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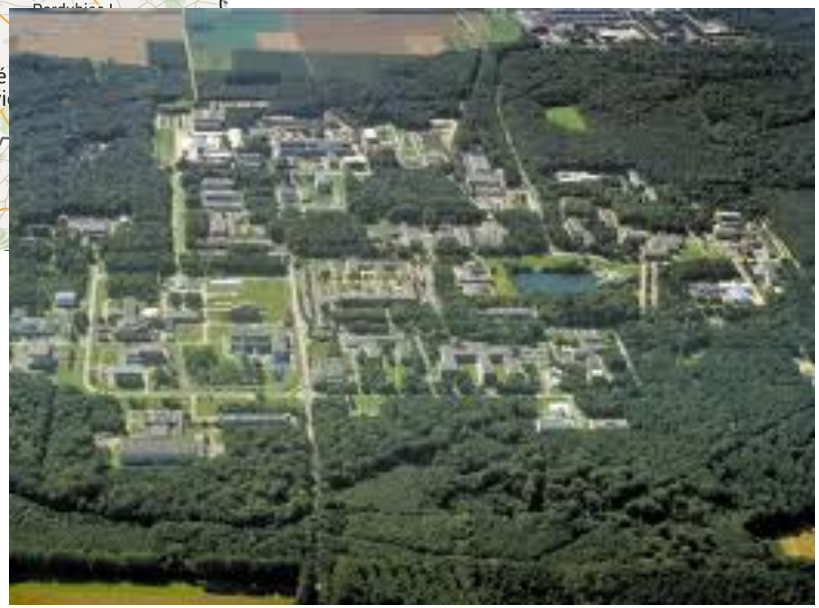
From single cells to intricate multi-cell interactions in blood flow

Dmitry A. Fedosov

Institute of Complex Systems and Institute for Advanced Simulation,
Forschungszentrum Jülich, 52425 Jülich, Germany

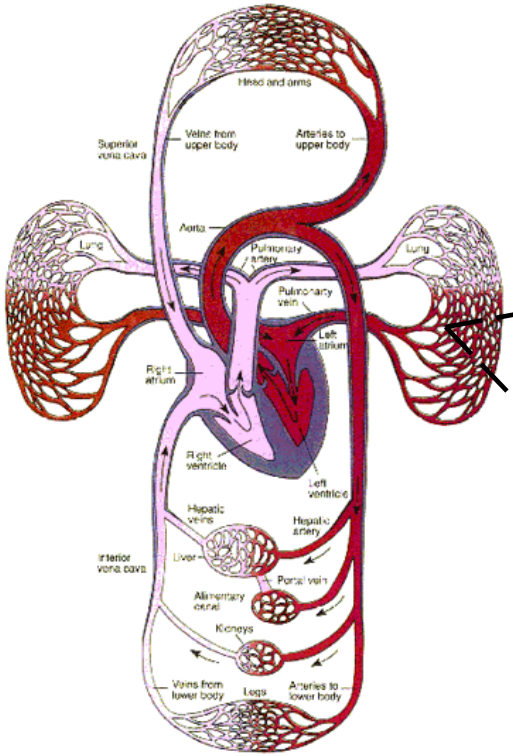
Forschungszentrum Jülich



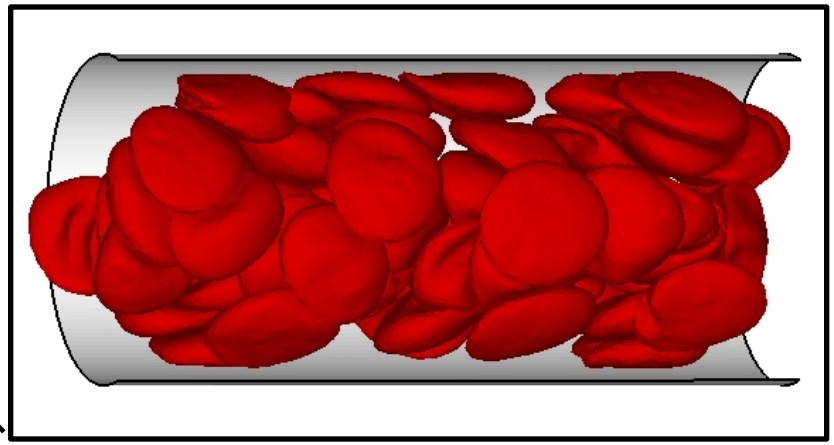
- One of the largest research centers in Germany with nearly 5000 employees
- Research includes energy, health, materials, etc.

Blood flow

- Blood transports oxygen and nutrients to cells of the body, removes waste products, and circulates molecules and cells which mediate various organism functions
- Abnormal blood flow and rheology is often associated with some blood disorders and diseases such as hypertension, anemia, malaria, and thrombosis

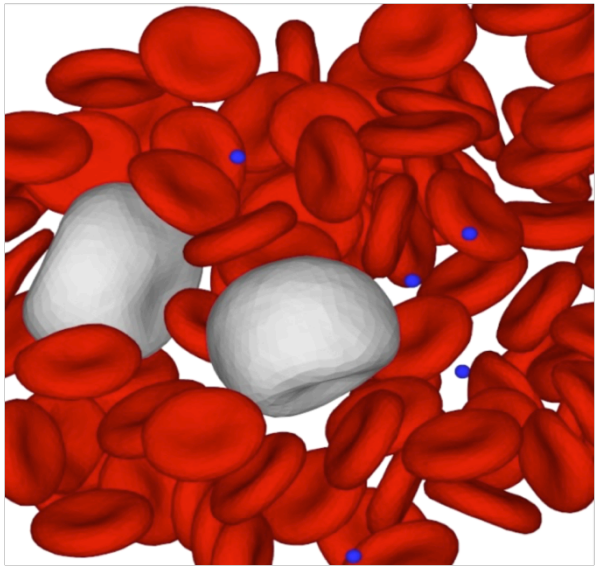


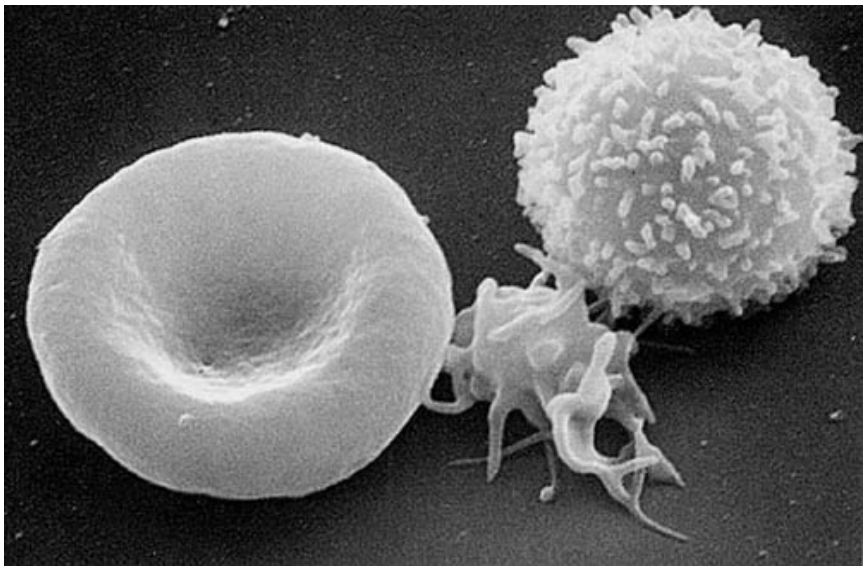
- Biomedical and bioengineering applications: blood substitutes, blood flow assisting devices, lab-on-a-chip, and drug delivery



Blood

- Adults have about 5 liters of blood formed by erythrocytes (red blood cells) - 45%, leukocytes (white blood cells) - 0.7%, blood plasma – 54%, thrombocytes (platelets)
- Blood plasma consists of about 92% water, 8% proteins and other materials
- One microliter of blood has about 4-6 million RBCs, 4-10 thousand WBCs, and half a million platelets





Modeling fluid flow

Incompressible Navier-Stokes equation

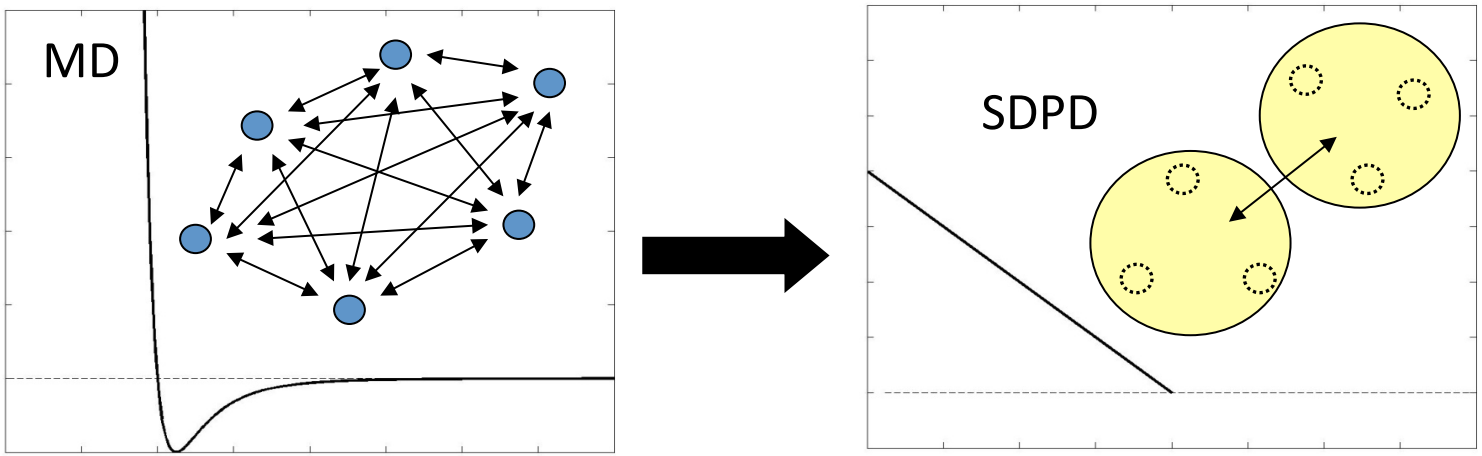
$$\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla)\vec{u} = -\frac{1}{\rho}\nabla p + \nu \nabla^2 \vec{u}$$

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

There exist different methods for solving NS equation:

- Eulerian discretization – finite difference, finite volume, finite element, etc.
- Lagrangian discretization – particle-based methods, etc.

Smoothed dissipative particle dynamics method

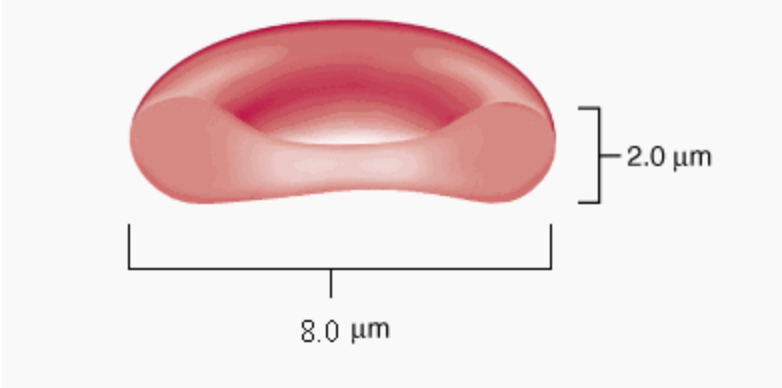


- SDPD is a mesoscopic particle-based hydrodynamics method
- Particles interact through a simple pair-wise potential
- The time evolution of positions and velocities are given by

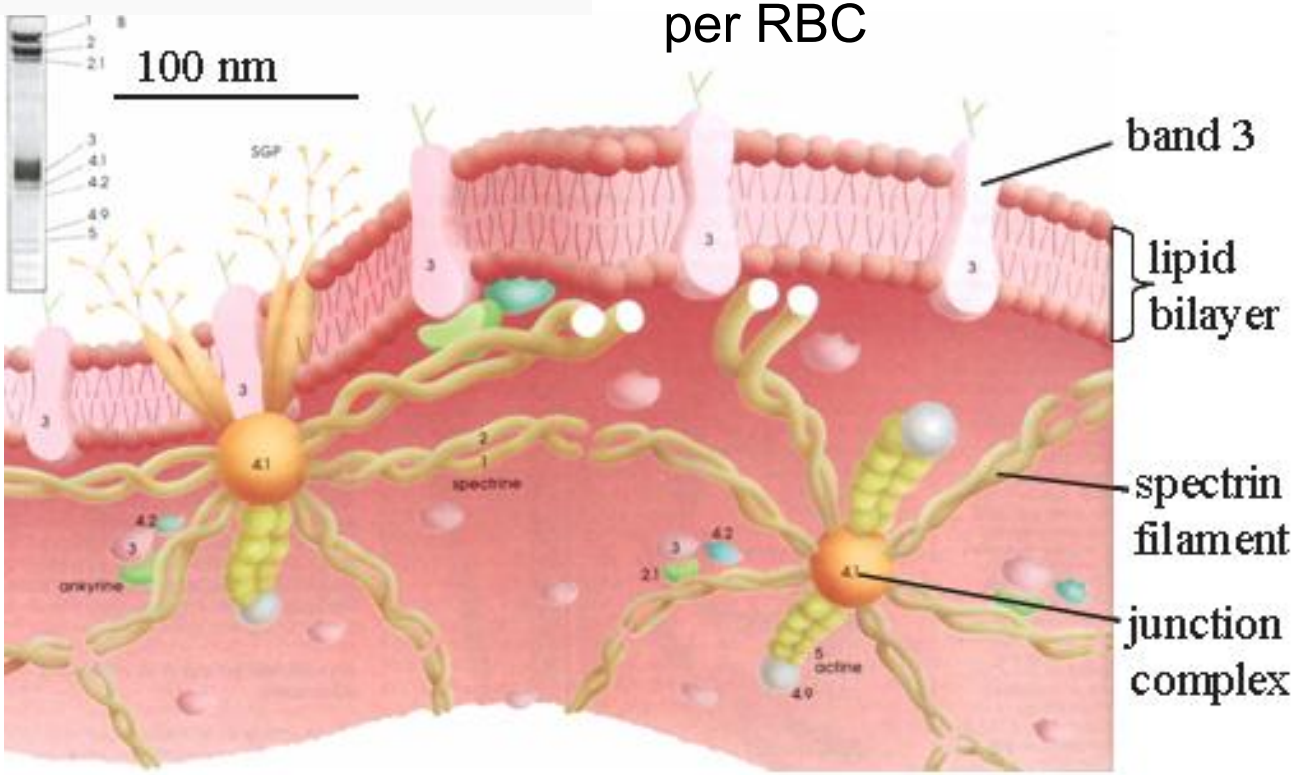
$$d\mathbf{r}_i = \mathbf{v}_i dt \qquad d\mathbf{v}_i = \mathbf{F}_i dt$$

Espanol and Revenga, *Phys. Rev. E*, 67:026705, 2003; Müller et al., *J. Comp. Phys.*, 281:301, 2015

Red blood cells



- No nucleus, organelles, and inner cytoskeleton
- Membrane: lipid bilayer with an attached spectrin network
- 50-100 nm spectrin length between junctions, 27000 – 40000 of junctions per RBC



Membrane model

Triangular network:

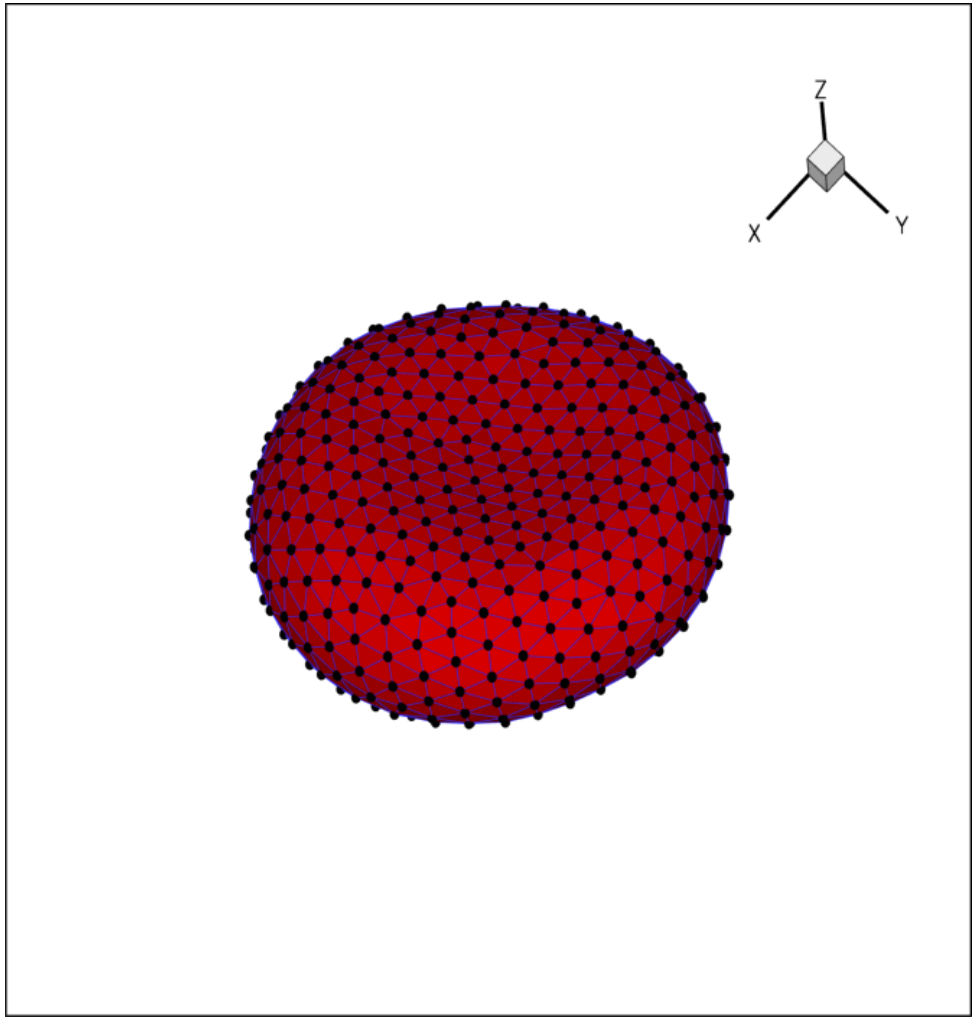
1) vertices – membrane particles

2) edges – viscoelastic springs

3) bending energy between faces

4) constant surface area (local or global)

5) constant volume



Fedosov et al., *Biophys. J.*, 98:2215, 2010

Deformation and dynamics of blood cells in microfluidics

Microfluidics

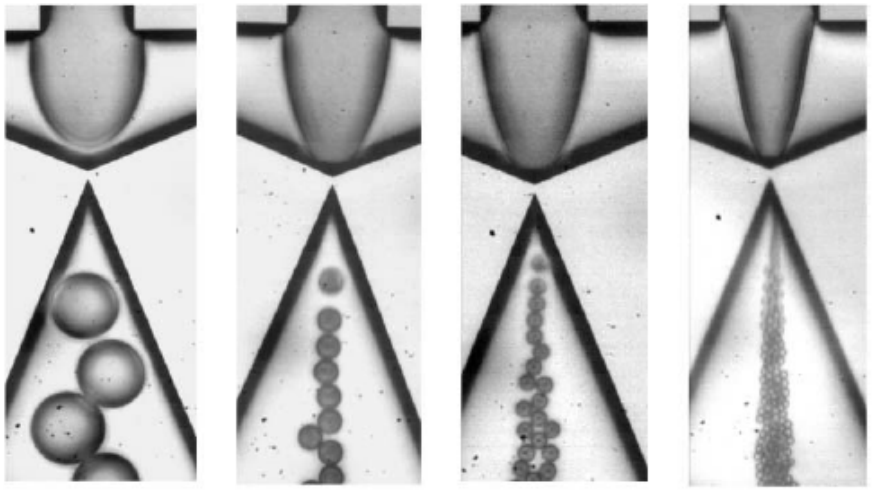
Biomedical and engineering applications

Analysis and detection of suspended particles

Sorting and separation

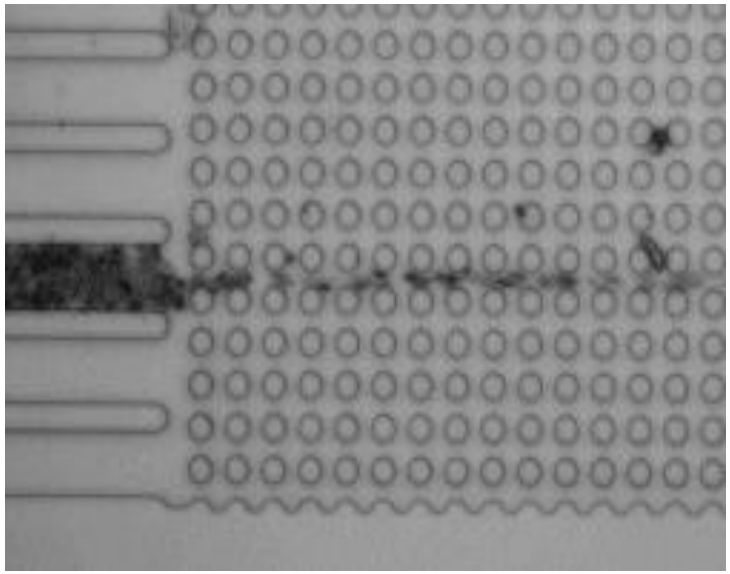
Manufacturing of micro-particles

Droplet microfluidics



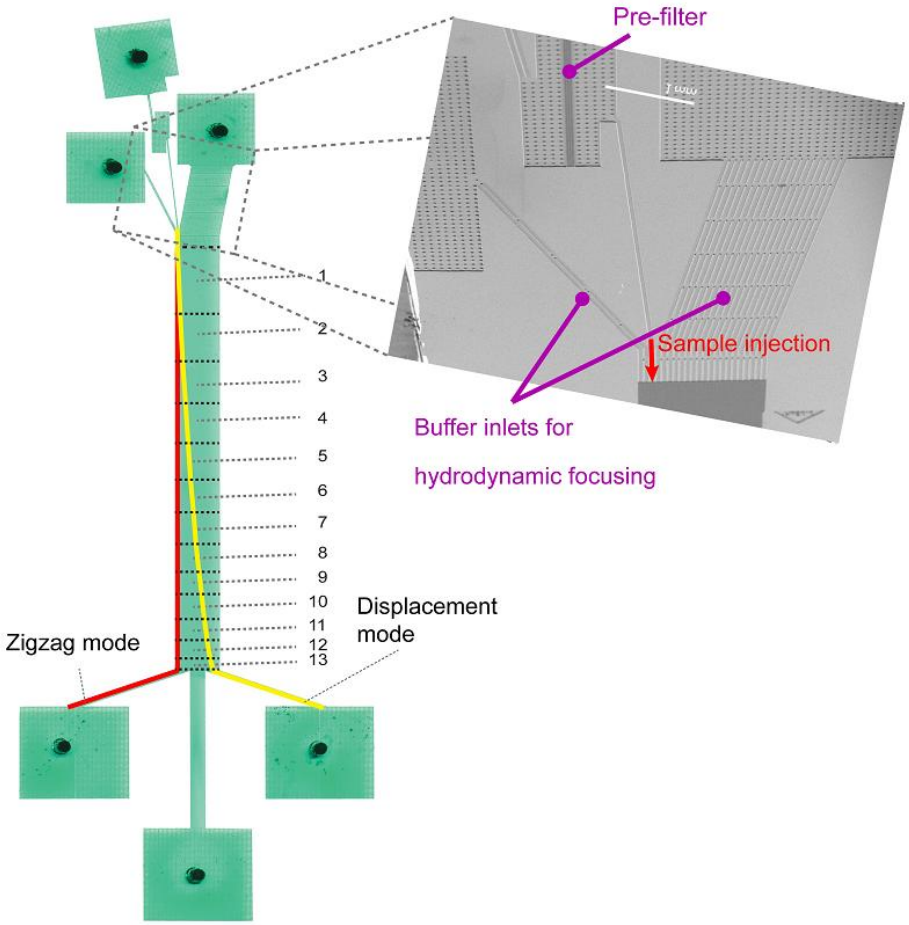
Yobas et al., *Lab Chip*, 6: 1073, 2006

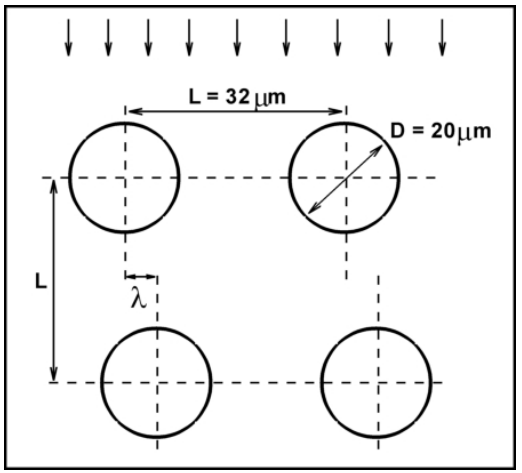
Bumper arrays

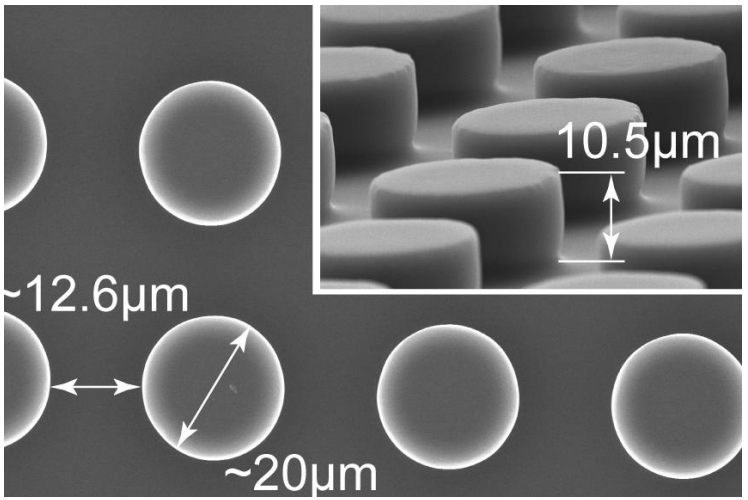


Holm et al., *Lab Chip*, 11: 1326, 2011

Deterministic Lateral Displacement (DLD) Devices





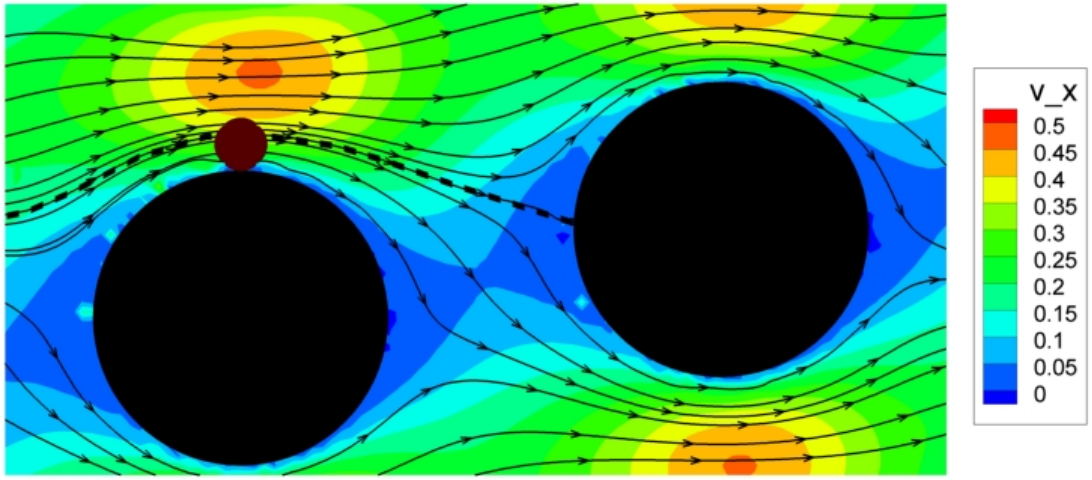


Holm et al., *Lab Chip*, 11: 1326, 2011

Basic principle of DLDs

DLD devices can be used efficiently for the separation of colloidal particles based on their size

Can we efficiently sort deformable particles (e.g., cells) in DLD devices?

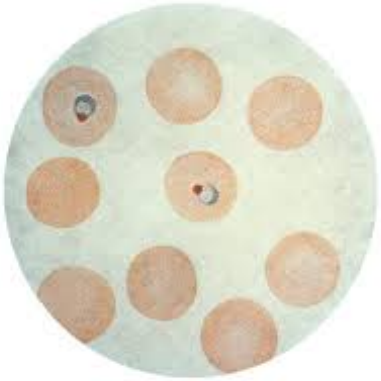


Understanding and optimization of obstacle array devices

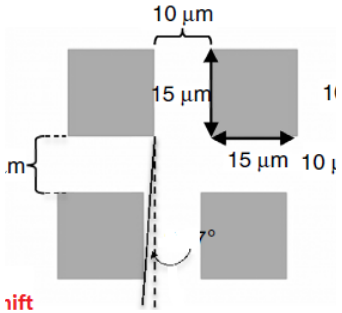
European FP7 program: LAPASO - Label Free Particle Sorting

Questions to address

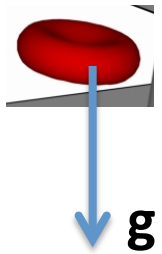
- How sensitive is a DLD to the moderate changes of various RBC properties such as the cell size, membrane elasticity and bending rigidity, and the viscosity contrast?



- What geometrical configuration (e.g., pillar shape and size, their arrangement) of a DLD provides an ‘optimal’ performance?

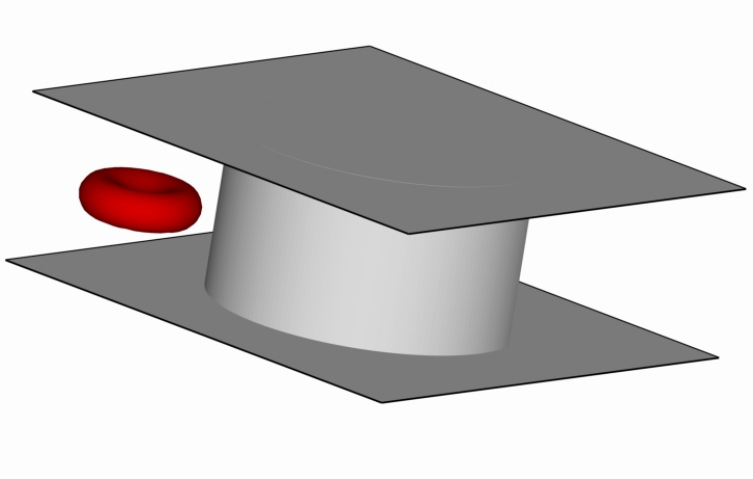


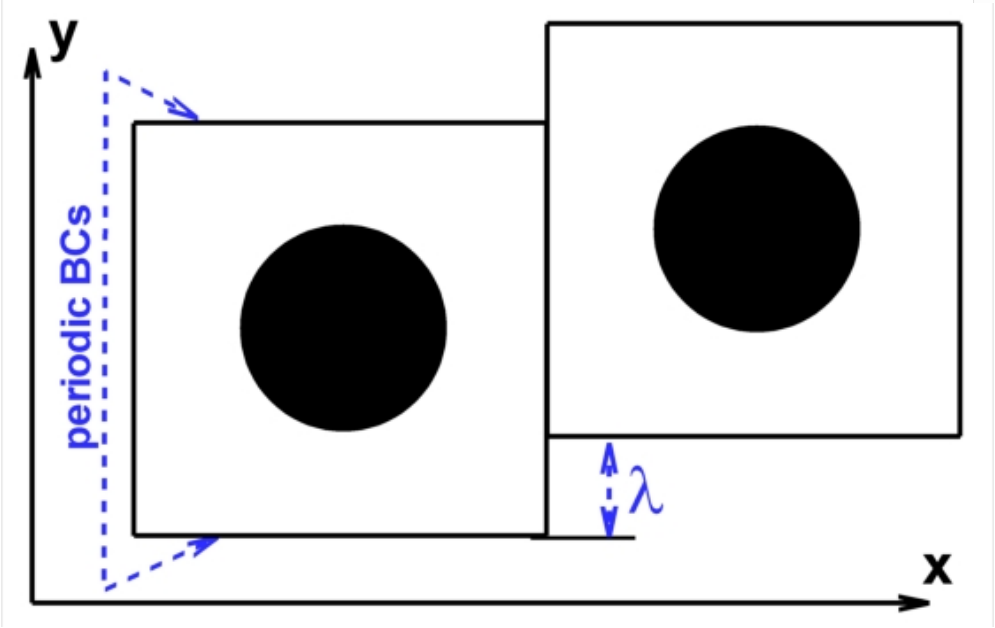
- Can we improve the separation through the application of various external fields (e.g., gravity, dielectrophoresis, acoustophoresis)?



Bumper array simulation

We are going to simulate only a single bumper!





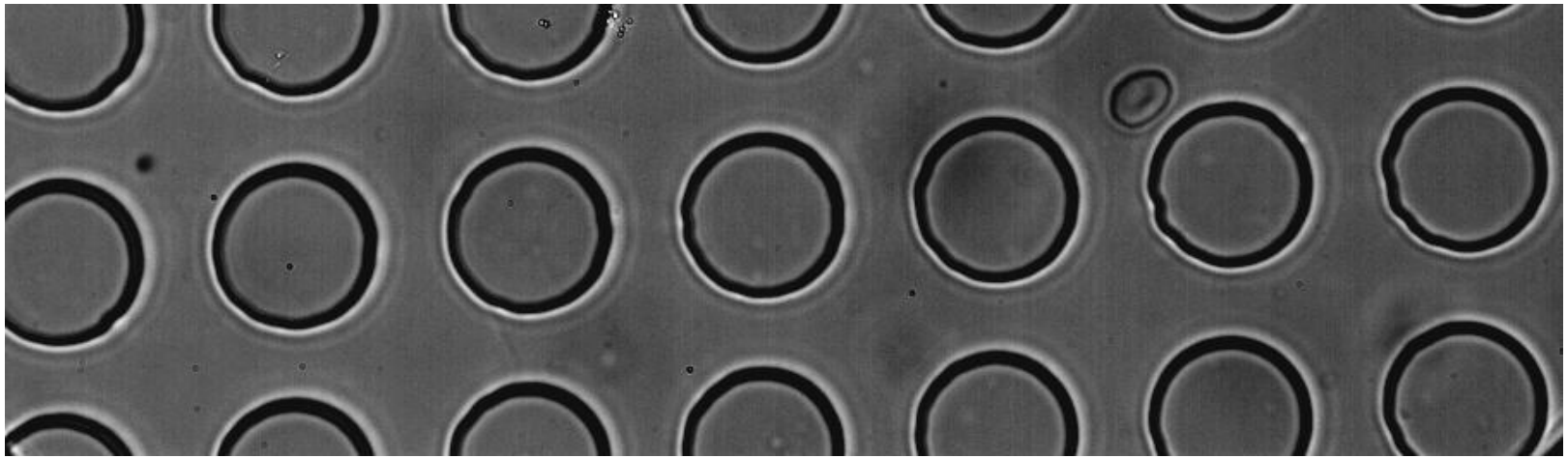
Boundary conditions:

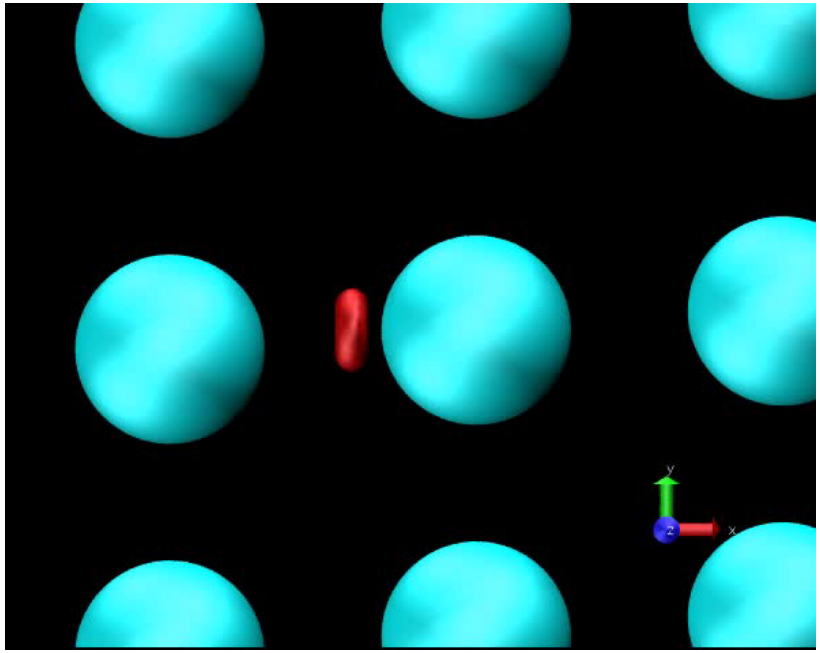
X – similar to Lees-Edwards BCs with the shift λ.

Y – periodis BCs.

Z – solid BCs.

Experiments & simulations

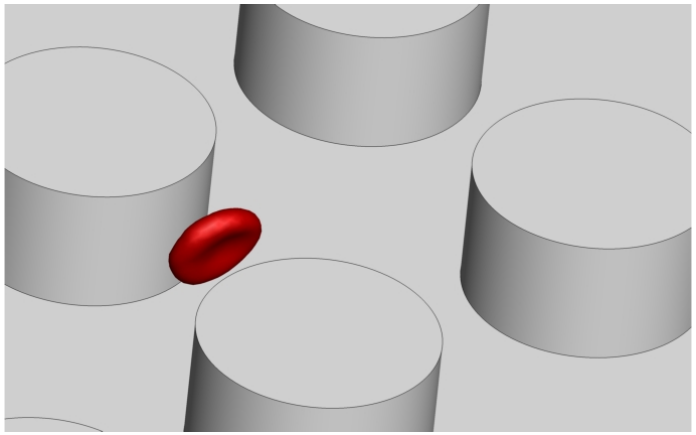




Section 4 of the device with the shift of 2 micron

Summary and conclusions

- Bumper arrays can exploit cell size, shape, and deformability for sorting and detection



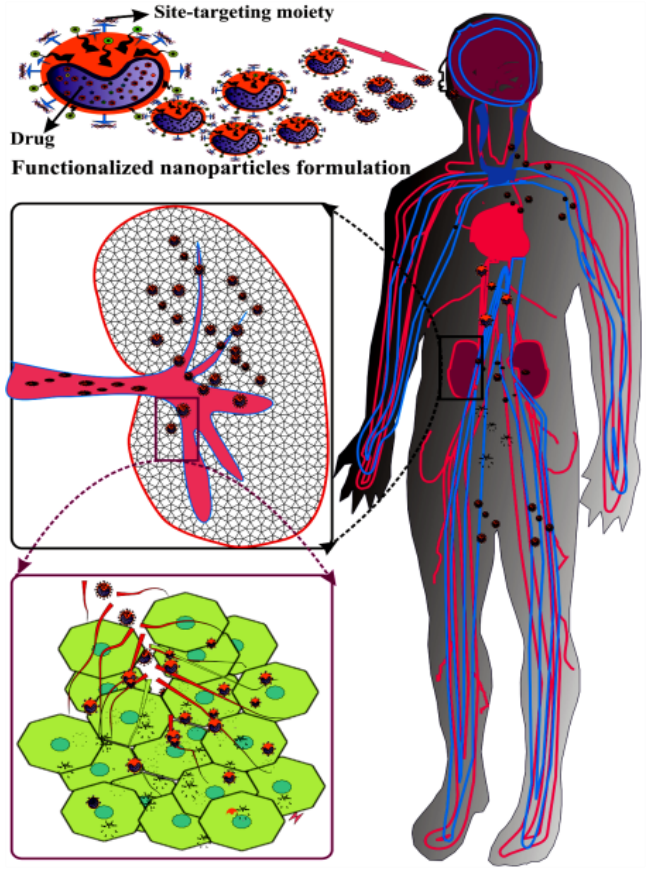
- Simulations allow us to observe in detail the cell dynamics, deformation, and orientation within the microfluidic device

- Microfluidics simulations can aid in the design of efficient micro-devices

Margination of micro- and nano-particles in blood flow

Targeted drug delivery

Drug delivery by micro- and nano-particles



An idea of targeted drug delivery is very simple:

i) Encapsulate drugs into "fully-functional" and "target-oriented" carriers
ii) Administer the carriers into human body
iii) Let the particles get delivered to specific targets
iv) Release drugs at the targeted sites

Bennet & Kim, *InTech*, DOI: 10.5772/58422, 2014

Realization steps of drug delivery

1) Fabrication of micro- and/or nano-particles

. . . .

2) Transport of the particles through a cardiovascular system

. . . .

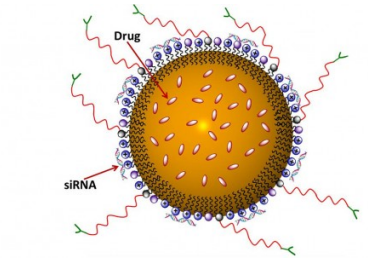
3) Transmigration of the particles through vascular walls and interstitial space

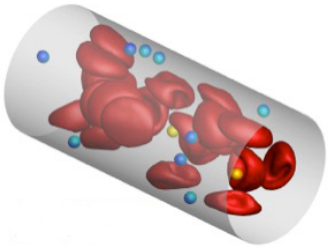
. . . .

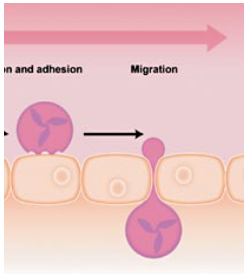
4) Particle uptake by cells and their transport within a cell

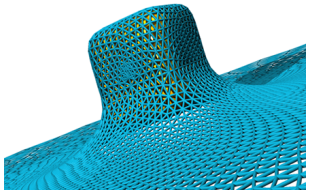
. . . .

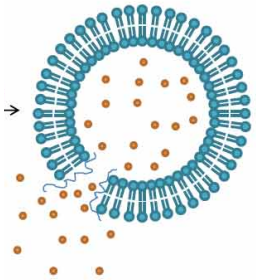
5) Release of drugs after a target has been reached





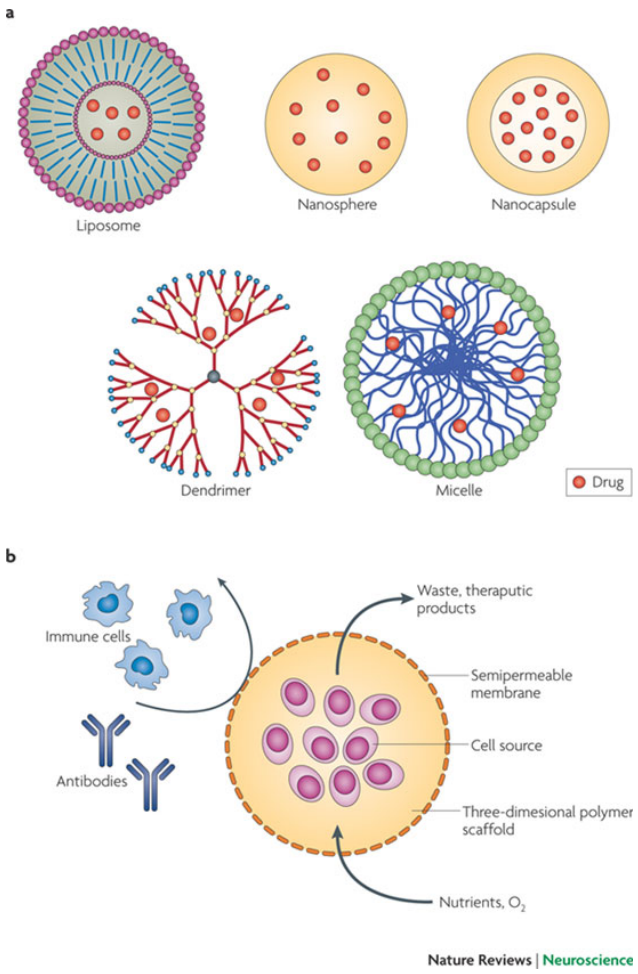






Properties of drug carriers

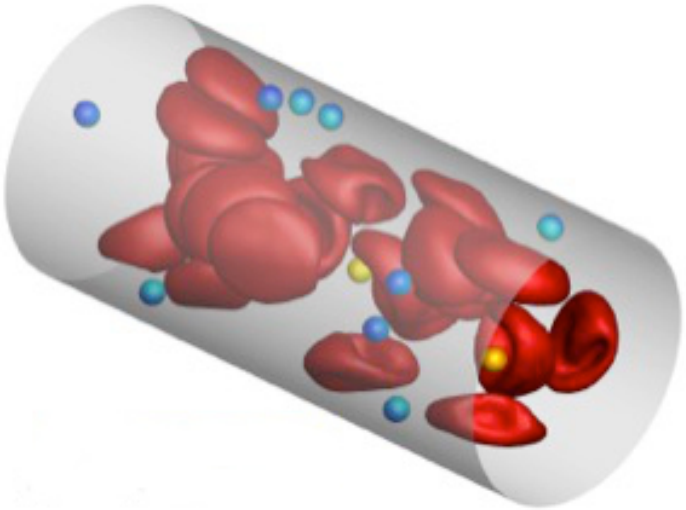
- Various sizes (from several nanometers to a few micrometers)
- Different shapes (e.g., sphere, ellipsoid, disk, rod-like)
- Different composition (e.g., polymers, lipids)
- Various functionalities (e.g., receptors, break-up, stealth properties)
- Multistage drug carriers
- …..



Orive et al., *Nat. Rev. Neurosci.*, 10:682, 2009

Vascular drug delivery

- Particle transport through vascular networks
- Interactions with other blood cells
- Adhesion to vascular endothelium



Müller et al., *Sci. Rep.*, 4:4871, 2014

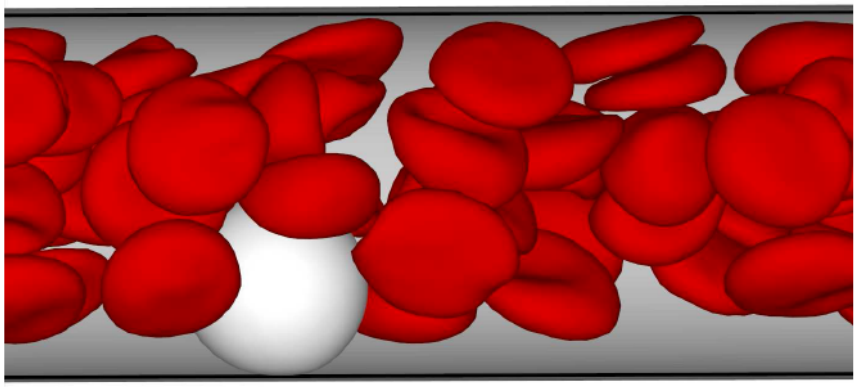
Questions:

- Effect of various blood flow conditions (e.g., flow rate, blood cell concentration) on the transport of particles
- Dependence of the transport on particle properties such as size, shape, deformability
- Interactions with other blood cells
- Adhesion to vascular endothelium

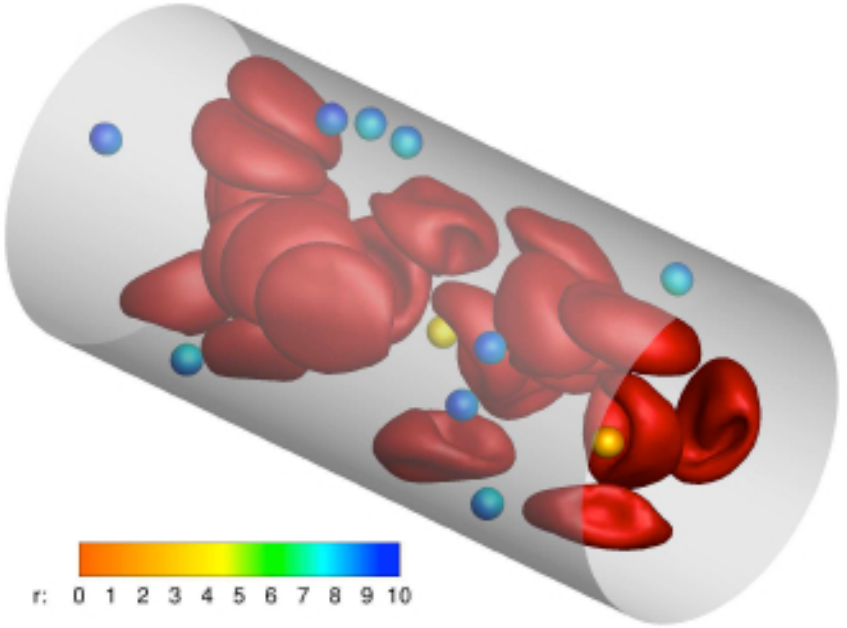
Particle margination

Margination of particles and cells in blood flow

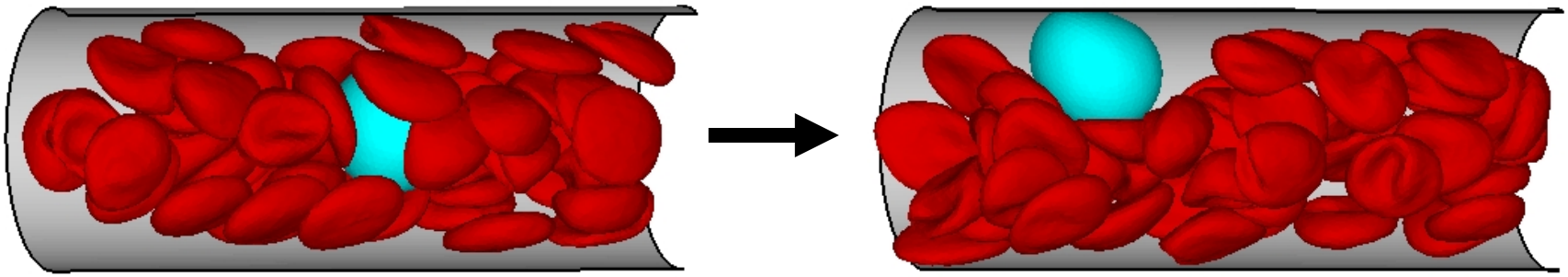
- white blood cells and platelets



- drug delivery carriers

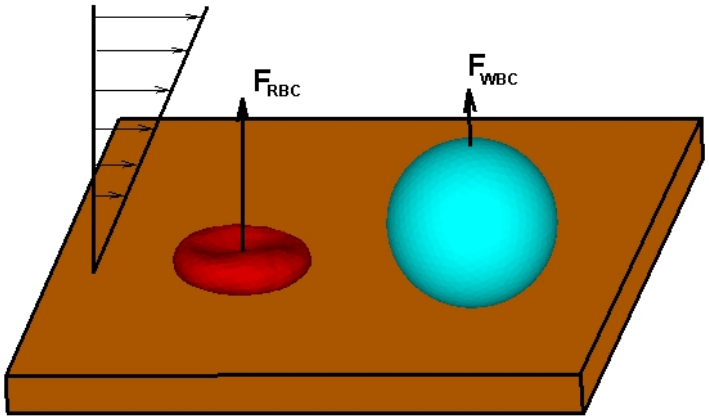


Margination mechanisms



Physical mechanisms and important factors?

"Lift" force?



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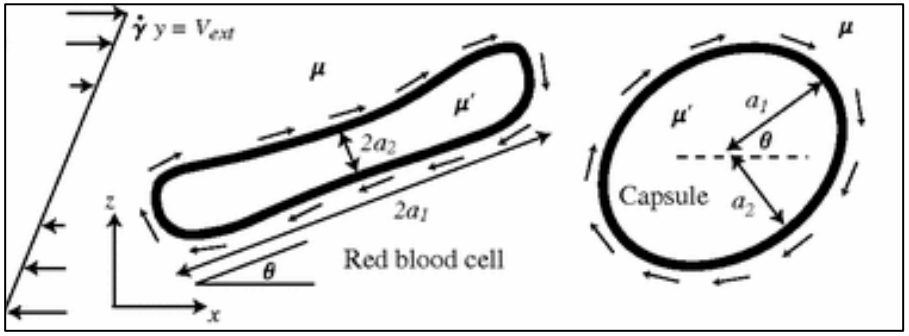
Shear induced diffusion or cell "collisions"?

Contributing factors: **Hematocrit, RBC aggregation, cell properties, flow rate and geometry**

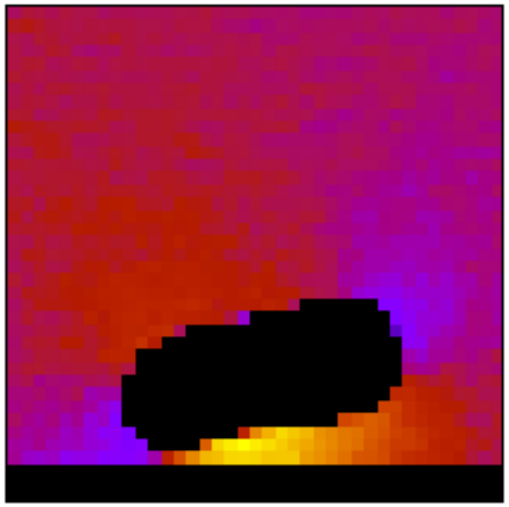
Lift force

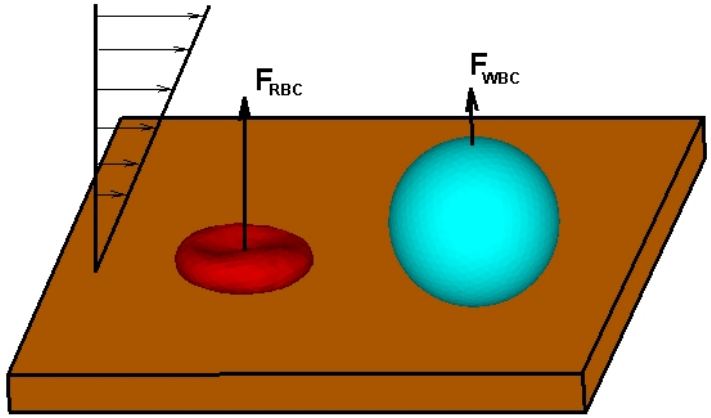
Due to hydrodynamic interactions of cells with a wall

- RBC alignment in flow
- tank-treading motion of a membrane
- pressure difference



Skotheim & Secomb, *Phys. Rev. Lett.*, 98:078301, 2007

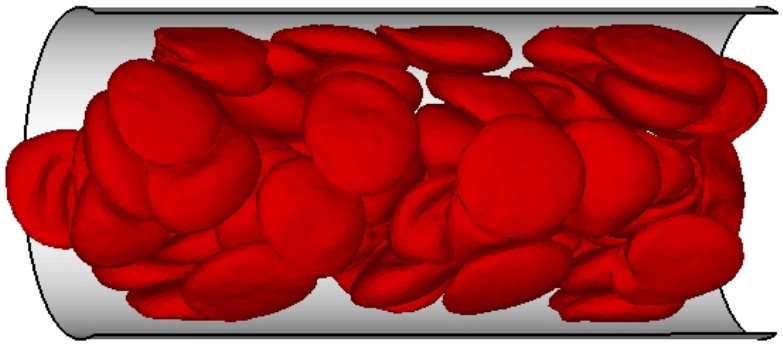




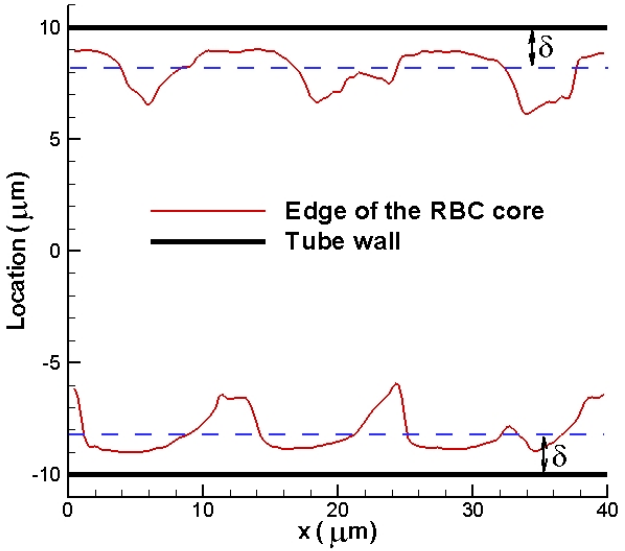
Messlinger et al., *Phys. Rev. E*, 80:011901, 2009

RBC free layer

Lift force on RBCs leads to a layer next to a wall void of RBCs



RBC-free layer (RBCFL)

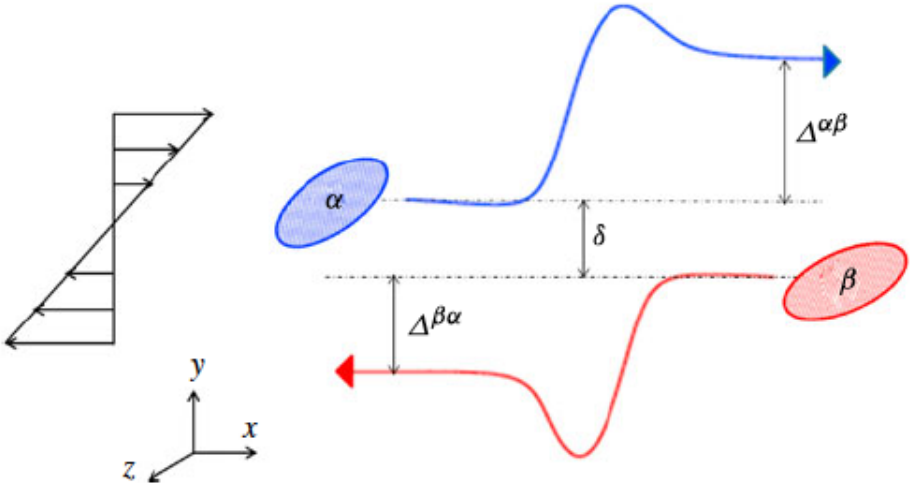


- RBCs migrate to the center of the tube forming a flow core
- Near the wall a RBC-free layer is formed absent of RBCs

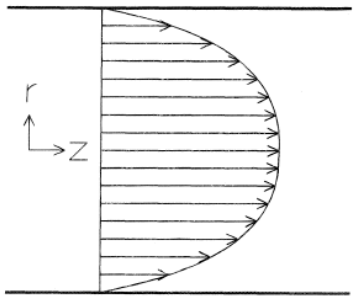
Shear-induced diffusion

Effective particle diffusion may be enhanced due to 'collisions' with RBCs

- Interactions of particles with RBCs lead to their enhanced diffusion
- Particle diffusion is non-uniform

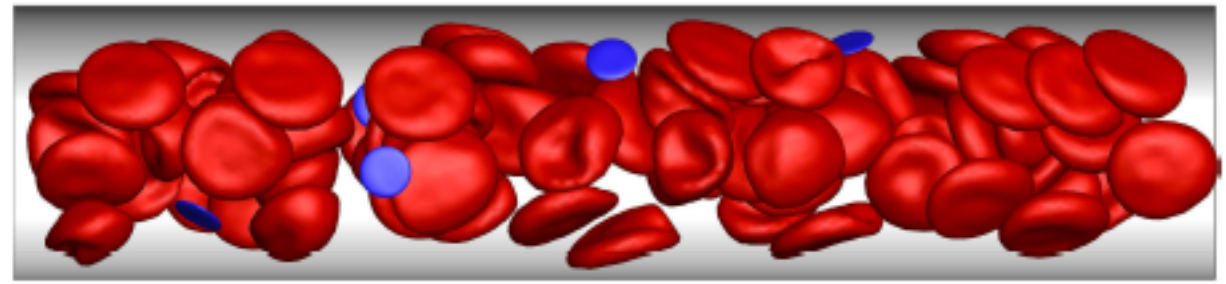


Kumar & Graham, *Phys. Rev. Lett.*, 109:108102, 2012

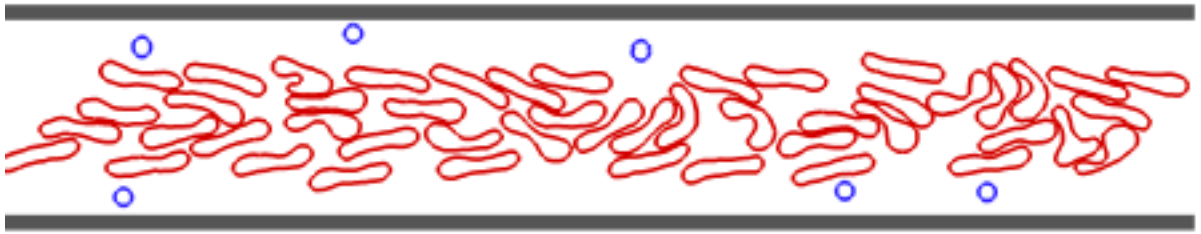


A gradient in the effective diffusivity leads to particle drift!

Simulation system



- 3D

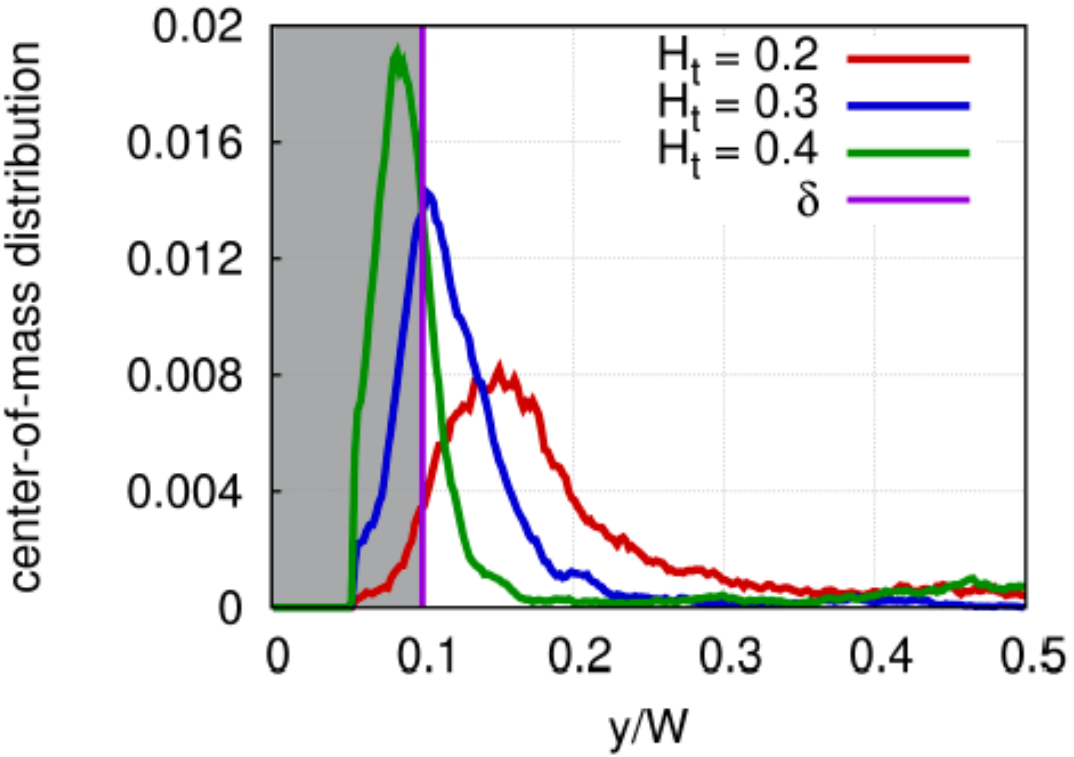


- 2D

Characterized by:

- hematocrit H_t
- non-dimensional shear rate $\dot{\gamma}^* = \bar{\dot{\gamma}}\tau = \frac{\bar{v}}{W}\frac{\eta D_r^3}{\kappa}$
- particle size D_p and shape (spherical and ellipsoidal)

Particle distribution



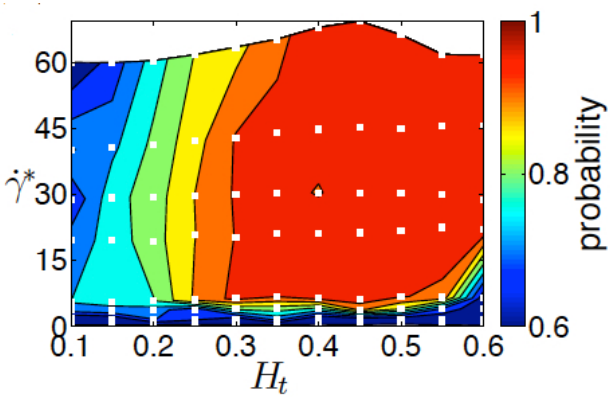
Margination probability is defined as a probability for a particle center of mass to be within the distance δ away from the wall.

Different choices of δ:

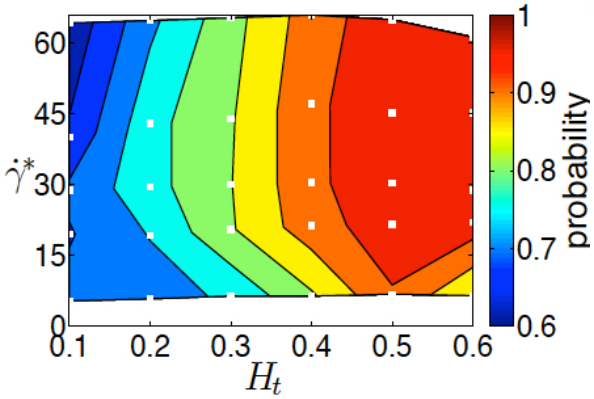
- RBC free layer, defined by the edge of RBC core
- δ = a fixed distance
- $\delta = D_p/2 + r$, a distance r between the wall and particle surface

Müller et al., *Sci. Rep.*, 4:4871, 2014

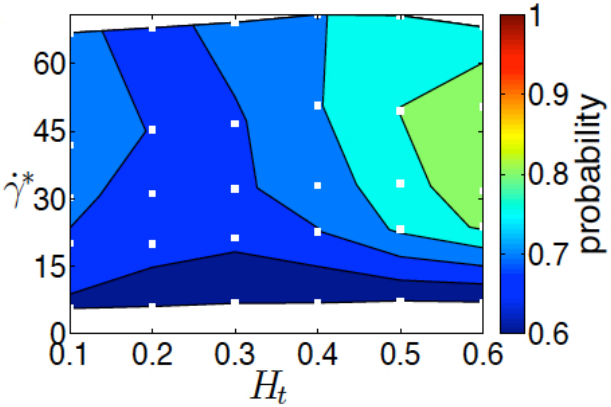
Margination of particles with different sizes



$D_p = 0.3D_r$ (1.83 µm)



$D_p = 0.15D_r$ (0.91 µm)

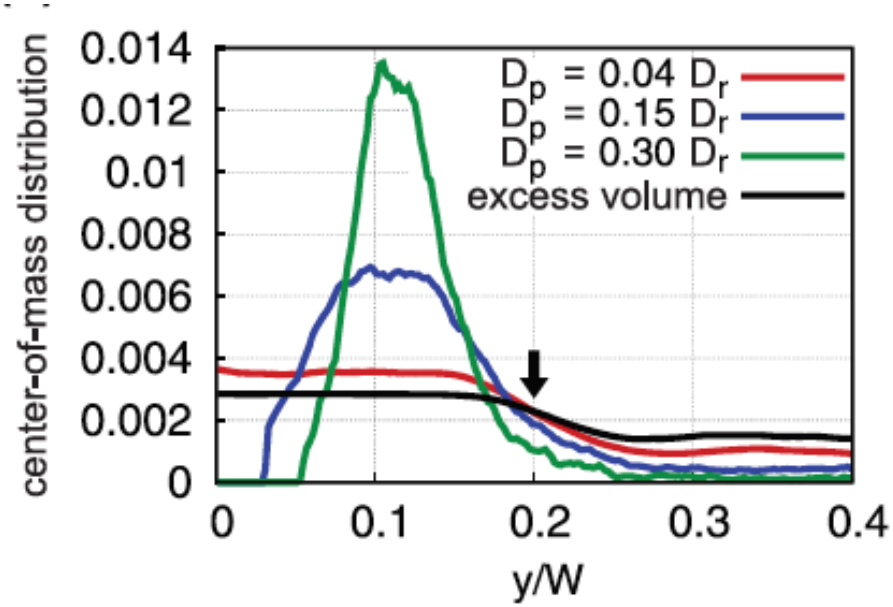


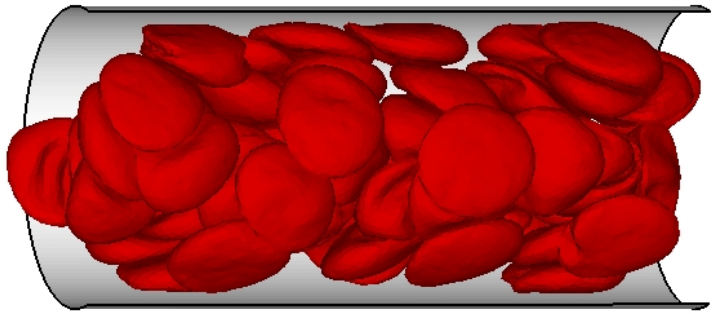
$D_p = 0.04D_r$ (0.25 µm)

- particle margination probability is based on the RBCFL thickness
- particle margination worsens as the particle becomes smaller
- margination of particles with a D_p smaller than about 200 nm can be described well by the distribution of blood plasma

Müller et al., *Sci. Rep.*, 4:4871, 2014

Distribution of small nano-particles



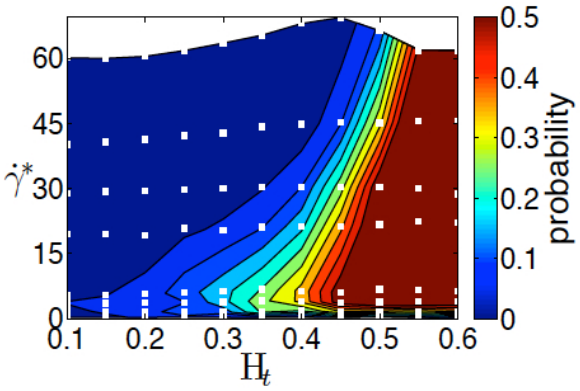


Margination of particles with a D_p smaller than about 200 nm can be described well by the distribution of blood plasma

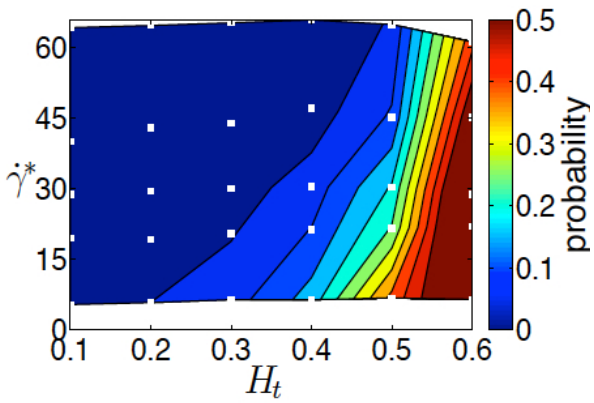
Müller et al., *Sci. Rep.*, 4:4871, 2014

Margination into the potential adhesion layer

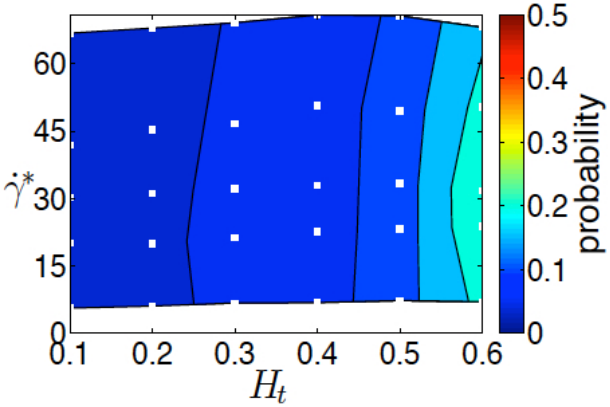
Potential adhesion layer ≈ 200 nm => $\delta = D_p/2 + 200$ nm



$D_p = 0.3D_r$ (1.83 µm)



$D_p = 0.15D_r$ (0.91 µm)



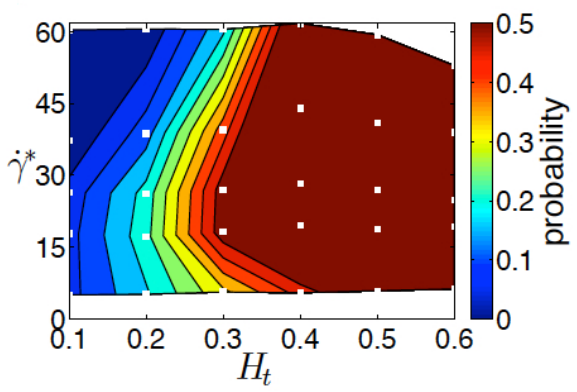
$D_p = 0.04D_r$ (0.25 µm)

Particle margination into the potential adhesion layer worsens as the particle becomes smaller

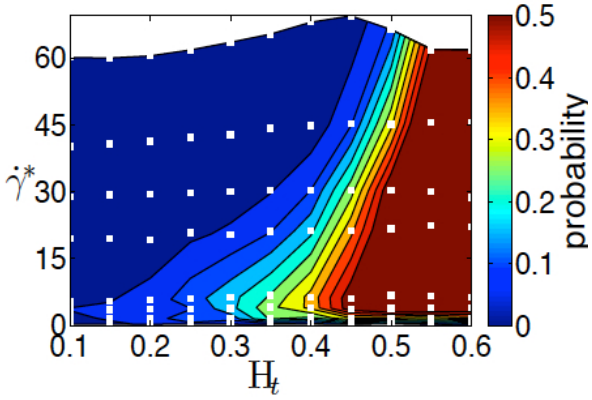
Müller et al., *Sci. Rep.*, 4:4871, 2014

Effect of vessel diameter on particle margination

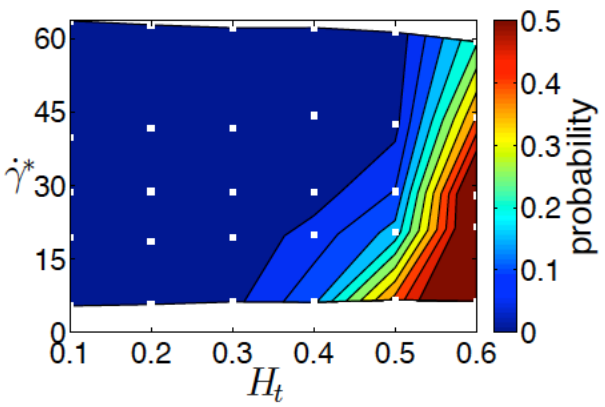
Potential adhesion layer ≈ 200 nm => $\delta = D_p/2 + 200$ nm



W = 10 µm



W = 20 µm

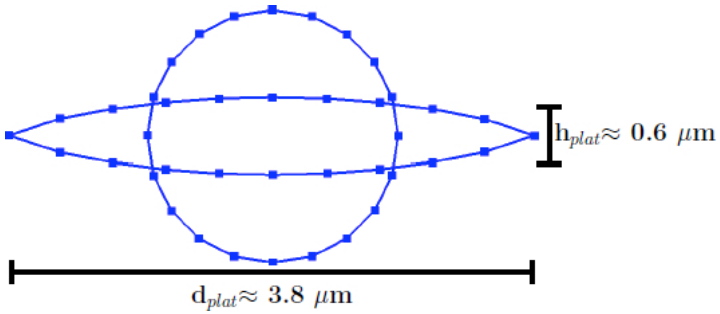


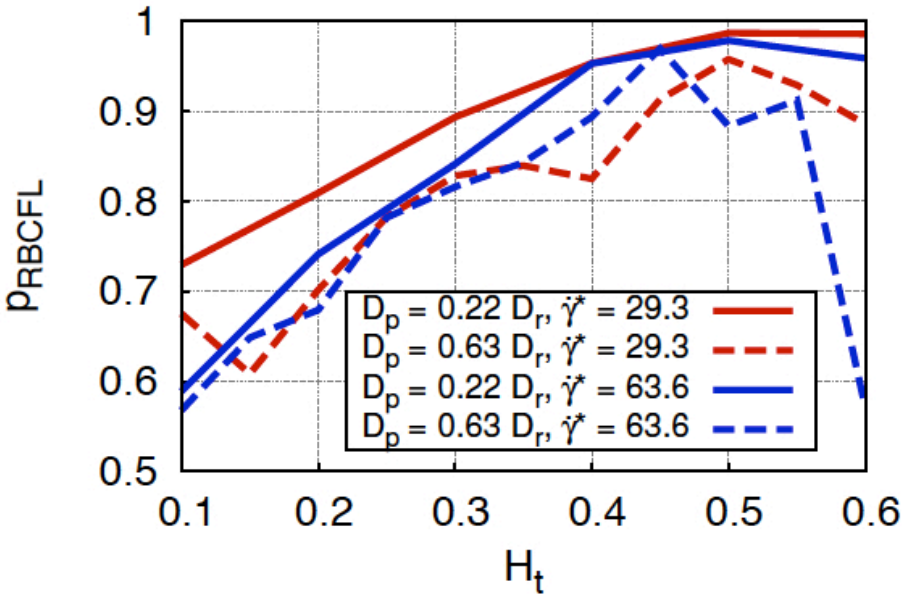
W = 40 µm

- particle margination into the potential adhesion layer with $\delta = D_p/2 + 200$ nm and for $D_p = 0.3D_r$ (1.83 µm)
- margination worsens as the vessel diameter is increased
- particle adhesion is mainly expected in small vessels

Müller et al., *Sci. Rep.*, 4:4871, 2014

Margination of particles with different shapes



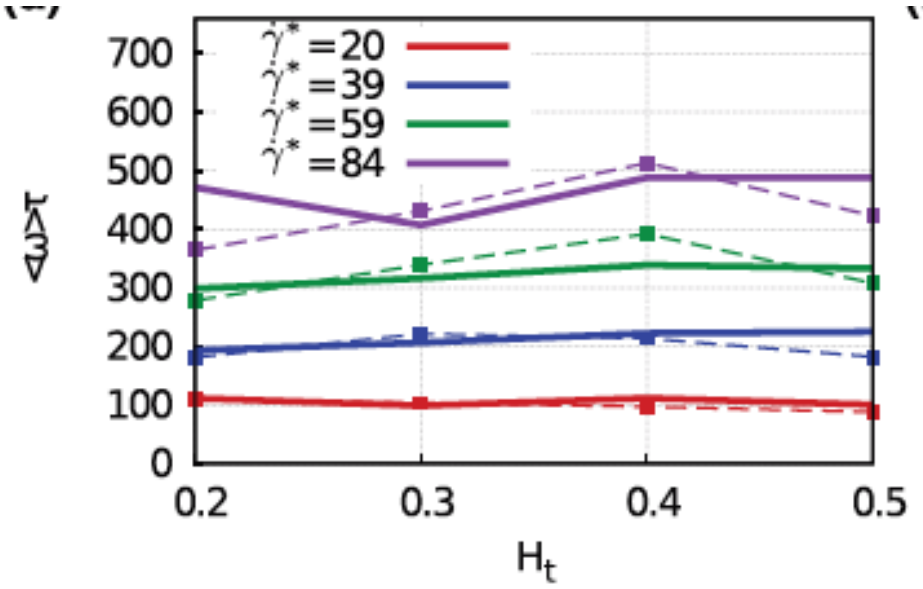


Ellipsoidal particles marginate slightly worse than spherical particles

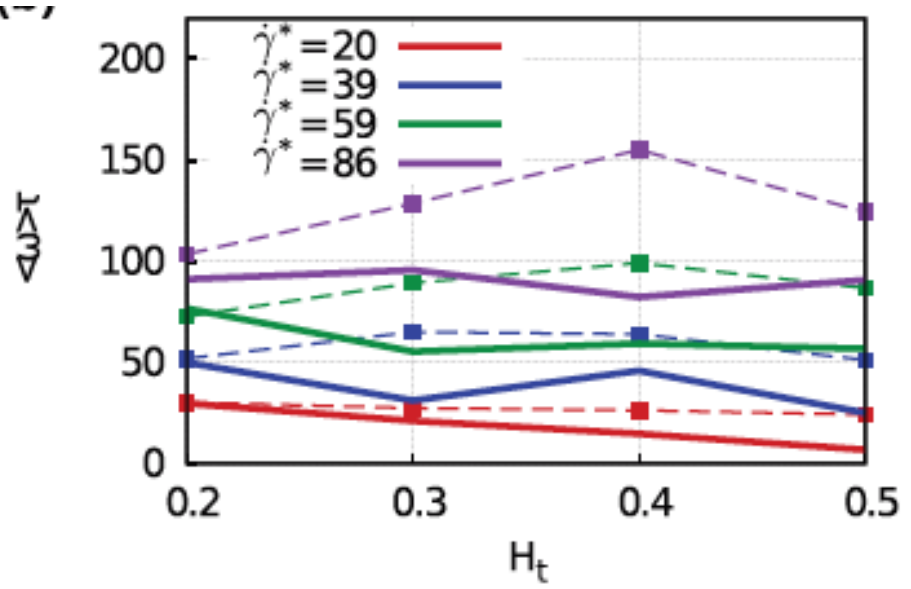
Müller et al., *Sci. Rep.*, 4:4871, 2014

Particle dynamics in the RBCFL

Sphere



Ellipsoid



Jeffery prediction in shear flow:

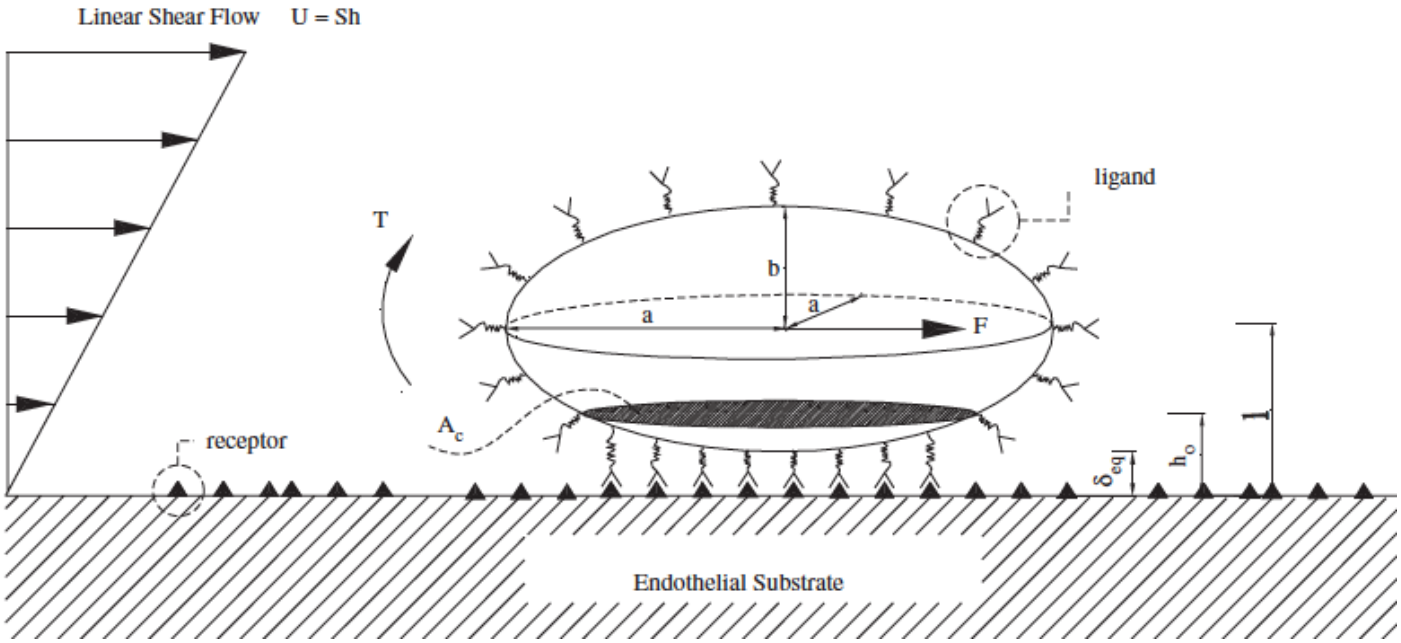
$$< \omega >= \frac{\dot{\gamma}}{r_e + 1/r_e}$$

Rotation (tumbling) of marginated ellipsoids within the RBCFL is slower than that of spheres leading to a longer interaction with a wall

Müller et al., *Sci. Rep.*, 4:4871, 2014

Particle adhesion

- Ellipsoidal particles adhere stronger than the spherical ones due to a larger area for particle-wall interaction
- Ellipsoidal particles rotate slower within the RBCFL
- Drag force on an adhered ellipsoidal particle appears to be smaller than on a spherical one having the same volume

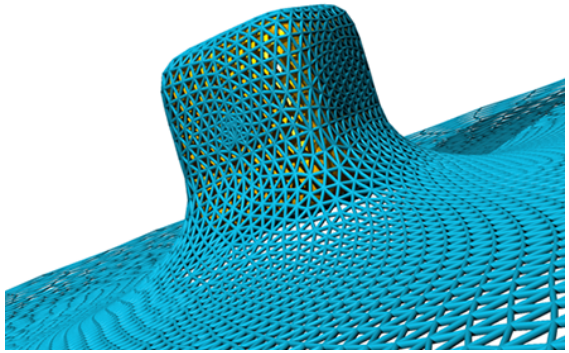


Decuzzi & Ferrari, *Biomaterials*, 27:5307, 2006

“Best” particle properties?

From the point of view of particle margination in blood flow the best particles for drug delivery are micron size ellipsoidal particles rather than spherical nanometer size particles.

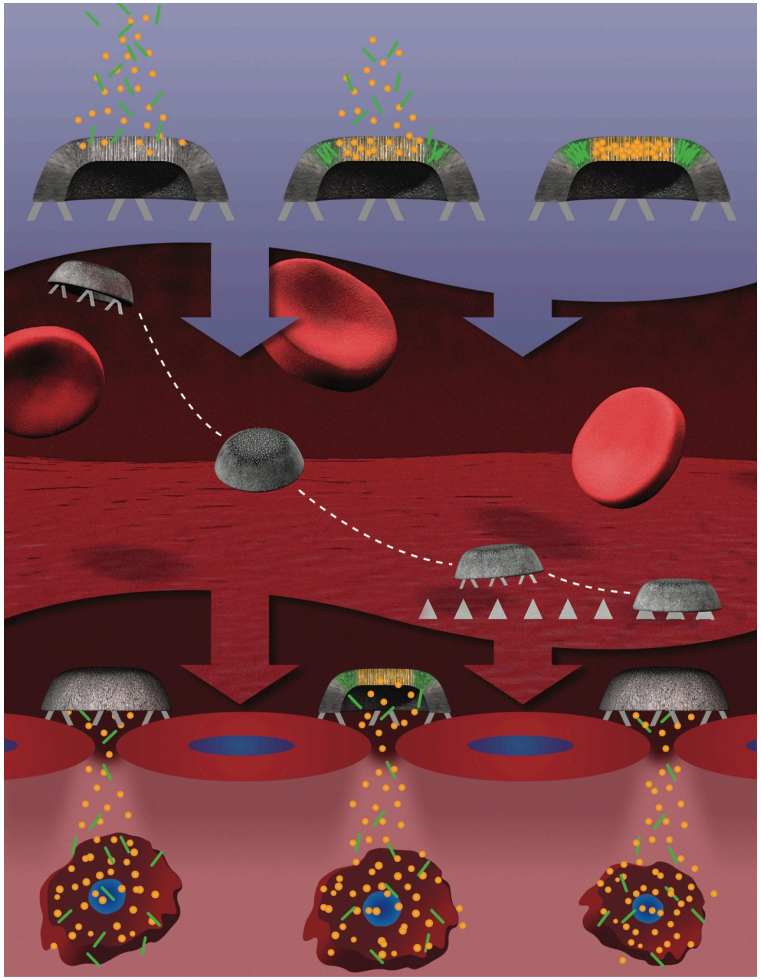
However, what particle properties are best for their transport through vascular walls and interstitial space, and their uptake by cells?



Dasgupta et al., *Nano Lett.*, 14:687, 2014

As a conclusion, we need to integrate the knowledge about particle performance at various drug delivery steps in order to decide on the optimal particle properties.

Multistage delivery systems



- May change their size at different stages of the drug delivery process
- Perform multiple tasks at different stages
- May include a number of different targets

Other ideas:

- active particles
- external forces
- ….

Martinez et al., *Chin. Sci. Bull.*, 57:3961, 2012

Summary and conclusions

- Larger particles (micron size) possess better margination properties than sub-micron particles
- Adhesion of drug carriers is mainly expected in small vessels
- Ellipsoidal particles are expected to adhere better due to slower rotational dynamics within the RBCFL and a larger area for adhesion
- From the vascular drug-delivery standpoint, ellipsoidal micron-size particles are likely to be advantageous for drug delivery
- However, an optimal strategy for drug delivery requires integration of the knowledge about particle performance at different delivery stages

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SEVENTH FRAMEWORK PROGRAMME

Jülich Supercomputing Centre (JSC)