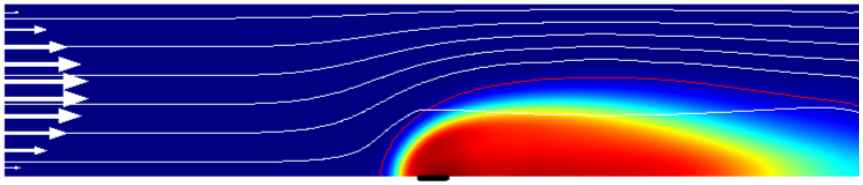
24th October 2013

Effects of flow and diffusion on blood coagulation in platelet poor plasma

A two-way coupling between hemodynamics and biochemistry

Diana Magnabosco, Henk van Ooijen,
Bart Bakker, Rene van den Ham,
Luca Formaggia



COMSOL CONFERENCE ROTTERDAM2013

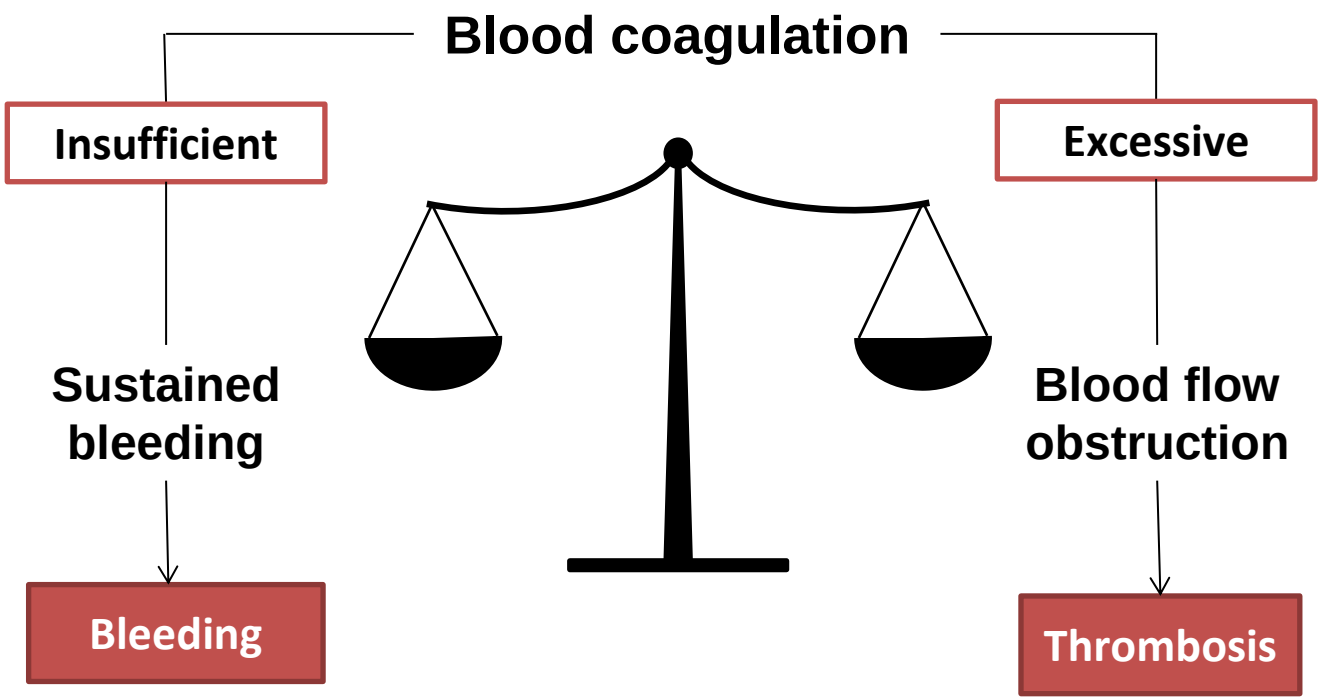
PHILIPS RESEARCH EINDHOVEN
Molecular Diagnostic Department

POLITECNICO DI MILANO
Mathematical Department
«F. Brioschi»

COMSOL CONFERENCE ROTTERDAM2013

Blood coagulation
Outline and motivation

- Biological background
- Mathematical and numerical model
- Results and analysis
- Conclusions

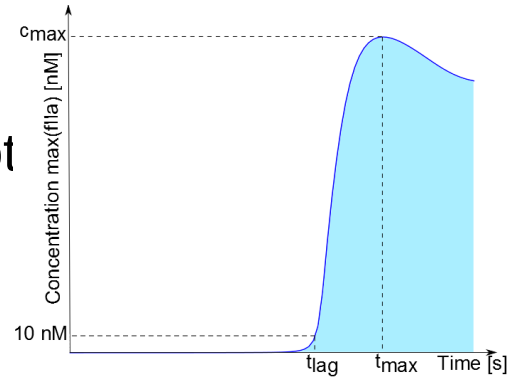


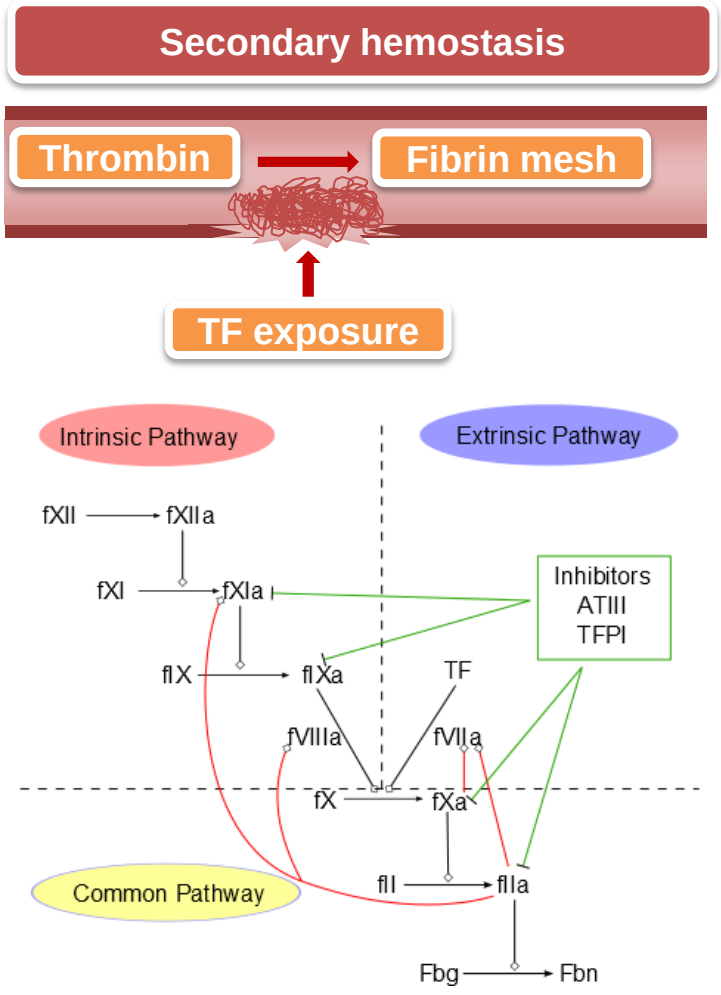
COMSOL CONFERENCE ROTTERDAM2013

Biological background
Secondary hemostasis in platelet poor plasma

Coagulation network
- Tissue factor: TF
- Inhibitors
- Feedback loops
- Thrombin: fIIa
- Fibrin: Fbn

Output parameters
- Thrombogram: t_{lag}, t_{max}, C_{max}
- TGD
- t_{clot} , A_{clot}
- Wound-Clot





COMSOL CONFERENCE ROTTERDAM2013

Mathematical and numerical method
Coagulation network

Plasma species in Ω, t>0

$$\frac{\partial \boldsymbol{c_p}(\boldsymbol{x},t)}{\partial t} - \mathrm{D}\nabla^2 \boldsymbol{c}_p(\boldsymbol{x},t) + \boldsymbol{u}(\boldsymbol{x},t)\cdot\nabla \boldsymbol{c_p}(\boldsymbol{x},t) = R_p(\boldsymbol{c}(\boldsymbol{x},t))$$

Membrane species on Γ_{down}, t>0

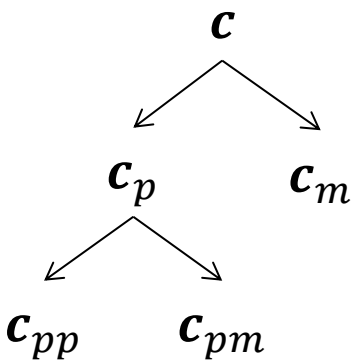
$$\frac{\partial \boldsymbol{c_m}(\boldsymbol{x},t)}{\partial t} = R_m(\boldsymbol{c}(\boldsymbol{x},t))$$

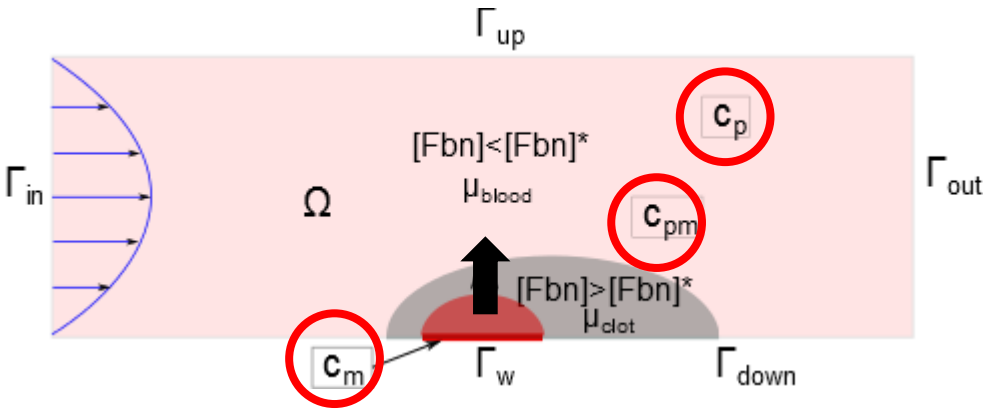
Coupling by boundary conditions on Γ_{down}, t>0

$$-\boldsymbol{n}\cdot D\nabla \boldsymbol{c_{pm}}(\boldsymbol{x},t) = R_{pm}\big(\boldsymbol{c}(\boldsymbol{x},t)\big)$$

46 PDEs
11 ODEs (Γ_{down})
1 ODE (Ω)
58 equations

Linear finite elements method with streamline and crosswind numerical diffusion





COMSOL CONFERENCE ROTTERDAM2013

Mathematical and numerical method
Blood flow

Modified **Navier-Stokes** equations in Ω, t>0

$$\rho \frac{\partial \boldsymbol{u}}{\partial t} + \rho \boldsymbol{u} \cdot \boldsymbol{\nabla} \boldsymbol{u} = \boldsymbol{\nabla} \cdot [-p\boldsymbol{I} + \mu(\boldsymbol{x}, t)(\boldsymbol{\nabla} \boldsymbol{u} + \boldsymbol{\nabla}^T \boldsymbol{u})]$$

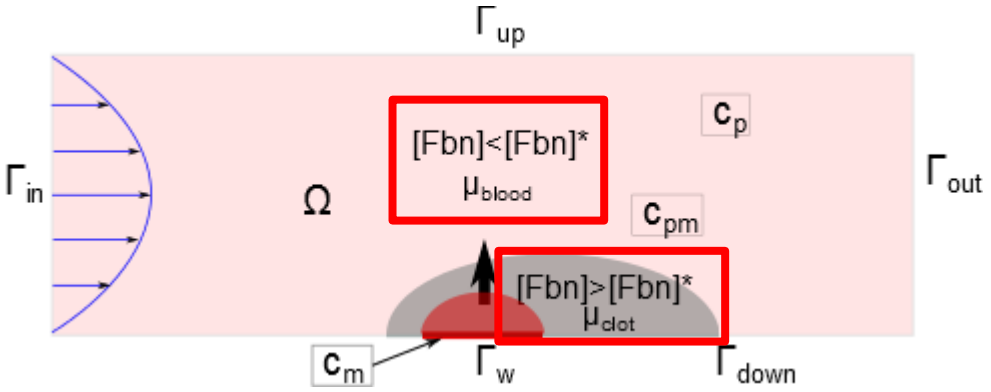
$$\boldsymbol{\nabla} \cdot \boldsymbol{u} = \boldsymbol{0}$$

Viscosity depending on fibrin (threshold [Fbn]*)

$$\mu(\boldsymbol{x}, t) = \mu([\mathrm{Fbn}]) = \begin{cases} \mu_{blood} & \text{if } [\mathrm{Fbn}] < [\mathrm{Fbn}]^* \\ \mu_{clot} & \text{if } [\mathrm{Fbn}] \geq [\mathrm{Fbn}]^* \end{cases}$$

Laminar flow

P_1P_1 with streamline and crosswind diffusion

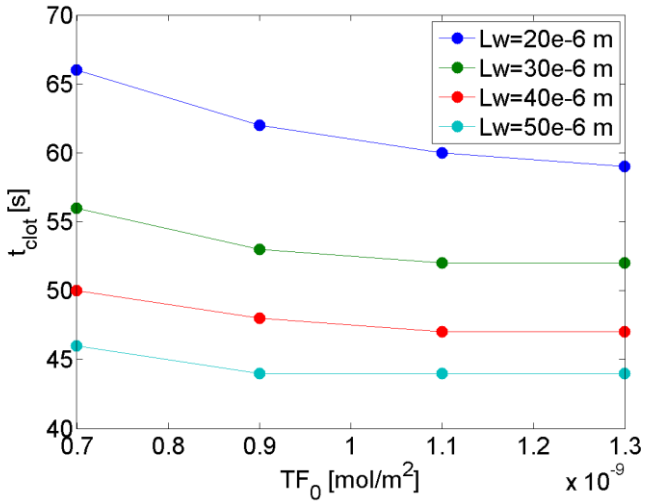


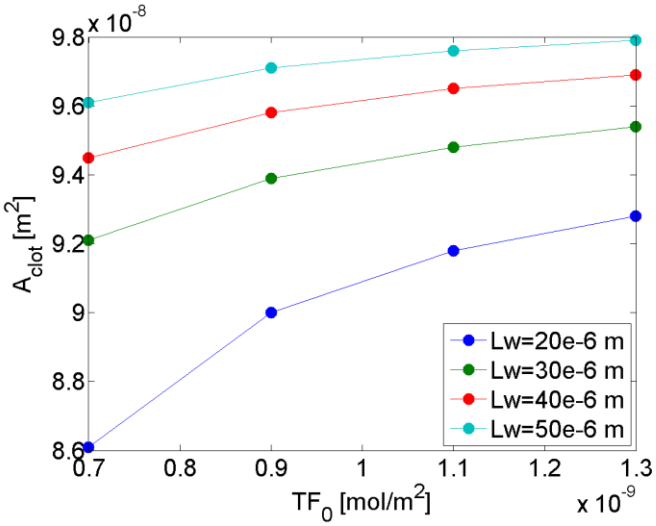
COMSOL CONFERENCE ROTTERDAM2013

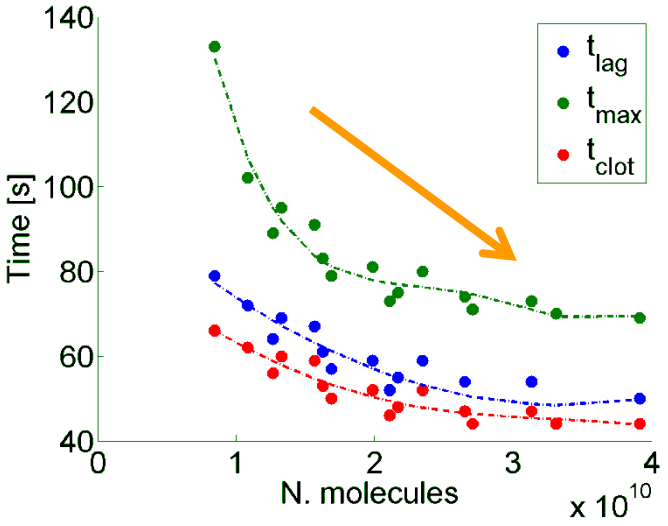
Results
Tissue factor and wound size

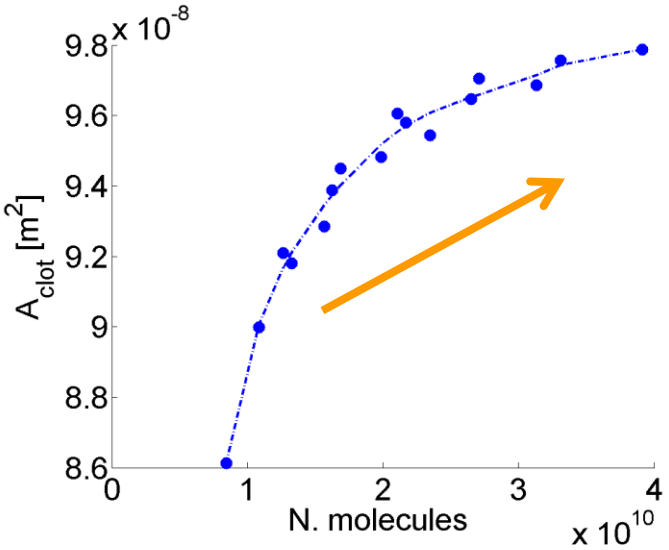
TF_0 [fmol/cm^2]	L_w [μm]
70	20
90	30
110	40
130	50

TF_0 or L_w↑	
t_{max}	↓
t_{lag}	↓
t_{clot}	↓
c_{max}	↑
A_{clot}	↑
TGD	↑







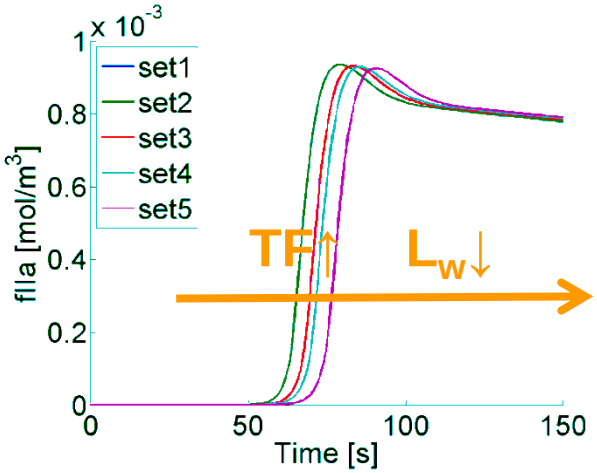


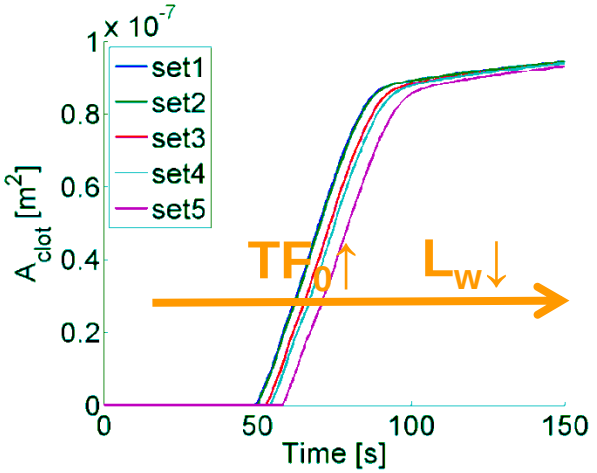
COMSOL CONFERENCE ROTTERDAM2013

Results
Constant number of molecules

Set	TF_0 [fmol/cm^2]	L_w [μm]
1	67.5	40
2	70	38.6
3	90	30
4	110	24.5
5	135	20

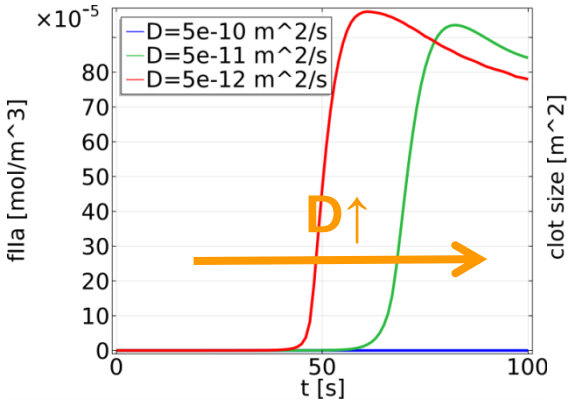
- Spatial distribution dominates over concentration level
- Contact region
- Contact time

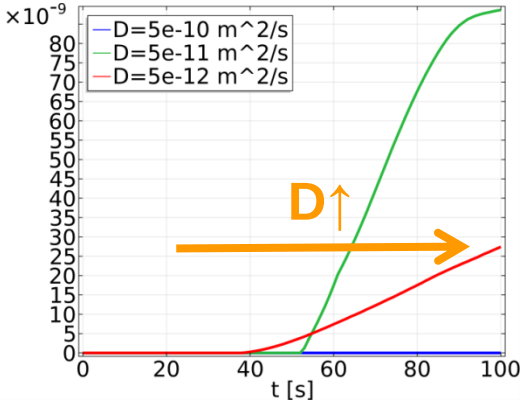




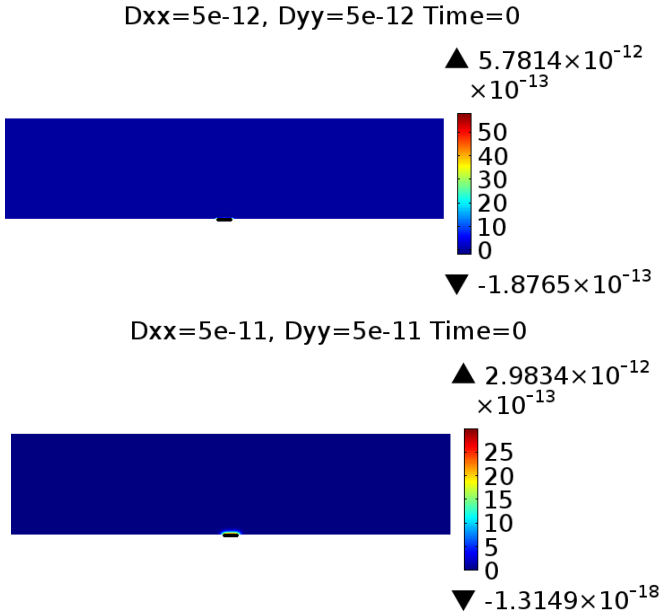
COMSOL CONFERENCE ROTTERDAM2013

Results
Flow and diffusion

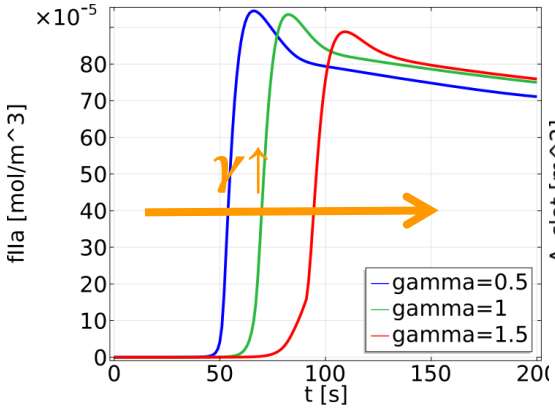


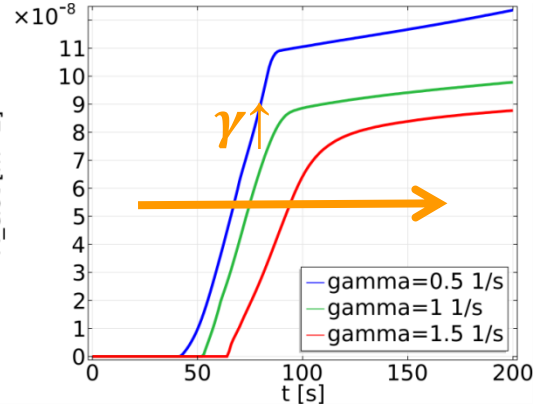


DIFFUSION

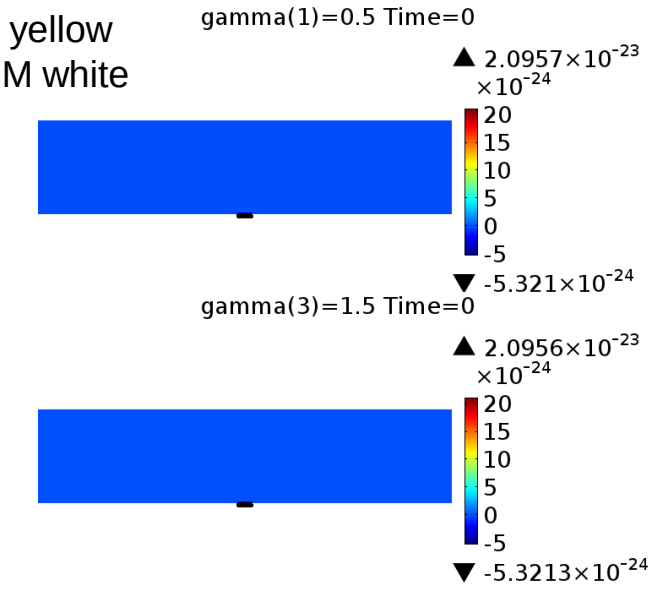


Contour level
- fIIa=10nM yellow
- Fbn=600nM white





FLOW



COMSOL CONFERENCE ROTTERDAM2013

Conclusions

- Increasing TF_0 or L_w enhances blood coagulation
  - stronger and accelerated burst
  - Larger clot and earlier clot occurrence

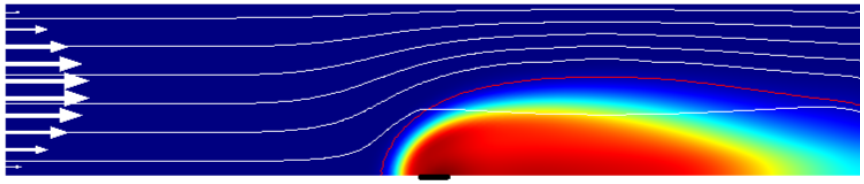
PRO-COAGULANT EFFECT

- Coagulation response is more sensitive to variation in L_w than TF_0
  - Contact region/time

- Flow and diffusion have a limiting role on blood coagulation
  - Delayed and damped burst
  - Domination of the anticoagulant effect

ANTI-COAGULANT EFFECT

Thank you for your attention
Questions



COMSOL CONFERENCE ROTTERDAM2013

- M. Anand, K. Rajagopal and K. R. Rajagopal, “A Model Incorporating Some of the Mechanical and Biochemical Factors Underlying Clot Formation and Dissolution in Flowing Blood,” *Journal of Theoretical Medicine*, vol. 5, 183–218 (2003).
- T. Bodnár and A. Sequeira. Numerical Simulation of the Coagulation Dynamics of Blood. Computational and Mathematical Methods in Medicine, 9(2):83–104, 2008.
- A. Sequeira, R. Santos and T. Bodnár, “Blood coagulation dynamics: mathematical modeling and stability results,” *Mathematical Biosciences and Engineering*, vol. 8, 425–443 (2011).
- M. Shibeko, E. S. Lobanova, M. A. Panteleev, and F. I. Ataullakhanov, “Blood flow controls coagulation onset via the positive feedback of factor VII activation by factor Xa.,” *BMC systems biology*, vol. 4, p. 5, Jan. 2010.