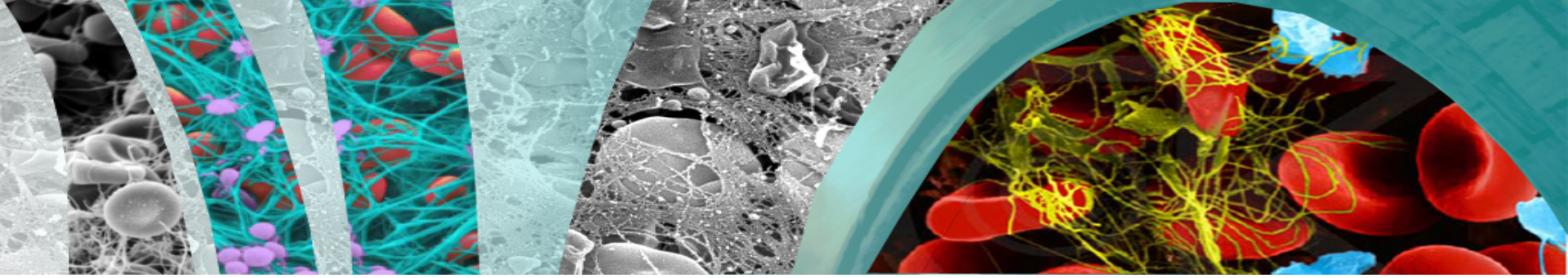

MATHEMATICAL MODELING OF THE EARLY STAGES OF ATHEROSCLEROSIS

Adélia SEQUEIRA

International Conference

Micro and Macro Systems in Life Sciences

Banach Center, Bedlewo, POLAND, June 8-13, 2015

TÉCNICO LISBOA

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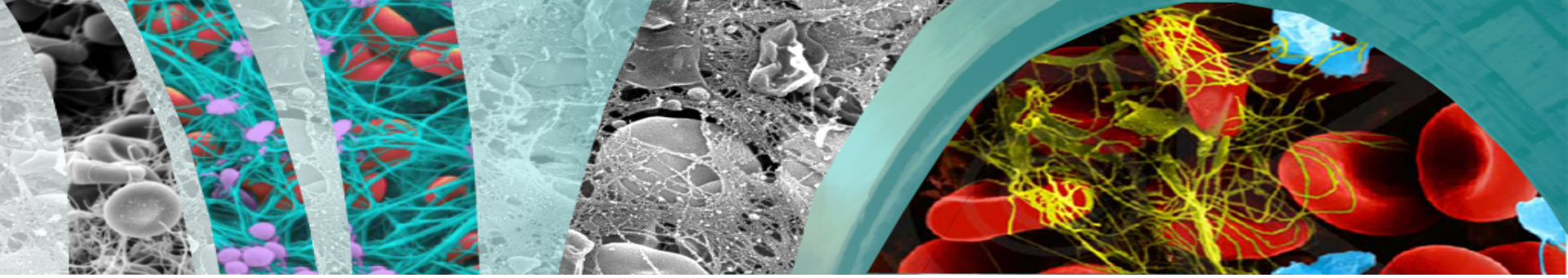
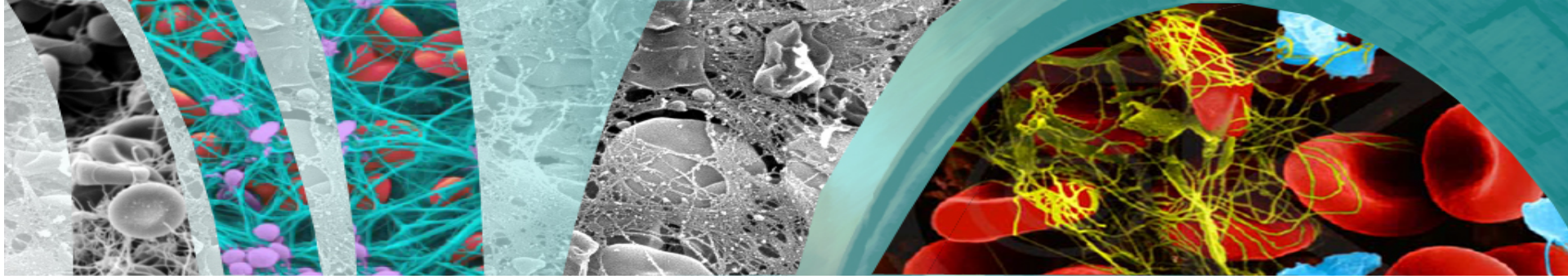


CARDIOVASCULAR DISEASES

- Leading cause of death in developed countries

- Modeling and simulations of blood flow behavior and the applied stresses help to:

    - Understand several diseases
    - Optimize surgical procedures
    - Design medical devices



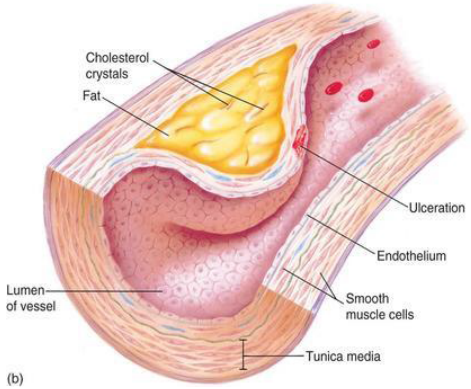
CARDIOVASCULAR DISEASES

Atherosclerosis

• Accumulation of fatty materials, fibrous elements and calcium in the intima of the arteries

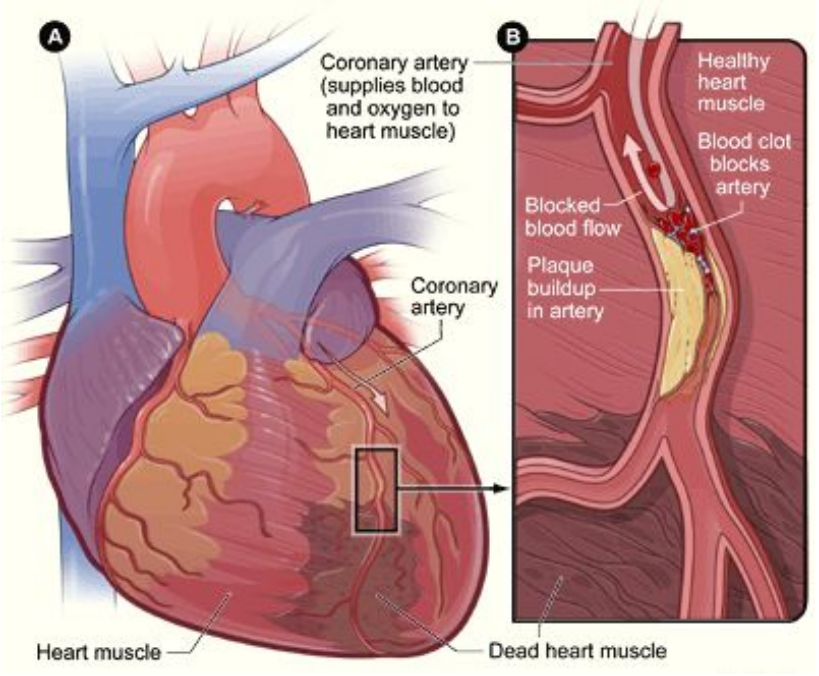
Causes:

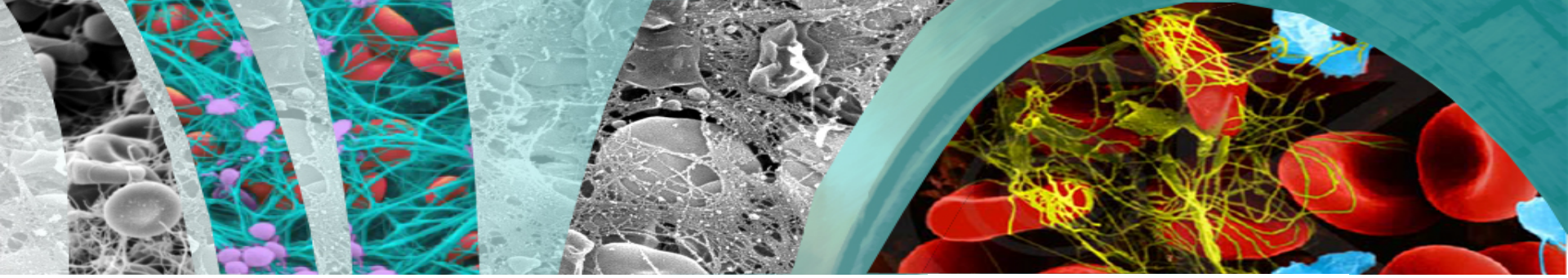
•Cholesterol
•High blood pressure
•Smoking



Consequences:

• Vessel narrowing
• Heart attack
• Stroke

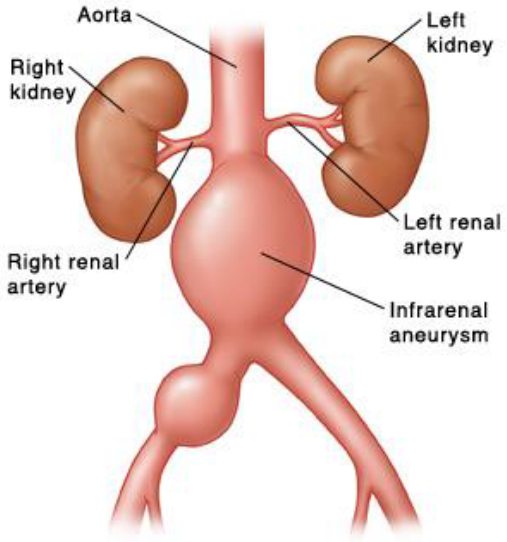


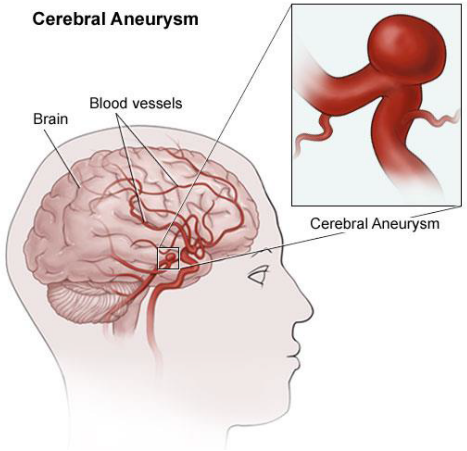


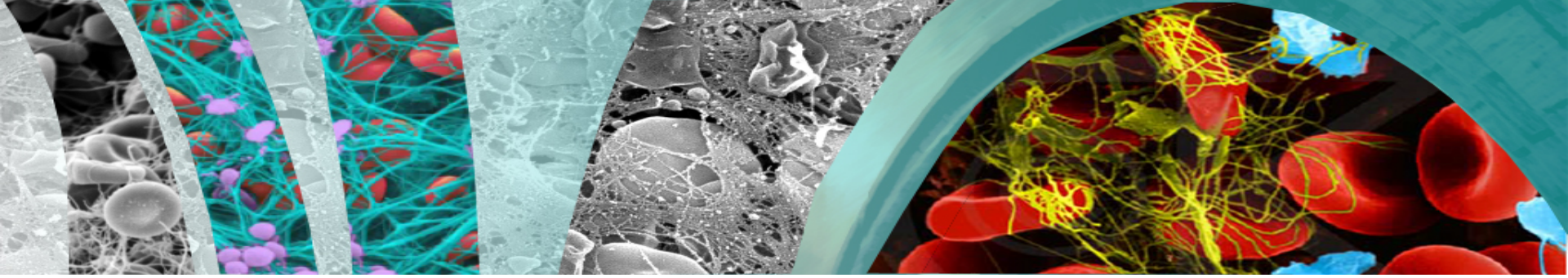
CARDIOVASCULAR DISEASES

Aneurysms

- Gradual dilation of an arterial segment
- <u>Consequences:</u>
  - Vessel stretches and becomes thinner
  - It can rupture causing hemorrage

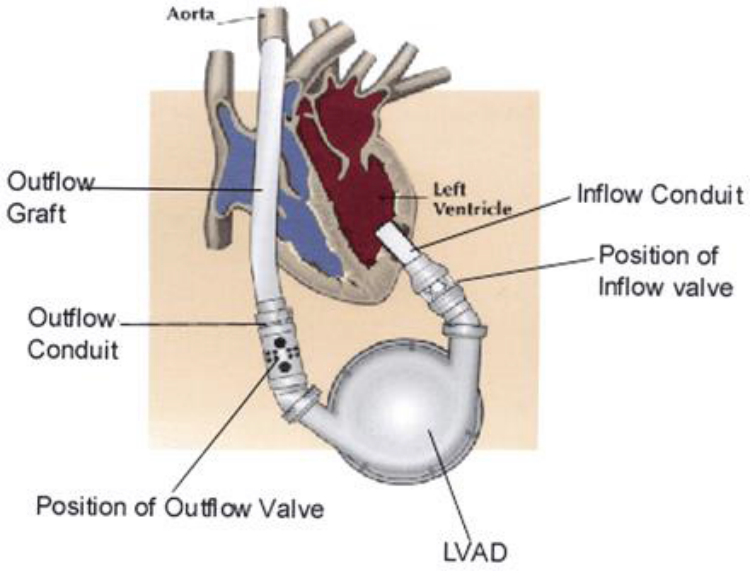




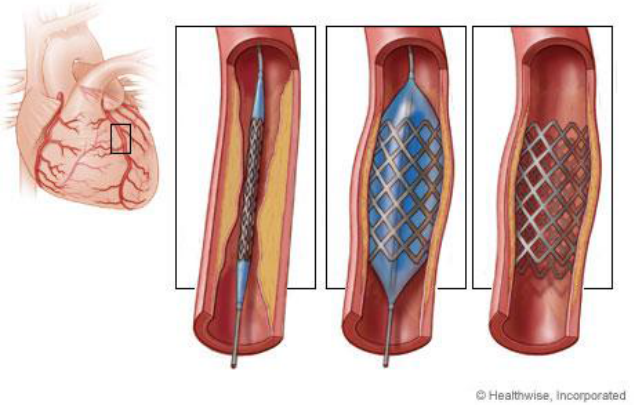


MEDICAL DEVICES

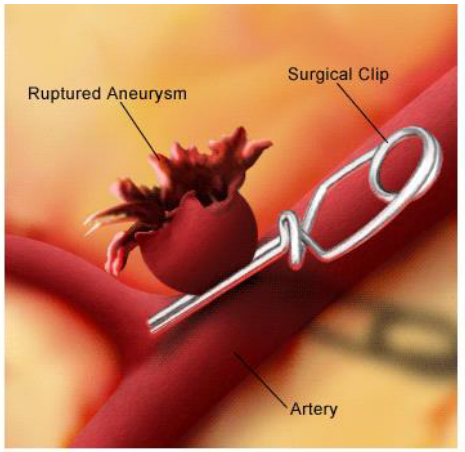
Ventricular Assist Devices (VAD)

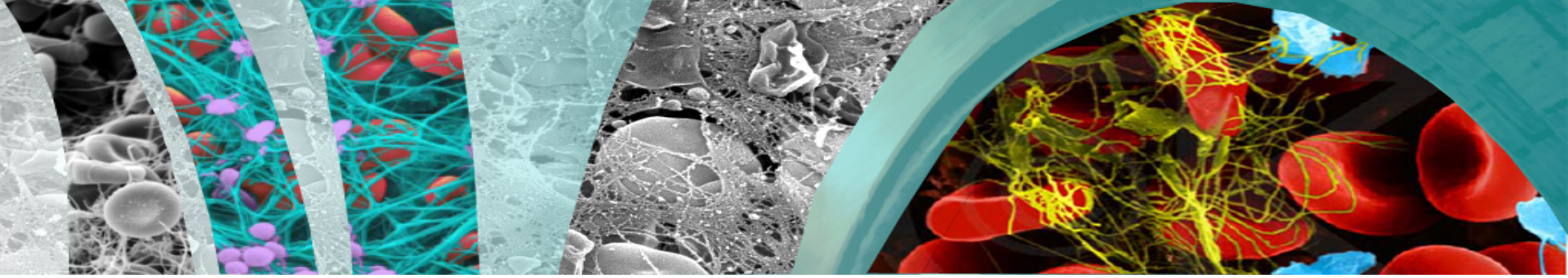


Stents



Aneurysm Clipping





OUTLINE

Atherosclerosis: the biological process

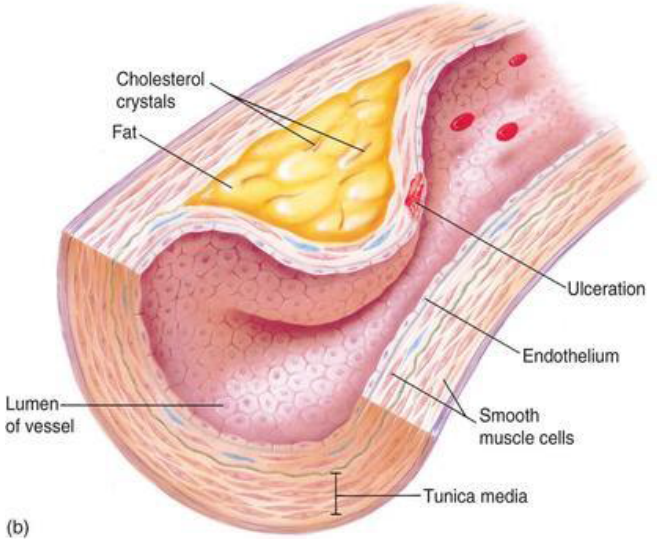
- Definition
- Atherosclerosis stages

Mathematical Modeling

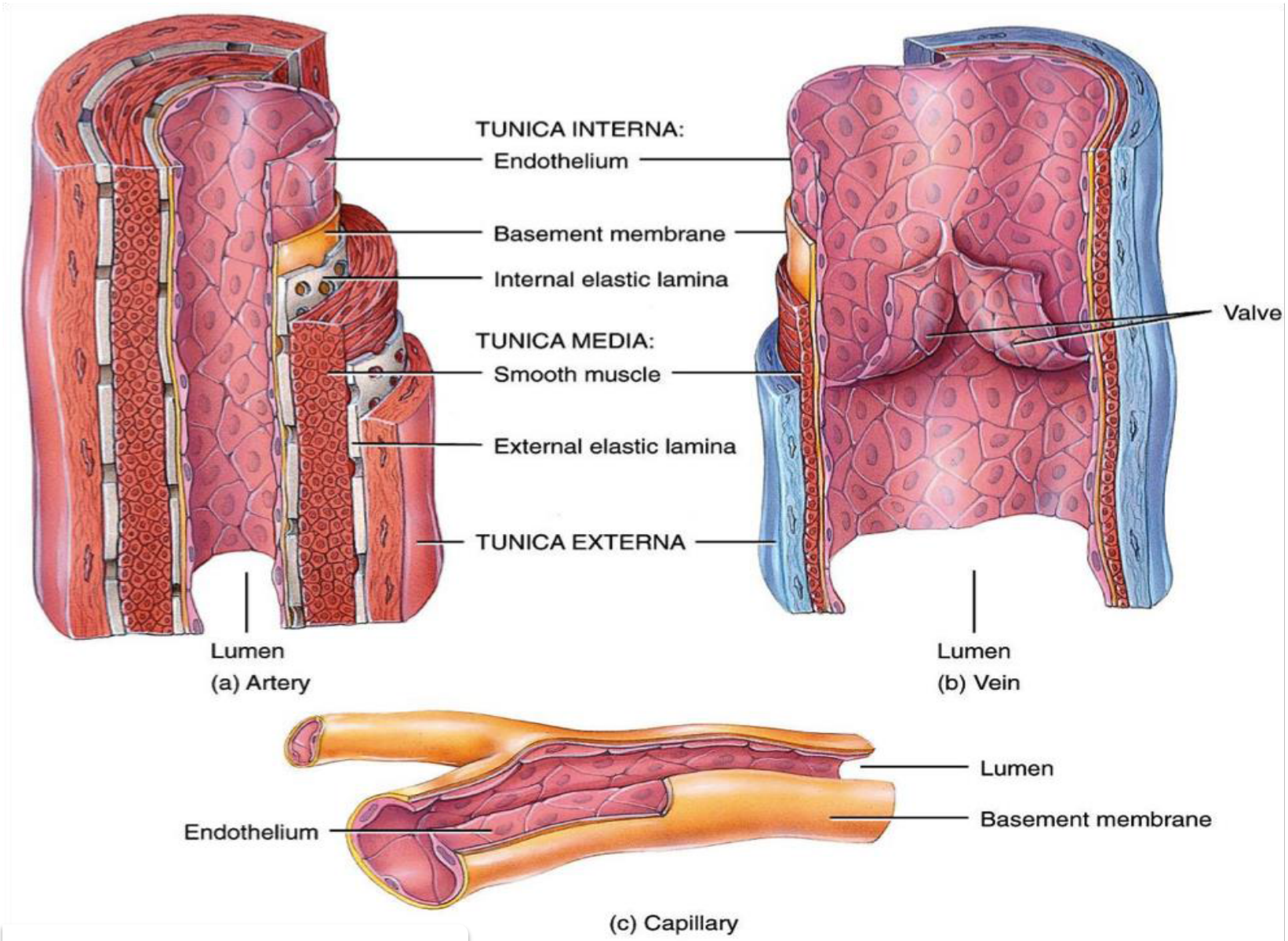
- Mathematical modeling of the inflammatory process
- The atherosclerotic plaque formation
- Coupling with the blood flow

Numerical Simulations

Blood Coagulation Modeling **(related topic)**

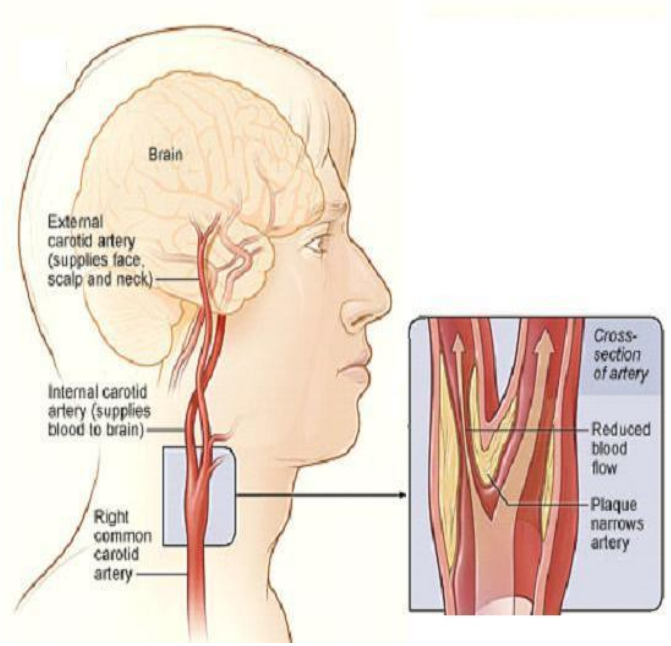


Structure of the blood vessels



What is Atherosclerosis?

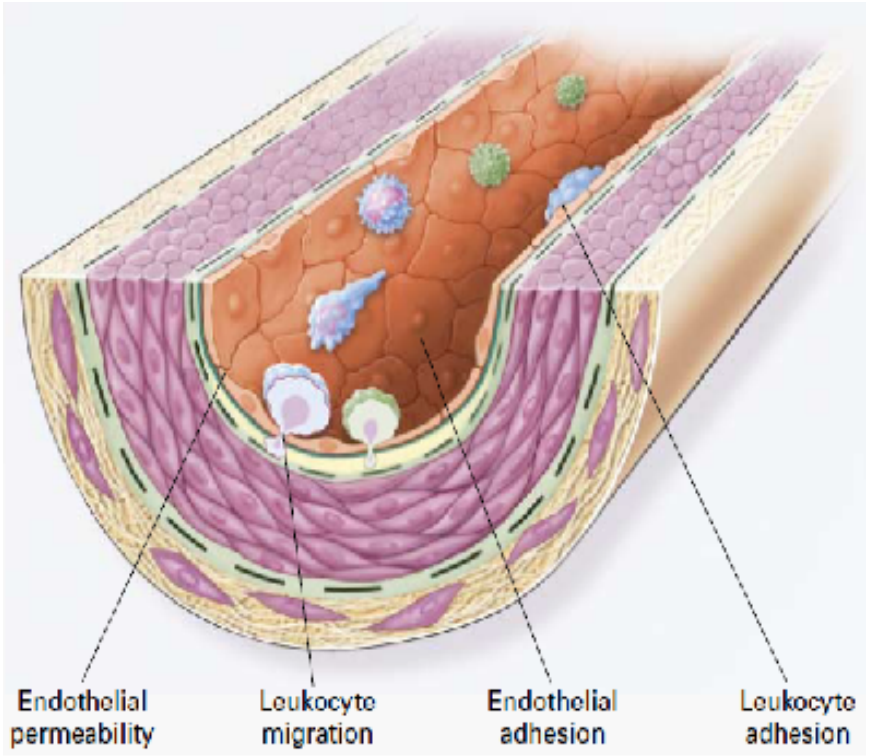
- Atherosclerosis is an inflammatory disease (R. Ross, 1999).
- The principal risk factor of atherosclerosis is the high concentration of **Low-Density-Lipoprotein (LDL-Cholesterol)** in the blood.
- Atherosclerotic lesions occur mainly in large and medium size arteries such as the **abdominal aorta**, the coronary arteries or the **carotid bifurcation**.



Atherosclerosis stages

I - Inflammation and Initiation

- **Low-Density Lipoprotein** (LDL) enters the intima and becomes oxidized - **oxLDL.**
- Endothelium Cells (ECs) send signals to the circulating blood Immune cells (eg. monocytes) .
- These immune cells are recruited to fight the unwanted substance (oxLDL).
- Once in the intima, monocytes are differentiated into active **macrophages**.

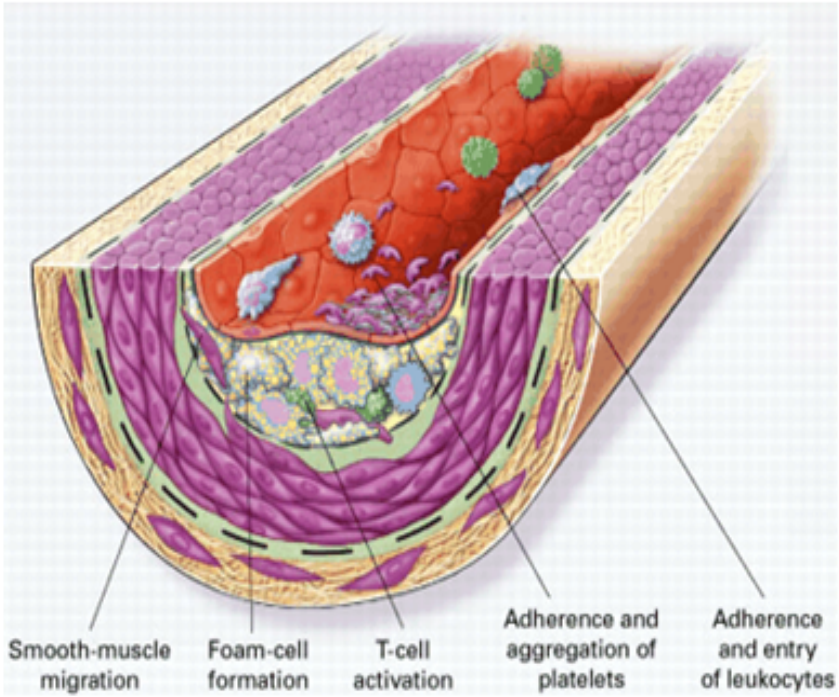


R. Ross (1999)

Atherosclerosis stages

II - Lipid Accumulation

- Active macrophages absorb oxLDL in the intima by phagocytosis process.
- This reaction transforms macrophages into **foam cells** (lipid-ladden cells) that should be removed by the immune system.
- A pro-inflammatory **signal** contributes to recruit new monocytes.
- An auto-amplification phenomenon occurs (chronic inflammatory reaction).



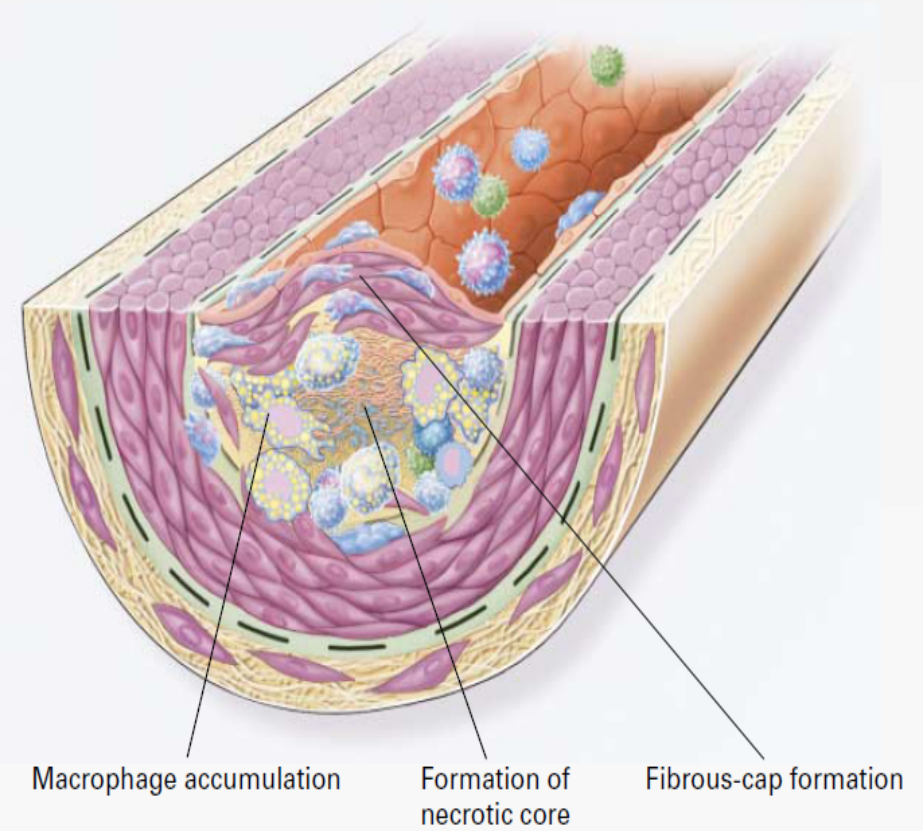
R. Ross (1999)

Atherosclerosis stages

III - Growth and Cap Formation

- The inflammation process involves the proliferation (the growth or production of cells by multiplication of their parts) and the migration of smooth muscle cells (SMCs) to create a fibrous cap over the lipid deposit.

- The fibrous cap changes the geometry of the vessel and modifies the blood flow.



R. Ross (1999)

Atherosclerosis stages

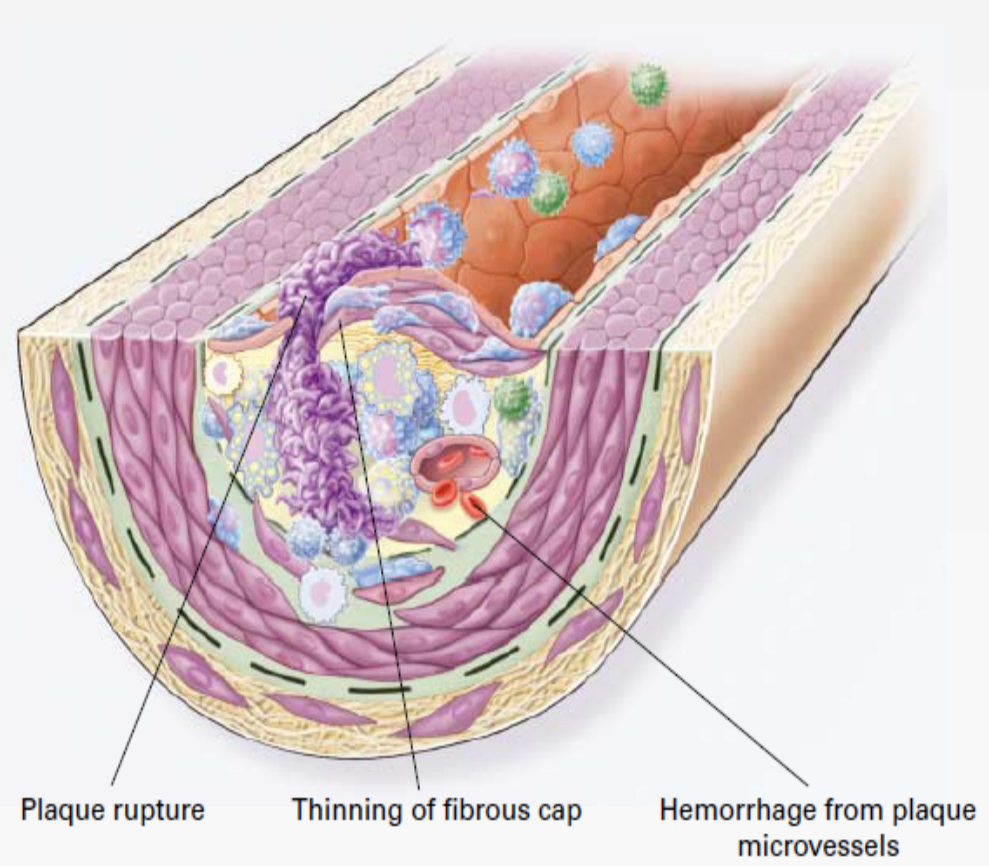
IV – Plaque Rupture

Due to several reasons:

- Local blood flow
- SMCs apoptosis
- ECs apoptosis

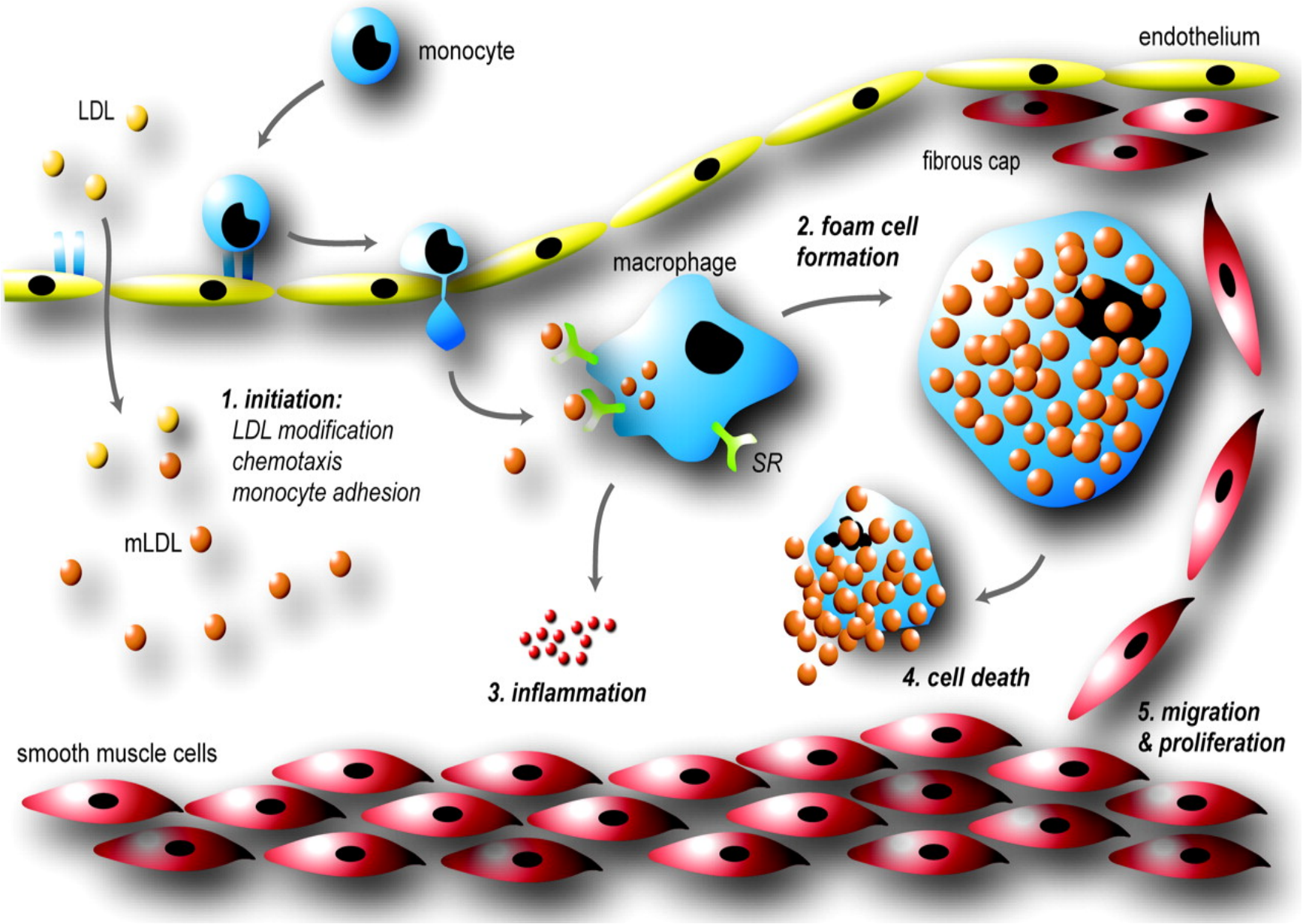
Leading to:

- The formation of a blood clot in the lumen and the subsequent obstruction of the artery
- Heart attack or Stroke



R. Ross (1999)

Atherosclerosis stages



Mathematical modeling of atherosclerosis

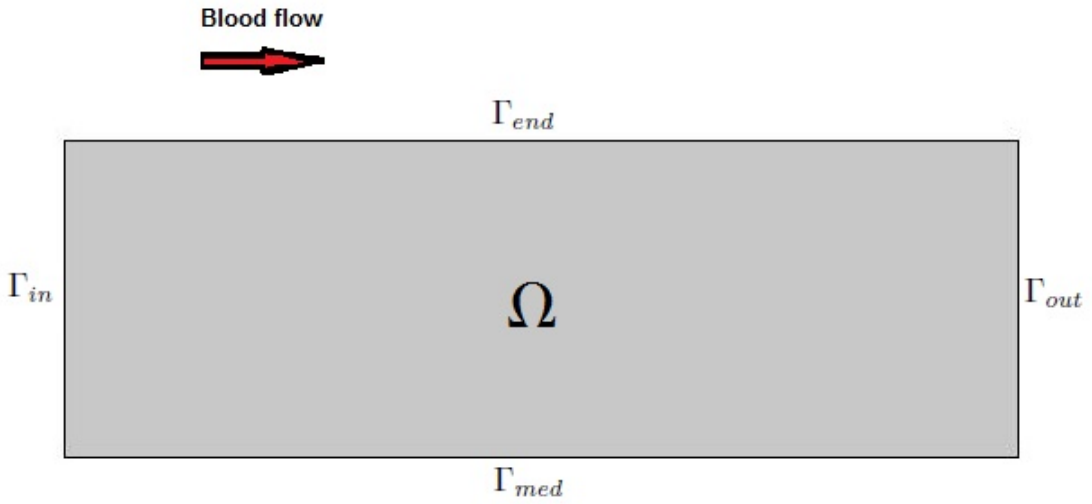
I and II stages – Early atherosclerotic lesions

II and III stages – Atherosclerotic plaque formation

IV stages - Plaque rupture

Mathematical modeling of atherosclerosis plaque formation

Geometry of the intima layer



$$\Omega = (0,L)\times(0,h)$$

$$\partial\Omega = \Gamma_{in} \cup \Gamma_{end} \cup \Gamma_{med} \cup \Gamma_{out}$$

V. Calvez, J. Houot, N. Meunier, A. Raoult and G. Rusnakova, Mathematical and numerical modeling of early atherosclerotic lesions, ESAIM Proceedings, 30 (2010), 1-14.

Mathematical modeling of atherosclerosis plaque formation

Evolution of Oxidized LDL – Ox

$$\begin{cases} \partial_t Ox + \underbrace{div(vOx)}_{\text{Lesion growth}} = \underbrace{d_1 \Delta Ox}_{\text{Diffusion}} - \underbrace{k_1 Ox \cdot M}_{\text{Ox+M}\rightarrow\text{LMA}}, & x \in \Omega,\ t \in [0, T], \\ \partial_y Ox = -\underbrace{\tau(x)}_{\text{Penetration}} C, & x \text{ on } \Gamma_{end},\ t \in [0, T], \\ \partial_n Ox = 0, & x \text{ on } \partial\Omega \setminus \Gamma_{end},\ t \in [0, T]. \end{cases}$$

Lesion growth
V=tissue displacement

Diffusion

Ox+M→LMA

Penetration
τ = permeability of the blood vessel

It reflects the conversion of macrophages into foam cells when they ingest the Ox

Assumptions:

Passive penetration of LDL in particular areas of the intima.

Law of Mass Action (LMA) states that the rate of an elementary reaction (a reaction that proceeds through only one transition state) is proportional to the product of the concentrations of the participating molecules.

Mathematical modeling of atherosclerosis plaque formation

Evolution of Macrophage (M)

$$\begin{cases} \partial_t M + \underbrace{div(vM)}_{\text{Vol. increasing}} = \underbrace{d_2 \Delta M}_{\text{Diffusion}} - \underbrace{k_1 Ox \cdot M}_{\text{Foam cells}}, & x \in \Omega, \ t \in [0, T], \\ \partial_y M = -\underbrace{f(S)}_{\text{Recruitment}}, & x \text{ on } \Gamma_{end}, \ t \in [0, T], \\ \partial_n M = 0, & x \text{ on } \partial\Omega \setminus \Gamma_{end}, \ t \in [0, T], \end{cases}$$

where, $f(S) = \dfrac{S}{1+S}$.

Assumptions:

- The incoming monocytes immediately differentiate into macrophages.
- The recruitment of new monocytes depends on a general pro-inflammatory signal S which gathers both chemokines and cytokines (chemoattractants).

Mathematical modeling of atherosclerosis plaque formation

Cytokines – Signal (S)

$$\begin{cases} \partial_t S = \underbrace{d_3 \Delta S}_{\text{Diffusion}} - \overbrace{\alpha S}^{\text{Degradation}} + \underbrace{k_1 Ox \cdot M}_{\text{Inflammatory}} + \underbrace{\beta \left(Ox - Ox^{th} \right)_+}_{\text{oxLDL detection}}, & x \in \Omega, \ t \in [0, T], \\ \partial_n S = 0, & x \text{ on } \partial\Omega, \ t \in [0, T]. \end{cases}$$

Assumptions:

Starting point of the signal emission is assumed to be a too high oxidized LDL concentration.

Mathematical modeling of atherosclerosis plaque formation

Foam Cells (F)

$$\partial_t F + \underbrace{div(vF)}_{\text{Lesion growth}} = \underbrace{k_1 Ox \cdot M}_{\text{Foam cells}}, \qquad x \in \Omega, \quad t \in \left[0, T\right].$$

Assumption:

Under a local incompressibilty assumption, when foam cells are created, the intima volume is locally increasing (lesion growth).

Mathematical modeling of atherosclerosis plaque formation

Biomass assumption: w denotes the biomass which is the rest of the intimal medium (extracellular matrix, SMCs,...) that does not contribute to the inflammatory process.

$$\partial_t w + div(vw) = 0, \qquad \mathrm{x} \in \Omega, \quad \mathrm{t} \in \left[0, T\right].$$

Local matter incompressiblity assumption: There exists A (total number of cells per unit volume – invariant in time) such that

$$w + F = A, \qquad \mathrm{x} \in \Omega, \quad \mathrm{t} \in \left[0, T\right]$$

Plaque growth

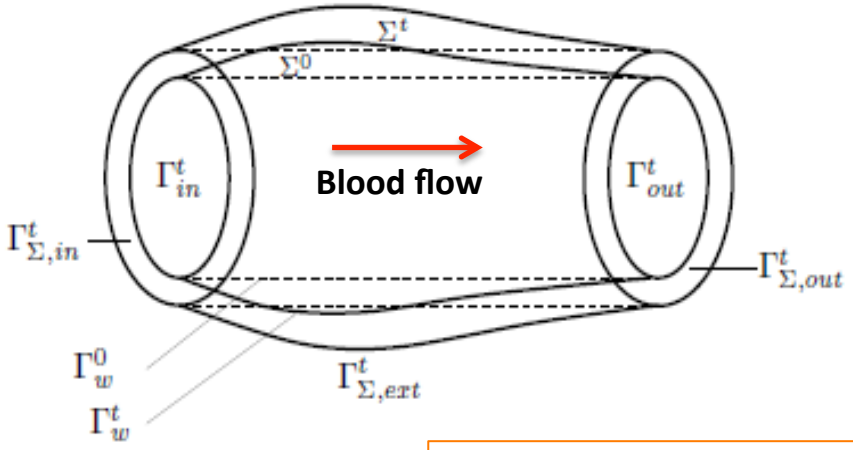
$$\nabla \cdot v = \frac{k_F}{A} Ox.M, \quad \mathrm{x} \in \Omega, \quad \mathrm{t} \in \left[0, T\right]$$

Mathematical modeling of atherosclerosis plaque formation

Foam cells, biomass and plaque growth

$$
\begin{aligned}
-\nabla \cdot D(v) + \nabla q &= 0, && \mathrm{x} \in \Omega, \ \mathrm{t} \in [0, T], \\
\nabla \cdot v &= \frac{k_F}{A} Ox.M, && \mathrm{x} \in \Omega, \ \mathrm{t} \in [0, T], \\
D(v)n - qn &= 0, && \mathrm{x} \ \text{on} \ \Gamma_{end}, \ \mathrm{t} \in [0, T], \\
v &= 0, && \mathrm{x} \ \text{on} \ \partial\Omega \setminus \Gamma_{end}, \ \mathrm{t} \in [0, T].
\end{aligned}
$$

Blood Flow Model



$$
\begin{aligned}
\rho(\partial_t u + (u.\nabla)u) - \nu\Delta u + \nabla p = 0, &\qquad x \in \Omega,\ t \in [0,T] \\
\nabla . u = 0, &\qquad x \in \Omega,\ t \in [0,T] \\
u = U_{in}, &\qquad x \in \Gamma_{in}, t \in [0,T] \\
T(u,p)n = -p_{out} n, &\qquad x \in \Gamma_{out}, t \in [0,T] \\
u.n = J_v, &\qquad x \in \Gamma_w, t \in [0,T] \\
u - (u.n)n = 0, &\qquad x \in \Gamma_w, t \in [0,T]
\end{aligned}
$$

where $T(u,p) = 2\nu D(u) - pId$ and $D(u) = \frac{1}{2}(\nabla u + \nabla u^T)$

Mathematical modeling of the inflammatory process

- Simplified model describing the concentration of OxLDL (Ox), Macrophages (M) and Cytokines (S) in the intima (Stages I and II)

System of three reaction-diffusion equations,

$$\partial_t Ox - d_{ox}\Delta Ox = -\beta Ox \cdot M \tag{1a}$$

$$\partial_t M - d_M \Delta M = -\beta Ox \cdot M \tag{1b}$$

$$\partial_t S - d_S \Delta S = \beta Ox \cdot M - \lambda S + \gamma\left(Ox - Ox^{th}\right) \tag{1c}$$

in Ω, for all $t \in \mathbb{R}^+$, with the boundary conditions

$$\nabla Ox \cdot (-\mathbf{n}) = \tau(x)\, C_{LDL} \quad \text{on } \Gamma_{end} \quad \text{and} \quad \nabla Ox \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \backslash \Gamma_{end} \tag{2a}$$

$$\nabla M \cdot (-\mathbf{n}) = g(S) \quad \text{on } \Gamma_{end} \quad \text{and} \quad \nabla M \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \backslash \Gamma_{end} \tag{2b}$$

$$\nabla S \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \tag{2c}$$

for all $t \in \mathbb{R}^+$ and the initial conditions

$$Ox(x,0) = Ox_0(x), \quad M(x,0) = M_0(x), \quad S(x,0) = S_0(x) \quad \text{in } \Omega. \tag{3}$$

Well-posedness of the time-dependent problem

- Parabolic problem with nonlinear boundary conditions:

The system (1)-(3) can be written as

$$\begin{aligned} \partial_t C_i - d_i \Delta C_i &= \Phi_i && \text{in } \Omega_T \\ \partial_{\mathbf{n}} C_i &= G_i && \text{on } \partial\Omega_T \\ C_i(x,0) &= C_{i,0}(x) && \text{in } \Omega \end{aligned} \tag{4}$$

for $i = 1, 2, 3$, where

$$\begin{aligned} (C_1(x,t), C_2(x,t), C_3(x,t)) &= (Ox(x,t), M(x,t), S(x,t)) \\ (d_1, d_2, d_3) &= (d_{ox}, d_M, d_S) \end{aligned}$$

$$\Phi_1 = \Phi_2 = -\beta C_1 \cdot C_2 \quad \text{and} \quad \Phi_3 = \beta Ox \cdot M - \lambda S + \gamma\left(Ox - Ox^{th}\right)$$

$$G_1 = -\tau(x) C_{LDL} \psi(x), \quad G_2 = -g(C_3)\psi(x) \quad \text{and} \quad G_3 = 0 \ \text{ on } \ \partial\Omega$$

$\Omega_T = \Omega \times (0, T]$ and $\partial\Omega_T = \partial\Omega \times (0, T]$ for an arbitrary finite $T > 0$.

Well-posedness of the time-dependent problem

Theorem (C. V. Pao, 1992)

Let $\tilde{\mathbf{C}} = \left(\tilde{C}_1, \tilde{C}_2, \tilde{C}_3\right)$ *and* $\hat{\mathbf{C}} = \left(\hat{C}_1, \hat{C}_2, \hat{C}_3\right)$ *be a pair of nonnegative* **coupled upper and lower solutions** *of* (4) *and let* $\mathbf{\Phi} = (\Phi_1, \Phi_2, \Phi_3)$ *and* $\mathbf{G} = (G_1, G_2, G_3)$ *be* **quasimonotone** *and satisfy the* **global Lipschitz condition** *in* $\mathbf{C} \in \left\langle \hat{\mathbf{C}}, \tilde{\mathbf{C}} \right\rangle$. *Then* **the upper and the lower sequences** $\left\{\overline{\mathbf{C}}^{(k)}\right\}, \left\{\underline{\mathbf{C}}^{(k)}\right\}$

(i) *possess the monotone property*

$$\hat{\mathbf{C}} \leq \underline{\mathbf{C}}^{(k)} \leq \underline{\mathbf{C}}^{(k+1)} \leq \overline{\mathbf{C}}^{(k+1)} \leq \overline{\mathbf{C}}^{(k)} \leq \tilde{\mathbf{C}} \quad \text{in } \overline{\Omega}_T \tag{5}$$

for every k *and*

(ii) *converge monotonically to a unique solution* $\mathbf{C} = (C_1, C_2, C_3)$ *with*

$$\left(\hat{C}_1, \hat{C}_2, \hat{C}_3\right) \leq (C_1, C_2, C_3) \leq \left(\tilde{C}_1, \tilde{C}_2, \tilde{C}_3\right) \text{ in } \Omega_T. \tag{6}$$

Well-posedness of the time-dependent problem

Let

$$\mathbf{C} = \left(C_i, [\mathbf{C}]_{a_i}, [\mathbf{C}]_{b_i}\right)$$

be the split notation of the vector $\mathbf{C}$, where $[\mathbf{C}]_{a_i}$, $[\mathbf{C}]_{b_i}$ are, resp., the a_i and b_i-components of the vector $\mathbf{C}$, with a_i, $b_i \in \mathbb{N}_0$ and $a_i + b_i = 2$.

Definition

(**Quasimonotone property**) A function $\mathbf{F} = (f_1, f_2, ..., f_n)$ is said to possess a quasimonotone property if for each i there exist nonnegative integers a_i, b_i with $a_i + b_i = n - 1$ such that $f_i\left(C_i, [\mathbf{C}]_{a_i}, [\mathbf{C}]_{b_i}\right)$ is monotone nondecreasing in $[\mathbf{C}]_{a_i}$ and monotone nonincreasing in $[\mathbf{C}]_{b_i}$.

Well-posedness of the time-dependent problem

Quasimonotone property

For Φ_i and for all $\mathbf{C} \geq 0$,

$$\begin{aligned} [\mathbf{C}]_{a_1} &= 0 && \text{and} \quad [\mathbf{C}]_{b_1} = C_2 \\ [\mathbf{C}]_{a_2} &= 0 && \text{and} \quad [\mathbf{C}]_{b_2} = C_1 \\ [\mathbf{C}]_{a_3} &= (C_1, C_2) && \text{and} \quad [\mathbf{C}]_{b_3} = 0. \end{aligned}$$

For G_i, since G_1 is linear and $G_3 = 0$, we will consider only G_2. Therefore, for all $\mathbf{C} \geq 0$,

$$[\mathbf{C}]_{\alpha_2} = 0 \quad \text{and} \quad [\mathbf{C}]_{\rho_2} = C_3.$$

The reaction function $\mathbf{\Phi} = (\Phi_1, \Phi_2, \Phi_3)$ and the boundary function $\mathbf{G} = (G_1, G_2, G_3)$ defined in (4), are quasimonotone in $\mathbf{C}$ for all $\mathbf{C} \geq 0$.

Well-posedness of the time-dependent problem

Upper and lower solutions

Definition

A pair of smooth functions $\tilde{\mathbf{C}} = \left(\tilde{C}_1, \tilde{C}_2, \tilde{C}_3\right)$, $\hat{\mathbf{C}} = \left(\hat{C}_1, \hat{C}_2, \hat{C}_3\right)$ in $C\left(\overline{\Omega}_T\right) \cap C^{2,1}\left(\Omega_T\right)$ is called **coupled upper and lower solutions** of (4) if $\tilde{\mathbf{C}} \geq \hat{\mathbf{C}}$ and if it satisfy

$$\partial_t \tilde{C}_I - d_I \Delta \tilde{C}_I \geq \Phi_I\left(\tilde{C}_I, \left[\tilde{\mathbf{C}}\right]_{a_i}, \left[\hat{\mathbf{C}}\right]_{b_i}\right) \quad \text{in } \Omega_T \tag{7a}$$

$$\partial_t \hat{C}_I - d_I \Delta \hat{C}_I \leq \Phi_I\left(\hat{C}_I, \left[\hat{\mathbf{C}}\right]_{a_i}, \left[\tilde{\mathbf{C}}\right]_{b_i}\right) \quad \text{in } \Omega_T \tag{7b}$$

$$\partial_n \tilde{C}_I \geq G_I\left(\cdot, \tilde{C}_I, \left[\tilde{\mathbf{C}}\right]_{\alpha_i}, \left[\hat{\mathbf{C}}\right]_{\rho_i}\right) \quad \text{on } \partial\Omega_T \tag{7c}$$

$$\partial_n \hat{C}_I \leq G_I\left(\cdot, \hat{C}_I, \left[\hat{\mathbf{C}}\right]_{\alpha_i}, \left[\tilde{\mathbf{C}}\right]_{\rho_i}\right) \quad \text{on } \partial\Omega_T \tag{7d}$$

$$\tilde{C}_I(x,0) \geq C_{I,0}(x) \geq \hat{C}_I(x,0) \quad \text{in } \Omega \tag{7e}$$

for $i = 1, 2, 3$.

Well-posedness of the time-dependent problem

Summary

The quasimonotone property of Φ and $\mathbf{G}$, the one-sided Lipschitz condition, the definition of upper and lower solutions and the iteration process are used to prove the monotone property

$$\hat{\mathbf{C}} \leq \underline{\mathbf{C}}^{(k)} \leq \underline{\mathbf{C}}^{(k+1)} \leq \overline{\mathbf{C}}^{(k+1)} \leq \overline{\mathbf{C}}^{(k)} \leq \tilde{\mathbf{C}} \quad \text{in } \overline{\Omega}_T.$$

From the quasimonotone property, the limits

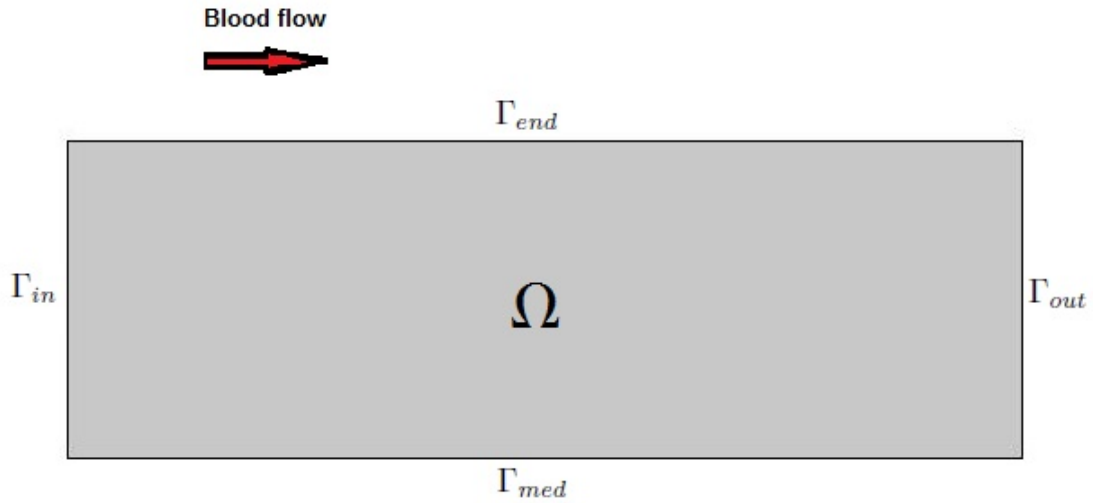
$$\lim_{k\to\infty} \overline{\mathbf{C}}^{(k)}(x,t) = \overline{\mathbf{C}}(x,t), \qquad \lim_{k\to\infty} \underline{\mathbf{C}}^{(k)}(x,t) = \underline{\mathbf{C}}(x,t)$$

exist and satisfy the relation

$$\hat{\mathbf{C}} \leq \underline{\mathbf{C}} \leq \overline{\mathbf{C}} \leq \tilde{\mathbf{C}} \quad \text{in } \overline{\Omega}_T.$$

The proof is completed by showing that $\overline{\mathbf{C}} = \underline{\mathbf{C}}$, which is the unique solution of (1).
The solution is global, since T is arbitrary.

Numerical Simulations



$$\Omega = (0,L) \times (0,h)$$

$$\partial\Omega = \Gamma_{in} \cup \Gamma_{end} \cup \Gamma_{med} \cup \Gamma_{out}$$

L= 0.5 cm h= 0.167 cm

$$\tau(x) = \begin{cases} 1 & on\ \Gamma_{end}^{p} \\ 0 & on\ \Gamma_{end} \end{cases}$$

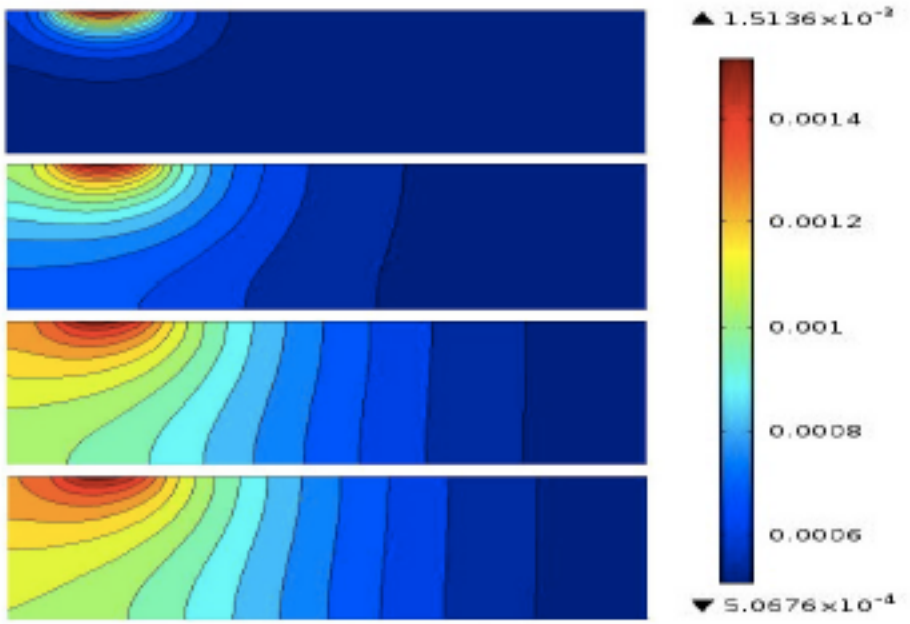
$$d_{ox} = d_S = 10^2 \times d_M = 10^{-3}\ cm/s$$
$$\lambda = 10\ s^{-1}$$
$$\beta = 1\ cm/(g \cdot s)$$
$$\gamma = 1\ s^{-1}$$

$$C_{LDL}^{-} = 0.1 g/cm^3$$

When the RD equations are coupled with the fluid, τ(x) is an absorption rate – function of the WSS

Numerical Simulations

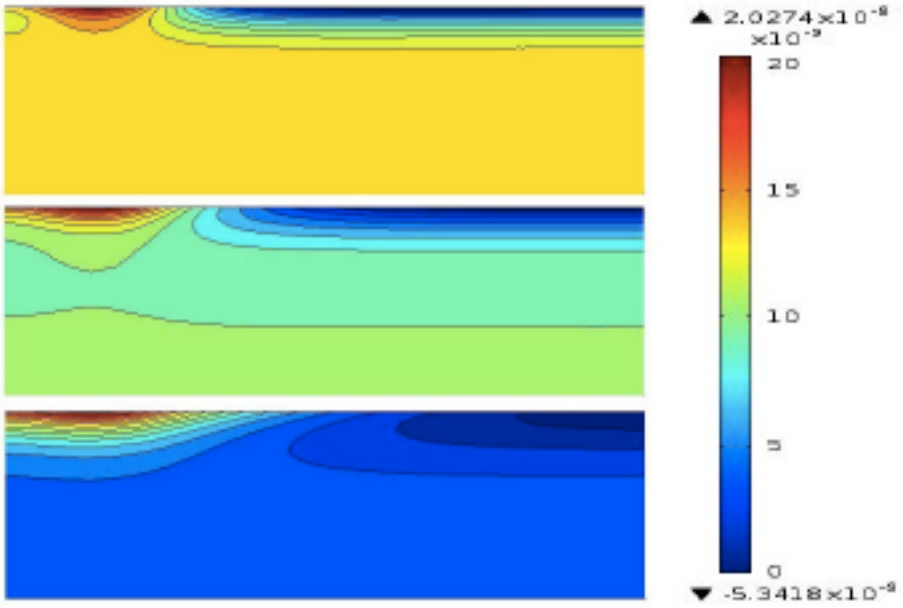
Results - OxLDL



Evolution in time of the concentration of OxLDL in a region of LDL penetration, with initial condition equal to zero (T=1, 10, 50, 100 s). The diffusion effect is also visible in this region.

Numerical Simulations

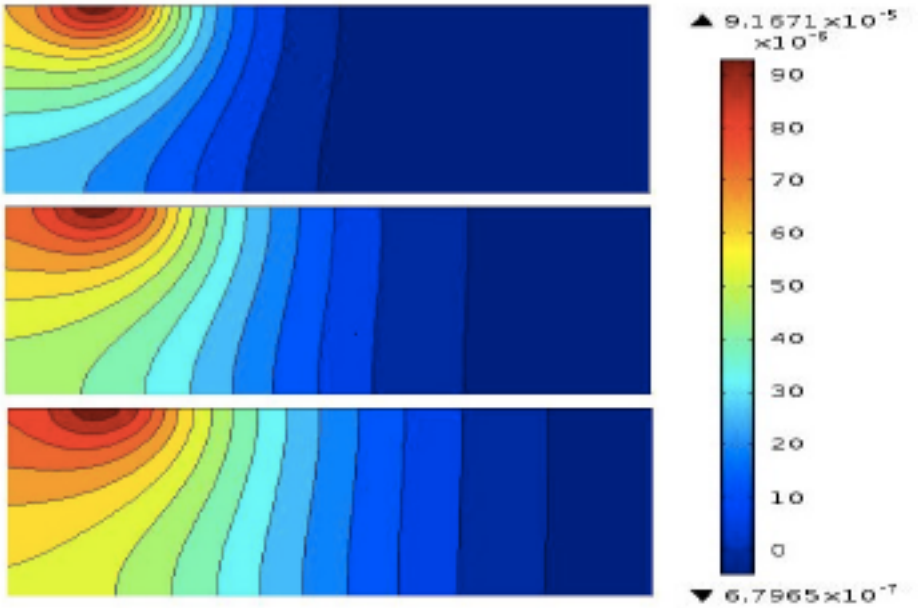
Evolution in time Macrophages concentration



T=30, 50, 100 s

Numerical Simulations

Evolution in time of Cytokines concentration



T=30, 50, 100 s

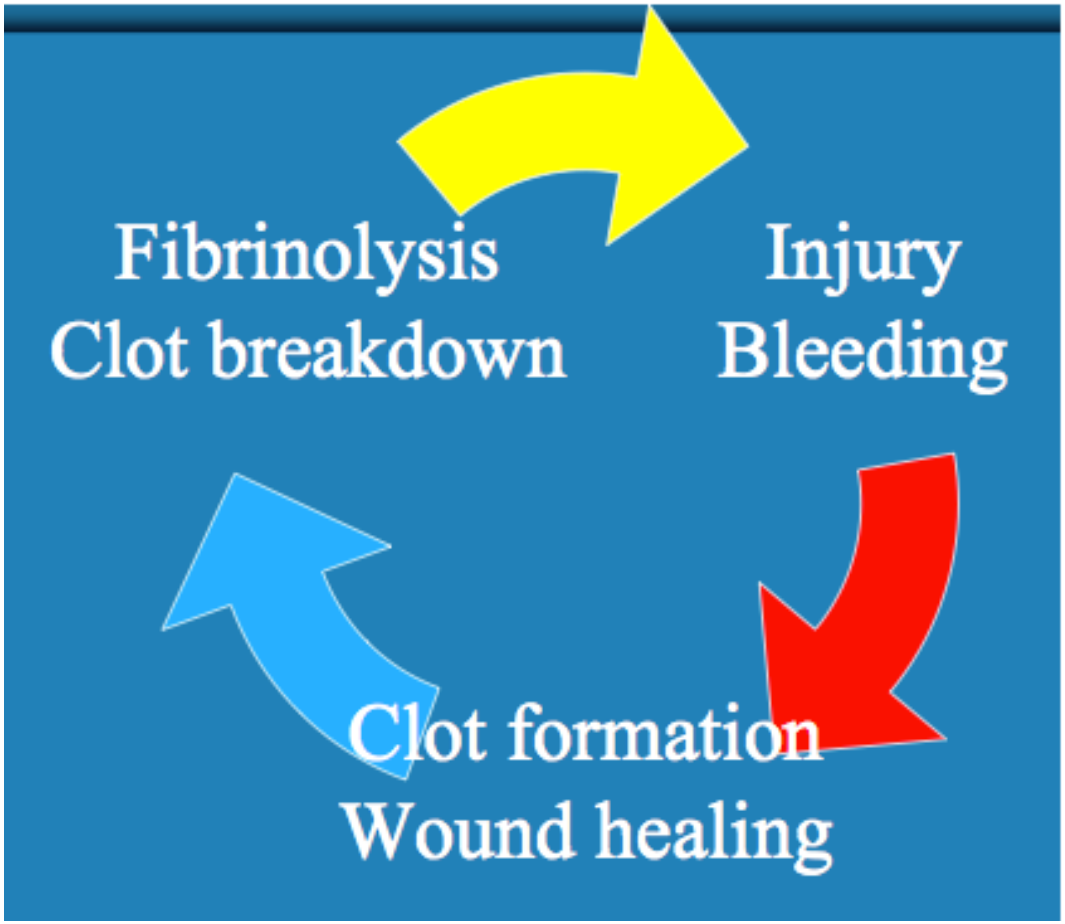
BLOOD COAGULATION MODELING AND SIMULATIONS

What is coagulation for ? How is it promoted?

Blood coagulation is an impressively complex process by which blood forms clots

- It is responsible for maintenance of hemostasis in the vascular system
- Provides localized response to the injury and triggers healing of the vessels
- Participates in the inflammatory response and atherosclerosis
- **The clotting mechanism is set in motion only when it is really necessary**, remaining silent in normal conditions and terminating before it occludes the vessel, allowing blood to flow normally **(fibrinolysis).**

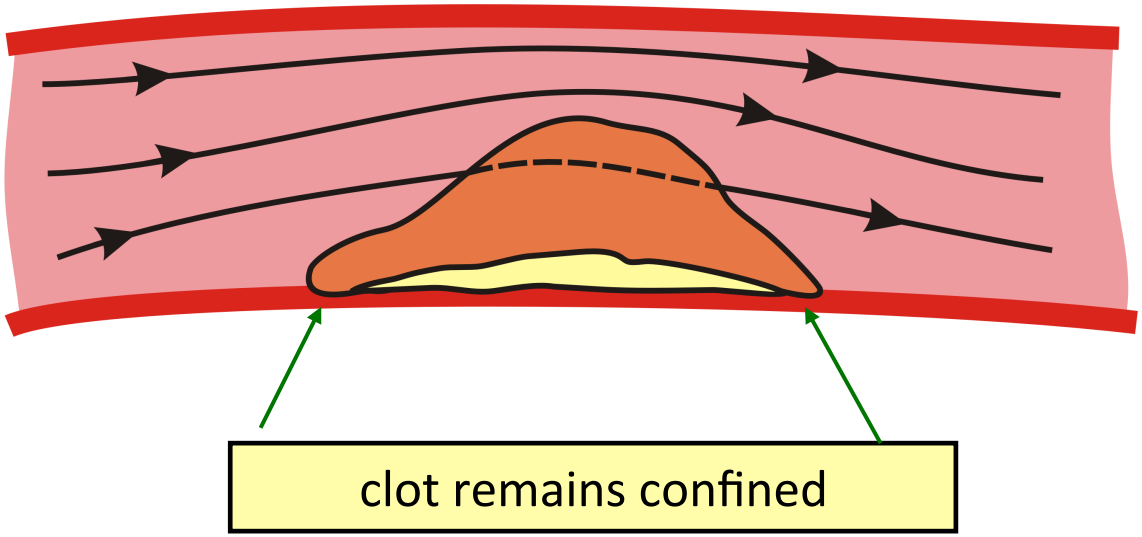
Constant Cycle: Hemostasis



A two-steps process

- primary hemostasis: platelets bind to von Willebrand Factor and collagen at the wound site, forming the so-called “white thrombus”

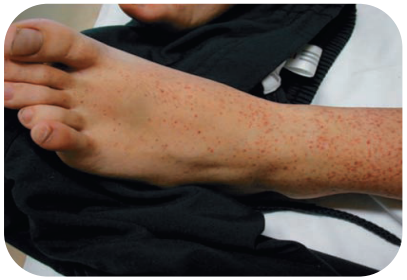
- secondary hemostasis: goes through a chemical cascade in which many “Factors” intervene



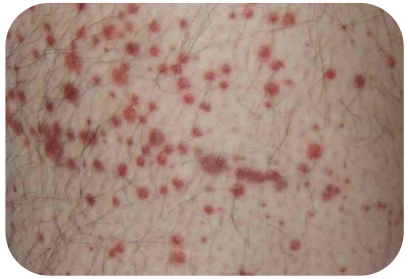
Disorders of coagulation can lead to an increased risk of

Spontaneous bleeding (hemorrhage)

Bleeding can occur **internally**, where blood leaks from blood vessels inside the body or **externally**



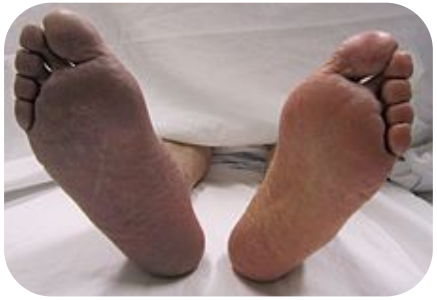
Petechiae around the ankles in an otherwise healthy 16-year old girl with acute idiopathic thrombocytopenic purpura.



Purpura of the type associated with ITP

Obstructive clotting (thrombosis) (excessive coagulation)

Thrombosis is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system

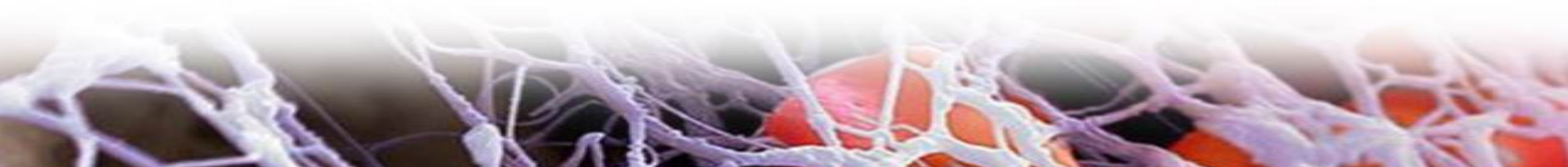


Acute arterial thrombosis of the right leg
(note the blue discoloration)

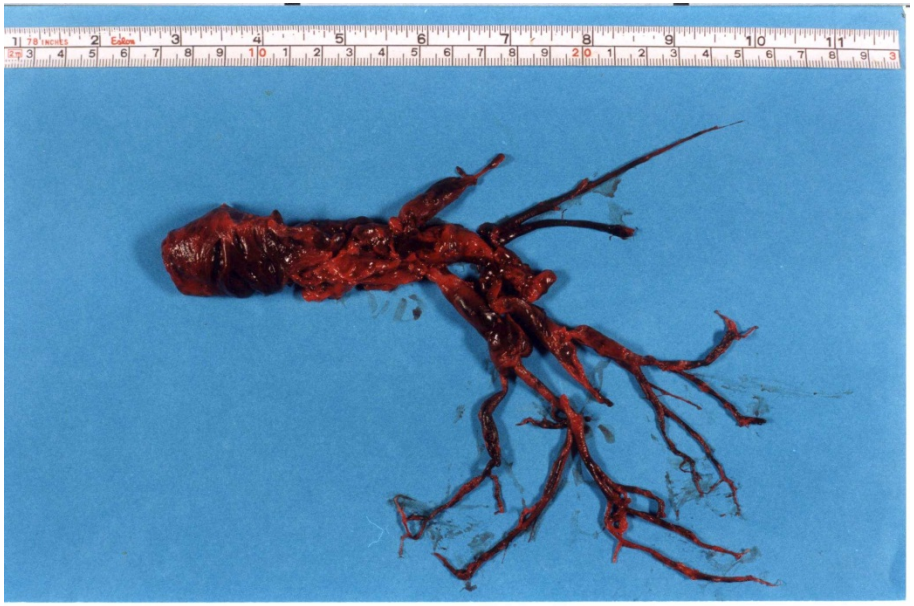
Congenital bleeding disorders

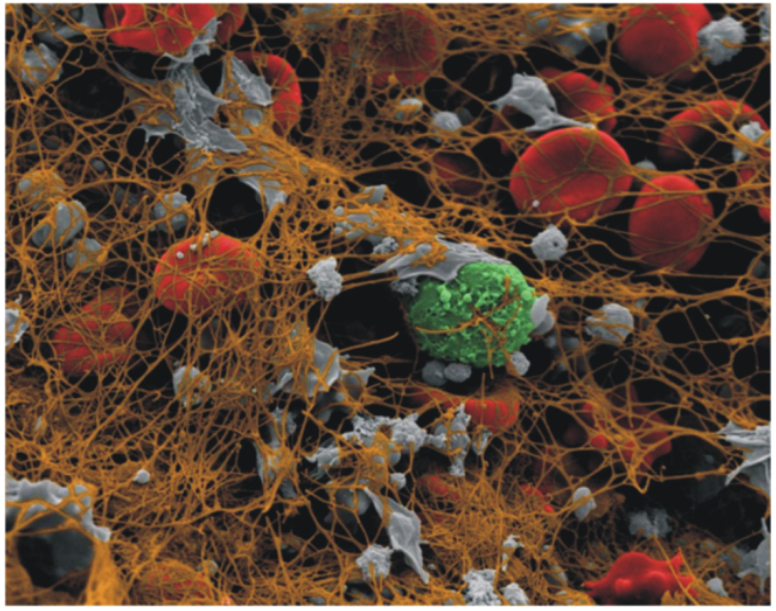
- Hemophilia A (FVIII deficiency)
- Hemophilia B (FVIX deficiency)
- Hemophilia C (FXI deficiency)
- Parahemophilia (FV deficiency)
- Combined FV+FVIII deficiency
- von Willebrand Disease (vWD: vWF deficiency)
- Thrombocytopenia (scarcity of platelets)
- Dysfunctions of platelets receptors
- Thrombophilia
- Deep Vein Thrombosis
- FXII deficiency

Biological Background



Clot is a gel like structure consisting of a polymer (Fibrin) network entrapping various blood components





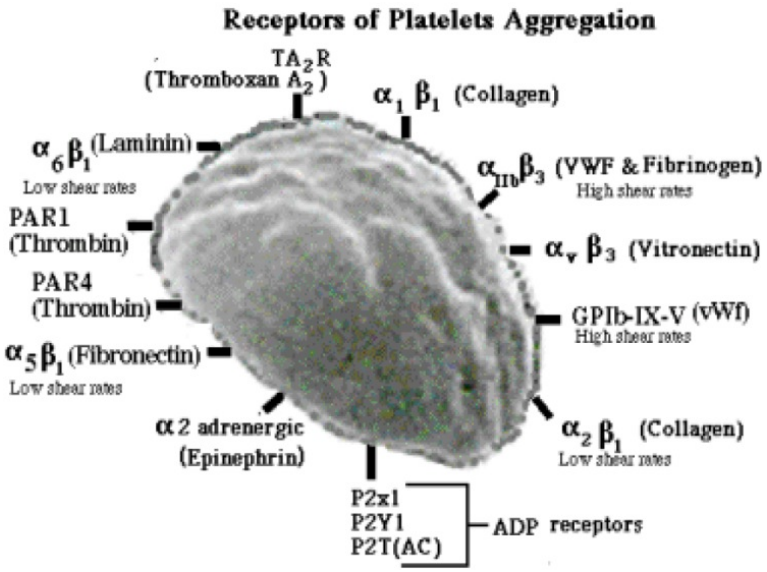
Not only cell reaction mechanisms but also the flow of blood and the interactions with the arterial wall become important in modelling thrombus formation

* The image is taken from www.scopeblog.stanford.edu

More about coagulation ...

Platelets have a number of receptors on their membrane which intervene in many processes:

- aggregation,
- binding to specific molecules,
- reacting to stress,
- etc.



"Activated" platelets are able to activate more platelets (aspirin acts as an Anticoagulant at this level).

vWF is one of the many "Factors" entering the coagulation process

Some of the Factors have been labelled by Roman numbers in the order of their discovery: FI – FXIII

Usually they come in pairs: inactivated (usually a zymogen = enzyme precursor) and activated (usually an enzyme)

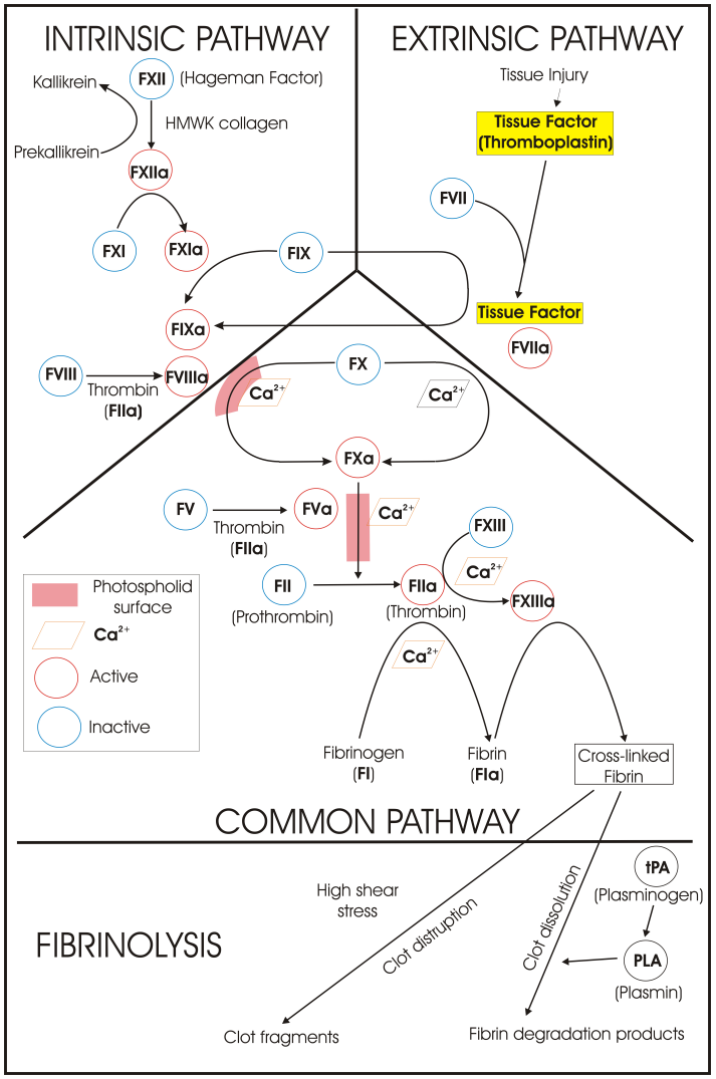
FI = fibrinogen ➔ *FIa = fibrin* : the polymer making the clot skeleton

FII = prothrombin ➔ *FIIa = thrombin* (has a key role)

etc.

They act through a *chemical cascade*

Cascade Model



The coagulation cascade model has two pathways which are series of biochemical reactions leading to **fibrin** formation:

- *contact activation pathway* (also known as the **intrinsic pathway**),
- and the *tissue factor pathway* (also known as the **extrinsic pathway**).

The intrinsic and extrinsic pathways can independently produce coagulation

- the extrinsic pathway bypasses FVIII

FXII is still considered to have some importance.

For instance, since its discovery it is believed to undergo self-activation in the presence of artificial surfaces.

Cascade model

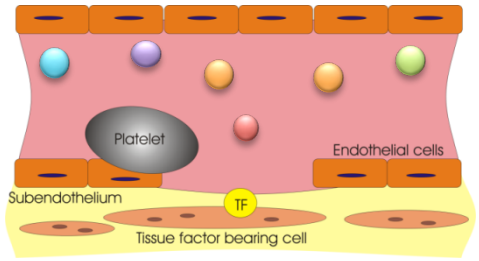
- Great advance in understanding of blood coagulation
- Accurate representation of the overall structure of the coagulation process as a series of proteolytic reactions
- Recognition of phospholipid surfaces required for the assembly of tenase and prothrombinase complexes

However, the role of cells, especially **platelets**,
was not described in the Cascade model

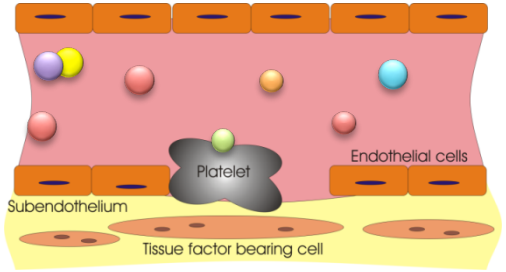
Cell-based model

Cell-based model

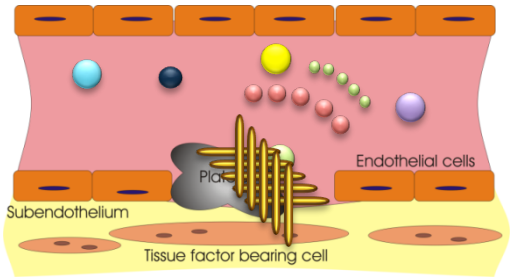
The three phases of coagulation occur on different surfaces:



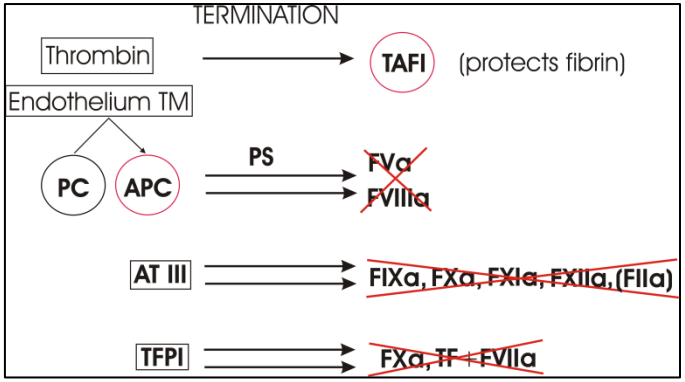
Initiation
on the Tissue Factor bearing cell

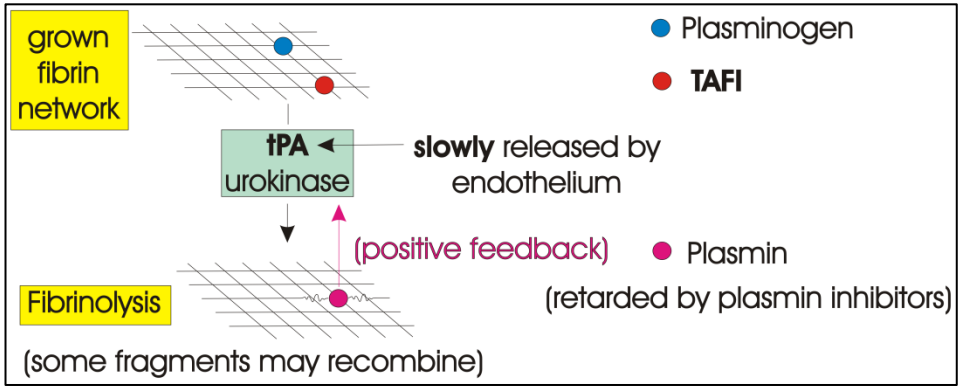


Amplification
on the platelets
when they become activated



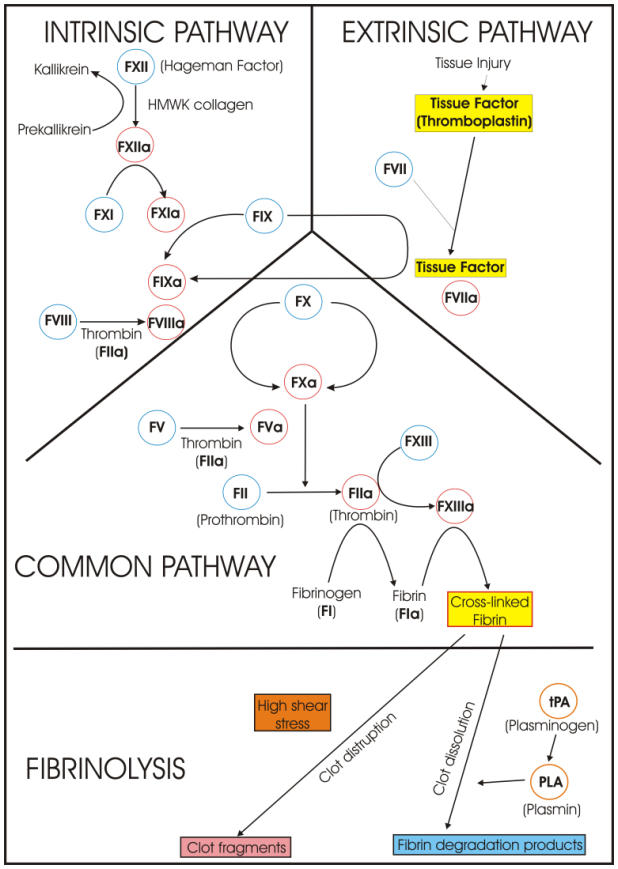
Propagation
on the activated platelets surface





Biological Models

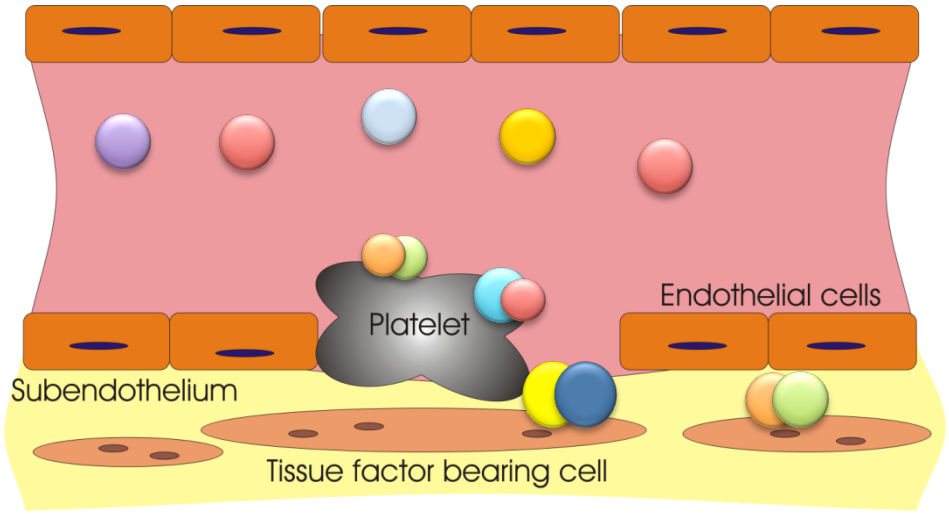
Coagulation cascade



Cell-based model

The three phases of coagulation occur on different surfaces:

- **Initiation** on the Tissue Factor bearing cell
- **Amplification** on the platelets as it becomes activated
- **Propagation** on the activated platelets surface
- **Termination**



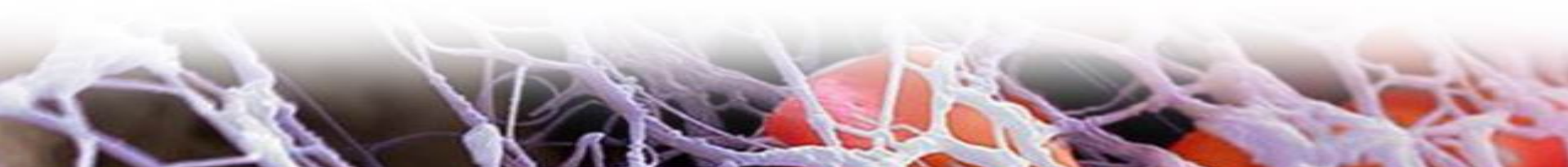
Motivations and Modeling

- Conceptualize and understand this complicated process
- Optimize design of artificial devices
- Identify the regions of the arterial tree susceptible to the formation of thrombotic plaques and possible rupture in stenosed arteries

A good model should be

- Simple enough in order to be applied in numerical simulations
- Able to capture the process complexity
- Predict effects of specific perturbations in the hemostatic system that can't be done by laboratory tests
- Assist in clinical diagnosis and therapies of blood coagulation diseases

Mathematical Modeling



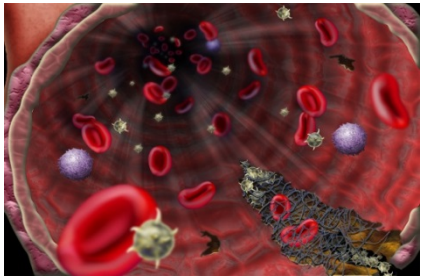
Mathematical model

M. Anand, K. Rajagopal and K.R. Rajagopal, A model for the formation, growth, and lysis of clots in quiescent plasma. A comparison between the effects of antithrombin III deficiency and protein C deficiency, Journal of Theoretical Biology 253 (2008) 725-738

A. Fasano, J. Pavlova and A. Sequeira, A synthetic model for blood coagulation including blood slip at the vessel wall Clinical Hemorheology and Microcirculation 51 (2013) 1-14

Full model

- **Extrinsic pathway**
- **Fibrinolysis**



- 23 RAD equations nonlinear Reactions
- Nonhomogeneous boundary conditions
- Non-Newtonian fluid

Reduced model

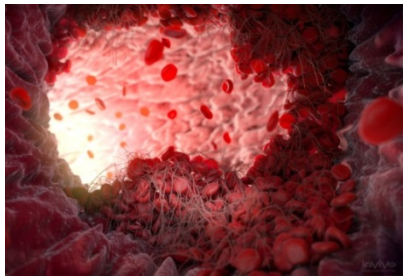
- **Propagation**
- **Termination**
- **Fibrinolysis**

+

PLATELETS

+

Slip BC



- 13 RAD equations with nonlinear reaction terms
- Homogeneous boundary conditions
- Non-Newtonian fluid

Image sources: www.chemistrylearning.com, robgarlington.com

Biochemical reactions and Platelets

Chemical reactions in the cascade leading to fibrin production are modeled in the form:

$$(C_i)_t + div(C_i u) - div(D_i \nabla C_i) = R_i, \quad i = 1,....13 \quad in\ \Omega$$

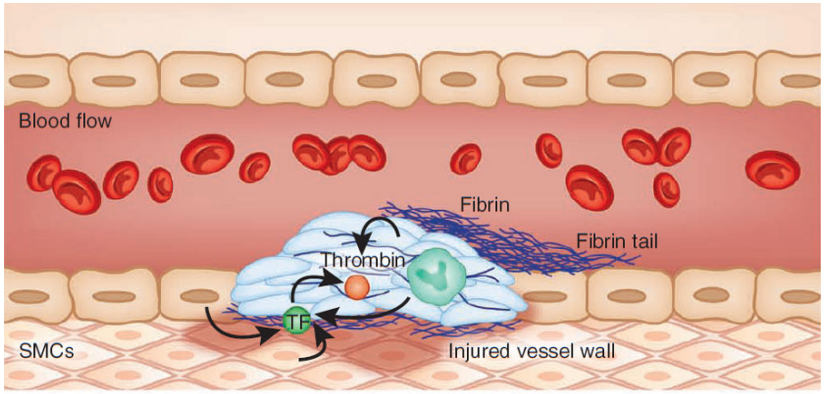


Image source: www.nature.com

- All equations with the appropriate initial and boundary conditions should be solved in a domain Ω representing the blood vessel hosting the clot.
- Moreover, the differential system (with low convection) has to be solved in the clot domain

Chemical Reactions Cascade

The rate of depletion of zymogens is equal to the rate of its activation into the corresponding enzyme, which is depleted by inactivation due to inhibitors

$$R_W = k_W C_P[IIa] - (h_{1W}[APC] + h_{2W}[ATIII])[W]$$

$$R_{II} = -\frac{k_2[W][II]}{K_{2M} + [II]}$$

$$R_{IIa} = -R_{II} - h_2[IIa][ATIII]$$

$$R_I = -\frac{k_1[IIa][I]}{K_{1M} + [I]}$$

$$R_{Ia} = -R_I - \frac{h_1[PLA][Ia]}{H_{1M} + [Ia]}$$

$$R_{ATIII} = -h_2[IIa][ATIII] - h_{2W}[W][ATIII]$$

$$R_{PC} = -\frac{k_{PC}[IIa][PC]}{K_{PCM} + [PC]}$$

$$R_{APC} = -R_{PC} - h_{PC}[APC][\alpha_1 AT] - h_{1W}[APC][W]$$

$$R_{\alpha_1 AT} = -h_{PC}[APC][\alpha_1 AT]$$

$$R_{tPA} = 0$$

$$R_{PLS} = -\frac{k_{PLA}[tPA][PLS]}{K_{PLAM} + [PLS]}$$

$$R_{PLA} = -R_{PLS} - h_{PLA}[PLA][\alpha_2 AP]$$

$$R_{\alpha_2 AP} = -h_{PLA}[PLA][\alpha_2 AP]$$

Propagation Phase

Termination Phase

Fibrinolysis

Virtual chemical reaction

$$R_W = k_W \widehat{C}_P [II_a] \left(1 - \frac{[II_a]}{[II_a]^*} \right) - \left(h_{1W} [APC] + h_{2W} [ATIII] \right) [W]$$

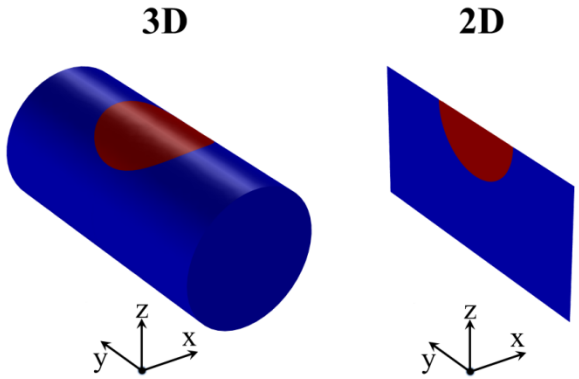
- A direct production of Prothrombinase (W) from Thrombin (IIa), which is a result of a complex reaction chain, going through several steps with the activation of many other factors (V, VIII, IX, X, XI) and the Tenase complex (VIIIa-IXa);
- A direct action of Activated Protein C (APC) and Antithrombin III (ATIII) on prothrombinase, while they are inhibitors of various activated factors eventually contributing to the creation of Prothrombinase

All the **rate constants** should be selected in a way to produce results comparable to the ones of the real cascade.

Coupled System

FEM was applied to a Generalized Newtonian blood flow model coupled with a system of RAD equations

$$\rho(u_t + u.\nabla u) = div\sigma(u,p) \quad in\ \Omega$$
$$divu = 0 \quad in\ \Omega$$
$$n^T\sigma(u,p)n = \alpha n.u = 0 \quad on\ \partial\Omega_{slip}$$
$$n^T\sigma(u,p)\tau_1 = \beta u.\tau_1 \quad on\ \partial\Omega_{slip}$$
$$n^T\sigma(u,p)\tau_2 = \beta u.\tau_2 \quad on\ \partial\Omega_{slip}$$
$$\sigma(u,p)n = 0 \quad on\ \partial\Omega_{out}$$
$$u(x,t) = u^* \quad on\ \partial\Omega_{in}$$
$$u(x,0) = u^0 \quad in\ \Omega$$



$$\sigma(u,p) = 2\mu(\dot{\gamma})D(u) - pI$$

$$(C_i)_t + div(C_iu) - div(D_i\nabla C_i) = R_i, \quad i = 1,....13 \quad in\ \Omega$$
$$-(D_i\nabla C_i + uC_i).n = 0 \quad on\ \partial\Omega_{slip} \cup \partial\Omega_{out}$$
$$C_i(x,t) = C_i^{blood} \quad on\ \partial\Omega_{in}$$
$$C_i(x,0) = C_i^0 \quad in\ \Omega$$

$$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = \frac{1}{1 + (\dot{\lambda\gamma})^m}$$

Cross viscosity model

SUPG stabilization

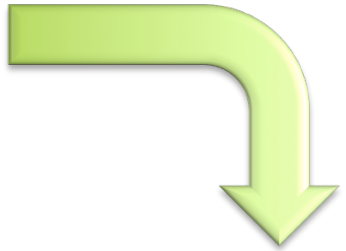
Boundary conditions for the blood flow problem

Navier's slip conditions are used to account for the extra supply of activated platelets:

$$n^T \sigma(u,p) n = \alpha n.u = 0 \qquad on\ \partial\Omega_{slip}$$

$$n^T \sigma(u,p) \tau_1 = \beta u.\tau_1 \qquad on\ \partial\Omega_{slip}$$

$$n^T \sigma(u,p) \tau_2 = \beta u.\tau_2 \qquad on\ \partial\Omega_{slip}$$



Slip provides an extra supply of activated platelets

Whole process is accelerated

Clot boundary

The **clot boundary** is defined as a level set of fibrin concentration

$$[Ia] = [Ia]^*$$

$[Ia]^*$ is a threshold concentration:

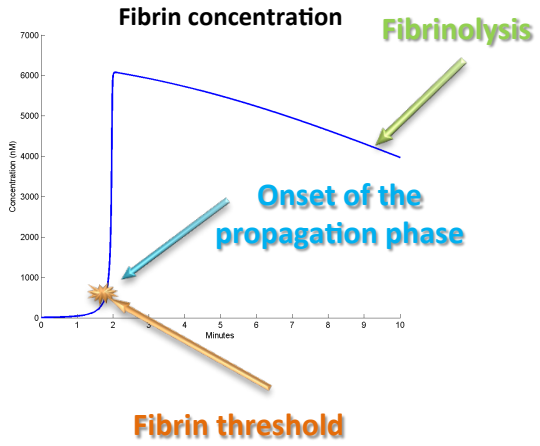
It can be identified with the value at the exit of the amplification phase of coagulation

Thus the **clot region** can be identified as the set

$$[Ia] > [Ia]^*$$

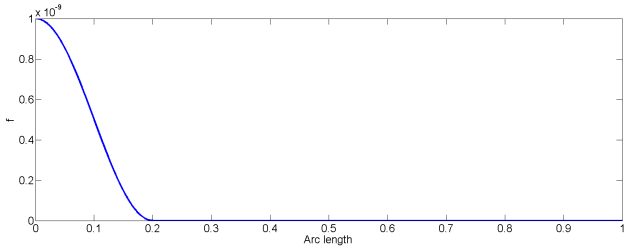
The choice of initial conditions and parameter adjustment

According to the 1D solution of the full RD system



Ovanesov, M.V., Krasotkina, J.V., Ulyanova, L.I., Abushinova, K.V., Plyushch, O.P., Domogatskii, S.P., Vorobev, A.I., Ataullakhanov, F.I., 2002. Hemophilia a and b are associated with abnormal spatial dynamics of clot growth. BBA-Gen. Subjects 1572 (1), 45–57.

- For **non active species** (FII, PLS, PC, ATIII, AT, tPA and FI) we use the data taken from experimental results
- **Activated chemical species** (FIIa, PLA, APC, FIa and Prothrombinase complex W) are defined as smooth decreasing functions:



Difficulties in Solving the RD System

- The stiffness arising from the reaction terms requires very small time steps
- Diffusion and reactions exhibit different temporal and spacial characteristics

To deal with these problems we use an

Operator splitting method

Biochemical problem

$$\begin{cases} (C_i)_t + \mathrm{div}(C_i\mathbf{u}) - \mathrm{div}(D_i\nabla C_i) = R_i, & \text{in } \Omega, \\ -(D_i\nabla C_i + \mathbf{u}C_i)\cdot\mathbf{n} = 0, & \text{on } \partial\Omega_{slip} \cup \partial\Omega_{out}, \\ C_i(\mathbf{x},t) = C_i^{blood}, & \text{on } \partial\Omega_{in}, \\ C_i(\mathbf{x},0) = C_i^0, & \text{on } \Omega. \end{cases}$$

- Large number of equations
- Stiff reactions
- High convection
- Slow diffusion

Operator splitting method

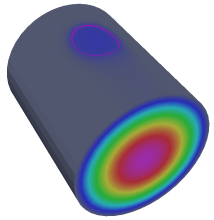
$$\begin{cases} \dfrac{\partial C^*}{\partial t} = R(C^*), \quad \text{on } (t_n, t_{n+\frac{1}{2}}), C^*(t_n) = C(t_n), \\ \dfrac{\partial C^{**}}{\partial t} = D\Delta C^{**} - \mathbf{u}\cdot\nabla C^{**}, \quad \text{on } (t_n, t_{n+1}), C^{**}(t_n) = C^*(t_{n+\frac{1}{2}}), \\ \dfrac{\partial C^{***}}{\partial t} = R(C^{***}), \quad \text{on } (t_{n+\frac{1}{2}}, t_{n+1}), C^{***}(t_{n+\frac{1}{2}}) = C^{**}(t_{n+1}), \end{cases}$$

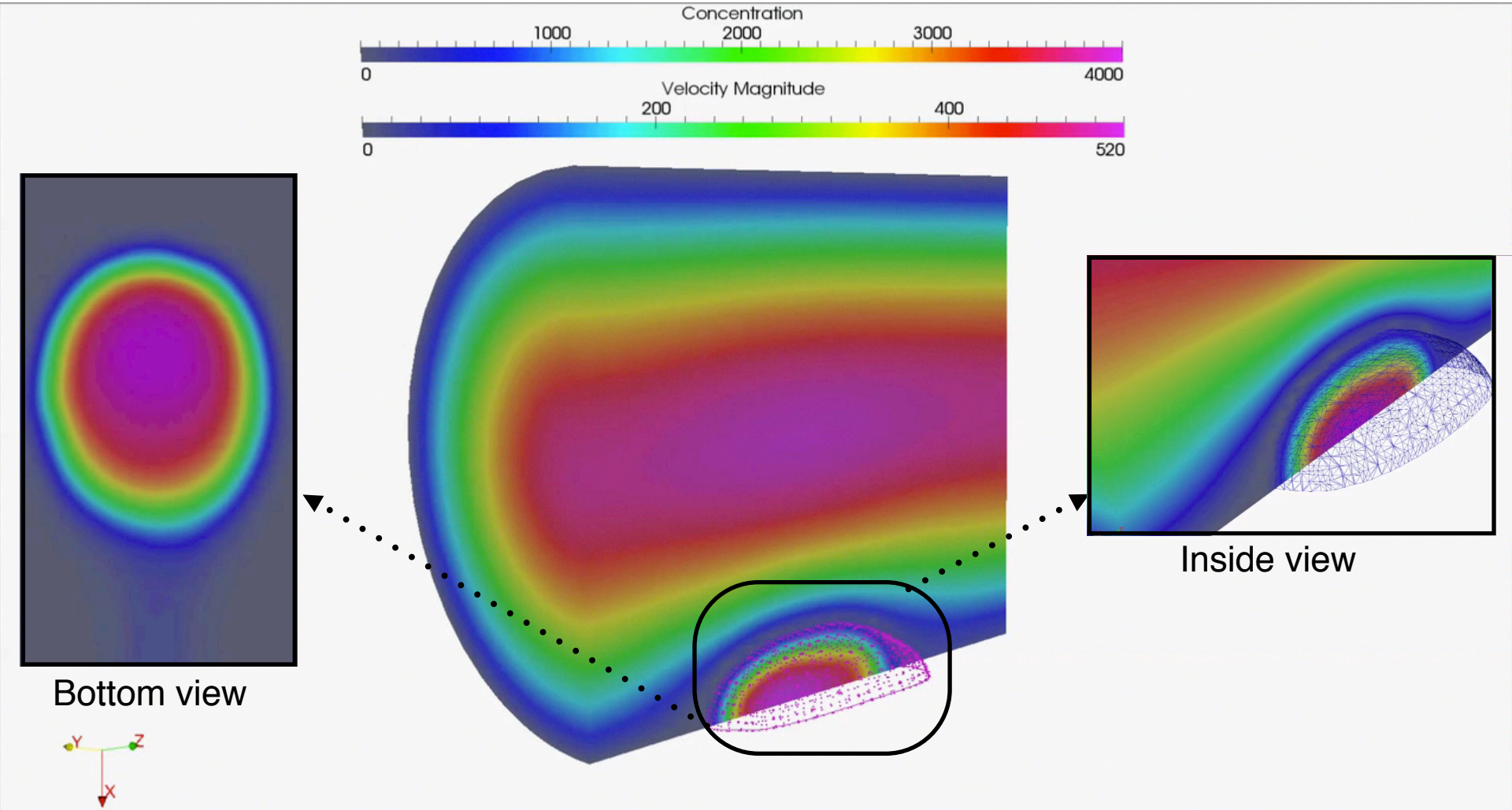
with $C(t_{n+1}) = C^{***}(t_{n+1})$.

Numerical Results

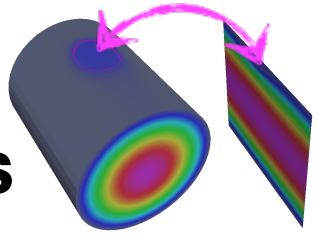
- 3D simulations
- Blood slip efficiency
- Pathological cases

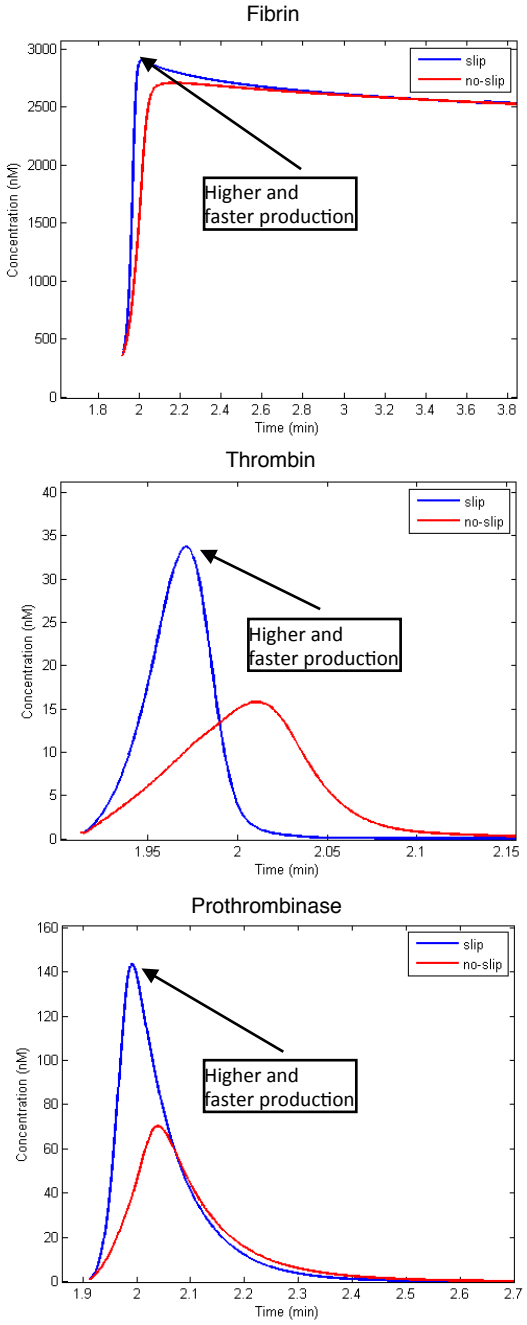
Clot formation

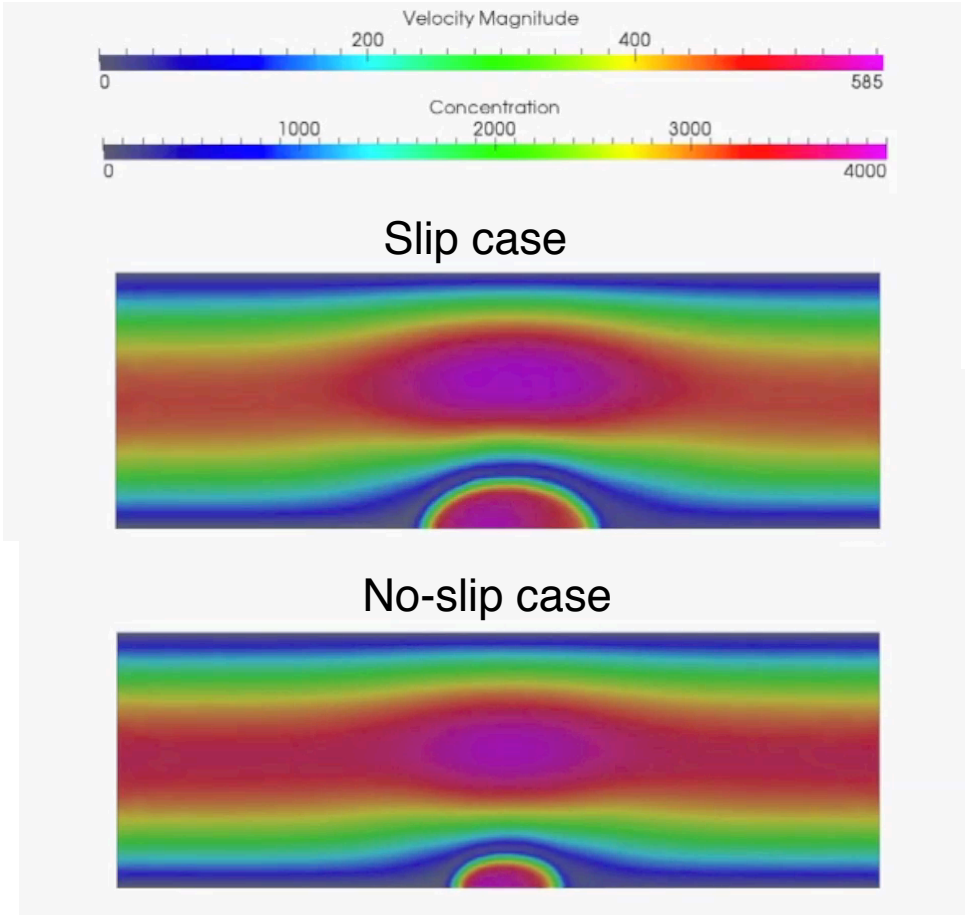




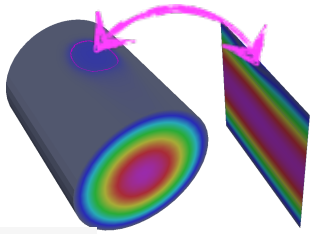
Slip vs no-slip boundary conditions

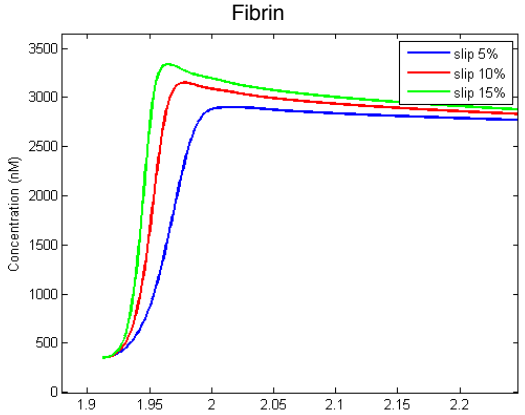


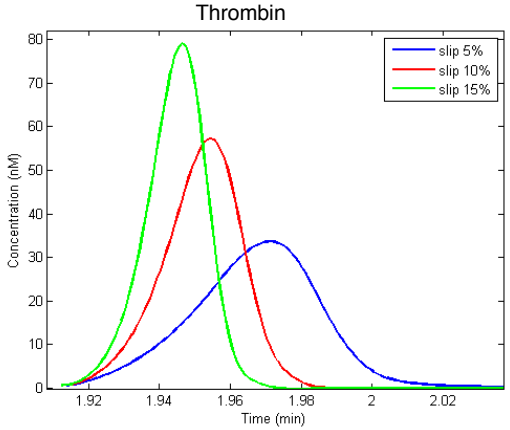


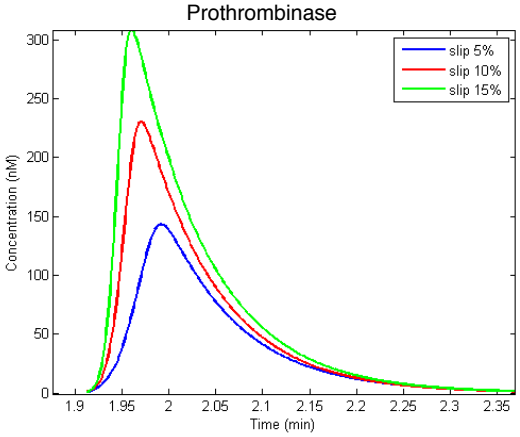


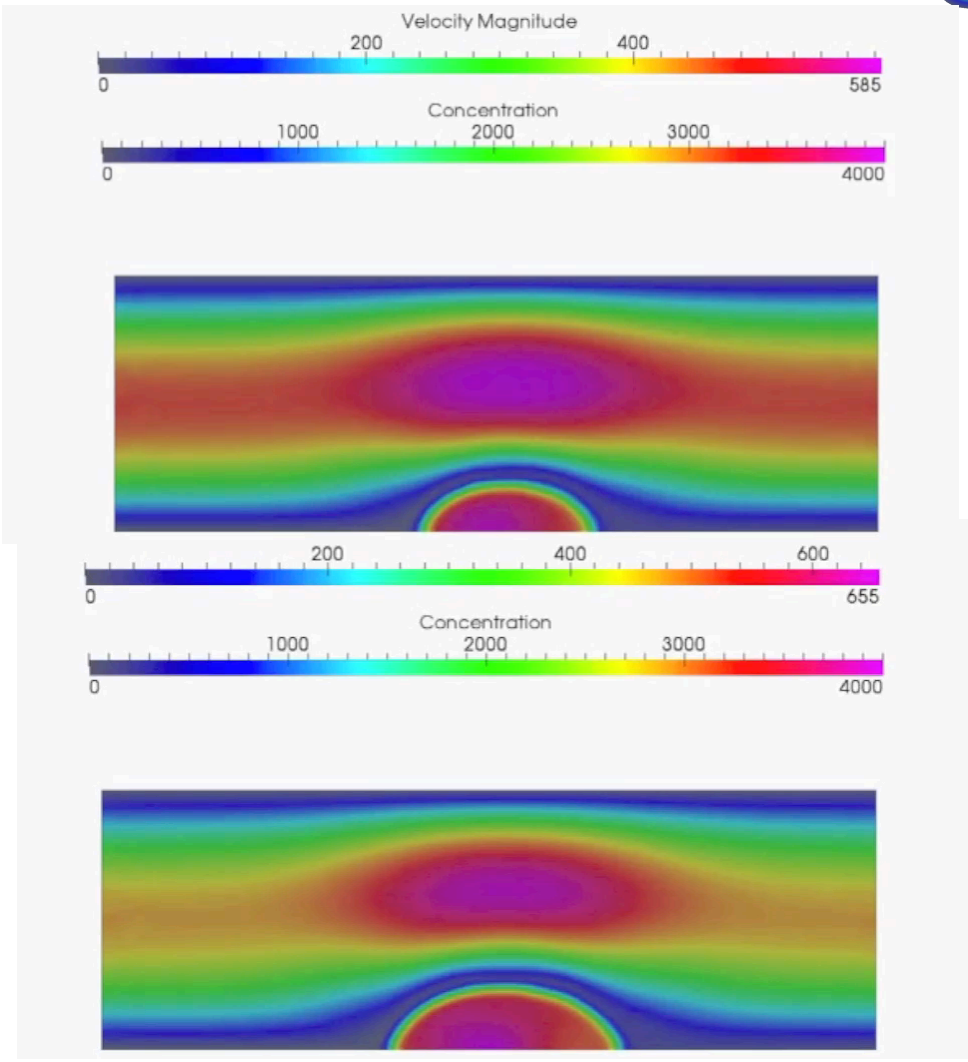
Blood Slip impact







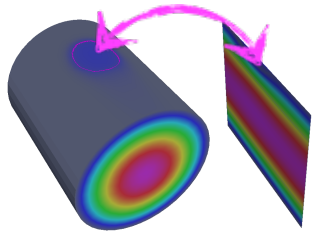




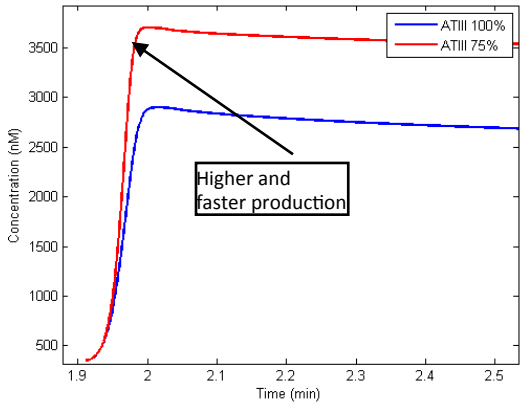
5% Slip velocity

10% Slip velocity

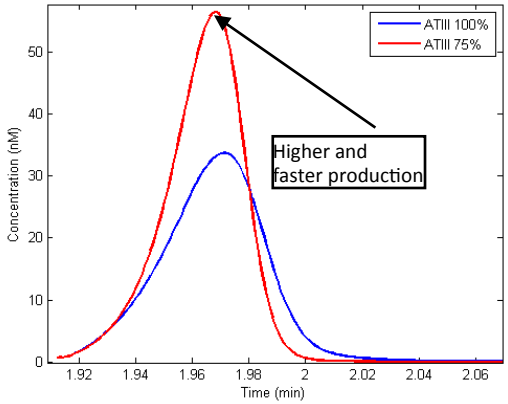
Decrease in ATIII concentration



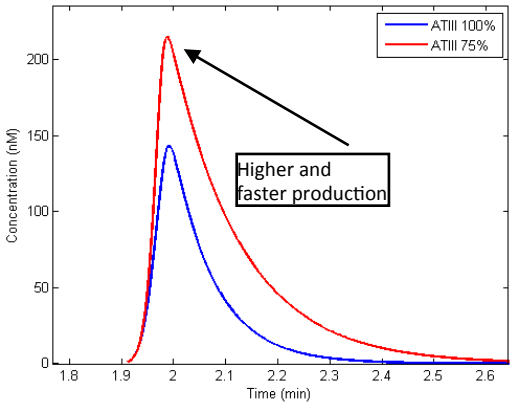
Fibrin

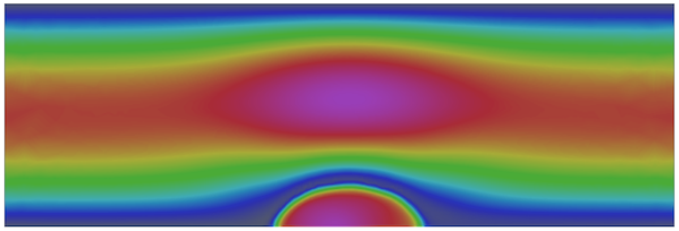


Thrombin

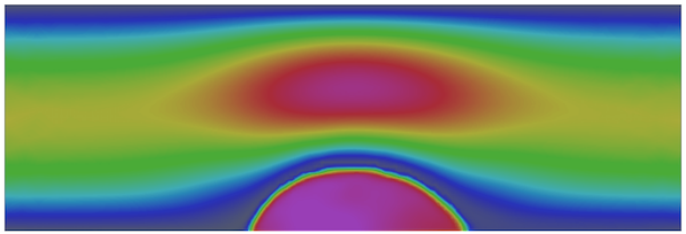


Prothrombinase



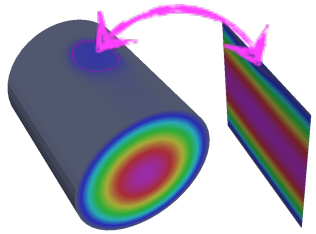


Normal case



Hypercoagulation case

Increase in ATIII concentration



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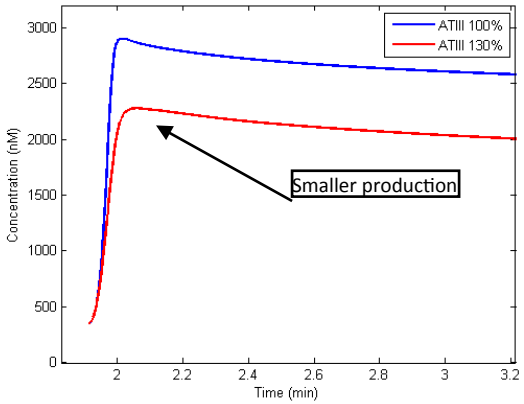

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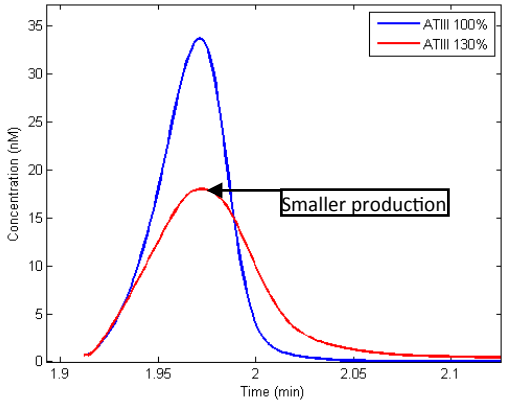

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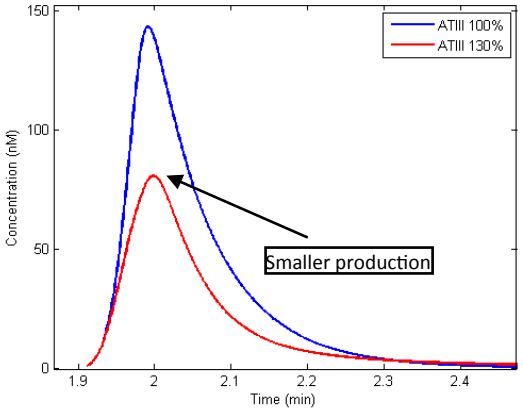
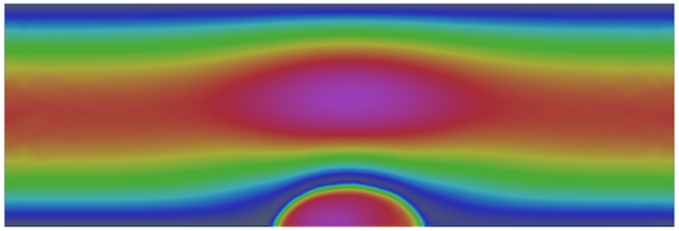
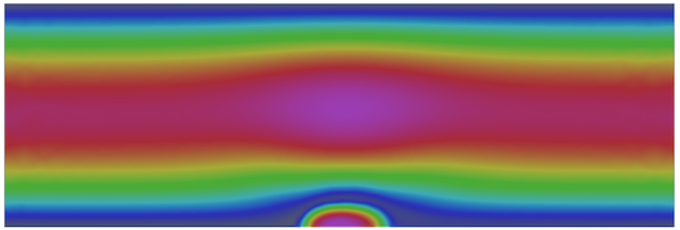


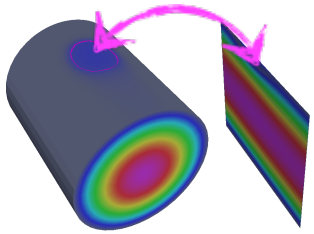


Normal case



ATIII dominance case

Platelets deficiency



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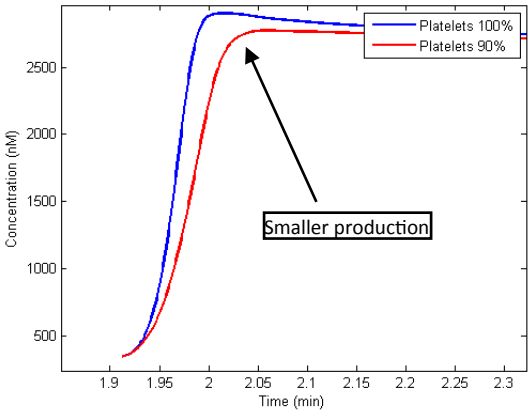

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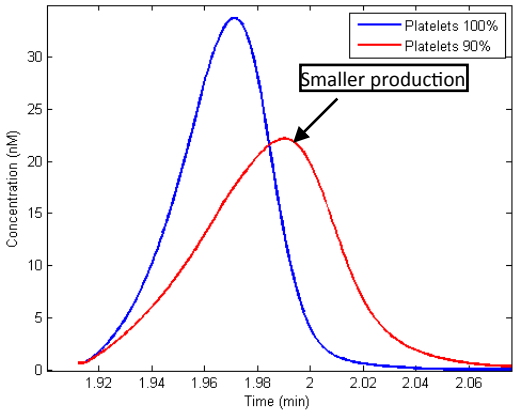
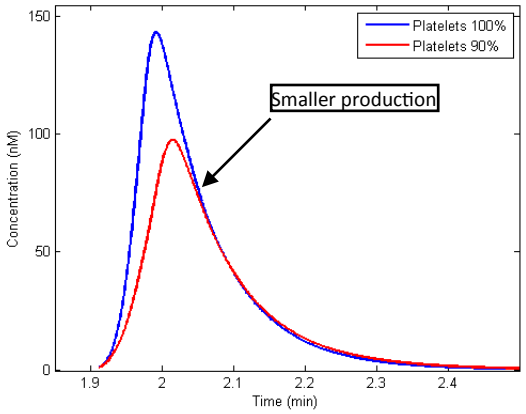
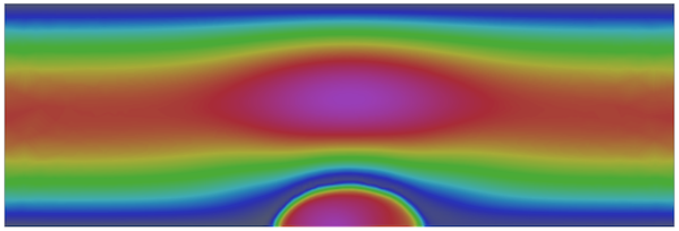
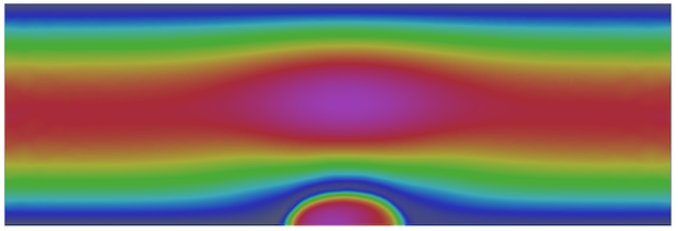


Prothrombinase





Normal case

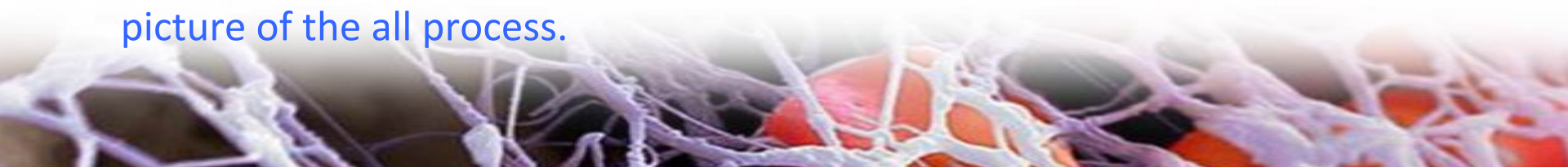


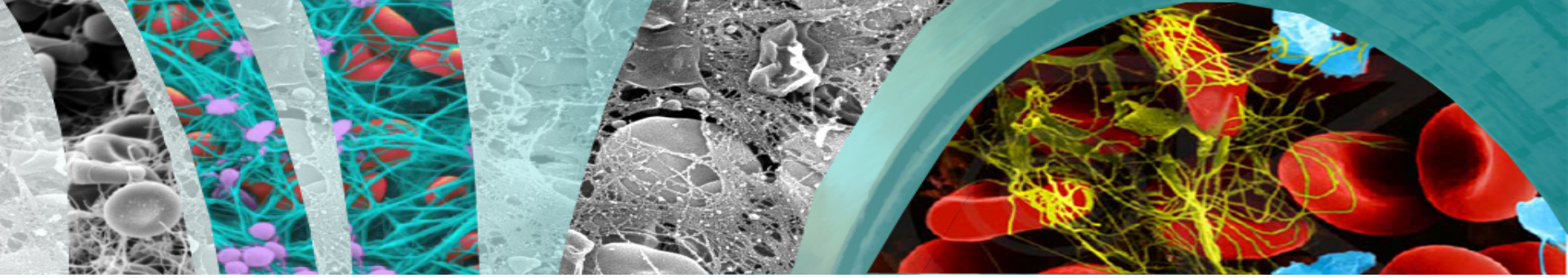
Platelets deficiency

Conclusions

- Mathematical model reduction through a virtual equation for the prothrombinase production
- Platelets role inclusion
- Extra supply of activated platelets due to the slip boundary conditions
- Concentrations evolution
- The capacity of the model has been tested to predict some disorder cases:
  - Inhibitors deficiency: ATIII deficiency (hypercoagulation)
  - platelets deficiency - delay in thrombin production

Blood clotting is extremely complex and requires modeling and simulations in close coordination with experiments to build an integrated picture of the all process.





Project: EXCL/MAT-NAN/0114/2012 [2013 – 2016]

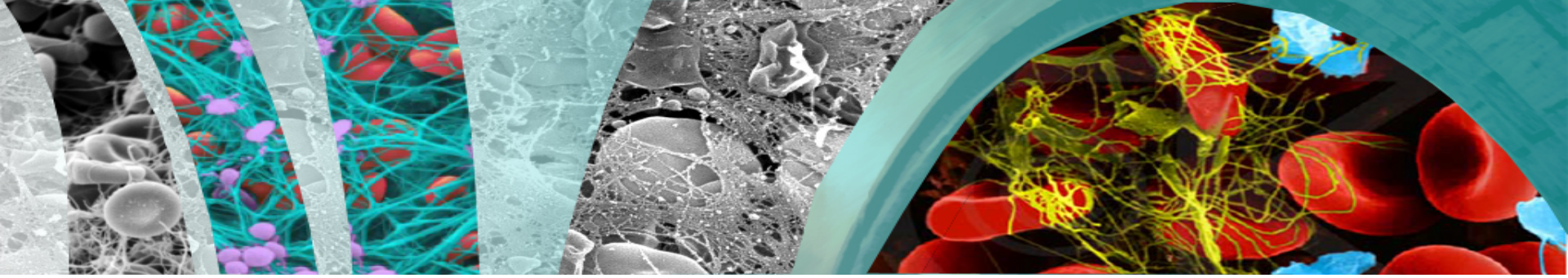
PHYSIOMATH

Mathematical Modeling and Simulations of the Human Physiological System

PI: Adélia Sequeira (IST-UL) with C. Saldanha (IMM), R. Pereira (IBILI/CHUC), L. Rosário (AIDFM)

External Collaborations:

Alfio Quarteroni (EPFL), A. Fasano (U Firenze), Willi Jäger (U Heidelberg)



Project: UT Austin|Portugal Program
in Advanced Computing [2014 – 2016]

MRI-Based Computational Modeling of Blood Flow and Nanomedicine Deposition in Patients with Peripheral Arterial Disease: Insights into Disease Management

PIs: Thomas J.R. Hughes (ICES – UTAustin), Adélia Sequeira (IST-UL)