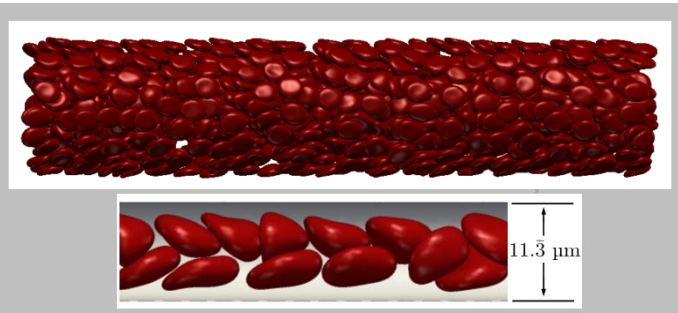
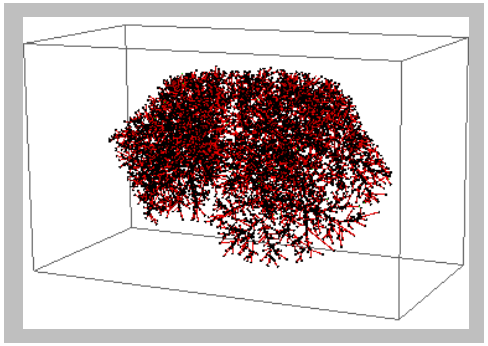
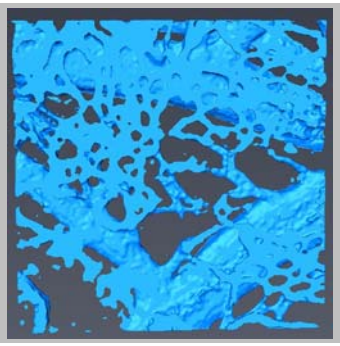
SAND2017-11008C

nano Crispr

Society of Rheology Annual Meeting
October 8-12 , 2017
Denver, Colorado







Continuum Modeling of Nanoparticles Transport in the Vasculature

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Georgia Institute of Technology

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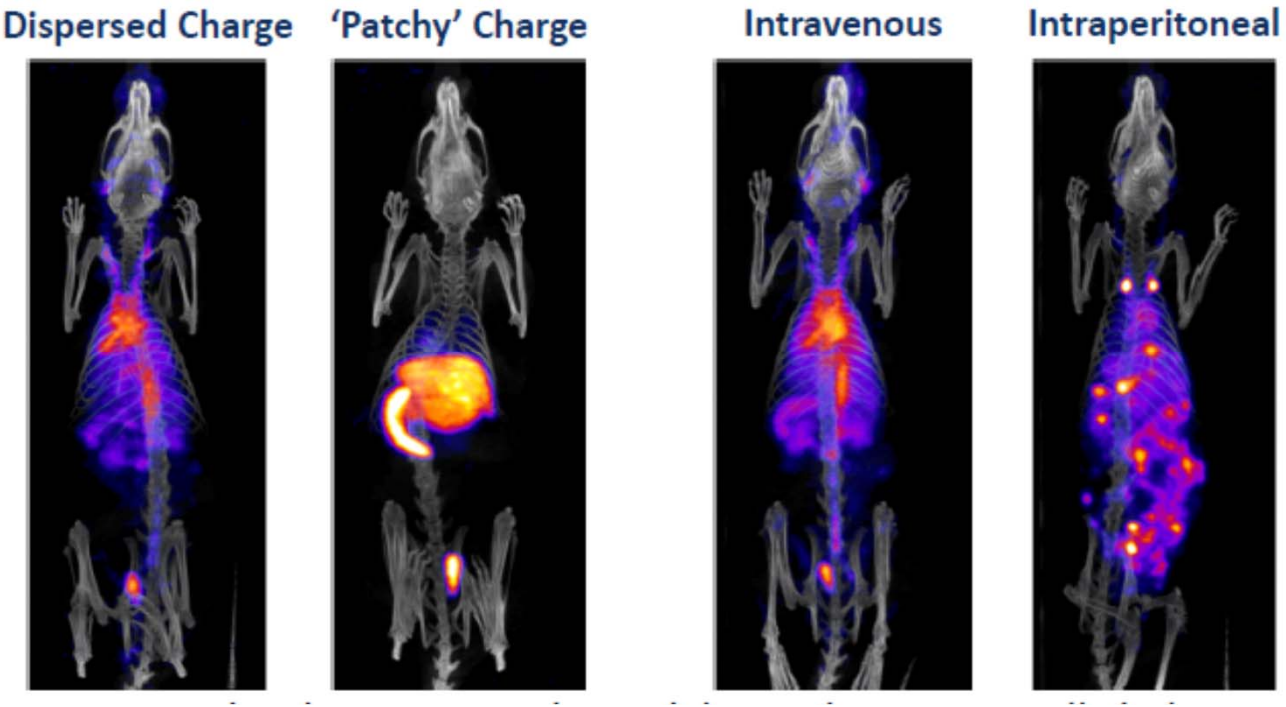
Nanotherapeutics: Develop Understanding of Nanoparticle Transport in Vivo for Targeted Drug Delivery

Sandia National Laboratories

"SPEC CT Images of NP Biodistribution in Mice"
Brinker Group
Sandia and UNM



Myth – Biodistribution is determined by hydrodynamics

- Misleading paradigm in nanotherapeutics – 100nm particles always accumulate in the liver

In reality, the biodistribution is much more complex

- We have rules of thumb, but no clear physics-based understand of why

Modeling can provide fundamental information on NP transport in vivo

- Use multiscale modeling to determine transport of NPs based on size, shape, and surface properties of the NPs

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Cellular Nature of Blood and Complexity of the Vasculature

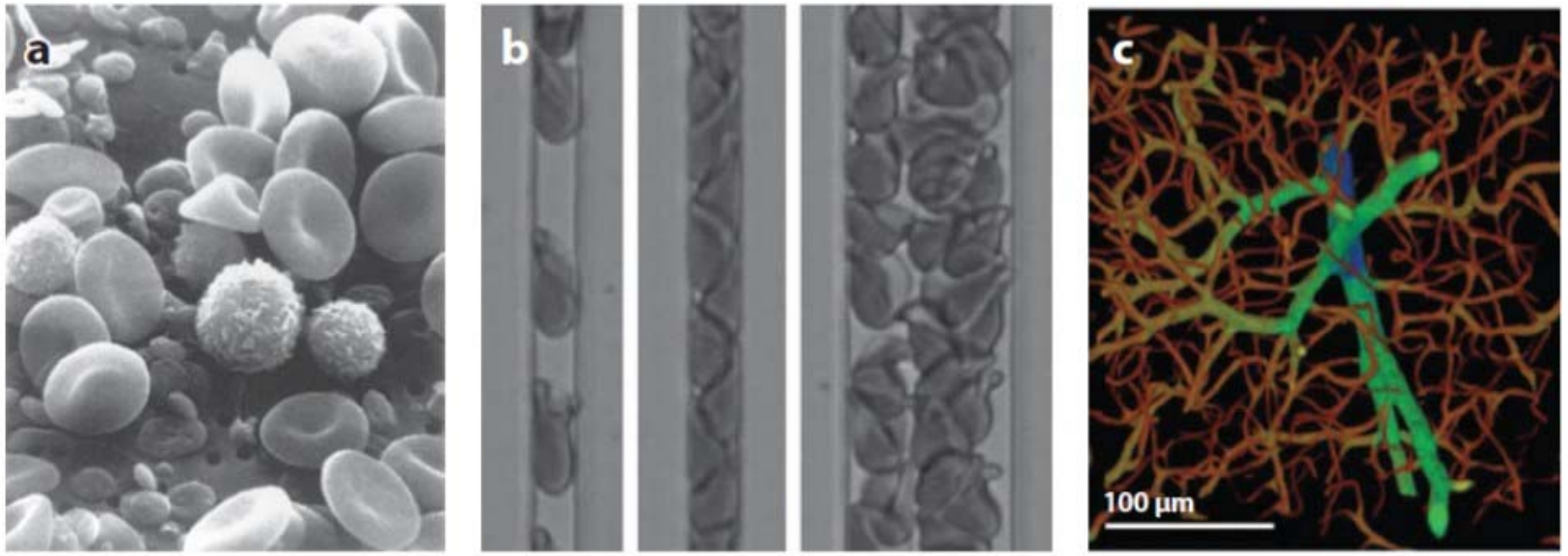


Figure 1

(*a*) Red and white blood cells and platelets at rest (Wetzel & Schaefer 1982) and (*b*) red blood cells flowing in a microfluidic device (Burns et al. 2012). (*c*) A mouse brain microvasculature scan showing its intricate geometry (Mayerich et al. 2011).

RBC Respond Differently Depend on Tube Diameter

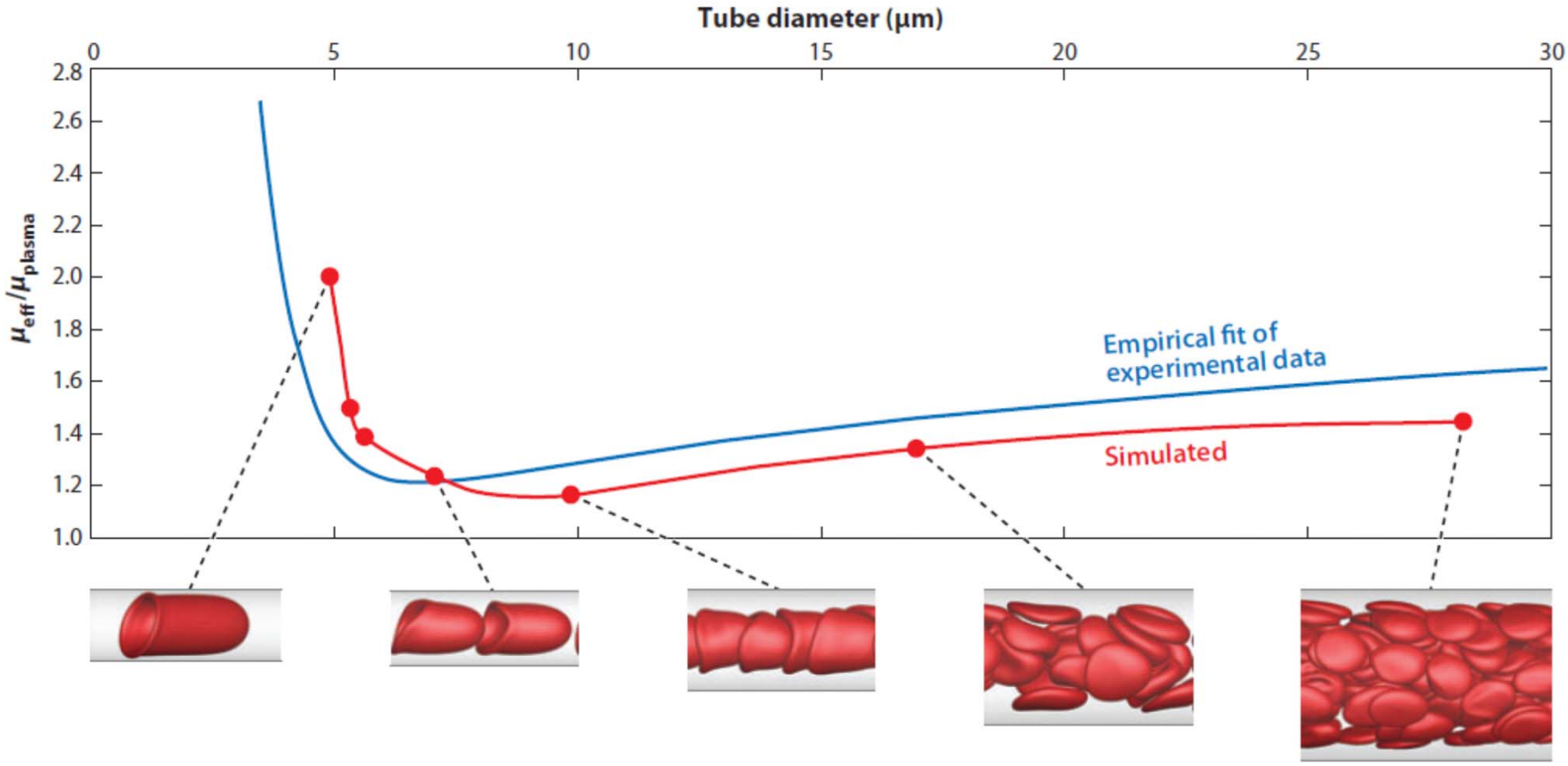
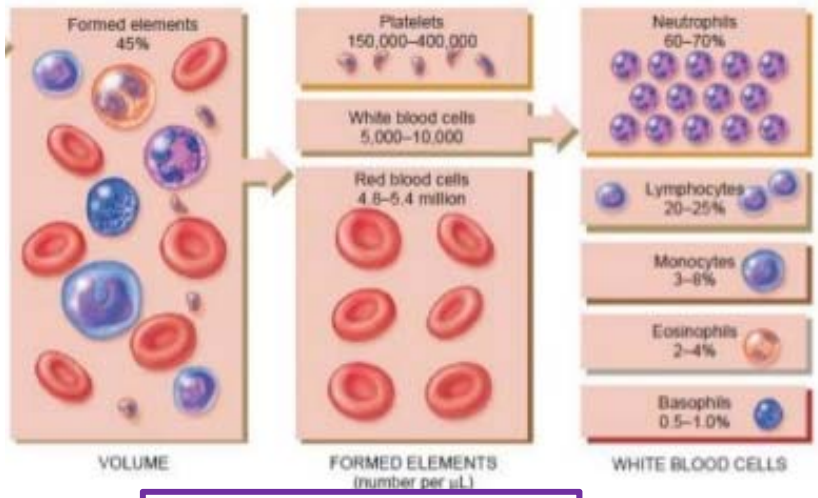


Figure 3

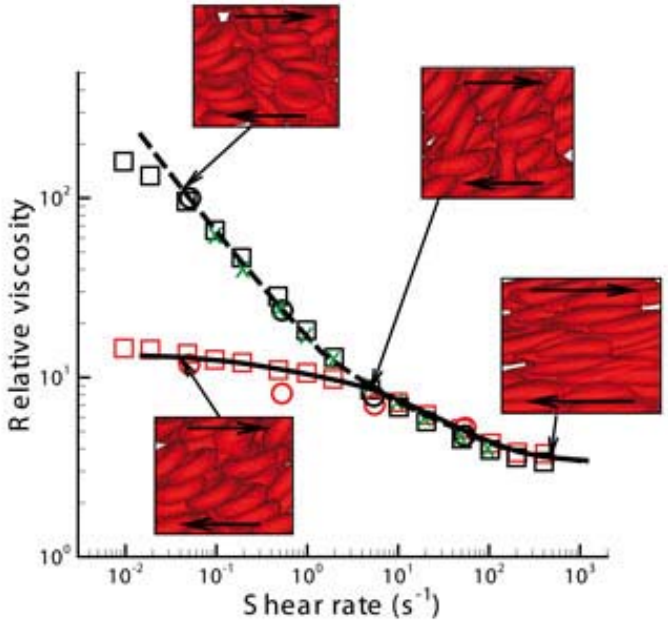
Simulated effective Newtonian-fluid Poiseuille-flow viscosity versus tube diameter (*symbols*) for hematocrit $H_c = 0.30$ (*red line*). The blue line is an empirical fit through a wide range of experimental data (Pries et al. 1992). Figure reprinted with permission from Zhao et al. (2010).

Blood Composition and Rheology



Doshi, SlideShare, LinkedIn, 2014

- Blood is a dense suspension of deformable red blood cells (RBC), platelets, and white blood cells in plasma
- Plasma is an aqueous suspending fluid with proteins
- Inherently two-phase and the flow behavior is a strong function of hematocrit or the concentration of RBCs

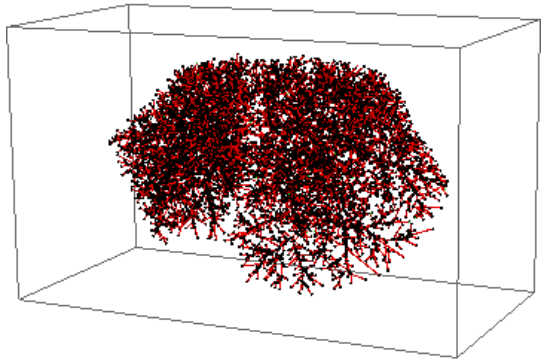


- Non-Newtonian effects such as yield stress, shear-thinning, hysteresis and viscoelasticity can be seen and lead to thixotropy
- Enhanced or hindered diffusivity of NPs via margination as small particles move toward the vessel walls
- Migration of smaller particles, e.g. platelets

Fedesov et al, PNAS, 2011

Multiscale Approach

small-scale capillaries



Organ-scale model of mouse liver (0.1 cm)

Multiscale approach is necessary for modeling

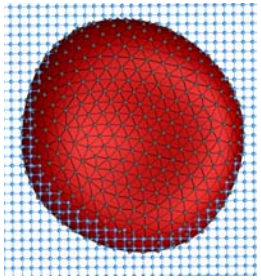
- Direct numerical simulation (DNS) of cellular scales
- Modeling of arterial-scale using a continuum approach
- Modeling of organ vasculature using network models

NP may move more slowly than the bulk flow due to adhesion, or more quickly due to velocity fluctuations. Modeling can determine which situation is dominant

Simulation of Cellular-Length Scales

Strategic partnership with Georgia Tech to add nanoparticles to cell-scale models

- Lattice-Boltzmann/spectrin-link code developed at Georgia Tech
- Demonstrated scalability on capability class clusters
- Langevin equation used for NP and coupled to RBCs

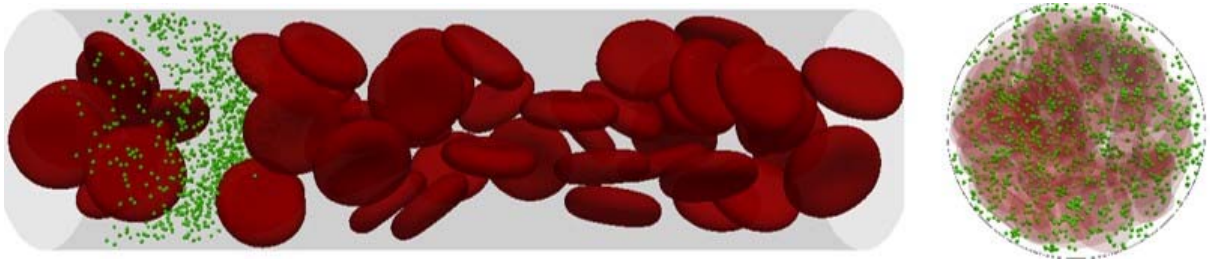


Red blood cell (RBC) model with surrounding fluid mesh

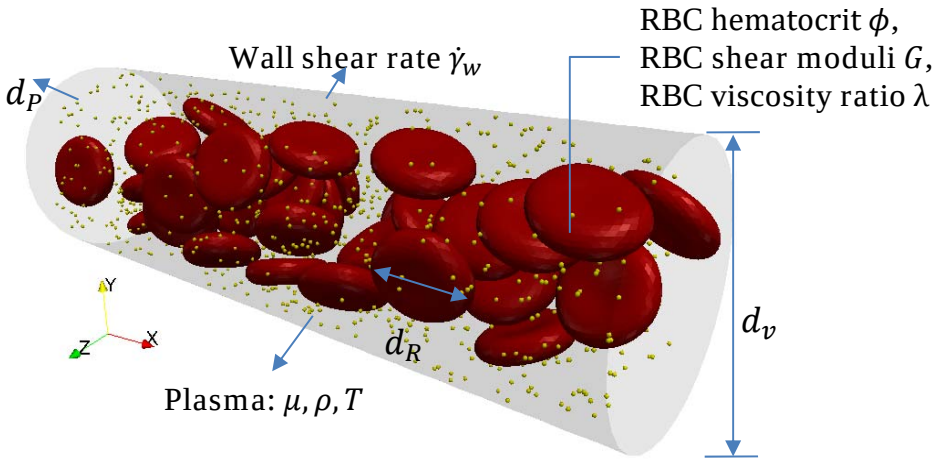
"Parachuting" of RBCs in capillaries

- Aidun, Lu, & Ding, *JFM*, 373, 1998.
- MacMeccan, Clausen, Neitzel, & Aidun, *JFM*, 618, 2009.
- Reasor, Clausen, & Aidun, *IJNMF*, 2011.

Deformable RBCs in a capillary with nanoparticles



NP Diffusion in A Capillary Vessel: Relevant Parameters



$$D^*_{rr} = \Phi\left(d^*_v, \phi, Pe, Ca_w\right)$$

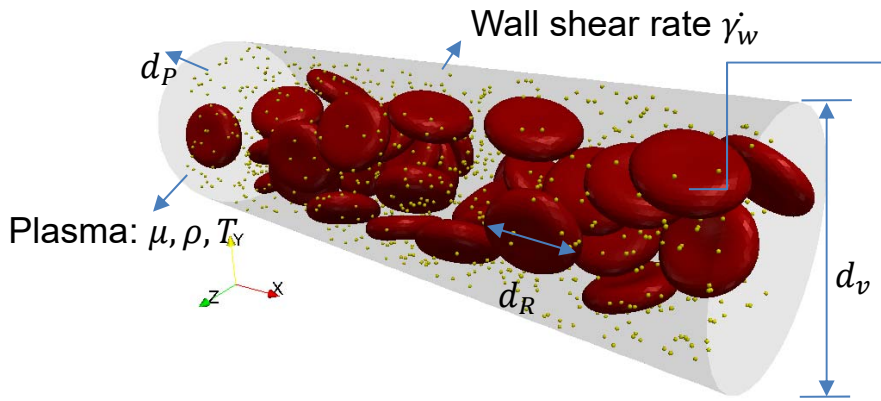
Note: In capillary vessels, Re << 1. Not a critical parameter.

Normalized Radial diffusivity:

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

- **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** $Ca_w = \frac{\mu\dot{\gamma}_w d_R}{2G}$;

NP Diffusion in A Capillary: Simulation Setup



$$D^*_{rr} = \Phi\,(d^*_v, \phi, Pe, Ca_w)$$

Fung (2013)
Zweifach (1974)

Physiological ranges of relevant parameters	
$d_v\ (\mu m)$	8 ~ 30
ϕ	10% ~ 26%
$\dot{\gamma}_w\ (s^{-1})$	50 ~ 1200
$d_p\ (nm)$	50 ~ 500

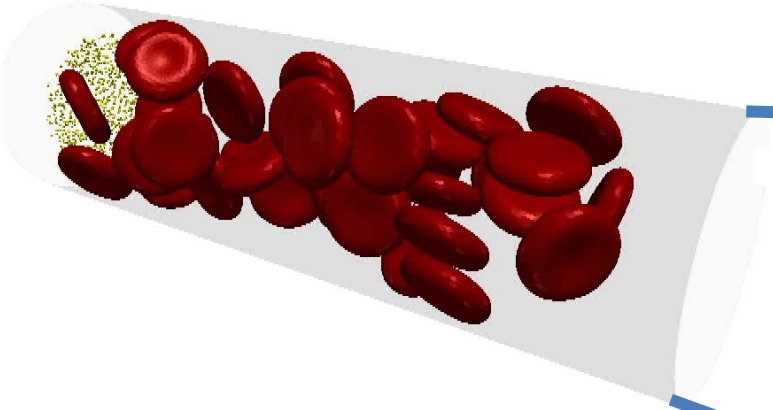
Non-dimensional Parameters	
d^*_v	1.0 ~ 3.8
ϕ	10% ~ 26%
Ca_w	0.04 ~ 0.90
Pe	0.004 ~ 100.0

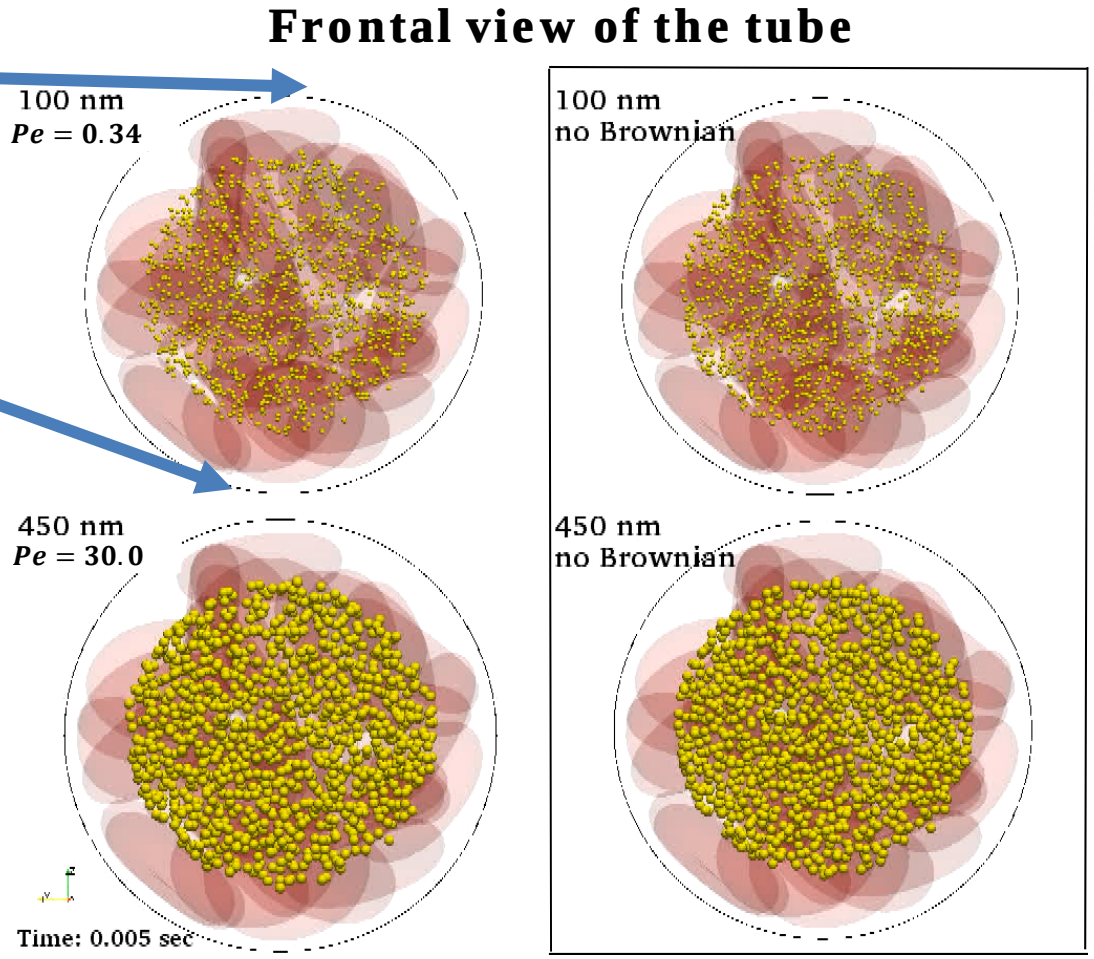
To study the effect of Peclet number on NP diffusion

Selected Parameters	
d^*_v	2.5
ϕ	20%
Ca_w	0.37
Pe	0.04, 0.34, 30.0, ∞

By "turn off" Brownian effect

Radially Outward RBC-enhanced Diffusion of Nanoparticles





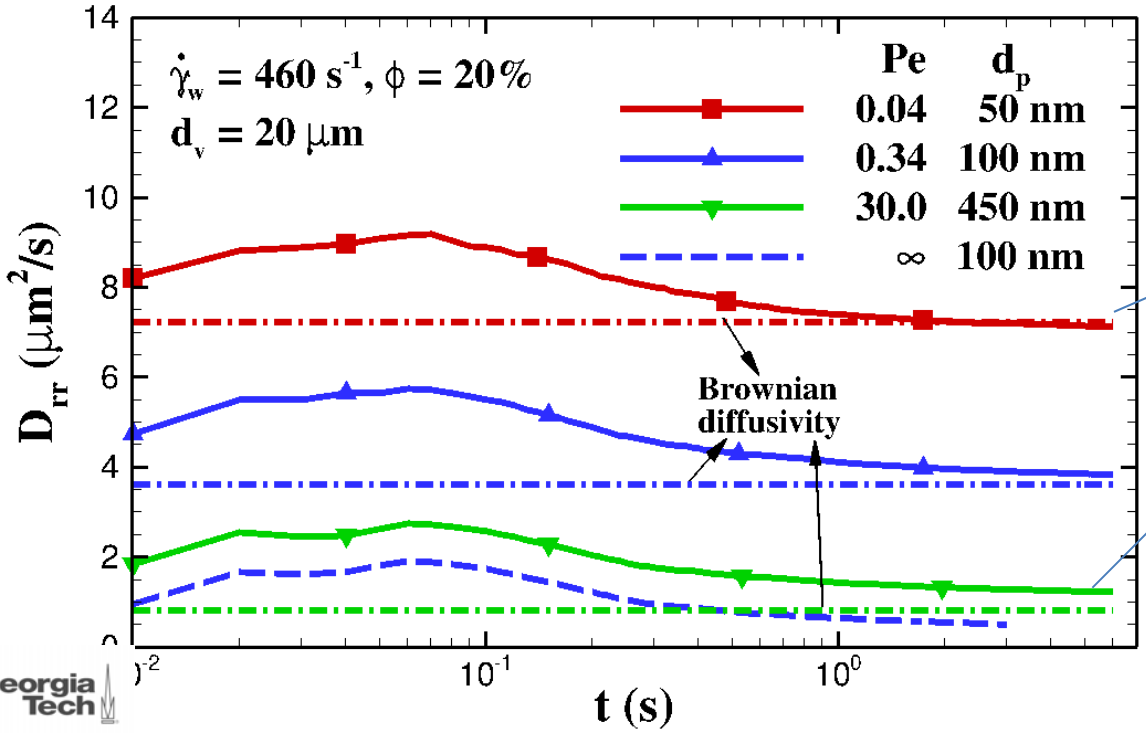
Non-dimensional Parameters		
d_v^*	2.5	2.5
ϕ	20%	20%
Ca_w	0.37	0.37
Pe	0.34	30.0

NP Diffusion in A Capillary : NP Radial Diffusivity

Mehrabadi, Ku, & Aidun, *Ann. Biomed. Eng.*, 2015.

- **Total Diffusion = Brownian diffusion + RBC-enhanced diffusion**

$$D_{rr} = D_{rr}^{B} + D_{rr}^{RBC}$$



For micro-sized particles:

Pe~∞ → $D_{rr}^{B}/D_{rr}^{RBC} \ll 1$

At equilibrium:

- **Pe ~ 0.04 (nano-sized):** $D_{rr}^{B}/D_{rr}^{RBC} \gg 1$
- **Pe ~ 30.0 (submicro-sized):** $D_{rr}^{B}/D_{rr}^{RBC} \sim 1$

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

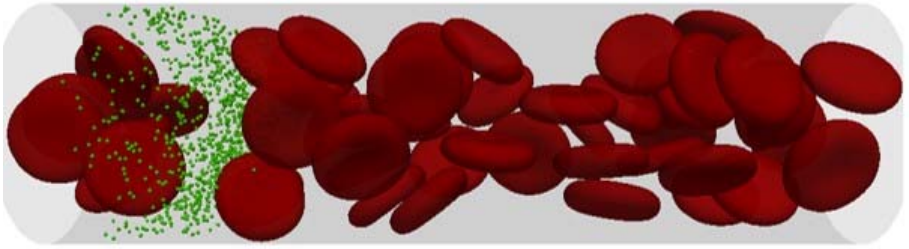
Continuum Model: NP Transport

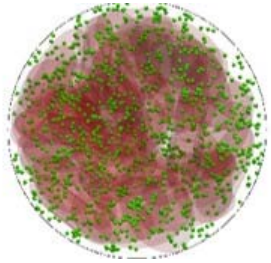
- Suspension model for RBC to give local concentration of cells (Phillips model)
- Assume neutrally buoyant particles
- Use Zydney & Colton for of diffusion NP, which will move away from RBCs

RBC migration

$$\frac{\partial \phi}{\partial t} + v \bullet \nabla \phi = -\frac{\nabla \bullet J_s}{\rho}$$

$$\frac{J_s}{\rho} = -\left(\phi K_c \nabla(\dot{\gamma}\phi) + \phi^2 \dot{\gamma} K_\eta \nabla(\ln \eta) \right)$$



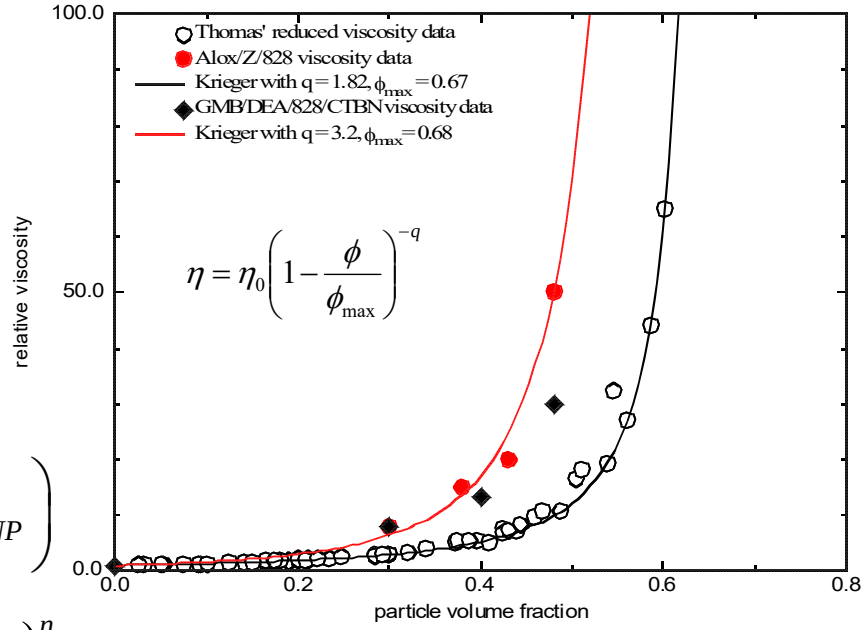


NP migration

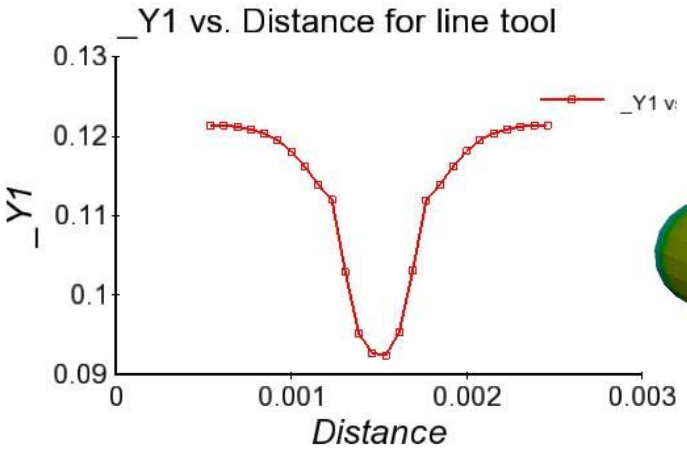
$$\frac{\partial \varphi_{NP}}{\partial t} + v \bullet \nabla \varphi_{NP} = -\frac{\nabla \bullet J_{NP}}{\rho}$$

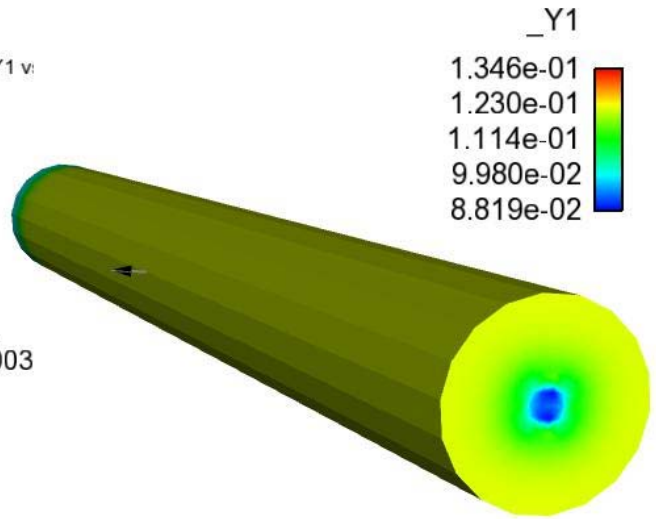
$$\frac{J_{NP}}{\rho} = -\left(\varphi_{NP} K_c \nabla(\dot{\gamma}\varphi) + \varphi_{NP} \varphi \dot{\gamma} K_\eta \nabla(\ln \eta) + D_{eff} \nabla \varphi_{NP} \right)$$

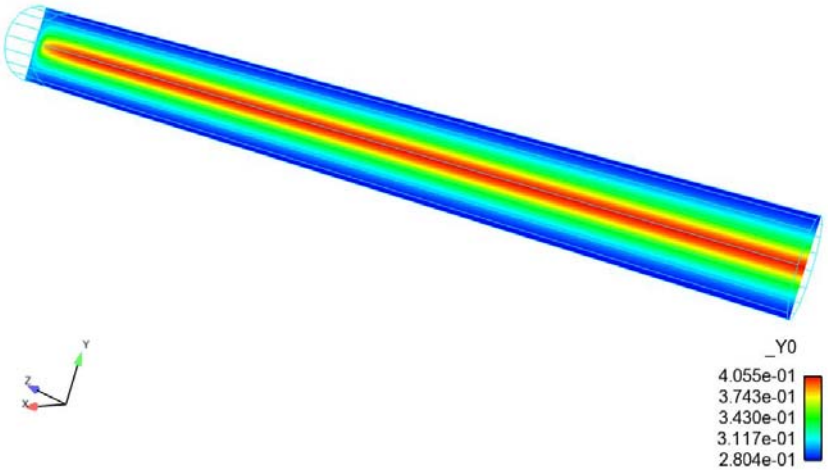
$$D_{NP} = \frac{k_B T}{3\mu d_{NP}} \qquad D_{eff} = D_{NP} + k a_{RBC}^2 \dot{\gamma} \phi_{RBC} (1 - \phi_{RBC})^n$$

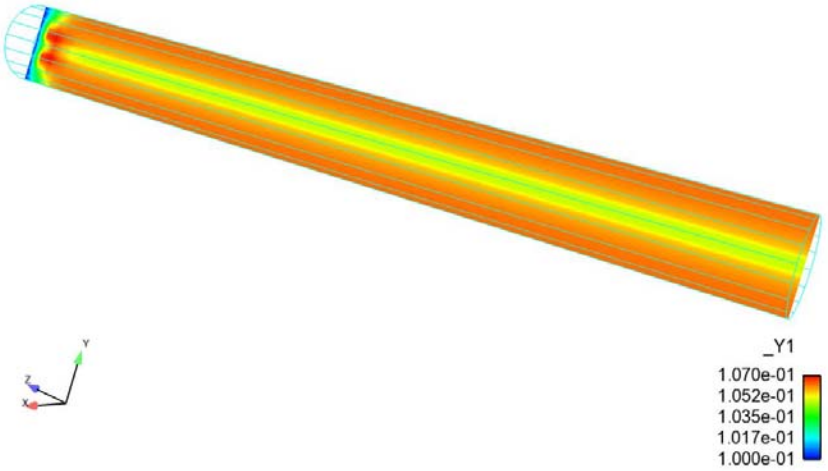


Continuum Model: NP Transport in A Capillary

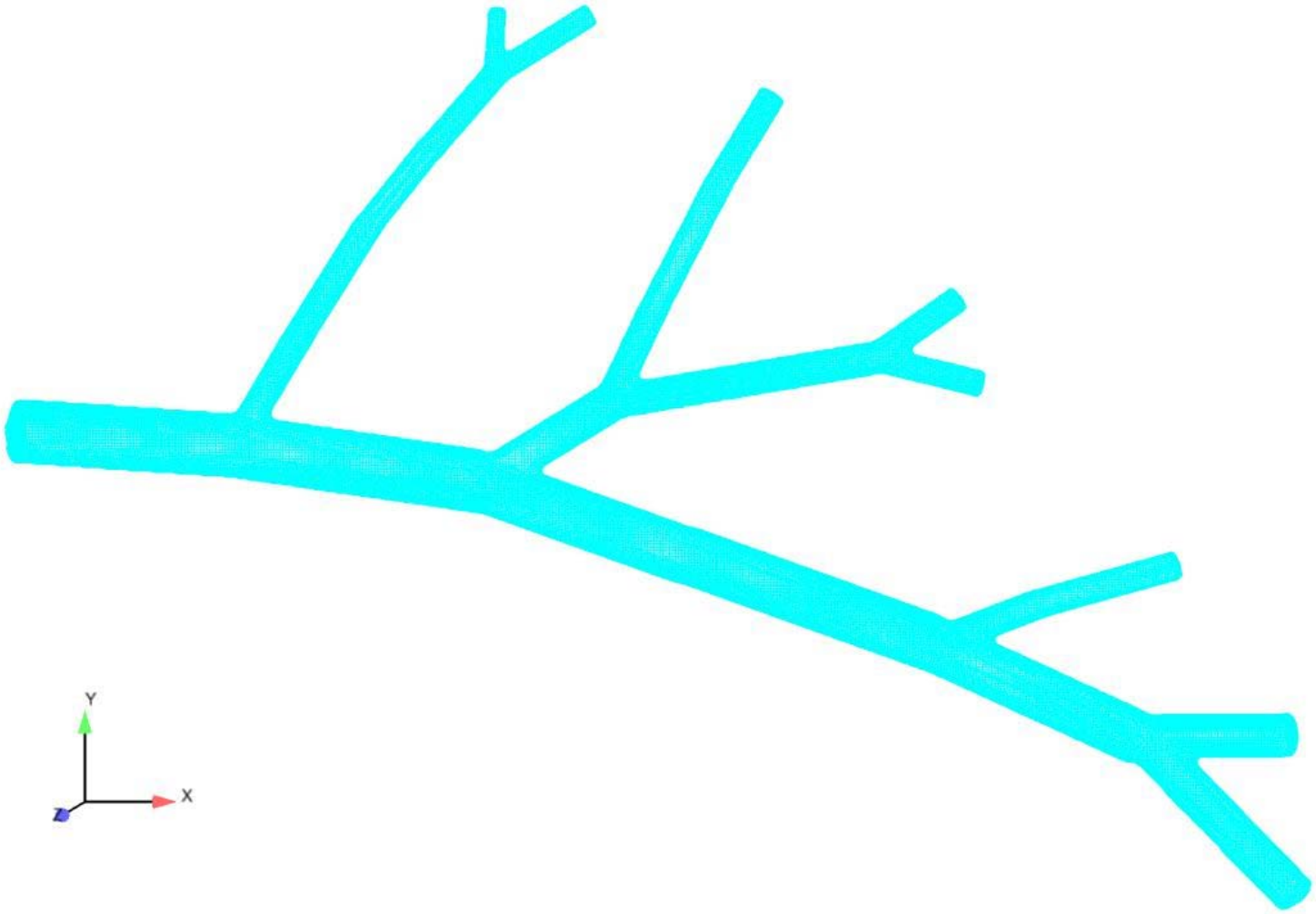




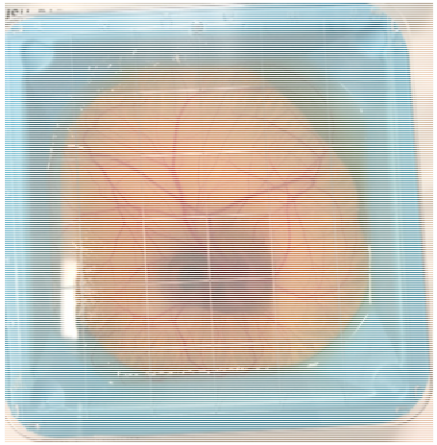




Synthetic Branching Microvessels

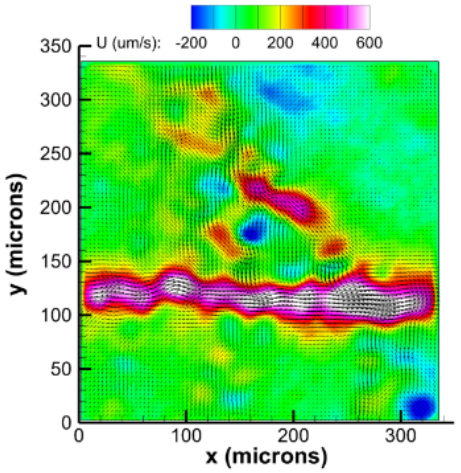


Experimental Approach for Validation Data

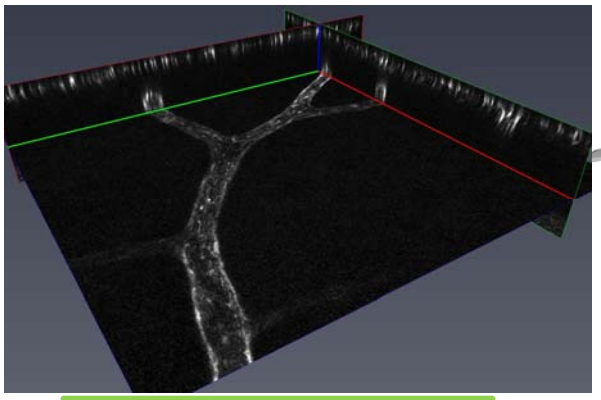


Chicken Embryo (CAM)

- Imaging large vessels in CAM which are deeper and required a new lens
- Two-photon data on the large vessels in the CAM 2D image slices into a 3D reconstruction and create a finite element mesh using CDFEM
- Working on new PIV data for large vessels. Kim Butler has just obtained usable new data and Justin Wagner is processing it for velocities!

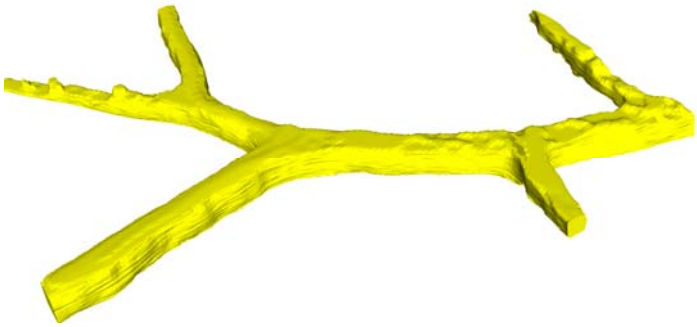


Early PIV of large vessels



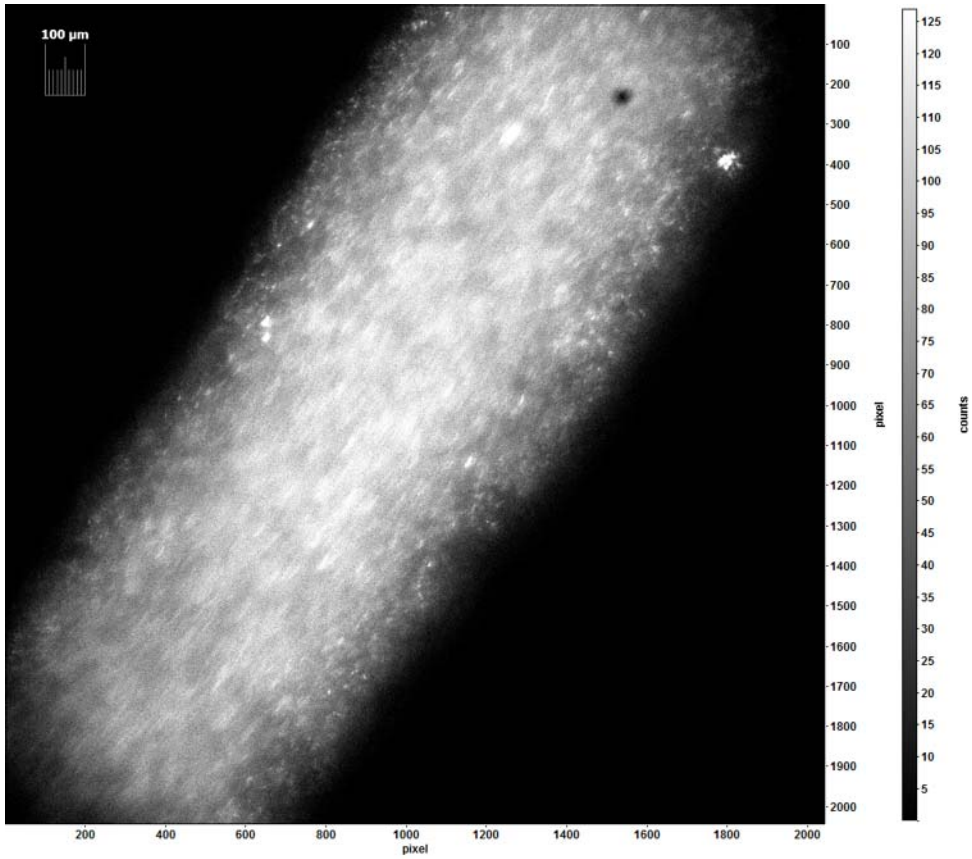
CAM two-photon data

3D reconstruction from AVISO



Finite element mesh from CDFEM

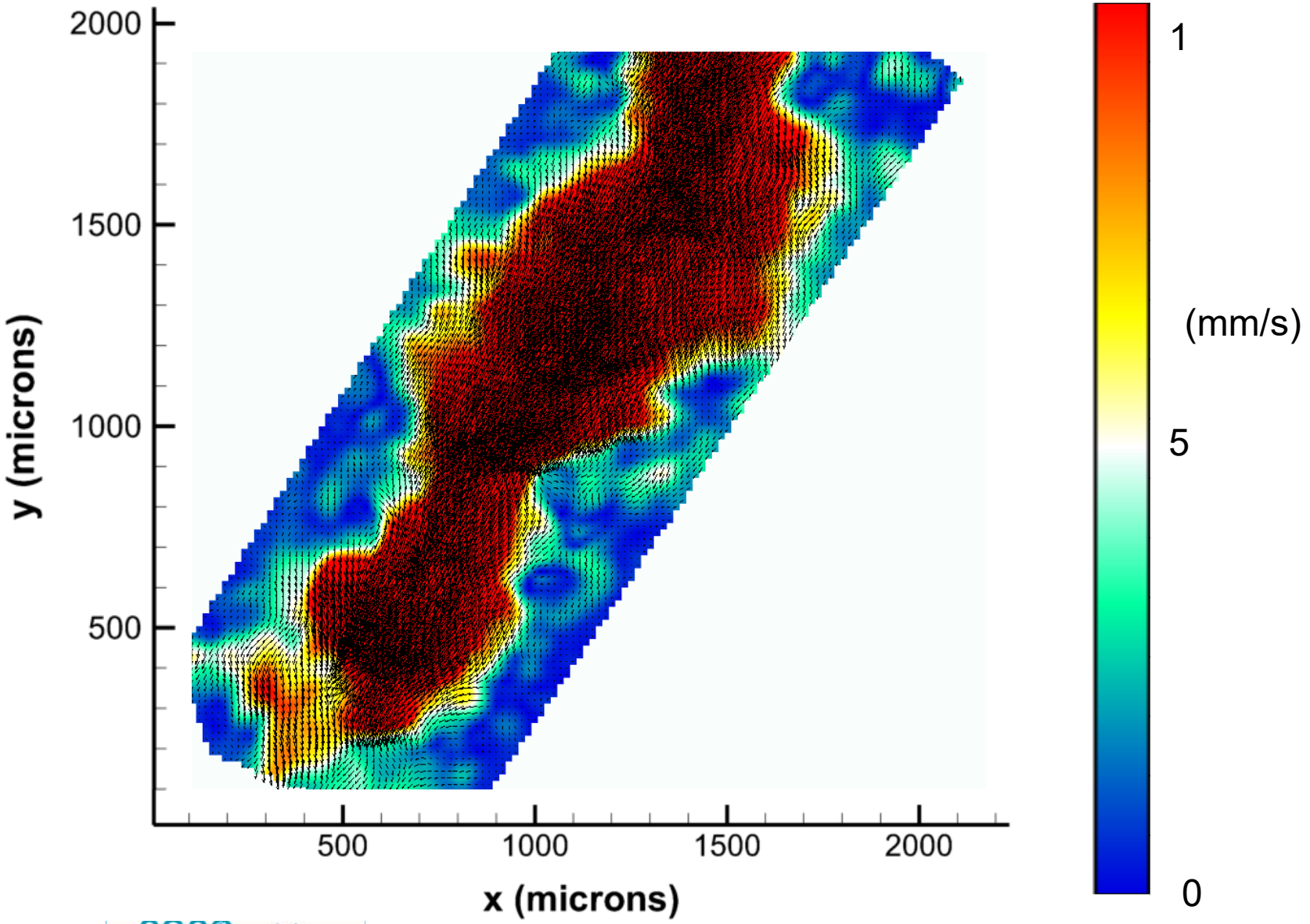
High-magnification Imaging of a Deep, Large Vessel in the CAM



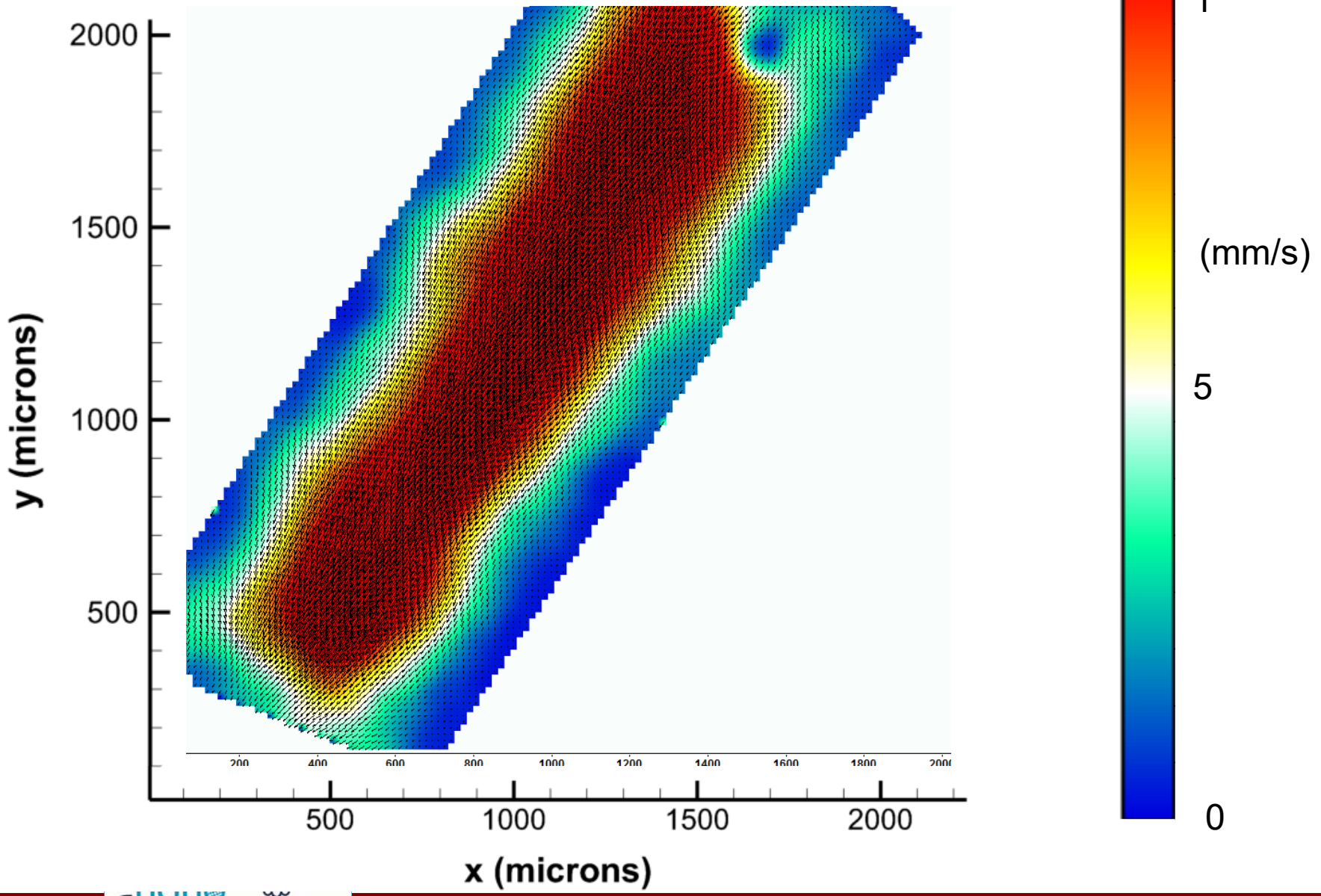
- Fluorescent particles having 180 nm diameter, no cargo
- *Water immersion lens to view deeper into CAM model*
- Particle images are blurry at peak velocities, but we can lower exposure some to improve image quality

Though non-ideal we can use these data as a first cut to measure velocity profiles across the vessel

Movie of Instantaneous Velocity Magnitude

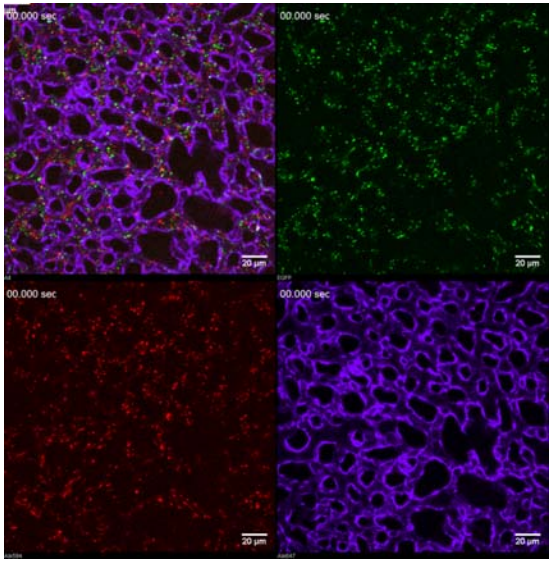


Mean Velocity Magnitude

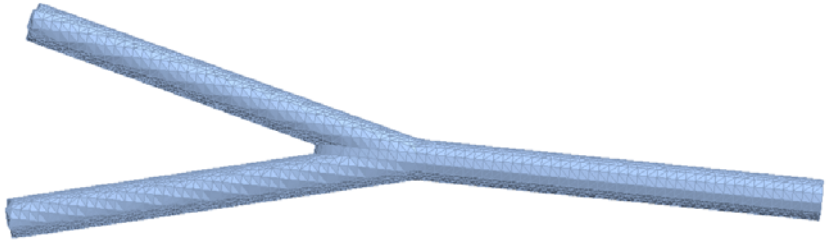


Conclusions and Next Steps

- Next steps:
  - Run viscometric flows RBC/NP statistics to support diffusion models
  - Use more advanced model for RBC transport for nanoparticle transport with RBCs and compare to available data
  - Complete network model for the mouse liver and compare to available data – complete journal article
  - Image deep vessels in CAM/PIV for NP transport in vessel with bifurcation. Microfluidic experiments for mock CAM.



CAM confocal imaging of red and green fluorescent NPs with vascular stain
-Hon Sing Leong (Western University and the Mayo Clinic)



Idealized branch structure – abstraction of the CAM deep vessels

Computational Approach

Sandia National Laboratories

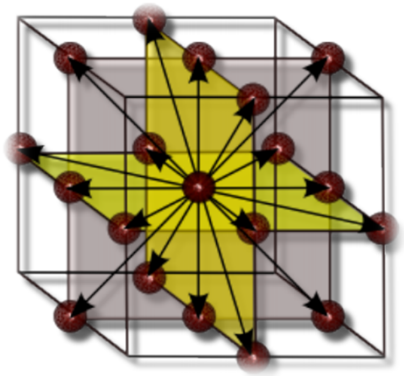
Multi-scale

Meso-scale

Lattice-Boltzmann (LB) method for fluid

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

Aidun & Clausen. Annual Rev. Fluid Mech., 42, 2010.



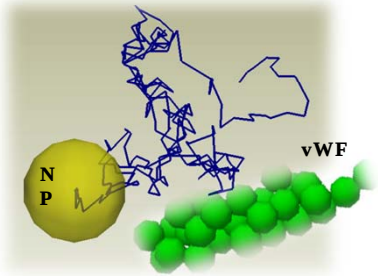
LB-LD two-way coupling

Aidun et. al. J. Fluid Mech., 1998.

Fluid-cell two-way coupling

Comprehensive two-way couplings

Nano-scale



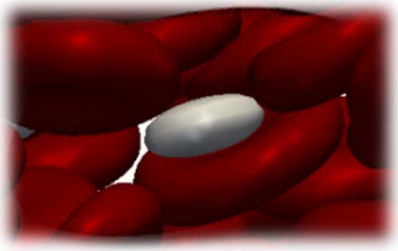
Langevin dynamics (LD) for NP/Nano-proteins

Micro-scale

Cell models:

- **RBC: Spectrin-link (SL) method**
- **Platelet, etc.**

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



Lennard–Jones potential, Morse potential.

Jones, Proc. R. Soc. London. Ser. A, 106, 1924.
Neu & Meiselman, Biophys. J., 83, 2002.