Margination of a leukocyte in a model microvessel

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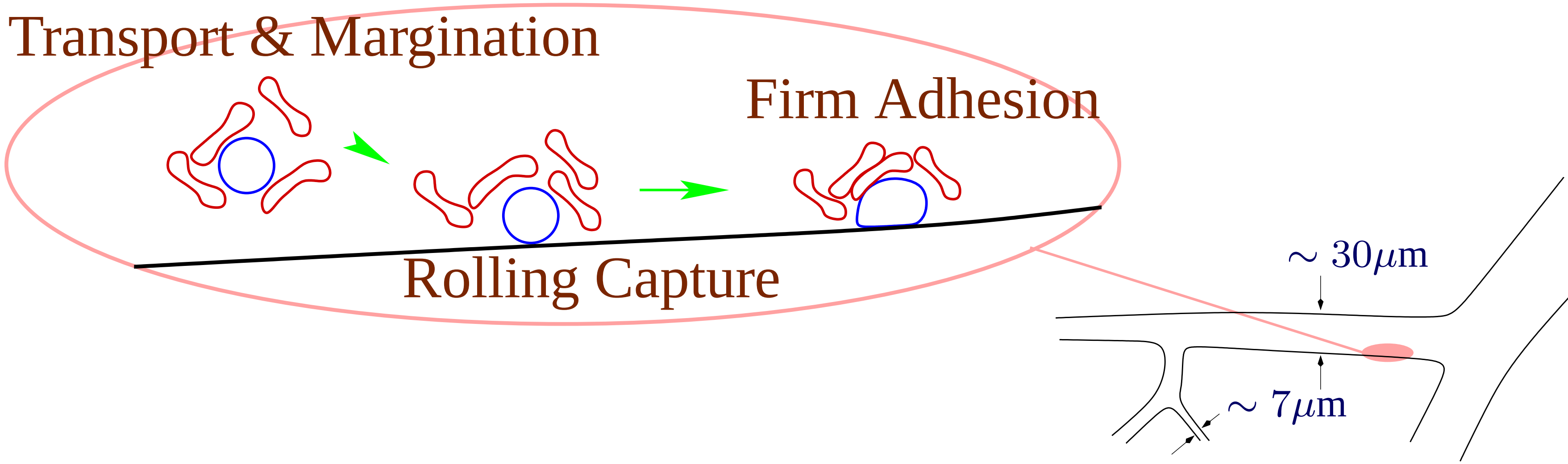
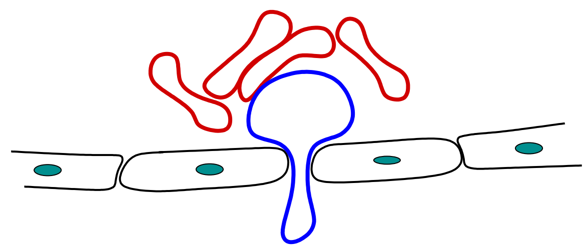
Inflammation Response

- Leukocyte (white cell) recruitment to endothelium
  - typically in post-capillary venules ($\sim 10\mu$m to $\sim 100\mu$m)



  - followed by *emigration* between endothelial cells



Inflammation Response

- Usually it's a good thing: fighting infection, *etc.*

Inflammation Response

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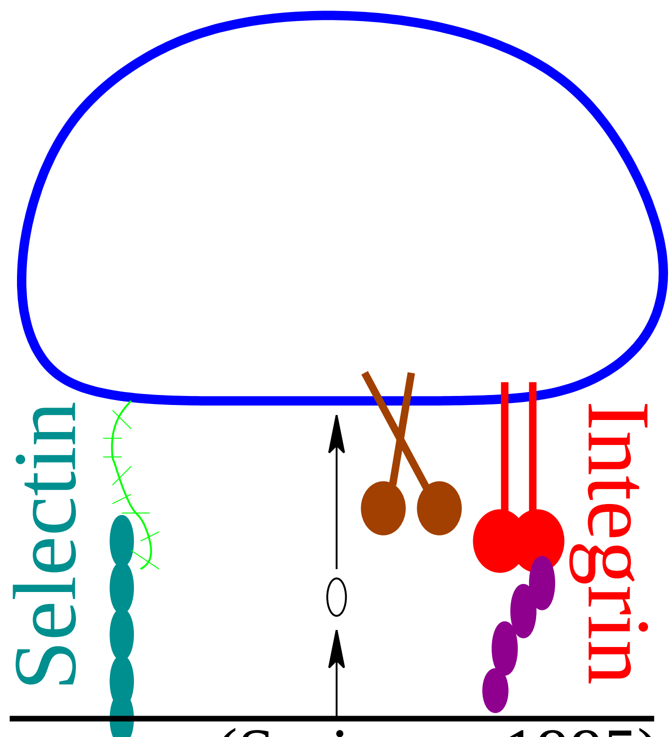
- but it can be a bad thing ...
  - Rheumatoid arthritis
  - Multiple sclerosis
  - Atherosclerosis
  - Ischemia reperfusion

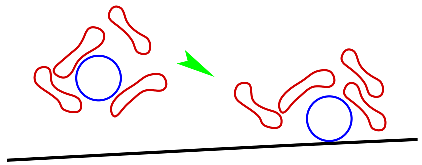
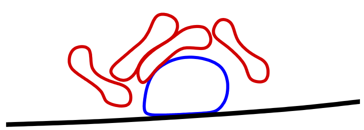
Inflammation Response

- Biochemistry/molecular biophysics well studied
- Binding in two stages
  - rolling capture stage by *selectin* binding
  - *chemoattractants* from endothelium activate *integrin*
  - immobilization by *integrin* binding



(Springer, 1995)

Hydrodynamics

- Multiple stages involve hydrodynamics
- Margination 
  - the transport of the leukocyte to the wall
  - not a simple Stokes flow effect
    - leukocytes are rigid (symmetric)
  - must involve multi-body flow dynamics
- Adhesion 
  - must resist flow
  - interactions with red cells probably important

Hydrodynamic Effects

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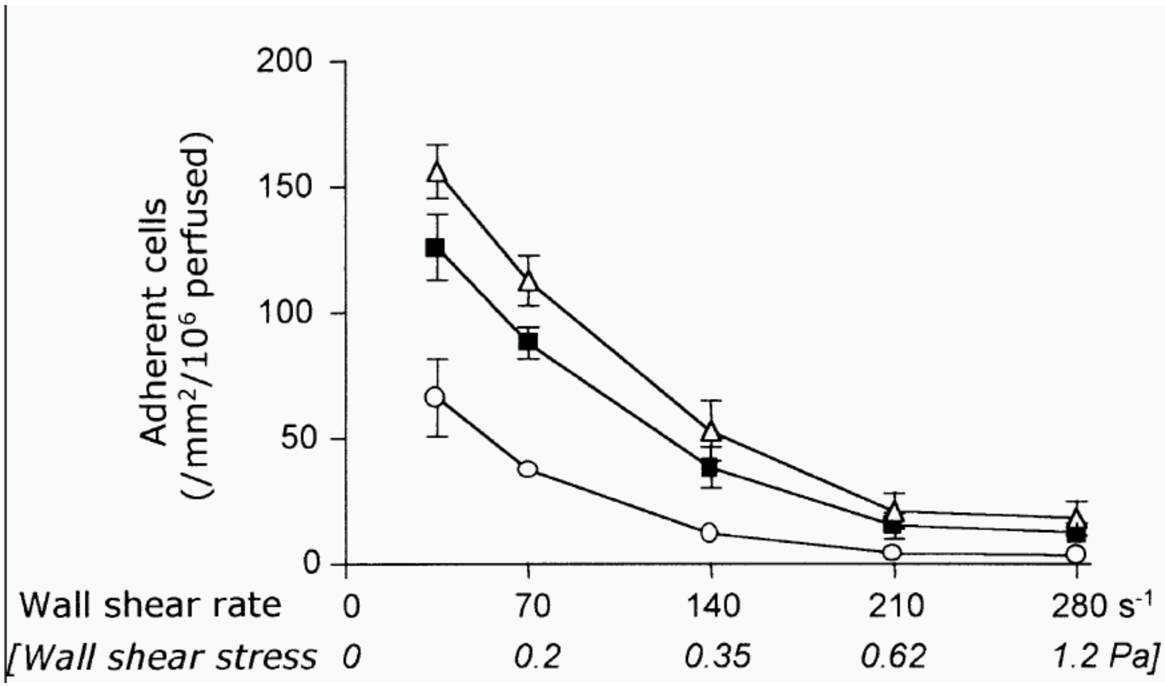
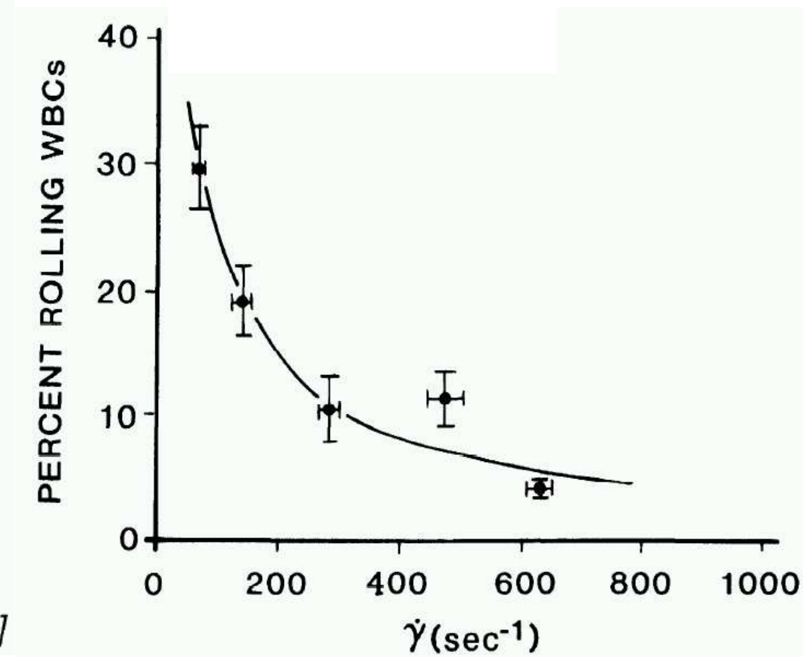
- On-wall probability sensitive to shear rate (flow rate)

Abbitt & Nash (2001)
in vitro: channel flow



Firrell & Lipowsky (1989)
in vivo: rat mesentery



- Mechanism?

RBC Aggregation

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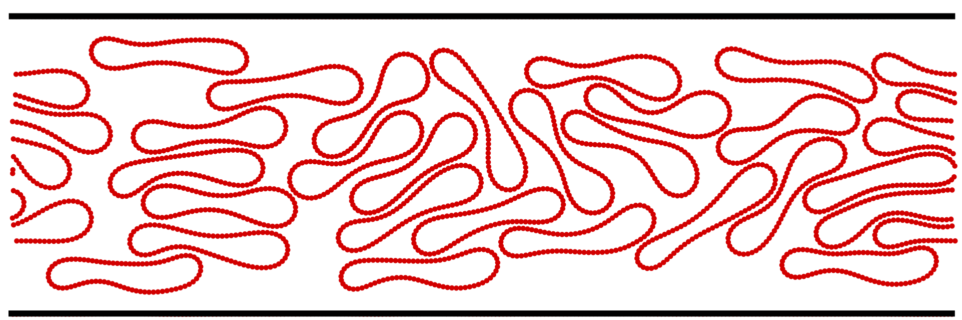
- At low strain rates, RBCs aggregate (in “athletic” species)
- RBC aggregation augmentation promotes margination/adhesion
  - Pearson & Lipowsky (2000), *in vivo* experiments, rat mesentery
  - Abbitt & Nash (2003), *in vitro* experiments
- Is aggregation necessary?
  - Direct observations do not suggest significant agg. needed
  - But 50kDa dextran (Dx50), which inhibits aggregation, still decreases adhesion (Pearson & Lipowsky 2000)???

Background: the F-L effect

- Key microcirculation feature: Fåraæus-Lindqvist effect
  - RBCs cluster toward vessel center
  - Reduced net resistance relative to Poiseuille flow



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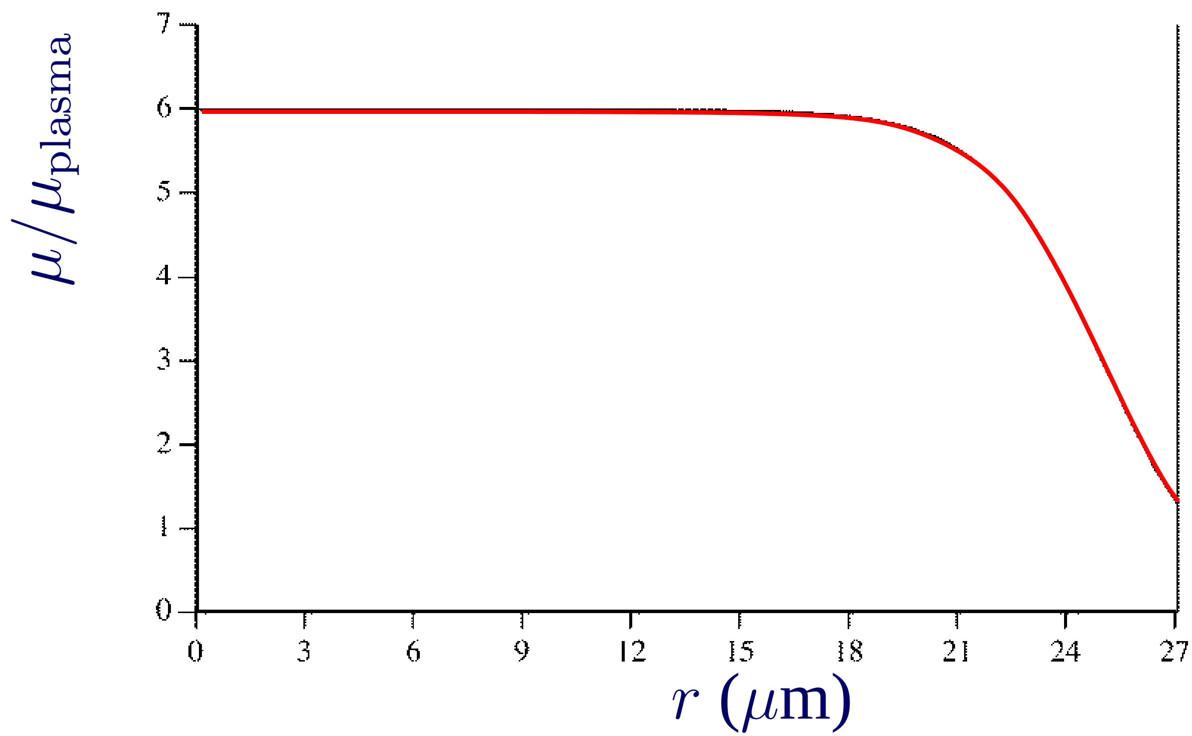


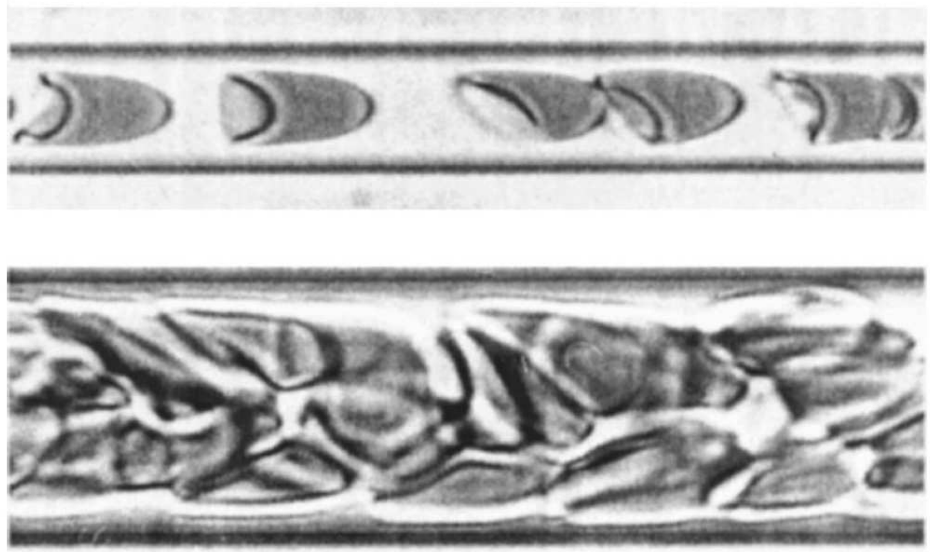
Experiment: Long *et al.*, *PNAS* (2004)

Background: the F-L effect

- Key microcirculation feature: Fåræus-Lindqvist effect
  - RBCs cluster toward vessel center
  - Reduced net resistance relative to Poiseuille flow
- Leukocyte margination seems counter to F-L effect

Questions Summary

- Do hydrodynamics alone marginate? Aggregation necessary?
- Dependence on RBC flexibility?



Pries

- Source of shear-rate/flow-rate dependence?
- Role of cell-free F-L layer?
- Mechanisms for Dx50 adhesion inhibition?

Simulation Model

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- Blood: cellular suspension in Stokes flow
- Matched interior/exterior cell viscosity
- Two dimensional

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- Blood: cellular suspension in Stokes flow
- Matched interior/exterior cell viscosity
- Two dimensional

- Not a quantitative model of the microcirculation but...
  - includes several key components
  - will reproduce key phenomena

Simulation Model

- Finite-deformation massless shell model for cell walls
  - reasonable model for RBCs — very simple cells
  - linear constitutive model

$$m = M(\kappa - \kappa_o) \qquad \tau = T\left(\frac{ds}{ds_o} - 1\right)$$

  - membrane traction on fluid

$$\Delta\boldsymbol{\sigma} = \frac{\partial \mathbf{t}\tau}{\partial s} + \frac{\partial}{\partial s}\left(\frac{\partial m}{\partial s}\mathbf{n}\right)$$

m	bending moment	τ	tension
M	bending modulus	T	tension modulus
κ	curvature	s	arc length
κ_o	reference curvature	s_o	referential arc length

Boundary Integral Formulation

- Boundary integral formulation (*e.g.* Pozrikidis *et al.*)

$$u_j(\mathbf{x}) = U_\infty + \frac{1}{(4\pi\mu)} \int_\Omega \Delta\sigma_j(\mathbf{y}(s)) S_{ij}(\mathbf{x}(s) - \mathbf{y}(s))\, ds$$

Ω	all surfaces
$\Delta\sigma_j$	j-th component of membrane traction
S_{ij}	fundamental solution for Stokes operator

Surface Discretization

- Evenly spaced points in referential s_o coordinate: $\mathbf{x}^m = \mathbf{x}(s_o^m)$
- Assume $\mathbf{x}^m$ are interpolated by harmonics

$$\mathbf{x}^m = \sum_{l=-N/2}^{N/2-1} \hat{\mathbf{x}}^l e^{ik_l s_o^m}$$

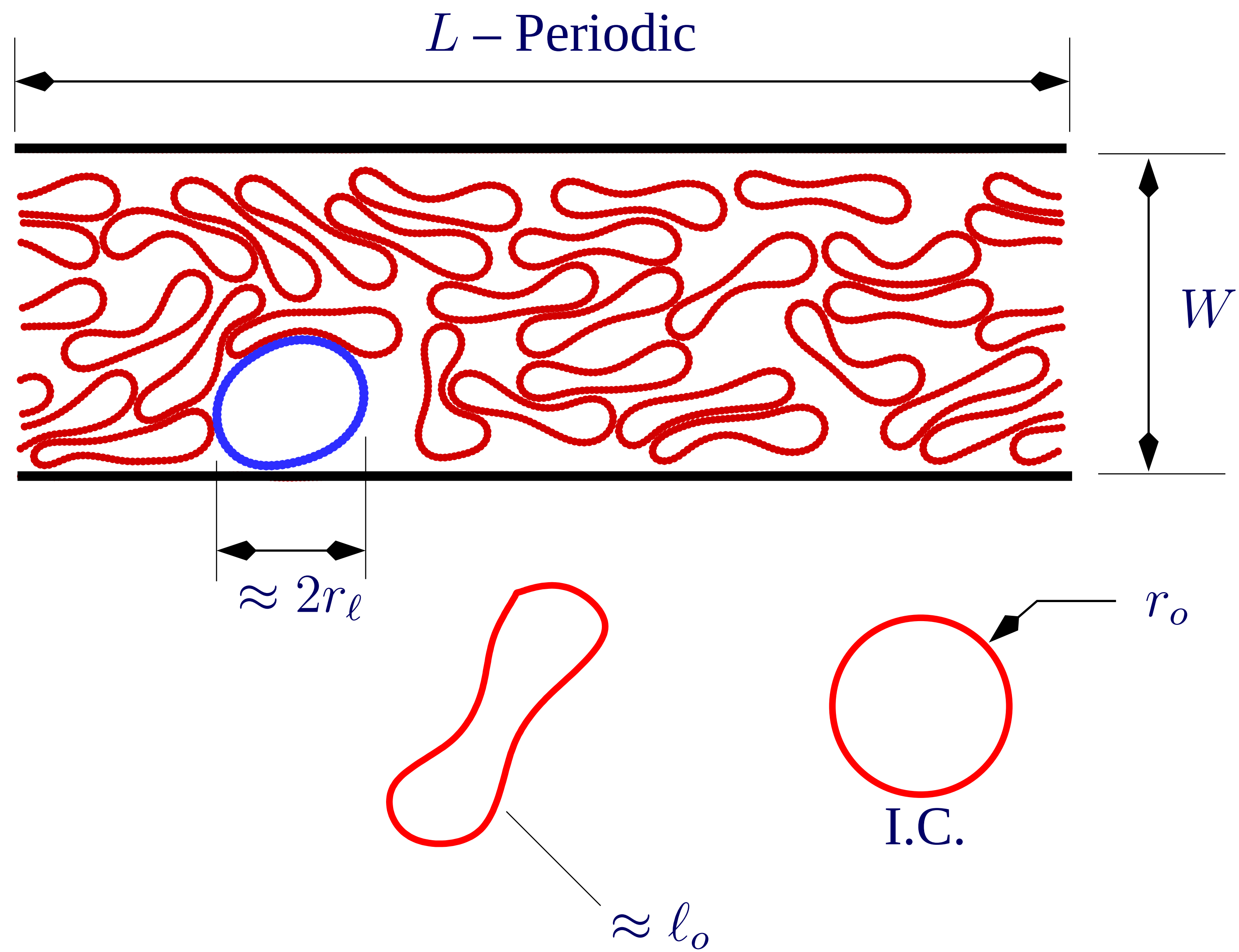
  - Efficient for given accuracy for smooth shapes
  - Dealiasing
  - Consistent accurate quadratures: $N_a > N$
    - integrand harder to resolve than cell shape
    - only N restricts time step

Fast Particle-Mesh Methods

- Particle-Mesh-Ewald (PME) or Particle-Part./Particle-Mesh (P^3M)
  - Darden *et al.* (1993), Essmann *et al.* (1995), Metsi (2000), Saintillan *et al.* (2005), Hockney & Eastwood (1988)
- FFTs on mesh: $O(N \log N)$ relatively small coefficient
- Significantly faster than multipole methods for typical N
- Standard for electrostatics in molecular biophysics codes

Configuration and Cases

Flow Configuration



Parameters

- **Fixed, anticipated important**

r_ℓ	leukocyte radius
r_o	RBC initial radius
ℓ_o	RBC reference length
ρ	hematocrit (0.45, 0.33, 0.20)
μ	viscosity
W	channel width

- **Fixed, anticipated unimportant for selected values**

M_ℓ	leukocyte moment modulus
T_ℓ	leukocyte tension modulus
L	channel length

- **Varied**

M	RBC moment modulus
T	RBC tension modulus
U_∞	driving flow

Constant Groups

$$r_o^2 \frac{T}{M} = 50 \quad [100]$$ RBC property

$$\frac{\ell_o}{r_o} = 1.6(2\pi)$$ RBC property

$$\frac{r_\ell}{r_o} = 1.75$$ leukocyte radius

$$\frac{L}{r_o} = 27$$ channel length

$$\frac{W}{r_o} = 7.8$$ channel width

Time Scales (Variable)

- Advection:

$$\tau_{\text{adv}} = \frac{r_o}{U_m}$$

- Shear:

$$\tau_{\text{sh}} = \frac{1}{\sigma_m} \qquad \text{where} \qquad \sigma_m = \left.\frac{du}{dy}\right|_w$$

- Relaxation:

$$\tau_{\text{rlx}} = \frac{\mu r_o}{T}$$

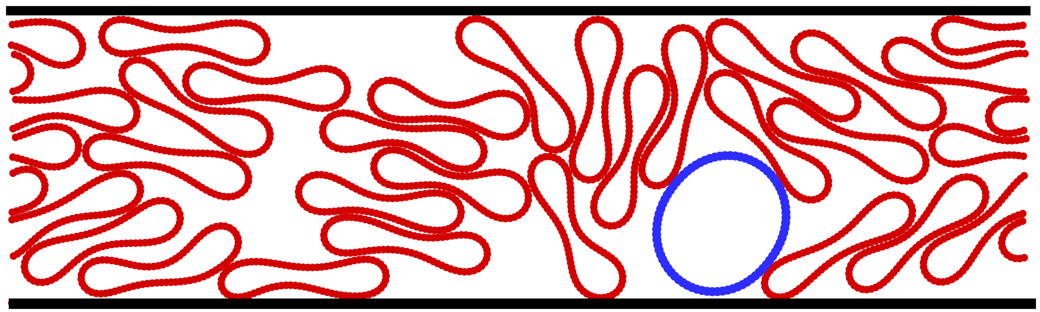
Cases

Case	$\frac{\mu U^\infty}{T}$	$\frac{\tau_{\text{rlx}}}{\tau_{\text{sh}}} = \frac{\mu r_o \sigma_m}{T}$	$\frac{\tau_{\text{rlx}}}{\tau_{\text{adv}}} = \frac{\mu \mathbf{u}_m}{T}$	$\frac{\tau_{\text{adv}}}{\tau_{\text{sh}}} = \frac{r_o \sigma_m}{\mathbf{u}_m}$	N	N_a
a1		0.120	0.109	1.10		
a2		0.120	0.106	1.13		
a3	0.80	0.115	0.100	1.15	32	128
a4		0.114	0.094	1.21		
a5		0.122	0.084	1.44		
b	0.6	0.090	0.077	1.16	32	128
c	0.4	0.060	0.039	1.45	32	128
d1		0.028	0.020	1.40		
d2	0.20	0.0281	0.017	1.64	20	80
d3		0.0245	0.014	1.73		
e	0.067	0.0073	0.0036	2.02	20	80
f1		0.0055	0.0040	1.36	16	64
f2	0.05	0.0057	0.0037	1.54	16	64
f3		0.0053	0.0032	1.64	20	80

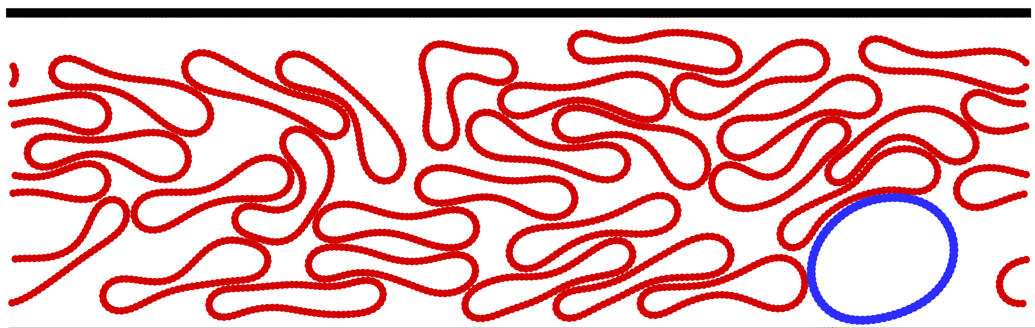
Basic Results

Visualizations/Animations

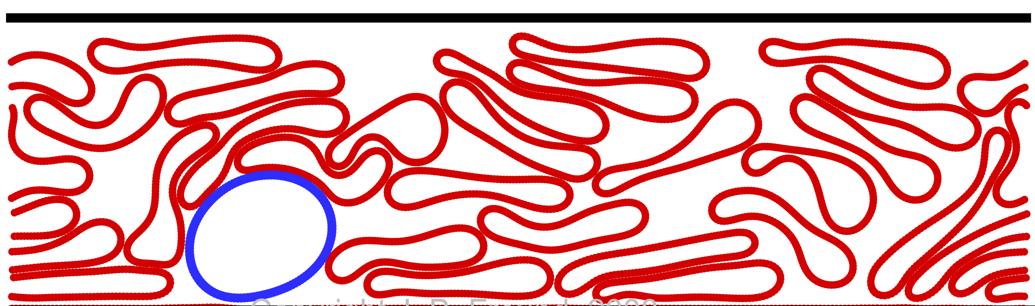
- $\frac{\mu U_\infty}{T} = 0.05$



- $\frac{\mu U_\infty}{T} = 0.2$

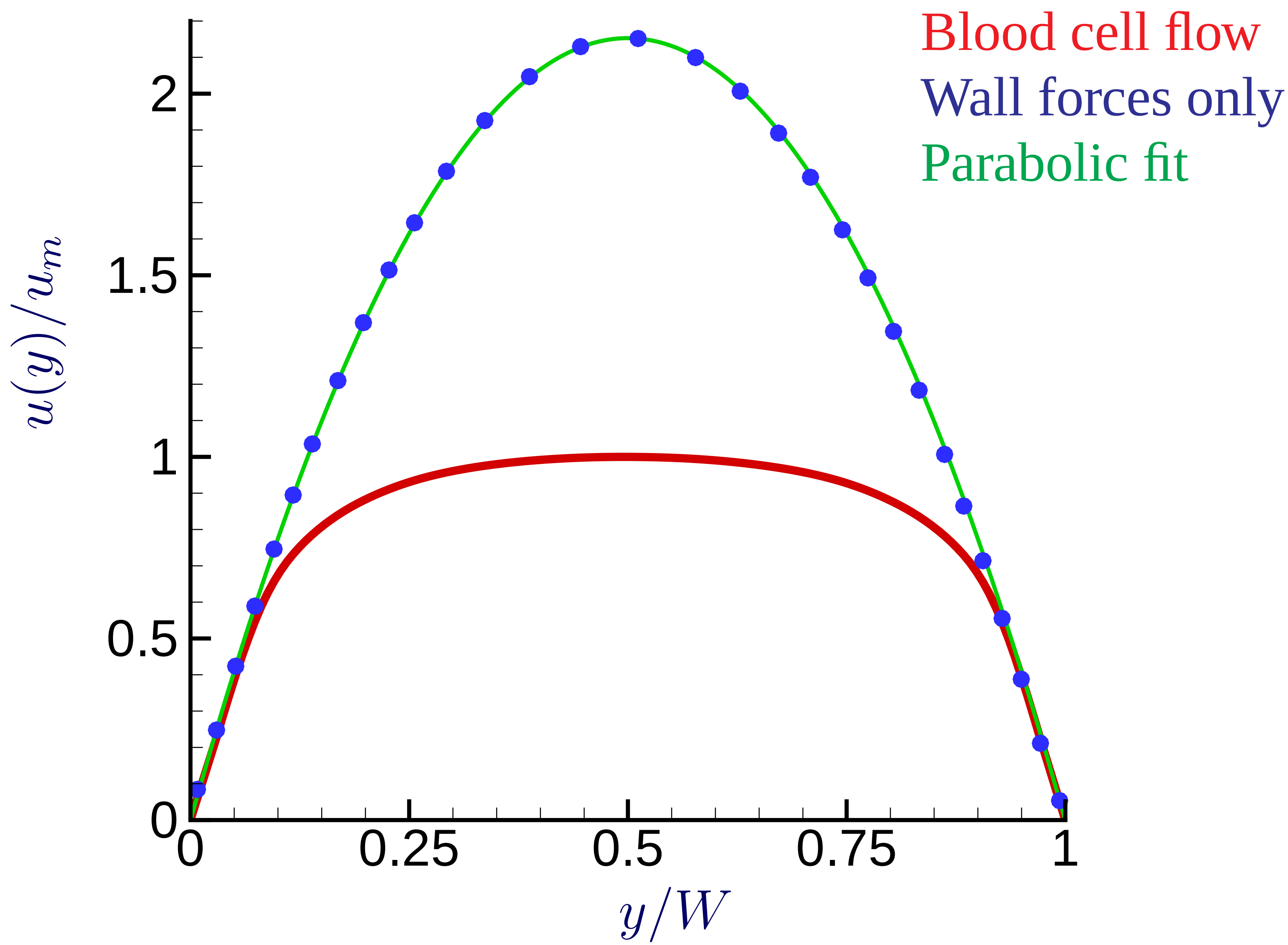


- $\frac{\mu U_\infty}{T} = 0.8$

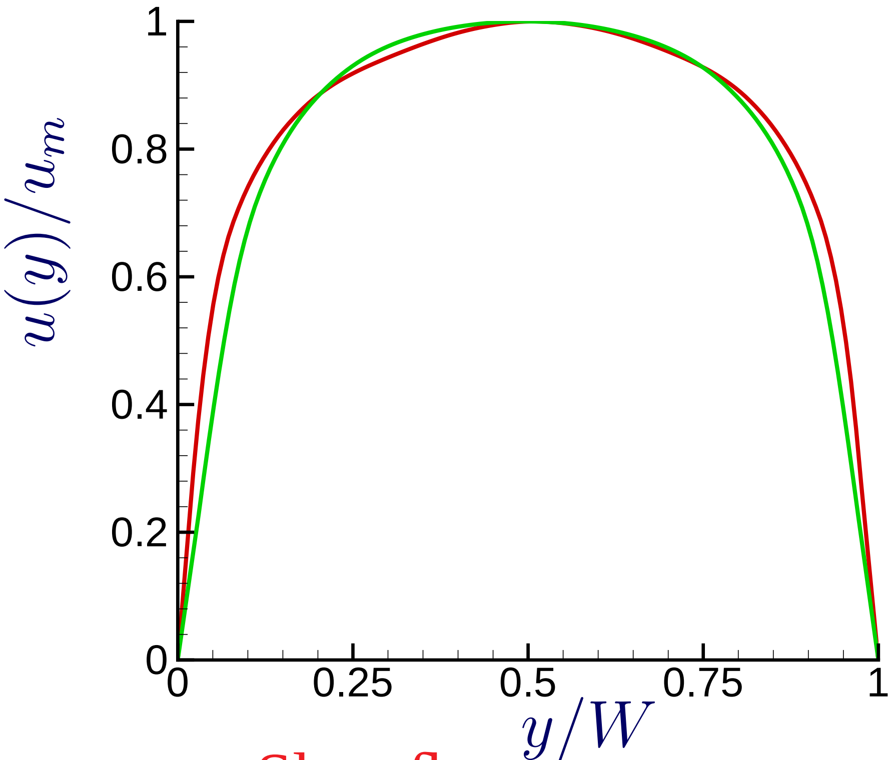


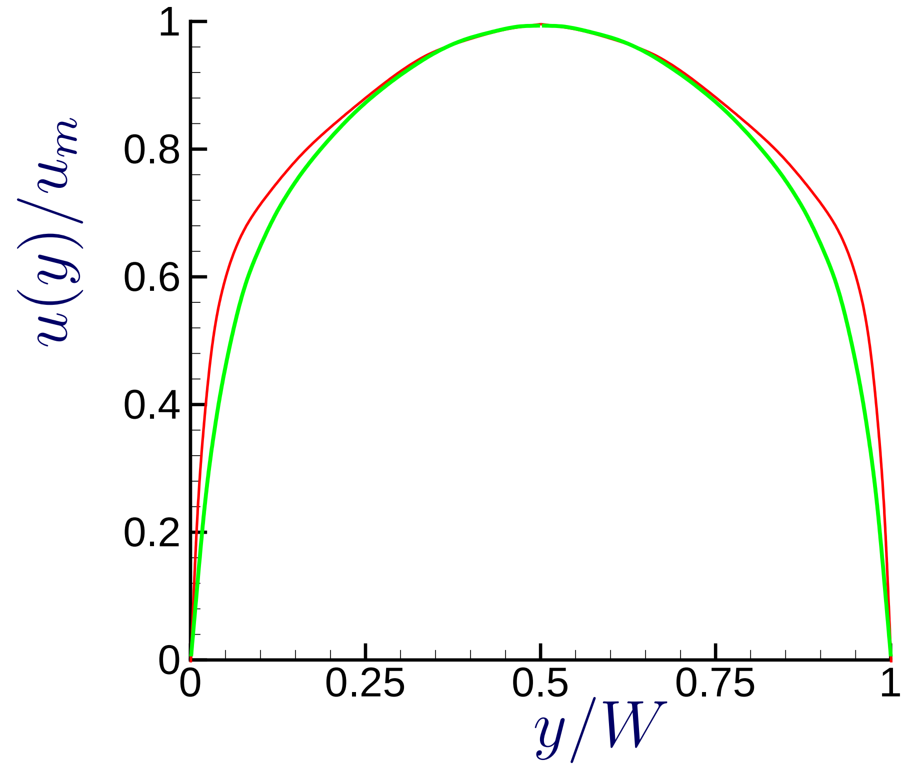
Floppier, Constant U_∞

Mean Velocity Profile



Velocity Profile Bluntness

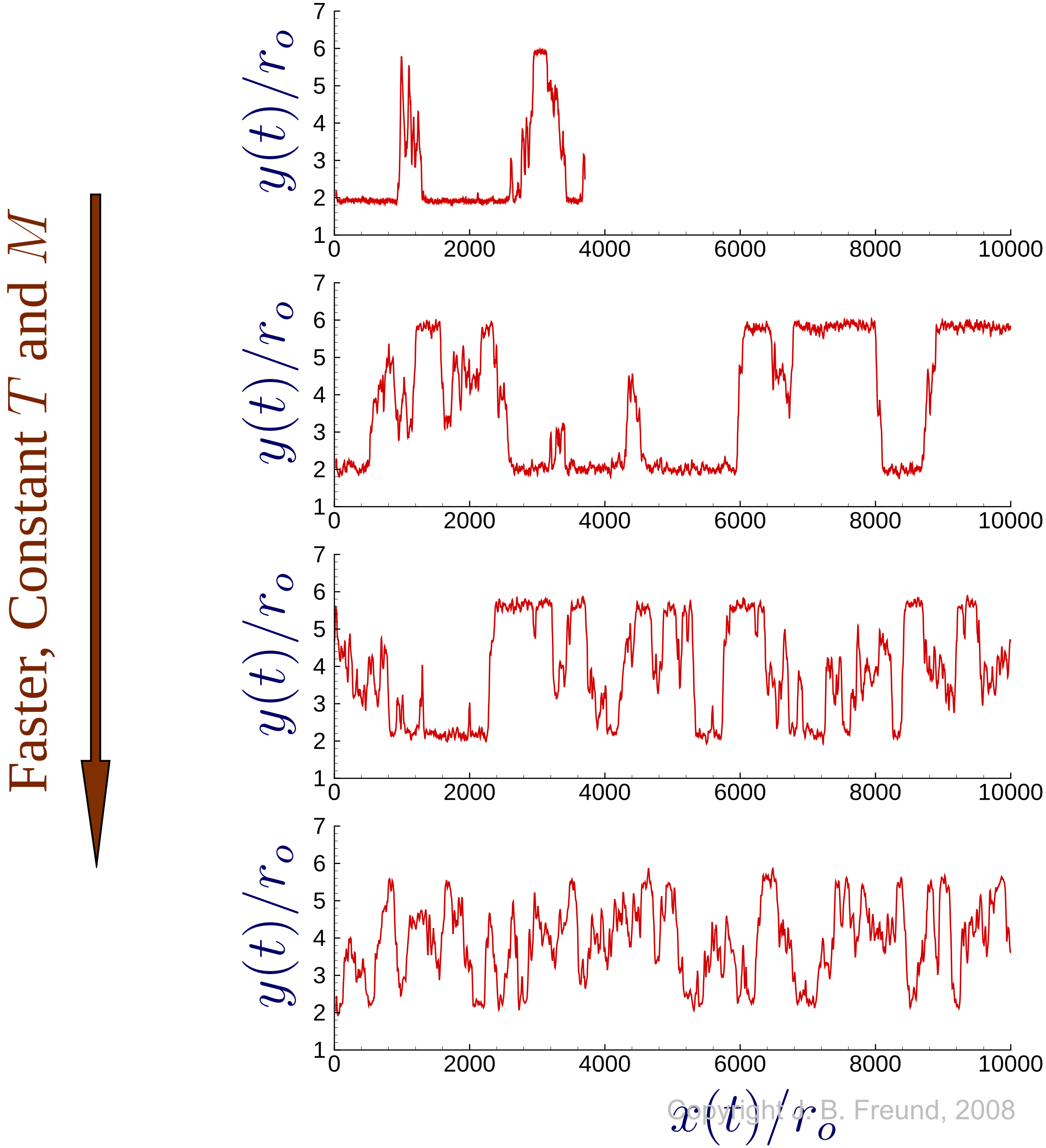




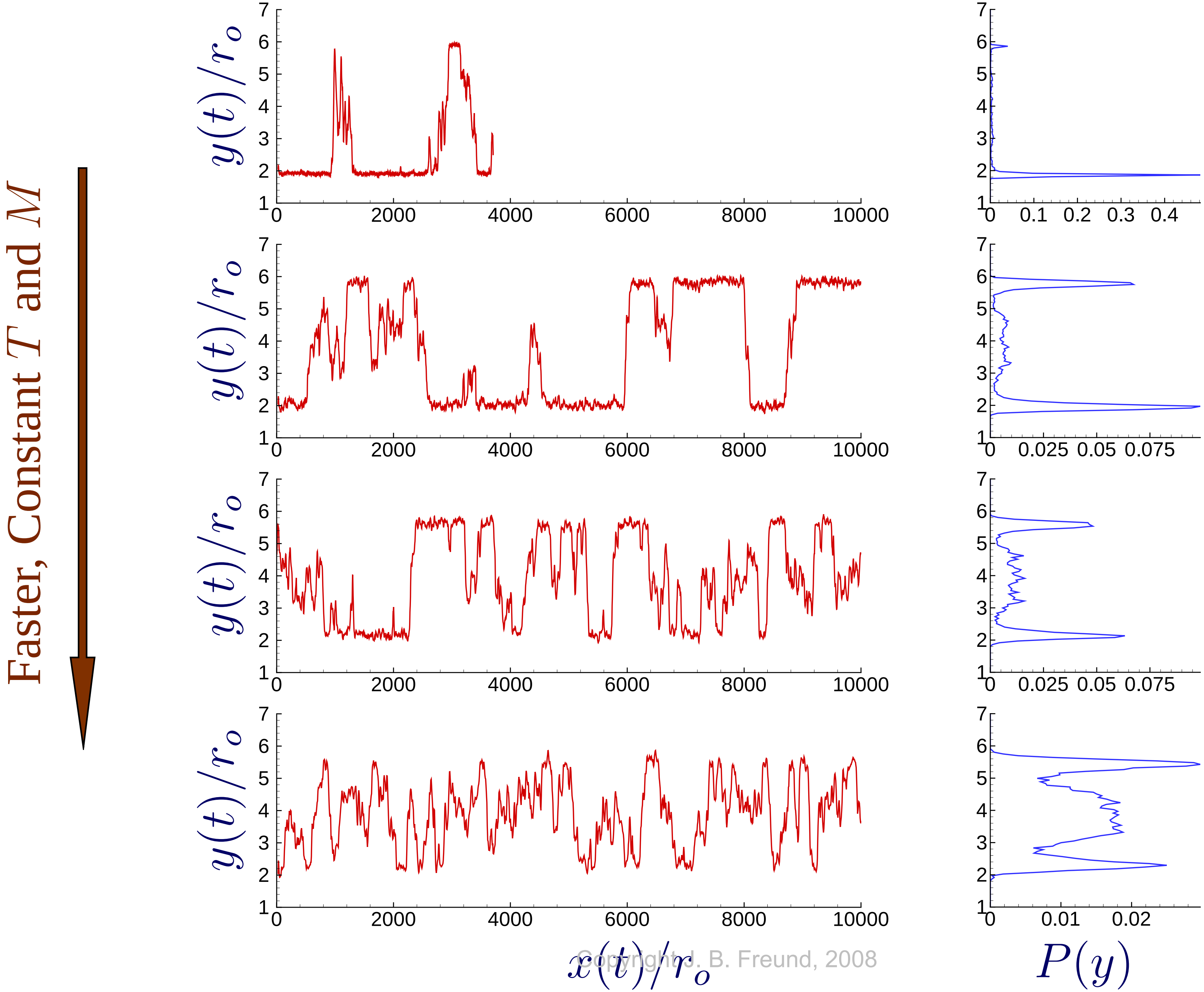
Slow flow
Fast flow
(same cell properties)

Slow Flow
Fast Flow
Long (2005); mouse blood
$\sim$29.7μm ($\approx 15r_o$) glass tube

Leukocyte Path: $M, T = consts$



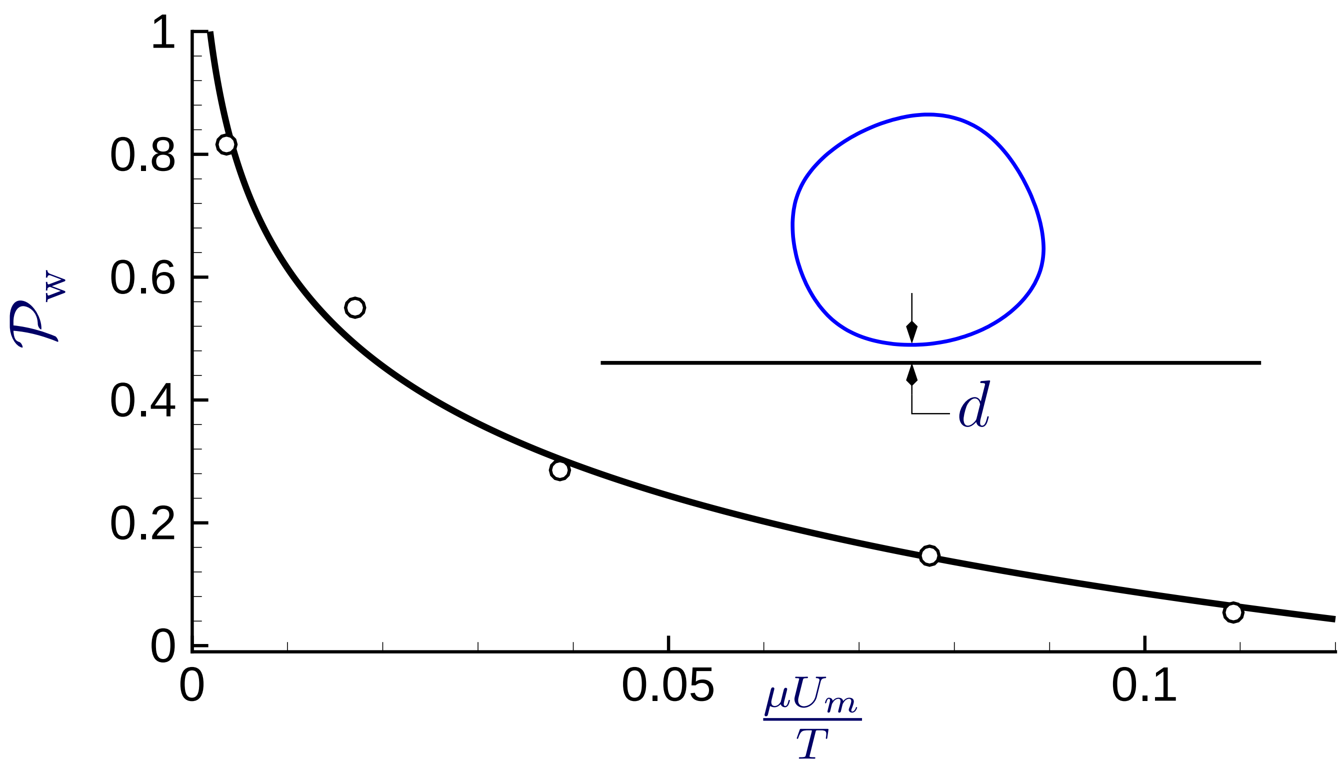
Leukocyte Path: $M, T = consts$



Near-Wall Probability

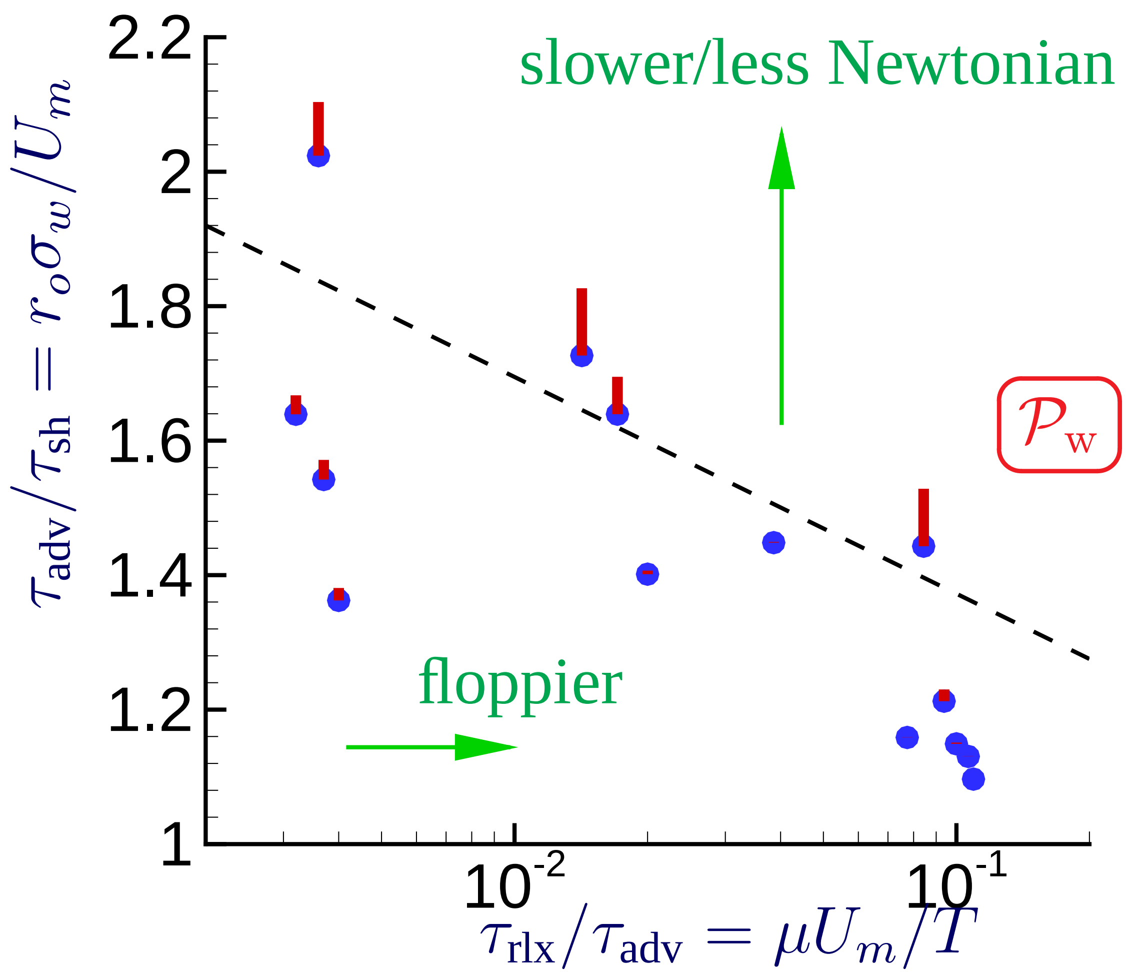
- Probability $d < d_c = 0.4 r_o$:

$$\mathcal{P}_{\mathrm{w}} = \int_0^{d_c} P(d)\, dd$$



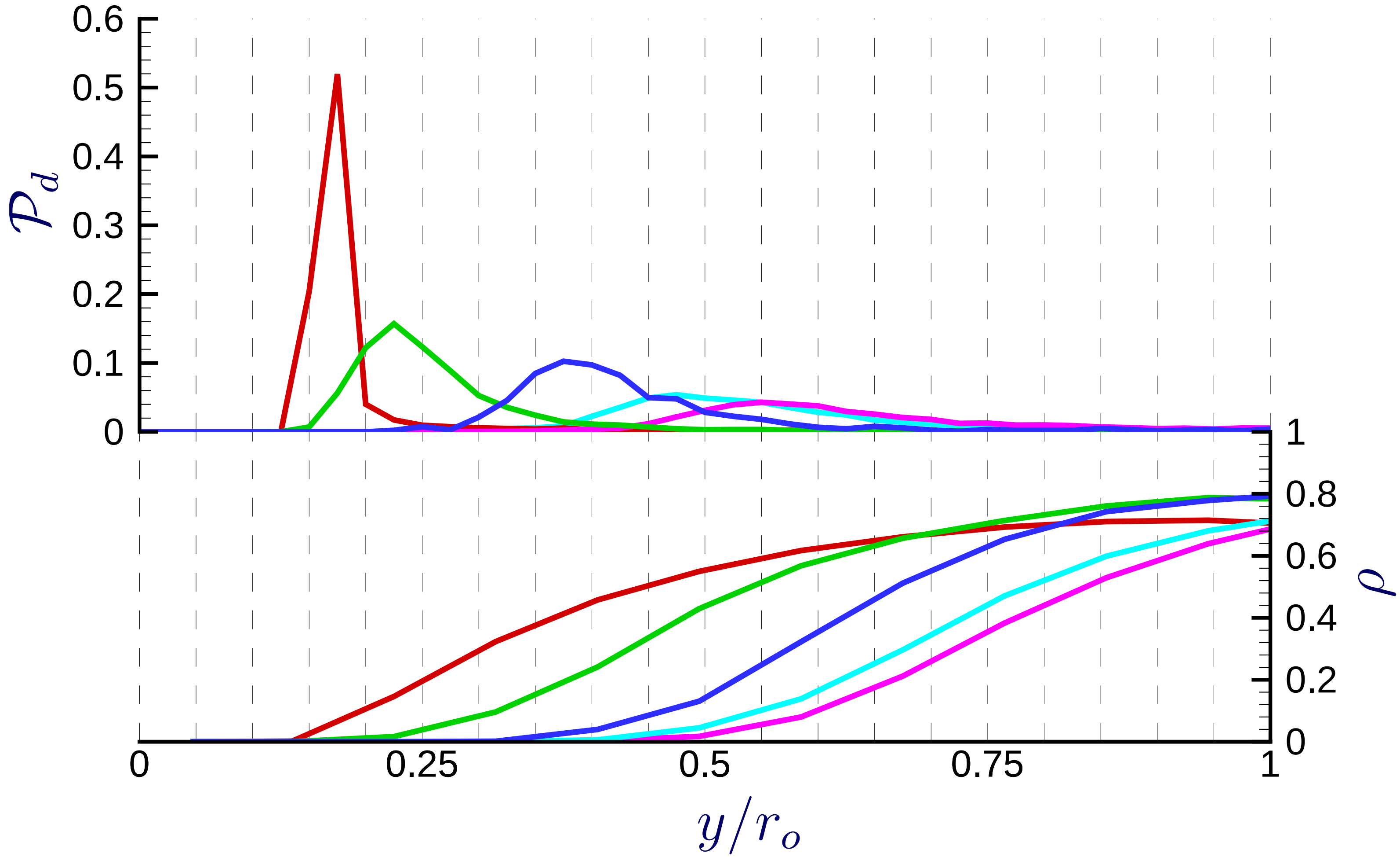
- Qualitatively similar to experiments

Near-Wall Probability



- Insensitive to RBC stiffness
- Sensitive to profile bluntness...?

Most Probable Luk. Location

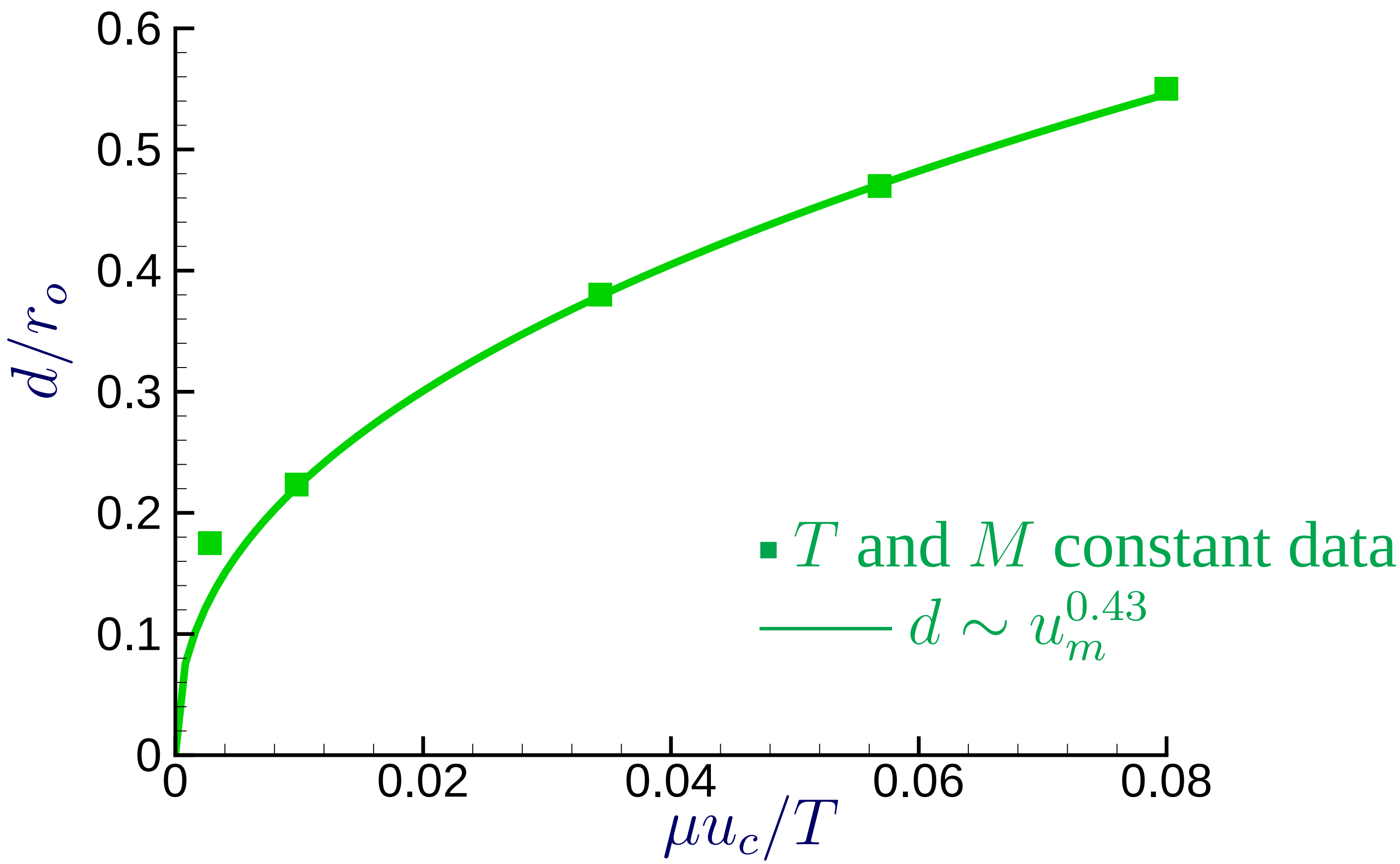


$\tau_{\text{rlx}}/\tau_{\text{adv}} = \mu u_m/T$ = 0.0036; 0.017; 0.039; 0.077; 0.11

Constant cell properties

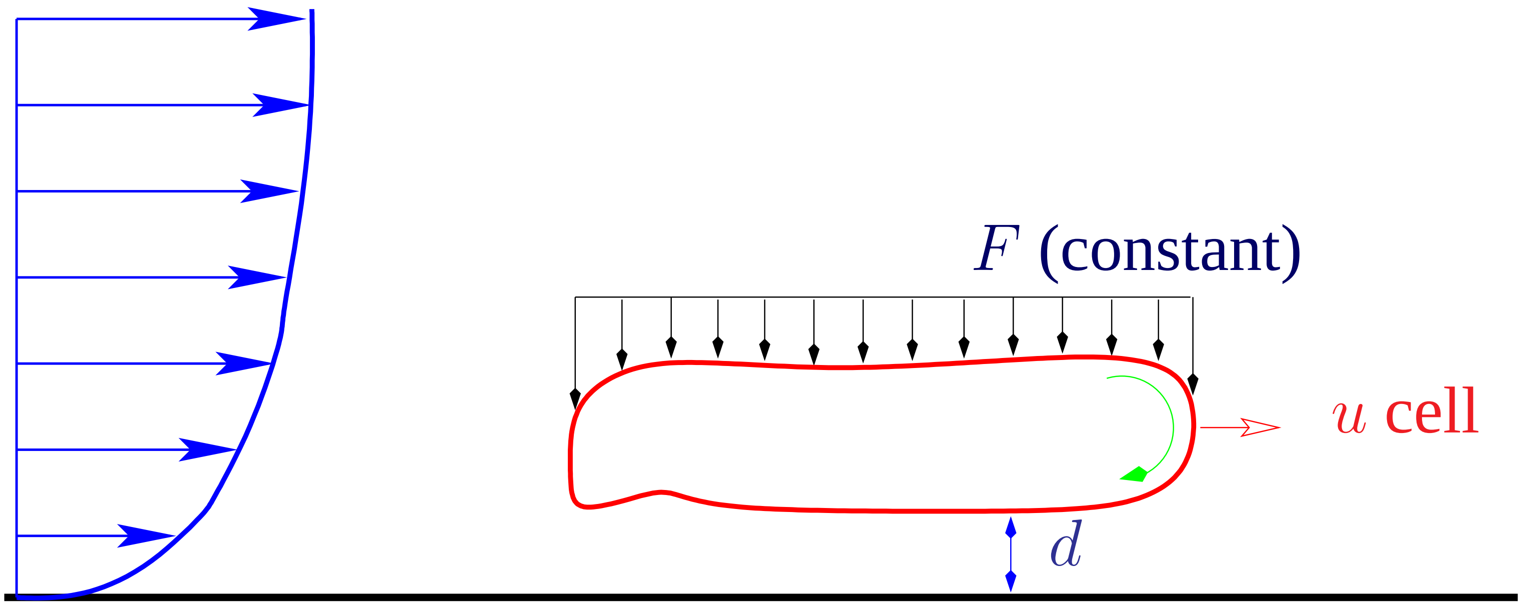
- Leukocyte sits at edge of cell free layer

Cell Free Layer Thickness

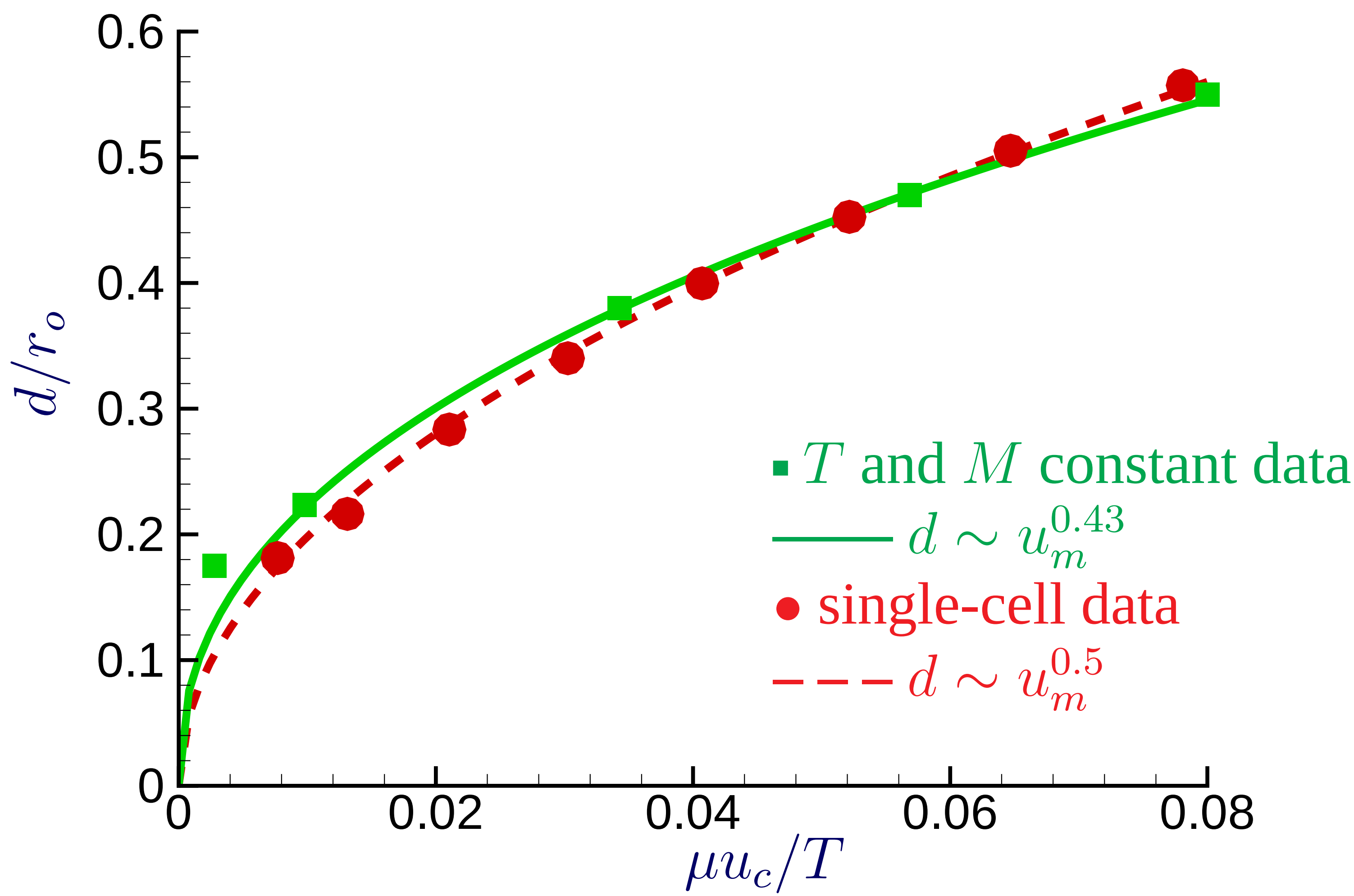


- Lubrication scaling $d \sim \sqrt{u}$ for constant "force"?

Single-Cell “Lift” Test



Cell Free Layer Thickness



- Why is leukocyte at same height?

3D

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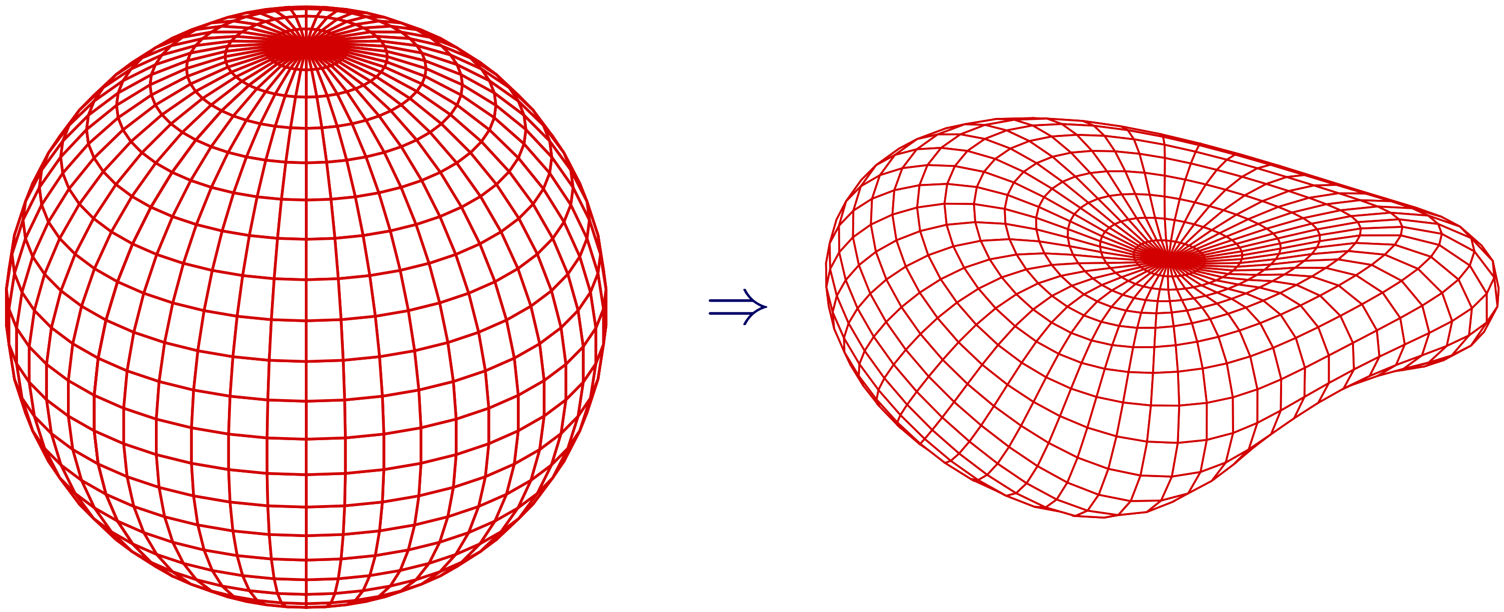
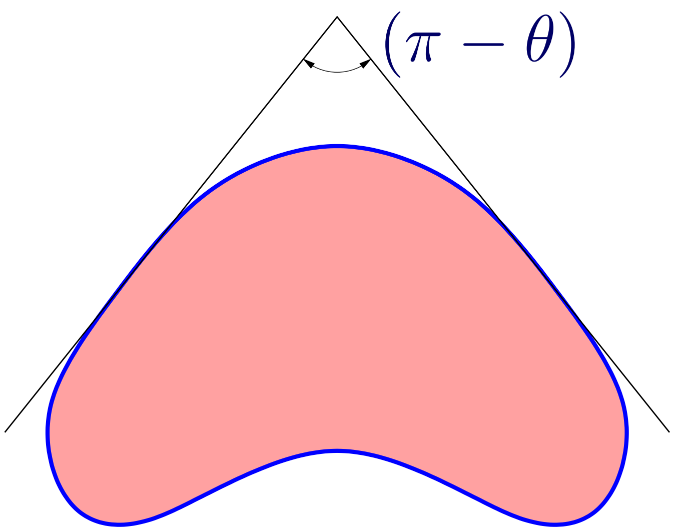
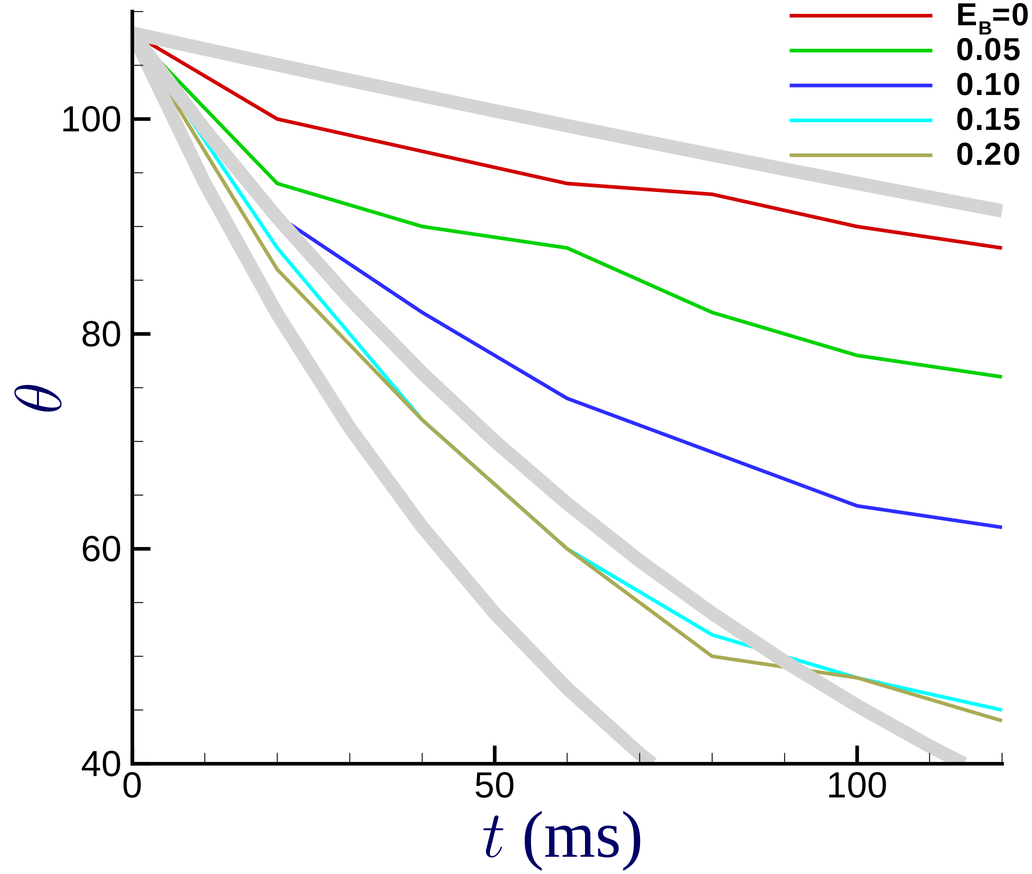
3D



- Spherical harmonics with dealising
- GMRES for mismatched viscosity implicit system

Deformation Relaxation

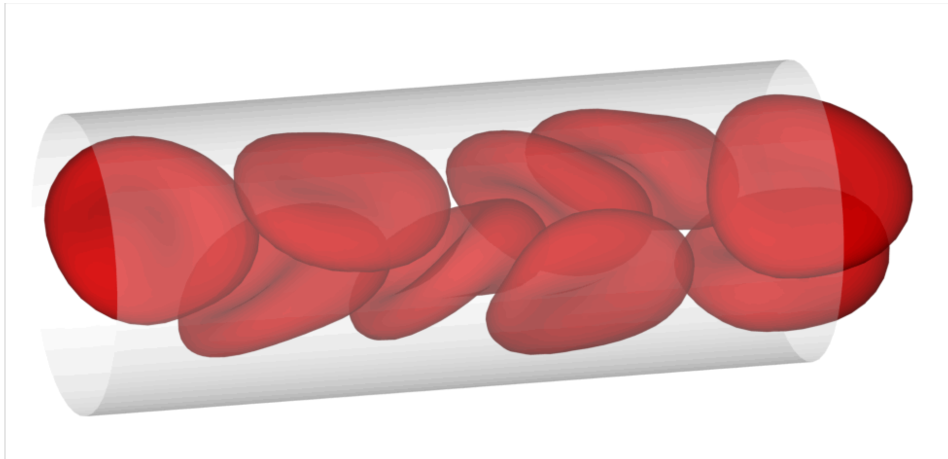


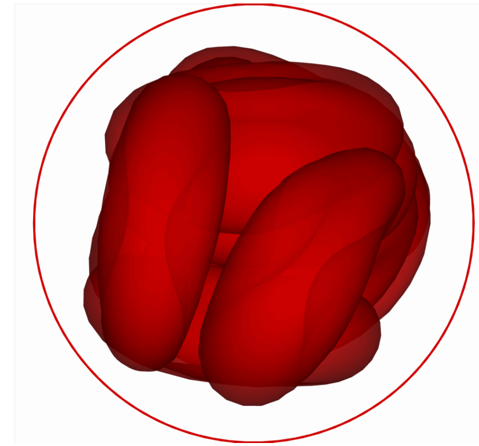


- Relaxation times with expected bending moduli match experiments of Bronkhorst *et al.*

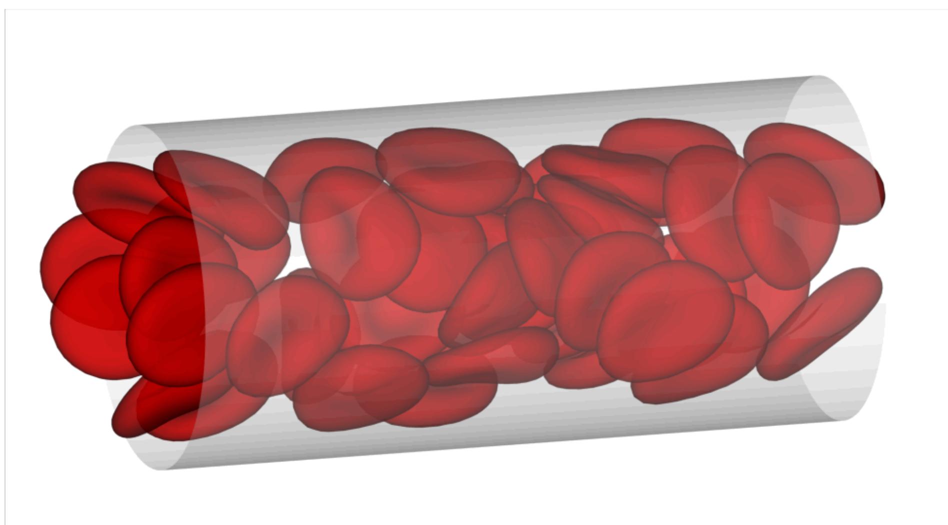
Cellular flow in cylindrical tubes

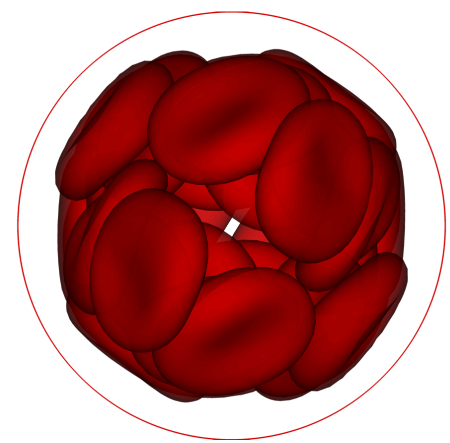
$D = 11.4\mu$m
$H_T = 30\%$



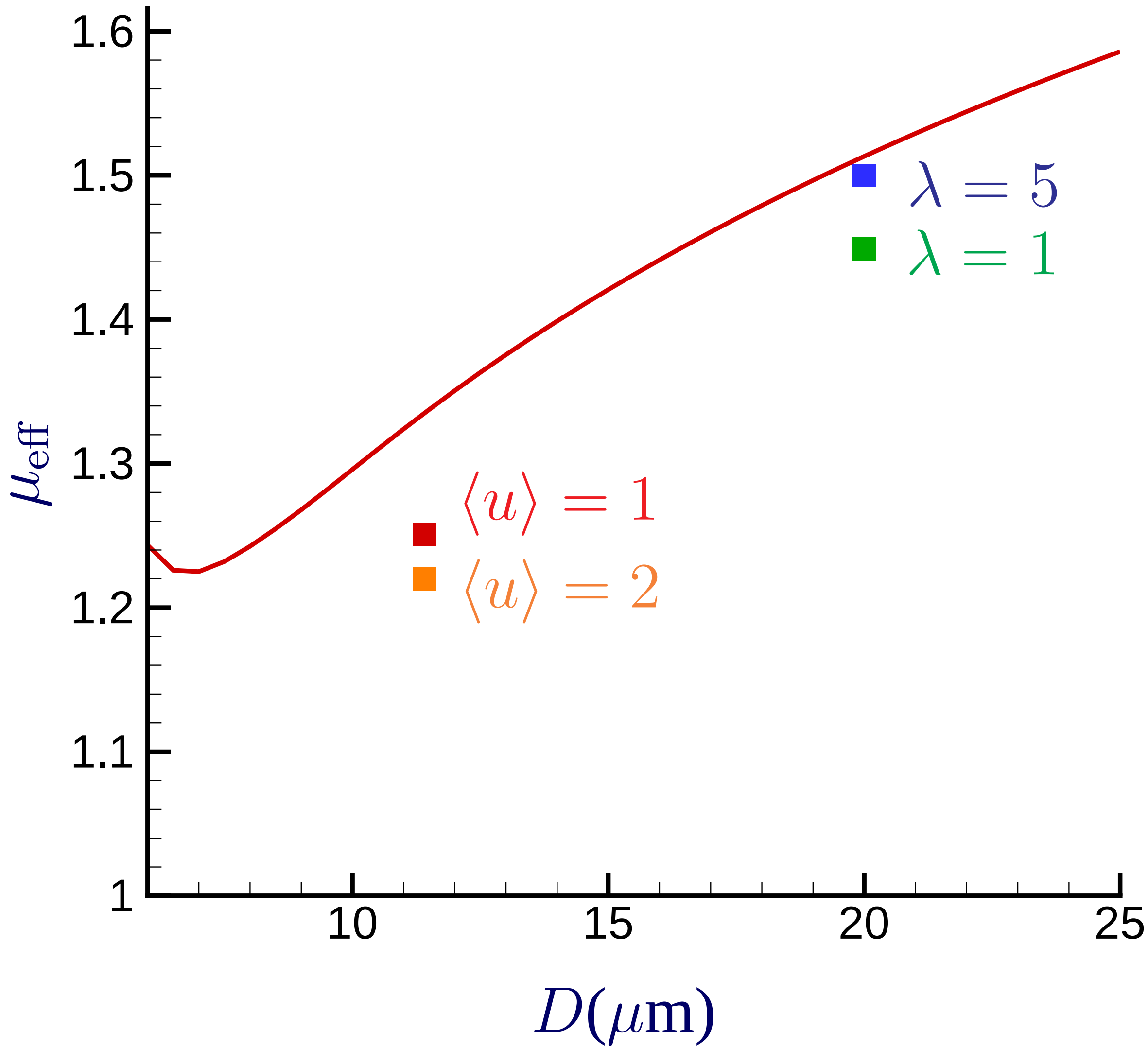


$D = 20.0\mu$m
$H_T = 30\%$

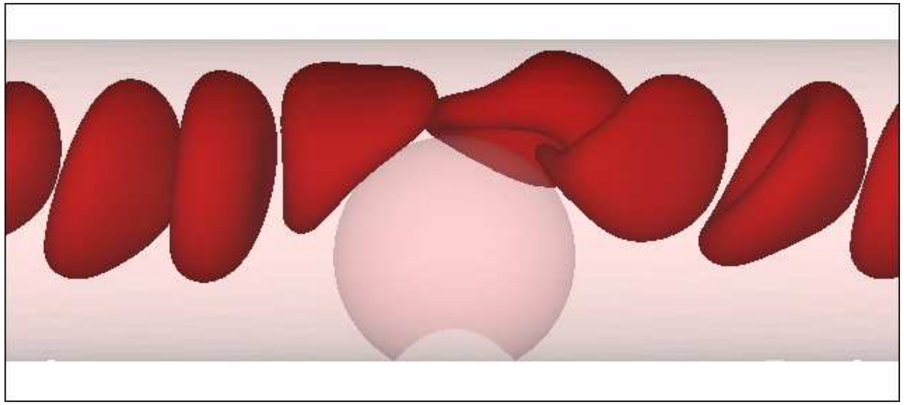


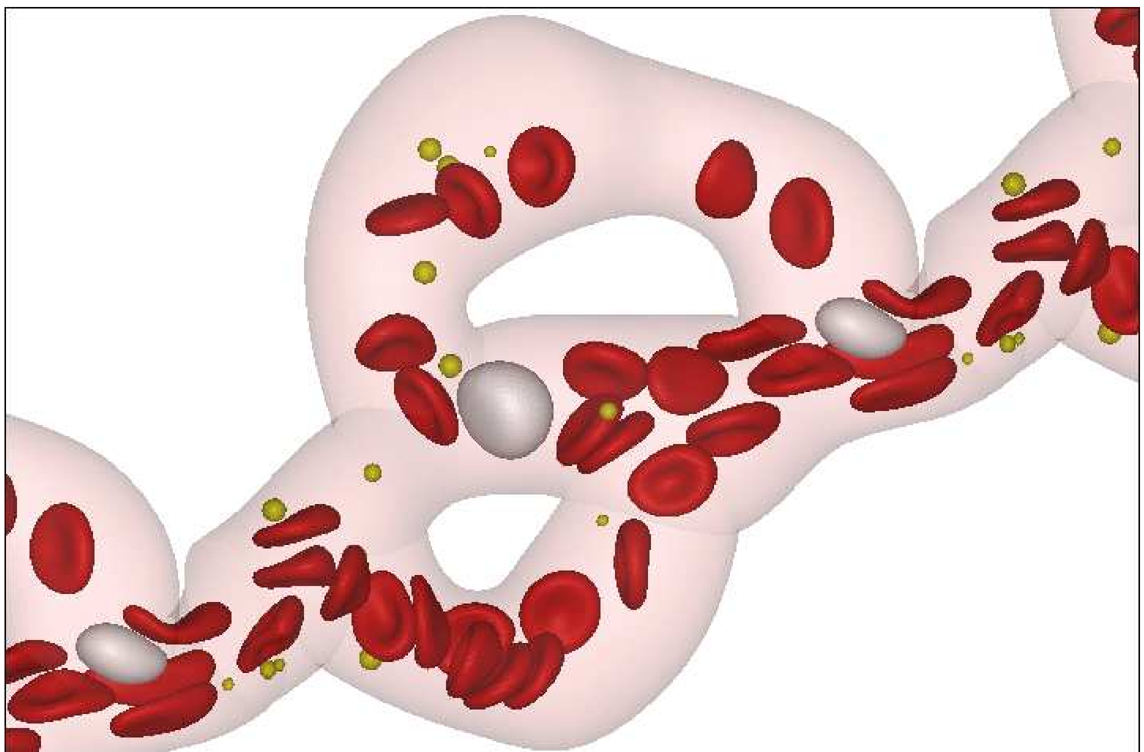


Effective Viscosity



Complex Geometries

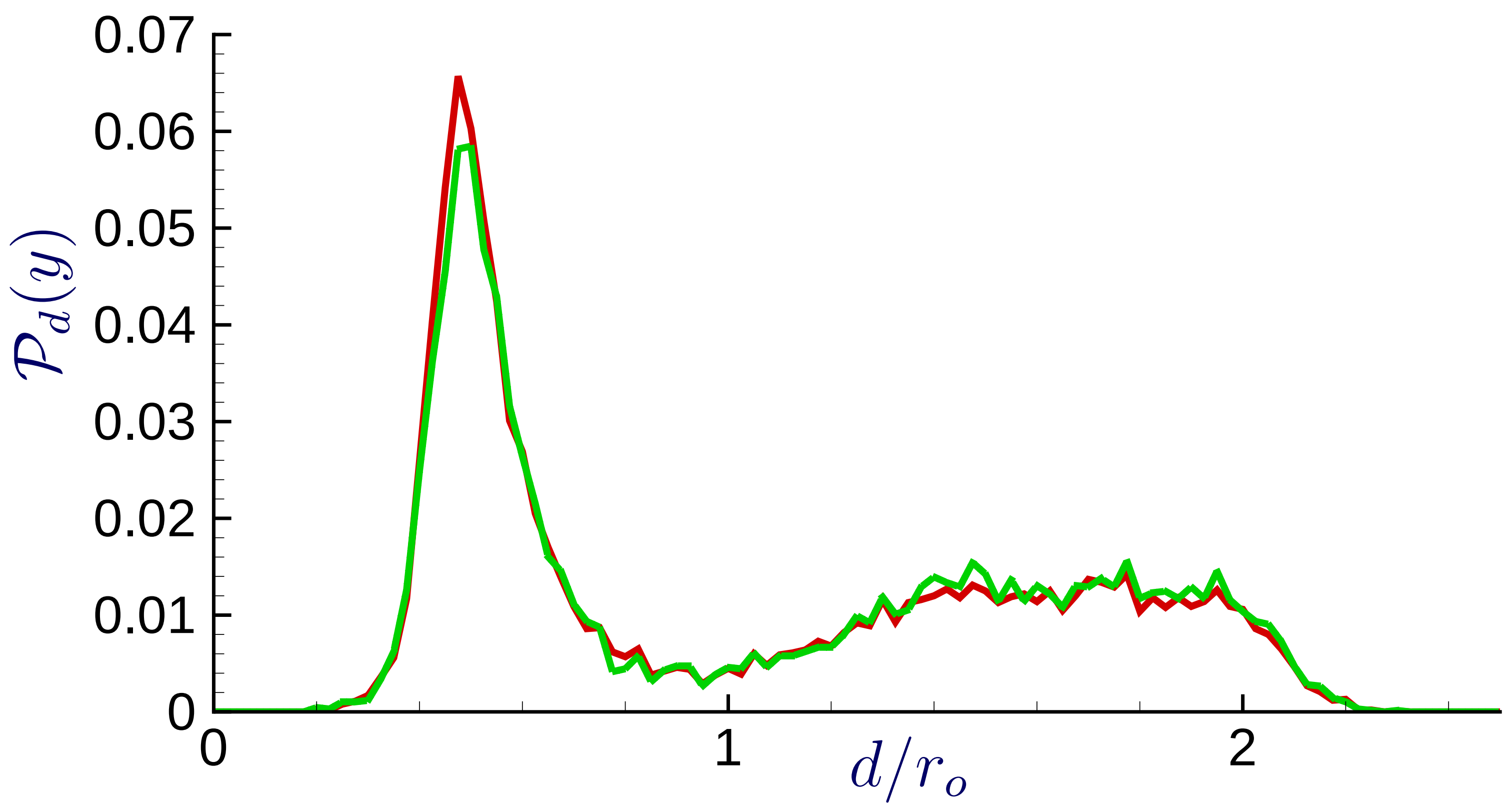




Conclusions

- More probable on-wall corresponds to longer periods on-wall
- Margination does not require RBC agglomeration
- Relatively insensitive to RBC stiffness
- Leukocyte most probably at edge of cell-free layer
- Cell-free layer thickness scales nearly as $\sqrt{u}$.
  - Lubrication with constant wall-ward force?
- Emerging Picture: lubrication forces lift RBC putting leukocyte into less stable configuration
  - consistent with Dx50, which increases μ plasma
- 3D: preliminary validations underway

Role of Leukocyte Flexibility



Leukocyte three time stiffer than leukocyte

- Insensitive to (small) leukocyte flexibility
- Lubrication forces lift RBC destabilizing leukocyte