Lecture 2. Biomedical applications

Part 2a. Cardiovascular system and diseases

Atherosclerosis

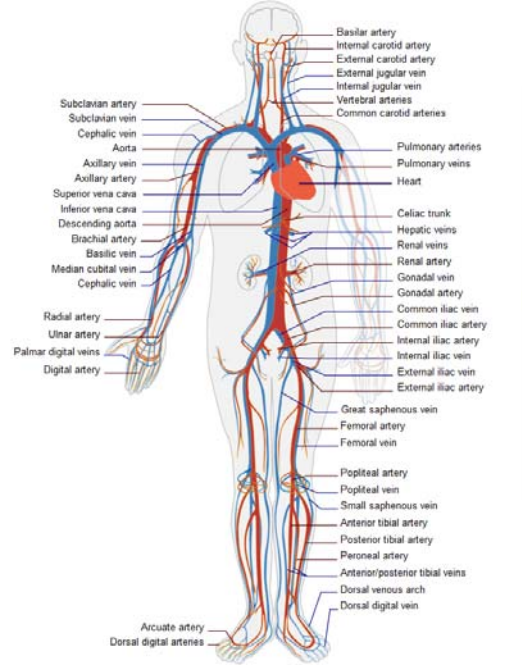
Blood coagulation and thrombosis

Methodology

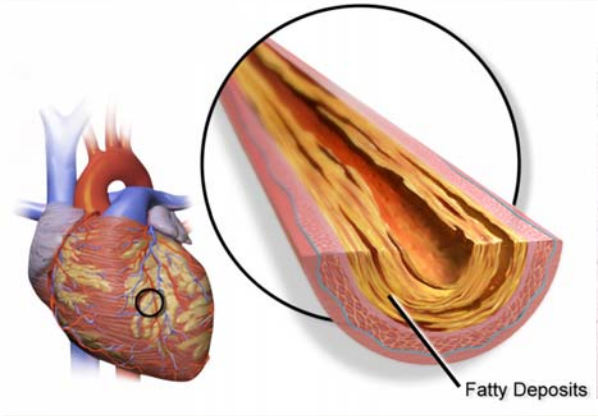
- Physiological background
- Modelling with reaction-diffusion equations
- Simulations and other methods of modelling

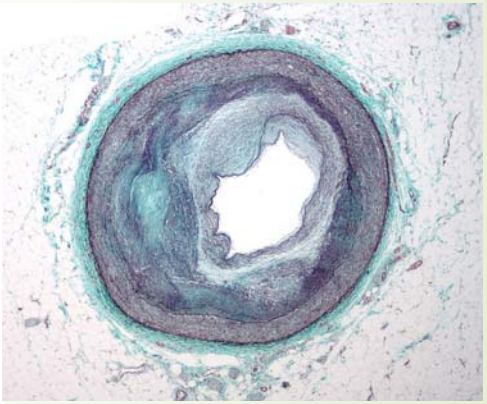
Atherosclerosis

Cardiovascular diseases: overview



Coronary artery disease ← Atherosclerosis (vs arteriosclerosis)





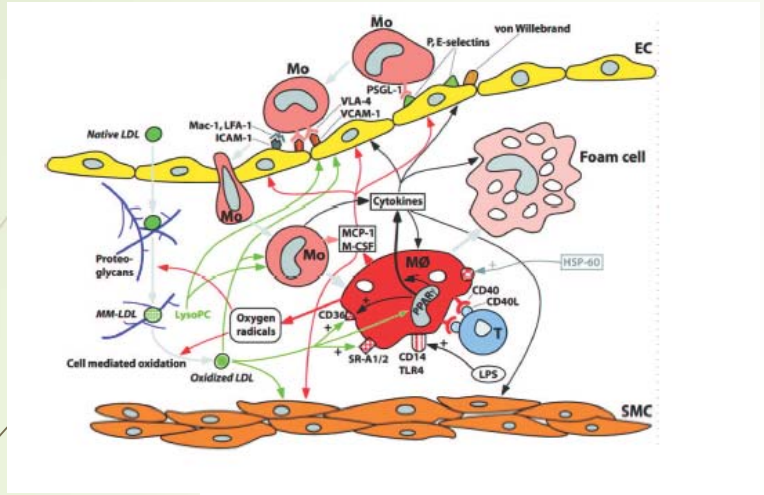
Myocardial infarction, arrhythmia, Fibrillation → clot formation → stroke

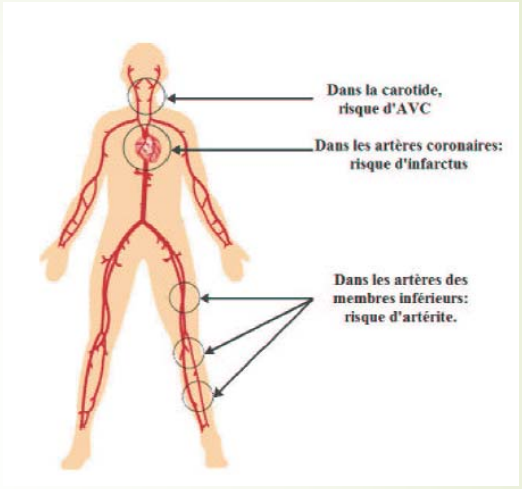
Chronic inflammation of blood vessel walls

Atherosclerosis

https://www.youtube.com/watch?v=njT428_JYzI

Biology of atherosclerosis





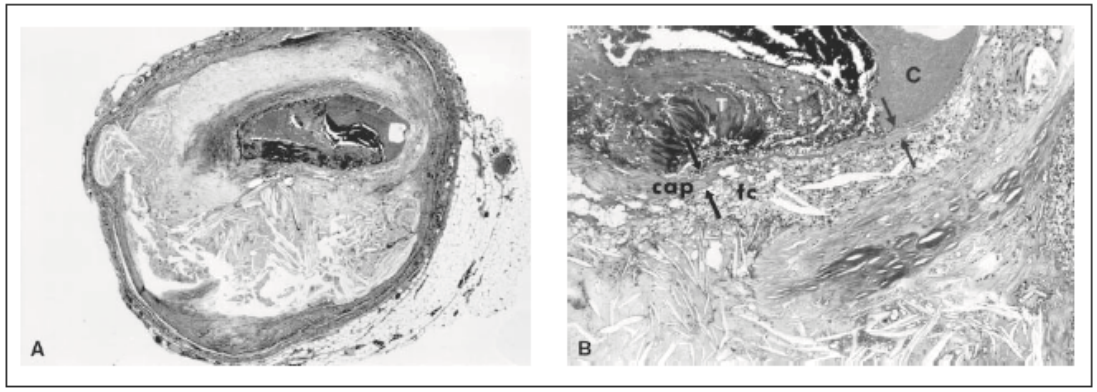
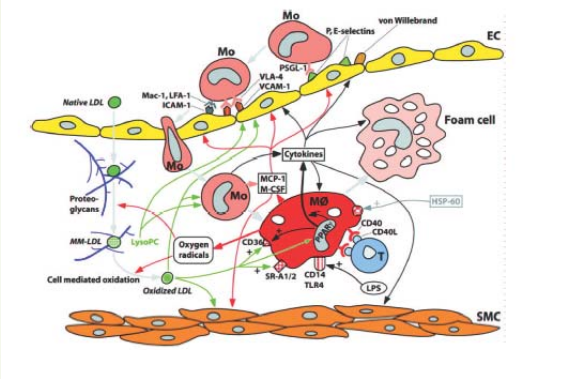


Figure 1: Plaque disruption and thrombosis. **A.** A stenotic coronary plaque containing a huge atheromatous core that is separated from the vascular lumen by a very thin cap of fibrous tissue, ie, a "vulnerable plaque". The fibrous cap is disrupted with superimposed non-occlusive luminal thrombosis. **B.** Higher magnification of the plaque-thrombus interface. The fibrous cap is very thin (between arrows) and heavily infiltrated by foam cells (fc), probably of macrophage origin. C: contrast medium injected post mortem; T: thrombus

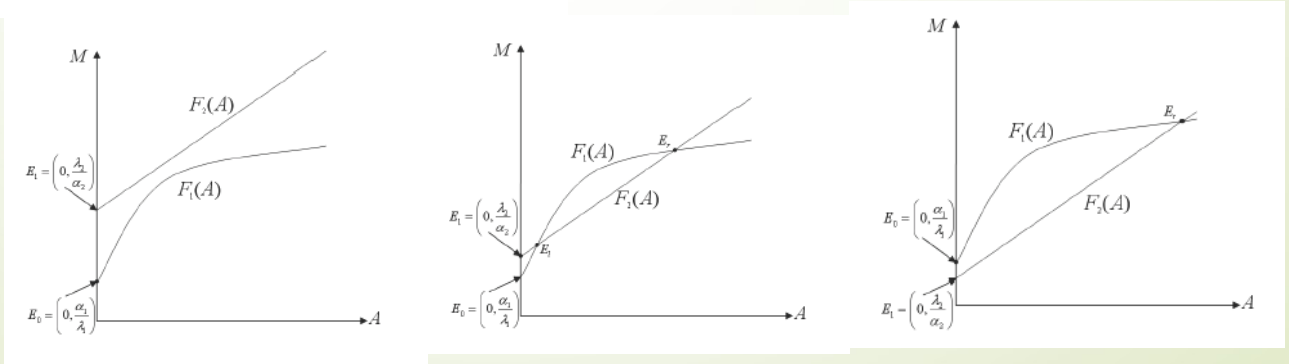
Modelof atherosclerosis (Genieys, El Khatib, VV, MMNP, 2007)



$$\begin{cases} \dfrac{dM}{dt} = f_1(A) - \lambda_1 M \\ \dfrac{dA}{dt} = f_2(A)M - \lambda_2 A \end{cases}$$

$$f_1(A) = \frac{\alpha_1 + \beta_1 A}{1 + A/\tau_1} \qquad f_2(A) = \frac{\alpha_2 A}{1 + A/\tau_2}$$

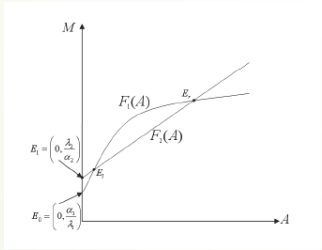
Cholesterol level:

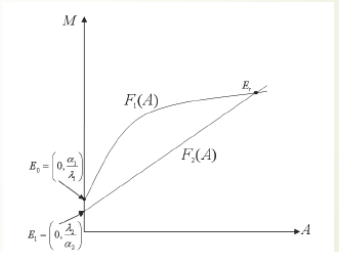


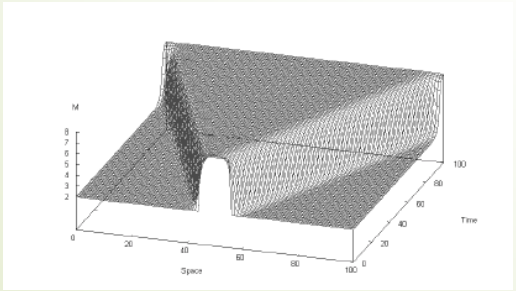
small **intermediate** **high**

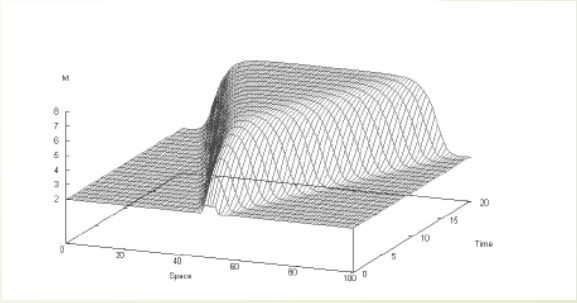
Reaction-diffusion system: existence and stability of waves

$$\begin{cases} \dfrac{\partial M}{\partial t} = d_1 \dfrac{\partial^2 M}{\partial x^2} + f_1(A) - \lambda_1 M \\ \dfrac{\partial A}{\partial t} = d_2 \dfrac{\partial^2 A}{\partial x^2} + f_2(A) M - \lambda_2 A \end{cases}$$





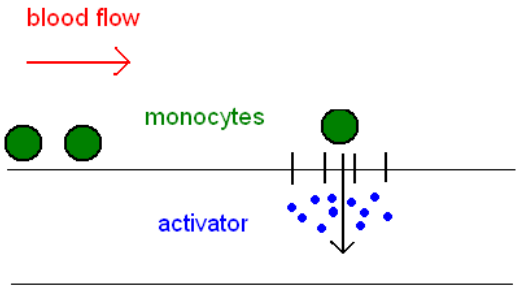




Summary

- Development of atherosclerosis depends on the concentration of LDL
- Low LDL concentration: a single globally stable point – no disease development
- Intermediate LDL concentration: two stable points; bistable wave, threshold
- Large LDL concentration: monostable wave, disease develops for any initial condition

2D model: nonlinear boundary conditions



$$\frac{\partial M}{\partial t} = d_M \Delta M - \beta M,$$

$$\frac{\partial A}{\partial t} = d_A \Delta A + f(A)M - \gamma A + b$$

in the two-dimensional strip $\Omega \subset \mathbb{R}^2$,

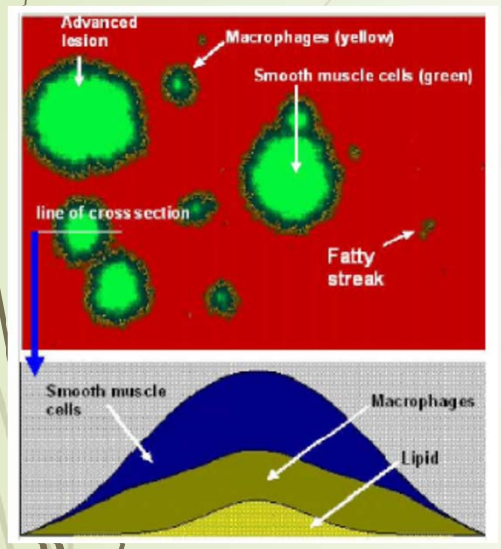
$$\Omega = \{(x, y), -\infty < x < \infty,\ 0 \le y \le h\}$$

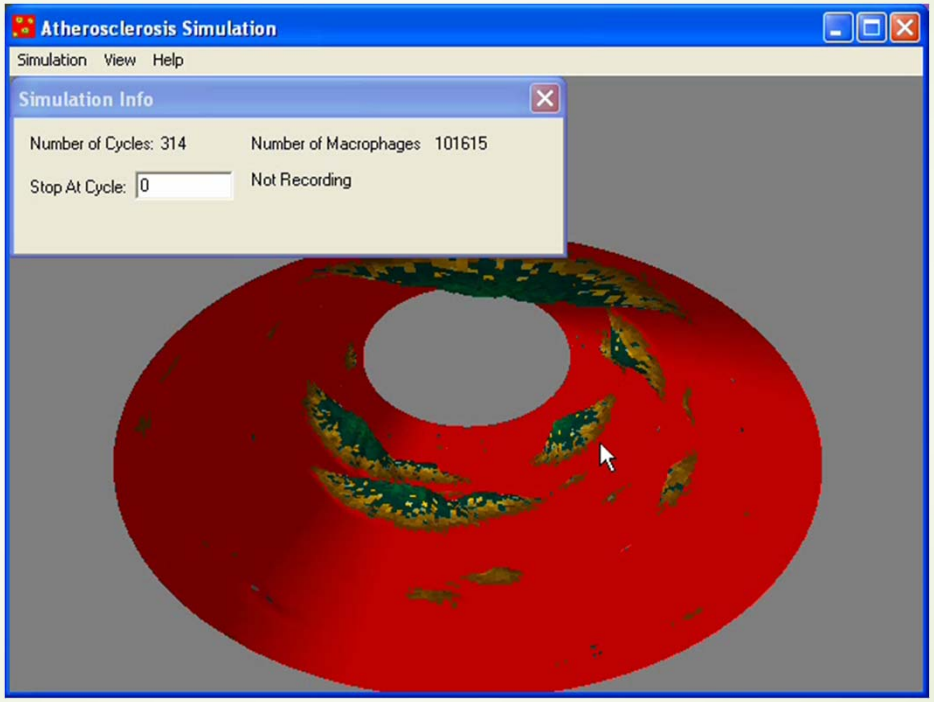
with the boundary conditions

$$y = 0: \ \frac{\partial M}{\partial y} = 0, \ \frac{\partial A}{\partial y} = 0, \quad y = h: \ \frac{\partial M}{\partial y} = g(A), \ \frac{\partial A}{\partial y} = 0$$

Atherosclerosis: cellular automata

(Poston, MMNP 2007)





Fluid-plaque interaction

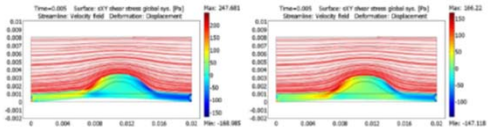


Figure 2: SSS distribution and deformation of structures in the case of moving wall. Left: Newtonian model. Right: non-Newtonian Carreau model

fluid

$$\begin{cases} \rho_f \frac{\partial \mathbf{u}}{\partial t} + \rho_f((\mathbf{u}-w)\cdot\nabla)\mathbf{u} - \nabla\cdot(2\mu(\sigma(\mathbf{u}))\triangle\mathbf{u}) + \nabla p = 0, & \text{in } \Omega_f \times (0,T), \\ \nabla\cdot\mathbf{u} = 0, & \text{in } \Omega_f \times (0,T), \\ 2\mu(\sigma(\mathbf{u}))\triangle\mathbf{u}\cdot\nu - p\nu = \mathbf{h}, & \text{on } \Gamma_{in} \times (0,T), \\ 2\mu(\sigma(\mathbf{u}))\triangle\mathbf{u}\cdot\nu - p\nu = 0, & \text{on } \Gamma_{out} \times (0,T), \\ \mathbf{u}\cdot\nu = 0 \text{ and } 2\mu(\sigma(\mathbf{u}))\triangle\mathbf{u}\cdot\nu - p\nu = \gamma, & \text{on } \Gamma_{w_1} \times (0,T), \\ \mathbf{u} = 0, & \text{on } \Gamma_{w_2} \times (0,T), \\ \mathbf{u} = \mathbf{u}_0, & \text{for } t = 0 \text{ in } \Omega_f \end{cases}$$

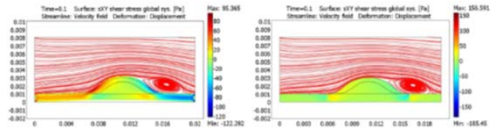


Figure 4: Blood recirculations downstream of the stenosis for non-Newtonian Carreau model. Left: moving wall. Right: fixed wall

solid

$$\begin{cases} \rho_s \frac{\partial^2 \eta}{\partial t^2} - \nabla\cdot((\mathbf{I}_2 + \nabla\eta)\Sigma_s(\eta)) = 0, & \text{in } \Omega_s \times (0,T), \\ \eta = 0, & \text{on } \Gamma_D \times (0,T), \\ ((\mathbf{I}_2 + \nabla\eta)\Sigma_s)\nu = 0, & \text{on } \Gamma_N \times (0,T), \\ \eta(x,0) = \eta_0(x), & \text{in } \Omega_s, \\ \frac{\partial \eta}{\partial t} = \dot{\eta}_0(x), & \text{in } \Omega_s. \end{cases}$$

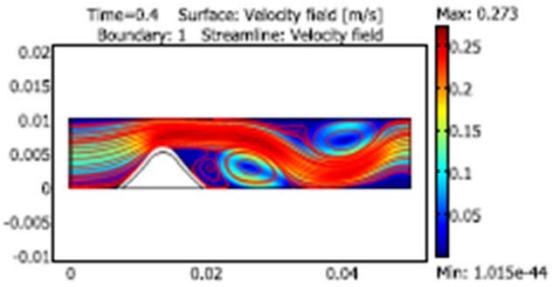
coupling

1. The continuity of velocity

$$\mathbf{u} = \frac{\partial \eta}{\partial t}, \quad \text{on } \Gamma_{w_1} \times (0,T).$$

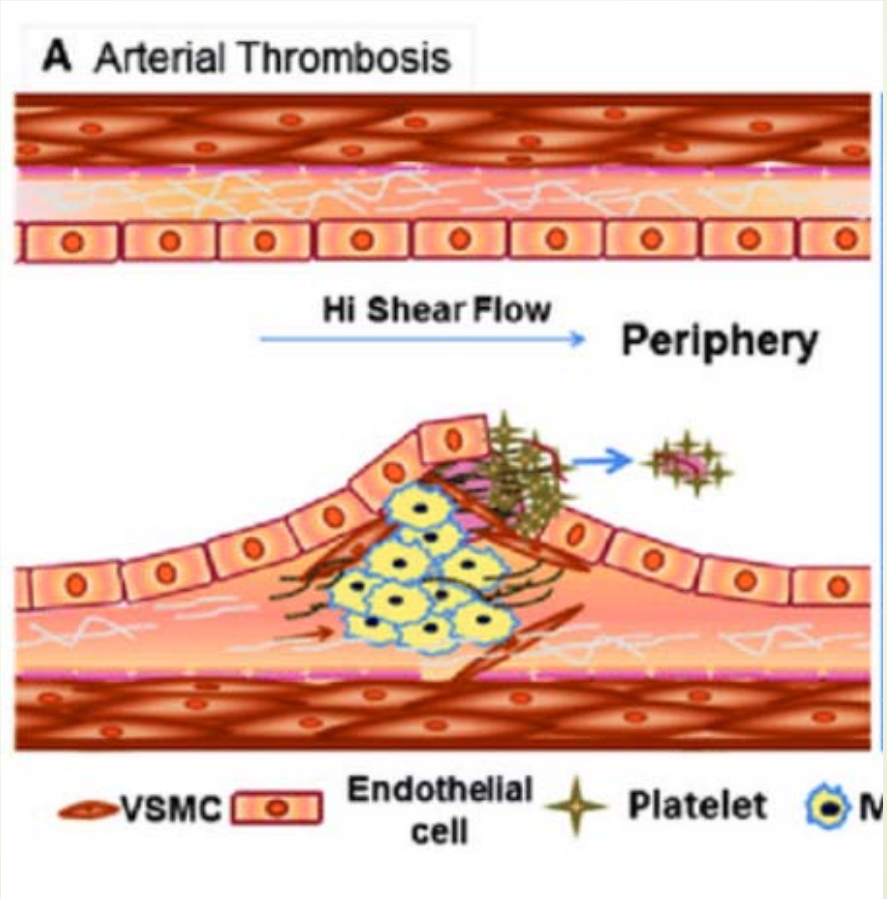
2. Mechanical equilibrium

$$-(2\mu(\sigma(\mathbf{u}))\triangle\mathbf{u} - p\mathbf{I}_2)\nu = (\Sigma_s(\eta))\nu, \quad \text{on } \Gamma_{w_1} \times (0,T).$$



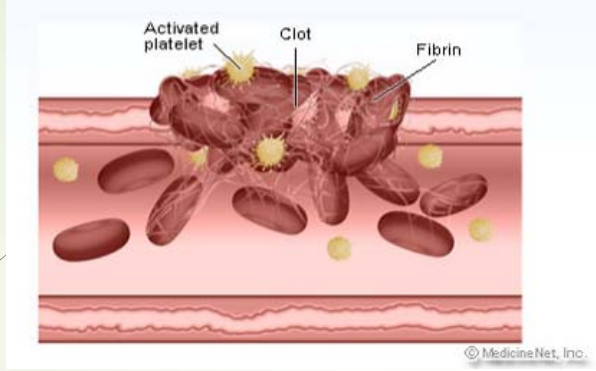
S. Boujena, O. Kafi, N. El Khatib. *A 2D mathematical model of blood flow and its interactions in an atherosclerotic artery.* Math. Model. Nat. Phenom., 9 (2014), No. 6, 46-68.

Plaque rupture: arterial thrombosis

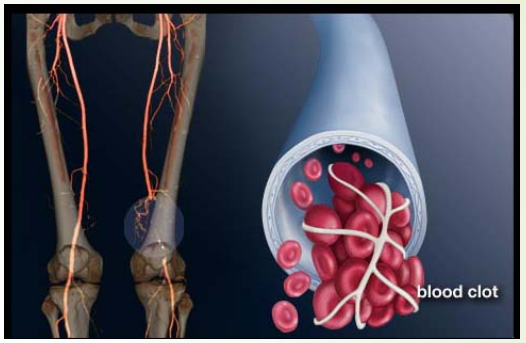


Blood coagulation

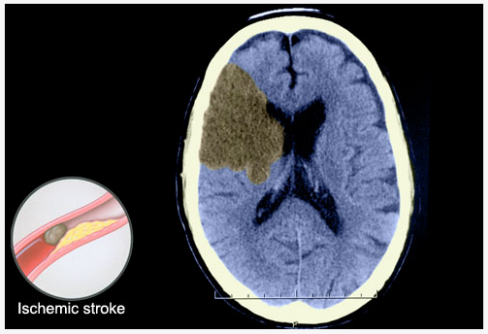
Blood coagulation and related pathologies



Clot growth



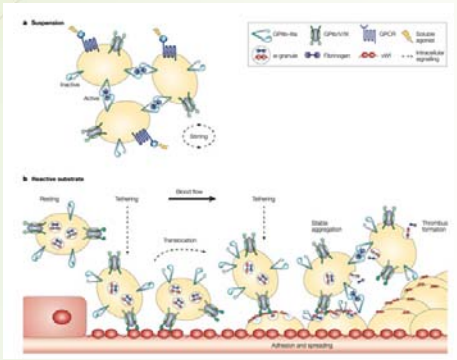
Deep vein thrombosis



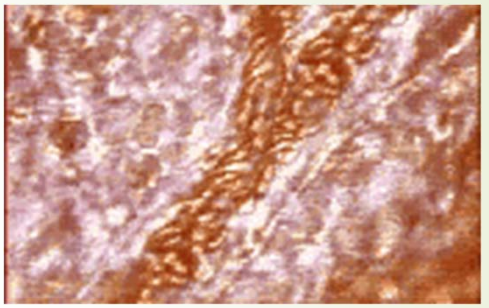
The most common type of stroke is known as an ischemic stroke. Nearly nine out of 10 strokes fall into this category. The culprit is a blood clot that obstructs a blood vessel inside the brain. The clot may develop on the spot or travel through the blood from elsewhere in the body.

Blood coagulations: main factors

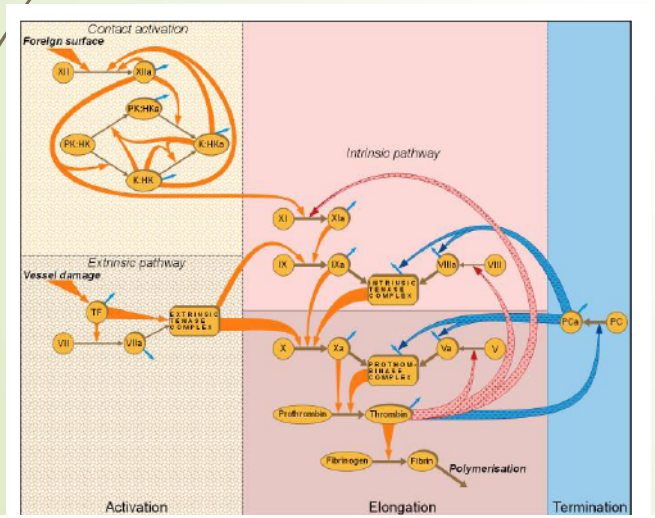
Platelet aggregation



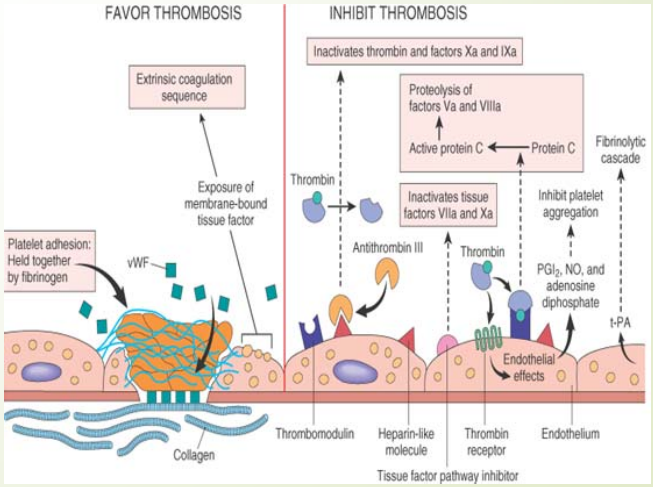
Blood flow



Coagulation cascade



Endothelial cells



Thrombin generation curves (TGC)

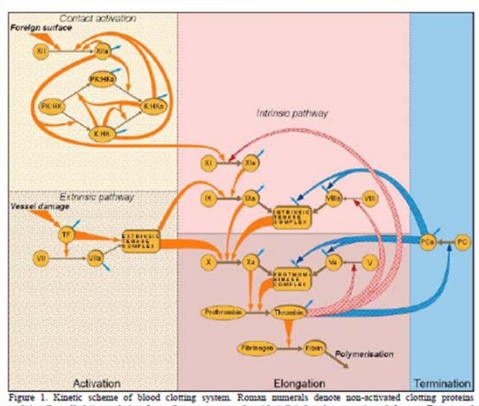
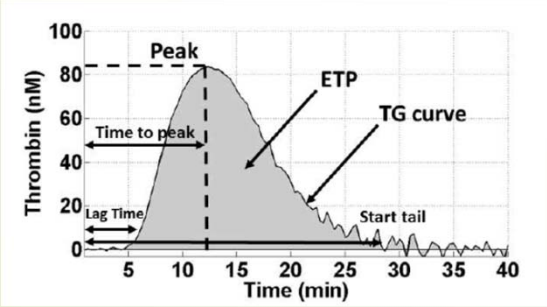


Figure 1. Kinetic scheme of blood clotting system. Roman numerals denote non-activated clotting proteins traditionally called "coagulation factors", roman numerals with "a" index denote activated factors. Tenase and



Reference	N_{var}	$N_{reactions}$	N_p
Models of *in vitro* coagulation kinetics			
Xu, 2002	6	13	16
Qiao, 2004	6	15	19
Xu, 2005	7	16	17
Jones, 1994	19	12	20
Hockin, 2002	34	27	42
Bungay, 2003	73	46	105
Luan, 2007	92	93	148
Chatterjee, 2010	76	57	105
Xu, 2010	50	43	63
Braescu, 2009	36	50	66
Khanin, 1998	25	17	26
Tyurin, 2006	32	50	72
Zhu, 2007	36	55	75
Panteleev, 2006	24	51	65
Zarnitsina, 1996	10	23	25
Panteleev, 2006	27	65	85
Models of *in vivo* coagulation kinetics			
Kuharsky, 2001	59	43	97
Wajima, 2009	76	49	85
Anand, 2003	27	27	32
LaCroix, 2012	28	34	51
Hund, 2010	7	20	12
Bodnar, 2011	25	21	38
Jordan, 2011	17	19	36
Biasetti, 2012	18	12	19

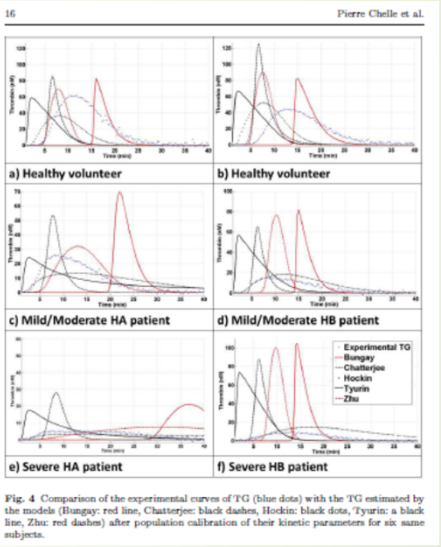


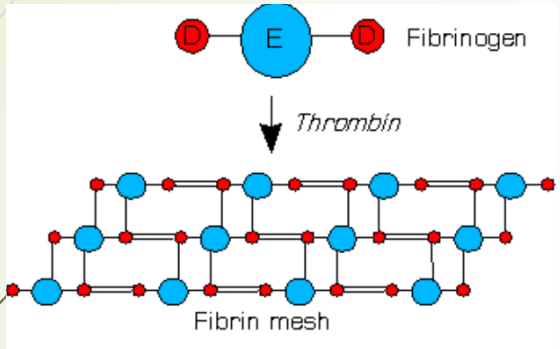
Fig. 4 Comparison of the experimental curves of TG (blue dots) with the TG estimated by the models (Bungay: red line, Chatterjee: black dashes, Hockin: black dots, Tyurin: a black line, Zhu: red dashes) after population calibration of their kinetic parameters for six same subjects.

Evaluation of In Silico Models of Thrombin Generation using Experimental Data from Healthy and Haemophilic Subjects

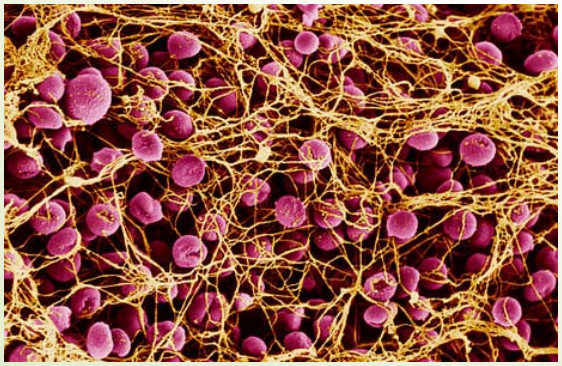
Pierre Chelle · Claire Morin · Aurélie Montmartin · Michèle Piot · Michel Cournil · Brigitte Tardy-Poncet

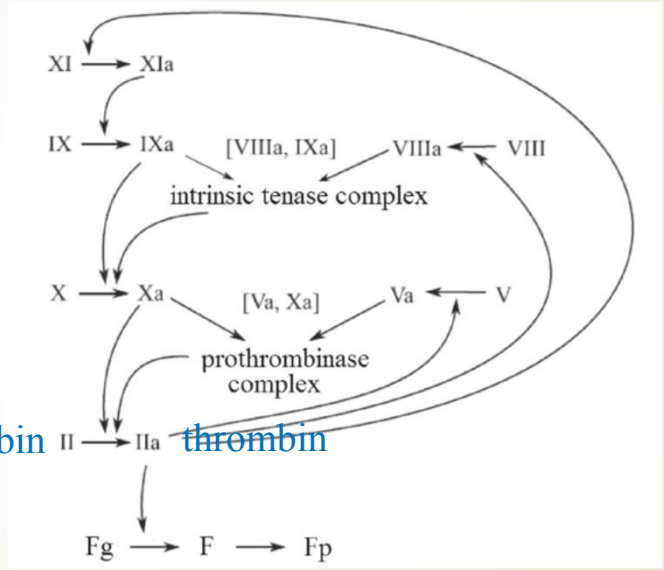
In spite of many models and results, description of TGC is not yet completely clear.
Important point: patient specific parameters.

Fibrin polymerization



wikipedia





prothrombin ~~thrombin~~

Fibrinogen → fibrin → fibrin polymer

Existence and stability of the traveling wave solutions

Monotone system

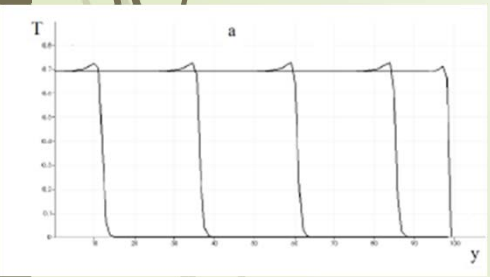
$$
\begin{aligned}
\frac{\partial T}{\partial t} &= D\Delta T + \left(k_2 U_{10} + \overline{k_2}\frac{k_{510}}{h_{510}} U_{10}U_5\right)\left(1 - \frac{T}{T_0}\right) - h_2 T,\\
\frac{\partial U_{11}}{\partial t} &= D\Delta U_{11} + k_{11}T - h_{11}U_{11},\\
\frac{\partial U_9}{\partial t} &= D\Delta U_9 + k_9 U_{11} - h_9 U_9,\\
\frac{\partial U_{10}}{\partial t} &= D\Delta U_{10} + k_{10}U_9 + \overline{k_{10}}\frac{k_{89}}{h_{89}} U_9 U_8 - h_{10}U_{10},\\
\frac{\partial U_8}{\partial t} &= D\Delta U_8 + k_8 T - h_8 U_8,\\
\frac{\partial U_5}{\partial t} &= D\Delta U_5 + k_5 T - h_5 U_5.
\end{aligned}
$$

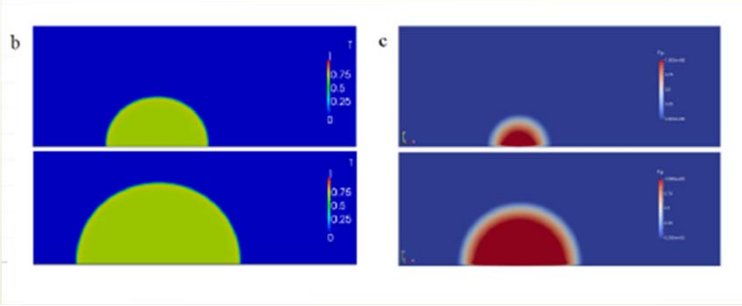
One-equation model

$$\frac{\partial T}{\partial t} = D\Delta T + F(T),$$

$$F(T) = \kappa T^n (P_0 - T) - \sigma T$$

$$
\begin{aligned}
U_{11} &= \frac{k_{11}}{h_{11}}T,\ U_9 = \frac{k_9 k_{11}}{h_9 h_{11}}T,\ U_5 = \frac{k_5}{h_5}T,\ U_8 = \frac{k_8}{h_8}T,\\
U_{10} &= \frac{k_9 k_{11}}{h_{10} h_9 h_{11}}\left(k_{10}T + \overline{k_{10}}\frac{k_{89}}{h_{89}}T^2\right)
\end{aligned}
$$

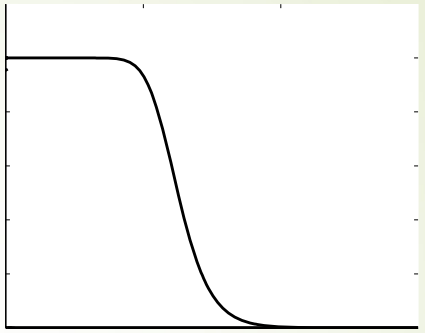


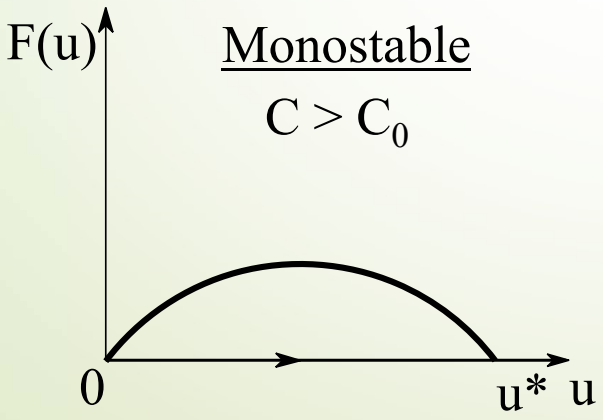


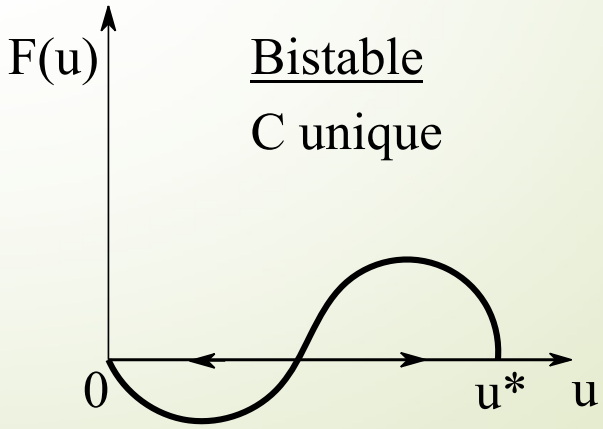
Thrombin propagation: traveling wave solutions

$$\frac{\partial u}{\partial t} = D\Delta u + F(u),\ \frac{\partial F_i}{\partial u_j} \geq 0,\ \forall i \neq j.$$

$$u(x,t) = w(x - ct),\ w(-\infty) = w_*,\ w(+\infty) = 0$$







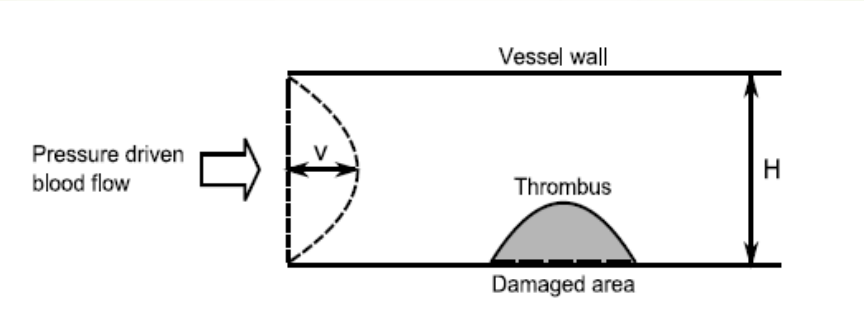
Existence of pulses and wave initiation

Pulse exists if and only if the wave speed is positive

Solution converges to the wave (clot growth) if the initial condition is greater than the pulse solution

Modelling of blood coagulation and clot growth

- Thrombin generation
- Modelling of blood coagulation in a quiescent plasma (reaction-diffusion equations)
- The influence of blood flow
- The influence of platelets



Hemophilia and speed of thrombin propagation

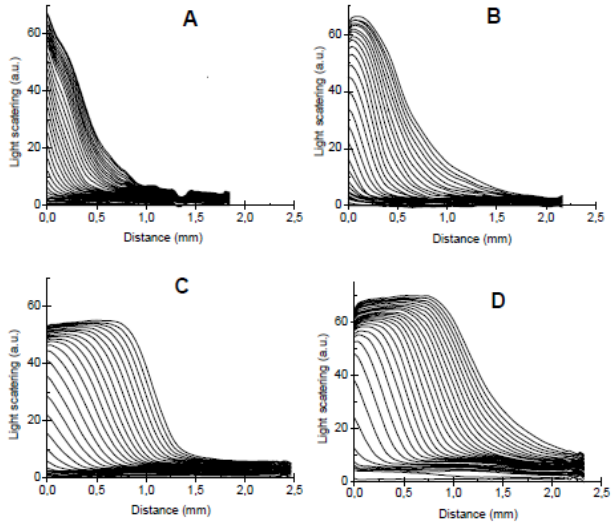
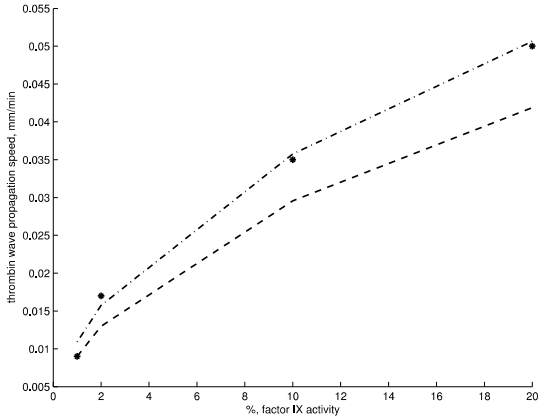


Figure 5. Clot growth from the glass surface in plasma of patients with (A) less than 1%, (B) 1.8%, (C) 2.8%, and (D) 5.5% of normal FIX clotting activity. The first curve was recorded in less than 1 minute after the start of the experiment; all other curves were recorded at a 2-minute intervals.



$$\hat{c_1} = \sqrt{D}\frac{bII_0^2 - \frac{4}{5}bII_0^3 - 2h_2}{\sqrt{2\left(bII_0^2 - \frac{4}{5}bII_0^3\right)}}$$

$$b = \frac{k_9 k_{11}\overline{k_{10}} k_8 k_{89}\overline{k_2} k_5 k_{510} II_0^2}{h_9 h_{10} h_{11} h_8 h_{89} h_5 h_{510}}$$

Spatial Dynamics of Contact-Activated Fibrin Clot Formation *in vitro* and *in silico* in Haemophilia B: Effects of Severity and Ahemphil B Treatment

A.A. Tokarev[*,1,@], Yu.V. Krasotkina[*,1], M.V. Ovanesov[1,3], M.A. Panteleev[1], M.A. Azhigirova[2], V.A. Volpert[4], F.I. Ataullakhanov[1, 5, 6] and A.A. Butilin[5]

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]:

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

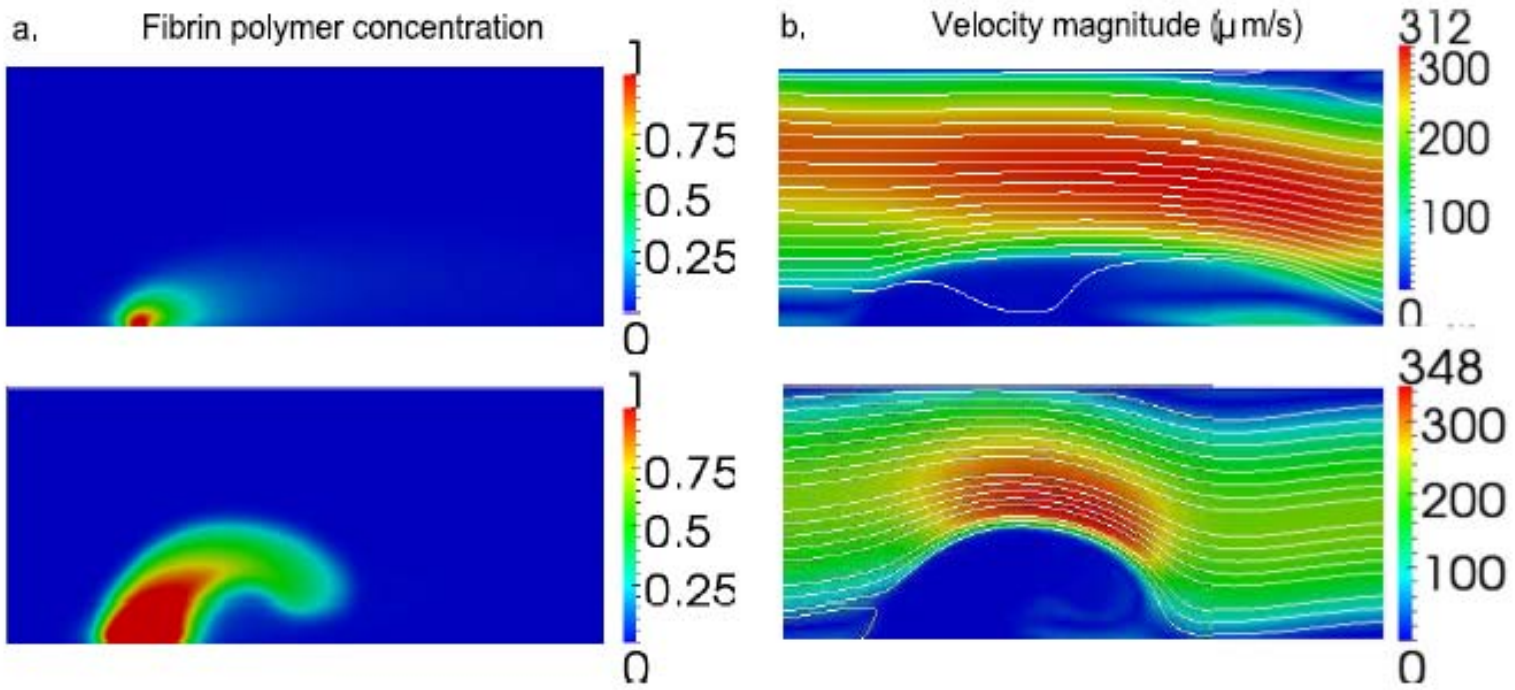
The factor α should express viscosity and fiber radius. In this simulation, we consider that $\alpha=0.02$.

[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 clot growth regimes

Partially occlusive thrombosis

Thrombin concentration:



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

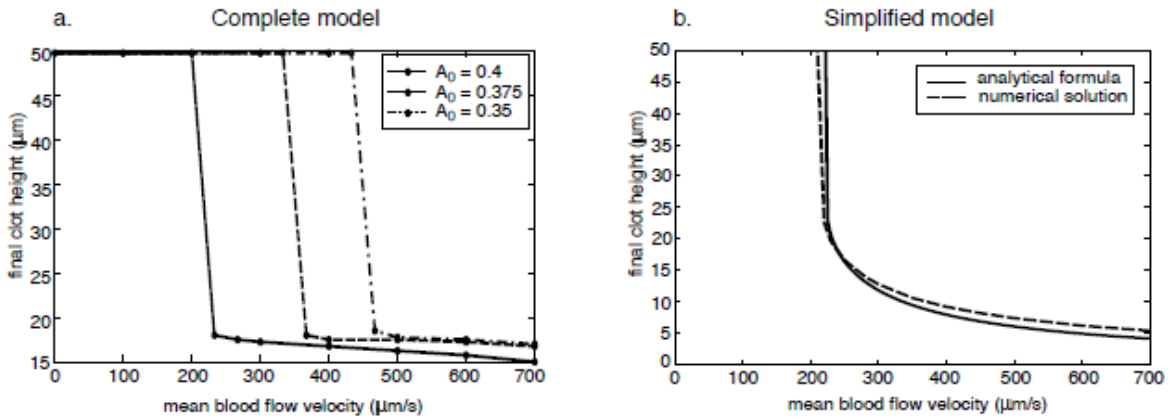
$$\Phi(T, y) = (k_3 B_a(y) + k_4 T^3)(P_0 - T) - \sigma(y)T,$$

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

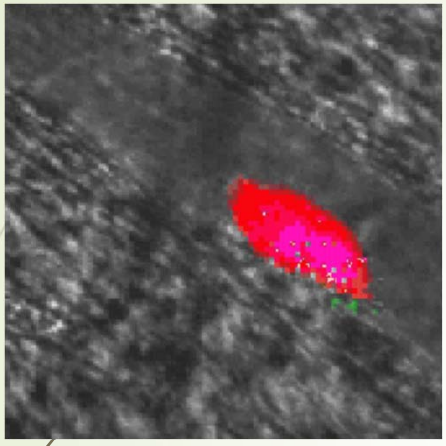
$$\int_0^{T^*} \Phi(T, y)dT > 0. \tag{13}$$

Conditions of vessel occlusion in flow

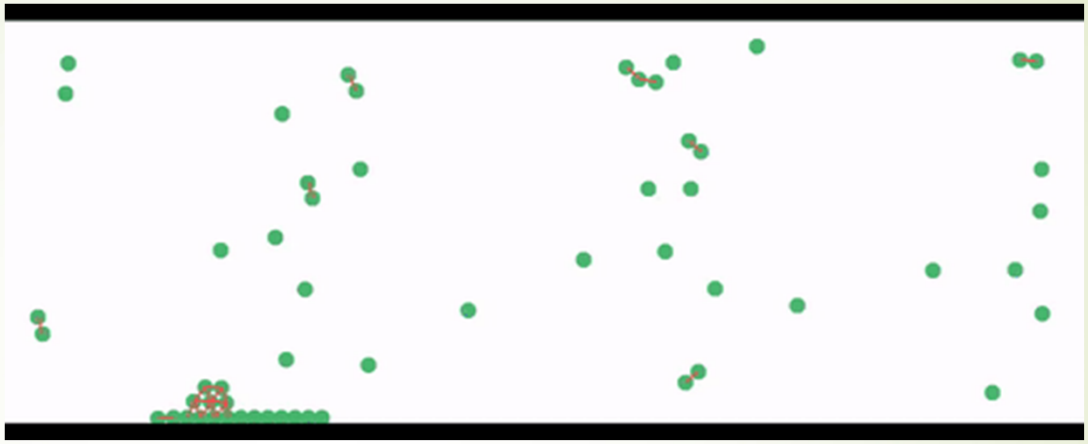
Blood flow limits clot growth and determine the regimes of vessel occlusion



Comparison with experiment

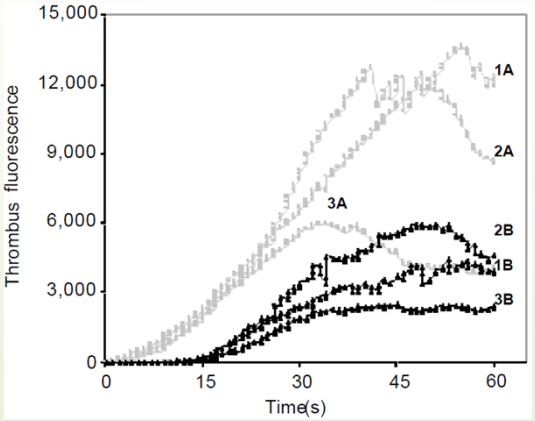


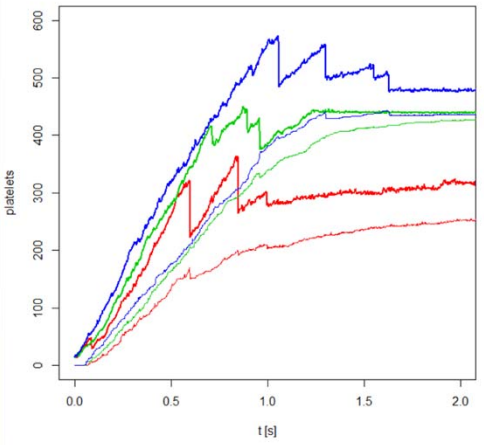
Falati et al. (2002)



Tosenberger et al. (2015)

Kamocka et al. (2010)

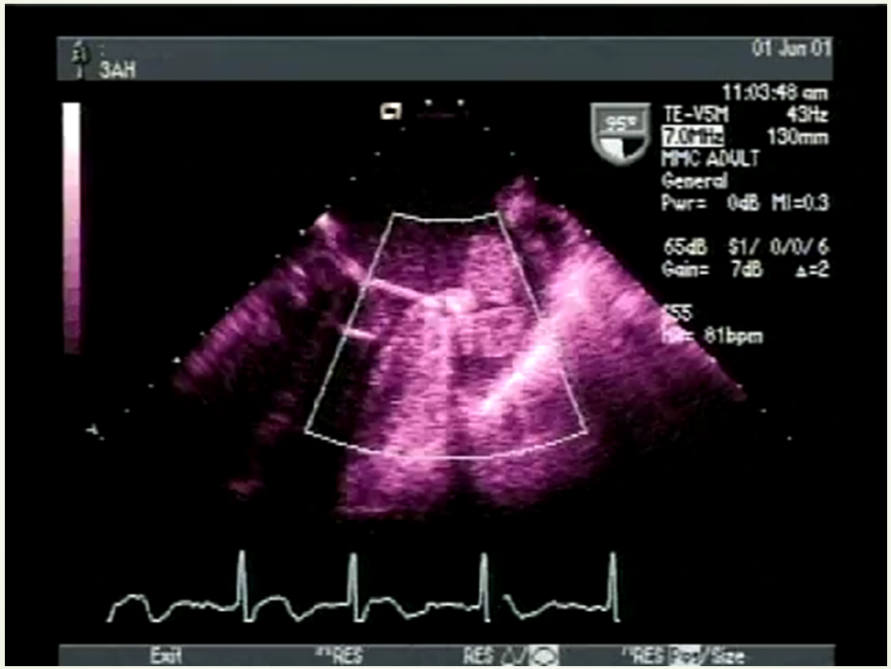




Blood coagulation and related disorders

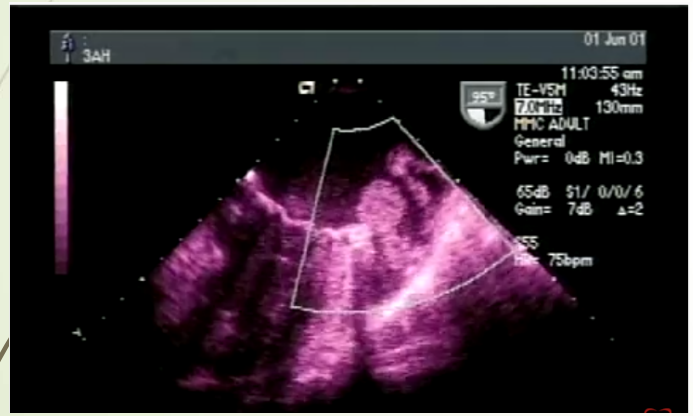
- Arterial thrombosis (atherosclerosis)
- Deep vein thrombosis
- Bleeding disorders (hemophilia, …)
- …
- Chronic inflammations
- Coronavirus disease

Atherosclerosis-fibrillation-LAA thrombus



https://www.youtube.com/watch?v=q7vsdY_fTMo

Atherosclerosis – heart fibrillation – LAA thrombus - stroke



Clot from the heart moves to the brain

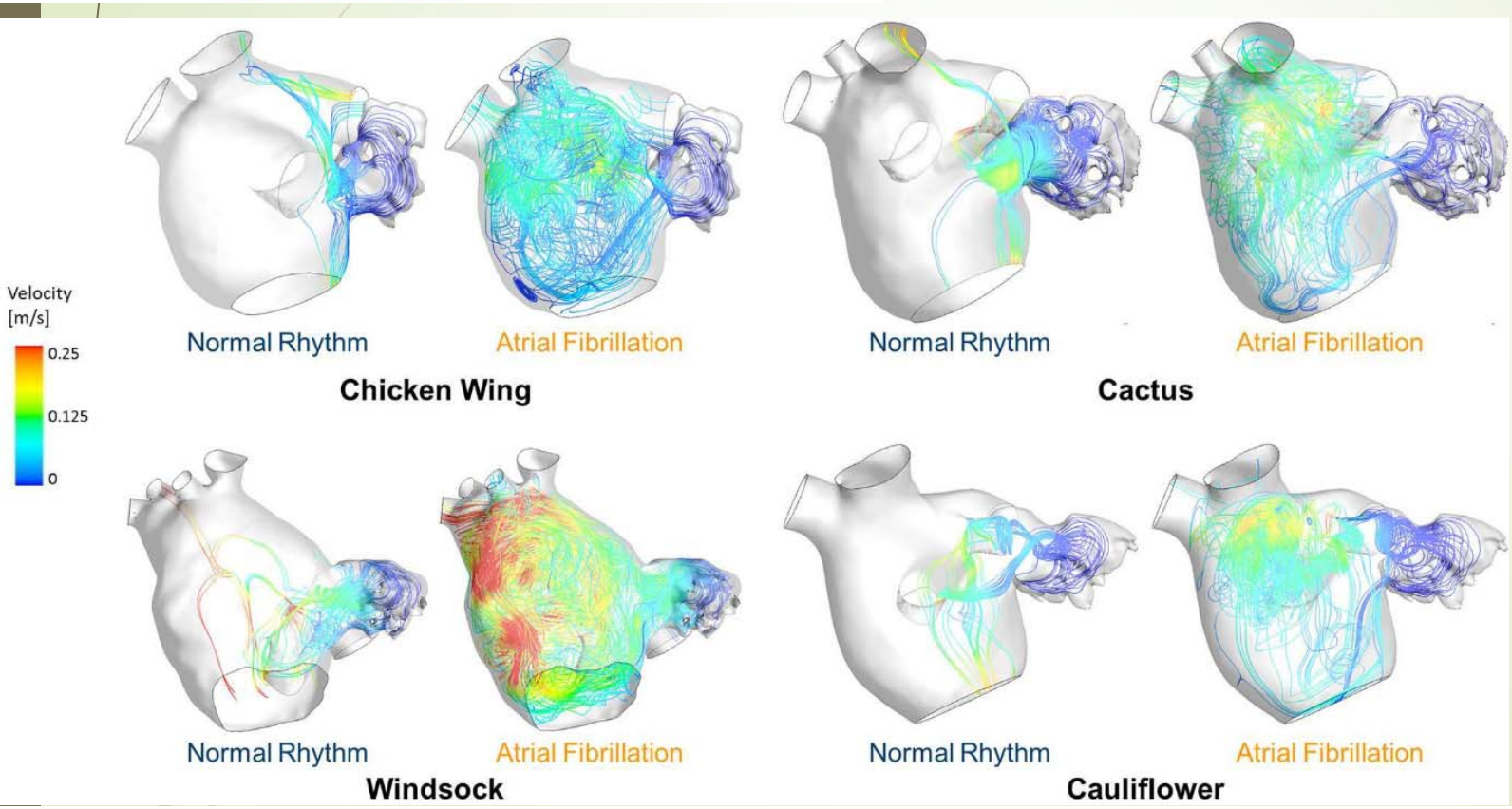
frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 04 April 2018
doi: 10.3389/fcvm.2018.00034

Computational Fluid Dynamic Analysis of the Left Atrial Appendage to Predict Thrombosis Risk

*Giorgia Maria Bosi [1], Andrew Cook [2], Rajan Rai [1], Leon J. Menezes [3], Silvia Schievano [2], Ryo Torii [1] and Gaetano Burriesci [1,4]**

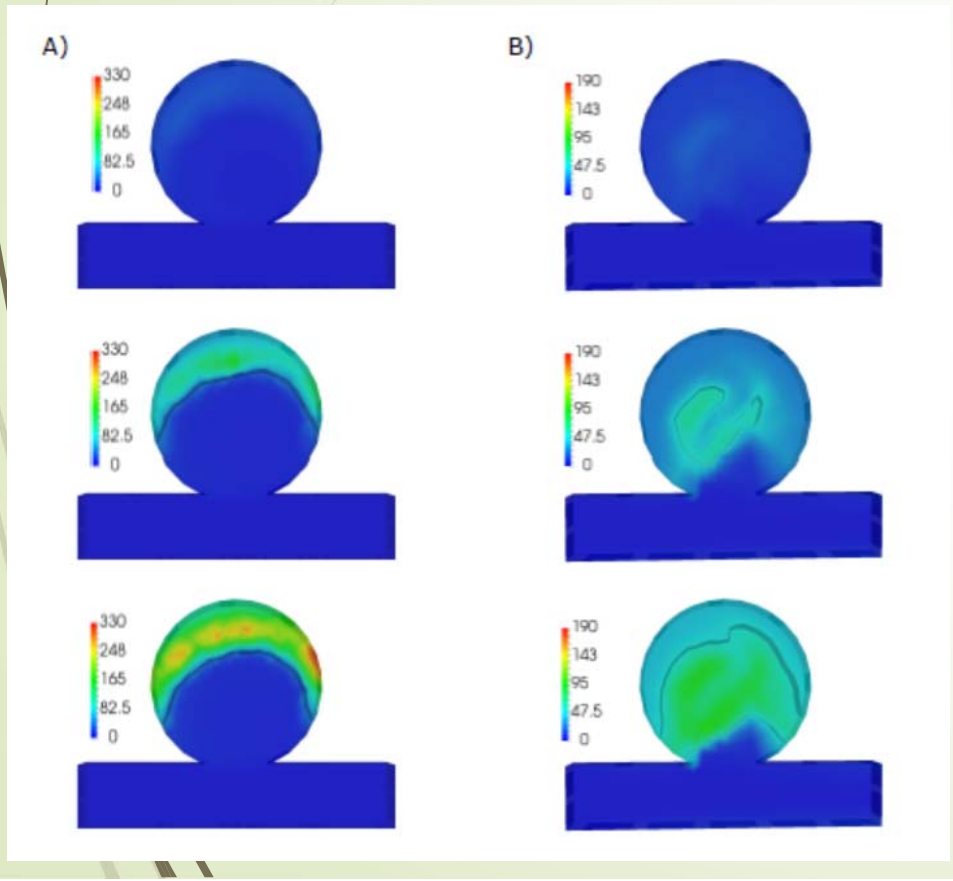
LAA thrombus modelling

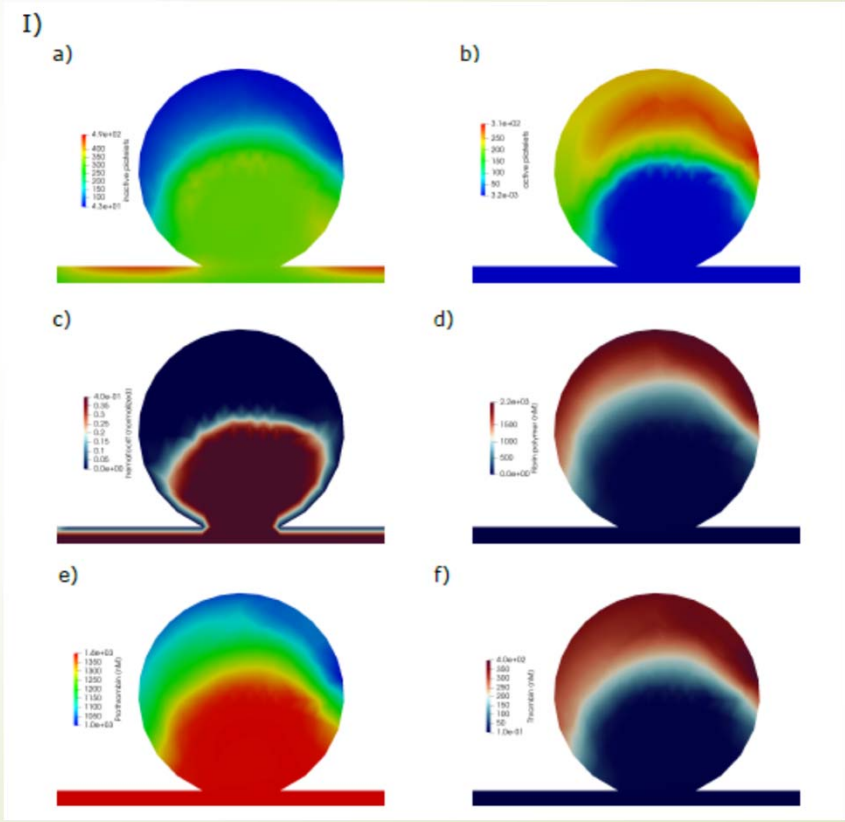


Multiphase continuum modeling of thrombosis in aneurysms and recirculation zones

Anass Bouchnita,[1] Aleksey V. Belyaev,[2, a)] and Vitaly Volpert[3, 4, 5]

Clot formation in aneurysm





Rheumatoid arthritis

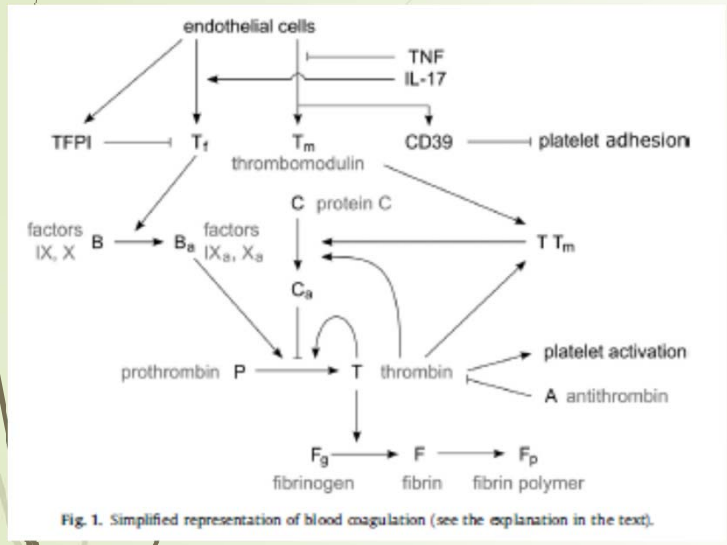
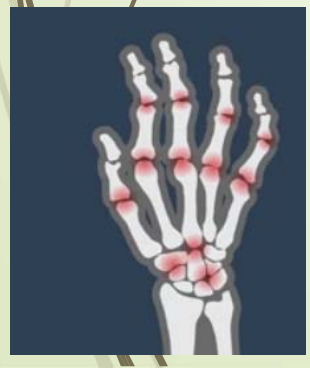
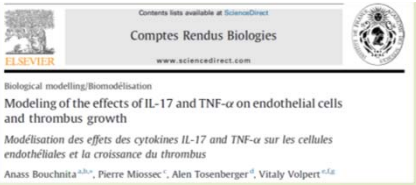


Fig. 1. Simplified representation of blood coagulation (see the explanation in the text).





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Biological modelling/Biomodélisation

Modeling of the effects of IL-17 and TNF-α on endothelial cells and thrombus growth

Modélisation des effets des cytokines IL-17 and TNF-α sur les cellules endothéliales et la croissance du thrombus

Anass Bouchnita[a,b,*], Pierre Miossec[c], Alen Tosenberger[d], Vitaly Volpert[e,f,g]

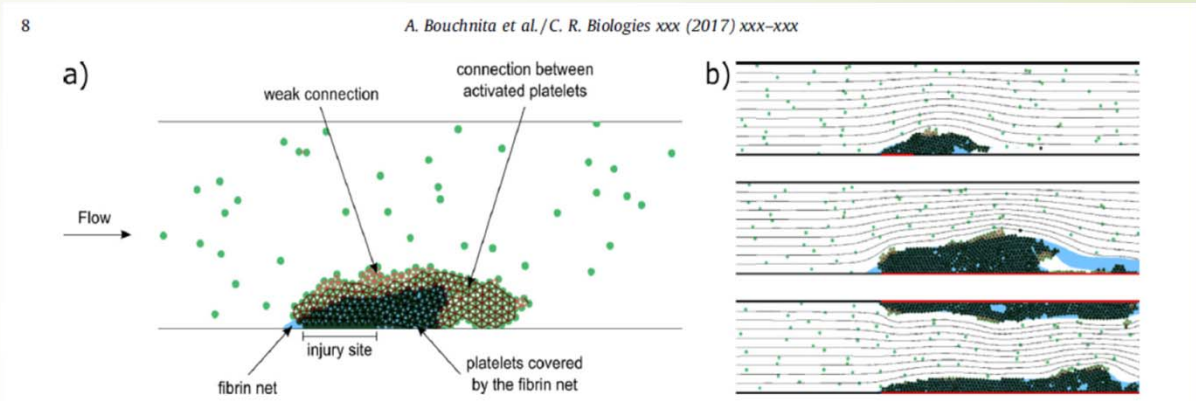
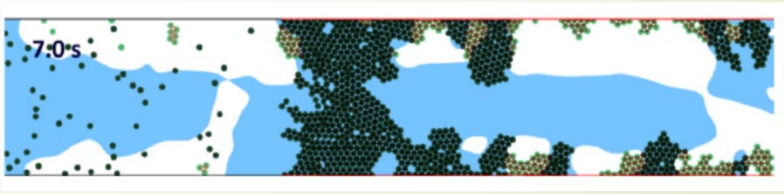


Fig. 6. (a) A scheme of clot structure (snapshot from a simulation). The connections between platelets are shown as red intervals between their centers. Light red lines correspond to weak GPIb connections, dark red to medium connections between activated platelets, and black to strong connections between platelets covered by a fibrin net. Dark green platelets are covered by a fibrin net, which is shown in blue [34]. (b) Final stages of clot growth for different sizes of inflamed areas of vessel wall (shown in red). From top to bottom: short inflamed area at the bottom wall, long area at the bottom wall, long area at both walls. The black lines denote flow streamlines.



Inflammation can lead to excessive blood coagulation, thrombosis, sepsis