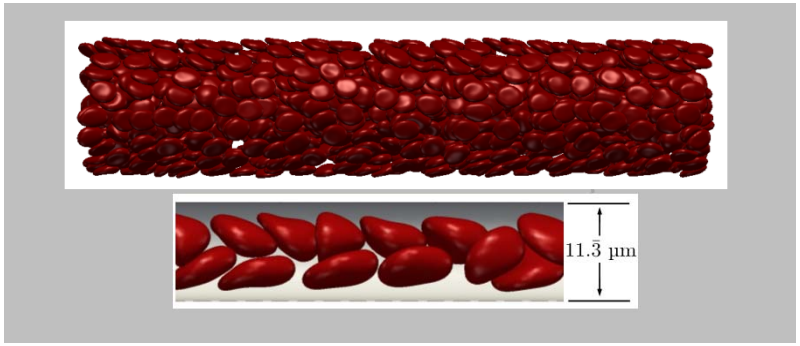
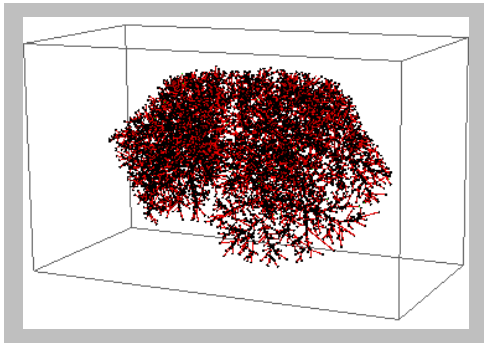
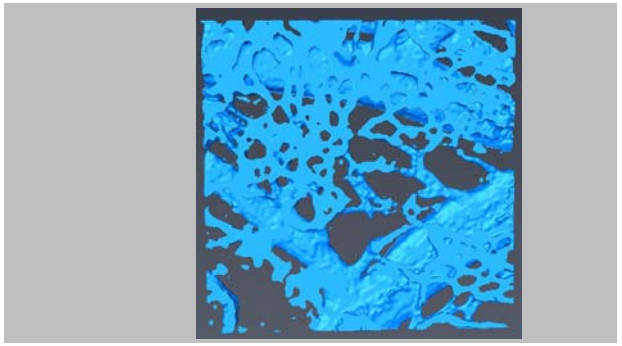
SAND2017-1434C

nanoCrispr

Society of Rheology Annual Meeting
February 12-16, 2017
Tampa, Florida







Towards Modeling Biodistribution of Nanoparticles in Vivo

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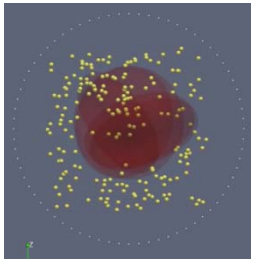
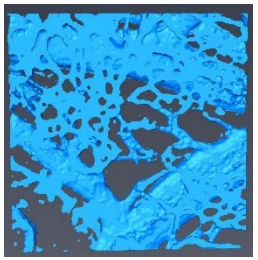
Objectives

Overall goal – Biodistribution predictions for CAM and mouse liver

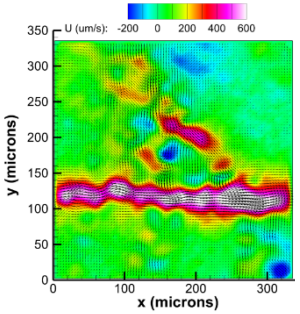
1. Overview of Blood Rheology
2. Multi-scale Modeling Approach
3. Discussion of Modeling Progress to Date
   a. Red Blood Cell Scale
   b. Continuum Scale
   c. Network Scale
   d. *Experimental discovery and validation*
4. Next Steps
5. Conclusions



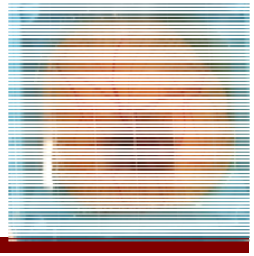
NP and RBC interactions



Surface mesh CAM



NP PIV from CAM

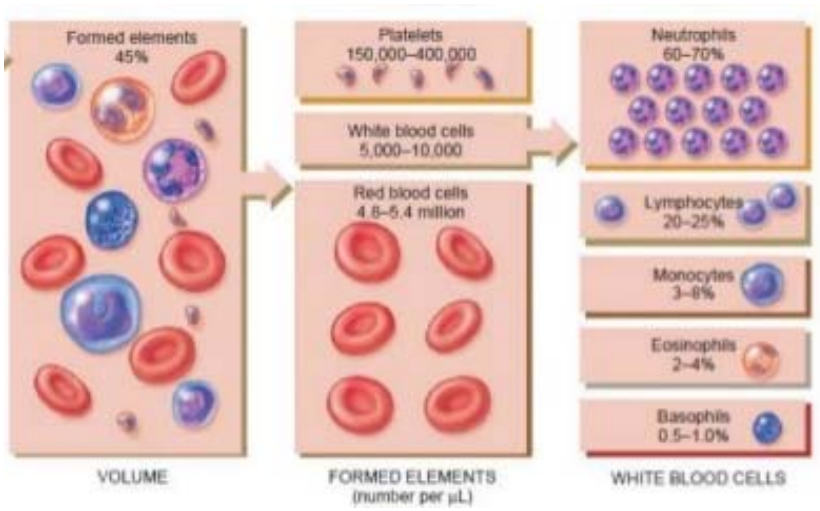


Cross-cut: Data needed for all models – characterization, discovery and validation

Outline of Biodistribution Modeling

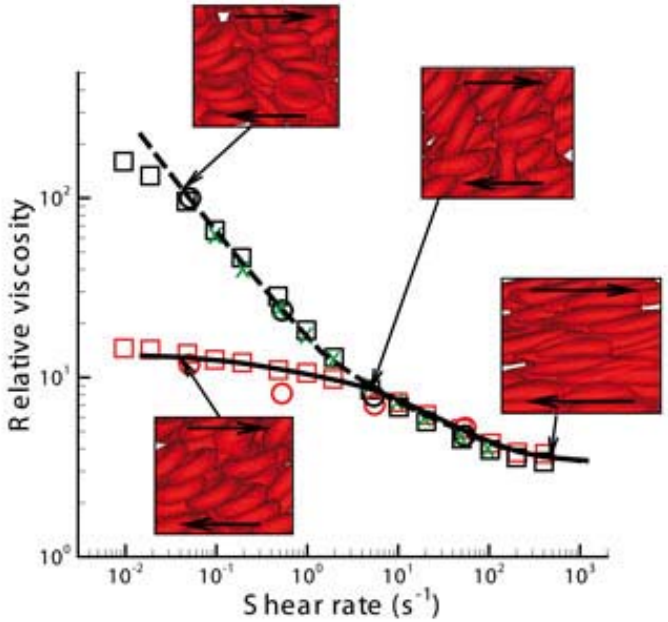
1. Overview of Blood Rheology
2. Multi-scale Modeling Approach
3. Discussion of Modeling Progress to Date
    a. Red Blood Cell Scale
    b. Continuum Scale
    c. Network Scale
    d. *Experimental discovery and validation*
4. Next Steps
5. Summary and Impact

Blood Composition and Rheology



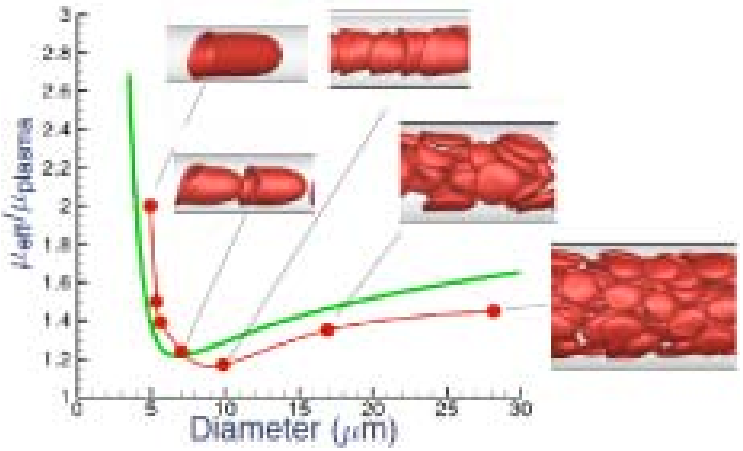
- Blood is a dense suspension of deformable red blood cells (RBC), platelets, and white blood cells in plasma
- Plasma is an aqueous suspending fluid with proteins
- Inherently two-phase and the flow behavior is a strong function of hematocrit or the concentration of RBCs

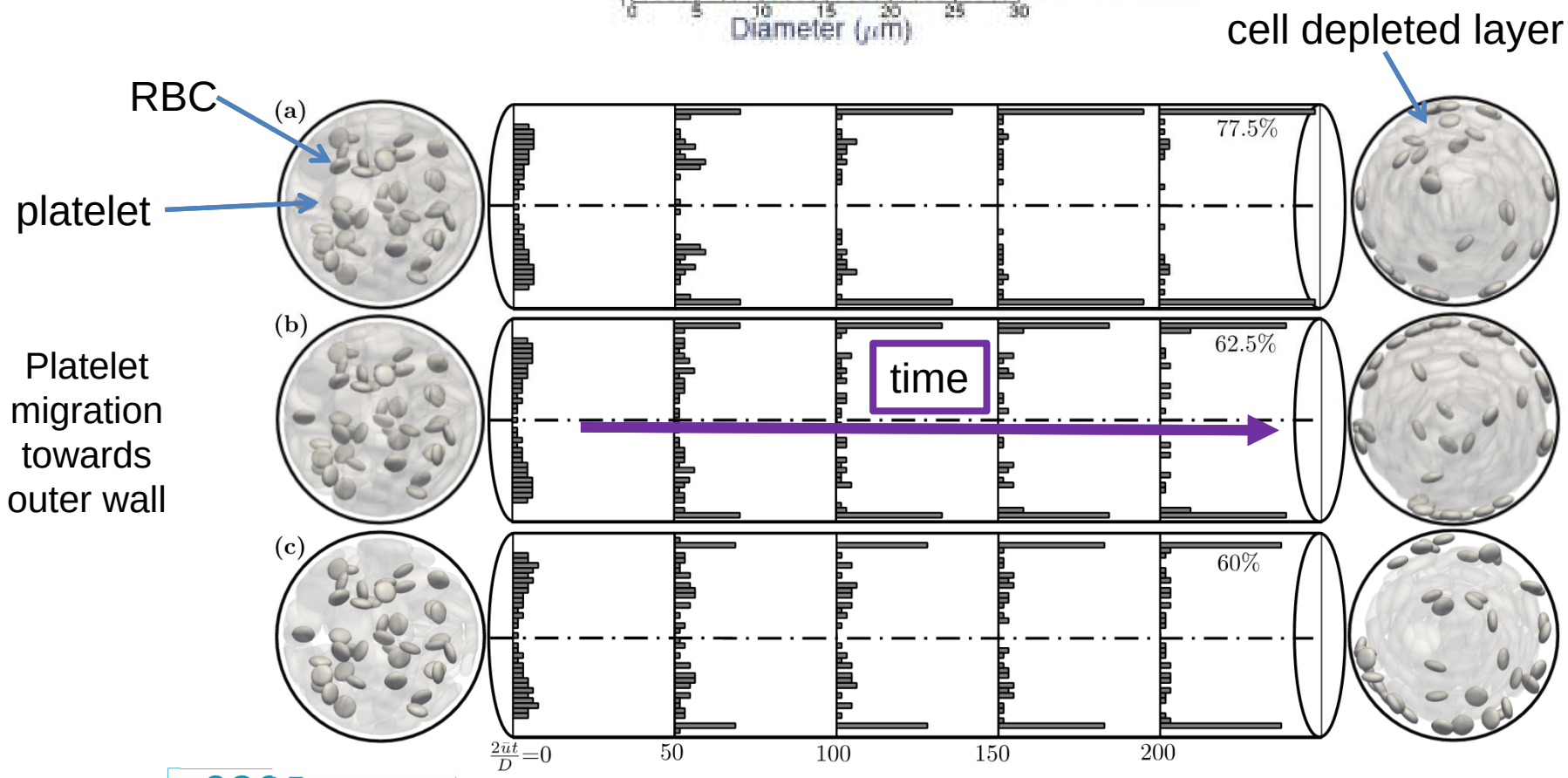
- Non-Newtonian effects such as yield stress, shear-thinning, hysteresis and viscoelasticity can be seen and lead to thixotropy
- Enhanced or hindered diffusivity of NPs via margination as small particles move toward the vessel walls
- Migration of smaller particles, e.g. platelets



Blood Flow

- Inherently two-phase
- Enhanced diffusivity
- Migration of smaller particles, e.g. platelets

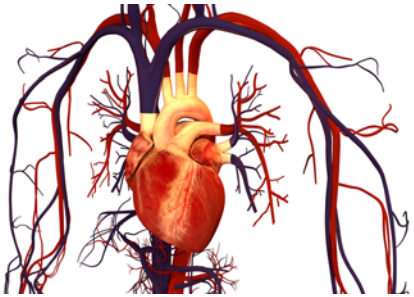




Multiscale Approach

small-scale capillaries

source: wikipedia.org



complete circulatory system
aorta diameter O(1 cm)

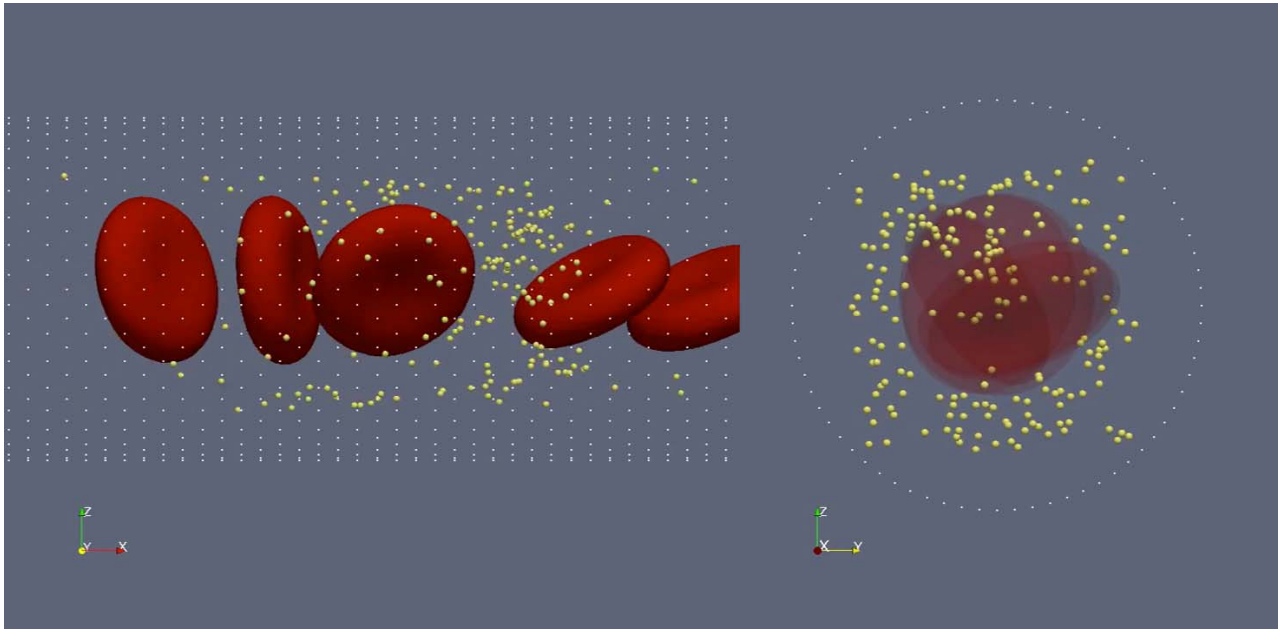
Multiscale approach is necessary for modeling

- Direct numerical simulation (DNS) of cellular scales
- Modeling of arterial-scale using a continuum approach
- Modeling of complete circulatory-scale 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

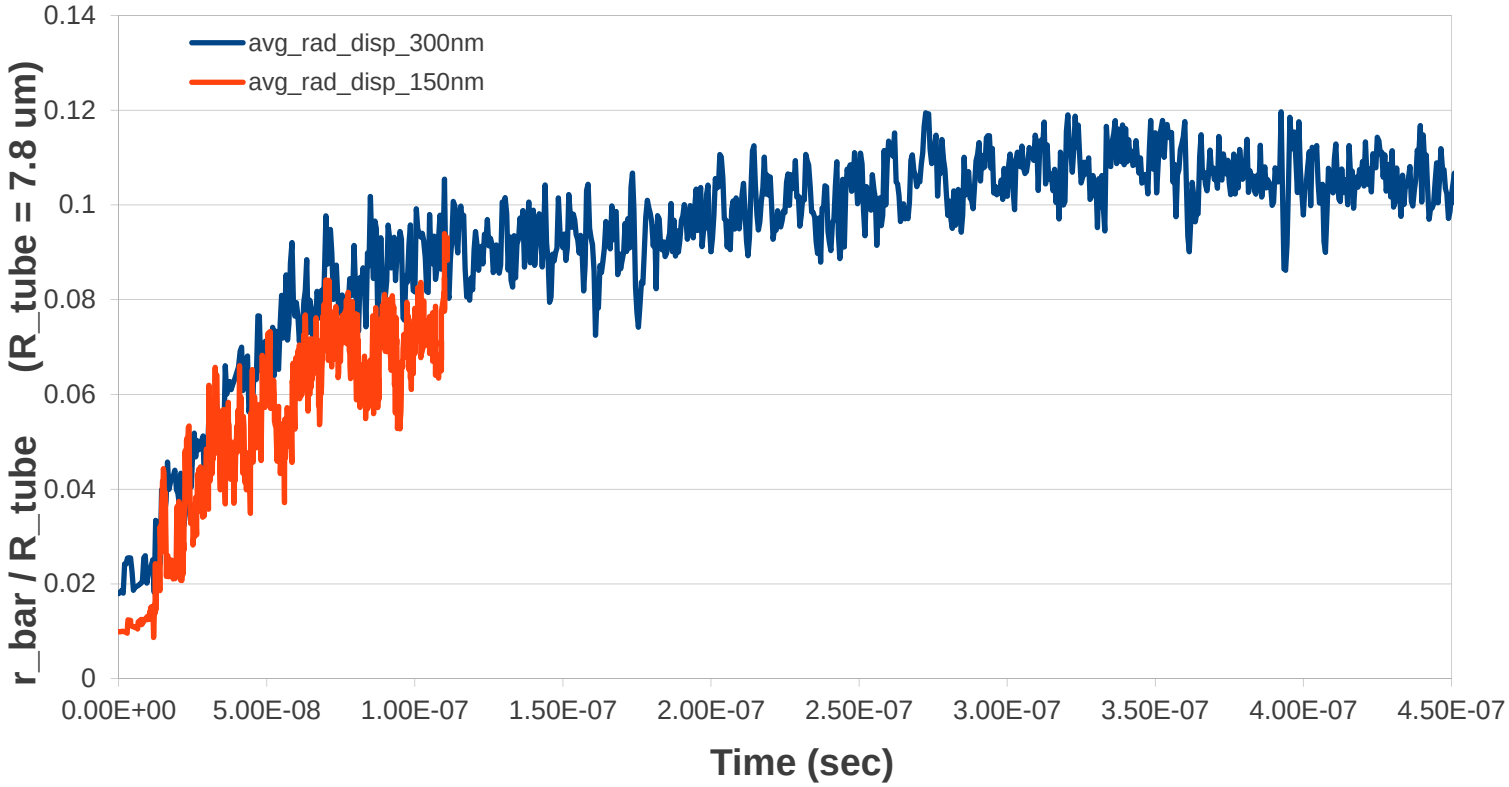
Capillary with 300 nm particles

- Tube diameter 15.6 µm
- Tube length 31.2 µm
- 150 nm and 300 nm
- Re = $1x10^{-4}$
- Ca_{RBC}=0.57
- No Brownian diffusion (yet)

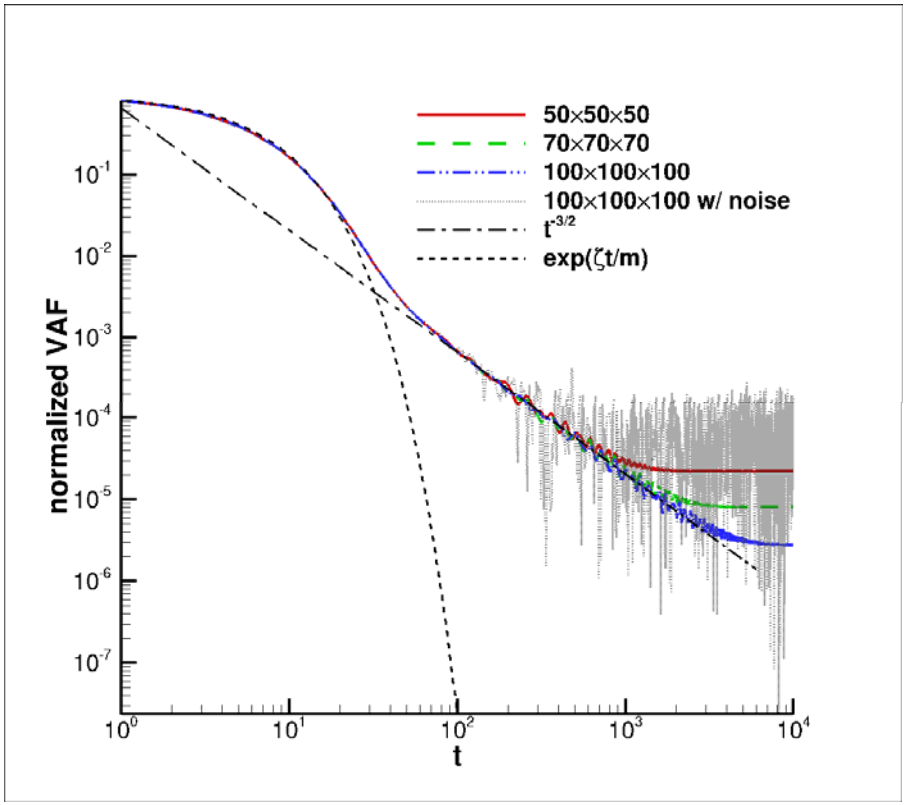


Nanoparticle Displacements

Margination is seen as NPs move towards the walls. This is similar to what is seen with much larger spherical platelets. This implies the platelet shear-induced diffusion model should be extensible to NP transport if we include Brownian motion

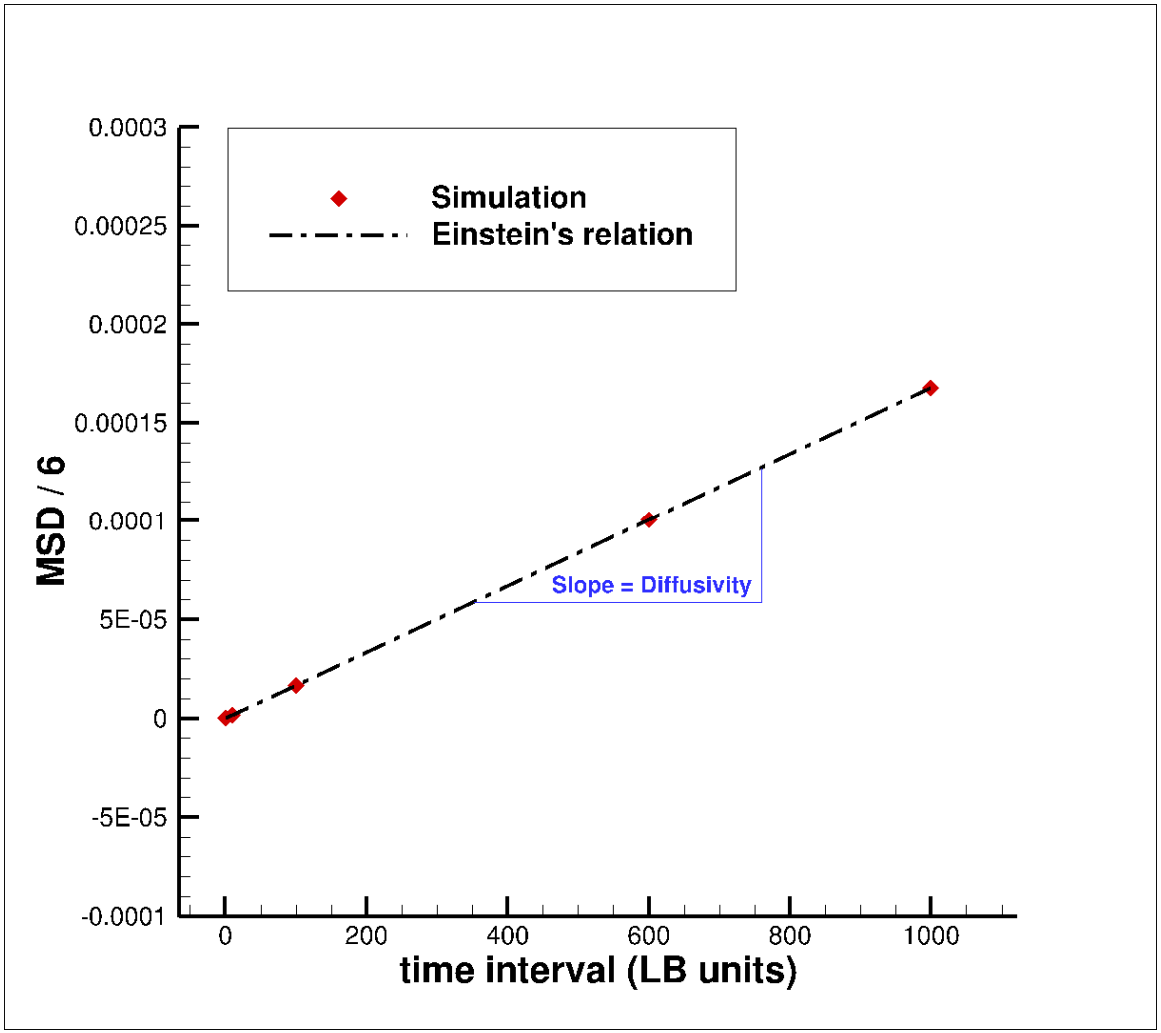


Particle Self-Diffusion Studies: Verification Study for Point Particles



- We are capturing the correct particle short-time behavior(by matching the asymptotic behavior), i.e.,
- We are correctly solving the Langevin equation and performing the particle-fluid coupling.

Particle Self-Diffusion Studies: Verification Study for Point Particles



- Diffusivity based on calculating mean squared displacement (MSD).
- The slope of the MSD/6-t curve is essentially the diffusivity.

Case Studies

Actual Parameters	Case 1:	Case 2	Case 3
NP diameter (nm) (10 to 200)	50.00	200	500
tube diameter (um) (15 to 25)	15.60	15.6	15.6
tube length (um) (2-3 tube dia)	31.20	31.2	31.2
wall shear rate s^-1	76.92	76.92	76.92
Ht	10%	10%	10%
RBC Ca#	0.0571	0.0571	0.0571
RBC Re#	0.0010	0.0010	0.0010
tube Re#	0.0020	0.0020	0.0020
NP Peclet#	0.4952	7.9235	49.5221
NP Peclet-like# (shear induced diffusion/brownian diffusion)	0.0025	0.1625	2.5396
NP #	596.34	596.34	596.34
NPs Concentration (# of particles/ml)	1.00E+08	1.00E+08	1.00E+08

Case Studies

Simulation Parameters	Case 1	Case 2	Case 3
NP diameter (nm) (10 to 200)	50.00	200.00	500
tube diameter (um) (15 to 25)	15.60	15.60	15.60
tube length (um) (2-3 tube dia)	31.20	31.20	31.20
wall shear rate s^-1	7692.00	7692.00	7692.00
Ht	10%	10%	10%
RBC Ca#	0.0571	0.0571	0.0571
RBC Re#	0.9750	0.9750	0.9750
tube Re#	1.9500	1.9500	1.9500
NP Peclet#	0.4952	7.9235	49.5221
NP Peclet-like# (shear induced diffusion/brownian diffusion)	0.0025	0.1625	2.5396
NP #	5.96E+02	5.96E+02	5.96E+02
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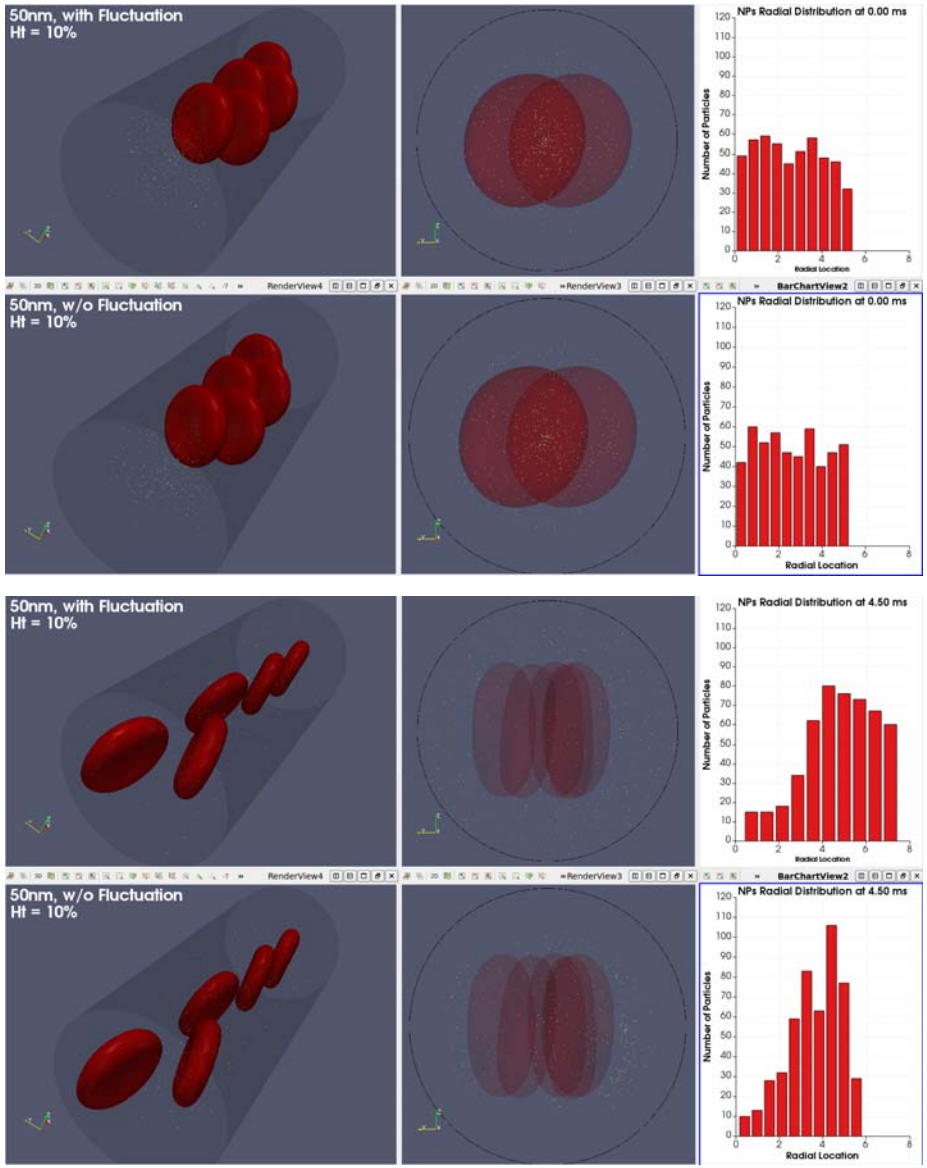
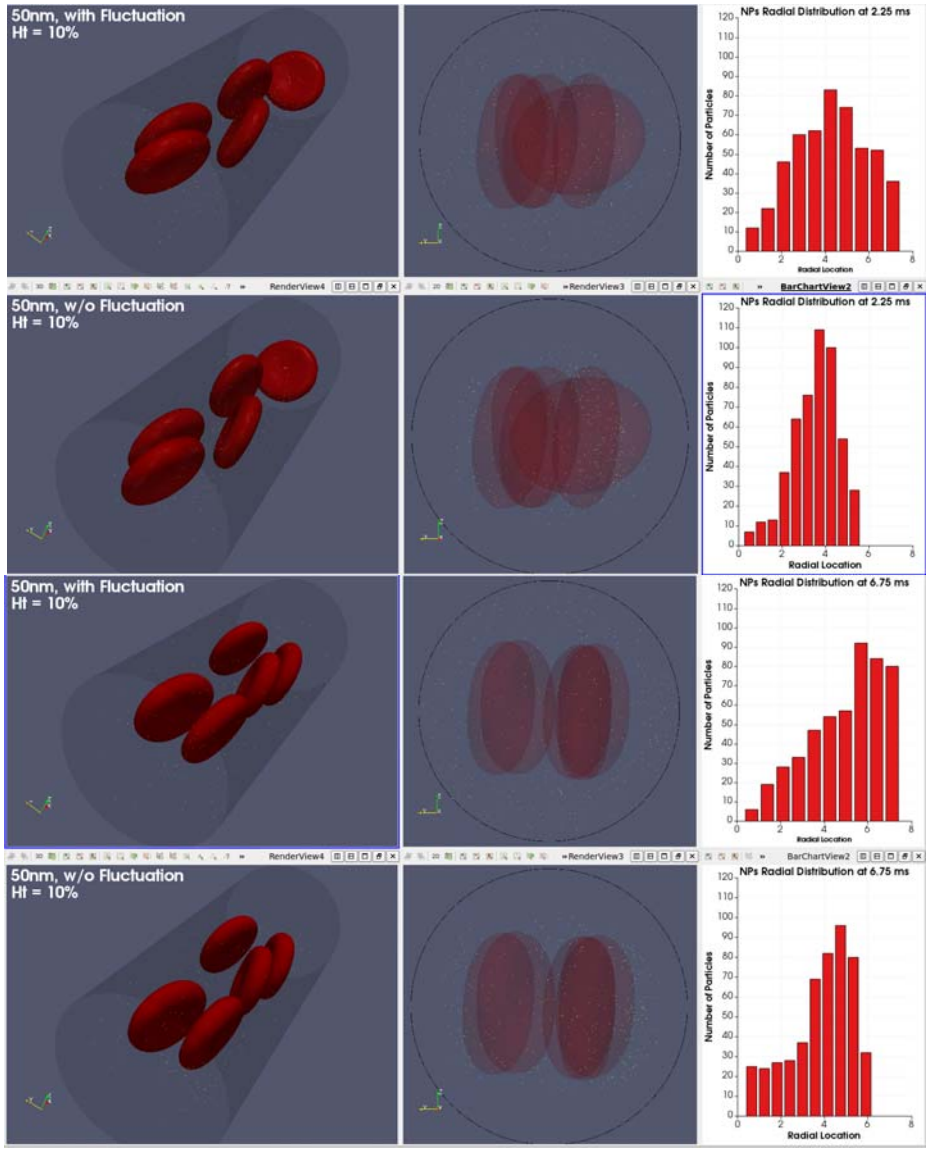
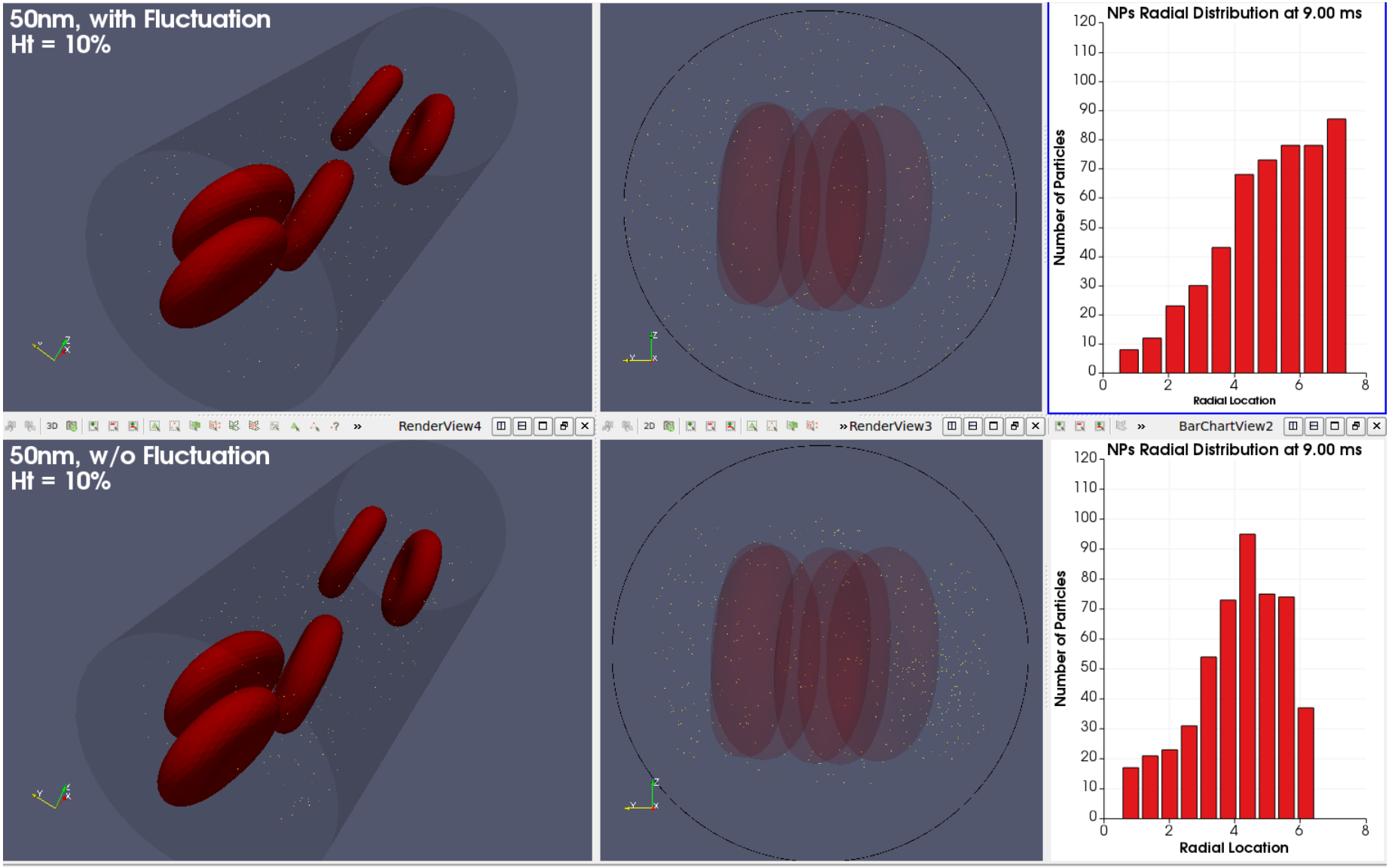
50nm Results

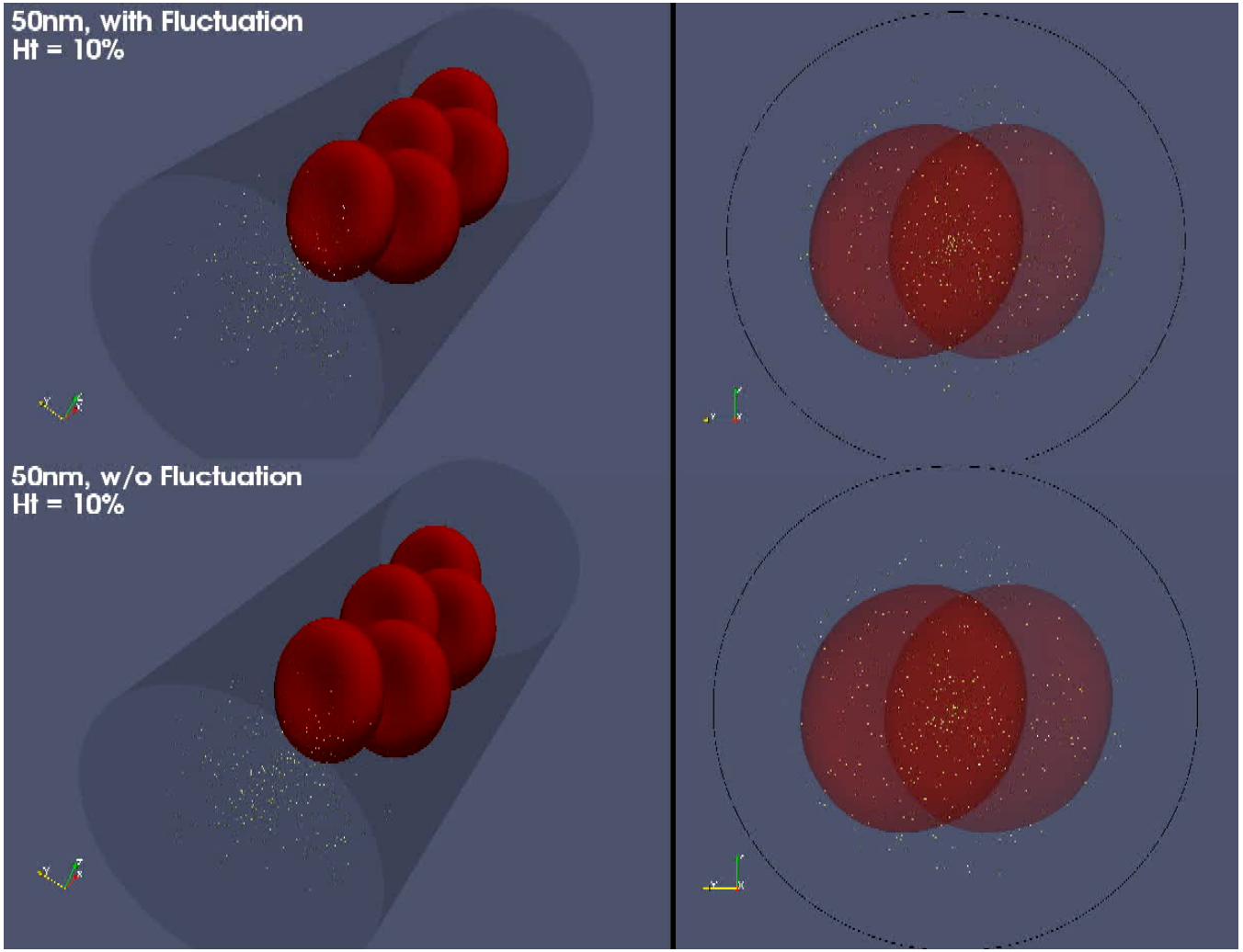




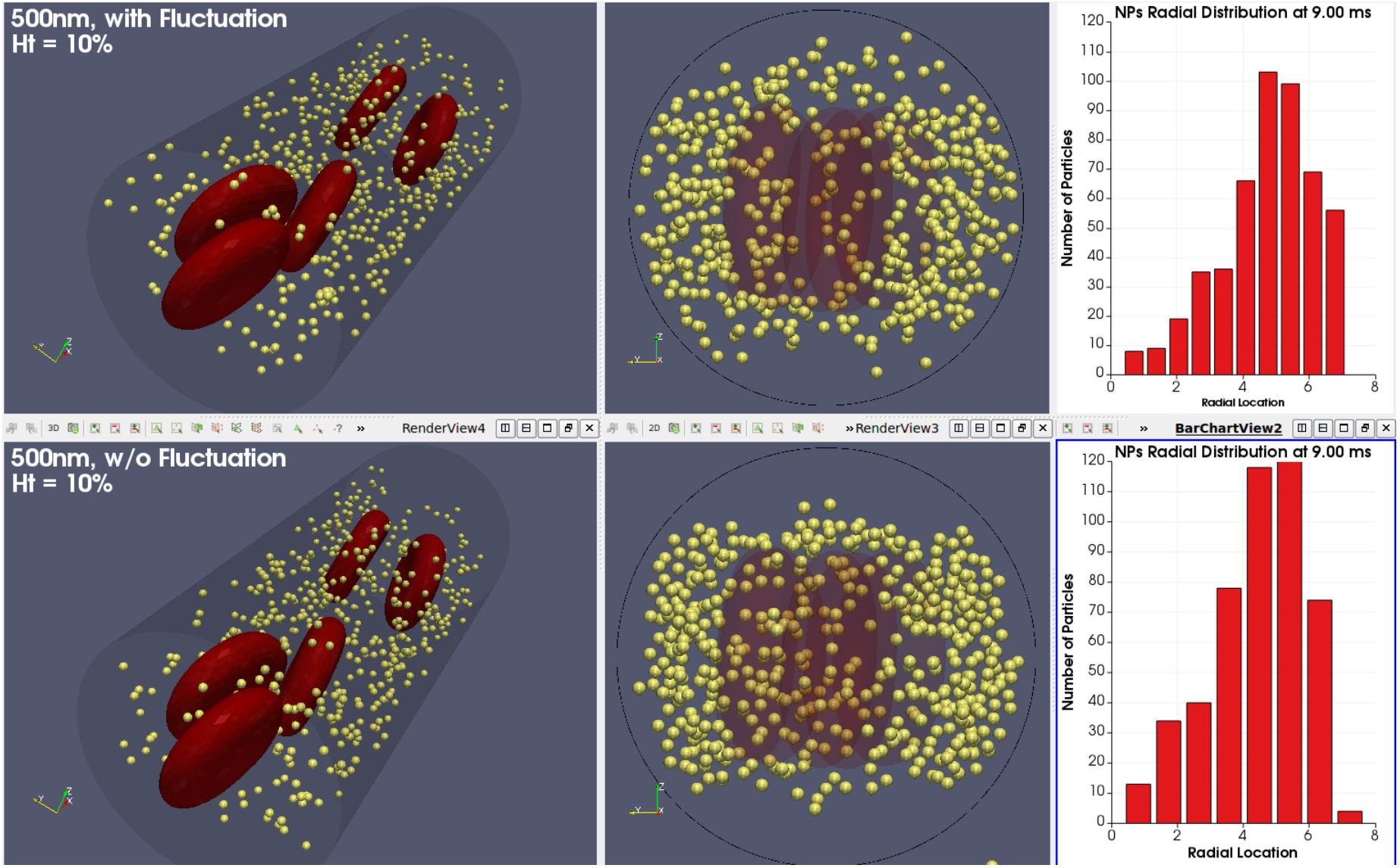
50nm Results



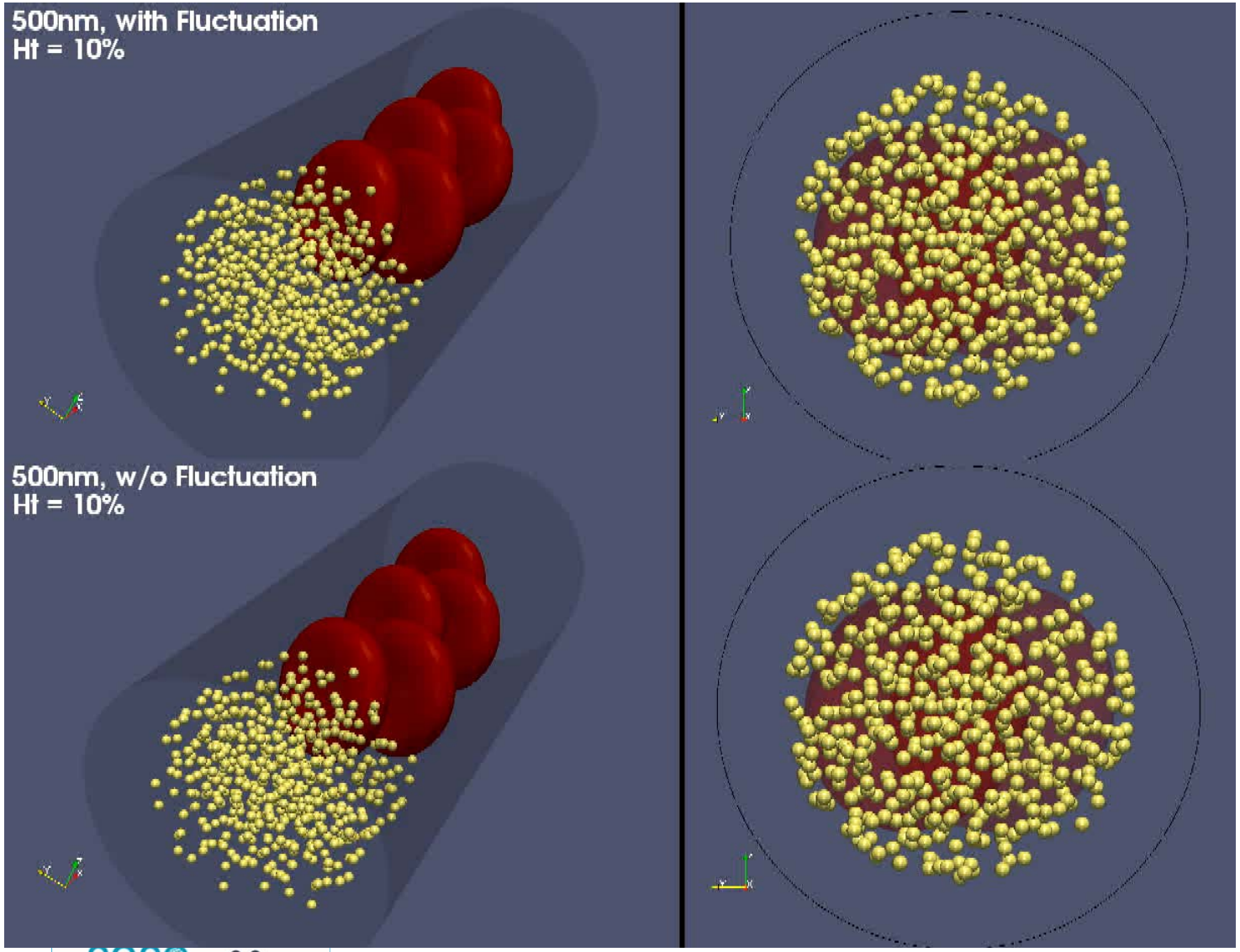
50 Nm Results



500 Nm Results

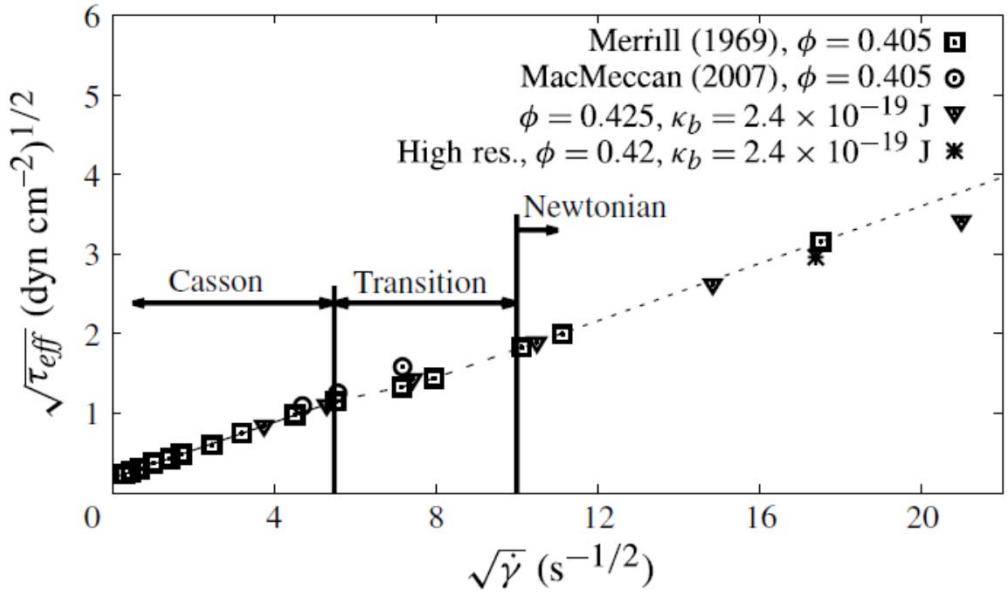


500 Nm Results



Continuum Model in Sierra Mechanics

Blood Rheology



Hossain et al., 2013 using their convective-diffusion-adsorption models

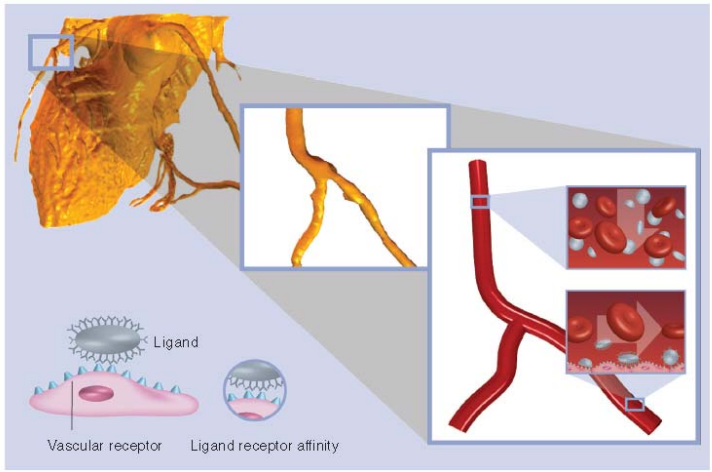


Figure 1. Reconstructing the patient-specific vascular geometry. The image shows, from left to right, the isocontour of a human heart, path extraction and editing of a small bifurcation portion from the left coronary artery and reconstruction of the geometry ready for isogeometric analysis. In addition, a nanoparticle with its ligand molecules is shown interacting with the receptor molecules decorating the surface of the endothelial cells in the vasculature.

Equations of Motion:

$$\dot{\gamma} = \nabla \mathbf{v} + \nabla \mathbf{v}^t$$

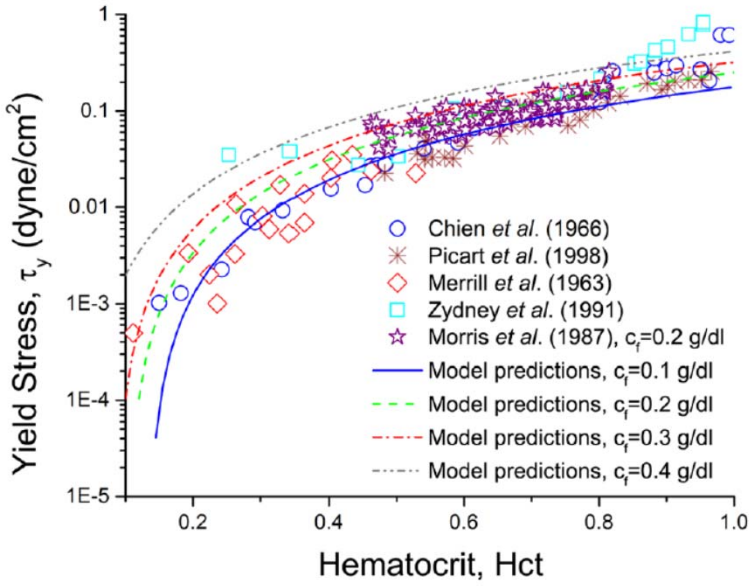
$$\rho \frac{\partial \mathbf{v}}{\partial t} = -\rho \mathbf{v} \bullet \nabla \mathbf{v} - \nabla p + \nabla \bullet \tau_{eff} + \rho \mathbf{g}$$

$$\nabla \bullet \mathbf{v} = 0$$

New Stress Model: Casson equation with yield stress

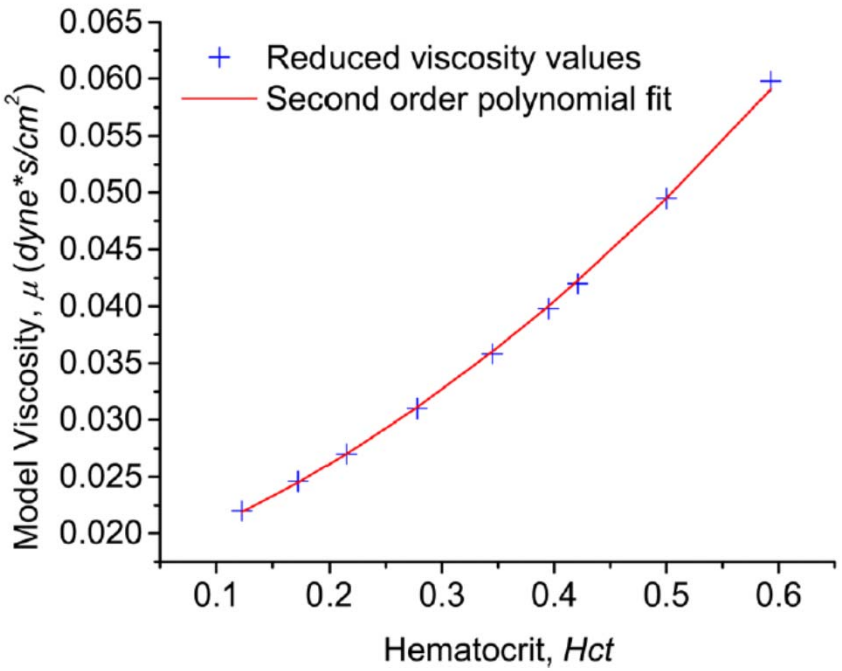
$$\sqrt{\tau_{eff}} = \sqrt{\tau_o} + \sqrt{\mu_a \dot{\gamma}}$$

Blood Rheology: Viscosity and Yield Stress



Blood yield stress is a function of hematocrit (Hct), critical hematocrit (Hctc) and fibrinogen concentration (cf)

Blood viscosity is a function of hematocrit (Hct) and temperature



Blood velocities range from 40-.03 cm/s

Continuum Model: NP Transport Bulk

Convective-diffusion-reaction equation for NP transport:

- Diffusivity tensor to be populated from RBC models – start with isotropic
- How do we include Brownian motion or fluctuations
- Homogeneous reaction could be irreversible sticking to RBC – to make this reversible we would need to add a RBC surface species

$$\frac{\partial C_{NP}}{\partial t} + v \bullet \nabla C_{NP} = \nabla \bullet D_{NP} \nabla C_{NP} - S_{NP}$$

$$S_{NP} = k C_{NP}^{n}$$

$$D_{NP} = \begin{pmatrix} D_{11} & D_{12} & D_{13} \\ D_{21} & D_{22} & D_{23} \\ D_{31} & D_{32} & D_{33} \end{pmatrix}$$

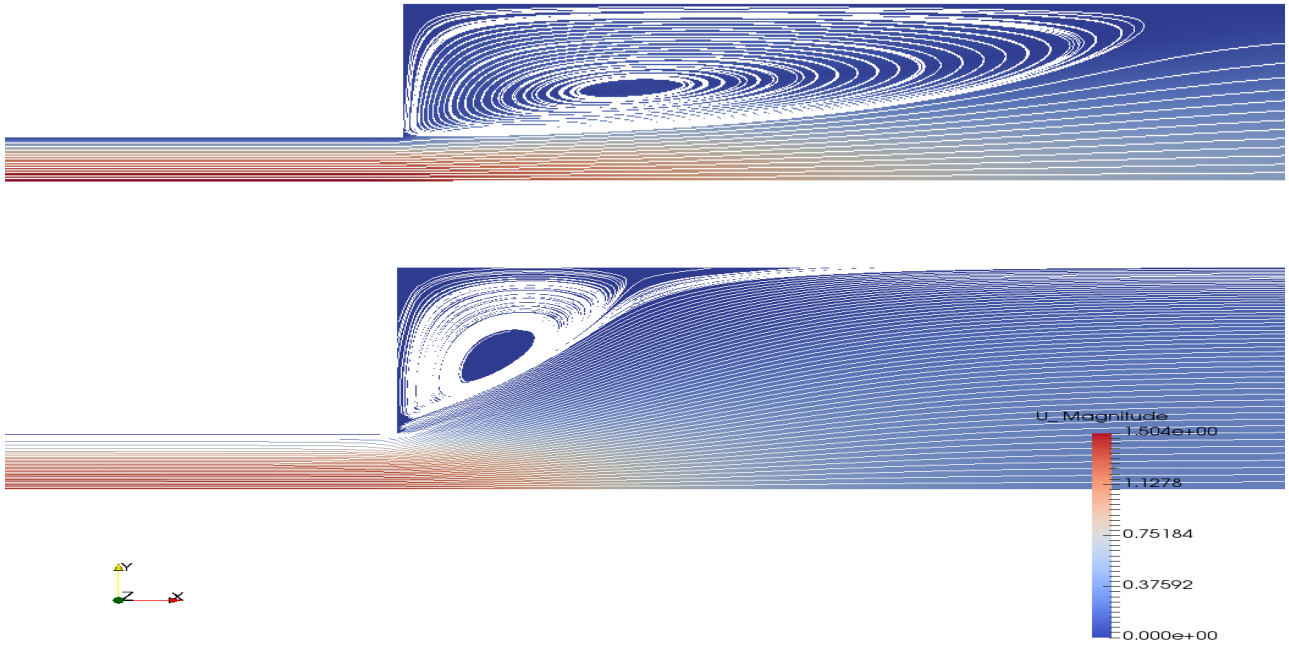
$$D_{NP} = D_{Einstein} I = \frac{k_B T}{3 \mu d_p}$$

Hossain et al, 2013 use Stokes-Einstein diffusivity, which is isotropic. What do we use for viscosity in this relationship?

Boundary conditions include:

- Prescribed concentration
- No flux
- Flux to the wall with adhesion

Verification of Casson Model in Sierra/Aria



Re=50 Ca=0

Re=50 Ca=1.5

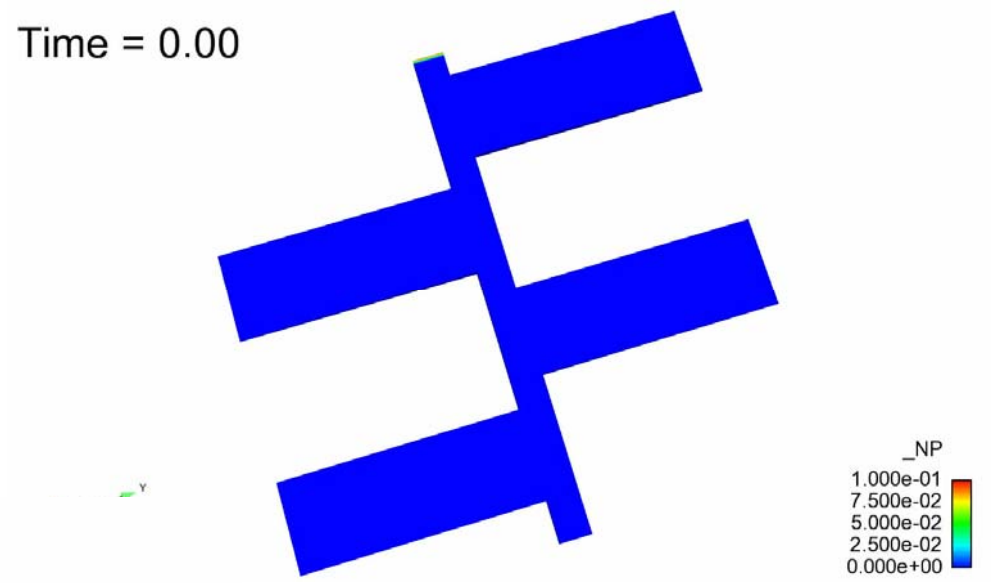
Verified Casson model with regularization of the yield stress and compared to published results

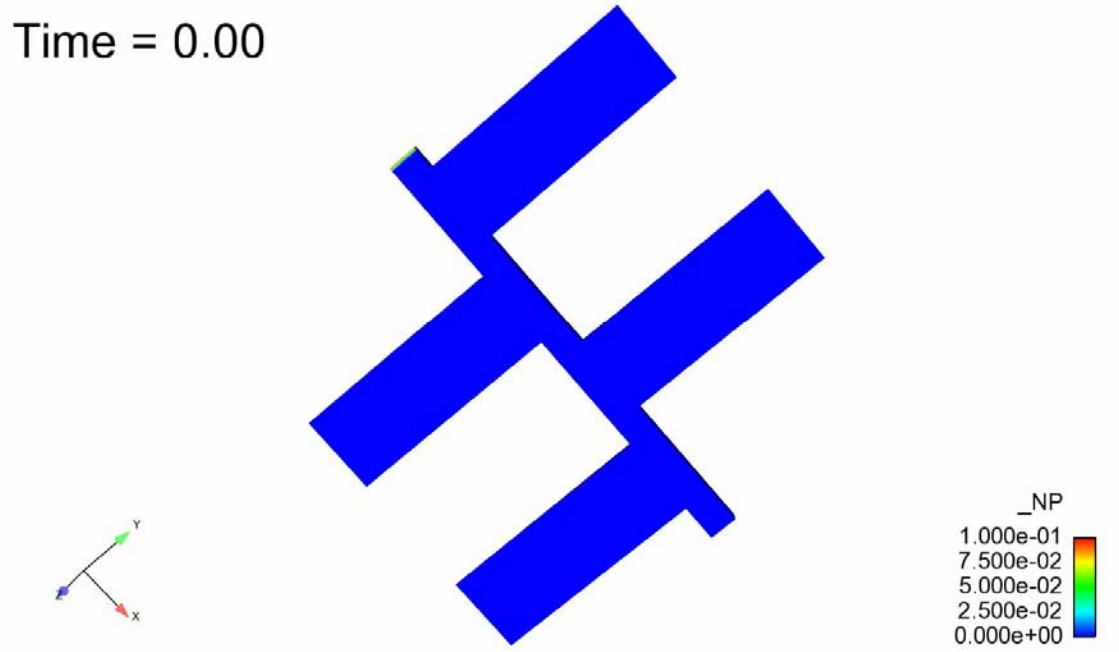
$$(\eta^*)^{1/2} = 1 + \left(\frac{\mathrm{Ca}}{\dot{\gamma}^*}\right)^{1/2} \{1 - \exp[-(m\dot{\gamma}^*)^{1/2}]\}$$

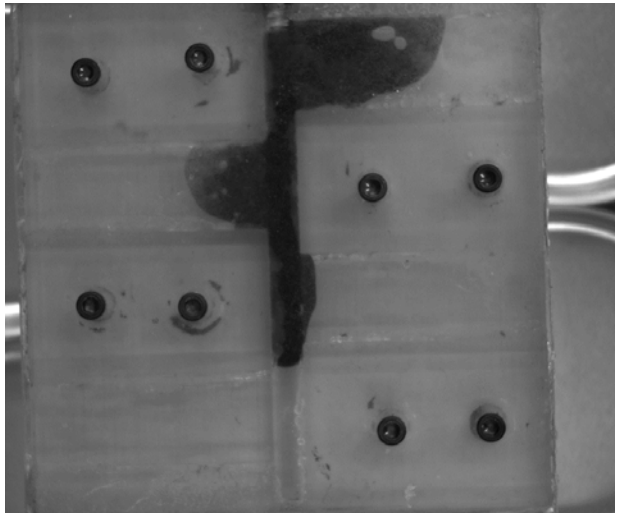
$$\eta^*(\dot{\gamma}^*) = \frac{\eta(\dot{\gamma})}{\eta_0}; \quad \dot{\gamma}^* = \frac{\dot{\gamma}}{u_0/L}; \quad \mathrm{Ca} = \frac{\tau_0 L}{\eta_0 u_0}$$

Preliminary Results: Casson Model in Branched Structure

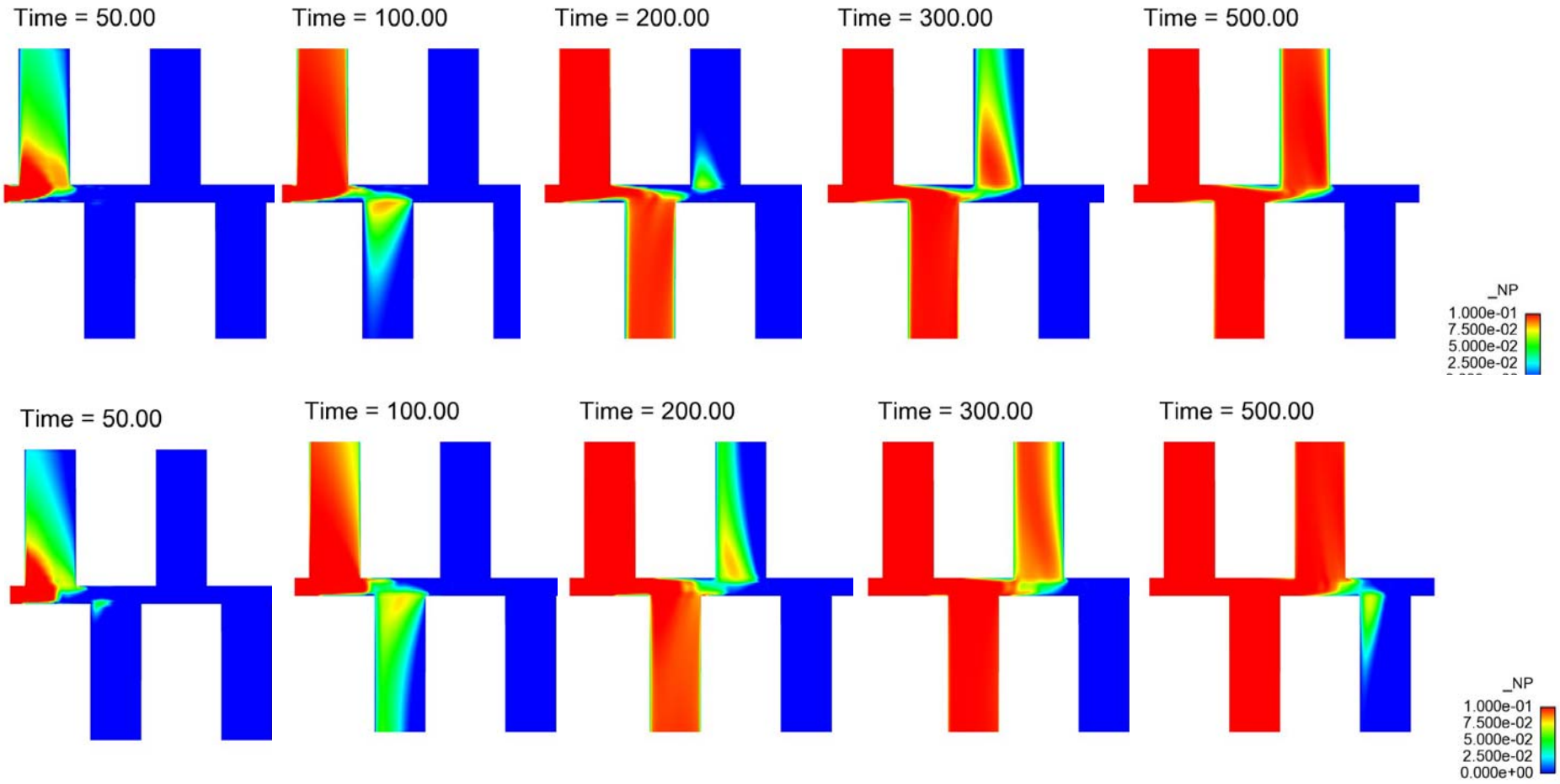
- Compare Casson and Newtonian Rheology
- Transport is affected by the background fluid even at low particle concentrations





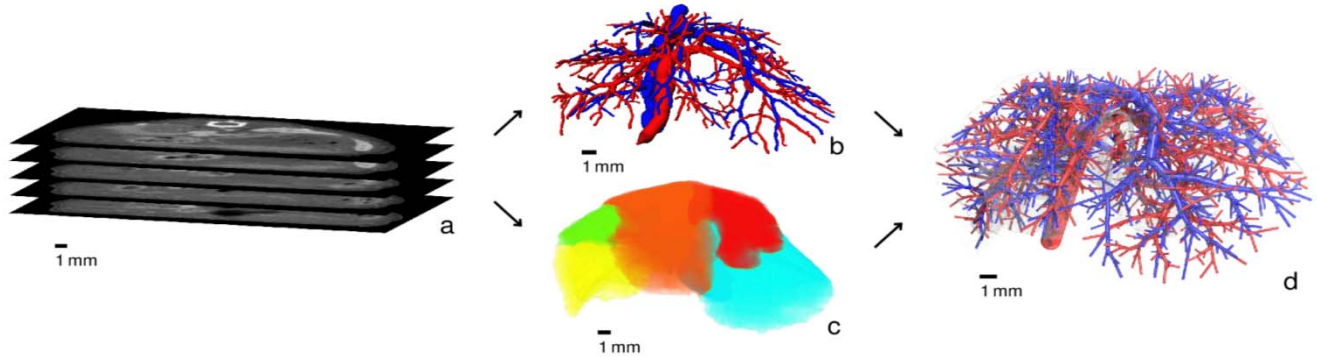


Preliminary Results: Casson Model versus Newtonian in Branched Structure



Mouse liver structure

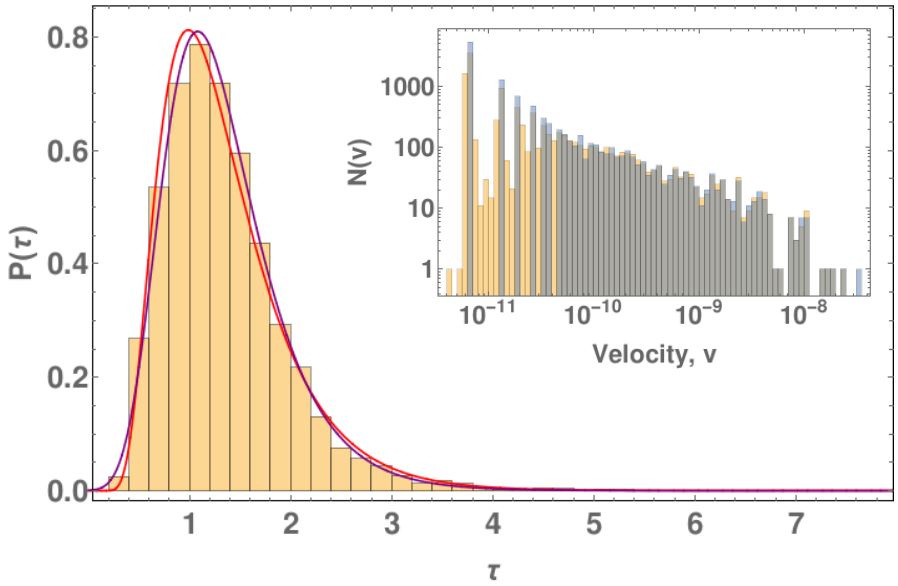
- Have network structure of Portal (supply) and Hepatic (drain) veins
  - Implement network construction algorithm
    - What about Hepatic Artery system?
    - What about details down to terminal venual and arteriole (lobule) level
    - Other organs, and systems (e.g., CAM embryonic chicken model)
- Have liver lobes segmented
- Initially, assume
  - Steady, Poiseuille flow of Newtonian, incompressible fluid (standard in literature)
  - Particle transport is advection dominated (ignore diffusion and fluctuations for now)
- Inform model with details of nanoparticle transport in capillaries later

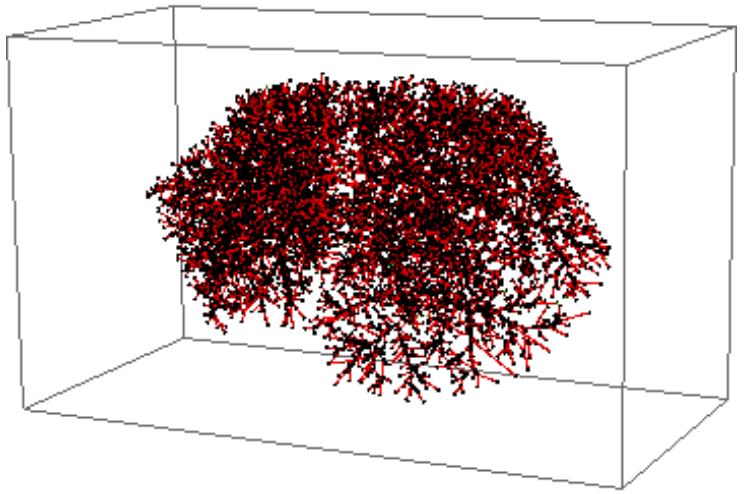


Schwen et al. (2014). PLOS Computational Biology, v. 10, pp. 1-17.

Flow Heterogeneity in Portal Vein Network

- Preliminary data for Portal vein network only
  - Based on pipe network representation of vasculature
    - Assumes constant pressure drop and Hagen-Poiseuille Flow
  - Result show inverse Gaussian distribution of transit times along unique vascular paths
    - Flow dispersion is relevant, but long-time tail is exponential
    - Work ongoing to assess vascular structure-transit time relationship





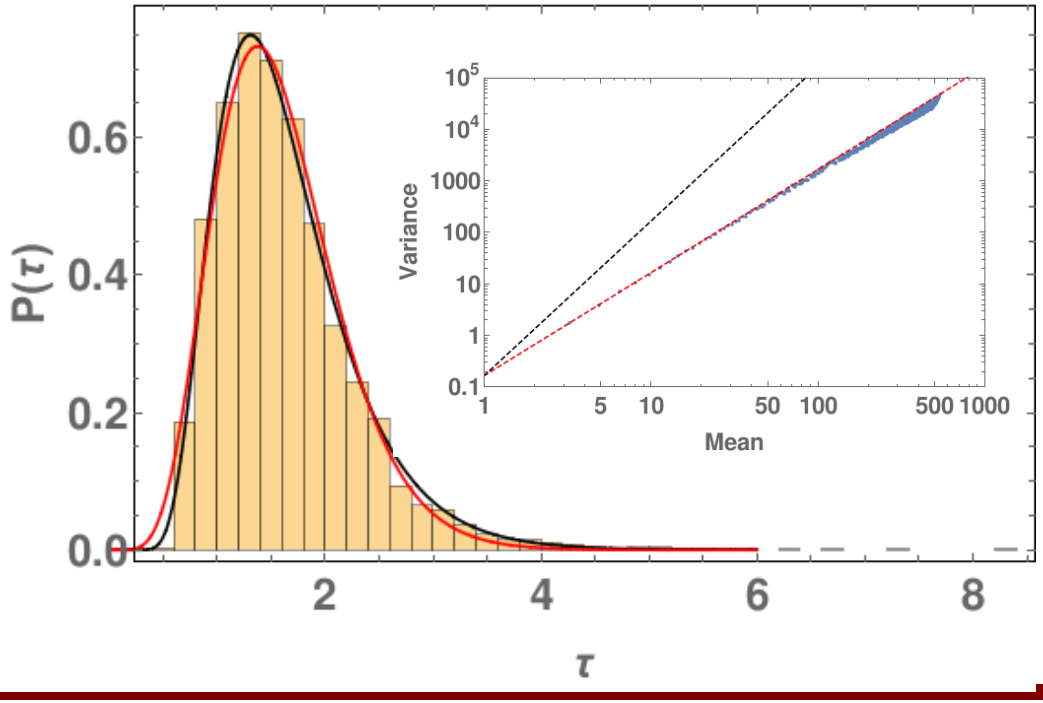
Bolintineanu, D.S., Grest, G. S., Lechman, J.B. & Silbert, L.E. (2015). Diffusion in Jammed Particle Packs. Phys.Rev. Let, 115(8), 088002-1-15.

Transit Time Distribution in Portal Vein Network

- Result show Inverse Gaussian (common in pharmo. lit.) or Gamma (common in blood flow heterogeneity lit.) distributions of transit times along unique vascular paths
  - Flow dispersion is relevant, but long-time tail is exponential – we capture first order phenomena
  - Can we decide between two candidate distributions?

Discovery!

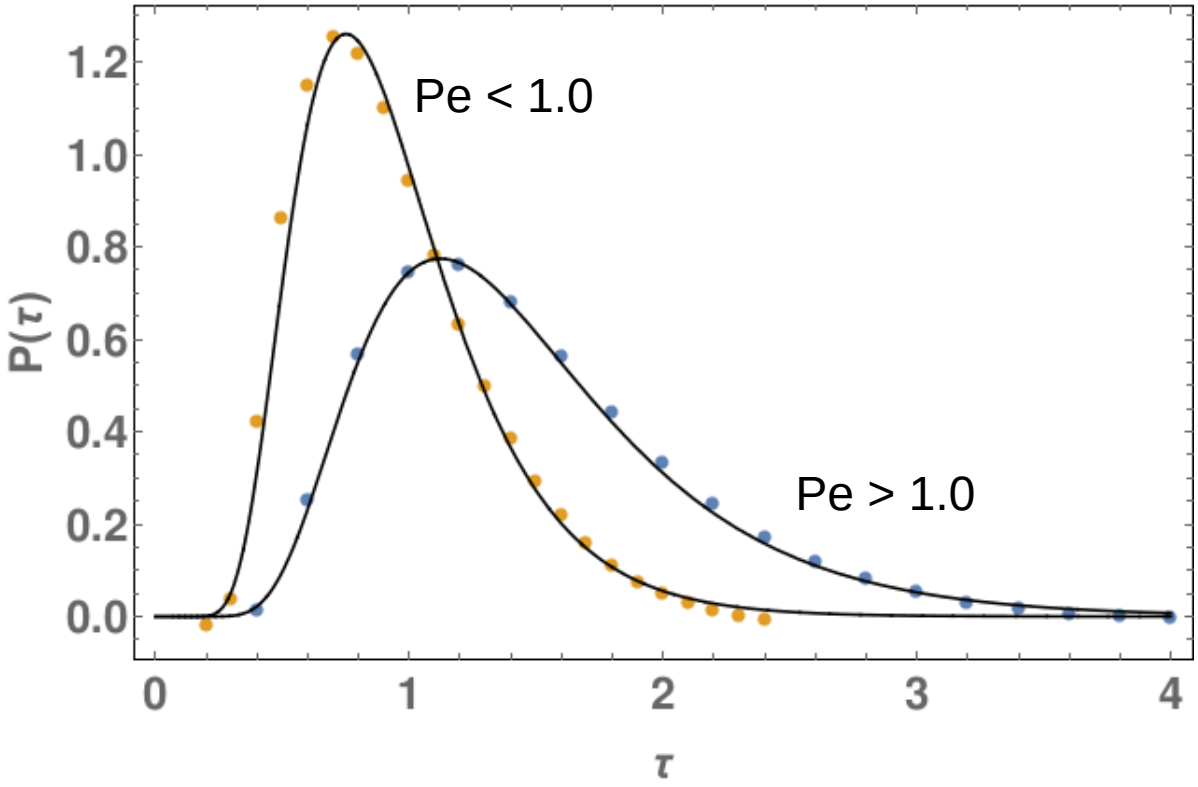
- Transit time distribution shows scaling consistent with Gamma distribution
- Link between blood flow heterogeneity due to vascular structure and macroscopic transit time distributions



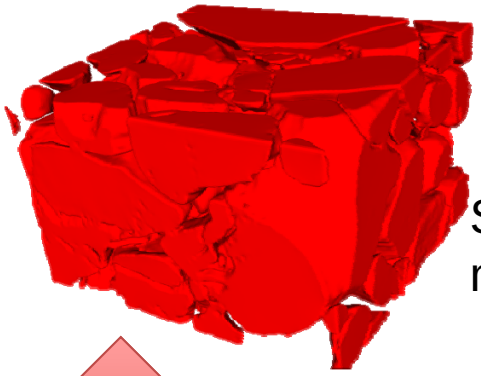
Mean First Passage Time Distribution in Portal Vein Network

- Preliminary results for large Pe and small limit
  - Difference between the two simulations is a factor of 10 in diffusivity
  - First interpretation is that the distribution is shifted to left for lower Pe
  - Shape of the distribution is relatively unchanged - Inverse Gaussian Distribution

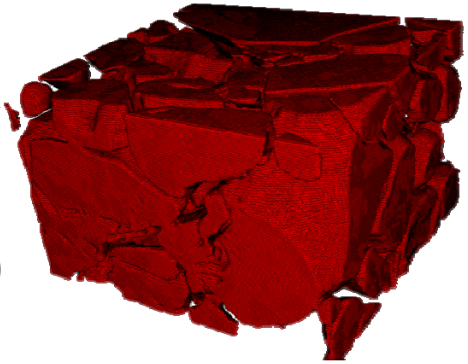
Enhanced Advection-Diffusion model

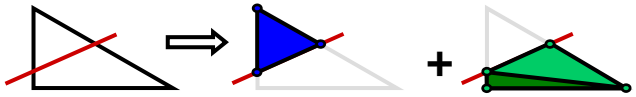


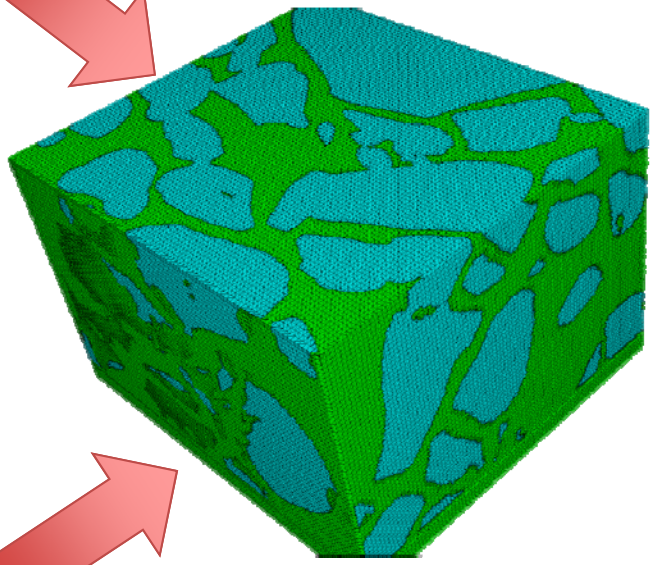
Represent Microstructure using Conformal Decomposition Finite Element Method (CDFEM)



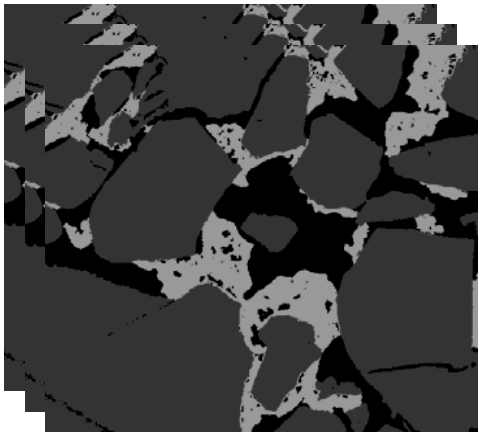
Surface mesh (STL)



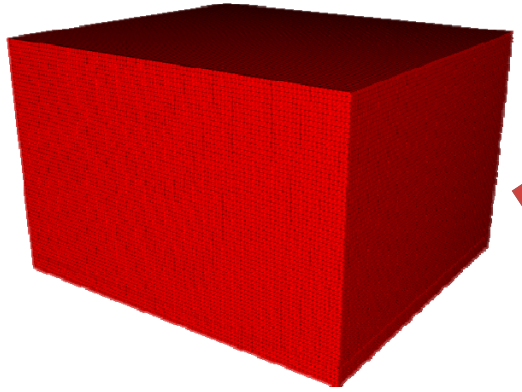




3D reconstruction

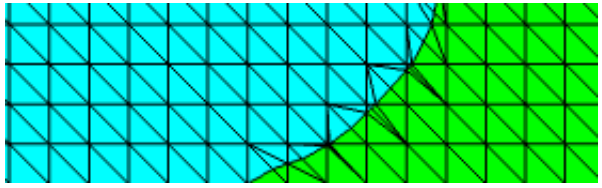


2D image stack

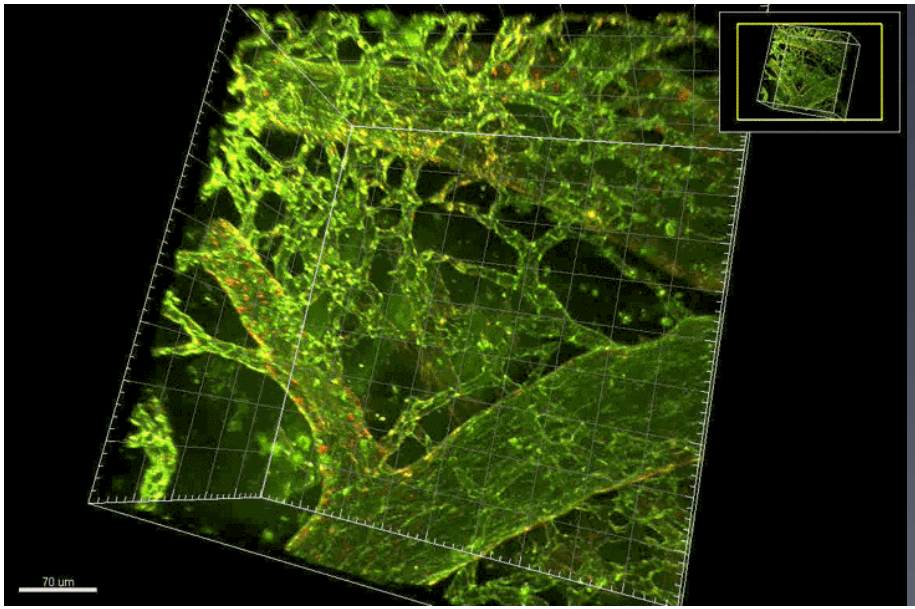


Background mesh

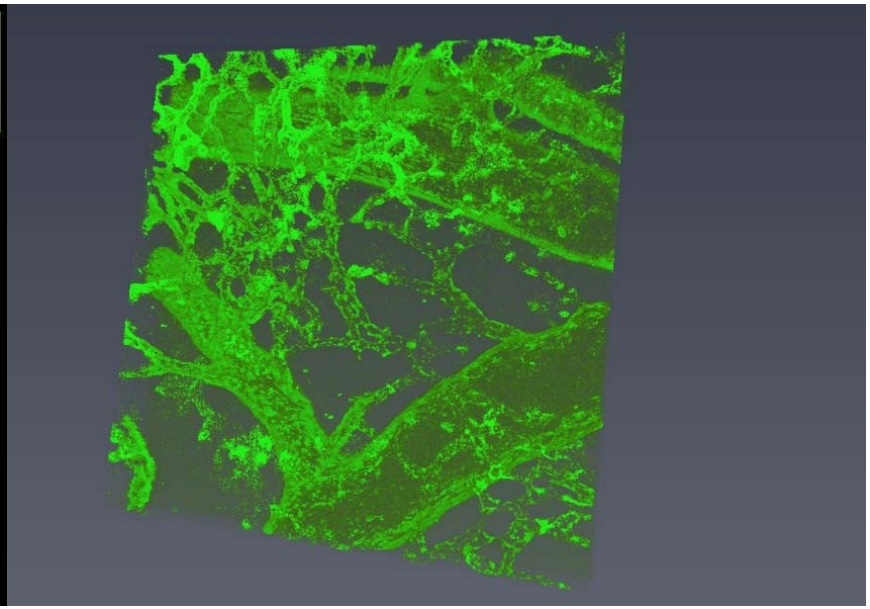
Decomposition of background mesh using CDFEM



Progress on Mesh Construction from Chick Chorioallantoic Membrane (CAM) Imaging



Original CAM volume reconstruction from multiphoton microscopy data by Dr. Kerfoot

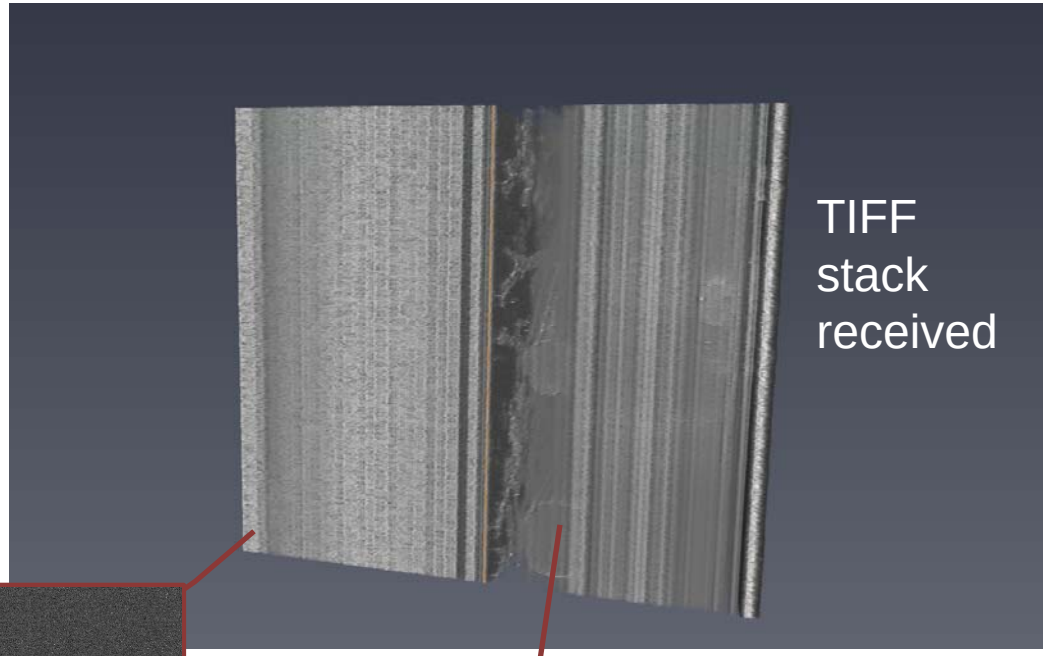


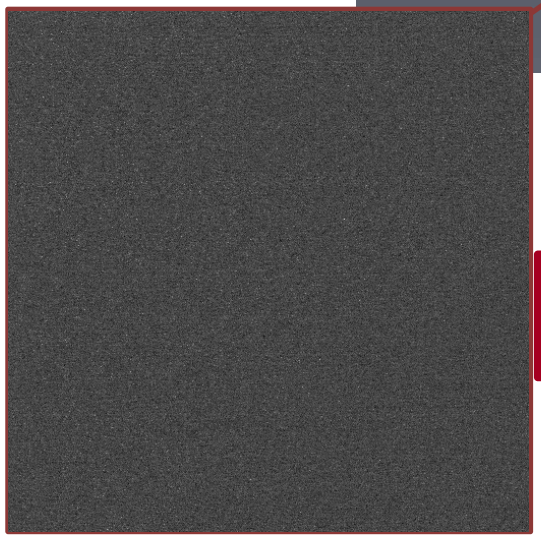
Avizo 9.1.1 volume reconstruction from raw image data sent as a tiff stack

Current problem: Only a small fraction of the tiff images are usable for surface construction.

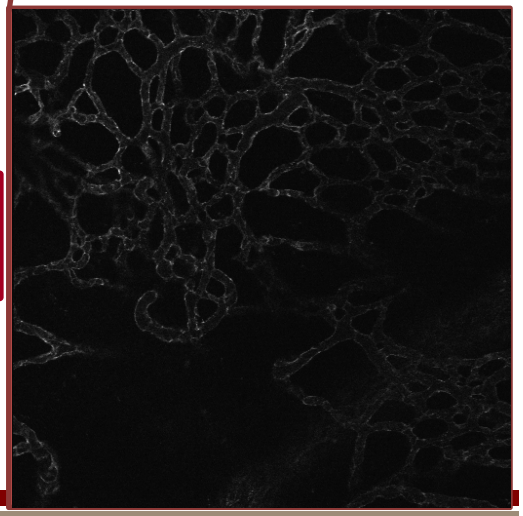
Full TIFF Stack Displayed through Volume Rendering in Avizo

- Many of these images have no discernable features for image processing.
- For the volume render on the previous slide, all “noisy” images were removed, leaving only ~25 slices where vasculature was visible.
- Different locations in the stack are at a different brightness, posing a challenge for image thresholding.

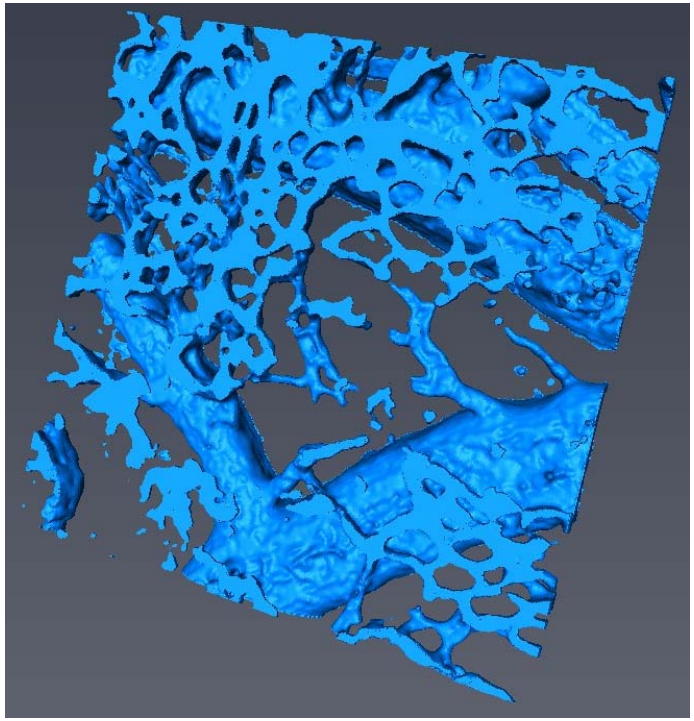


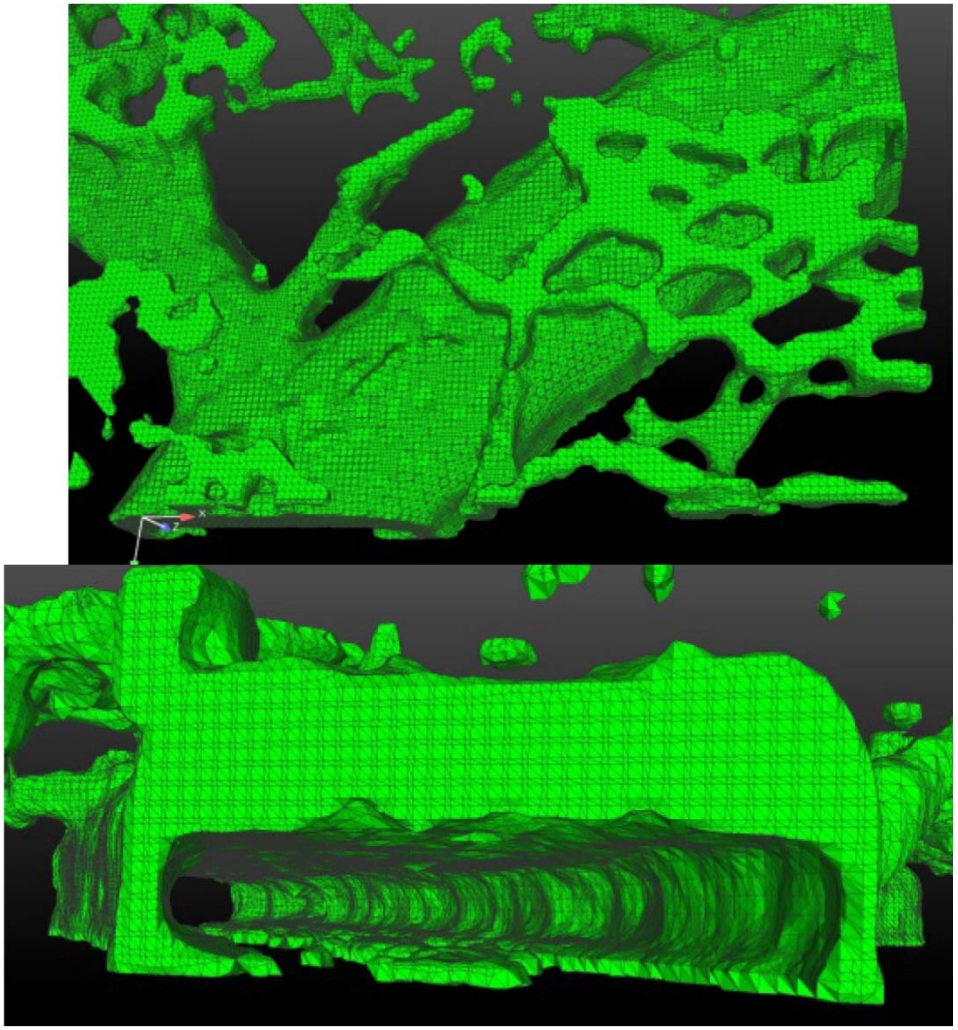


Representative slices



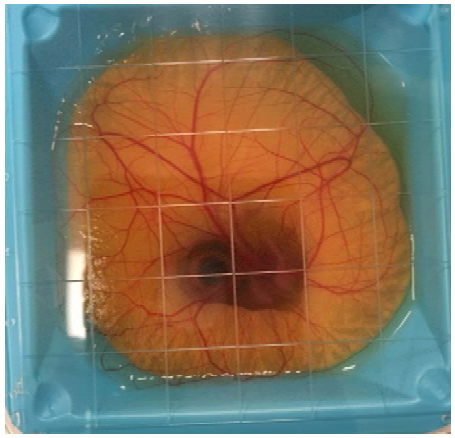
Rudimentary Mesh of CAM Generated in Avizo

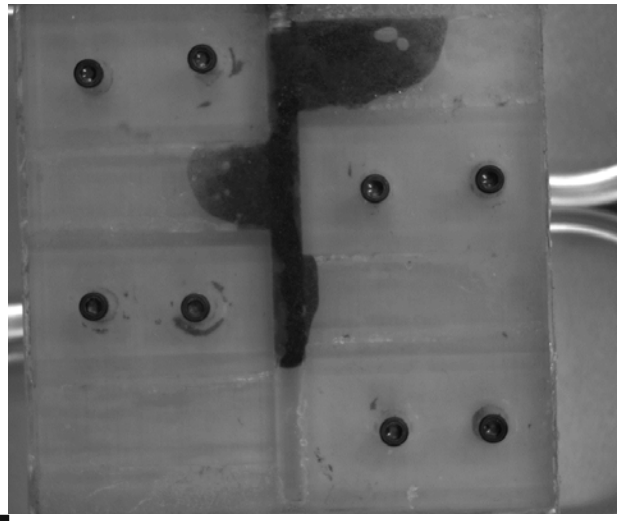


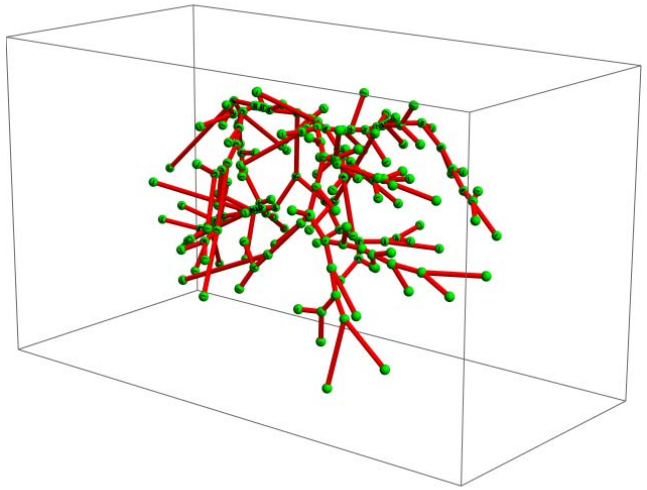


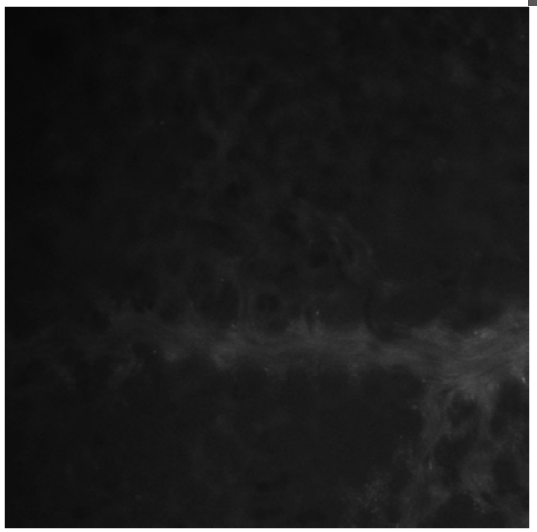
- A conformal surface mesh was generated.
- Due to excessive image noise, we are currently unable to obtain a surface representing a fully enclosed artery.
- Our best reconstructions result in truncated channels shown here on the right.

Experiments of Discovery and Validation





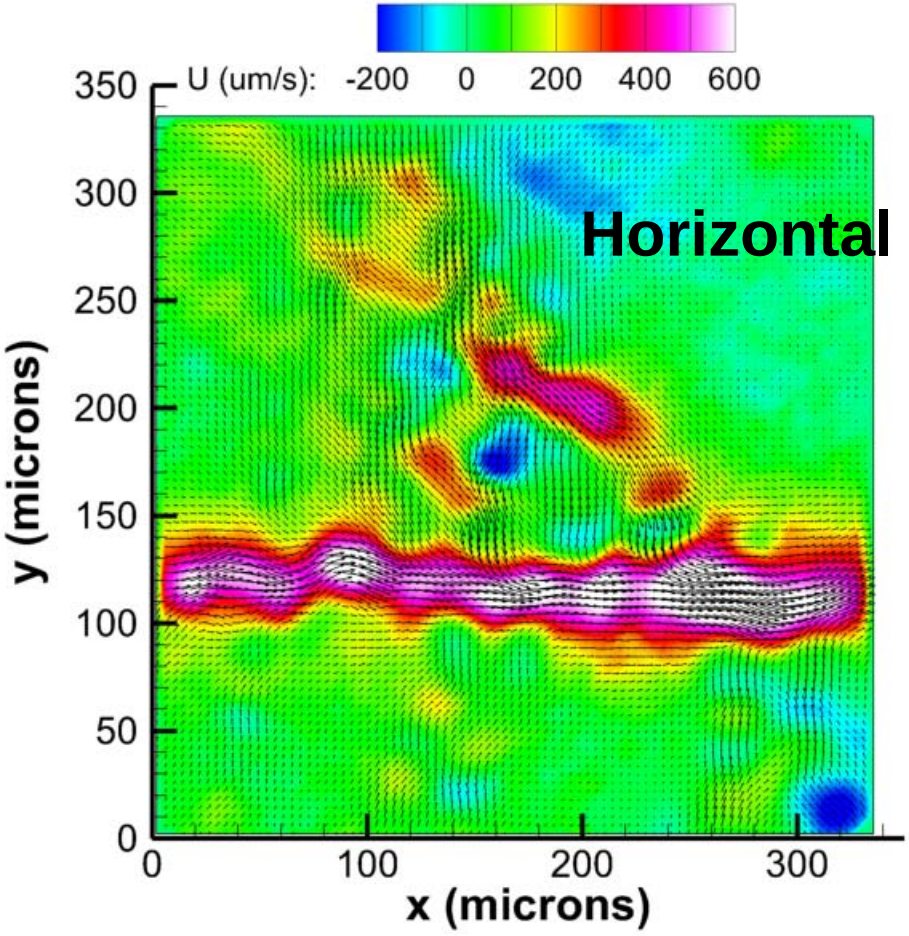




- Agile experimental technique developed with mesh and solid model generation and subsequent 3D printing and finite element analysis
- Possibly to print and design an experiment based on this geometry or something similar to a vascular structure

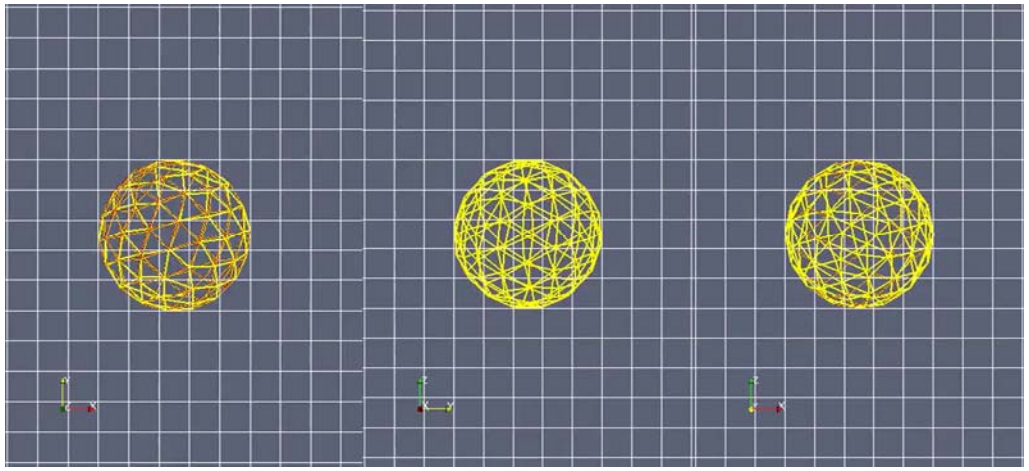
Particle Image Velocimetry (PIV) Can Give Mean Velocities

Large Vessel
100 frames / s 20 x magnification

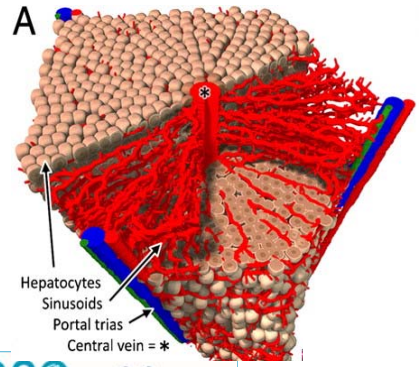


We have three other useful movies that we have successfully processed.

Next steps: Modeling



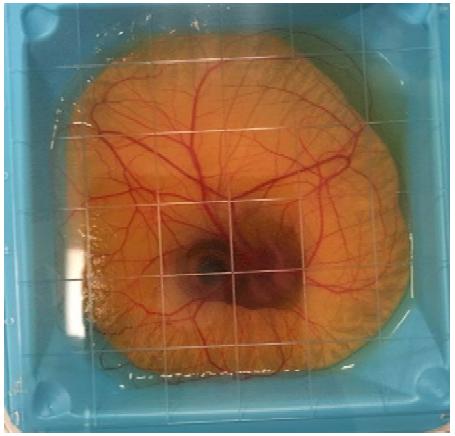
- Add Brownian motion for NPs
- Use shear-induced diffusivity plus Brownian motion to inform a continuum model for nanoparticle transport
  - Marmar, Ku, Aidun (2015)
- Complete mesh of CAM vasculature
- Complex NP boundary conditions :
  - Time-dependent velocities imitating blood flow
  - NP Flux to the wall with adhesion



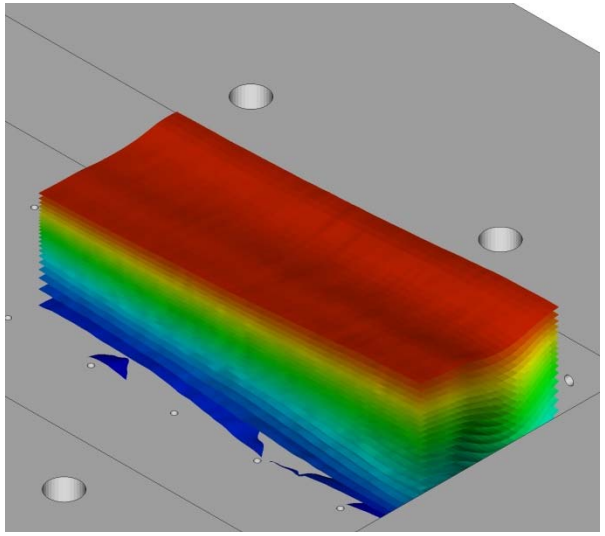
- Finish analysis by including Hepatic Vein network
- Add diffusion to network model
  - Hope to see tail stretch in transit time distribution
- Model effect of sinusoid and lobule structure
  - Stochastic models for linking PV and HV
  - Incorporate insights from microcapillary mod-sim

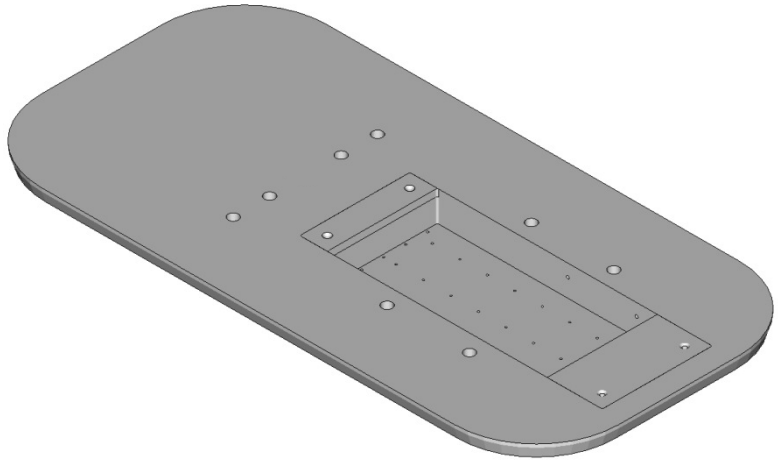
Next Steps: Experiments

Next we will obtain data at multiple z planes in the CAM model and attempt to reconstruct the velocity fields.



Example: Volumetric Reconstruction of cavity flow PIV data in SNL's Trisonic Wind Tunnel





Challenges: The current CAM PIV setup only provides two components of in-plane velocity. 3-component velocity data using a stereoscopic configuration might be required.

Conclusions

We have started on an ambitious modeling project for NP transport in vivo

- Modeling work on three scales:
  - Particle-scale for understanding diffusion of NPs in capillaries
  - Continuum-scale for full CAM
  - Network-scale for full organ
- Next Steps:
  - Develop hindered diffusion model for NPs with RBCs in small vessels
  - Complete network model for the mouse liver and compare to available data
  - Higher resolution data for vasculature and NP PIV