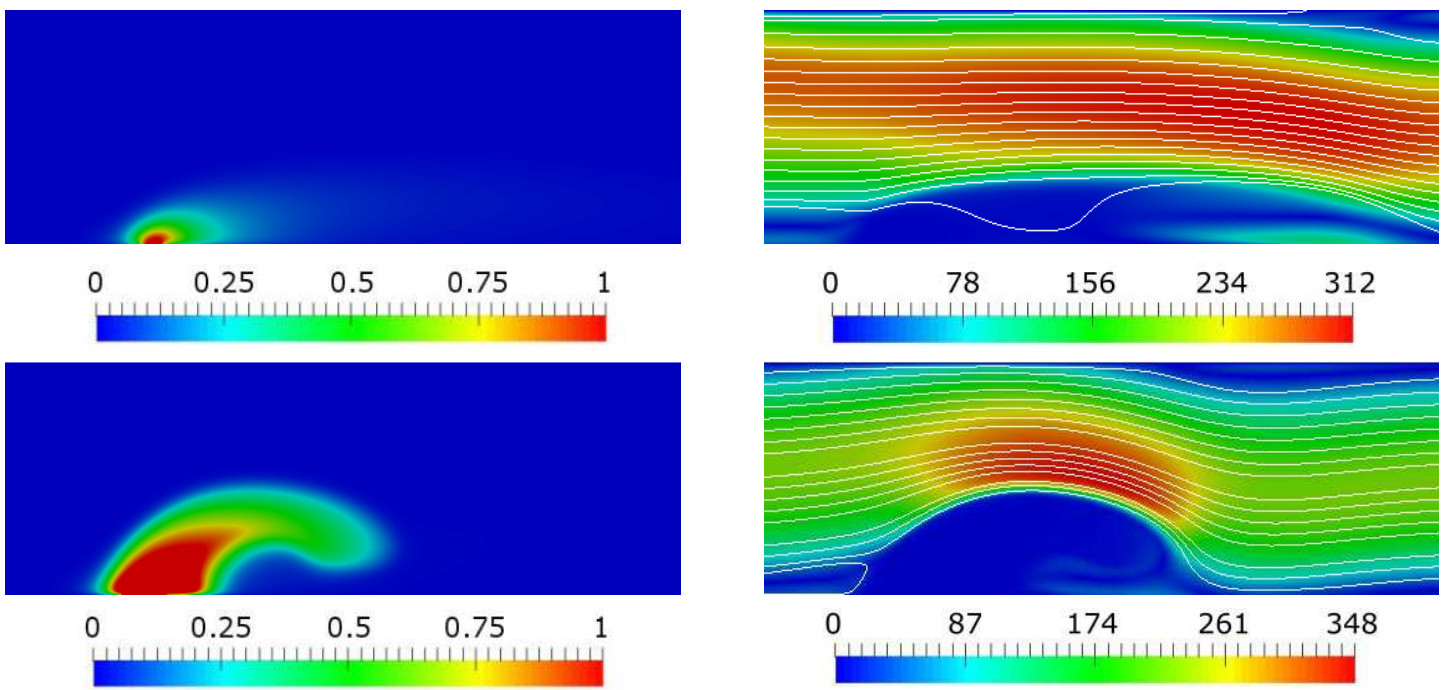
Numerical simulations of vessel occlusion regimes

Bouchnita, A., Galochkina, T., Kurbatova P., Nony, P. & Volpert, V. "Conditions of microvessel occlusion for blood coagulation in flow". International Jounal for Numerical Methods in Biomedical Engineering. Accepted.

Partially occlusive thrombosis

a. Fibrin polymer concentration

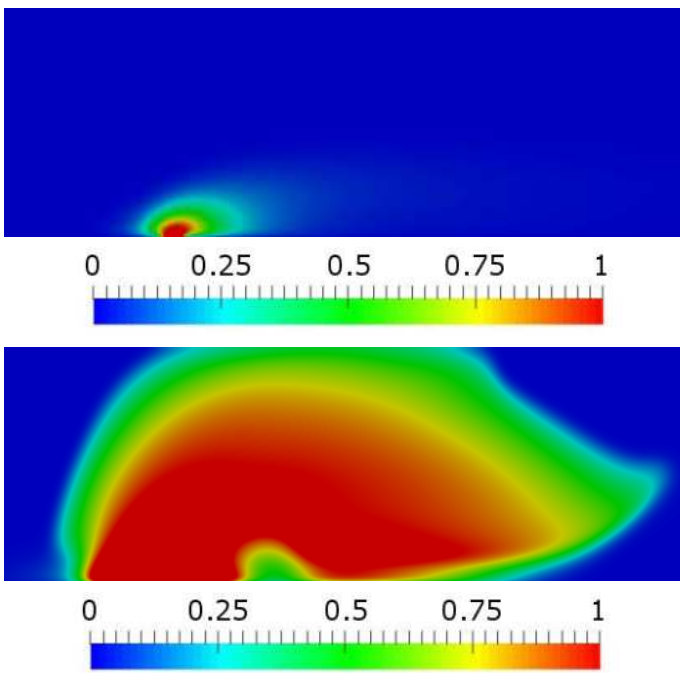
b. Velocity magnitude (μm/s)



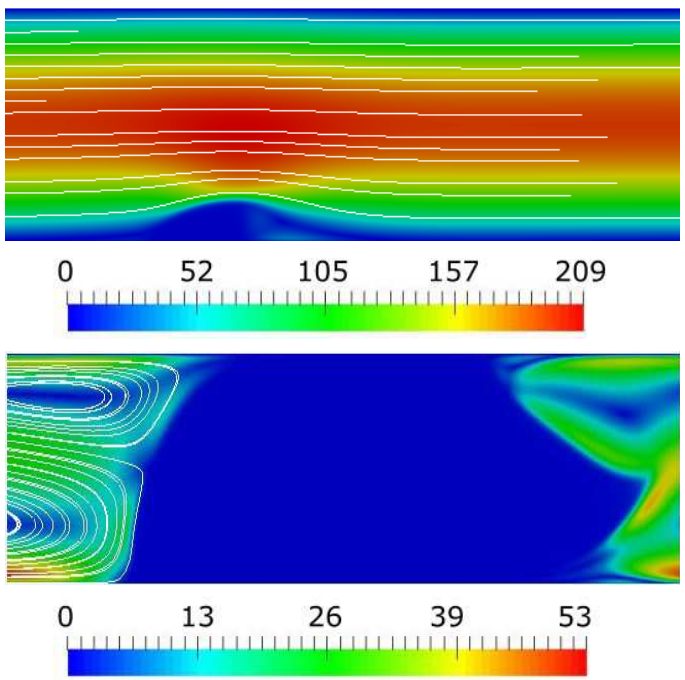
Blood occlusion regimes

Completely occlusive thrombosis

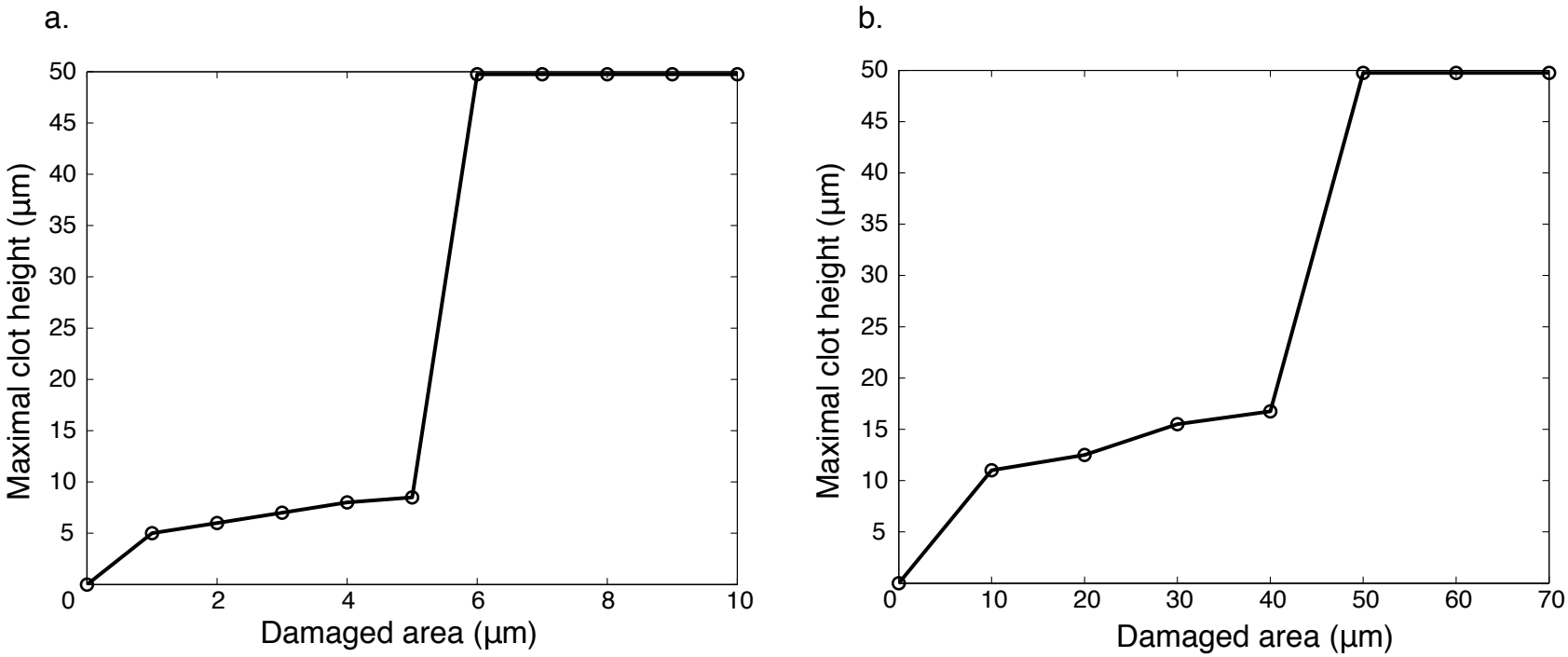
a. Fibrin polymer concentration



b. Velocity magnitude (μm/s)

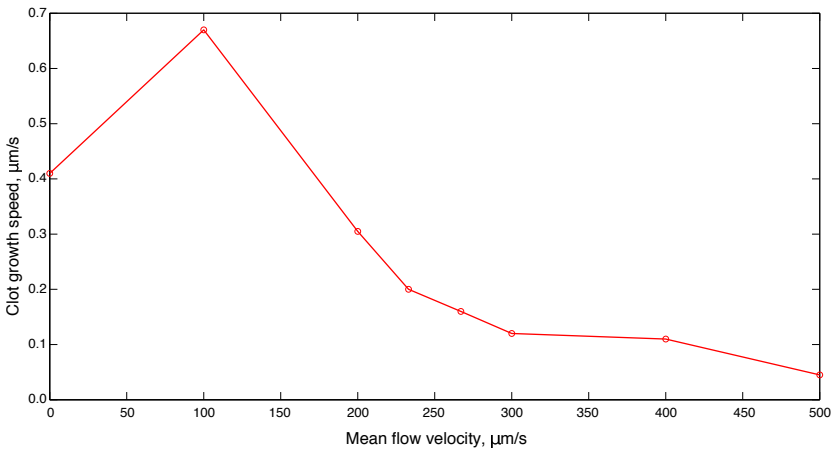


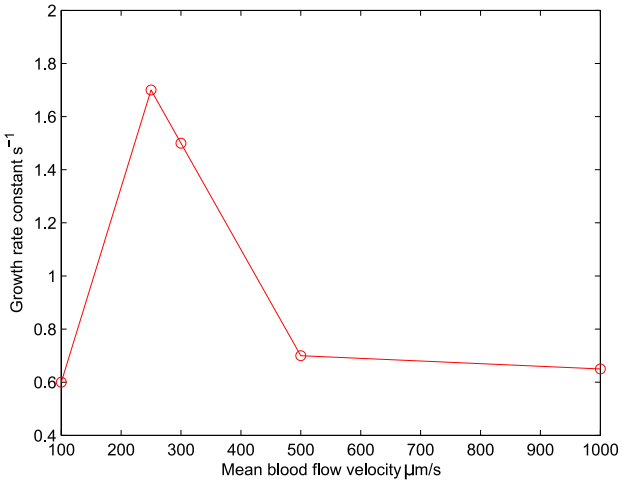
The injury size determines the regime of vessel occlusion



Left: without flow; Right: under flow

The regimes of clot growth velocity in flow





Left: numerical simulations results

Right: *In vitro* experiments from "Begent, Nicola, and G. V. R. Born. "Growth rate in vivo of platelet thrombi, produced by iontophoresis of ADP, as a function of mean blood flow velocity." Nature 227 (1970): 926-930."

Simplified model of thrombin distribution

For a sufficiently wide clot, we derive a model of thrombin concentration consisting of one equation:

$$\frac{\partial T}{\partial t} = D\frac{\partial^2 T}{\partial y^2} + \Phi(T, y), \tag{12}$$

where

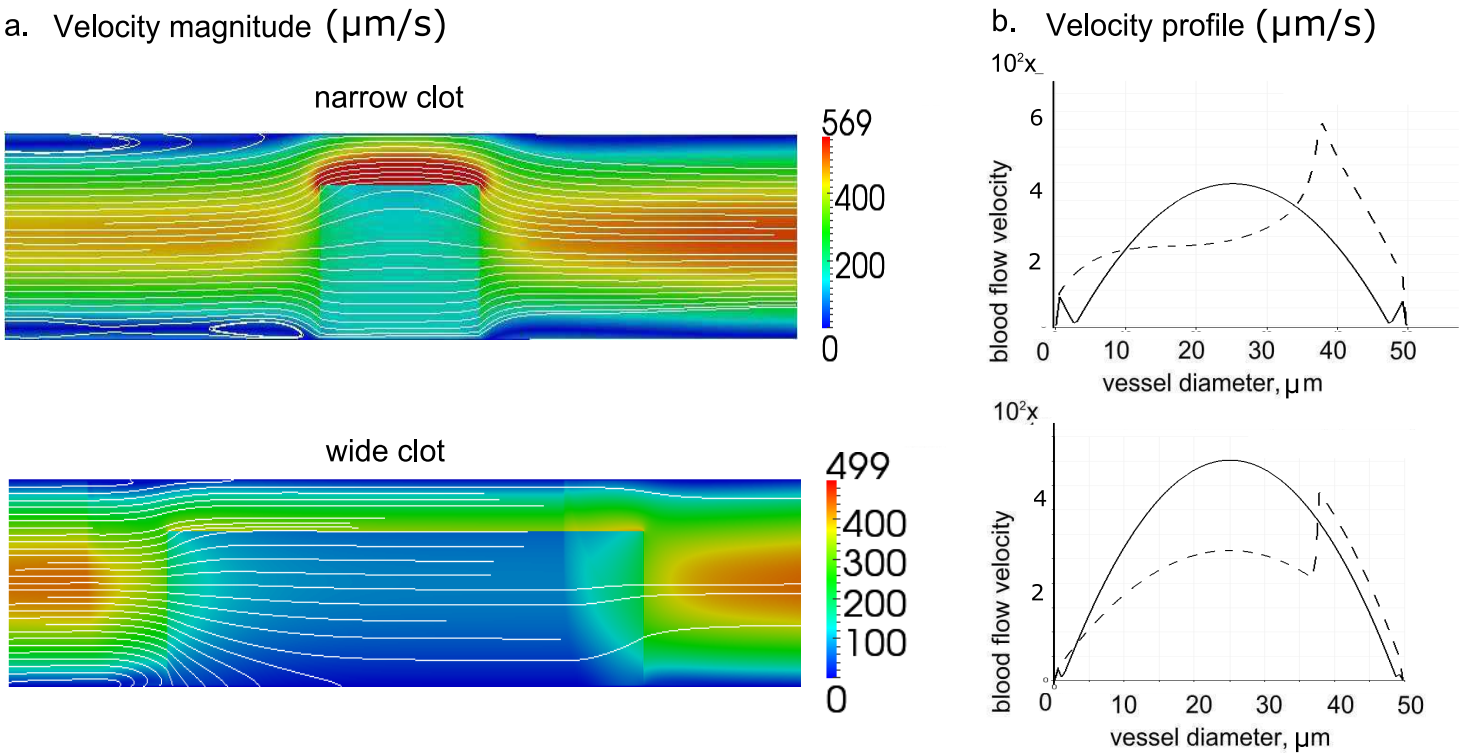
$$\Phi(T, y) = (k_3 B_a(y) + k_4 T^3)(P_0 - T) - \sigma(y)T,$$

The model sustain analytical investigation. For thrombin to propagate (i.e. clot growth):

$$\int_0^{T^*} \Phi(T, y)dT > 0. \tag{13}$$

Haemodynamics of clot growth

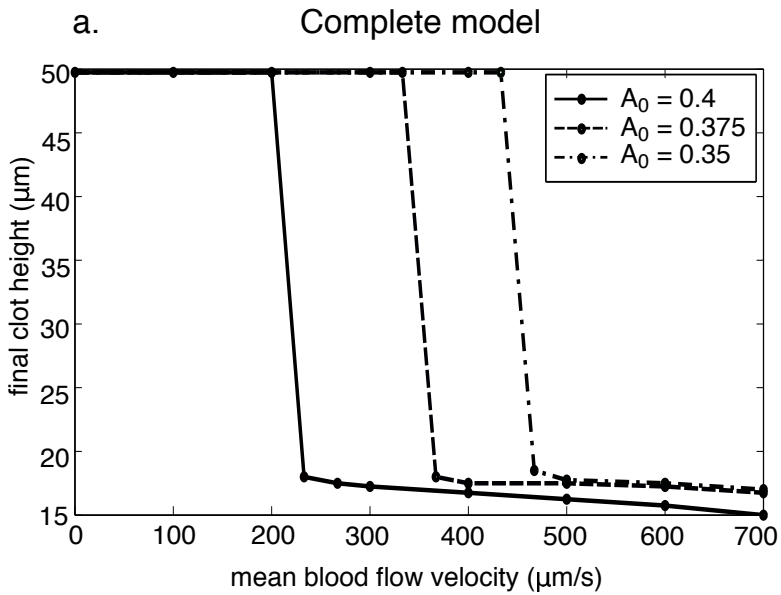
The size of the clot determines the profile of blood flow:

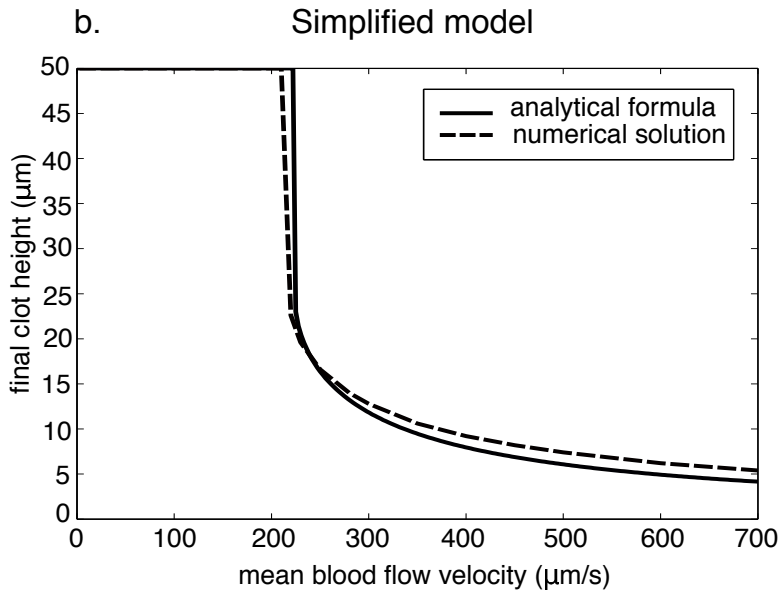


The analytical validation of the truncated parabolic profile hypothesis is provided in: "Beavers G S, Joseph D D. Boundary conditions at a naturally permeable wall. *Journal of fluid mechanics* 1967; **30**(01):197-207."

Conditions of vessel occlusion in flow

Blood flow limits clot growth and determine the regimes of vessel occlusion





Model of thrombus growth and platelet aggregation

The permeability of the clot depends on the concentrations of fibrin polymer and platelets attached to the endothelium (ϕ_b):

$$\frac{1}{K(\vec{x})} = \frac{1}{K_f(\vec{x})} \frac{1+\phi_b}{1-\phi_b},$$

Mobile platelets in the flow:

$$\frac{\partial \phi_f}{\partial t} + \nabla.(vk(\phi)\phi_f) = D_p \Delta(k(\phi)\phi_f) - \beta_1(F_0 - F_p)\phi_f\phi_c - \beta_2 T \phi_f, \tag{14}$$

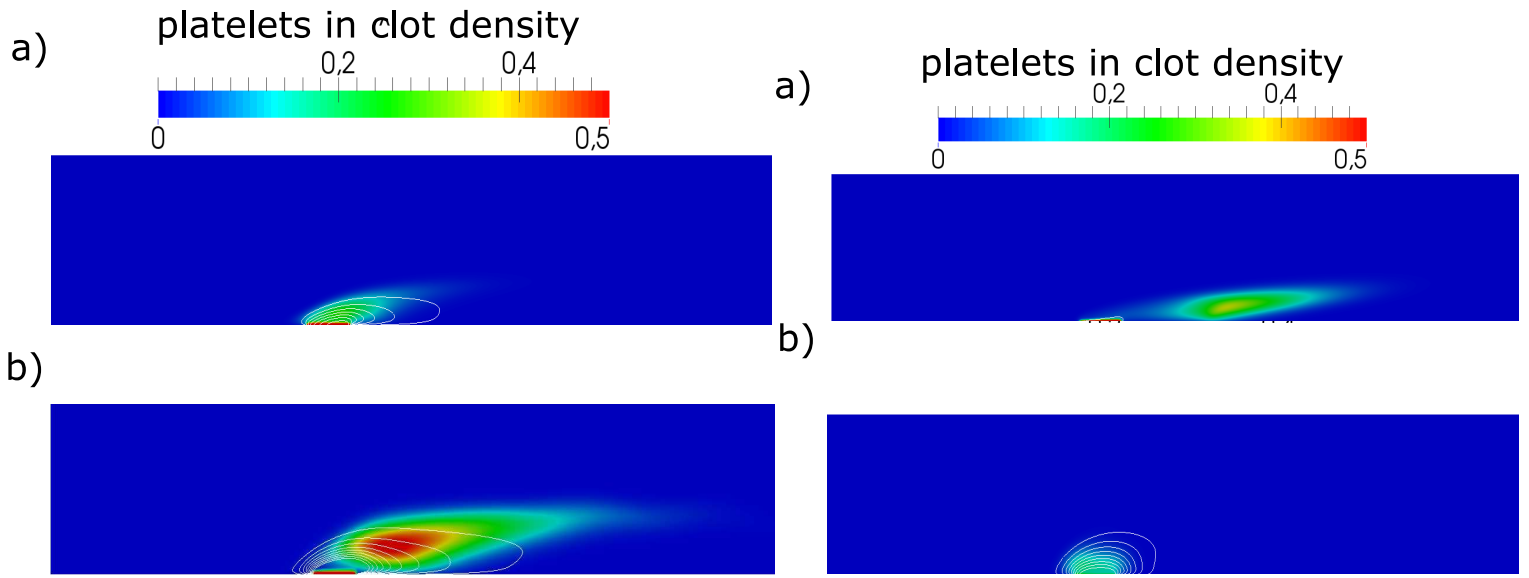
Mobile platelets in the clot:

$$\frac{\partial \phi_c}{\partial t} + \nabla.(vk(\phi)\phi_c) = D_p \Delta(k(\phi)\phi_c) + \beta_1(F_0 - F_p)\phi_f\phi_c + \beta_2 T\phi_f - \beta_3 \int_\Omega d(x_1 - x_2)\phi_b(x_2)dx_2\phi_c, \tag{15}$$

Bounded platelets to the endothelium:

$$\frac{\partial \phi_b}{\partial t} = \beta_3 \int_\Omega d(x_1 - x_2)\phi_b(x_2)dx_2\phi_c. \tag{16}$$

Model of thrombus growth and platelet aggregation

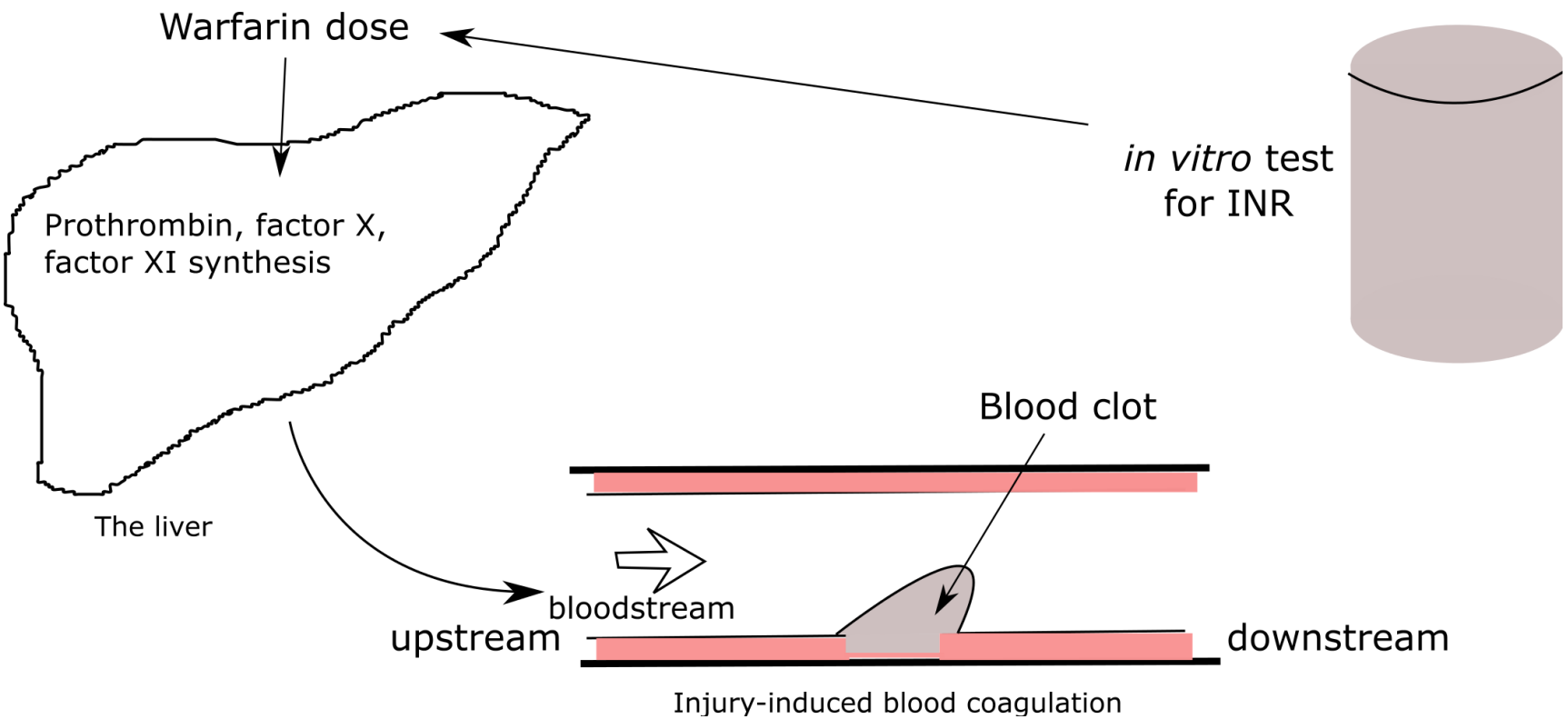


Left: fibrin polymer reinforces the clot and attaches the fixed platets in the endothelium with the rest of platets (white thrombus)

Right: fibrin polymer forms later and covers the attached platets after the detachment of activated platets (red thrombus)

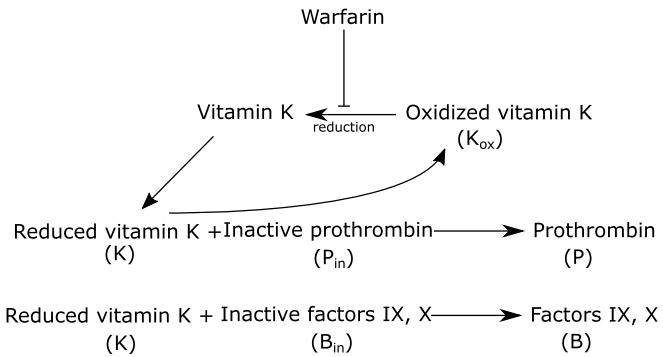
Application: Deep venous thrombosis prevention by warfarin

Bouchnita, A., Bouzaachane, K., Galochkina, T., Kurbatova, P., Nony, P. & Volpert, V. "An individualized blood coagulation model to predict INR therapeutic range during warfarin treatment". Submitted



Application: Deep venous thrombosis prevention by warfarin

PK-PD model of vitamin K dependent factors synthesis in the liver during warfarin treatment



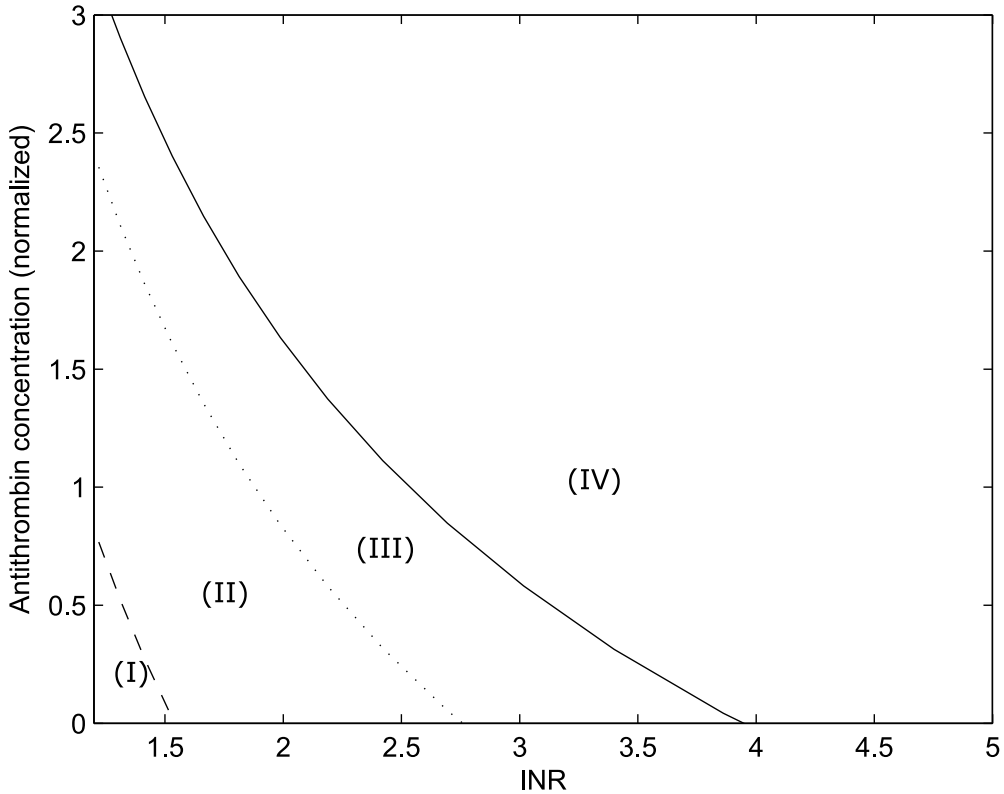
INR blood test model

$$INR = \frac{PT}{PT_{ref}}, \tag{17}$$

$$INR = \frac{k_1 B_a^* + k_2 P^{3*}}{k_1 B_a + k_2 P^3}, \tag{18}$$

Application: Deep venous thrombosis prevention by warfarin

Results for the individual INR therapeutic range depending on antithrombin and blood flow



Perspectives and ongoing works

- Quantitative study for the conditions of venous red thrombi vs. arterial white thrombi,
- 3D model of clot growth in complex geometries,
- Comparing the action of various anticoagulants such as NOACs, heparin ...

Thank you for your attention!