British Council Researcher Links Workshop

“Mathematical and Computational Modelling in Cardiovascular Problems”

# Erythrocytes – platelets – fibrin mesh interactions in blood flow:

## Basic regulation of the hemostatic and thrombotic processes

Alexey A. Tokarev, PhD

Federal Research and Clinical Centre of Pediatric Hematology, Oncology and Immunology and National Research Centre for Hematology,
Ministry of Healthcare of the Russian Federation

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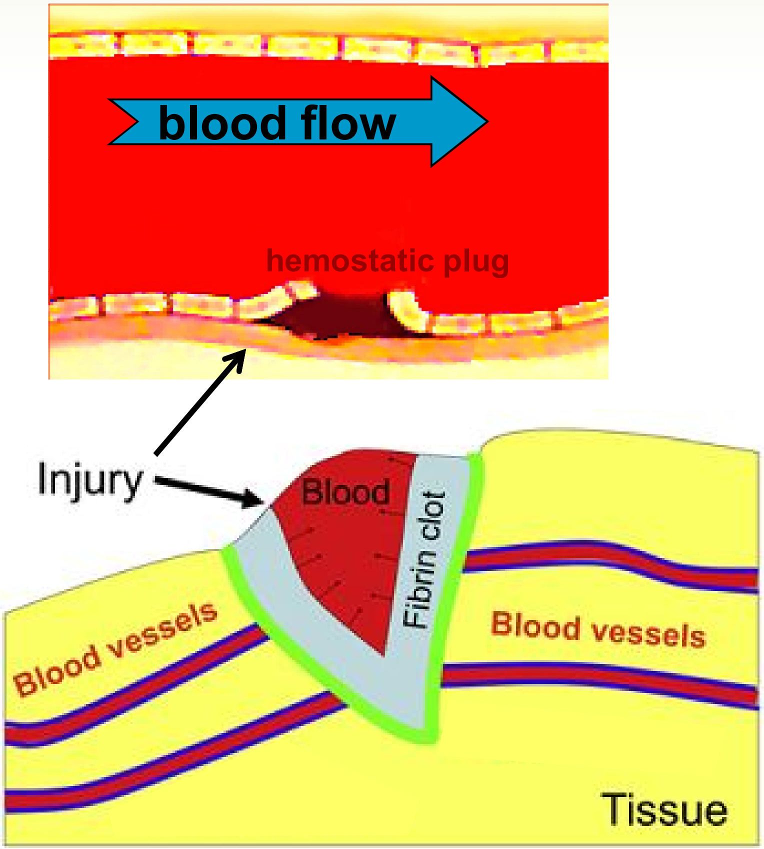
# Hemostasis

- body’s ability to stop bleedings
- body’s defense system that provides this ability

**Main property: the response is fast and strictly localized at the injury site**

• inside the injured vessel

• outside the vessels (e.g., in a wound)

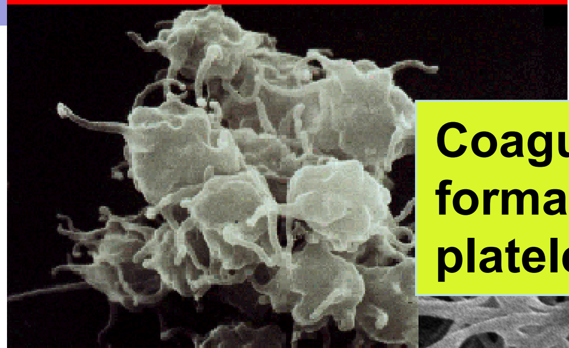


# Branches of hemostasis:
# vascular, cell (platelets), plasma (coagulation)

**Vasculature:**

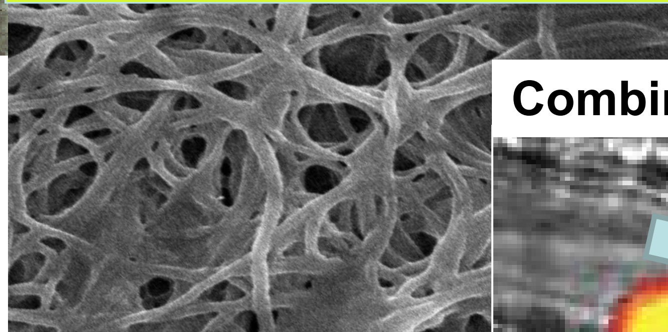
anticoagulation
vasoconstriction

**Platelets: activation, secretion, aggregation**



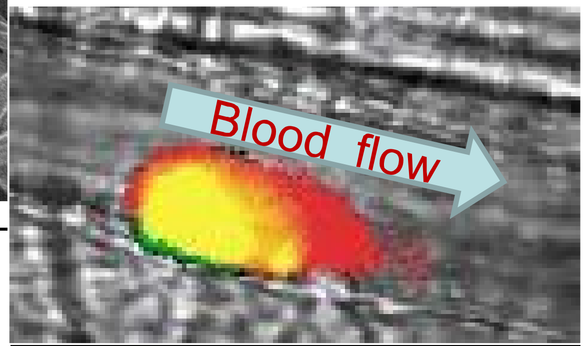
Platelet aggregate.
Ohlmann (2000)

**Coagulation: fibrin mesh formation between platelets or in slow flow**



Fibrin mesh. SEM made by Jean-Claude Bordet (Lyon, France).

**Combined:**

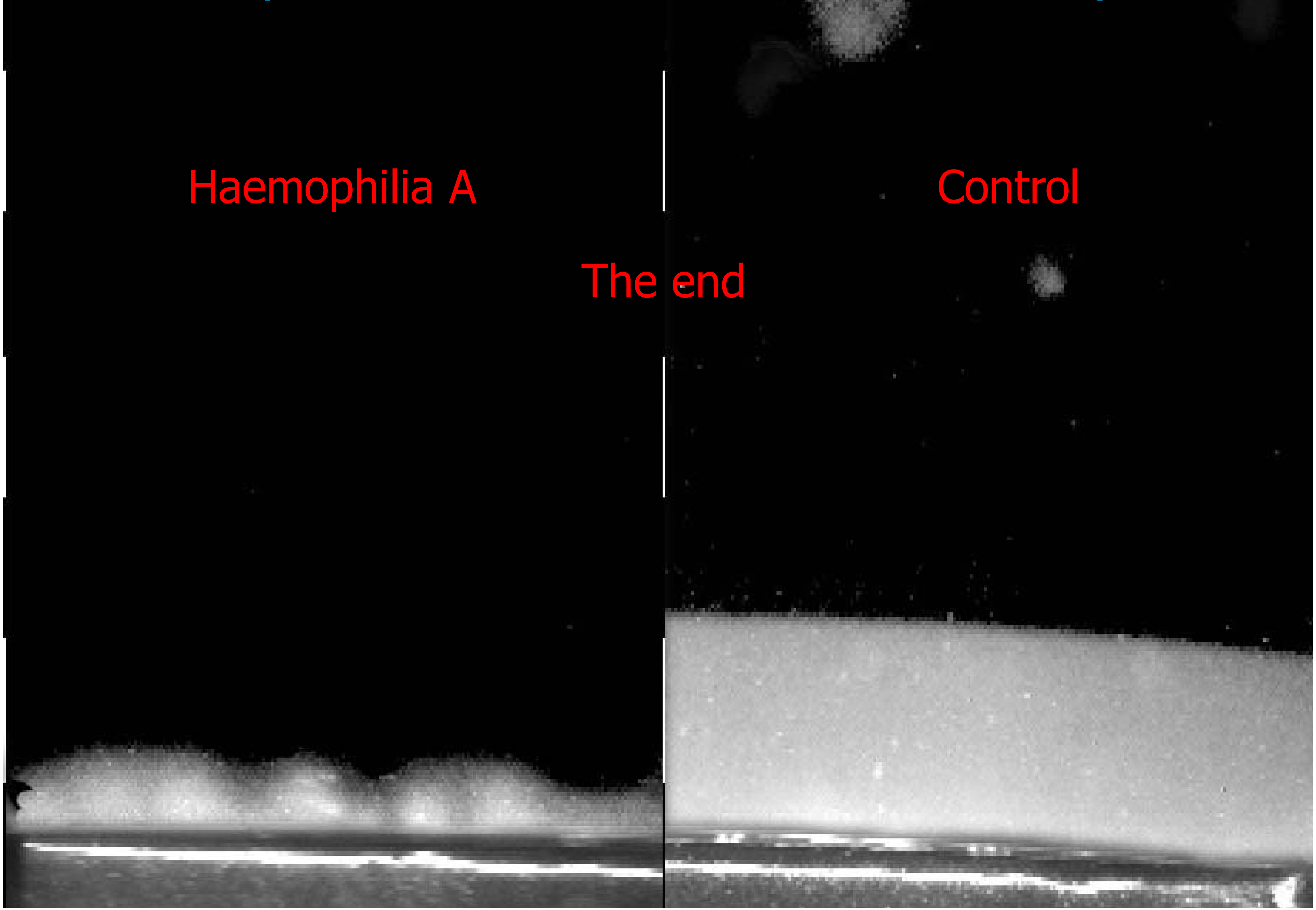



platelets fibrin
platelets+fibrin

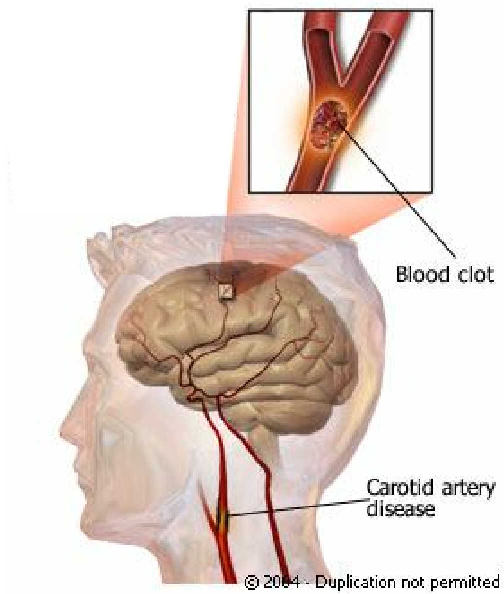
Experimental *in vivo* thrombosis.
Falati (2002)

**Insufficient hemostasis → Bleeding**
(Hemophilias, von Willebrand disease, DIC, etc.)

# Impaired hemostasis, *in vitro* example

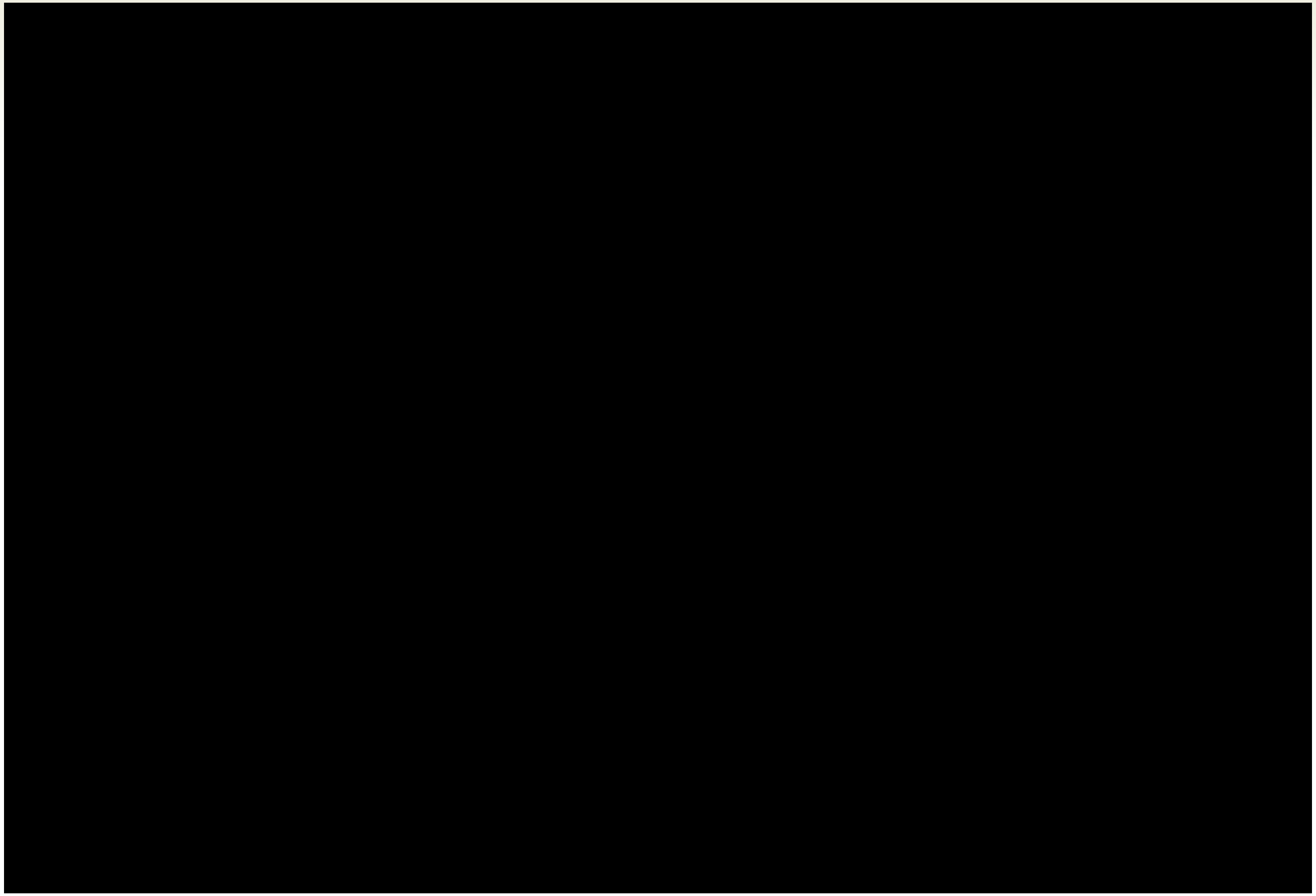


# Thrombosis


**Excessive (unregulated) hemostasis** → Thrombosis
(Ischemic Stroke, Cardiac Infarction, Gangrene of extremity, Blindness, Necrosis of the Ischemic organ, DIC)

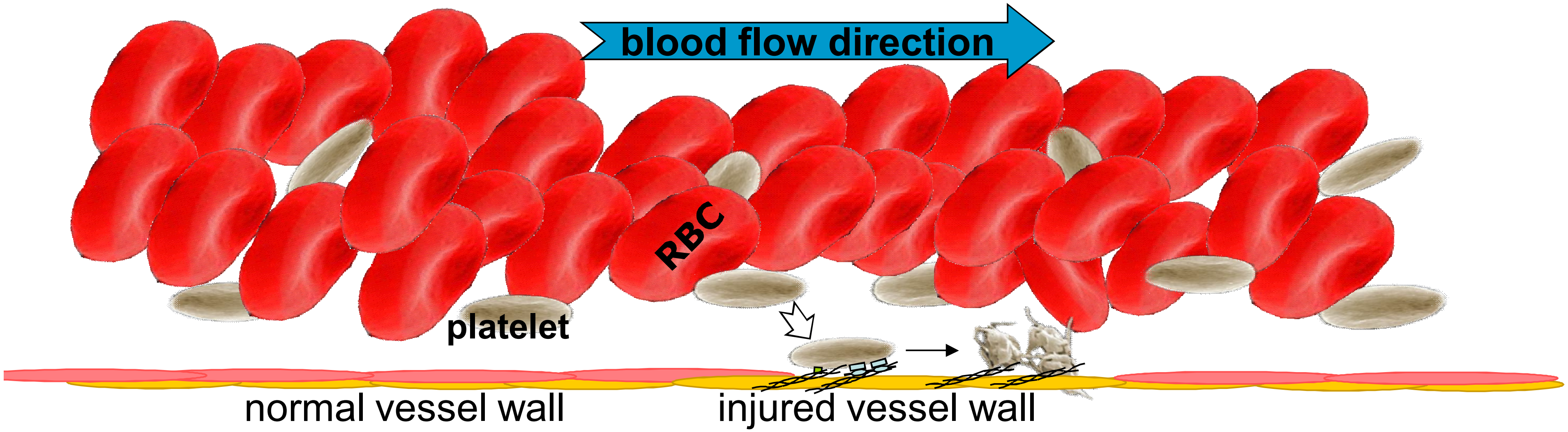
# Experimental thrombus formation, *in vivo example*



Chen et al., J. Biomed. Opt. (2010)

**We want to understand the basic biophysical regulation mechanisms of hemostasis and thrombosis:**

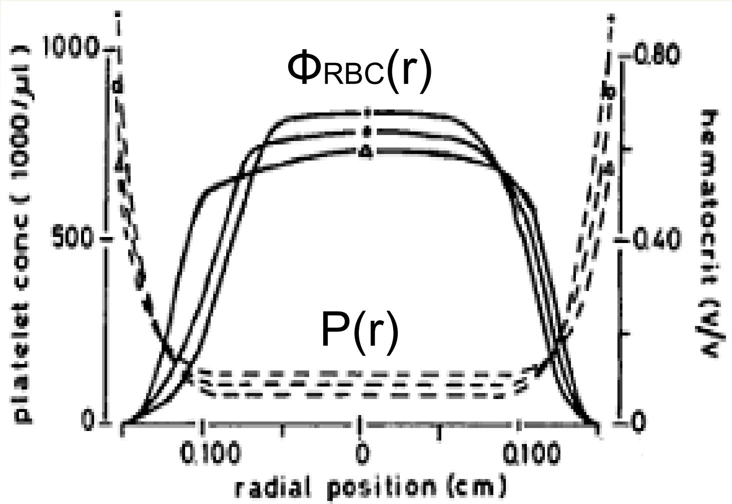
1. Platelet transport <u>across</u> the bulk of the flow (irrespective to the vessel wall injury)
2. Platelet adhesion from the flow to the active wall
3. Platelet plug (thrombus) growth
4. Plug (thrombus) growth termination



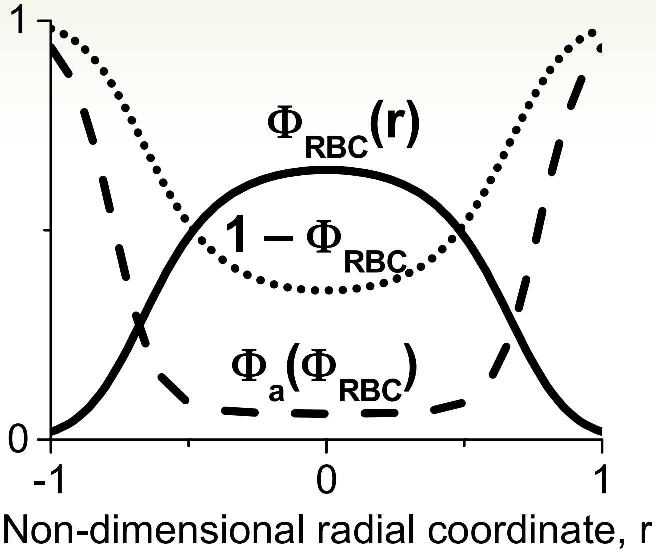

**Method:** <u>experiment-validated</u> mathematical modelling

**Q.1: What is the mechanism of platelet near-wall excess?**
**A.1: Finite platelet size impedes platelet positioning between densely packed RBCs in the flow core**

Tokarev, Butylin, Ermakova, Shnol, Panasenko, and Ataullakhanov. Biophys. J. 2011a


Aarts et al (1988)

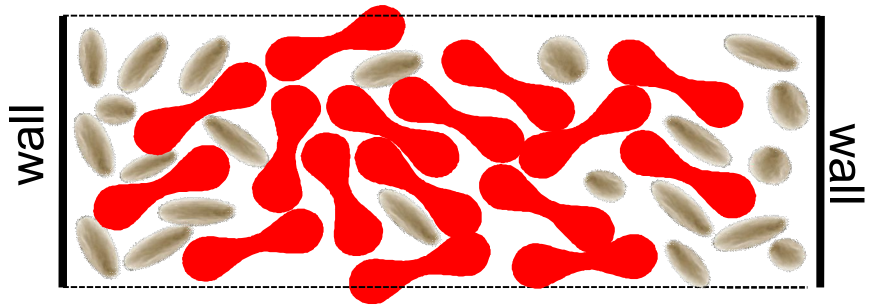


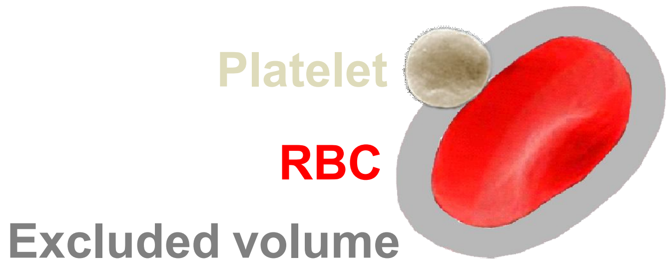

**Available volume hypothesis (Blackshear et al., 1977):**

$$P(r) \sim \Phi_a(r)$$

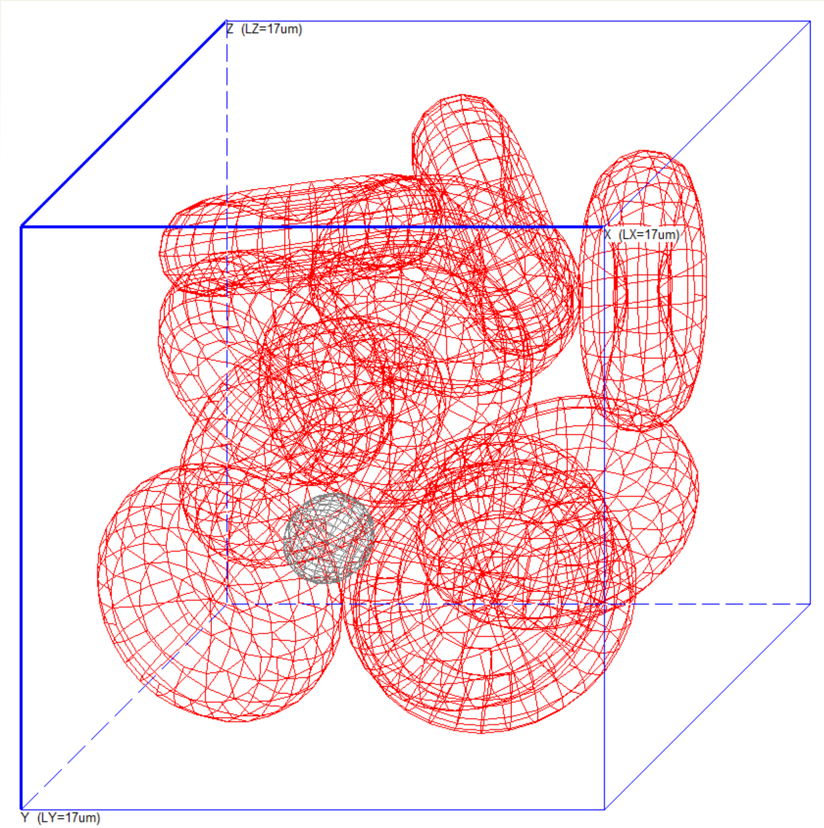
$$\Phi_a = 1 - \Phi_{RBC} - \Phi_{ex}$$

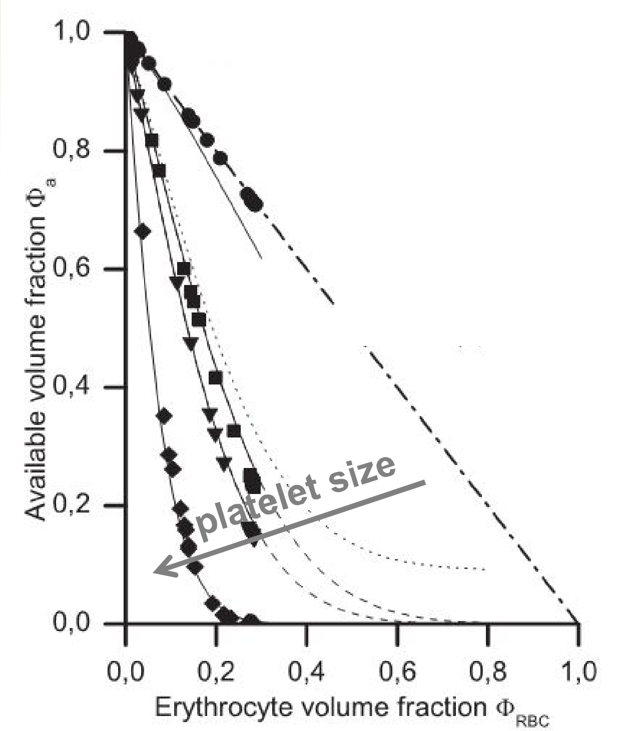
**$\Phi_a(\Phi_{RBC})$ – ?**



## Dependence of the available volume fraction on the erythrocyte volume fraction

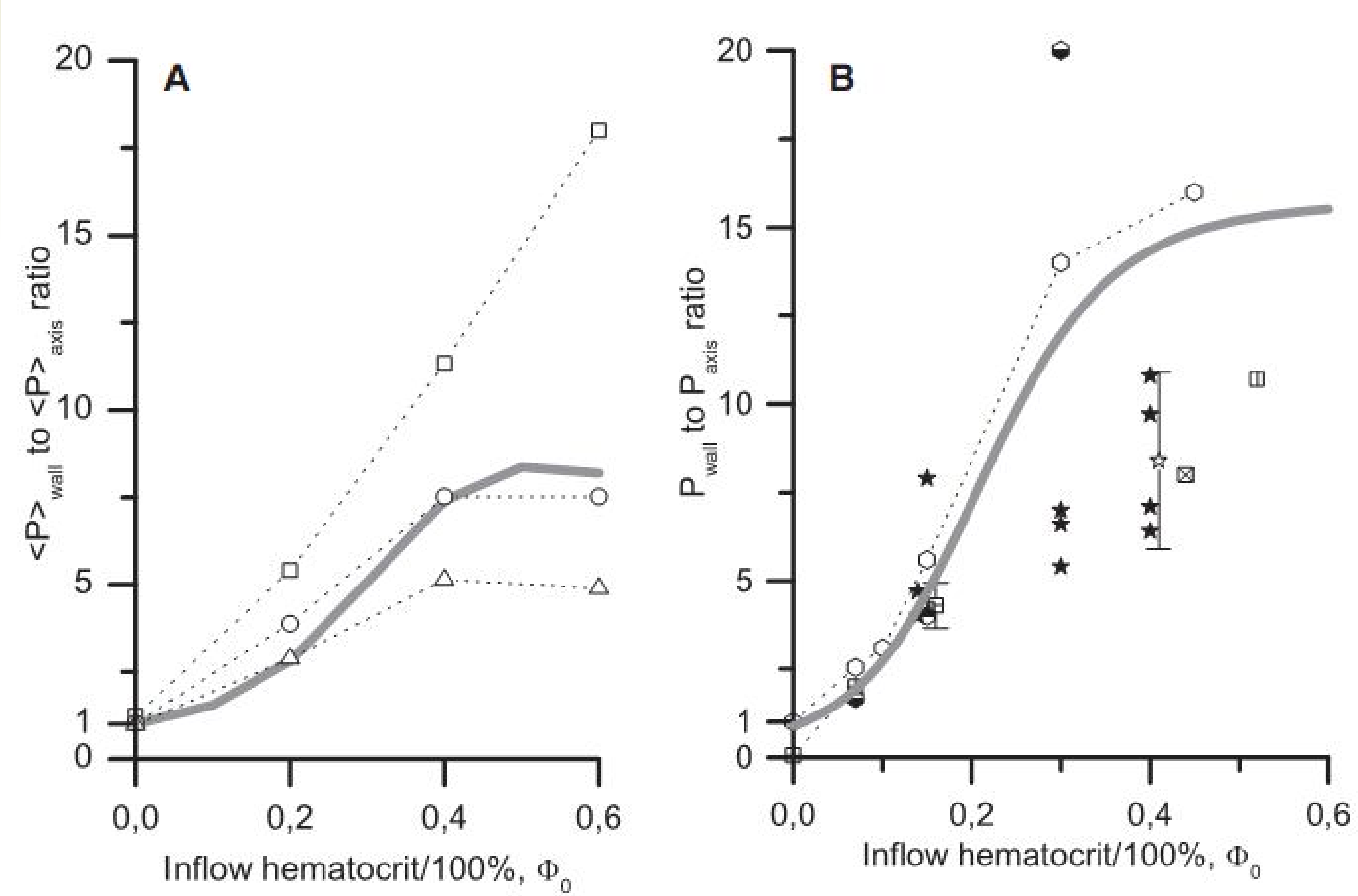



$$\Phi_a = \frac{\exp(-p \cdot \Phi_{\mathrm{RBC}} \cdot (2\Phi_{\mathrm{RBC}} + 1)) + f}{1 + f}$$

*Tokarev et al., Biophys. J., 2011, 101 (8): 1835-1843.*

# Hematocrit dependence for platelet NWE




Thick lines, theory.
Symbols, experiment. (A), platelets + RBC ghosts from Aarts (1988); (B), platelet-modeling particles + RBCs (from Eckstein group).

*Tokarev et al, Biophys. J. 2011a*

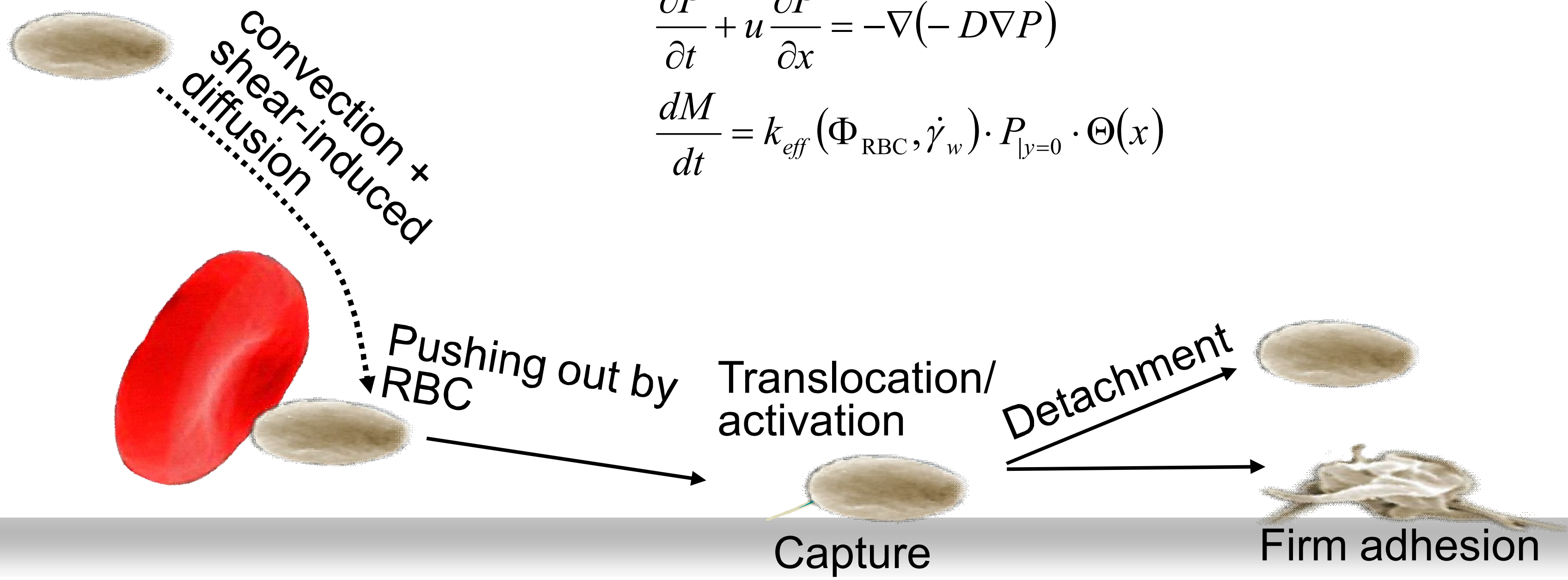
## Q.2: What is the mechanism of wall shear rate and hematocrit regulation of platelet adhesion?
## A.2: Platelet adhesion from shear blood flow is controlled by near-wall rebounding collisions with erythrocytes

Tokarev, Butylin and Ataullakhanov. Biophys. J., 2011b


**Full model** (convection-diffusion PDE + BCs based on Smoluchowsky's theory of collisions):

$$\frac{\partial P}{\partial t} + u\frac{\partial P}{\partial x} = -\nabla\left(-D\nabla P\right)$$

$$\frac{dM}{dt} = k_{eff}\left(\Phi_{\mathrm{RBC}}, \dot{\gamma}_w\right)\cdot P_{|y=0}\cdot\Theta(x)$$




**Reduced model** (analytical from the BC):

- only the near-wall platelet-RBCs collisions have been taken into account

$$\frac{dM^0}{dt} = k^0_{eff}\left(\Phi_{\mathrm{RBC}}, \dot{\gamma}_w\right)\cdot P_0$$

# Calculation of the effective adhesion rate constant

$$\beta = \frac{\dot{\gamma}}{\pi}\left(V_1^{1/3} + V_2^{1/3}\right)^3$$

$$\beta_1 = \frac{4}{3}\dot{\gamma}\left(k_1\frac{d_P}{2} + k_2\frac{d_{\mathrm{RBC}}}{2}\right)^3$$

1. Частота столкновений по Смолуховскому
2. Эффективный диаметр толкающей клетки – её главный диаметр ($d_{RBC}$ или $d_P$)
3. Тромбоцит касается стенки только если столкновение произошло в пристеночном слое толщиной порядка диаметра толкающей клетки ($d_{RBC}$ или $d_P$)
4. Длина тормозного пути захваченного тромбоцита по стенке << длины поверхности адгезии
5. Вероятность отрыва пропорциональна пристеночной скорости сдвига
6. Время активации слабо зависит от скорости сдвига
7. Поверхностная плотность захваченных тромбоцитов квазистационарна

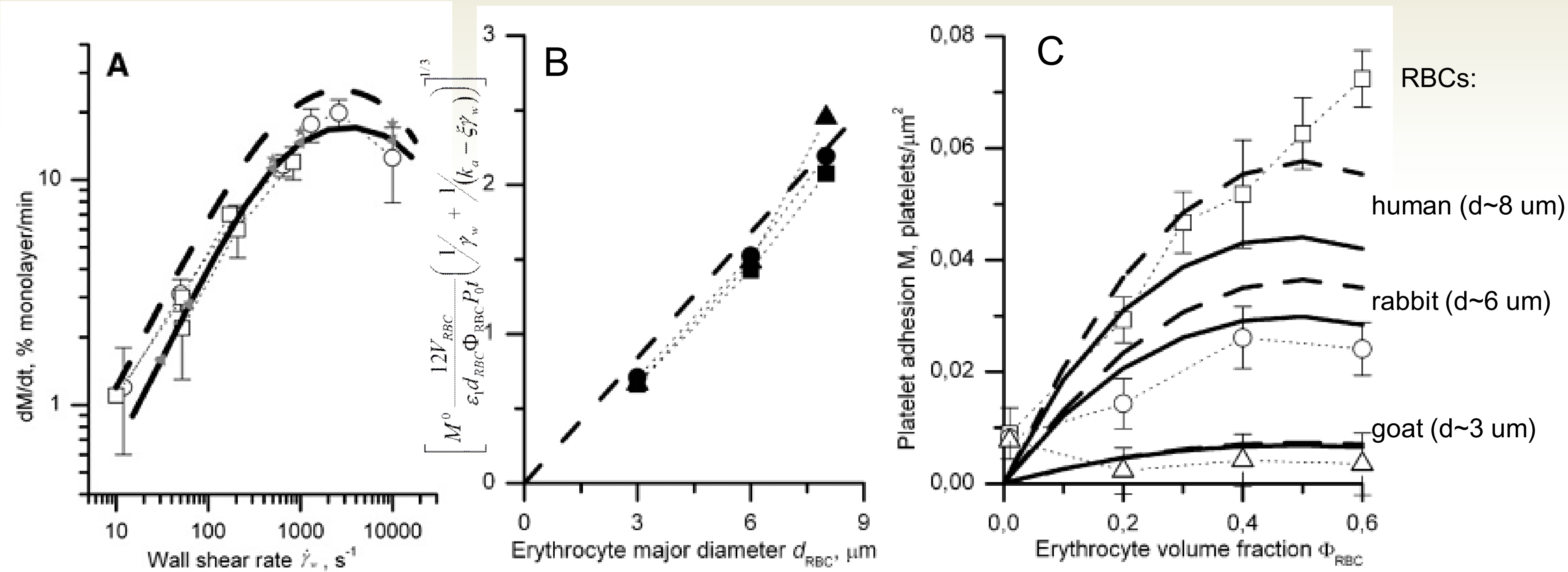
$$k_{eff} = \frac{\alpha Q}{1/\dot{\gamma}_w + 1/\left(k_a - \xi\dot{\gamma}_w\right)}$$

$$Q = \varepsilon_1 K_1 d_{RBC} \Phi_{\mathrm{RBC}} + \varepsilon_2 K_2 d_P V_{\mathrm{P}} P$$

$$K_1 = \frac{\left(k_1 d_P + k_2 d_{\mathrm{RBC}}\right)^3}{12 V_{RBC}}$$

$$K_2 = \frac{\left(k_1 + k_2\right)^3 d_P^3}{12 V_P}$$

# Wall shear rate-, RBC size- and hematocrit-dependence of the platelet adhesion rate




Solid lines, full model
Dashed lines, reduced model
Symbols, experiment (white in A from Turitto et al., 1975,1979; B, C from Aarts et al., 1983).

*Tokarev et al., Biophys. J., 2011b*

## Q.3: How wall shear rate and hematocrit control plug/thrombus growth rate?

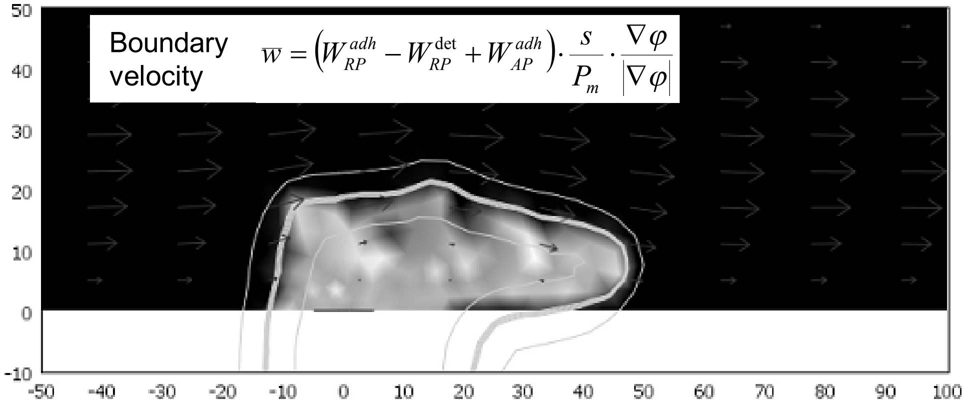
Tokarev, Sirakov, Panasenko, Volpert, Shnol, Butylin, Ataullakhanov. Russ.J. Num. Anal. Math. Model., 2012

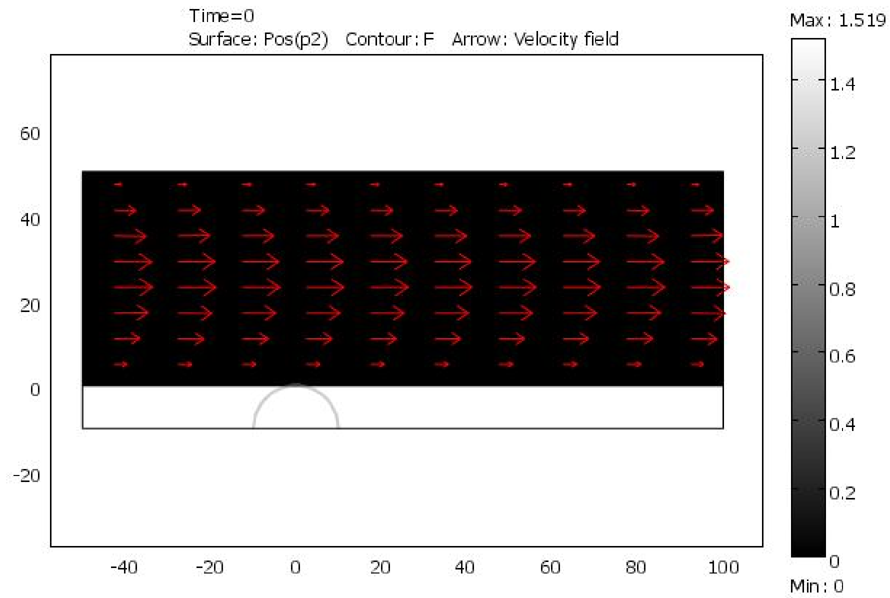
### Continuous Math Model of Platelet Thrombus Formation in Blood Flow:

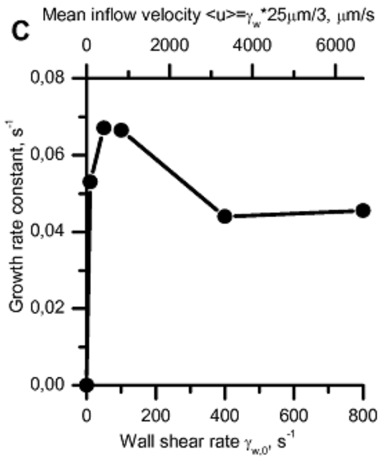
- 2 above models of platelet non-uniform distribution and platelet adhesion are included
- Moving thrombus boundary: platelet adhesion/detachment were distributed over a layer of the finite thickness *s* using the Level Set Function *φ*

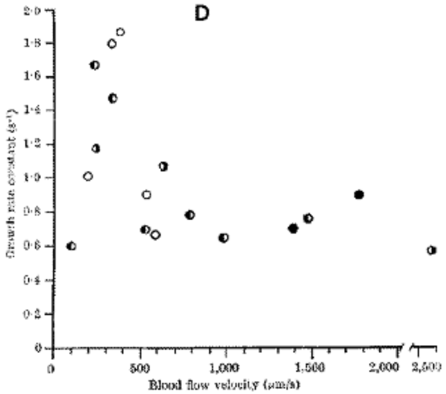
Boundary velocity

$$\vec{w} = \left(W_{RP}^{adh} - W_{RP}^{\det} + W_{AP}^{adh}\right) \cdot \frac{s}{P_m} \cdot \frac{\nabla\varphi}{|\nabla\varphi|}$$






Thrombus growth rate constant in the hamster cheek pouch venule. Begent, Born (1970)

**Problems:**

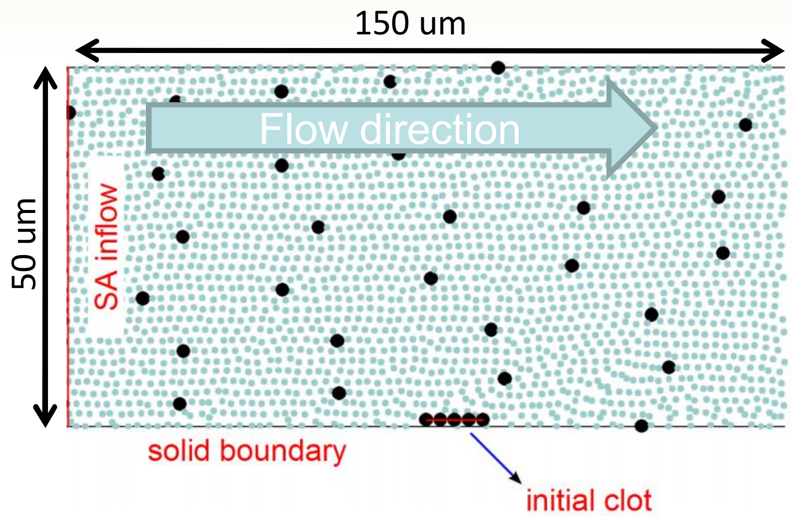
1) Platelets divide into subpopulations of different behavior
2) Platelet adhesion/activation mechanism is complex and has to be modeled on the molecular level

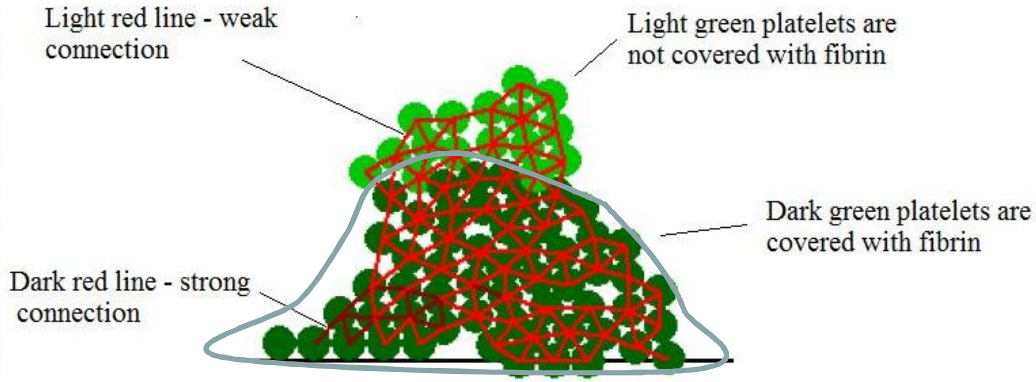
**Q.4: What controls the termination of a plug/thrombus growth?**
**A.4: Platelet shielding by a fibrin mesh can lead to this termination**

Tosenberger et al, Russ.J. Num. Anal. Math. Model., 2012; Tosenberger et al, J.Theor.Biol, 2013

**Hybrid math model:**

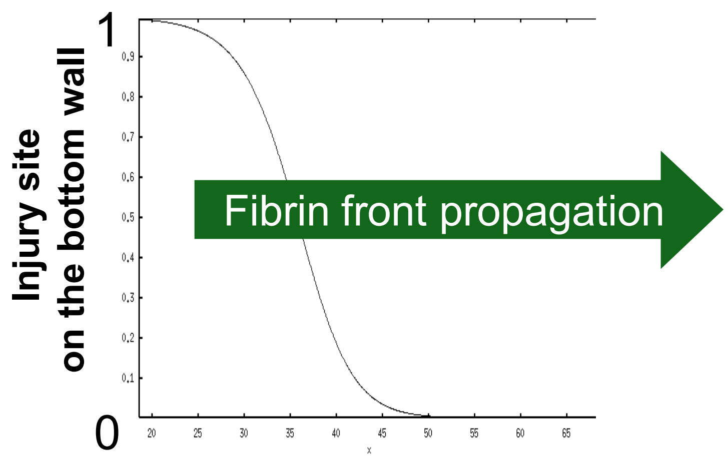
• plasma flow and platelet aggregation – DPD method, 2-step platelet adhesion



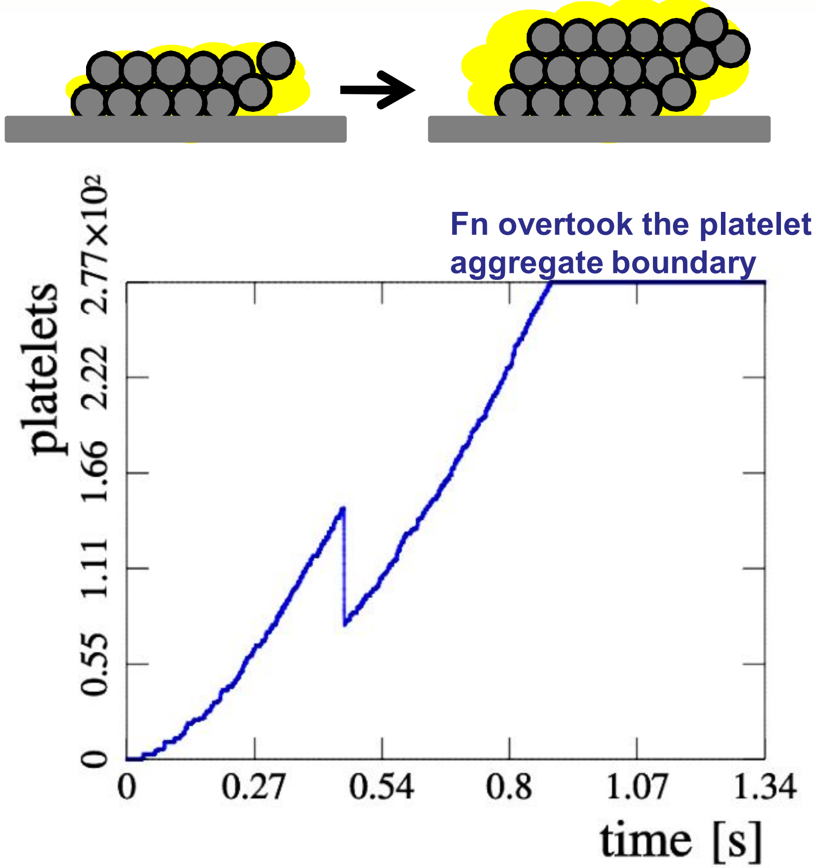

• plasma clotting – Fisher-KPP-type PDE (front of fibrin formation)

$$\frac{\partial u}{\partial t} = \alpha \Delta u - \nabla \cdot (\mathbf{v} u) + \beta u \,(1-u)$$

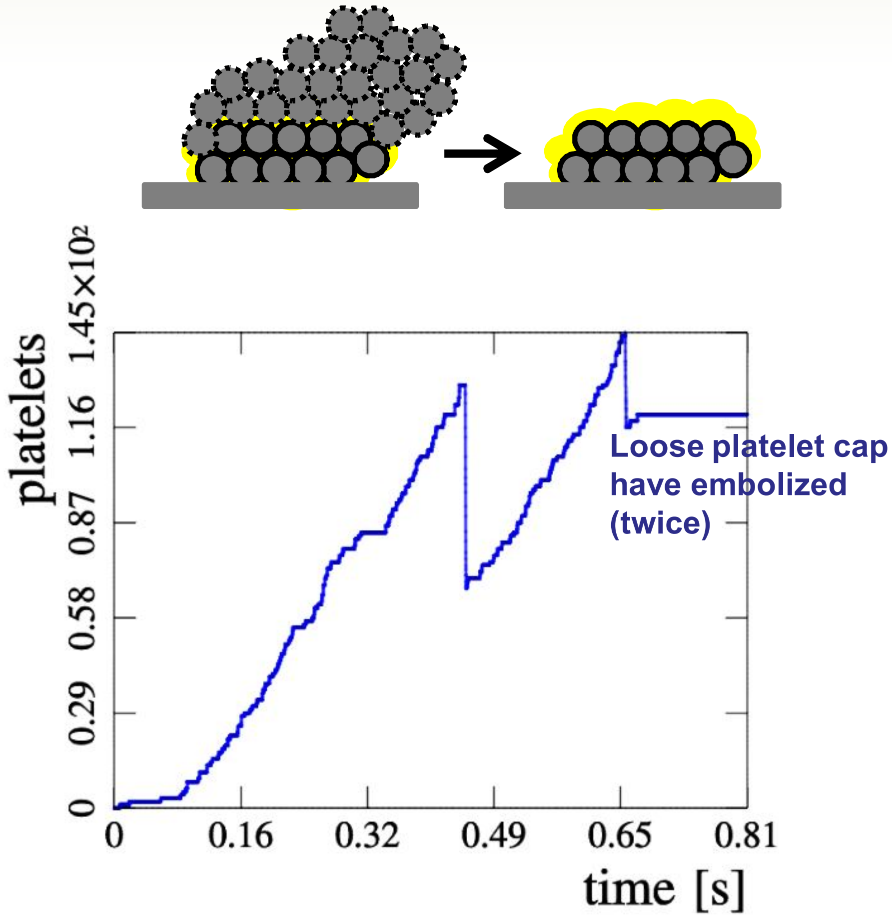


## Two regimes of thrombus growth termination differ in relative velocity of platelet plug growth and plasma coagulation

**“Fibrin network overgrowing“ regime:**
coagulation propagation velocity inside the platelet plug EXCEEDS the plug growth velocity




**“Loose cap embolization" regime:**
coagulation propagation velocity inside the plug is LESS than platelet plug growth velocity




Tosenberger et al, Russ.J. Num. Anal. Math. Model., 2012
Tosenberger et al, J.Theor.Biol, 2013

# Conclusions

1. Erythrocytes participate in hemostasis providing the passive transport of platelets to the vessel wall:

- strong non-uniformity of platelet distribution across blood vessel mainly results from the platelet expulsion from the core to the periphery of the flow due to finite platelet size, which impedes their positioning in between the densely packed erythrocytes in the core.

- platelet delivery from blood flow to the vessel wall is limited by near-wall rebounding collisions of platelets with erythrocytes.

Thus, platelet and erythrocyte sizes are the ruling parameters that should be accounted in every thrombosis modelling together with hematocrit and wall shear rate.

2. Fibrin “shield” formation on the top of platelet aggregate can terminate its growth.

# Our team (welcome to www.fazly.ru)



**Fazly Ataullakhanov**, **Andrey Butylin** and **Mikhail Panteleev** (Moscow lab)

**Nick Bessonov** (Institute of Problems of Mechanical Engineering, Russian Academy of Sciences, S.-Petersburg)



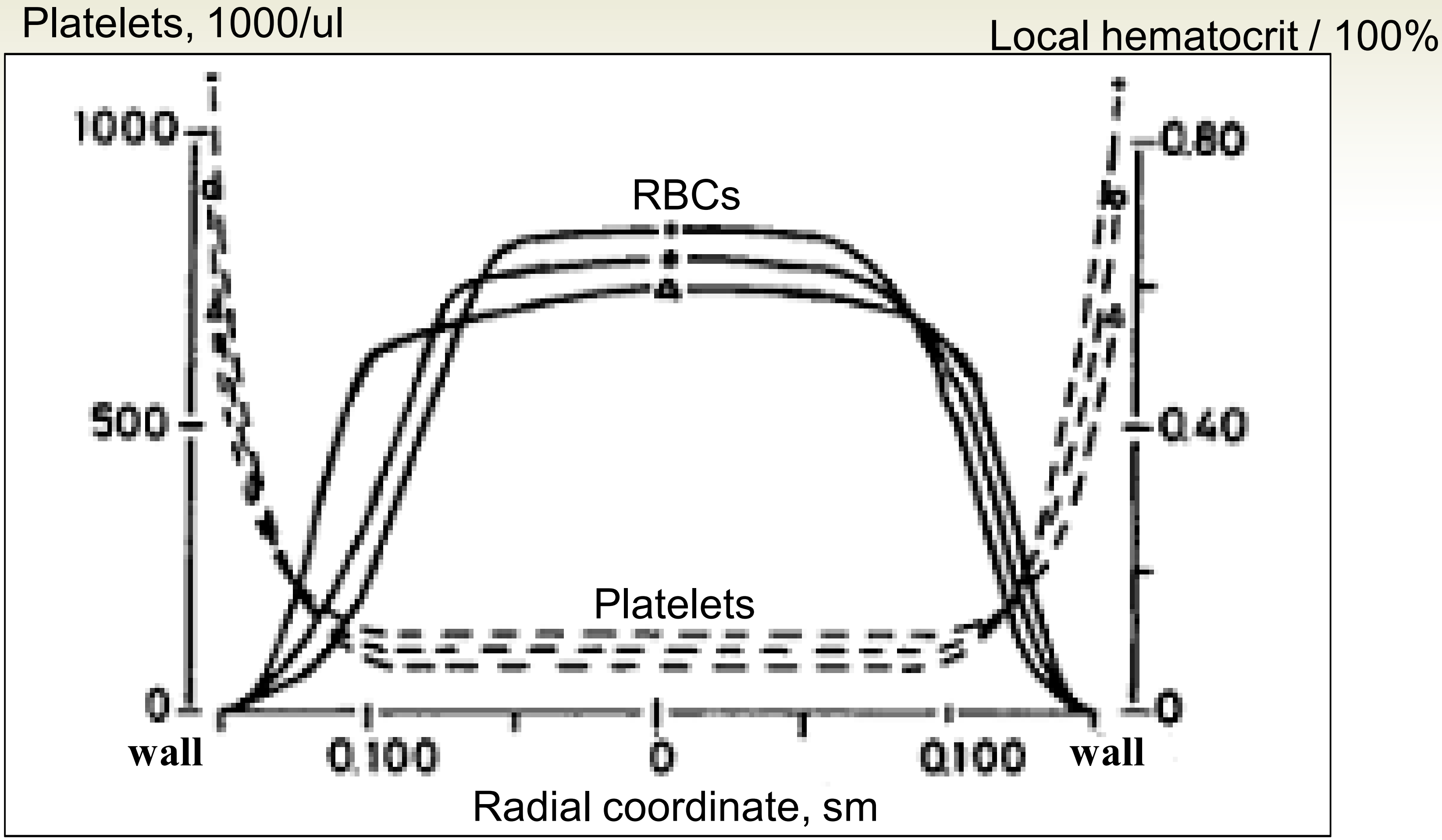
**Grigory Panasenko**, **Vitaly Volpert**, and **Alen Tosenberger** (Institut Camille Jordan, Université de Saint-Etienne and Université Claude Bernard Lyon 1, France)

# Thank you for your attention!

# Характерные параметры кровотока в организме человека

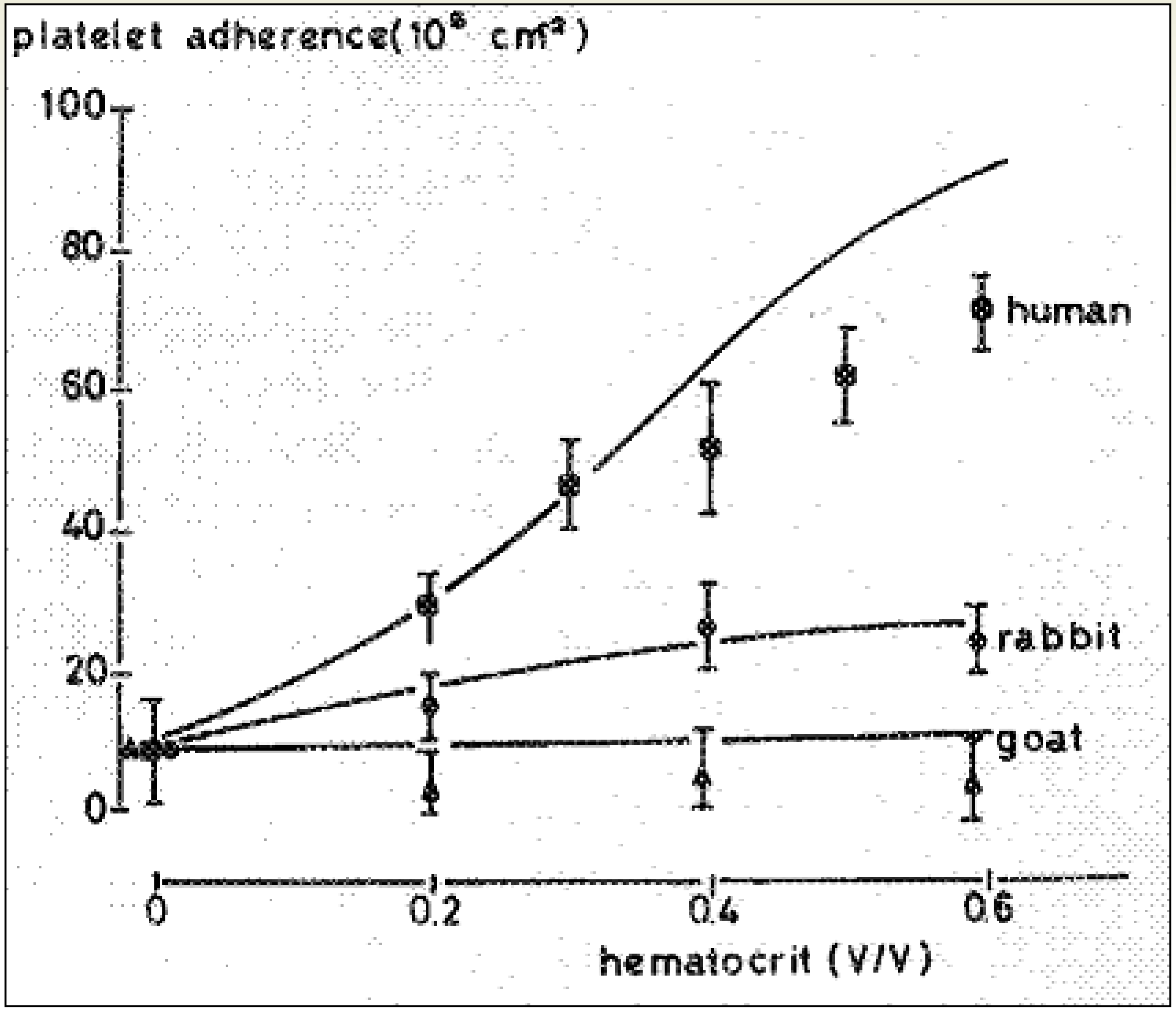
| Сосуды[2] | | Внутренний диаметр *d*, мкм | Длина, см | Количество в организме | Средняя скорость течения[3] *u*, см/с | Средняя скорость сдвига, 1/с | Пристеночная скорость сдвига[4] $\dot{\gamma}_w$, 1/с | Пристеночное напряжение сдвига[4] $\tau_w$, дин/см$^2$ | Число Рейнольдса[3] *Re* |
|---|---|---|---|---|---|---|---|---|---|
| Артерии большого круга кровообращения | Аорта | $(2\text{-}4)\cdot10^4$ | 80 | 1 | 30-60 | 100 | 50-300 | 2-10 (+45/-2) | $(1\text{-}6)\cdot10^3$ |
| | Большие артерии (бедренная, сонная, коронарные) | $(3\text{-}6)\cdot10^3$ | 20-40 | $\sim10^3$ | 20 | 400 | 220-460 | 8-16 | 100-1000 |
| | Малые артерии | 300 | 0.2-5 | $\sim10^8$ | 0.2-10 | >100 | 1500 | 53 | 5-10 |
| Микрососуды большого круга кровообращения | Артелиолы и прекапиллярные артериолы | 30 (20-100) | | | | | 1900 | 60 | 0.01-0.04 |
| | Капилляры | 6 (5-10) | 0.1 | $>10^9$ | 0.05-0.07 | 400 | 370-2800 | 14-100 | 0.001-0.003 |
| | Венулы и посткапиллярные венулы | 40 (20-200) | 0.2-1 | $\sim10^9$ | 0.1-1 | ~100 | нет данных | | 0.01-1 |
| Вены большого круга кровообращения | Вены | $(0.5\text{-}1)\cdot10^4$ | 10-30 | ~1000 | 10-20 | | 200 | 7 | 100-600 |
| | Полая вена | $2\cdot10^4$ | 50 | 2 | 10-20 | 50 | 40-60 | 1.5-2.1 | 300-1000 |
| Ширина диапазона (порядки) | | 4 | 3 | 9 | 4 | 1-2 | | | 6 |

# The presence of RBCs leads to great platelet near-wall excess



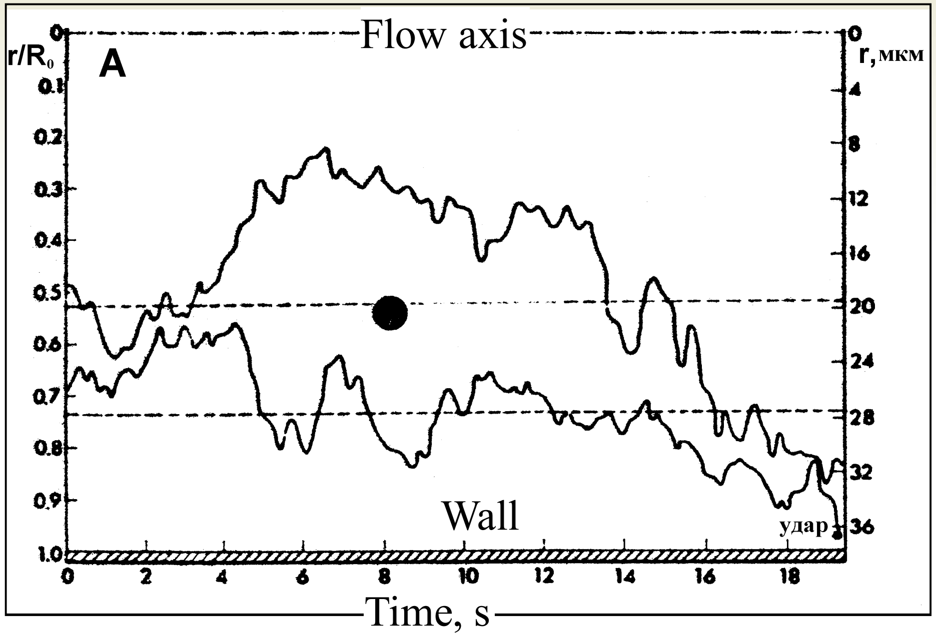

RBC (—) and platelet (– –) distribution across the flow *in vitro*.
Hematocrit 40%; wall shear rate 240 (Δ), 750 (○) and 1200 $s^{-1}$ (●).
*Aarts et al., 1988.*

# The presence of RBCs drastically increases the rate of platelet adhesion to various active surfaces




Human platelet adhesion *in vitro* in the presence of human (d~8 um), rabbit (d~6 um) and goat (d~3 um) RBCs. t=5 min. *Aarts et al.,1983.*

# The presence of RBCs leads to chaotic motion of blood cells across the flow

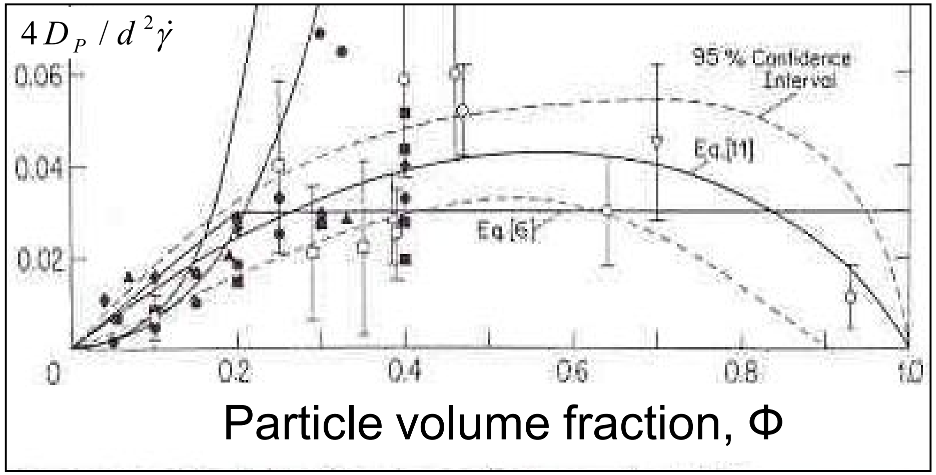



Trajectories of platelet-modelling microspheres in the suspension of RBC ghosts. *Goldsmith, 1971.*

Shear rate diffusion (dispersion) coefficient $D_p$ :

$$\text{at shear rate} \quad \dot{\gamma} = 100 \div 1000\,\text{s}^{-1}$$

$$D_P \sim 10^{-6} \div 10^{-5}\,\frac{\text{s}m^2}{\text{s}} >> D_{Br} \sim 10^{-9}\,\frac{\text{s}m^2}{\text{s}}$$




Shear-induced diffusion efficiency depends on the RBC volume fraction $\Phi_{RBC}$:

$$D_P \sim d_{RBC}^2 \cdot \dot{\gamma} \cdot \Phi_{RBC} \cdot (1 - \Phi_{RBC})$$

*Zydney and Colton, 1988.*