LONI Institute
First All Hands Meeting

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Modeling of cell adhesion using a multiphase flow approach

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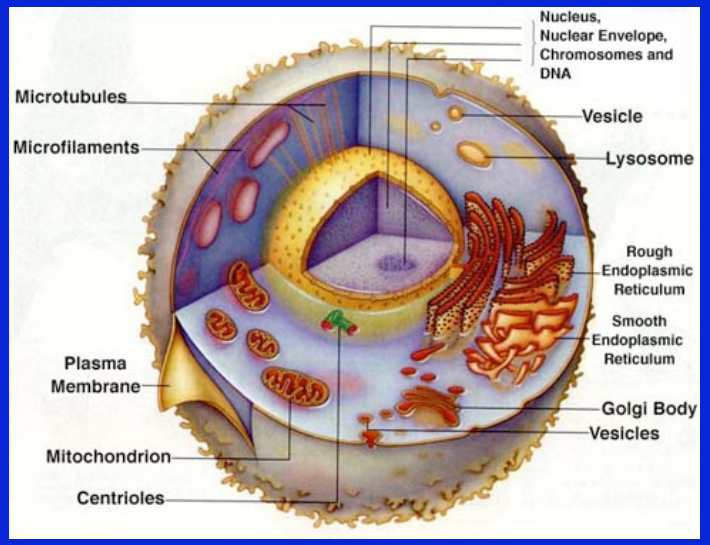
- **Multiphase systems**, i.e., mixtures of disperse immiscible phases form our atmosphere and oceans, the Earth's crust, and the **bodies of living beings**.

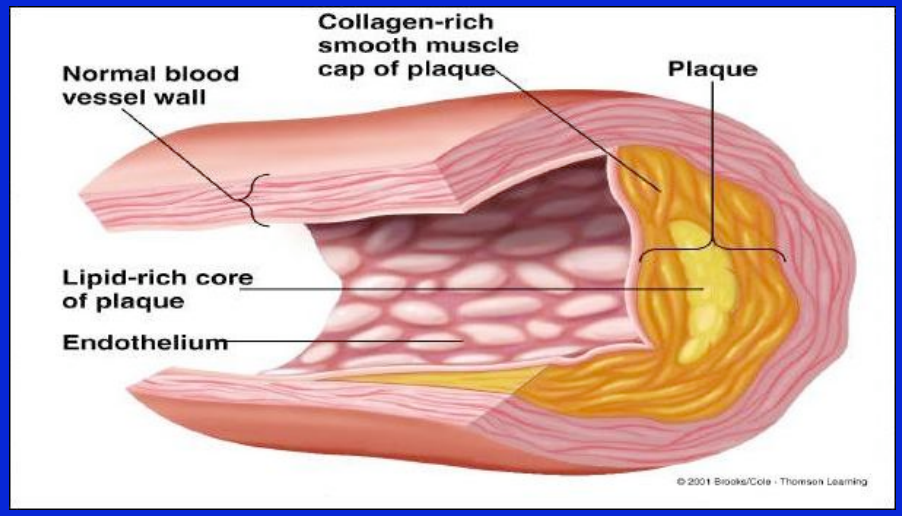
- The mechanics of multiphase systems, often called **multiphase flow**, **provides a more realistic description** of natural and industrial processes than single-phase fluid mechanics.

- Since biological systems are characterized by a significant level of heterogeneity, it is natural to use a multiphase flow approach to model the mechanics of biological systems.



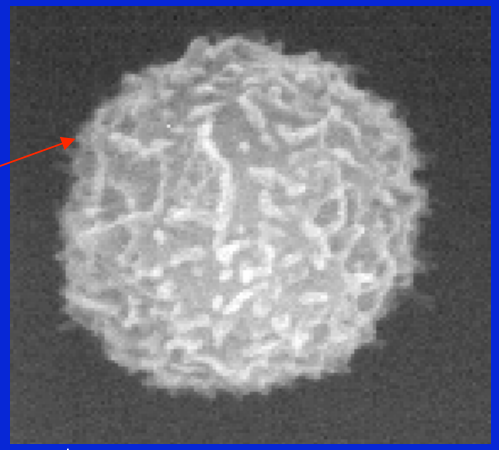
Goal 1: To develop a realistic computational model of leukocyte movement in inflammation

- **Inflammation** is the defense reaction of the body to tissue damage.
- The central stage of this process is recruitment of **leukocytes (white blood cells)** to the sites of infection or injury.

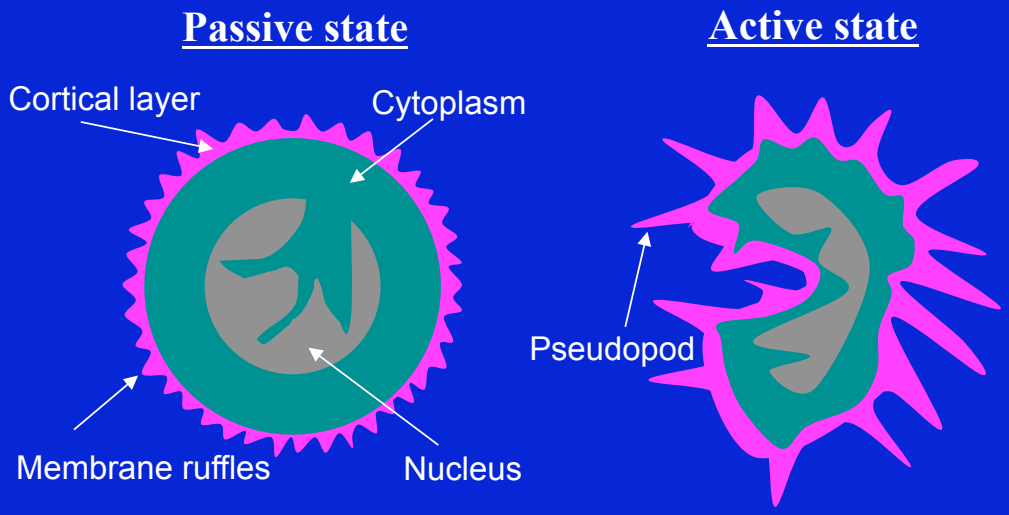


Atherosclerotic plaque.
From http://www.uvm.edu/~biology/Classes/255/

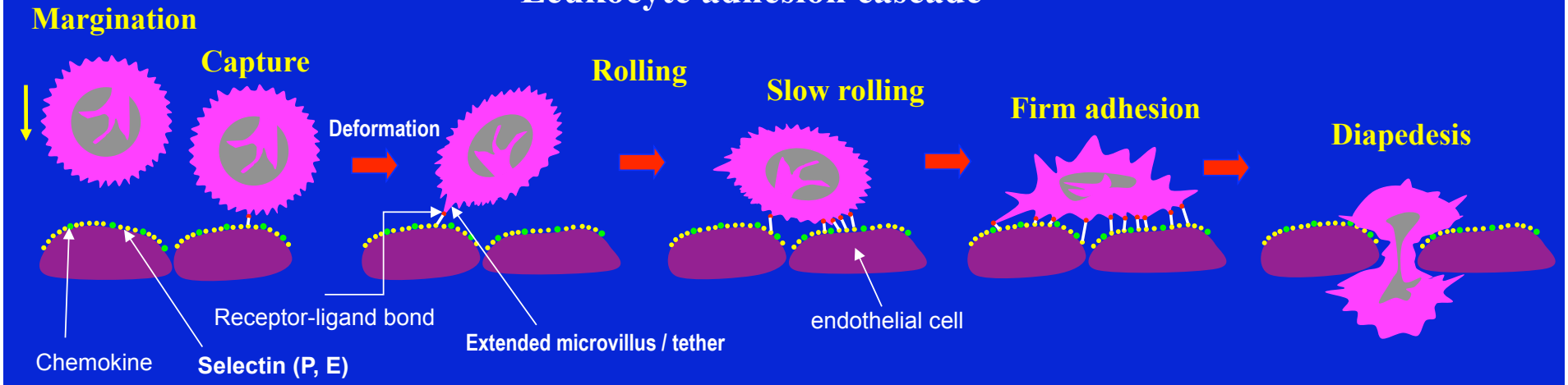
- **Leukocyte recruitment** into inflamed tissues is beneficial for host defense but **may also lead to various inflammatory disorders**, such as asthma, autoimmune diseases, ischemia-reperfusion injury, and **atherosclerosis**.
- Atherosclerosis **is a leading course of morbidity and mortality** in developed countries, including the United States.

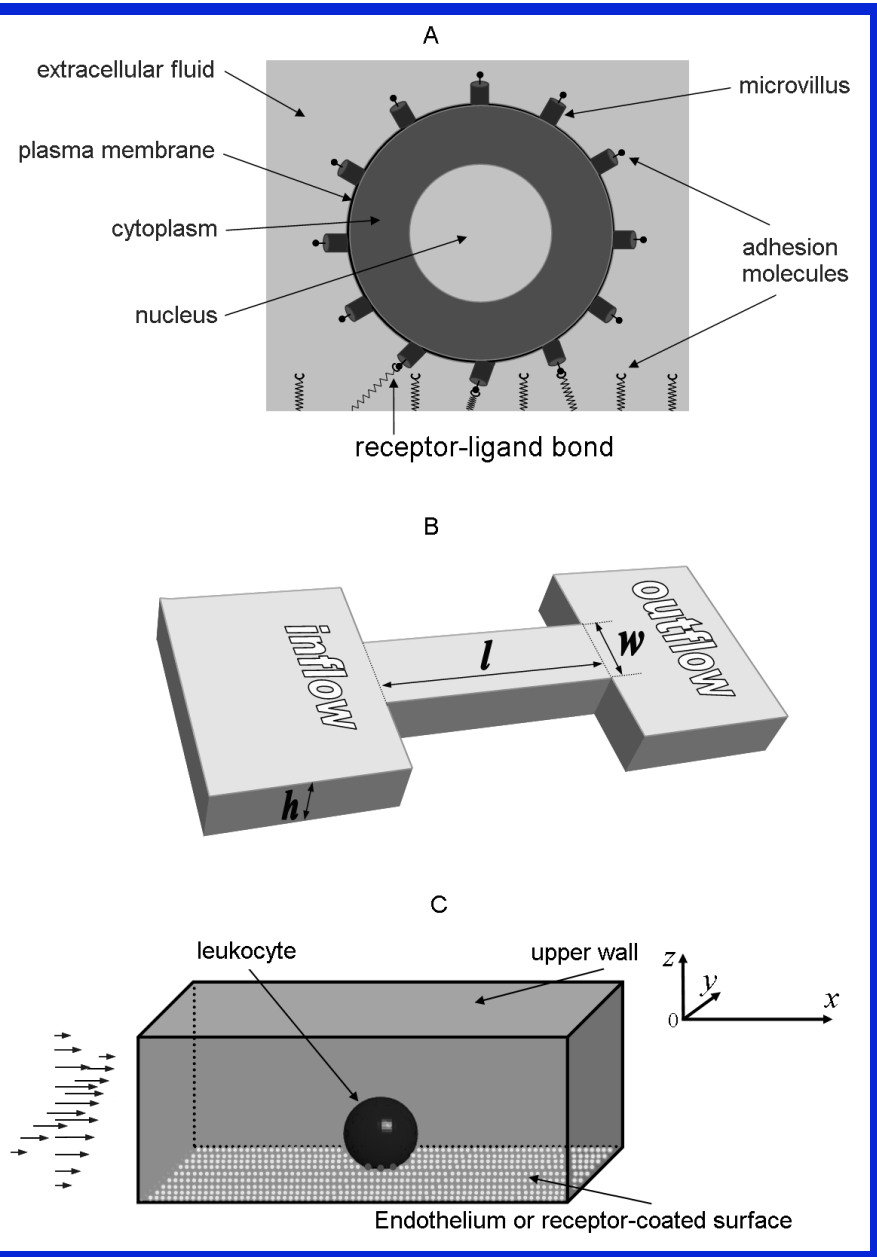


Scanning electron micrograph of a human neutrophil (provided by Robert M. Hochmuth, Duke University).



Leukocyte adhesion cascade





Compound viscoelastic drop model

- The leukocyte consists of two phases: **cytoplasm** and **nucleus**.
- Both phases are **viscoelastic**.
- The plasma membrane and an underlying cortex are treated as an infinitesimally thin layer with **cortical tension**.
- The leukocyte surface is coated with **microvilli** modeled as **massless elastic rods** of circular cross section.
- Leukocyte interaction with the substrate is mediated by **cell adhesion molecules** located on **tips of leukocyte microvilli** and on the **substrate**.
- The leukocyte is located in a rectangular **microchannel**.
- Startup or fully developed flow.

Numerical implementation

Step 1: Initialization (base flow, initial profile of the leukocyte, microvilli distribution)

Time Cycle:

Step 2: Piecewise-Linear Interface Calculation (PLIC): reconstruction of the interface

Step 3: Advection of microvilli and the interfaces: $C_1^{(n)} \rightarrow C_1^{(n+1)}$, $C_2^{(n)} \rightarrow C_2^{(n+1)}$

Step 4: Calculation of Continuous Surface Force (CSF)

Step 5: Calculation of the microvillus-bond force

Step 6: Calculation of an intermediate velocity using the semi-implicit factorized scheme for the Navier-Stokes equations: $\mathbf{u}^{(n)} \rightarrow \mathbf{u}^*$

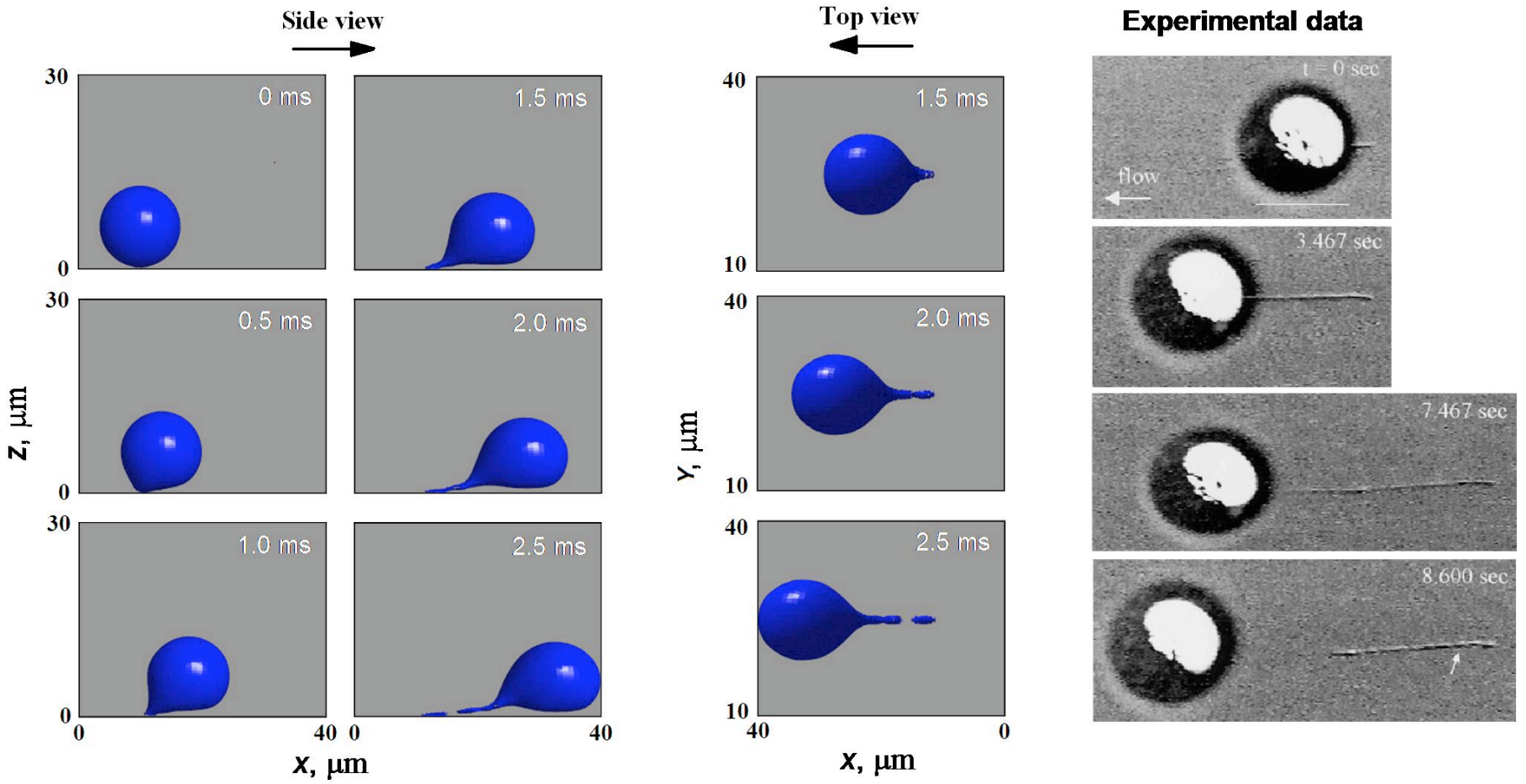
Step 7: Solving the Poisson equation for the pressure by the multigrid method

Step 8: Correction of the intermediate velocity by the pressure term: $\mathbf{u}^* \rightarrow \mathbf{u}^{(n+1)}$

Step 9: Calculation of the extra stress tensor using the semi-implicit factorized scheme for the Giesekus constitutive equation: $\mathbf{T}^{(n)} \rightarrow \mathbf{T}^{(n+1)}$

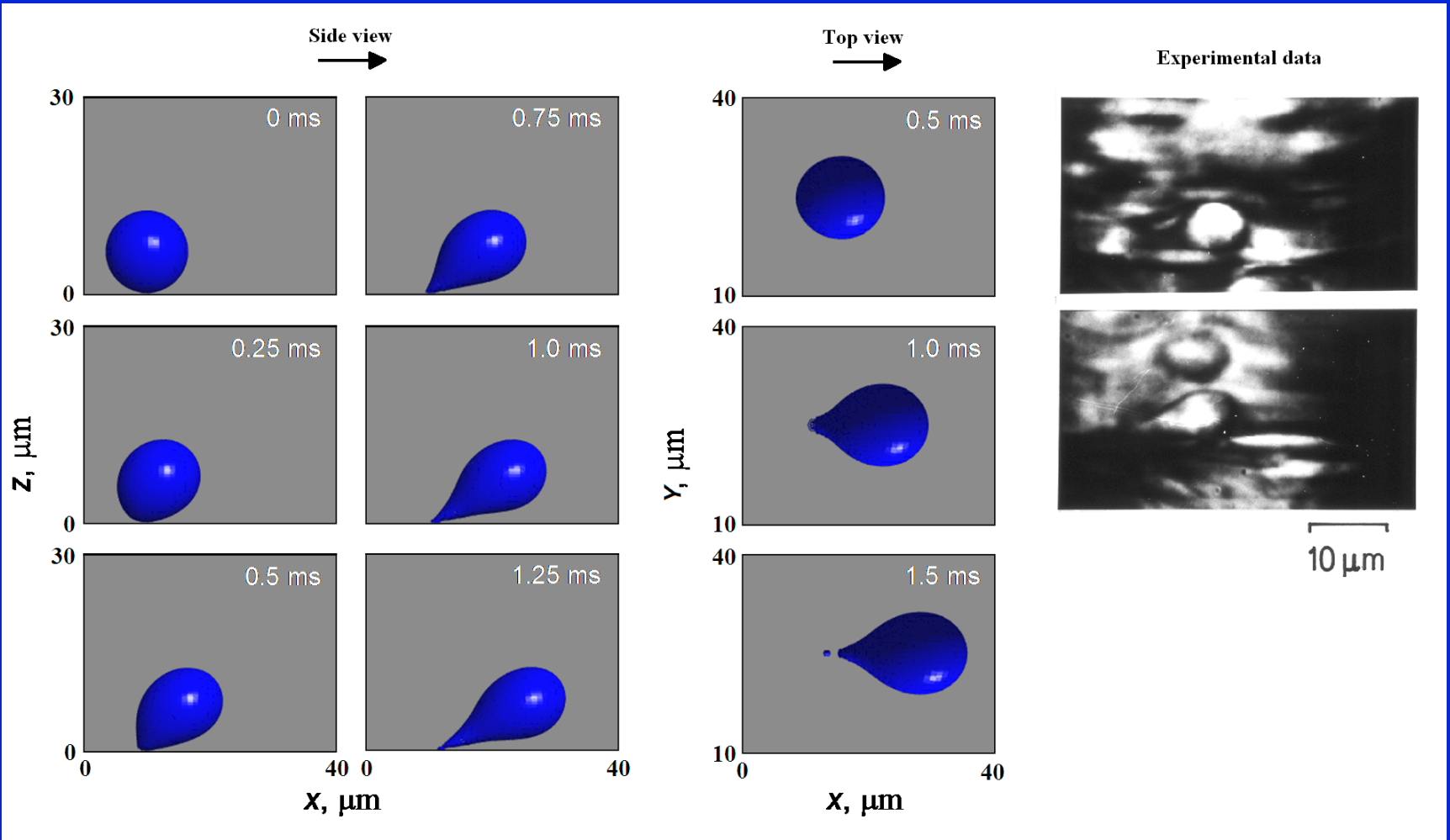
End of Cycle

Effects of deformability: Newtonian model



Comparison of computed shapes and in vitro images (right) of the adherent leukocyte. In vitro images show a neutrophil on a P-selectin-coated surface of the parallel-plate flow chamber at a wall shear rate of 150 s^{-1} (provided by the Diamond Laboratory, Institute for Medicine and Engineering, University of Pennsylvania). The computed shapes correspond to Mono Mac 6 modeled as a compound Newtonian drop. The nucleus occupies 20% of the cell body volume. The cytoplasmic and nuclear viscosities are 1.0 P and 10.0 P, respectively. 252 microvilli of length 0.09 μm are distributed uniformly. The wall shear stress is 4 Pa.

Effects of deformability: viscoelastic model



Comparison of computed shapes and in vivo images (right) of the adherent leukocyte. In vivo images show a rolling neutrophil in a postcapillary venule of the rat mesentery (provided by Klaus Ley, Department of Biomedical Engineering, University of Virginia). The computed shapes correspond to Mono Mac 6 modeled as a compound viscoelastic drop. The cytoplasmic and nuclear viscosities are 35.3 P and 100.0 P, respectively. 252 microvilli of length 0.09 μm are distributed uniformly. The wall shear stress is 4 Pa.

Monocyte rolling on P-selectin: Effect of cytoplasmic viscosity

In vivo data

GIF decompressor
are needed to see this picture.

The leukocyte cytoplasmic viscosity is a critical parameter for leukocyte-endothelial cell interactions

Numerical simulation: cytoplasmic viscosity = 50 poise

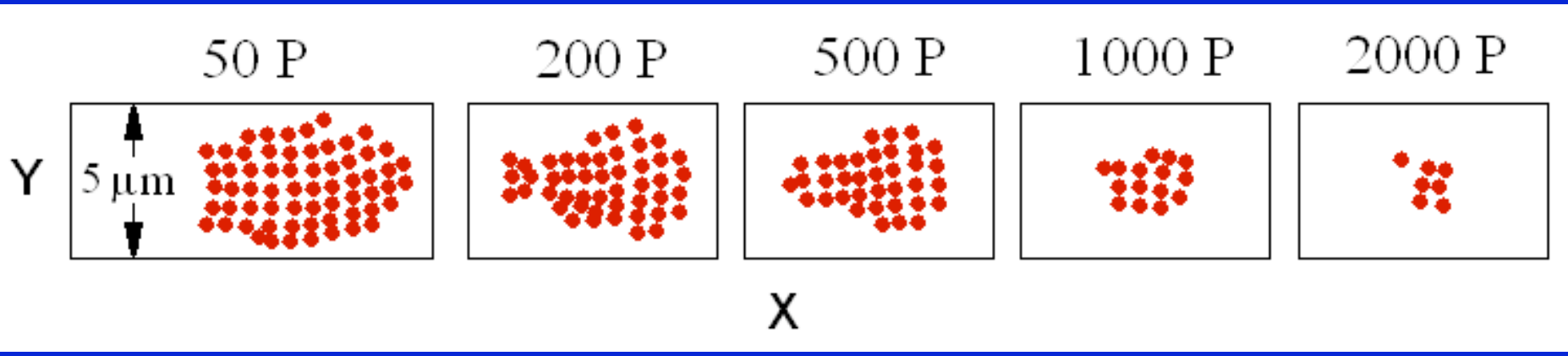
➡ Rolling and deformation to a tear-drop shape

Cytoplasmic viscosity = 500 poise, wall shear stress = 0.5 dyn/cm^2

➡ Detachment from the substrate

The case of high density of microvilli: 16.95 per μm^2. The P-selectin density is 145 sites/μm^2 ; 18,600 PSGL-1 molecules per cell (approximately 5 molecules per microvillus). The nucleus-to-cytoplasm viscosity ratio is fixed at 2.5. In the case of 50 poise, the simulation time is 3.5 s.

Monocyte rolling on P-selectin: microvilli footprints



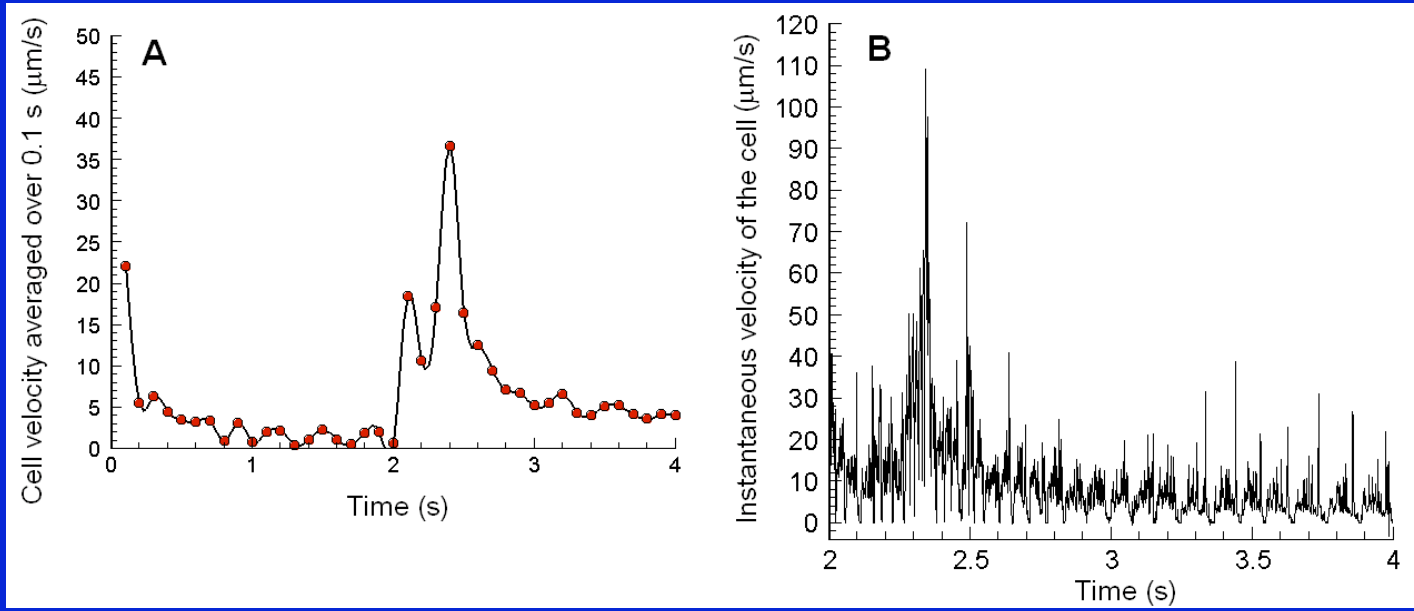
The case of low density of microvilli: 4.0 per μm^2. The wall shear stress is 0.25 dyn/cm^2. The P-selectin density is 145 sites/μm^2; 5 PSGL-1 molecules per microvillus. The nucleus-to-cytoplasm viscosity ratio is fixed at 2.5. The simulation time is 2.0 s.

A decrease in cytoplasmic viscosity leads to an increase in monocyte-to-substrate contact area and thus stabilizes the cell against detachment

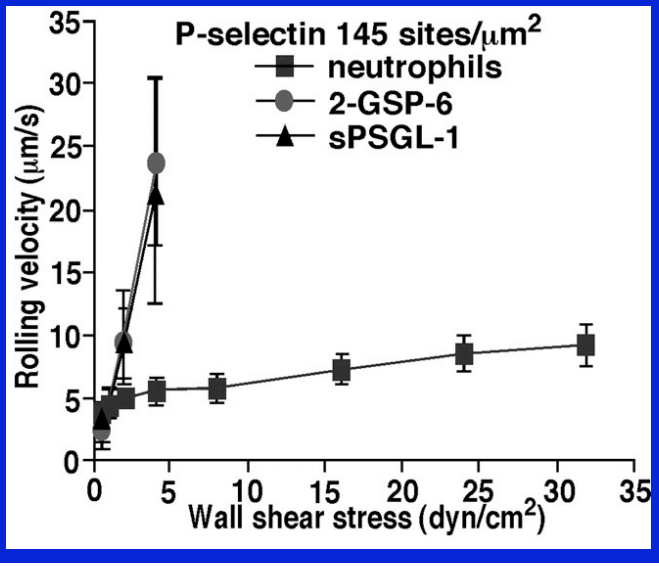
Monocyte rolling on P-selectin: rolling velocity

Numerical simulation (50 poise-viscosity cell)

The wall shear stress suddenly changes from 0.25 dyn/cm^2 to 1.0 dyn/cm^2 at t = 2 s.



in vitro (parallel-plate flow chamber)



Yago *et al. J. Cell Biol.* **158**, 787-799 (2002).

- Numerical predictions of the rolling velocity are within the range of experimental values.
- Our deterministic model is able to reproduce time variations in the rolling velocity.

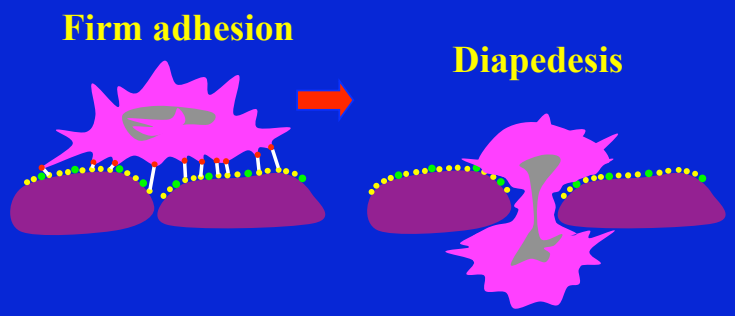
Possible collaboration: Cell motility and mechanotransduction phenomena

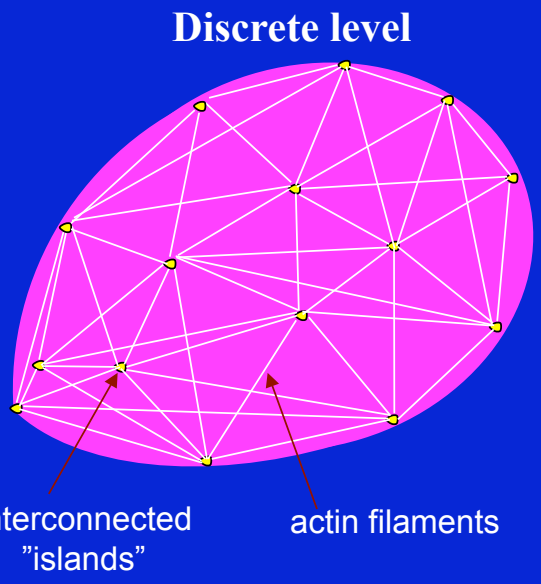
QuickTime™ and a
Photo decompressor
are needed to see this picture.

Migrating connective tissue cell. Image source: Cell Migration Gateway
http://www.cellmigration.org/science/index.shtml

My main interest is to integrate a multiphase model of the cell with biochemical networks to develop a comprehensive whole cell model that will be able to simulate cell migration, chemotaxis, division and other acitve mechanical processes in the cell.

Possible collaboration: Leukocyte motility and transmigration

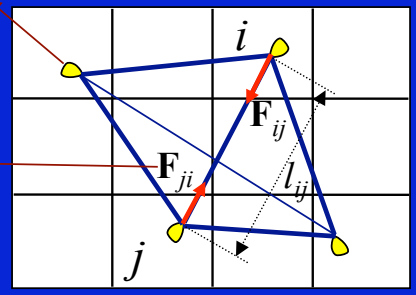




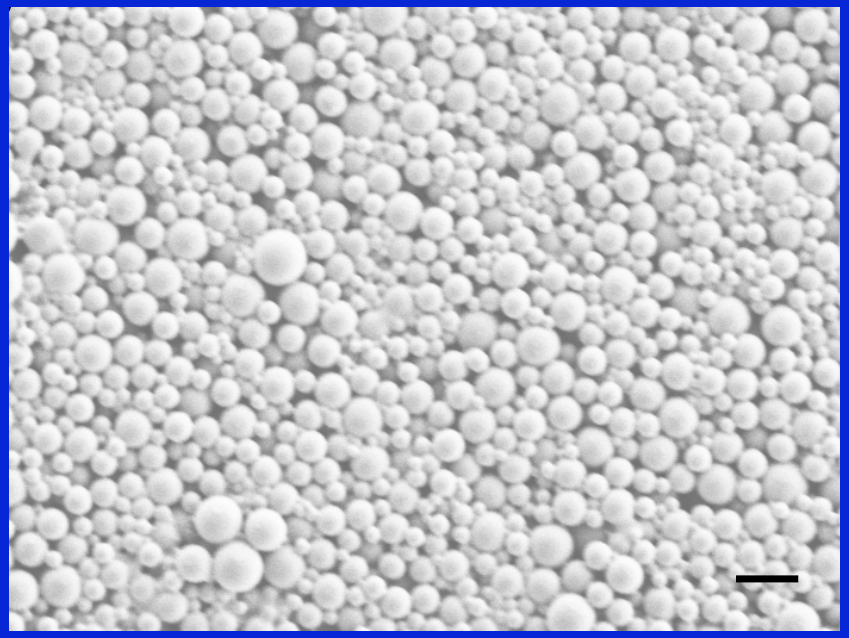
Objective: To develop and validate, through in vitro and in vivo experiments, a 3D computational model for leukocyte motility and transmigration. The proposed research will examine several mechanisms of **active force generation** in the leukocyte, including the polymerization force, Brownian ratchets, and molecular motor models.

The "islands" are advected by the velocity field

Elastic force exerted on a *j* "island" by a link between *i* and *j* "islands"



Possible collaboration: Optimization of polymer drug delivery systems

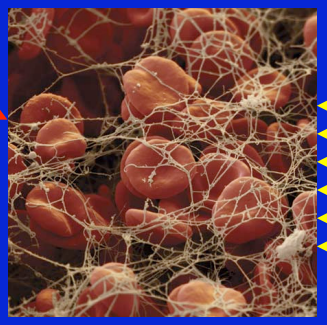


FE-SEM images of PLA microparticles at 3000X. PLA functionalized with mPEG2000-DSPEand b-PEG3350-DSPE. Scale bar is 2 μm. Provided by Joyce Wong (Boston U.)

The developed computational algorithm can be extended to simulate biodegradable polymer drug delivery systems targeted, for example, to inflamed endothelium

Goal 2: To develop a method for noncontact measurement of blood clot viscoelasticity through a combination of acoustic levitation experiments, analytical studies, and computational modeling. Collaboration with R. Glynn Holt (AME Dept., Boston U.).

Acoustically levitated blood clot



High-speed filming (CCD)

Data processing: evaluation of the frequency f and the decay factor δ

Standing wave

Sound Generator

Rough estimates of the relaxation and retardation times by the formulae:

$$\lambda_1 \approx \frac{2394}{1388\pi^2}\frac{\mu}{\rho_l R^2 f^2}, \quad \lambda_2 \approx \frac{\delta}{2\pi^2 f^2} - \frac{347}{2394}\frac{\rho_l R^2}{\mu}$$

D. B. Khismatullin and A. Nadim, “Shape oscillations of a viscoelastic drop,” *Phys. Rev. E* **63**, 061508 (2001)

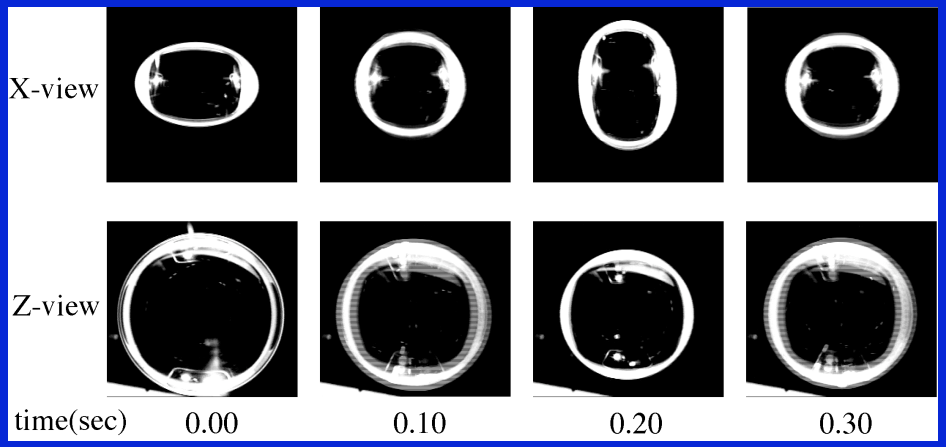
High-viscosity limit

Newtonian → Aperiodic decay

viscoelastic → Elasticity-driven shape oscillations

$$f_e = \frac{\omega_e}{2\pi} \approx \frac{1}{2\pi}\sqrt{\frac{2(n-1)(2n^2+4n+3)\mu}{(2n+1)(1+E_n)\rho_l R^2 \lambda_1}}$$

$$\delta_e \approx \frac{1}{2\lambda_1}\sqrt{1+\frac{2(n-1)(2n^2+4n+3)\mu\lambda_2}{(2n+1)(1+E_n)\rho_l R^2}}$$



Sequence of 4 video frames depicting a cycle of the normal mode oscillation (n=2, or quadrupole mode) of a spheroidal sample in an acoustic levitator. Images provided by R. G. Holt (Boston University).

Acknowledgements

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Geert Schmid-Schönbein, Ph.D. (UCSD)
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Ali Nadim, Ph.D. (Keck Graduate Institute)
R. Glynn Holt, Ph.D. (Boston U.)
Michael Renardy, Ph.D. (Virginia Tech)
Joyce Wong, Ph.D. (Boston U.)

Tiri Chinyoka, Ph.D.
Sundhar Ramalingam and Jason Leung (Duke U.)
Bo Li (Boston U.)