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A lattice-Boltzmann based multiscale approach for simulating nanoparticle transport in cellular blood flow

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07/19/2017

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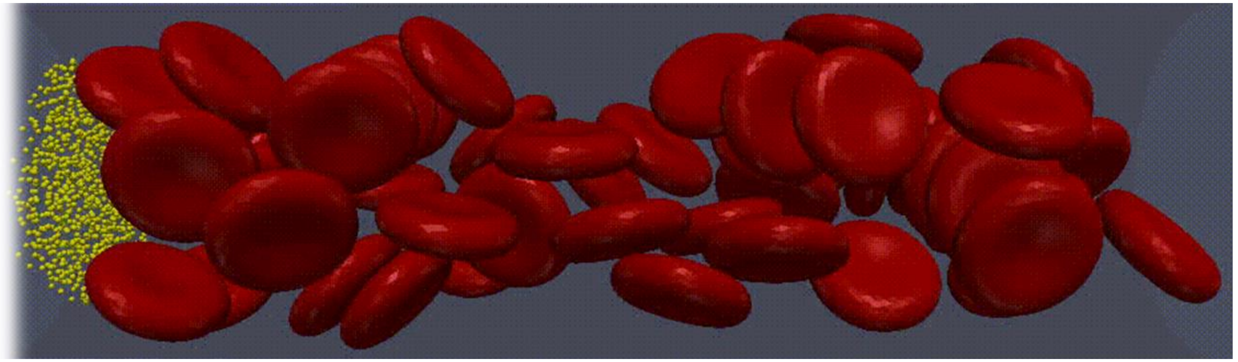
Outline

- **Motivation**
- **Computational Approach**
    - Lattice-Boltzmann (LB) method for fluid
    - Spectrin-link (SL) method for red blood cell (RBC) membrane
    - Langevin dynamics (LD) approach for nanoscale particles (NP)
    - Coupling of the LB-SL-LD method
- **Verification**
- **Application to NP diffusion in a capillary vessel**

Motivation

- **Nano-therapeutics:**
- The last 20 years have witnessed a plethora of studies focused on **using intravascularly injected NP systems to deliver drugs to biological targets** such as tumor.
- It is shown that NP therapeutics has the potential to improve current disease therapies because of their ability to **overcome multiple biological barriers** and **release therapeutic load in the optimal dosage range**.



Decuzzi et al., *Pharm. Res., 2009*
Alexis et al., *Mol. Pharm., 2008*
Blanco et al., *NATURE BIOTECHNOLOGY, 2015*

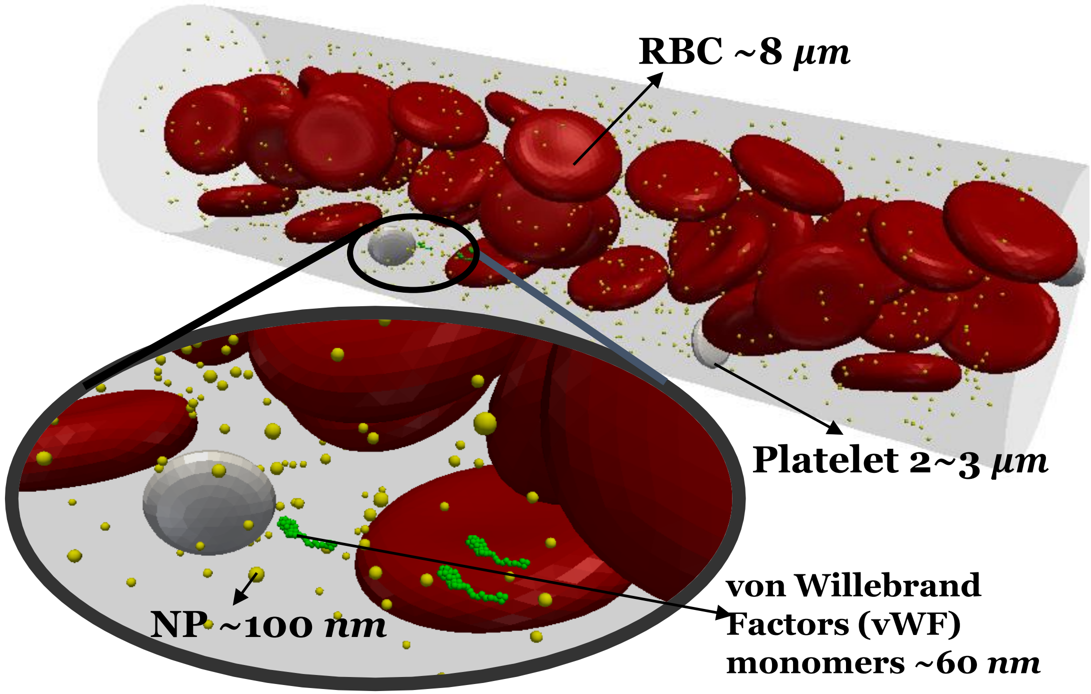
Motivation

- **Being able to computationally investigate the characteristics of NP transport in cellular blood flow is of strategic significance to the improvement the NP bioavailability in biological systems.**
- Support the realization of **controllable the NP circulating time** and **favorable pre-extravasation/adhesion states**.
- **Major challenges:**

1) To resolve the **large length-scale discrepancy** (2~3 orders of magnitude) between NPs and cells such as RBC, platelet, and white blood cell using one resolution of mesh remains challenging;
2) Capture the **NP dynamics** including Brownian effect and interactions with other cells.

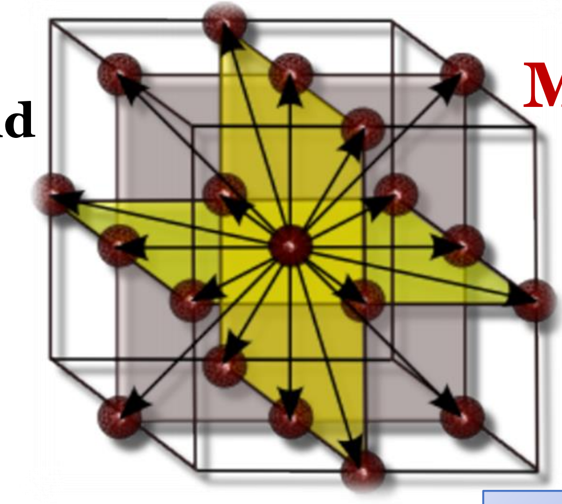
Specific Aim:

1) Develop an efficient computational approach **to resolve the multi-scale nature of NP transport in cellular blood flow**,
2) and understand the **fundamental physics of the NP diffusion process**.
3) **Support the development of targeted NP drug delivery system.**



Computational Approach

Lattice-Boltzmann (LB) method for fluid



Mesoscale

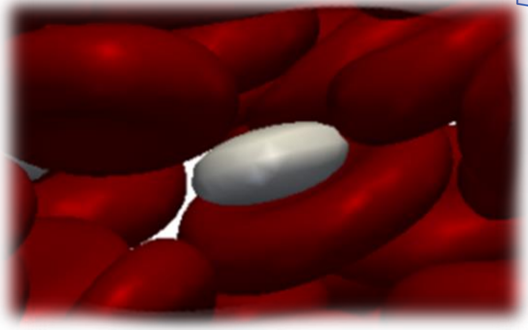
Multi-scale

Comprehensive two-way couplings

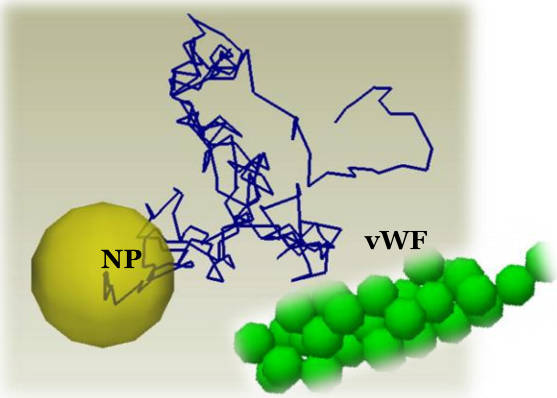
Microscale

Cell models:

- RBC: Spectrin-link (SL) method
- Platelet: rigid particle
- …



Nanoscale

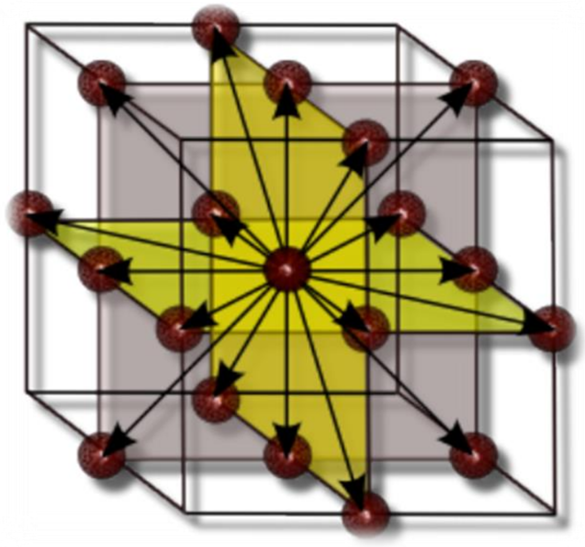


Langevin dynamics (LD) for nanoscale particles/proteins

Method: Lattice Boltzmann method for the fluid

- Solve the **discretized Boltzmann equation** in velocity space with the **collision term** treated by the single-relaxation-time **Bhatnagar, Gross, and Krook (BGK) operator and** a **forcing term** to represent the body force effect

$$f_i(\boldsymbol{r} + \Delta t_{LB}\boldsymbol{e}_i, t + \Delta t_{LB}) = f_i(\boldsymbol{r}, t) - \frac{1}{\tau}\left[f_i(\boldsymbol{r}, t) - f_i^{(eq)}(\boldsymbol{r}, t)\right] + f_i^S(r, t)$$



D3Q19
Lattice Stencil

- **Equilibrium distribution function:**

$$f_i^{(eq)}(\boldsymbol{r}, t) = \omega_i \rho\left[1 + \frac{1}{c_s^2}(\boldsymbol{e_i} \cdot \boldsymbol{u}) + \frac{1}{2c_s^2}(\boldsymbol{e_i} \cdot \boldsymbol{u})^2 - \frac{1}{2c_s^2}(\boldsymbol{u} \cdot \boldsymbol{u})\right]$$

Recovers incompressible Navier-Stokes equations at low Mach number limit $(\frac{u}{c_s} \ll 1)$

LB kinematic viscosity:

$$\upsilon_{LB} = \left(\tau - \frac{1}{2}\right) c_s^2 \Delta t$$

Pseudo-sound-speed:

$$c_s = \frac{\Delta r_{LB}}{\sqrt{3}\Delta t_{LB}}$$

- **Recovers the macroscopic properties:**

Density $\sum_i f_i(\boldsymbol{r}, t) = \rho$

Velocity $\sum_i f_i(\boldsymbol{r}, t)\, e_i = \rho \boldsymbol{u}$

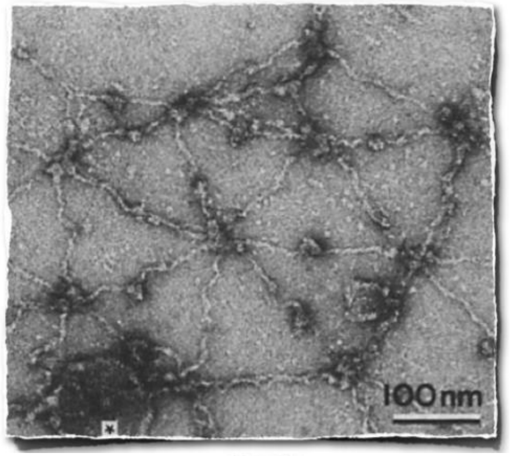
Pressure $\sum_i f_i(\boldsymbol{r}, t)\, \boldsymbol{e_i}\boldsymbol{e_i} = \rho c_s^2 \boldsymbol{I} + \rho \boldsymbol{u}\boldsymbol{u}$

D3Q19

- **weights** ω_i
- **lattice velocity** $\boldsymbol{e_i}$

Bhatnagar, Gross, & Krook, *Phys. Rev.*, 94(3), 1954.
He et. al. *J. Stat. Phys.*, 87, 1997.
Aidun, Lu & Ding, *J. Fluid Mech.*, 373, 1998.
Aidun & Clausen. Annual Rev. Fluid Mech., 42, 2010.

Method: Spectrin-link method for the RBC membrane



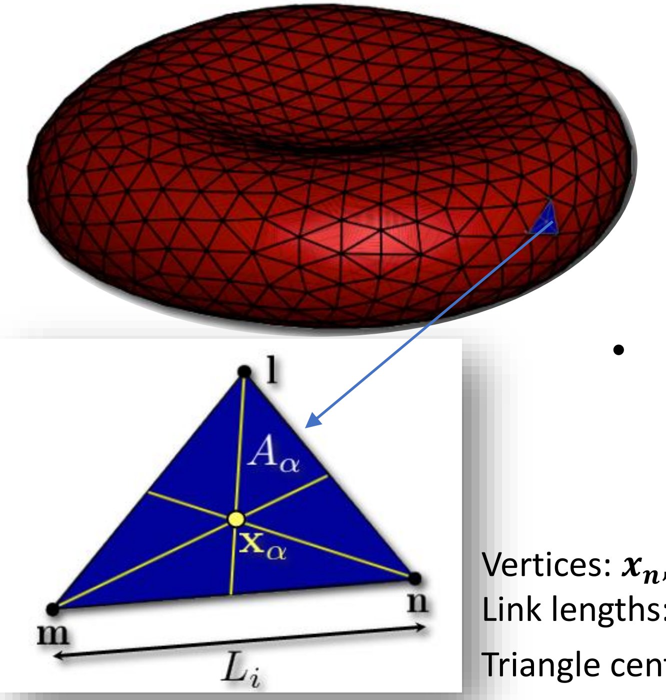
- The SL model for deformable RBC membranes is inspired by the **physiological structure of the RBC membrane.**
- **Course-graining** procedure to match material properties and enable dense suspension simulations.
- **The total Helmholtz free energy of the RBC membrane:**

$$E\{\boldsymbol{x_n}\} = E_{in-plane} + E_{bending} + E_{volume} + E_{area}$$

  - $E_{in-plane} = \sum_{i \in S} V_{WLC}(L_i) + \sum_{\alpha \in \Pi} C/A_{\alpha}$, (compressional + repulsive)
  - $E_{bending} = \sum_{adjacent\ \alpha,\beta} k_{bend}[1 - \cos(\theta_{\alpha\beta} - \theta_0)]$
  - $E_{volume}\ and\ E_{area}$ introduce constraints to the total volume and total area of the RBC
  - **SL forces**: $\mathbf{f_n} = -\frac{\partial E\{\boldsymbol{x_n}\}}{\partial \boldsymbol{x_n}}$.

- **Update according to Newton's equation of motion:**

$$\frac{d\boldsymbol{x_n}}{dt} = \boldsymbol{v_n}; \quad M\frac{d\boldsymbol{v_n}}{dt} = \mathbf{f_n} + \mathbf{f_n^{LB}} + \mathbf{f_n^{PP}}$$



Vertices: $\boldsymbol{x_n}$, $n \in 1, \ldots, N$
Link lengths: $L_i = |\boldsymbol{x_m} - \boldsymbol{x_n}|$, i $\in 1, \ldots, S$
Triangle centers: $\boldsymbol{x_\alpha} = \frac{1}{3}(\boldsymbol{x_m} + \boldsymbol{x_n} + \boldsymbol{x_l})$, α $\in 1, \ldots, \Pi$
Triangle Area: $A_\alpha = \frac{1}{2}|(\boldsymbol{x_m} - \boldsymbol{x_l}) \times (\boldsymbol{x_n} - \boldsymbol{x_l})|$

Liu et al., J. Cell Bio., 104:528–536, March 1987.
Li et. al, Biophysical J., 88, 2005.
Dao et. al, Mat. Sci. Engr. C-BioS., 26, 2006.
Pivkin & Karniadakis, Phys. Rev. Lett., 101, 2008.
Reasor, Clausen & Aidun, J. Num. Meth. Fluids, 14, 2010.

Method: Langevin dynamics for NPs

- **By treating each NP as a point particle, the NP dynamics can be described via the Langevin Equation:**

$$m_i \frac{d\boldsymbol{u}_p^i}{dt} = \boldsymbol{C}_p^i + \boldsymbol{F}_p^i + \boldsymbol{S}_p^i$$

- **Three driving forces:**

Conservative force:

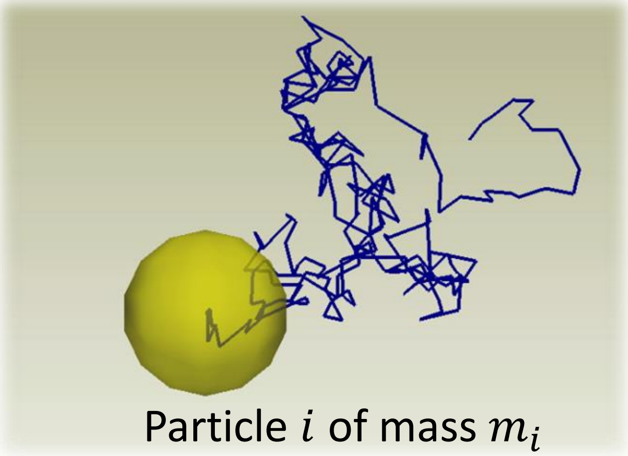
$$\boldsymbol{C}_p^i = -\frac{dU_{total}^i}{d\boldsymbol{r}_p^i}$$

Frictional force:

Local fluid velocity

$$\boldsymbol{F}_p^i = -\zeta[\boldsymbol{u}_p^i(t) - \boldsymbol{u}(\boldsymbol{r}_p^i, t)]$$

(Stokes' drag law: $\zeta = 3\pi\rho\nu d_p$)



Stochastic force $\boldsymbol{S}_p^i$ (source of the Brownian effect)

$$\begin{cases} \overline{S_{p,\alpha}^i(t)} = 0 \\ \overline{S_{p,\alpha}^i(t) S_{p,\beta}^j(t')} = 2k_B T\zeta\delta_{ij}\delta_{\alpha\beta}\delta(t-t') \end{cases}$$

the Cartesian component of $\boldsymbol{S}_p^i$ exhibit **a Gaussian distribution of zero mean**

Demonstration of the fluctuation-dissipation theorem

Hinch, *J. Fluid Mech.*, 72 1975.

Method: Langevin dynamics for NPs

- **Two critical time scales:**

1) Brownian relaxation time scale

$$\tau_r = \frac{m}{\zeta} = \frac{m}{3\pi\rho\nu d_p}$$

2) LB time scale

$$\tau_{LB} = \frac{\mathcal{L}^2 \nu_{LB}}{\mathcal{L}_{LB}^2 \nu}$$

$\mathcal{L}$: physical length
ν: physical viscosity
$\mathcal{L}_{LB}, \nu_{LB}$: corresponding properties in lattice units.

- **The LE is conditionally solved with first-order forward Euler method:**

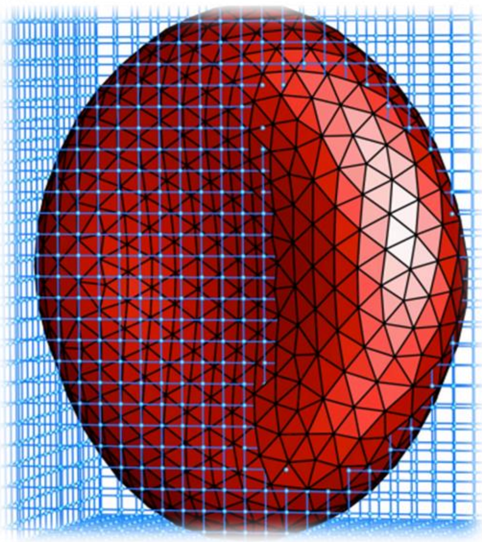
Velocity: $$\boldsymbol{u}_p(t + \Delta t_{LB}) = \begin{cases} \boldsymbol{u}_p(t) + \frac{1}{\zeta}\left[\boldsymbol{C}_p(t) + \boldsymbol{S}_p(t)\right] + \boldsymbol{u}(\boldsymbol{r}_p, t), & (\tau_{LB} > \tau_r) \\ \boldsymbol{u}_p(t) + \frac{\Delta t_{LB}}{m}\{\boldsymbol{C}_p(t) + \boldsymbol{S}_p(t) - \zeta[\boldsymbol{u}_p(t) - \boldsymbol{u}(\boldsymbol{r}_p, t)]\}, & (\tau_{LB} \leq \tau_r) \end{cases}$$

Displacement: $$\boldsymbol{r}_p(t + \Delta t_{LB}) = \boldsymbol{r}_p(t) + \Delta t_{LB}\, \boldsymbol{u}_p(t + \Delta t_{LB})$$

Journal Article in Preparation.

Method: Couplings

Cell-fluid coupling



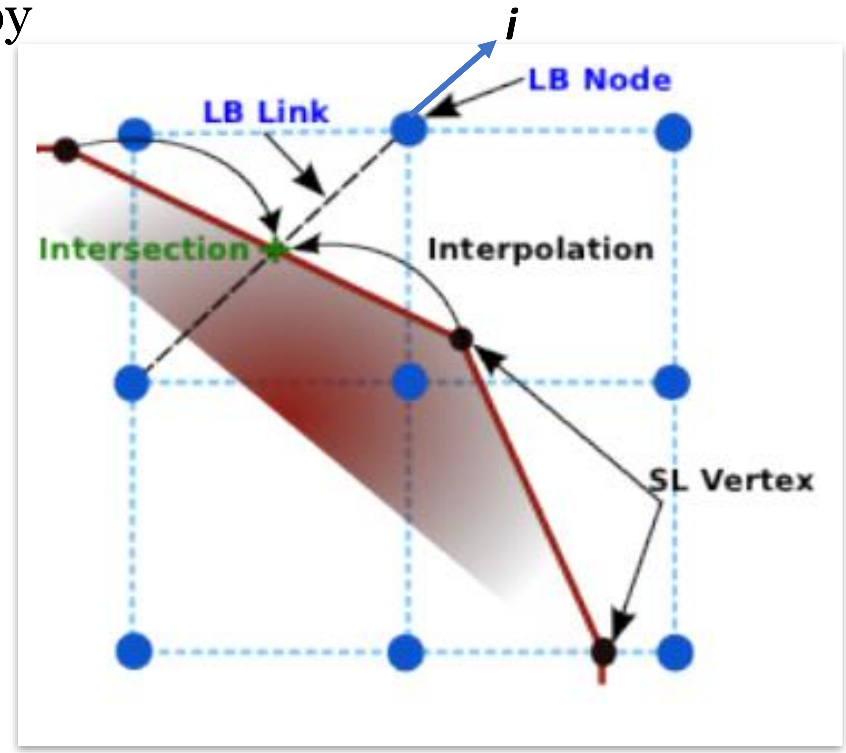
- **Standard bounce-back (SBB)**
- The distributions of the LB node at the end point of a LB link is adjusted by

$$f_i(\boldsymbol{r}, t+1) = f_{i'}(\boldsymbol{r}, t^+) + 2\frac{\rho\omega_i}{c_s^2}\boldsymbol{u}_b \cdot \boldsymbol{e}_i$$

- The LB fluid force acting on the SL surface vertex is determined by

$$f_n^{LB}\left(\boldsymbol{r} + \frac{1}{2}\boldsymbol{e}_i, t\right) = -2\boldsymbol{e}_i\left[f_{i'}(\boldsymbol{r}, t^+) + \frac{\rho\omega_i}{c_s^2}\boldsymbol{u}_b \cdot \boldsymbol{e}_i\right]$$

- Identical to no-slip boundary condition
- first-order accuracy in space due to intersection point not at midpoint



Aidun & Lu, *J. Stat. Phys.*, 81, 1995.
Aidun, Lu & Ding, *J. Fluid Mech.*, 373, 1998.
MacMeccan et. al, *J. Fluid Mech.*, 618, 2009.
Aidun & Clausen. *Annual Rev. Fluid Mech.*, 42, 2010.

Method: Couplings

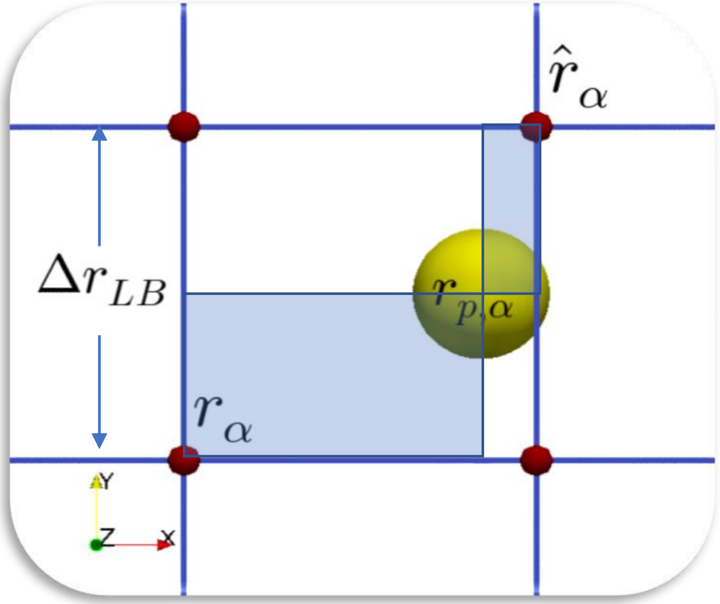
NP-fluid (LD-LB) coupling

- Two stencils can be adapted to interpolate $\boldsymbol{u}(\boldsymbol{r}_p, t)$ from neighboring LB nodes.
  1) Trilinear method

$$w(\boldsymbol{r}, \boldsymbol{r_p}) = \prod_{\alpha\in\{x,y,z\}} \frac{|\hat{r}_\alpha - r_{p,\alpha}|}{\Delta r_{LB}} \quad (1^{st}\ order)$$

  2) External boundary force (EBF) method

$$w(\boldsymbol{r}, \boldsymbol{r_p}) = \prod_{\alpha\in\{x,y,z\}} \frac{\{1+\cos\left[\frac{\pi(r_\alpha - r_{p,\alpha})}{2\Delta r_{LB}}\right]\}}{4\Delta r_{LB}} \quad (2^{nd}\ \text{order})$$



- The fluid velocity at the NP vicinity then reads

$$\boldsymbol{u}(\boldsymbol{r}_p, t) = \sum_{r\in N_c} w(\boldsymbol{r}, \boldsymbol{r_p})\boldsymbol{u}(\boldsymbol{r}, t)$$

- Fluid force in LD, including frictional force and the stochastic force, are then obtained as

$$\boldsymbol{F}_p^f = \boldsymbol{F}_p + \boldsymbol{S}_p = -\zeta[\boldsymbol{u}_p - \boldsymbol{u}(\boldsymbol{r}_p, t)] + \boldsymbol{S}_p$$

- To conserve momentum, the reactionary impulse density, $\boldsymbol{J}(\boldsymbol{r}) = -w(\boldsymbol{r})\frac{\boldsymbol{F}_p^f \Delta t_{LB}}{\Delta r_{LB}^3}$, is assigned back to the neighboring LB nodes

$$f_i^S(\boldsymbol{r}, t) = \frac{\omega_i \boldsymbol{J}(\boldsymbol{r}) \cdot \boldsymbol{e}_i}{c_s^2}$$

He et. al. *J. Stat. Phys.*, 87, 1997.
Aidun, Lu & Ding, *J. Fluid Mech.*, 373, 1998.
Ahlrichs & Dunweg, *J. Chem. Phys.*, 111, 1999.
C. S. Peskin, *Acta Numer.*, 11, 2002.
Wu & Aidun, *Int. J. Numer. Methods Fluids*, 2008.

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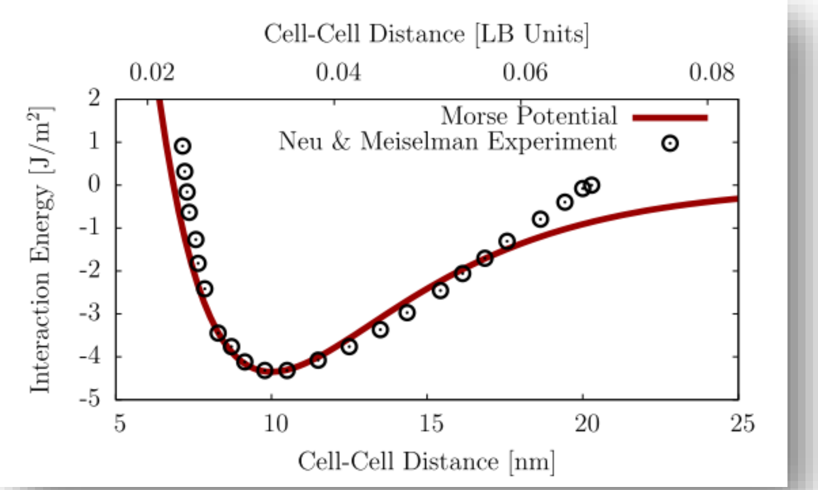
Method: Couplings

NP-Cell Interactions



- Mimic the way of cell-cell interaction through Morse potential with a cut-off distance at $r_e = 0.5d_p$

$$U_M(r_{pc}) = D_e\left[e^{2a(r_{pc}-r_e)} - 2e^{-a(r_{pc}-r_e)}\right], \quad (r_{pc} \leq r_e)$$

- Here r_{pc} denotes a particle-cell distance instead of a cell-cell distance.
- A search algorithm is implemented to efficiently locate the closest RBC triangulation with respect to each NP.

NP-NP interactions

- Standard Lennard–Jones potential is employed to resolve the NP-NP interaction forces

$$U_{LJ}(r_{ij}) = 4\epsilon\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right], \quad (r_{ij} \leq 3.0\sigma)$$

$$U_{total} = U_M + U_{LJ} + U_{other}$$

Jones, *Proc. R. Soc. London. Ser. A*, 106, 1924.
Neu & Meiselman, *Biophys. J.*, 83, 2002.
Liu et. al., *Int. J. Num. Meth. Fluids*, 46, 2004.

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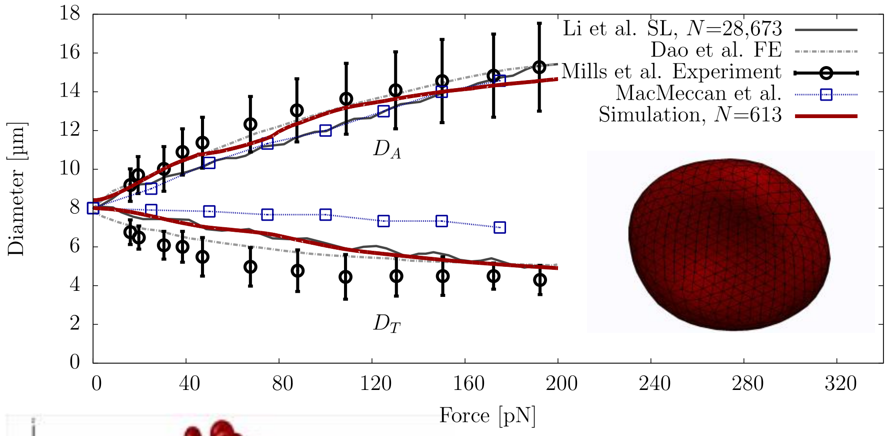
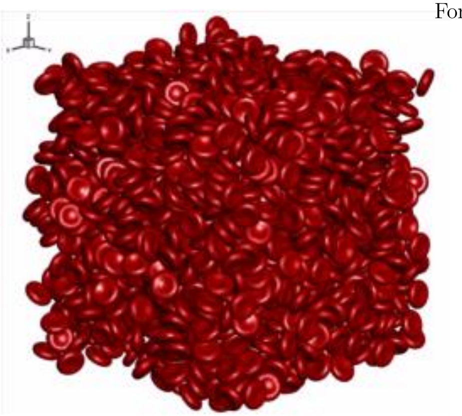
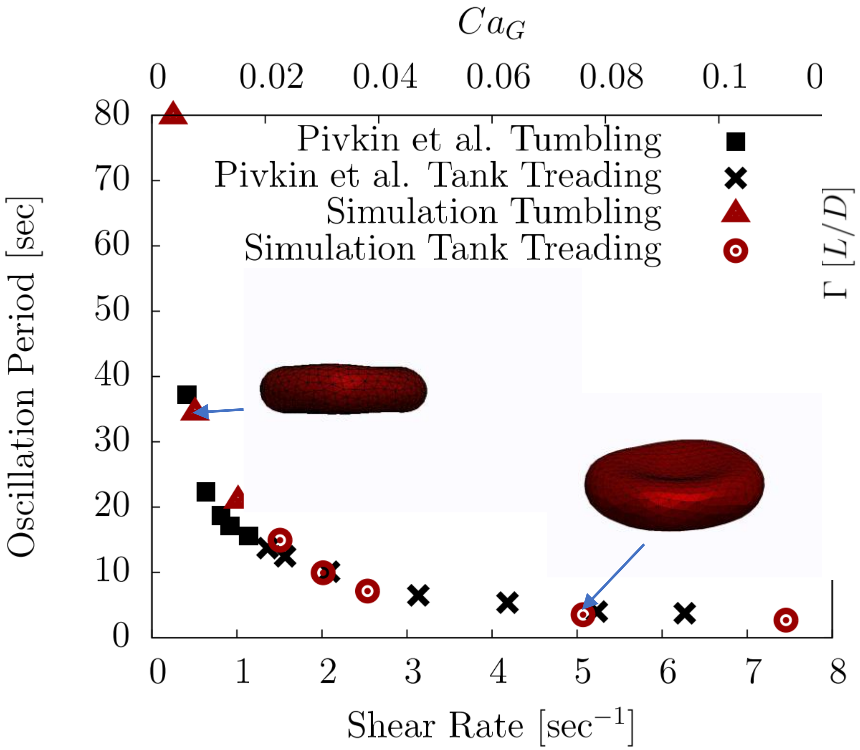
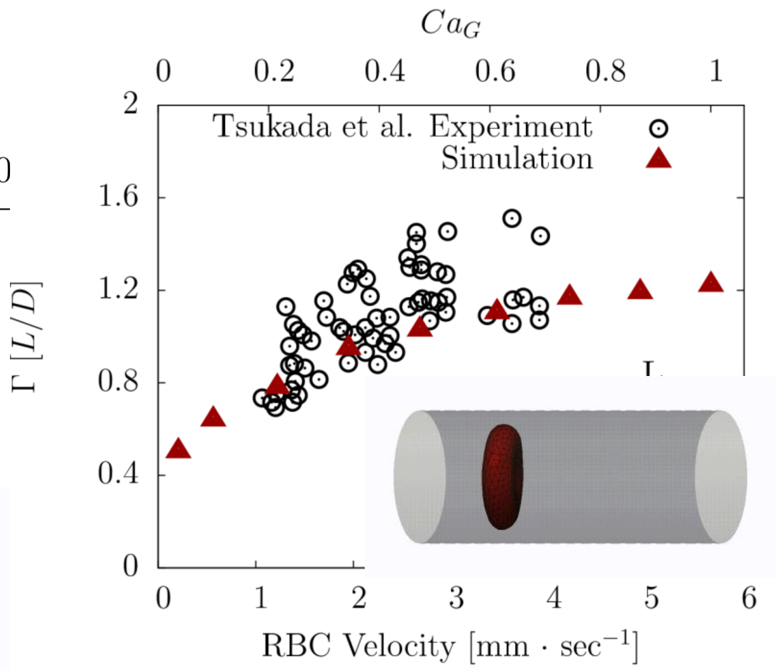
Verification: LB-SL coupling

- **The LB-SL coupling has been extensively validated with experiments and benchmark cases, proved to be successful** to capture both single RBC dynamics and rheology of dense suspensions of RBCs.









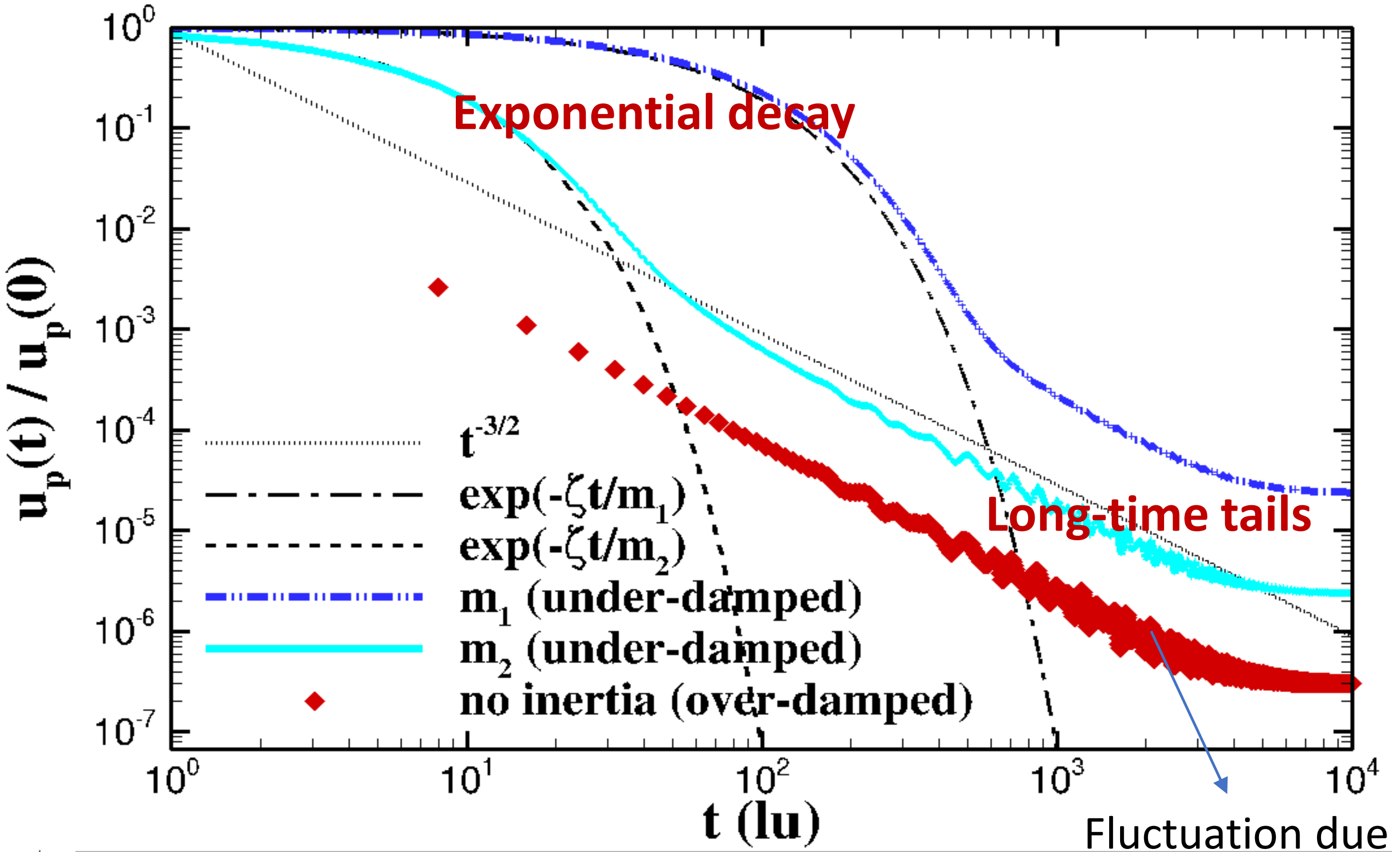
- **This work hereby intends to demonstrate the validity of the LB-LD coupling.**

Reasor, Clausen & Aidun, *J. Num. Meth. Fluids*, 14, 2010.
Reasor, Clausen, & Aidun, *J. Fluid Mech.*, 726, 2013.

Verification: LB-LD coupling

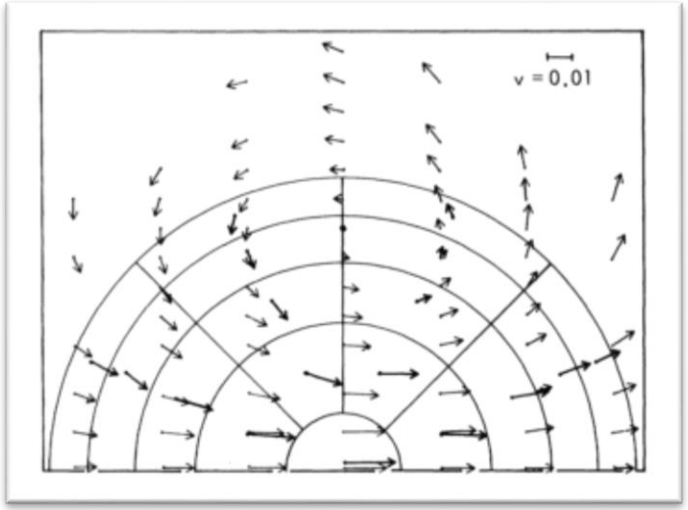
Velocity relaxation of a single particle

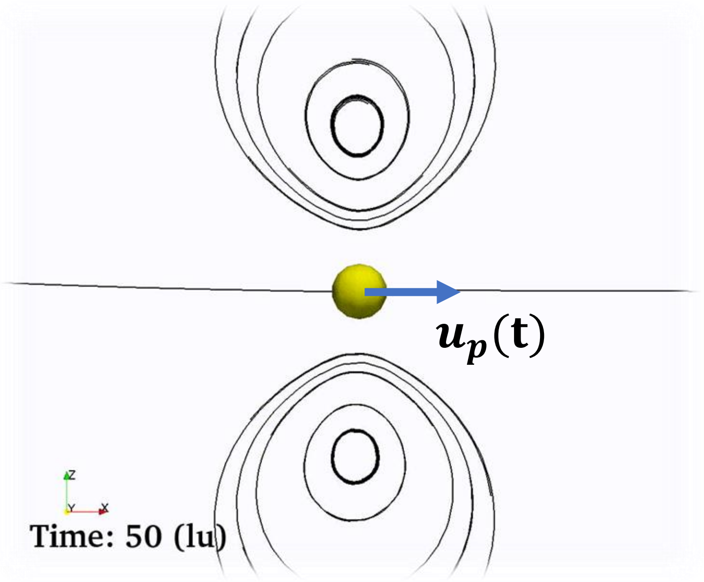
$m_1 = 29.3, m_2 = m_1/10,\ \zeta = 0.48,\ u_p(0) = 0.01$ all in lattice units (lu); simulation performed in a 100^3 cube with periodic BCs in all directions.



Fluctuation due to relatively large time steps.

Alder & Wainwright, *Phys. Rev. A*, 1, 1970.





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Journal Article in Preparation

Verification: self-diffusion of a single particle

- **Stokes-Einstein relation**

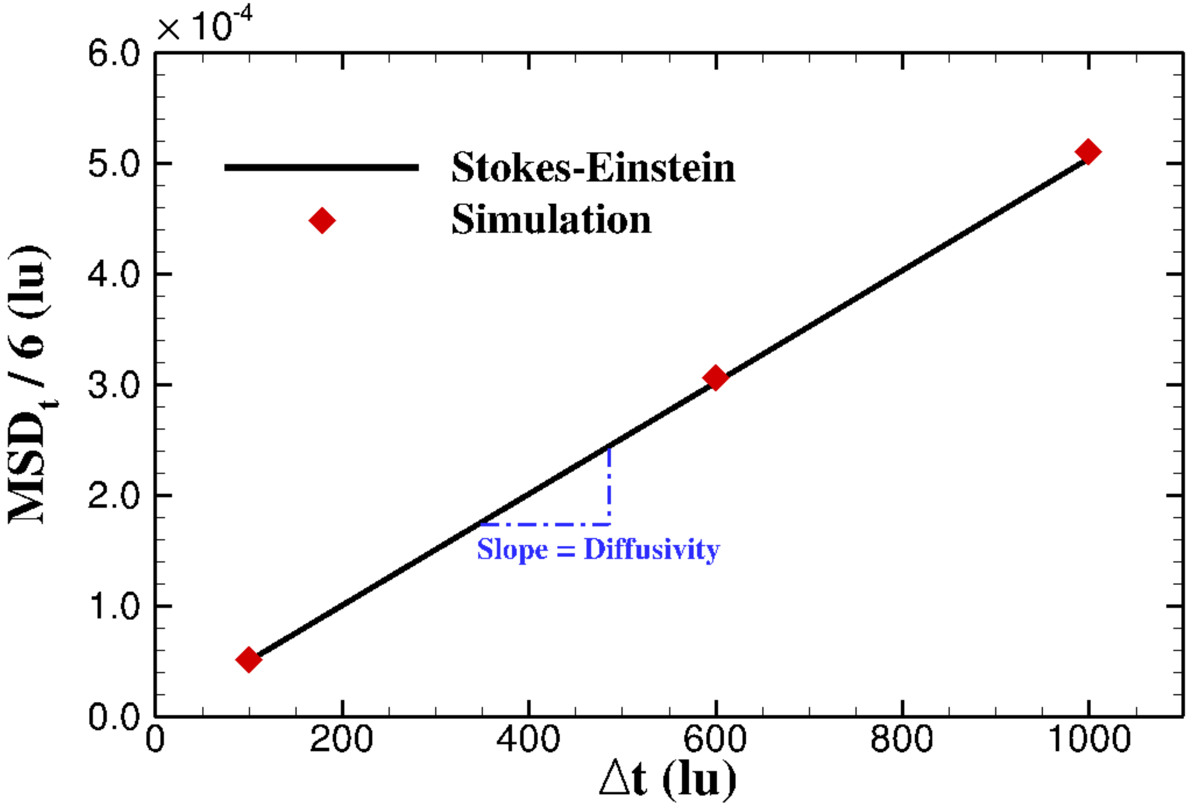
$$D_{theo} = \frac{k_B T}{\zeta}$$

where $\zeta = 3\pi\rho\nu d_p$.

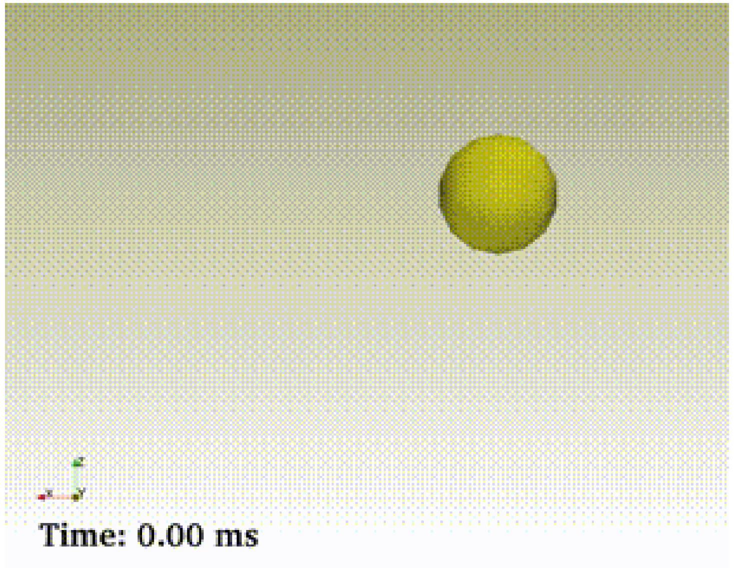
- **Measure the diffusivity through mean squared displacement**

$$D_{sim} = \lim_{\Delta t \to \infty} \frac{MSD_t}{6\Delta t}$$

where $MSD_t = \overline{\Delta r^2(t)}$.



100 nm particle self-diffusion in blood plasma at body temperature 298 K



Journal Article in Preparation.

Einstein, *Ann. Phys.*, 322, 1905.

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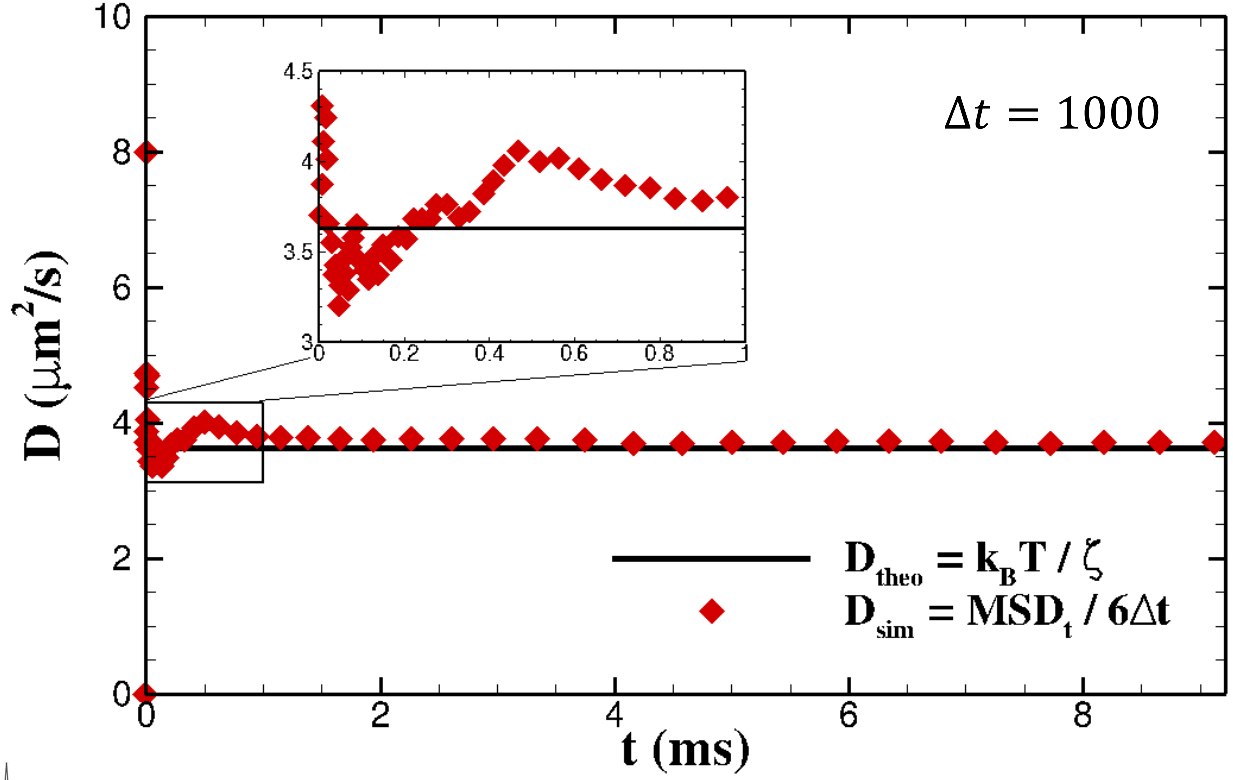

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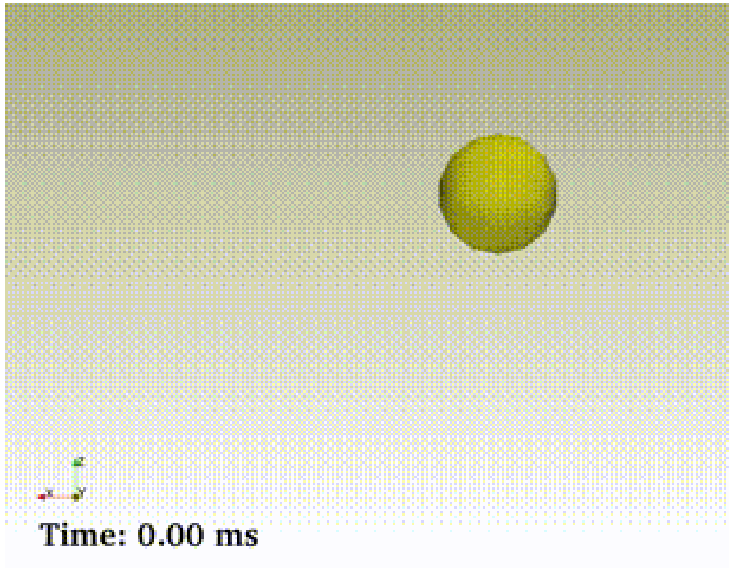

Journal Article in Preparation.

Einstein, *Ann. Phys.*, 322, 1905.

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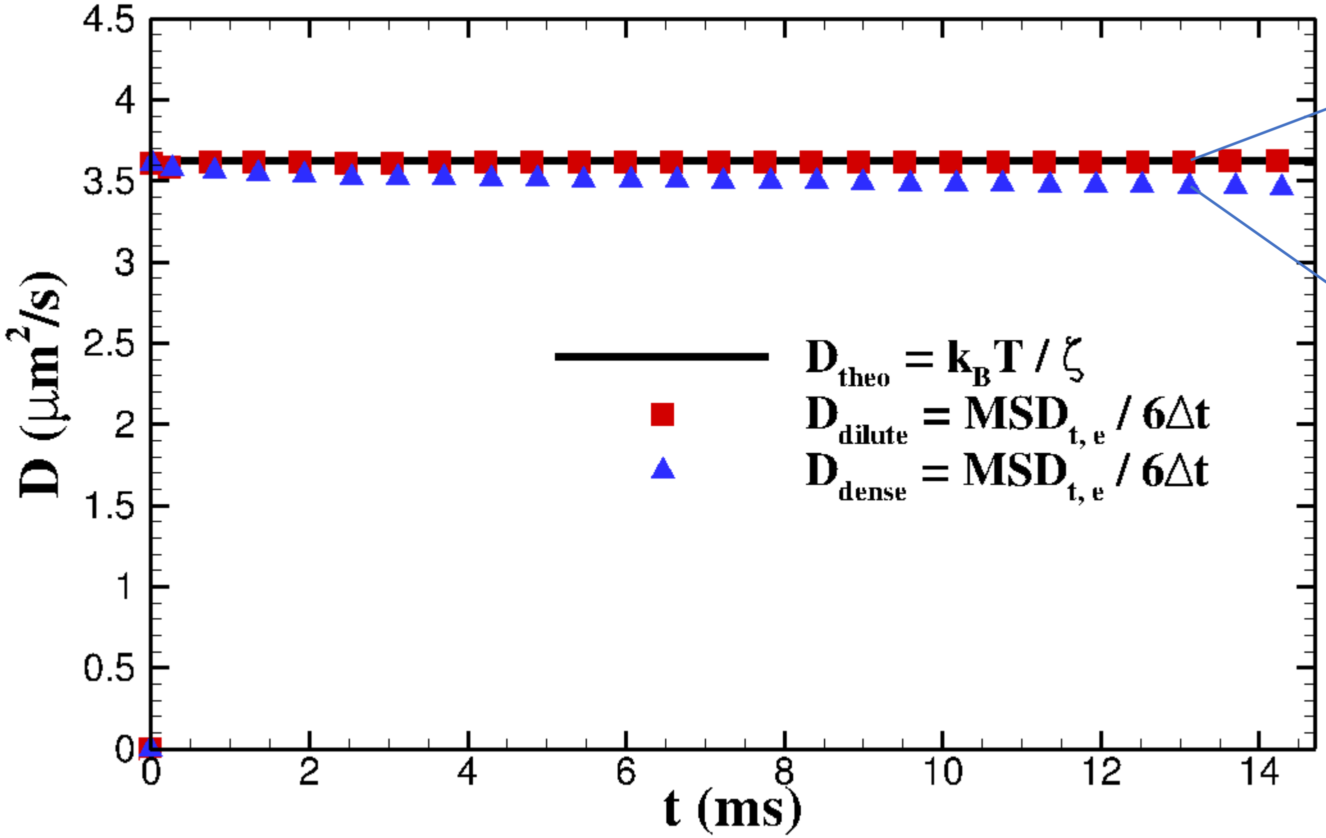
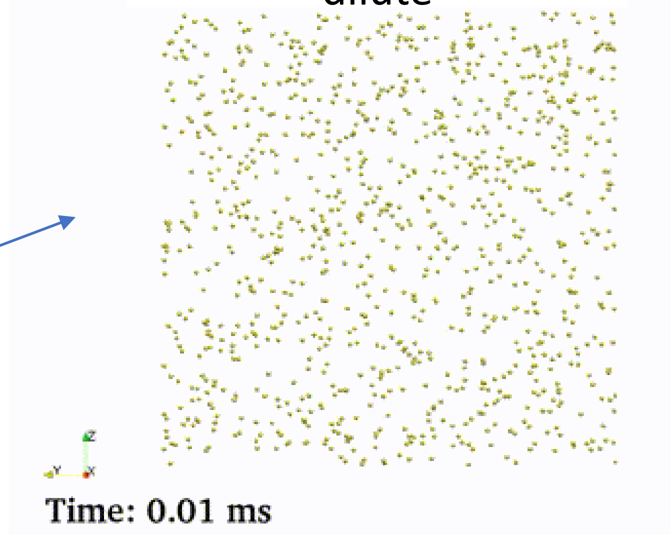
Verification: dispersion of a particle swarm

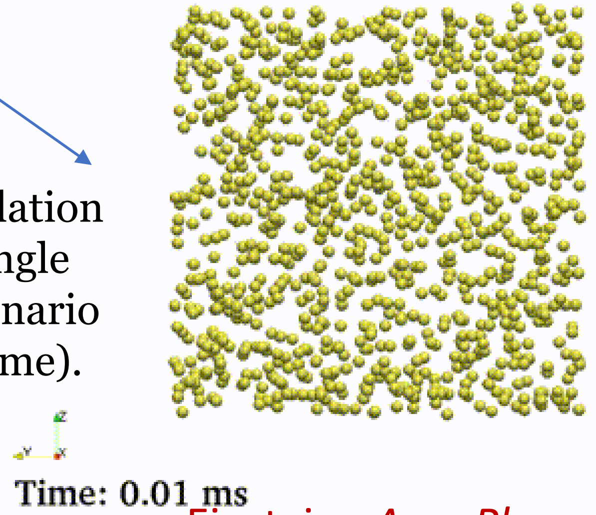
For dilute suspensions of nanoparticles, the **calculated diffusivity matches well with the theoretical counterpart** given by Einstein's relation.



100 nm, $\phi = 0.4\%$, dilute



100 nm, $\phi = 12\%$, dense



Einstein relation assumes single particle scenario (dilute regime).

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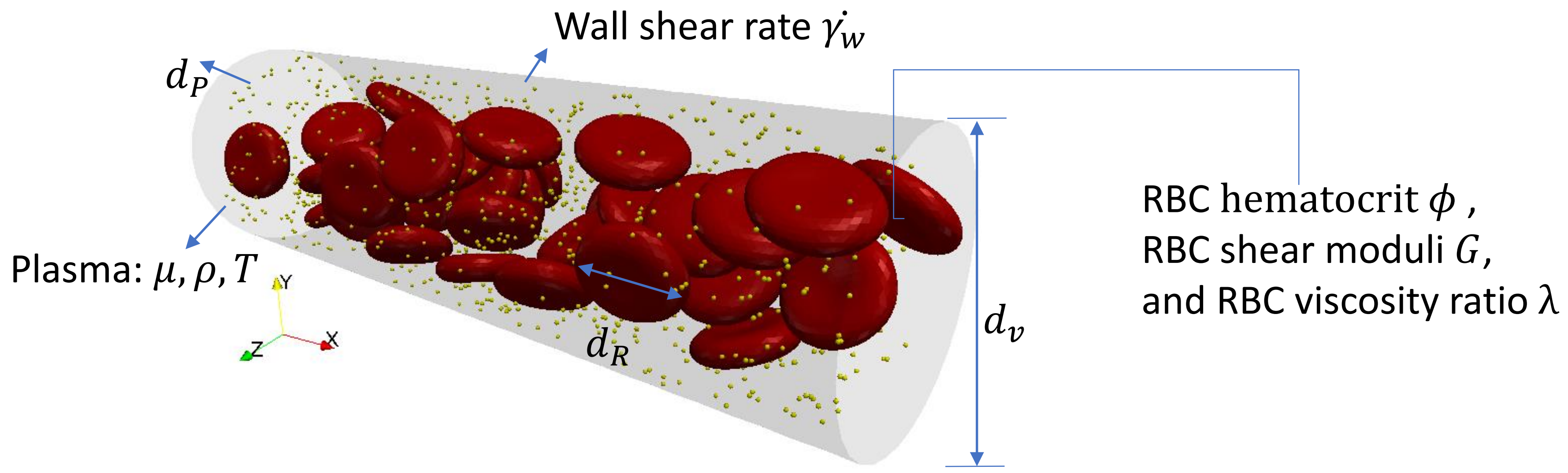
Journal Article in Preparation.

Einstein, *Ann. Phys.*, 322, 1905.

Application to NP diffusion in a capillary vessel

- **Non-dimensional Parameters:**



$$\boldsymbol{D_{rr}^{*} = \Phi\,(d_v^{*}, \phi, Pe, Ca_w)}$$

Normalized Radial diffusivity:

$$\boldsymbol{D_{rr}^{*} = \frac{D_{rr}}{\dot{\gamma}_w d_p^2}}$$

Confinement ratio: $d_v^{*} = \frac{d_v}{d_R}$

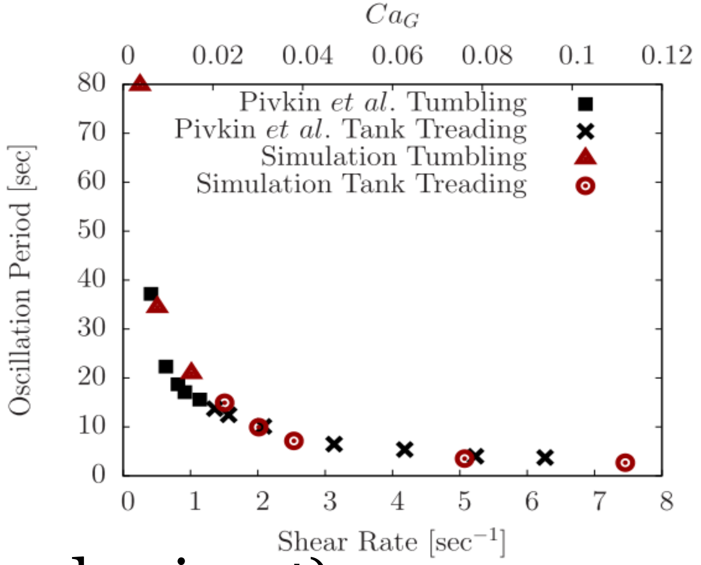
RBC hematocrit ϕ

NP Peclet number: $Pe = \frac{3\pi\mu\dot{\gamma}_w d_P^3}{4k_B T}$

RBC capillary number: $Ca_w = \frac{\mu\dot{\gamma}_w d_R}{2G}$

Application to NP diffusion in a capillary vessel

- $D^*_{rr} = \Phi\left(d^*_v, \phi, Pe_{NP}, Ca_{RBC}\right)$
- **Confinement ratio**:
  $d^*_v = 2.0 \sim 5.0$; $(d_v = 16 \sim 40\ \mu m)$
- **Hematocrit**:
  $\phi = 0\% \sim 20\%$; (capillaries)
- **NP Peclet number**:
  $Pe_P = 0.0 \sim 43.1$;
  (Brownian diffusion dominant → RBC-enhanced diffusion dominant)
- **RBC Capillary number**:
  $Ca_w = 0.04 \sim 0.37$;
  (tumbling → tank-treading)

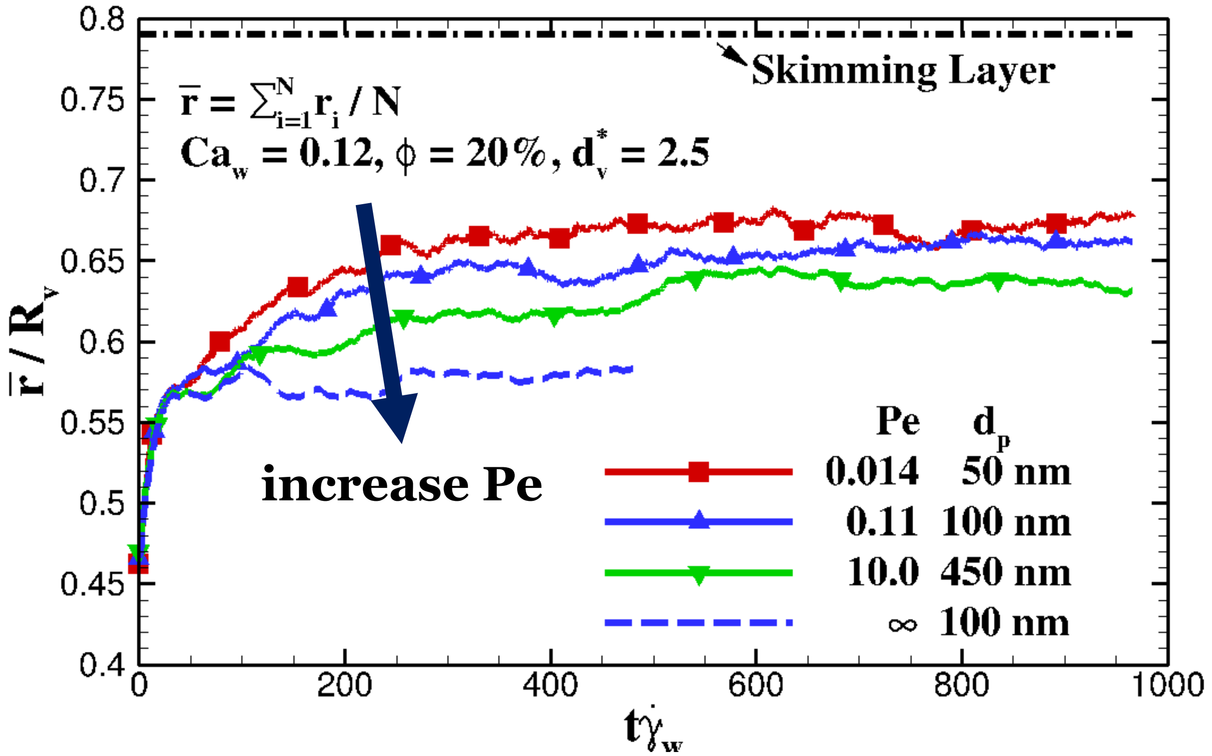


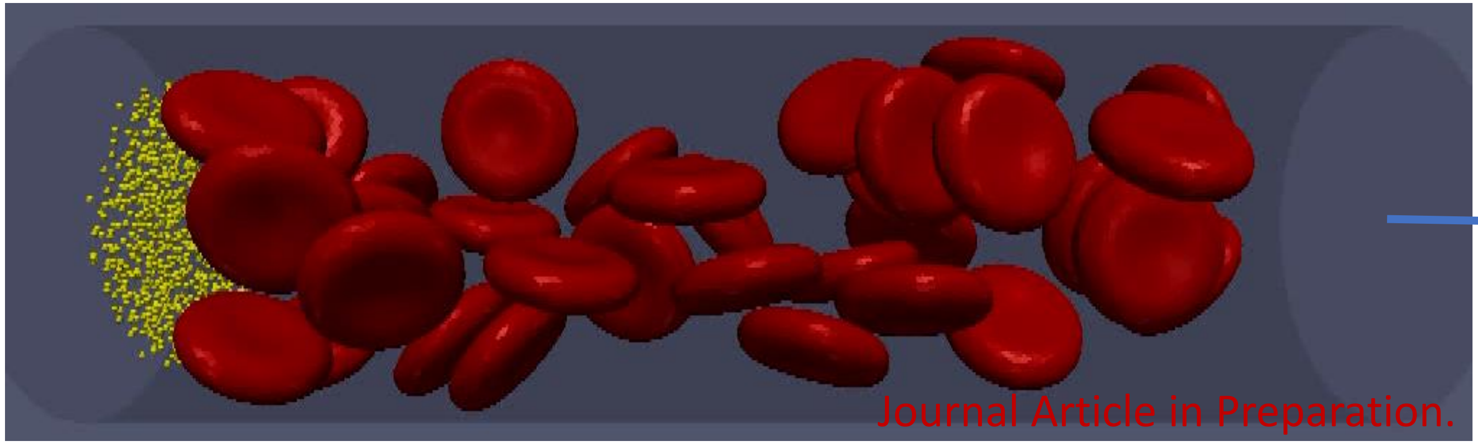
- $d^*_v = 2.5$, $\Phi = 20\%$, $Ca_w = 0.12$ are fixed with $Pe_P = 0.01, 0.1, 10.0$ *and* ∞ to **study the effect of Peclet number on NP diffusion.**

Reasor, Clausen & Aidun, J. Num. Meth. Fluids, 14, 2010.

Application to NP diffusion in a capillary vessel

$$Pe = \frac{3\pi\mu\dot{\gamma}_w d_P^3}{4k_B T}$$





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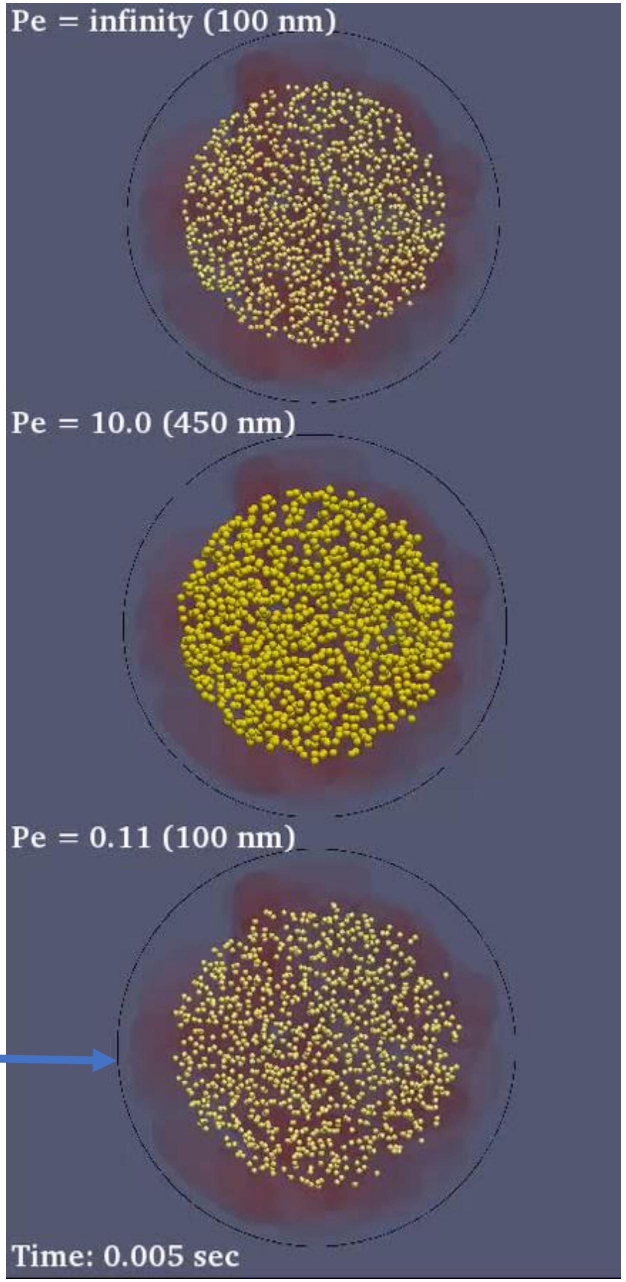

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Application to NP diffusion in a capillary vessel

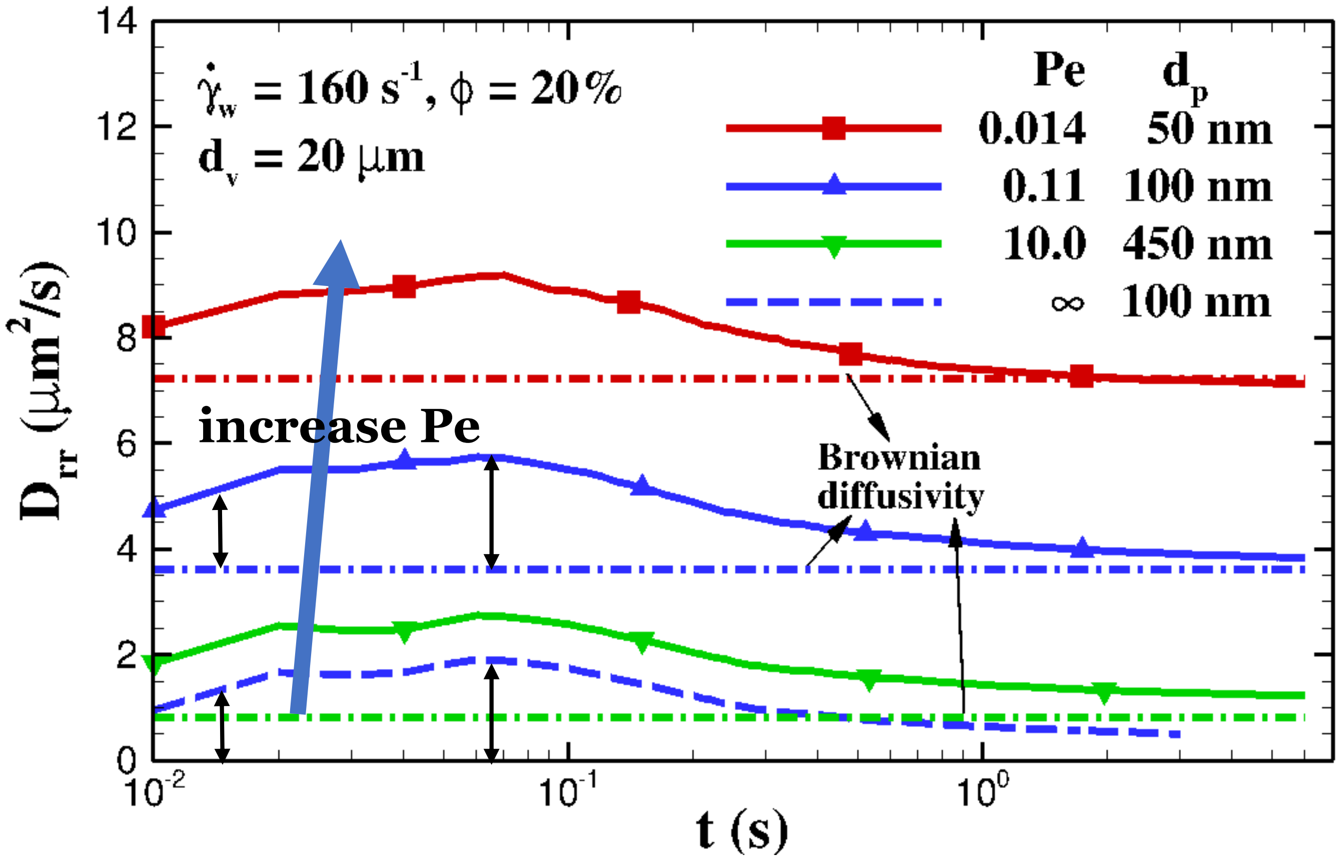
$$D_{rr} = \frac{MSD_t(\Delta r^2)}{2\Delta t} \quad (\Delta t = 1000)$$

$$D_{Brwn} = \frac{k_B T}{3\pi\rho\nu d_p}$$

Observations:

- $Pe \uparrow \rightarrow D_{rr} \uparrow$
- Brownian diffusivity is **linearly added (no coupling)** to the RBC enhanced diffusivity

- At equilibrium:
- For 0~100 nm particles, **Brownian diffusion is dominant**;
- For > 450 nm particles, **RBC enhanced diffusion is competing with Brownian diffusion.**



$$Pe_P = \frac{3\pi\mu\dot{\gamma}_w d_P^3}{4k_B T}$$

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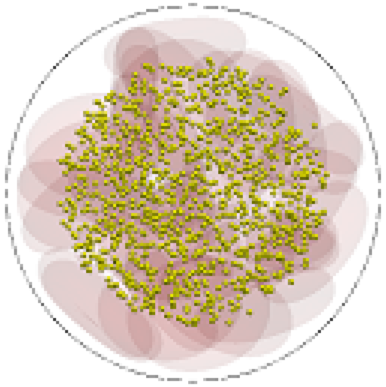
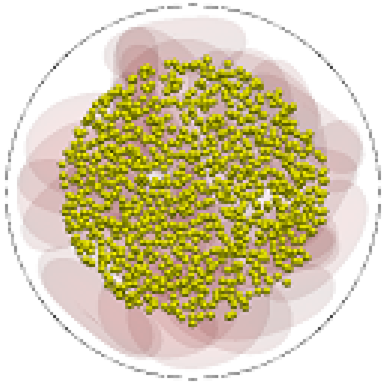
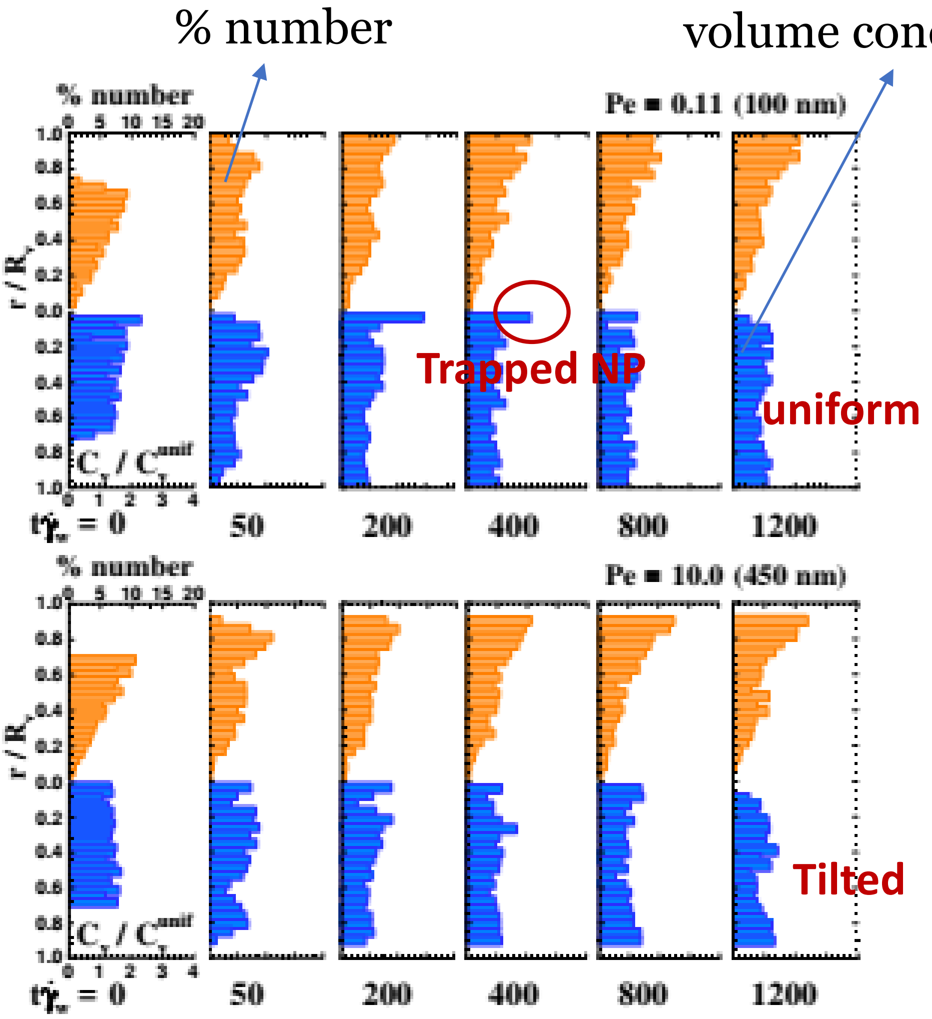
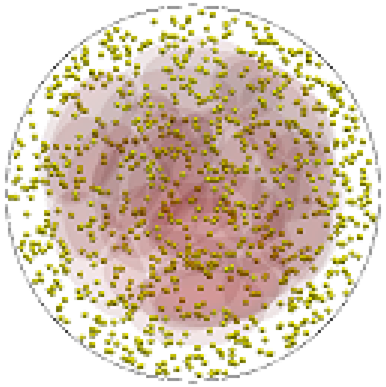
Application to NP diffusion in a capillary vessel

"Turn on" Brownian effect, yielding both Brownian diffusivity and RBC-enhanced diffusivity



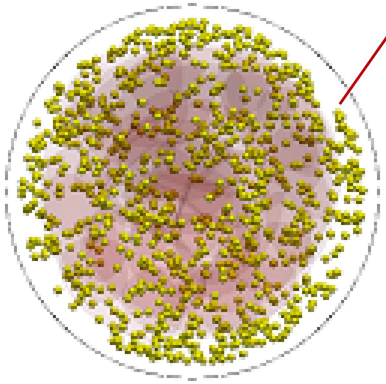






$Pe = 0.11$
$(100\ nm)$

Particle free zone.



$Pe = 10.0$
$(450\ nm)$

$$Pe = \frac{3\pi\mu\dot{\gamma}_w d_P^3}{4k_BT} = \frac{\dot{\gamma}_w d_p^2}{4k_BT/3\pi\mu d_p}$$

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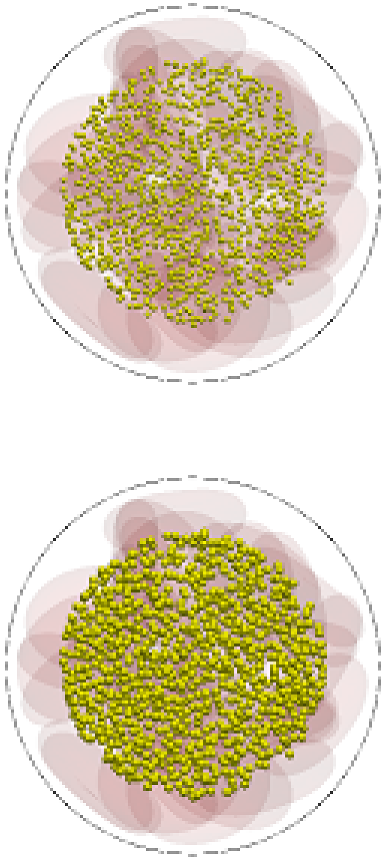
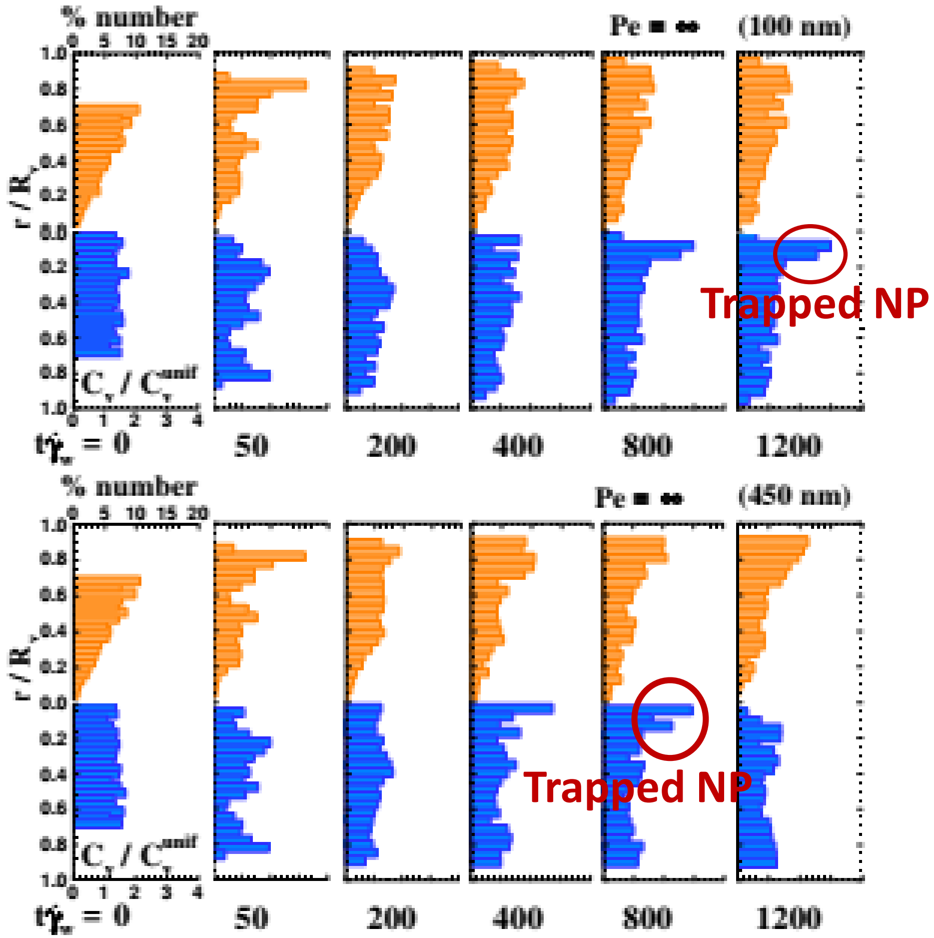
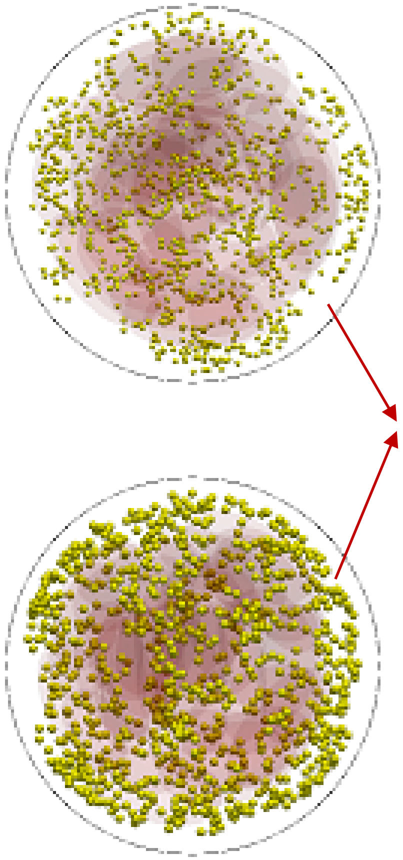
Application to NP diffusion in a capillary vessel

"Turn off" Brownian effect, yielding purely RBC-enhanced diffusivity.







$Pe = \infty$
$(100\ nm)$

Particle free zone.

$Pe = \infty$
$(450\ nm)$

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Conclusion

- **A lattice-Boltzmann based multiscale simulation approach for simulating nanoparticle transport in cellular blood flow has been developed and proved to be successful.**

- **Particles of low *Pe* tend to have higher averaging radial displacement owing to higher averaging radial diffusivity**; Brownian effect contributes the major differences.

- **Particles of high *Pe* could yield "particle free zone"** near the wall due to **low Brownian effect.**

- **Small particles (< 100 nm) are easier to be trapped in RBC-concentrated regions**; Brownian effect is critical for NPs to bypass RBCs.

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Thanks for your attention!

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