

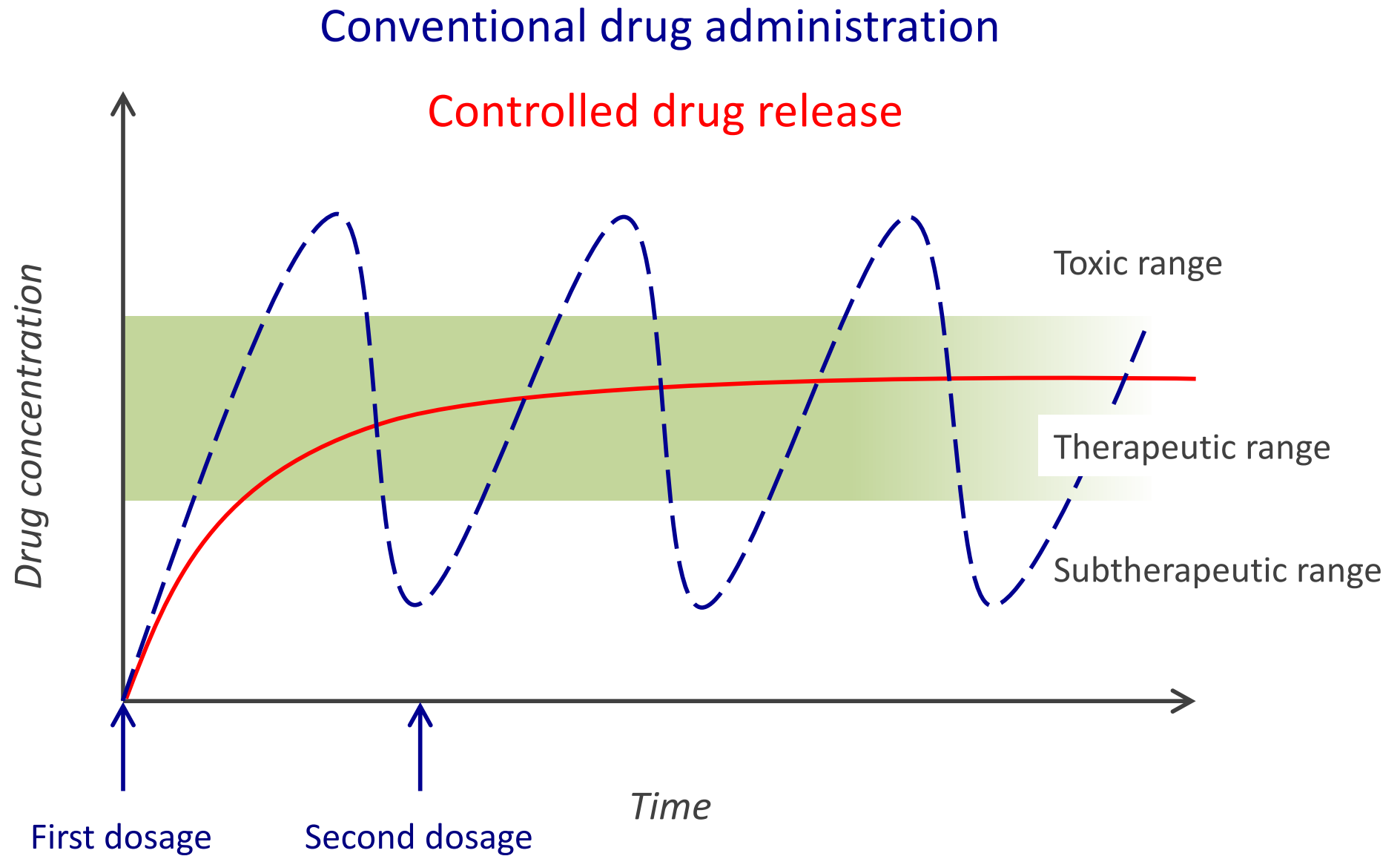


# Drug delivery in the bloodstream using particles: *A numerical study*

Badr Kaoui

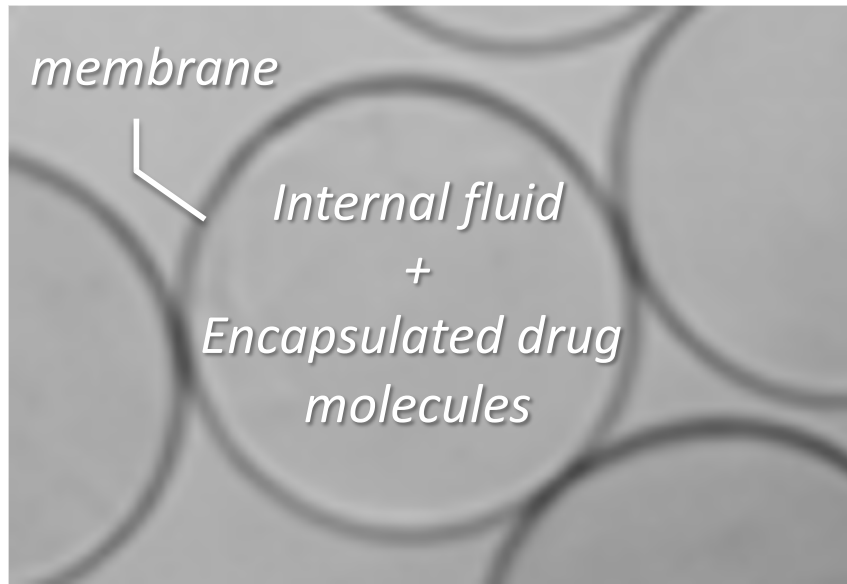
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CNRS and Université de Technologie de Compiègne  
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# Motivation: Drug delivery



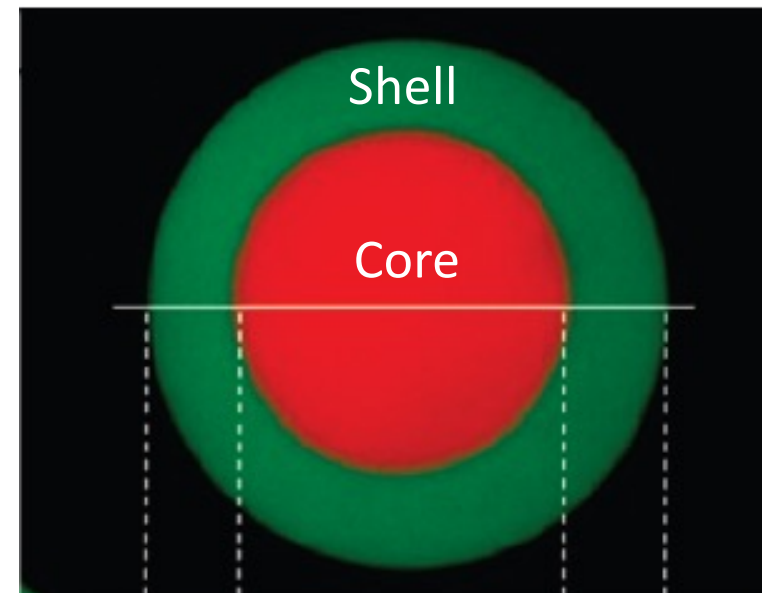
# Motivation: Drug-carrier micro-particles

## Fluid-filled deformable micro-particles



Capsules (closed polymeric gel membrane)

Liposomes (closed lipid membrane)



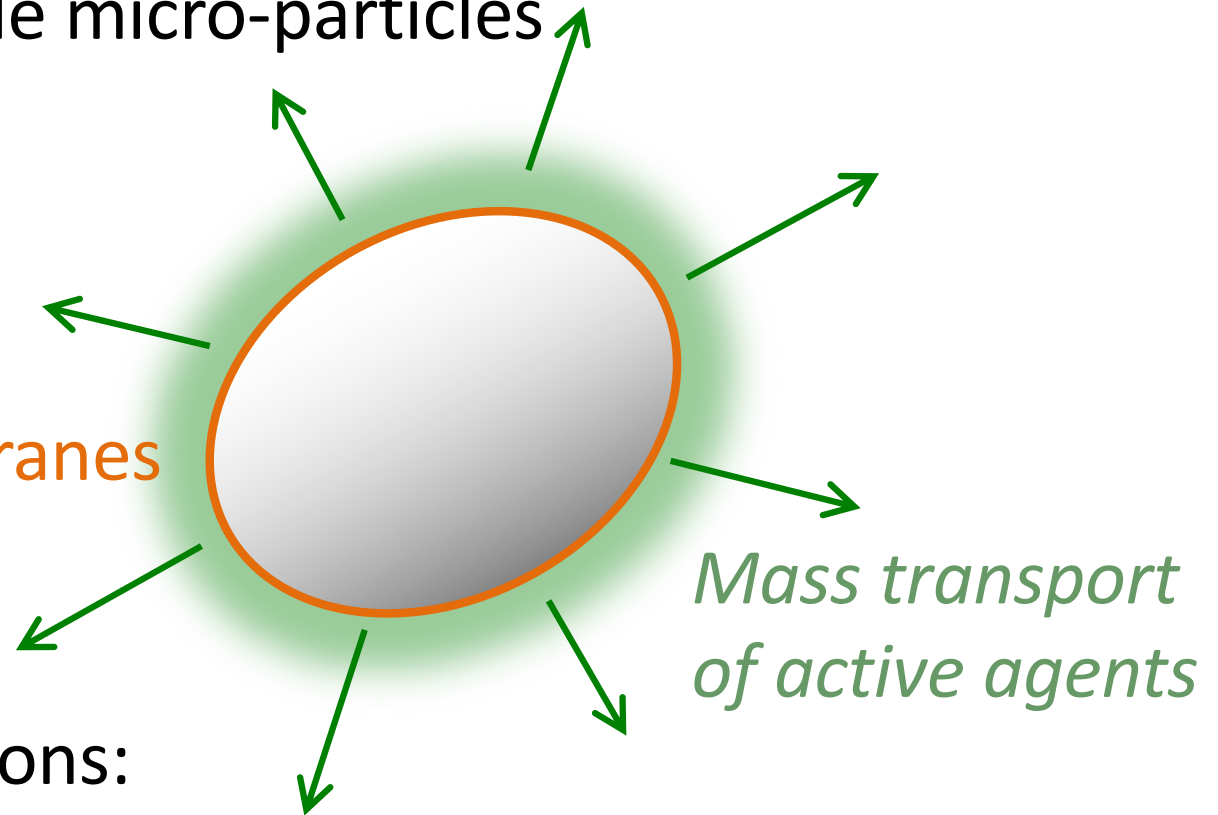
Core-shell reservoir

S. Seiffert *et al.*, J. Am. Chem. Soc. (2010)

# Motivation: Drug-carrier micro-particles

Fluid-filled deformable micro-particles

Closed lipid membranes

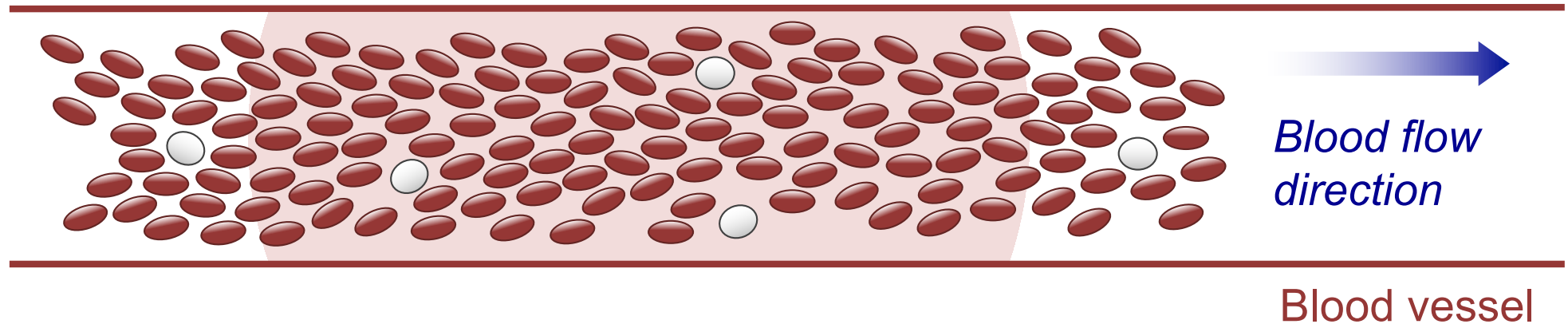


Biomedical applications:

- Targeted and controlled drug release from particles
- Contrast-agent release from liposomes for MRI
- Oxygen uptake and delivery by red blood cells
- B<sub>12</sub> vitamin uptake by particles in an artificial liver



# Problem statement



- Red blood cell
- Liposome / Capsule  
(a closed membrane)

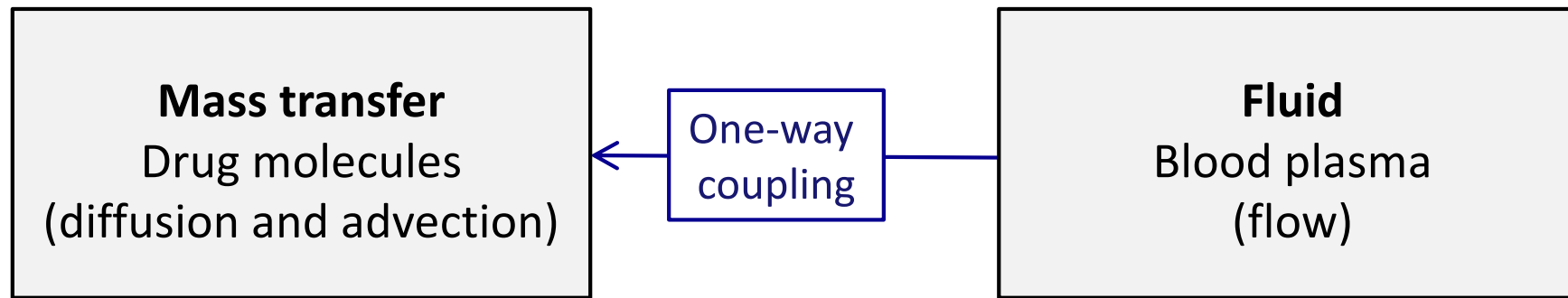
## 2D computer simulations

Multiphysics problem:

Biofluid mechanics + Fluid-structure interaction+ Transport phenomena

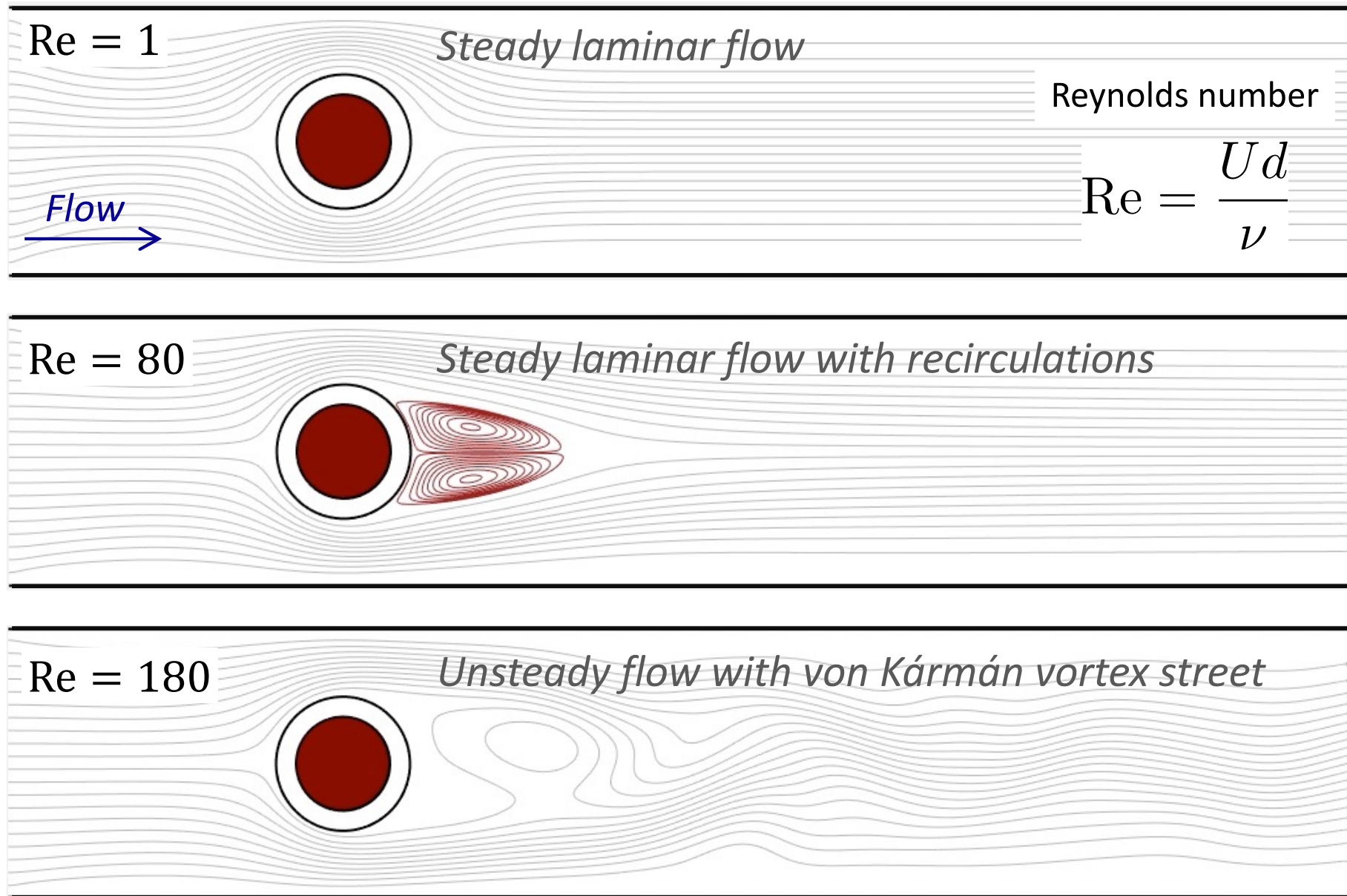
Polydisperse suspension

# 2D computer simulations: flow and mass transfer

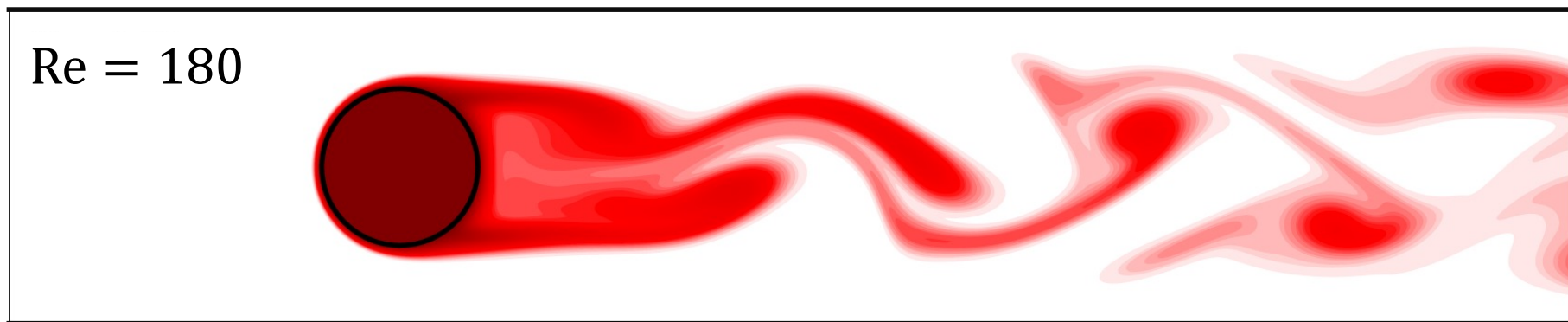
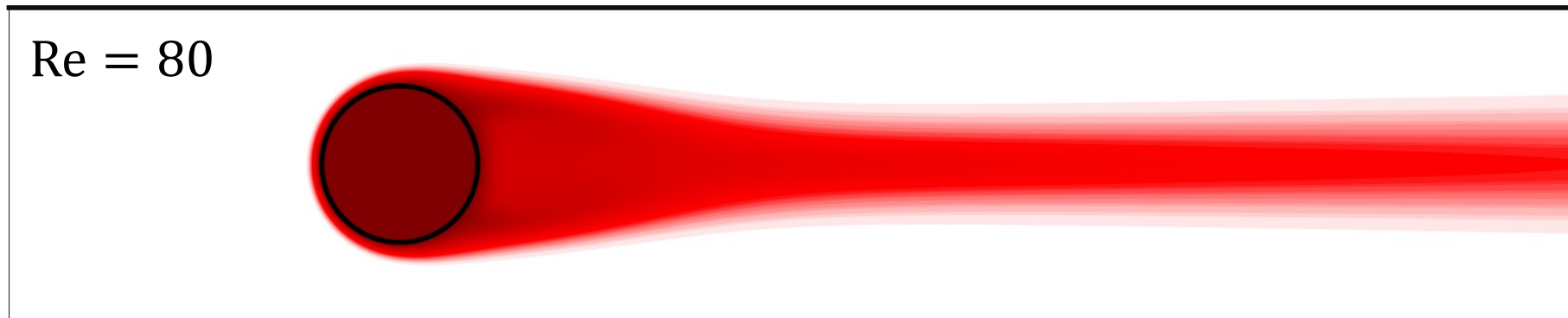
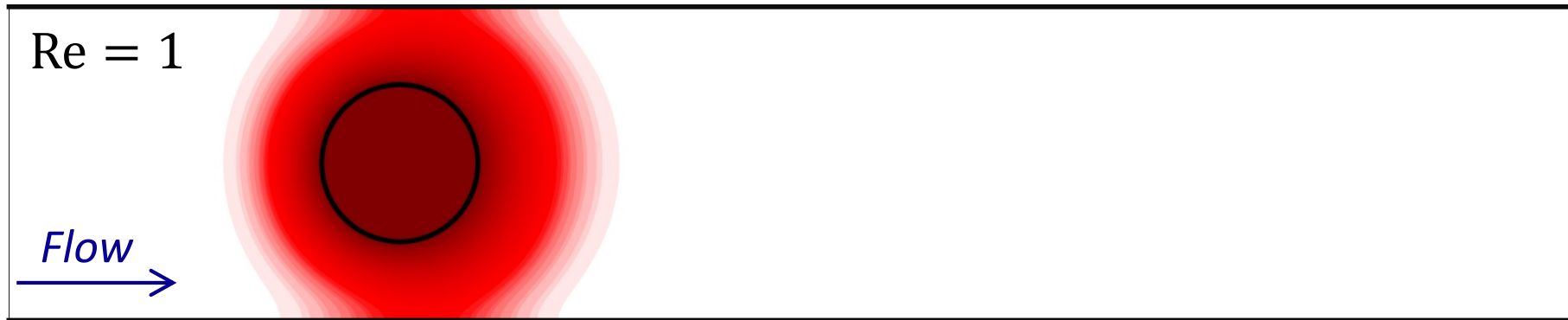


**Flow and mass transfer solver**  
Lattice-Boltzmann Method

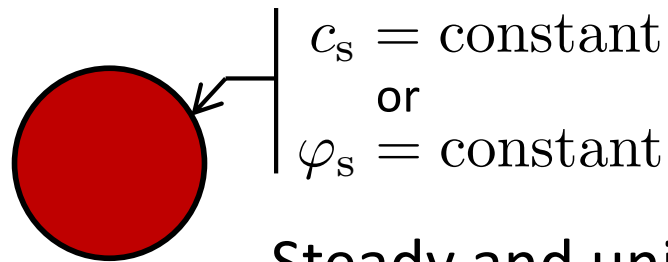
# Unsteady mass transfer from a core-shell cylinder



# Steady mass transfer from a simple cylinder



# Cylinders in crossflow: Classical studies



Steady and uniform boundary conditions

2 control parameters: Reynolds number      Schmidt number

$$\text{Re} = \frac{Ud}{\nu} \qquad \text{Sc} = \frac{\nu}{D_f}$$

Existing correlations for the Sherwood number:  $\text{Sh} = f(\text{Re}, \text{Sc})$

- Hilpert:**  $\text{Sh} = c\text{Re}^m \text{Sc}^n$ 

$$\text{Sh}(\theta, t) = 2 \frac{R}{D_f} h(\theta, t) \quad h(\theta, t) = -\frac{D_f}{c(R, \theta, t)} \left[ \frac{\partial c}{\partial r} \right]_{r=R}$$

Hilpert, Forschung auf dem Gebiet des Ingenieurwesens A (1933)

- Churchill-Bernstein:**

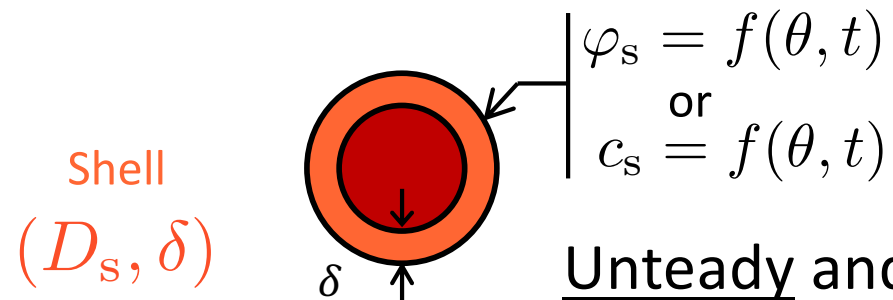
$$\text{Sh} = 0.3 + \frac{0.62\text{Re}^{1/2}\text{Sc}^{1/3}}{\left[1 + (0.4/\text{Sc})^{2/3}\right]^{1/4}} \left[1 + \left(\frac{\text{Re}}{282000}\right)^{5/8}\right]^{4/5}$$

Churchill & Bernstein, J. Heat Transfer. ASME (1977)

$\text{Sc Re} \geq 0.2$

# Cylinders in crossflow: Present study

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Unsteady and non-uniform boundary conditions

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3 control parameters:

Reynolds number

$$\text{Re} = \frac{Ud}{\nu}$$

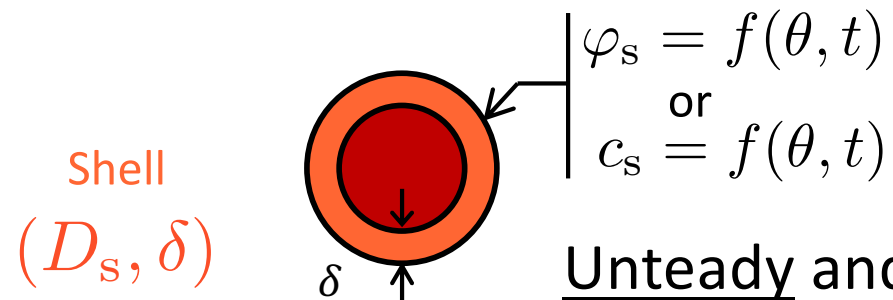
Schmidt number

$$\text{Sc} = \frac{\nu}{D_f}$$

Permeability

$$p = \frac{D_s}{\delta}$$

# Cylinders in crossflow: Present study



Unsteady and non-uniform boundary conditions

3 control parameters: Reynolds number      Schmidt number      Permeability

$$\text{Re} = \frac{Ud}{\nu}$$

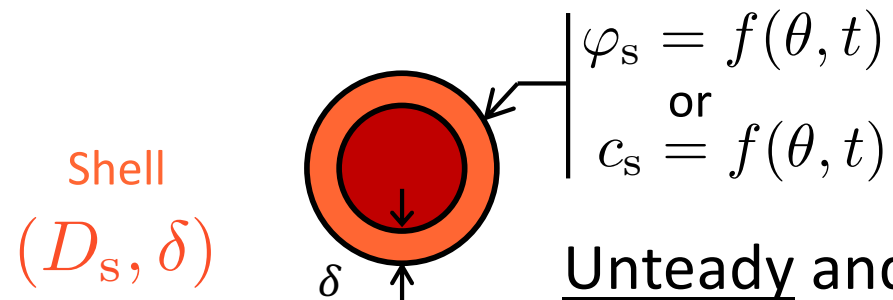
$$\text{Sc} = \frac{\nu}{D_f}$$

$$p = \frac{D_s}{\delta}$$

What is then the resulting correlation?

$$\text{Sh} = f(\text{Re}, \text{Sc}, P) \longleftarrow P = \frac{d}{D_f} p$$

# Cylinders in crossflow: Present study



Unsteady and non-uniform boundary conditions

3 control parameters: Reynolds number Schmidt number Permeability

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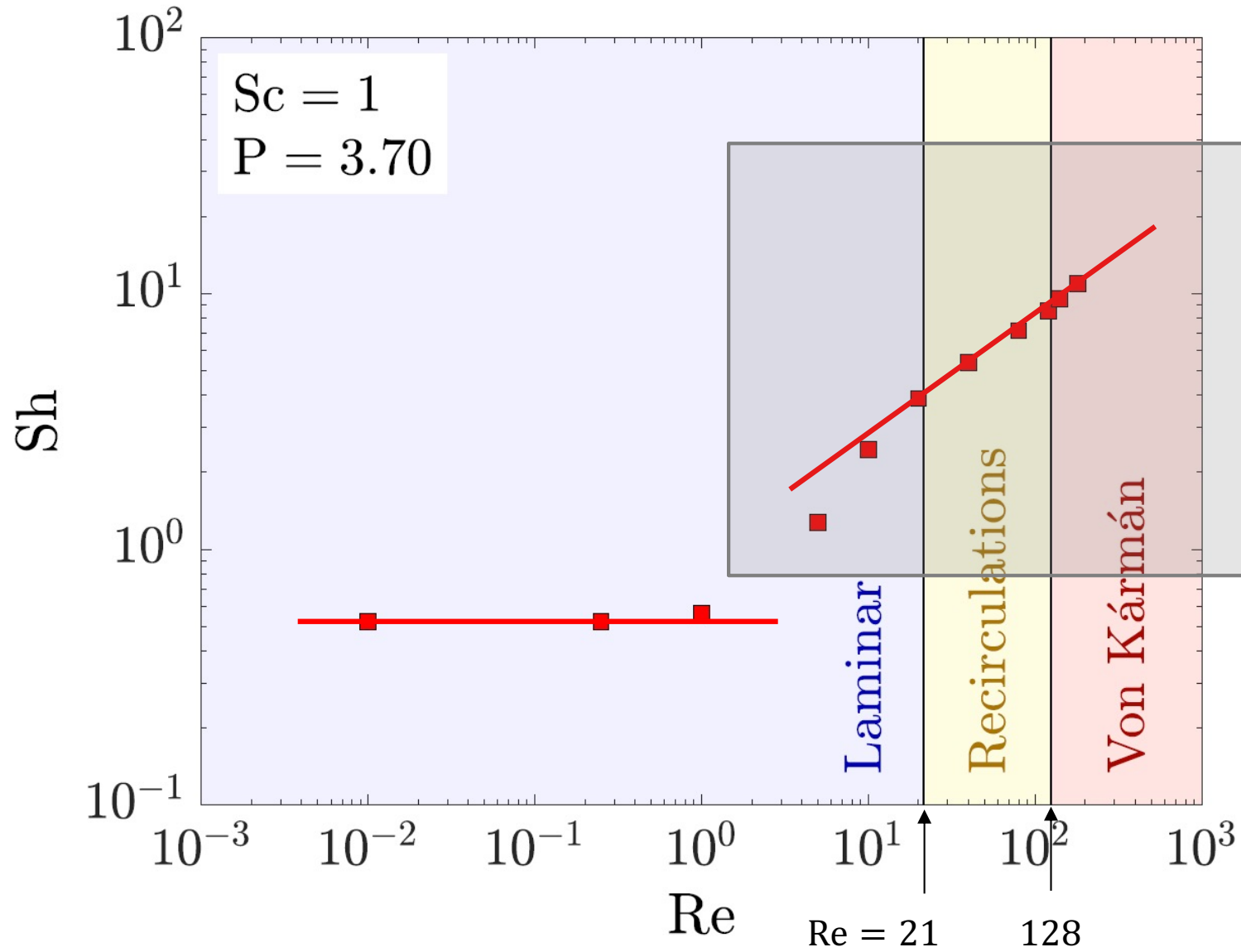
Clément Bielinski  
PhD Student



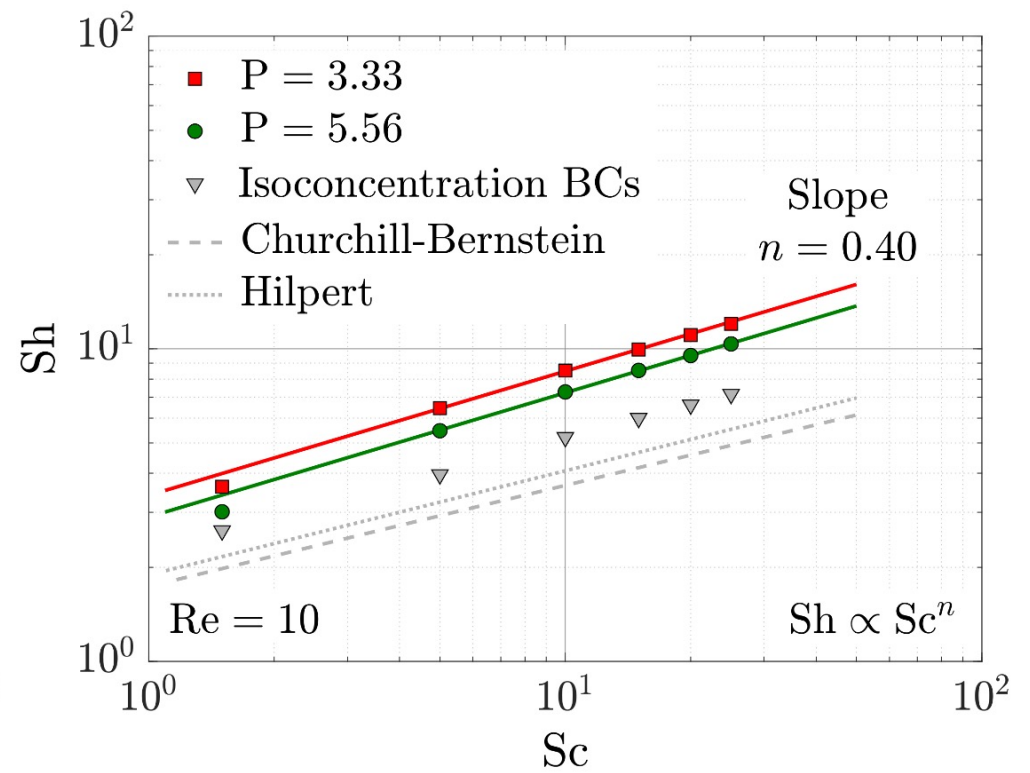
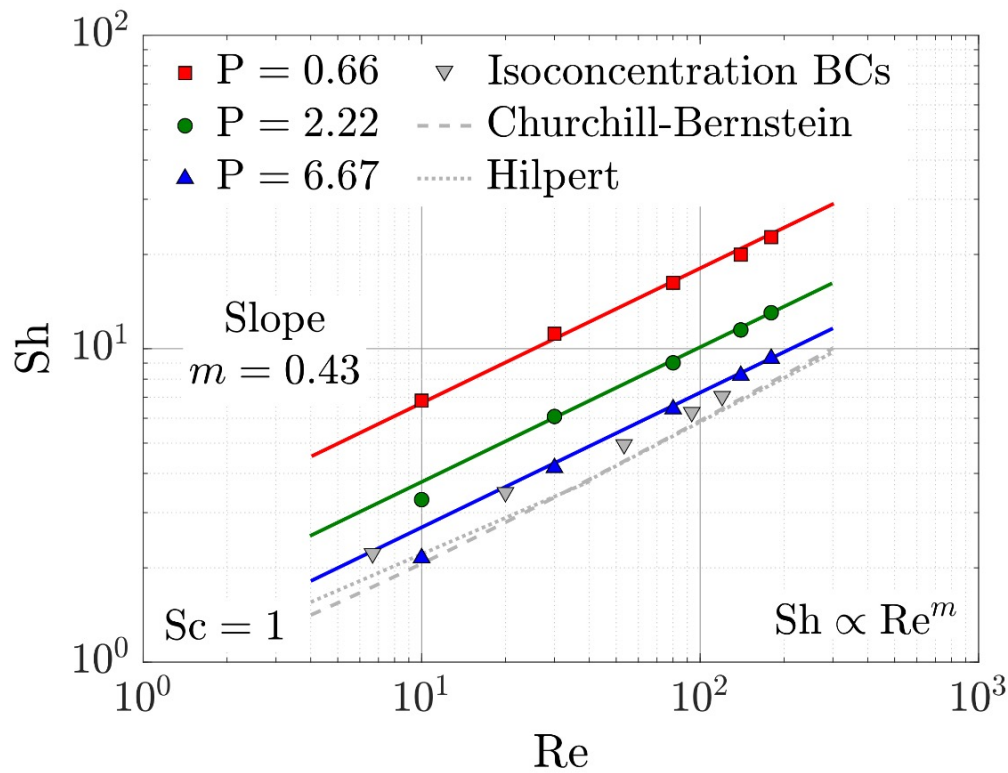
Nam Le  
MEng Student



# Sh vs Re: Impact of the flow regime

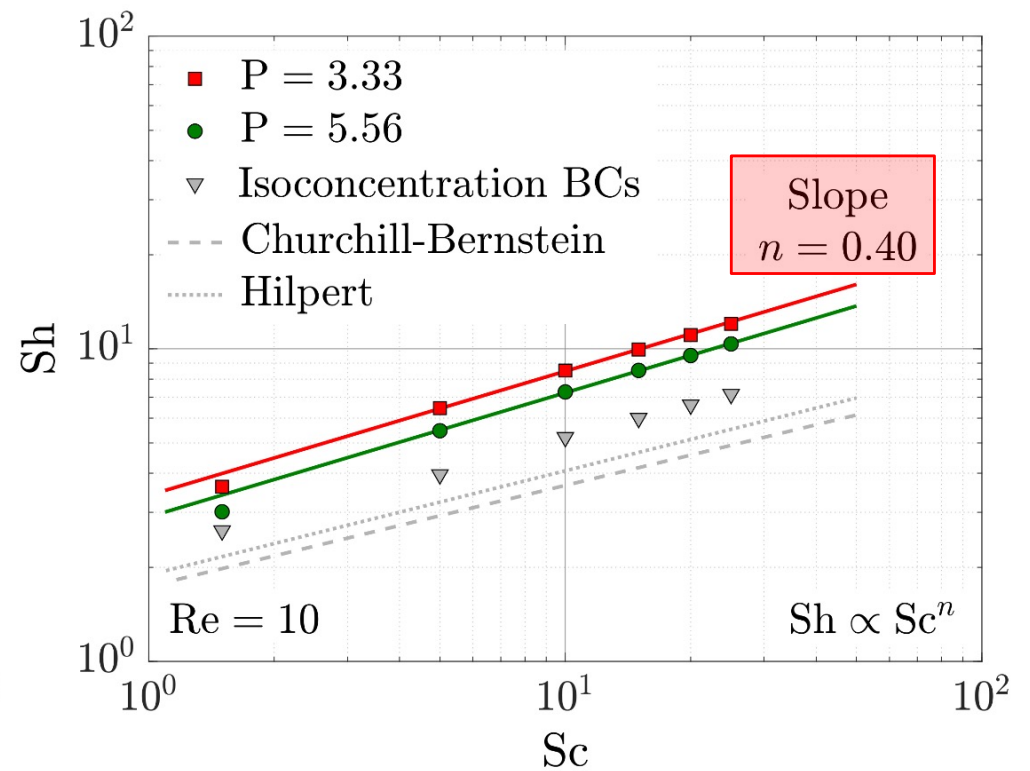
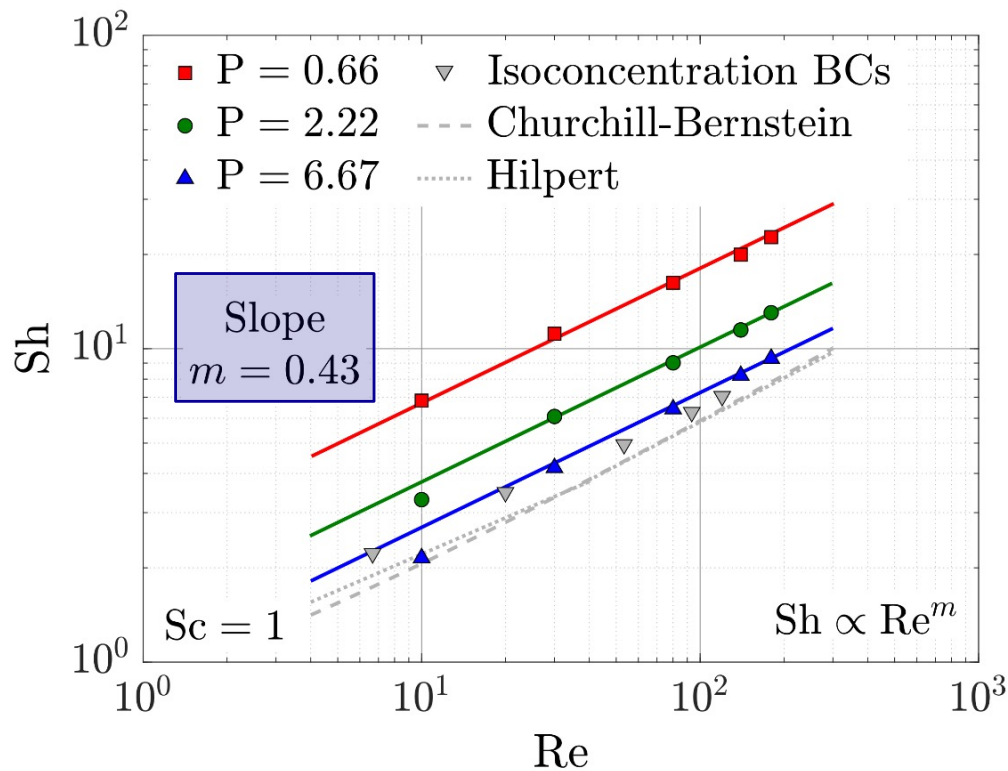


# 1st Step: Dependency of Sh on Re and Sc



The presence of the shell shifts Sh upwards to larger values

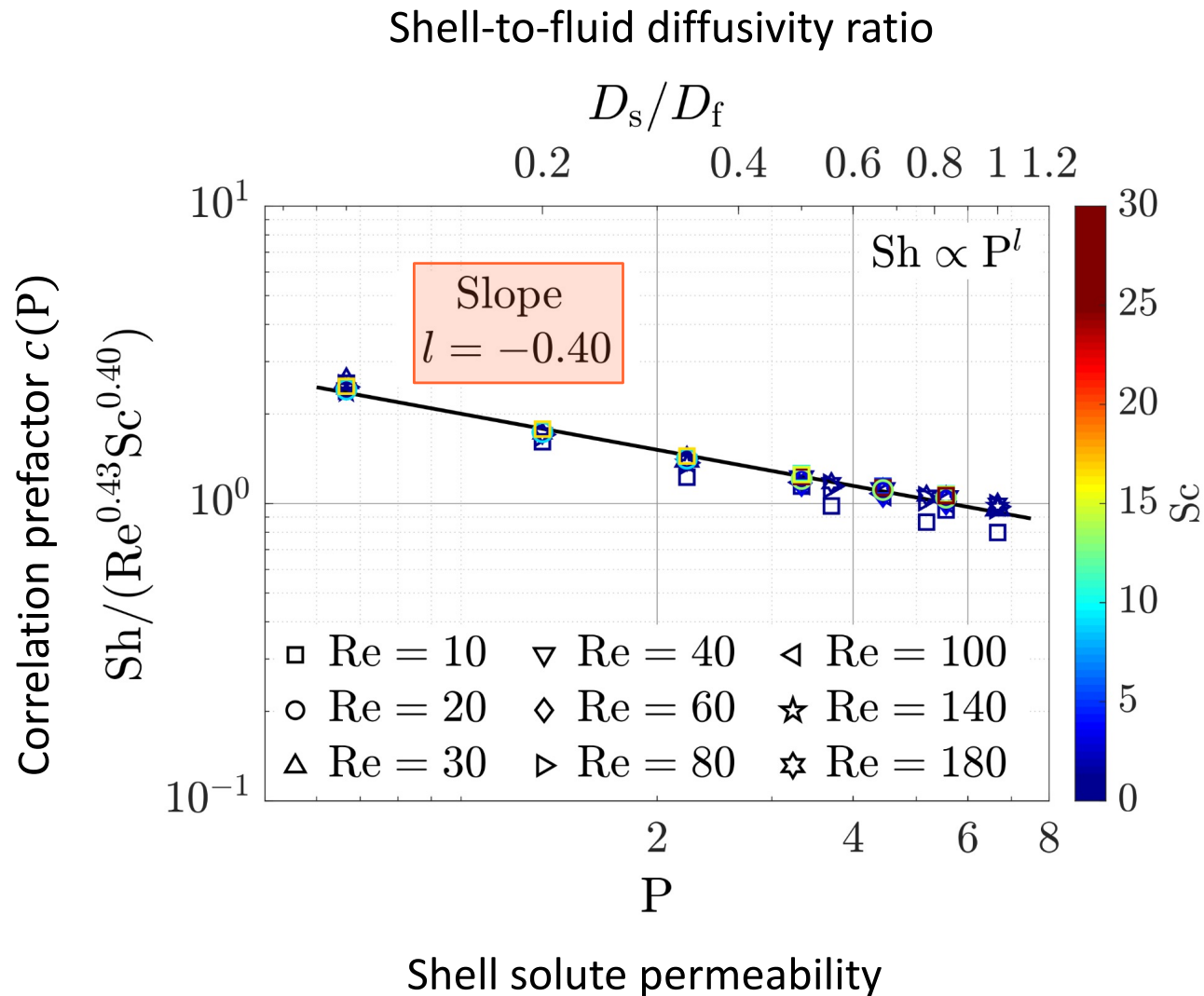
# 1st Step: Dependency of Sh on Re and Sc



Linear fit to extract the Reynolds and Schmidt exponents

$$Sh = c(P) Re^{0.43} Sc^{0.40}$$

## 2<sup>nd</sup> Step: Sh correlation as a function of P



$$Sh = 1.99 P^{-0.40} Re^{0.43} Sc^{0.40}$$

# Conclusions of the 1<sup>st</sup> part

- Core-shell reservoirs involve unsteady and non-uniform concentration and mass flux at the cylinder surface, in contrast to classical studies,
- Decreasing the shell solute permeability shrinks the concentration boundary layer, and consequently increases the Sherwood number,
- A correlation for cylindrical core-shell reservoirs, highlighting the shell solute permeability, is proposed for the first time.

$$Sh = 1.99P^{-0.40}Re^{0.43}Sc^{0.40}$$

$$10 \leq Re \leq 180$$

$$1 \leq Sc \leq 25$$

$$0.66 \leq P \leq 6.67$$

$$B = 0.5$$

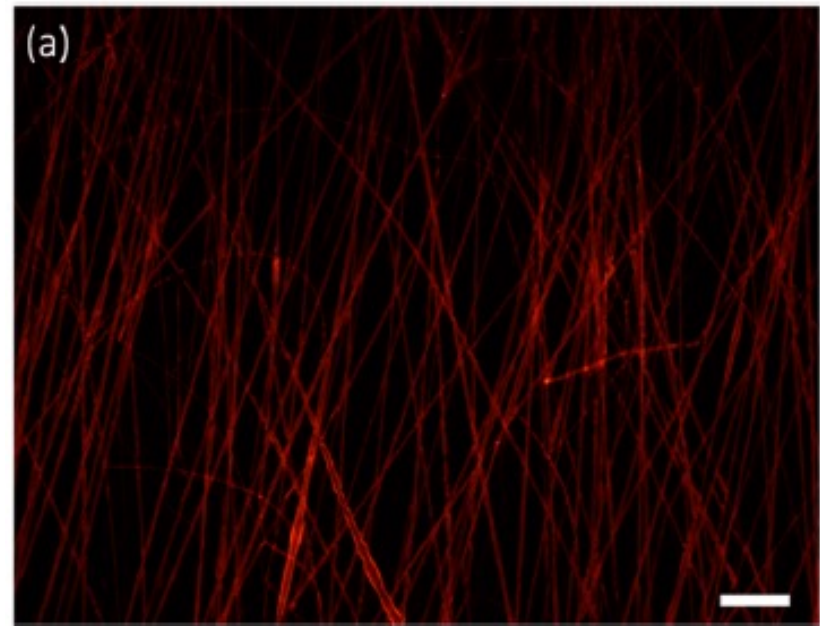
Blockage



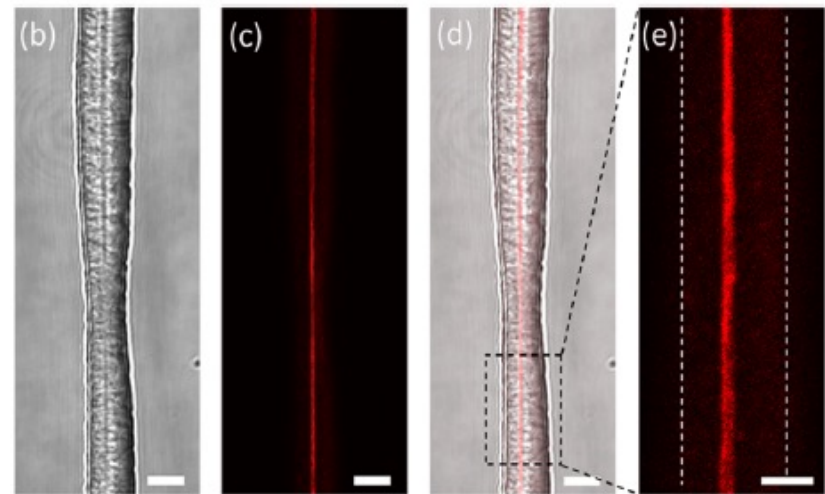
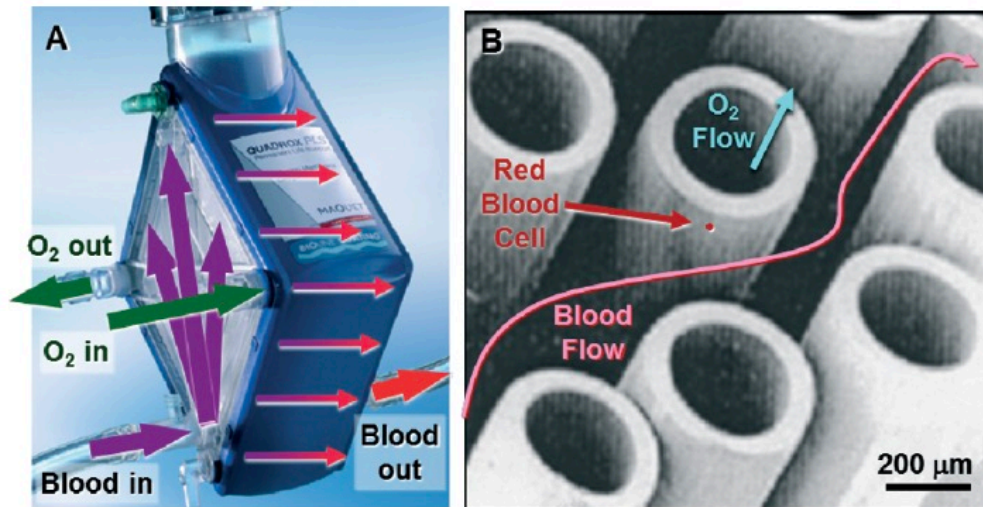
# Possible applications



## Core-shell electrospun fibers for controlled release



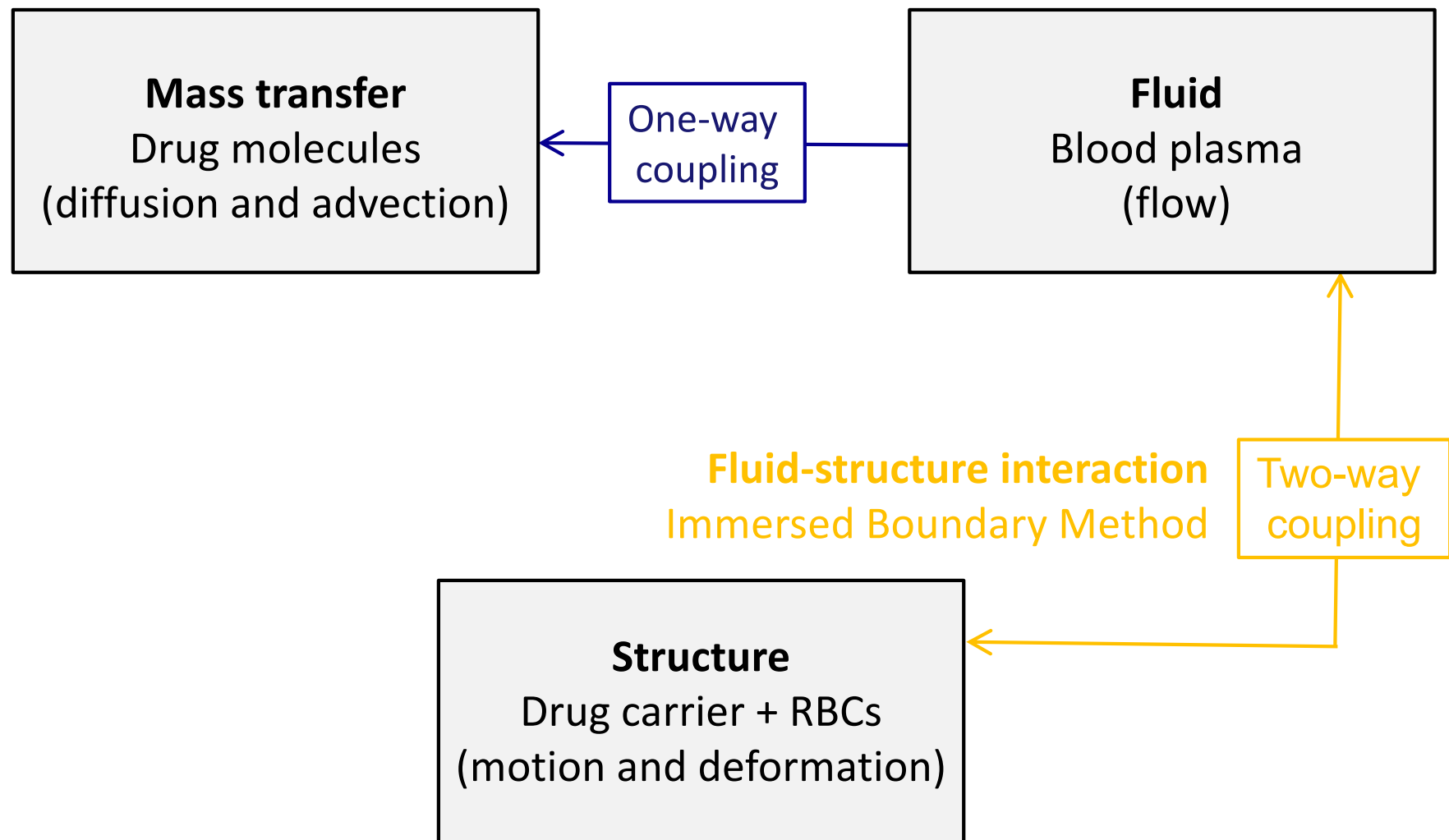
## Hollow-fiber artificial lung technology



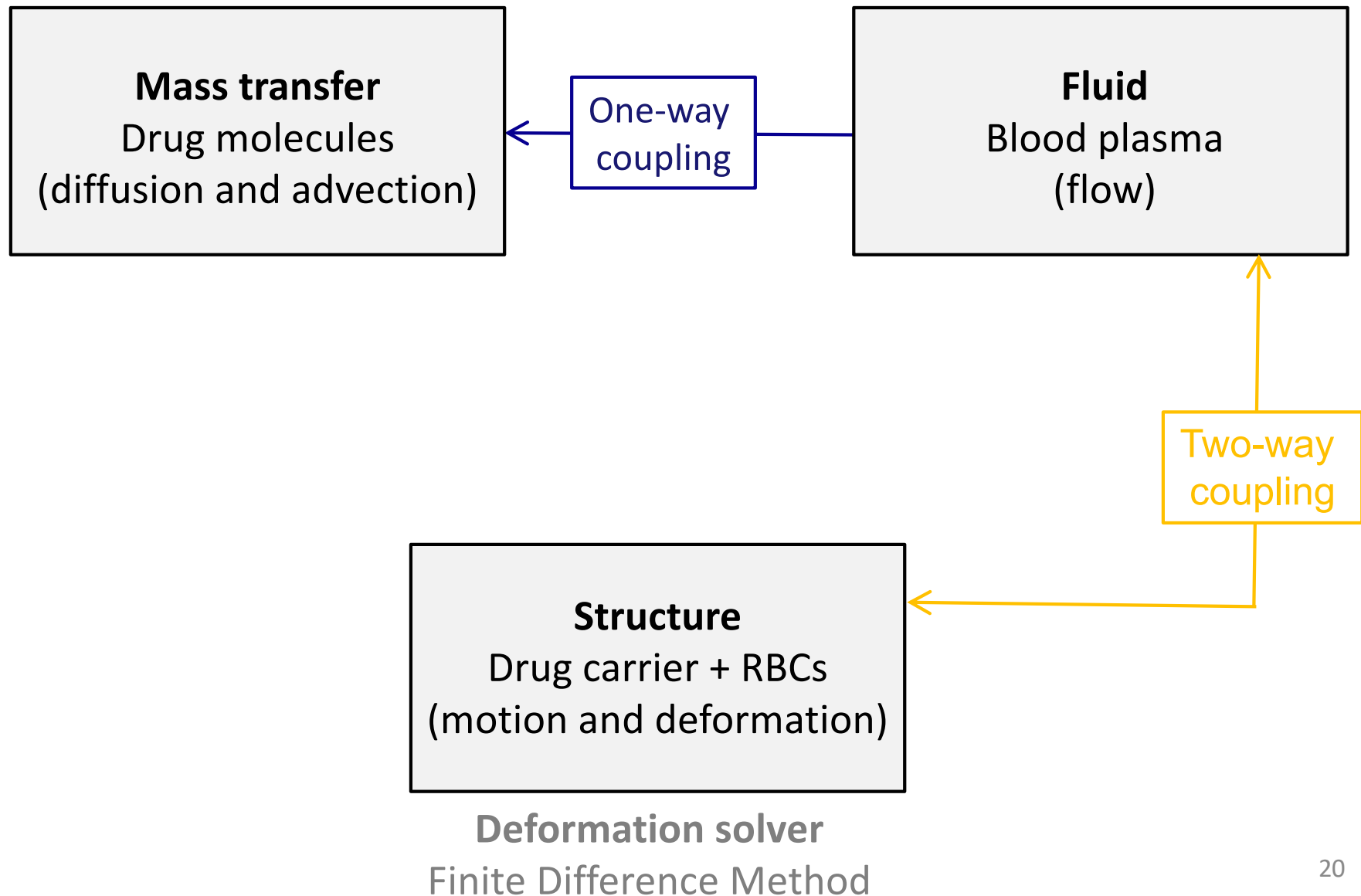
Potkay, Lab Chip 14, 4122 (2014)

L. Romano *et al.*,  
Mol. Pharmaceutics 13(3), 729 (2016)

# 2D computer simulations: FSI

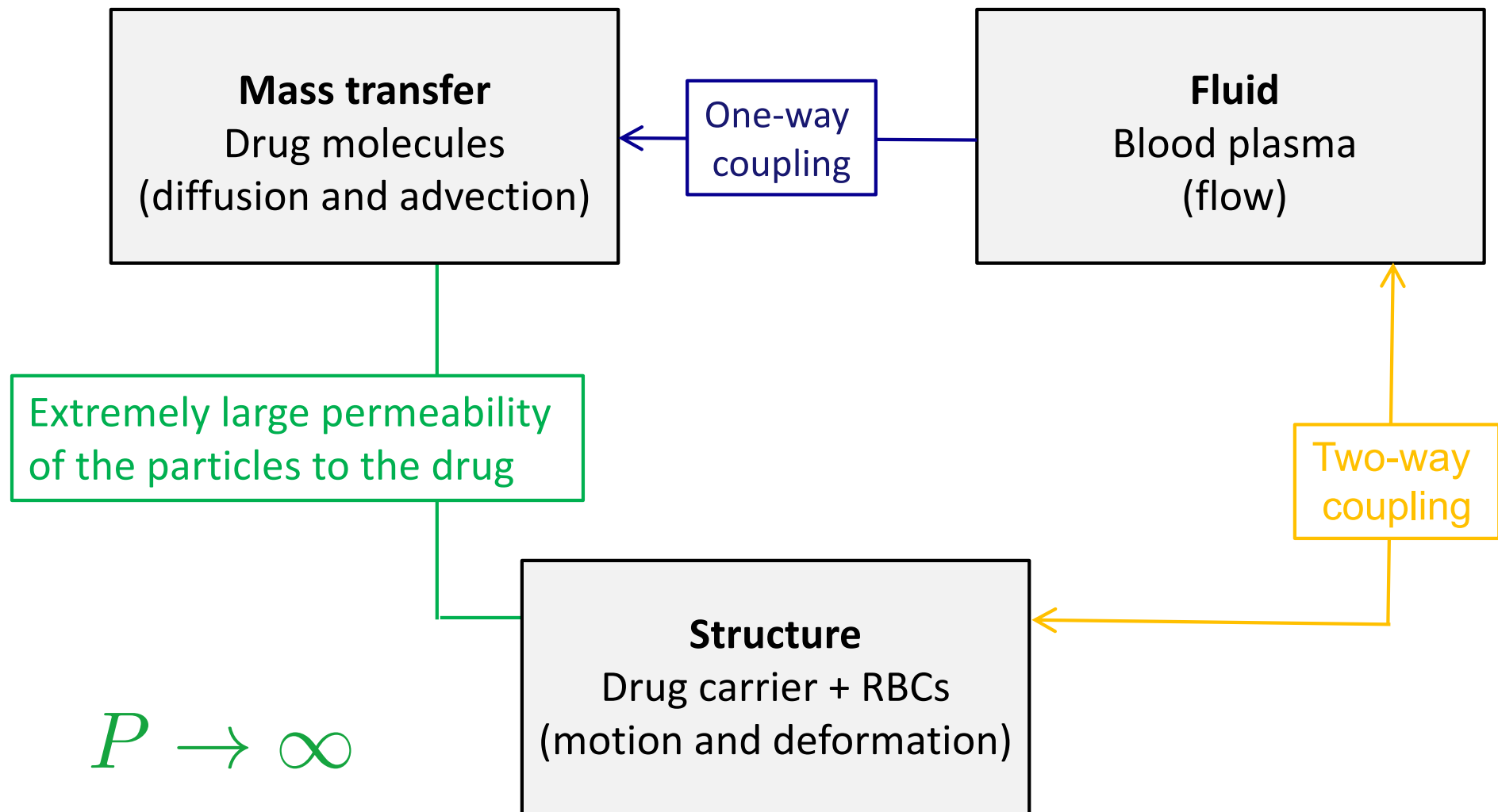


# 2D computer simulations: structure deformation





# 2D computer simulations: FSI + Mass transport

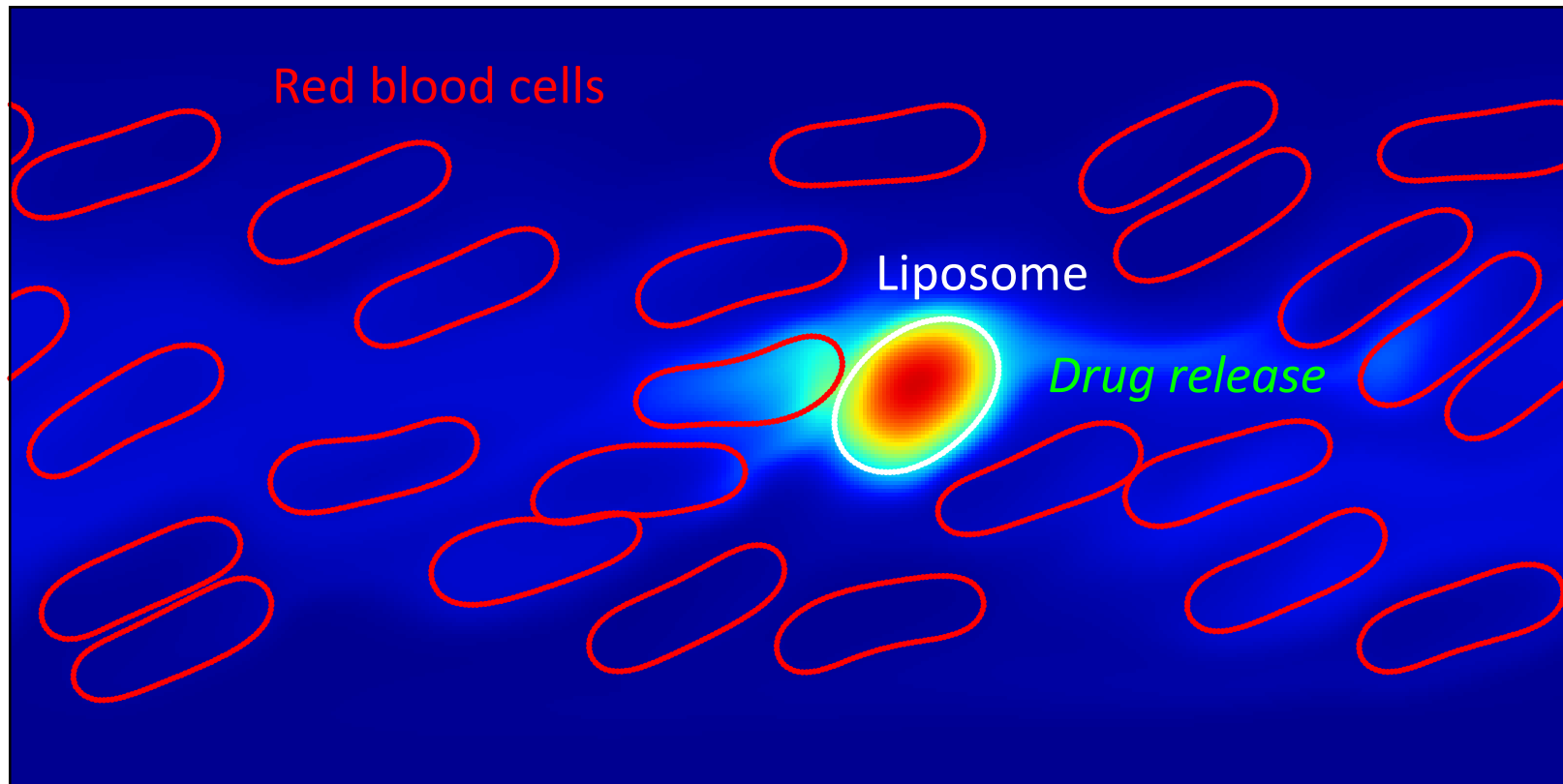


Continuity in the concentration and the mass flux at the boundaries

# Results: Drug molecules spatial distribution

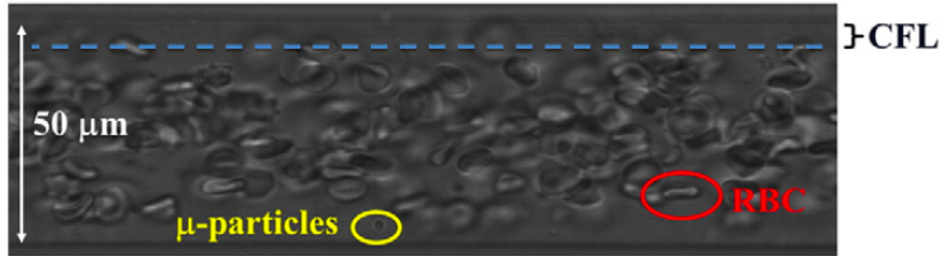
$$\text{Re} = 0.1 \quad \text{Sc} = 10^3 \quad N_p = 25 \quad \text{Ca} = \frac{\eta\gamma R^3}{E_B} = 1$$

Applied shear flow + Collective motion of particles = Complex flow



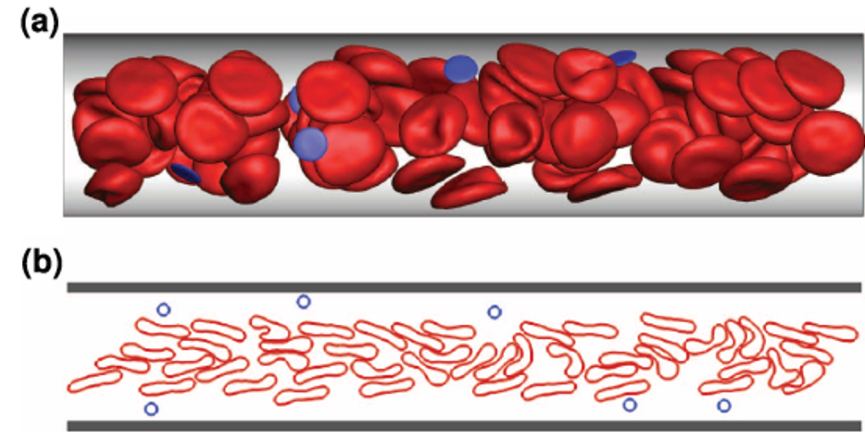
# Previous studies: Only margination effect

Only fluid-structure interaction,  
without mass transfer (i.e. no drug release and  
transport)



**Fig. 5.** Image of the flow of  $\mu$ -Ps and RBCs inside a 50- $\mu$ m microcapillary. The migration of RBCs towards the capillary center-line leaves a cell-free layer (CFL) of 6  $\mu$ m.

D'Apolito et al., Journal of Controlled Release 217 (2015)



**Figure 1 |** Snapshots of cell and particle conformations in microchannels in 3D and 2D. RBCs are colored in red and suspended particles in blue. (a) 3D simulation snapshot of blood flow for  $H_t = 0.3$  and  $\dot{\gamma}^* \approx 39$ . (b) 2D simulation snapshot of blood flow for  $H_t = 0.3$  and  $\dot{\gamma}^* \approx 29.3$ .

Mueller et al., Scientific Reports (2014)

# Previous studies: Only margination effect

Only fluid-structure interaction, without mass transfer (i.e. no drug release and transport)

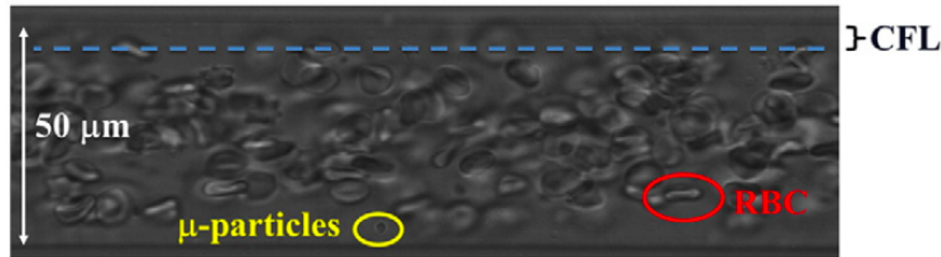


Fig. 5. Image of the flow of  $\mu$ -Ps and RBCs inside a 50- $\mu$ m microcapillary. The migration of RBCs towards the capillary center-line leaves a cell-free layer (CFL) of 6  $\mu$ m.

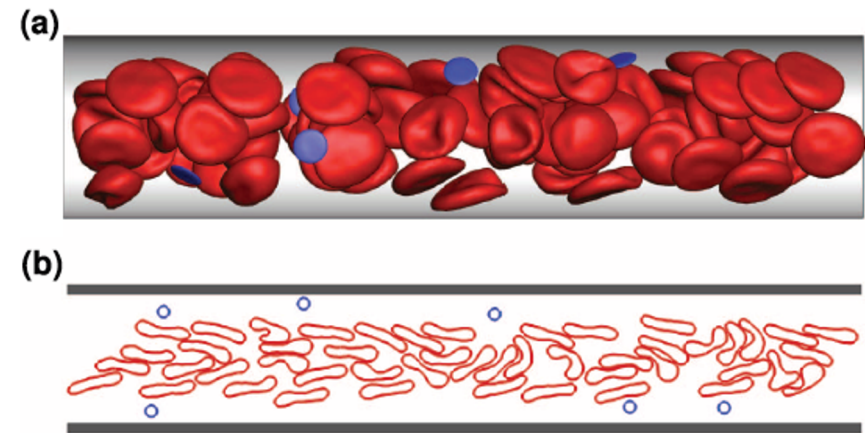
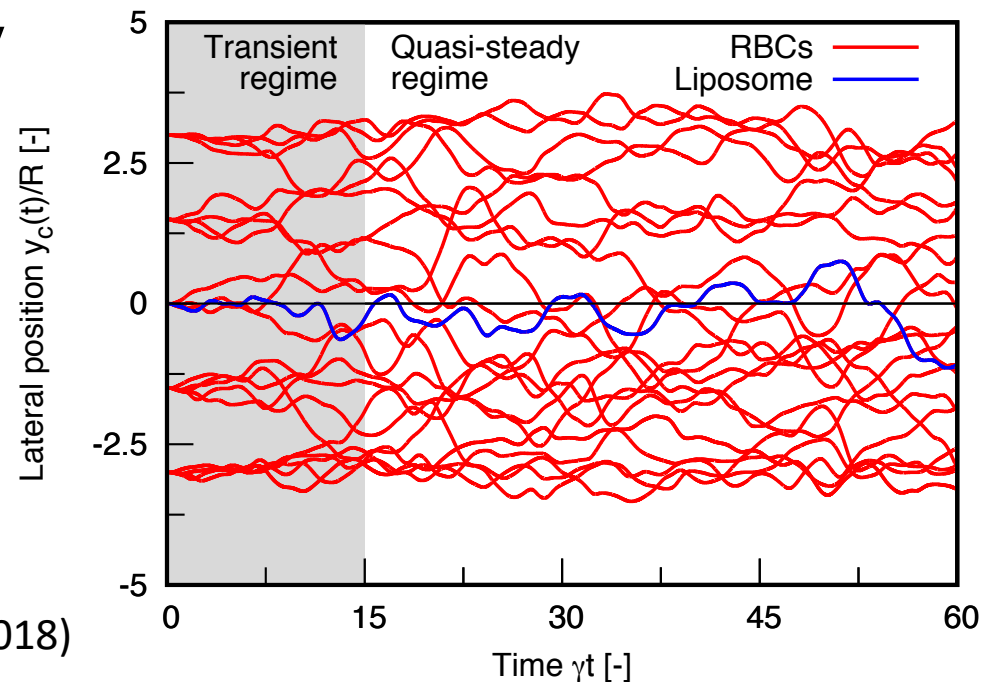


Figure 1 | Snapshots of cell and particle conformations in microchannels in 3D and 2D. RBCs are colored in red and suspended particles in blue. (a) 3D simulation snapshot of blood flow for  $H_t = 0.3$  and  $\dot{\gamma}^* \approx 39$ . (b) 2D simulation snapshot of blood flow for  $H_t = 0.3$  and  $\dot{\gamma}^* \approx 29.3$ .

D'Apolito et al., Journal of Controlled Release 217 (2015)

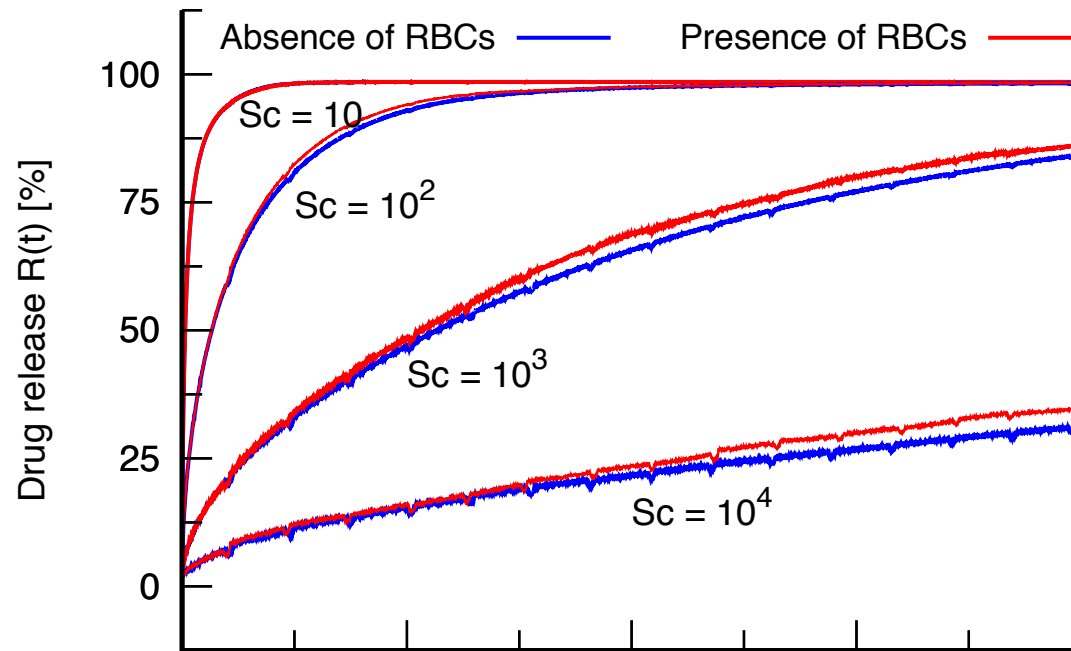
Mueller et al., Scientific Reports (2014)

# Present study



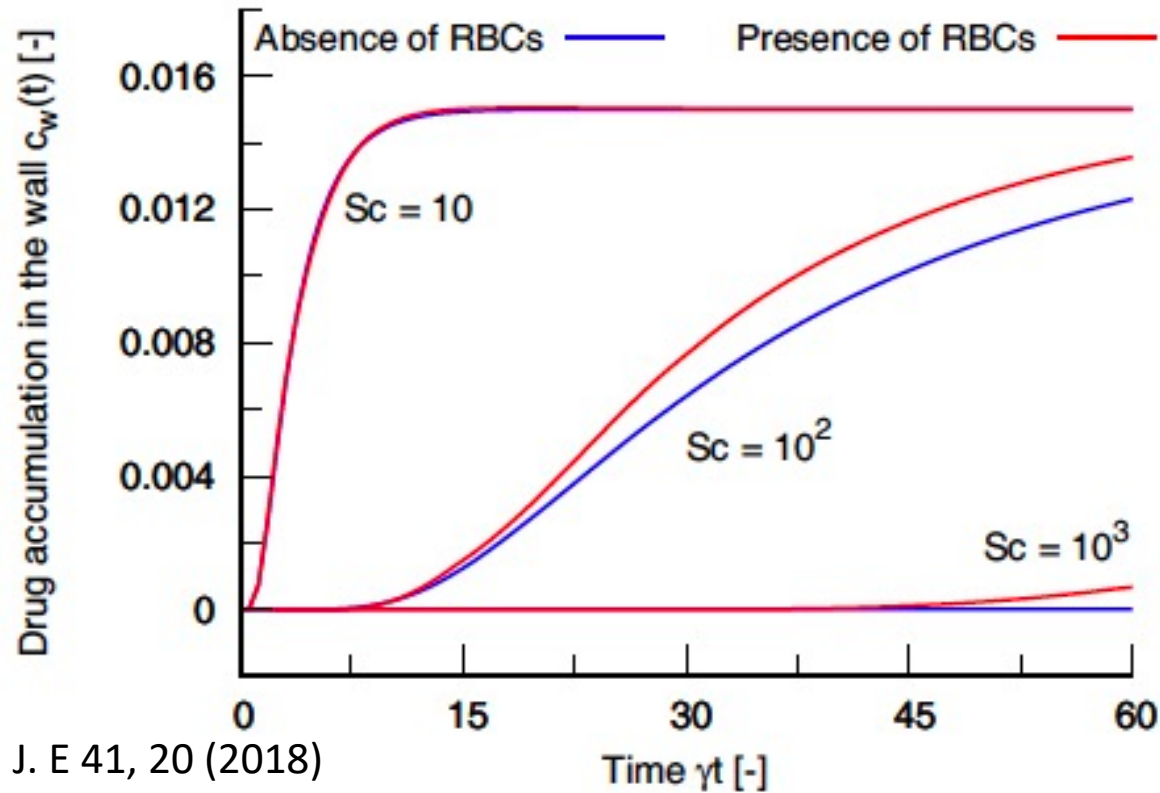
Kaoui, Eur. Phys. J. E 41, 20 (2018)

# Results

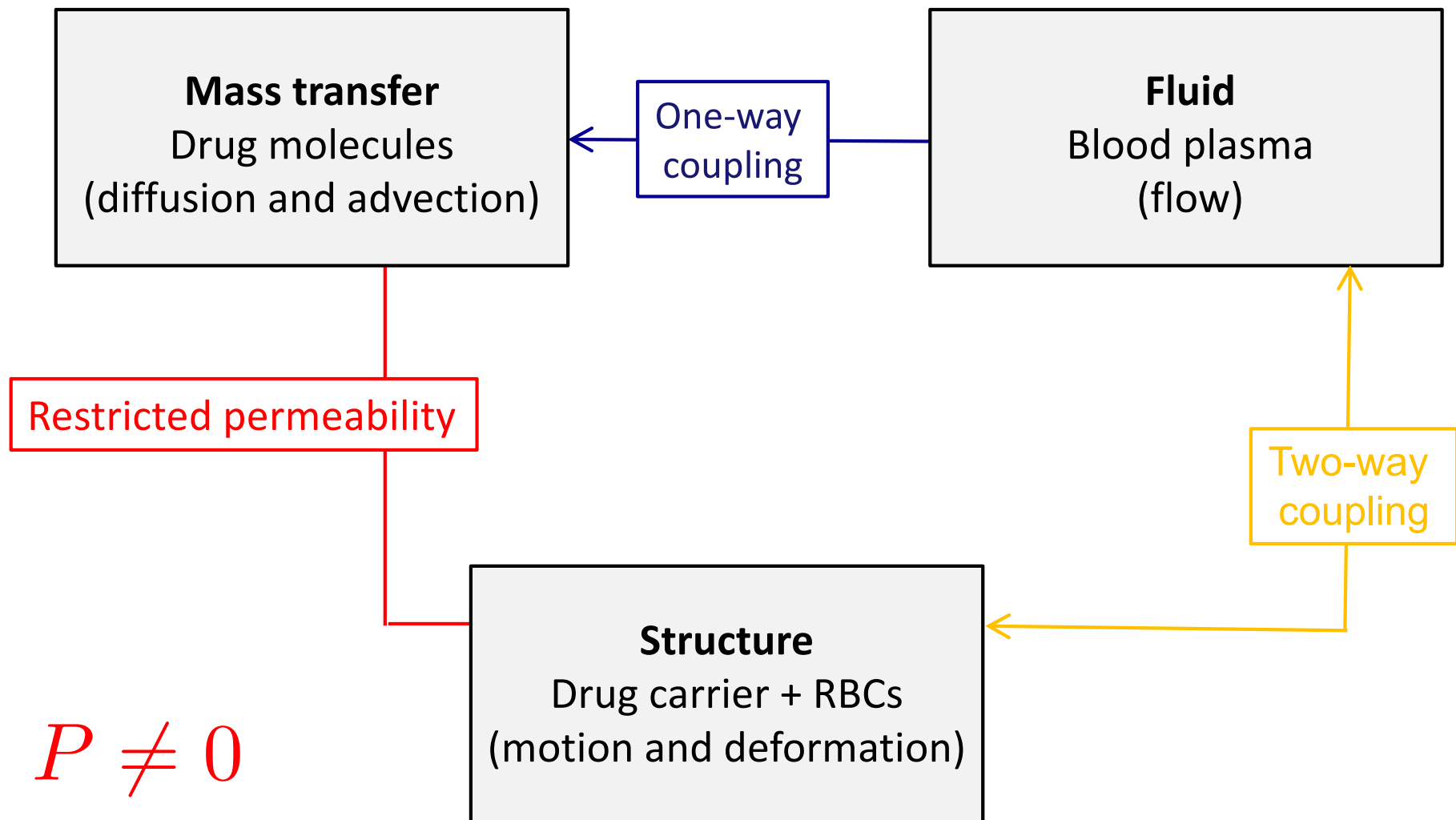


Schmidt number

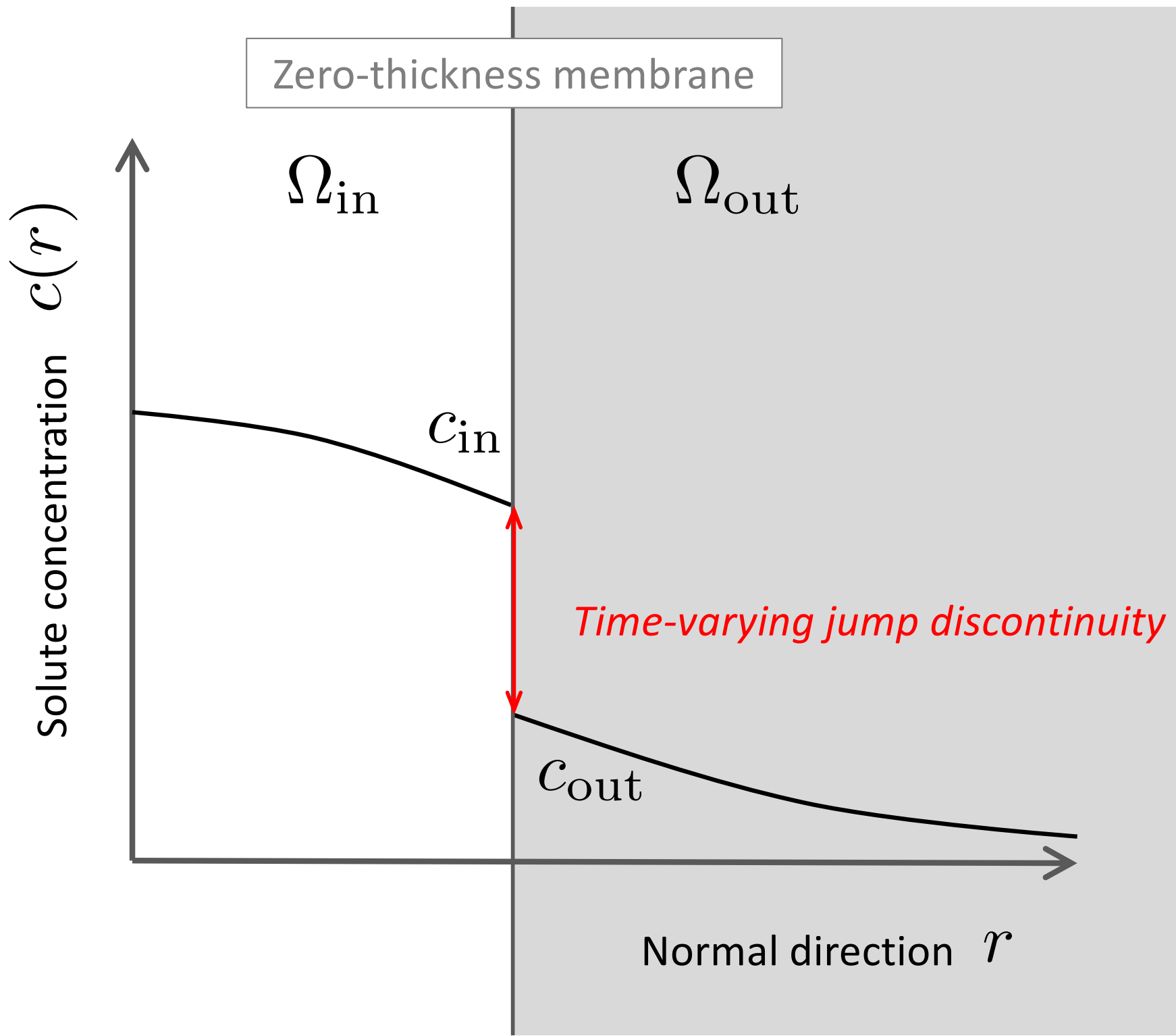
$$Sc = \frac{\nu}{D}$$



# 2D computer simulations: FSI + Mass transport



Unsteady jump boundary condition



Jump boundary condition

Membrane  
 $\partial\Omega$

Permeability

$$\mathbf{J} \cdot \mathbf{n} = -P (c_{\text{out}} - c_{\text{in}})$$

Mass flux

$\mathbf{n}$

A diagram showing a white, irregularly shaped region representing a volume. The boundary of this region is a black line. An arrow labeled  $\mathbf{n}$  points outwards from the boundary at a specific location. The region is surrounded by a gray background.



# Algorithm to implement unsteady jump boundary conditions within the lattice Boltzmann method

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$$g_i(\mathbf{r} + \mathbf{e}_i, t + 1) - g_i(\mathbf{r}, t) = -\frac{g_i(\mathbf{r}, t) - g_i^{\text{eq}}(\mathbf{r}, t)}{\tau_g} + \omega_i (\mathbf{Q}(x, y, t) \cdot \mathbf{e}_i)$$

Forcing term

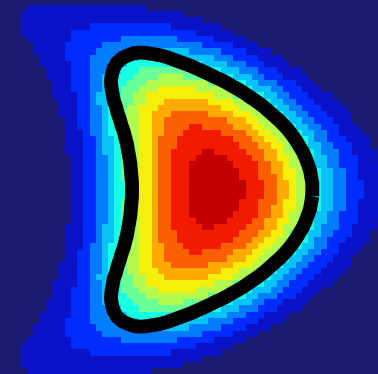
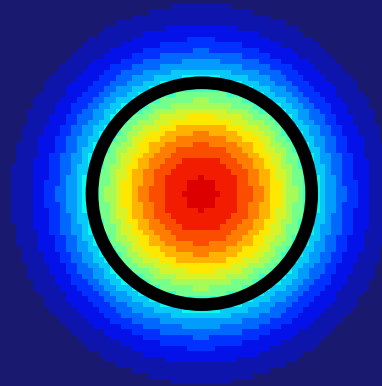
$$\mathbf{Q}(x, y, t) = \int_{\partial\Omega_m} \alpha(x, y, \mathbf{r}_m) \mathbf{q}(\mathbf{r}_m, t) ds \quad \mathbf{q}(\mathbf{r}_m, t) = -R [c_{\text{in}}(\mathbf{r}_m, t) - c_{\text{out}}(\mathbf{r}_m, t)] \mathbf{n}$$

# Results: Solute release from a fluid-filled particle

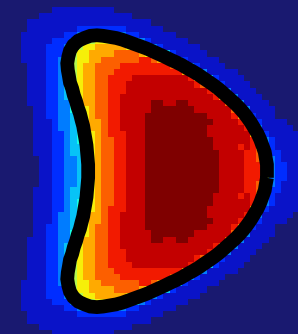
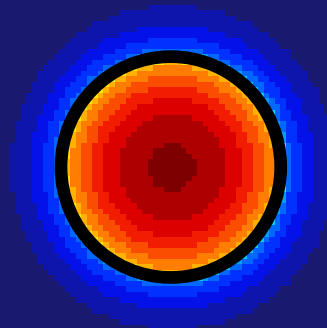
Under static conditions

Under flow conditions

Membrane with infinite permeability

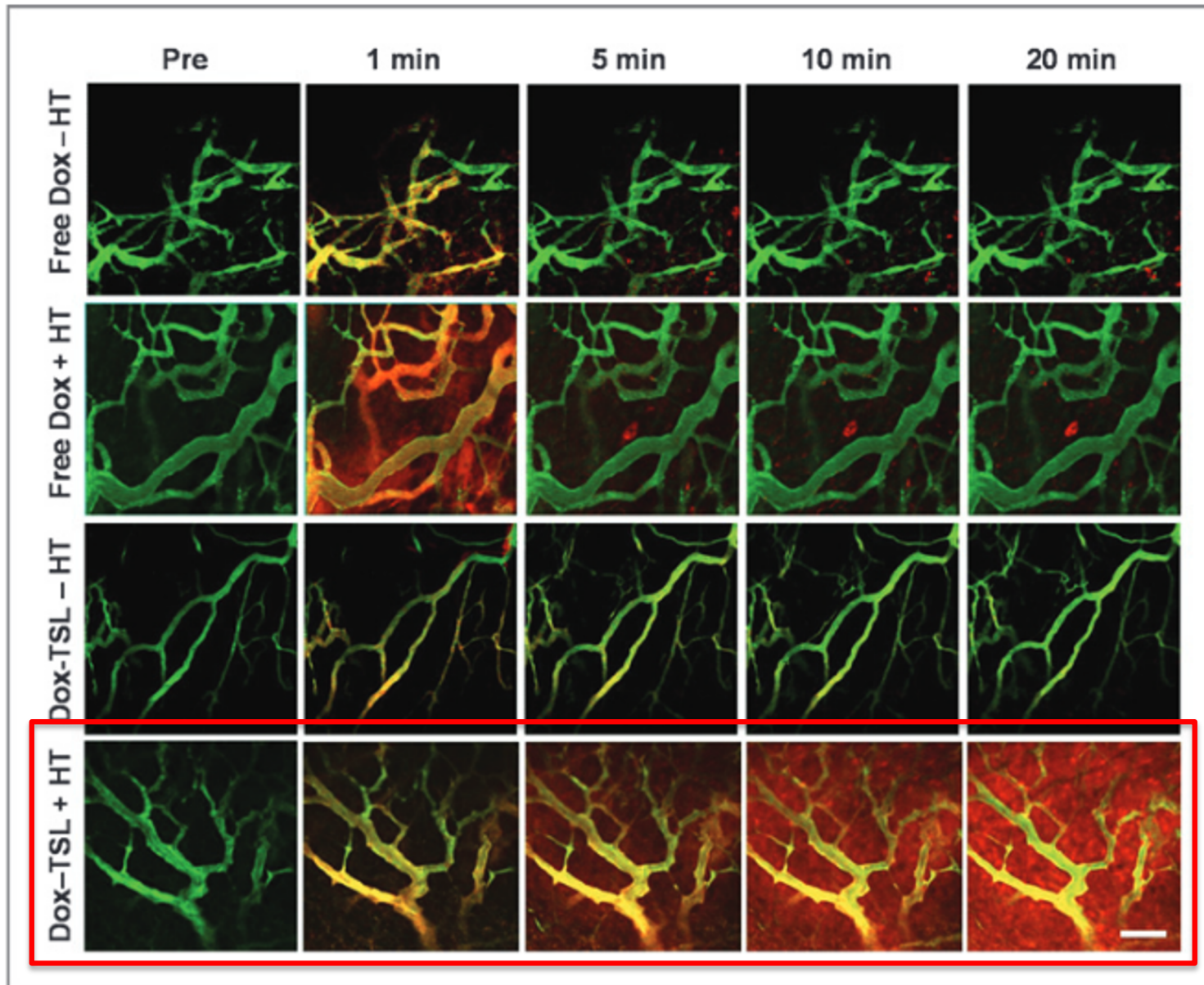


Membrane with finite permeability



# Complex geometry: Vascular system

Release of doxorubicin (anticancer drug) in the bloodstream



# Complex geometry: Vascular system

Release of doxorubicin (anticancer drug) in the bloodstream

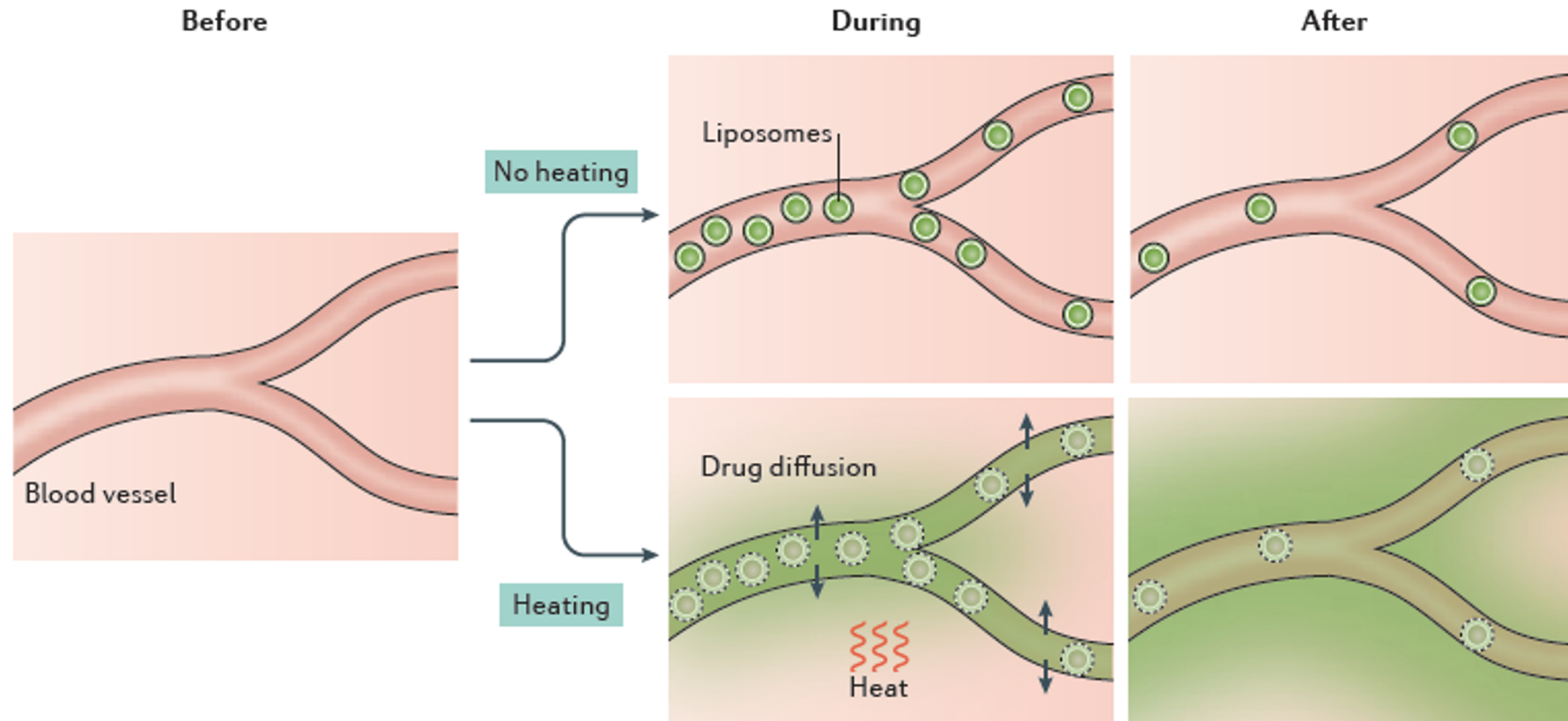
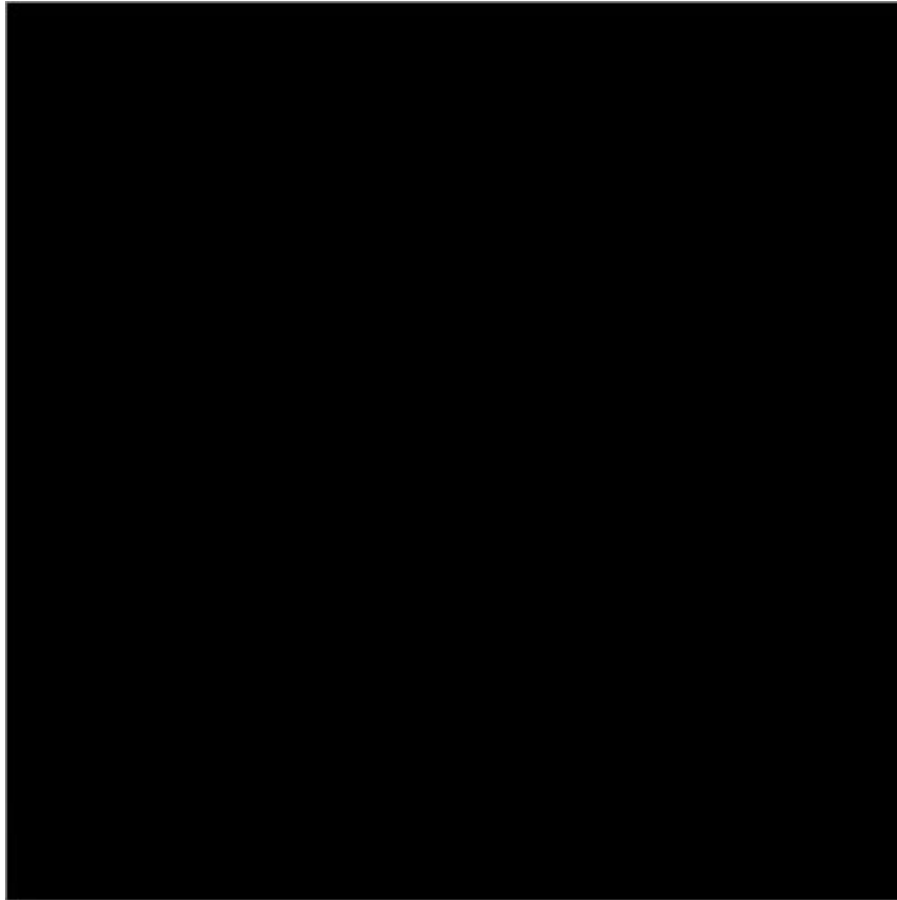


Figure 4 | **Principle of thermally triggered drug release from liposomes.** This illustration is based on experimental imaging of drug distribution<sup>54</sup>. Local application of heat during the delivery of liposomes causes pores to form in the lipid bilayer and thus release of drug, which diffuses into the tissue. With heating, penetration of liposomes through blood vessel walls into tissue is not required for drug delivery to tumour. Here, drug release occurs intravascularly. Green shading indicates the level of drug.

# Complex geometry: Vascular system

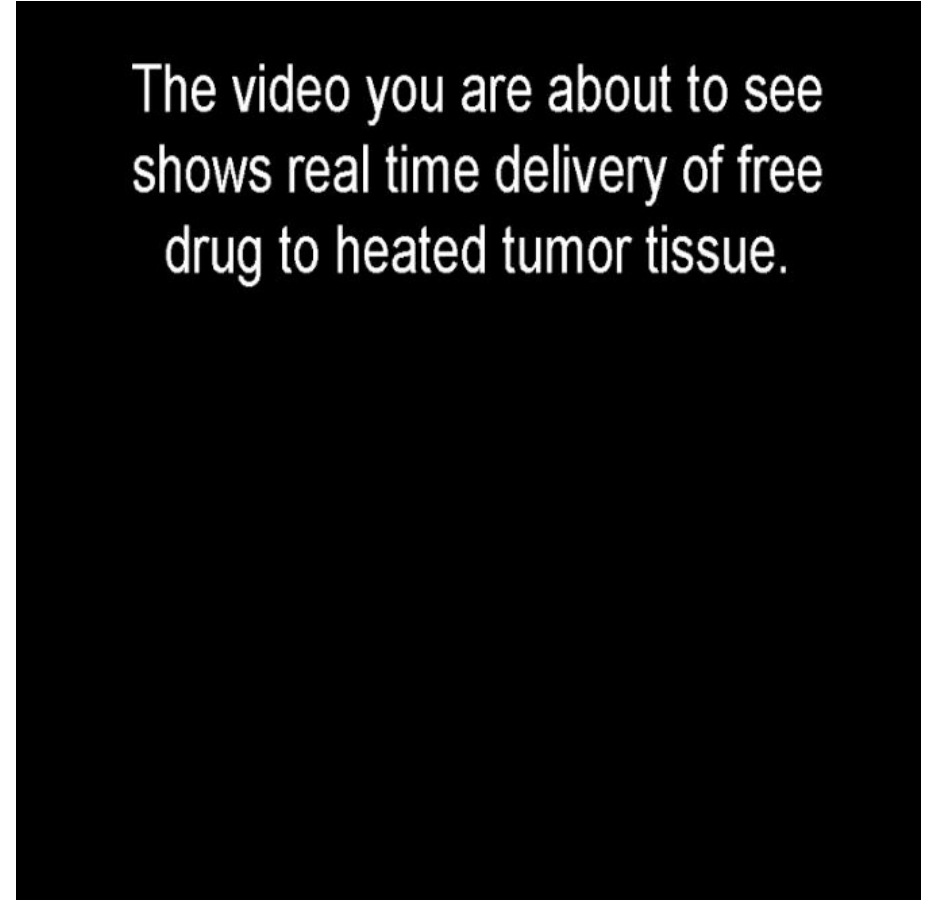
Release of doxorubicin (anticancer drug) in the bloodstream

Only drug-carrier particles



In Silico

Preliminary results



The video you are about to see shows real time delivery of free drug to heated tumor tissue.

In Vivo

Manzoor *et al.* Cancer Research (2012)

# Conclusions of the 2<sup>nd</sup> part

- The flow enhances the drug release: convection effect
- Red blood cells alter the released drug distribution in the blood vessel
- A new numerical tool to study and predict the impact of the plasma flow and red blood cells on drug mass transport in the bloodstream
- A new numerical tool to model solute mass transport across membranes with finite permeability: unsteady jump BCs



# Sherwood number : dimensionless mass transfer coefficient (eq. Nusselt number)



Local mass transfer coefficient

$$h(\theta, t) = -\frac{D_f}{c(R, \theta, t)} \left[ \frac{\partial c}{\partial r} \right]_{r=R}$$

Dimensionless mass transfer coefficient

$$\text{Sh}(\theta, t) = 2 \frac{R}{D_f} h(\theta, t)$$

Average Sherwood number

$$\text{Sh}_a(t) = \frac{1}{2\pi R} \int_{\theta=0}^{2\pi} \text{Sh}(\theta, t) ds(\theta)$$

