20.GEM GEM4 Summer School: Cell and Molecular Biomechanics in Medicine: Cancer

Summer 2007

Continuum Modeling of the Cell

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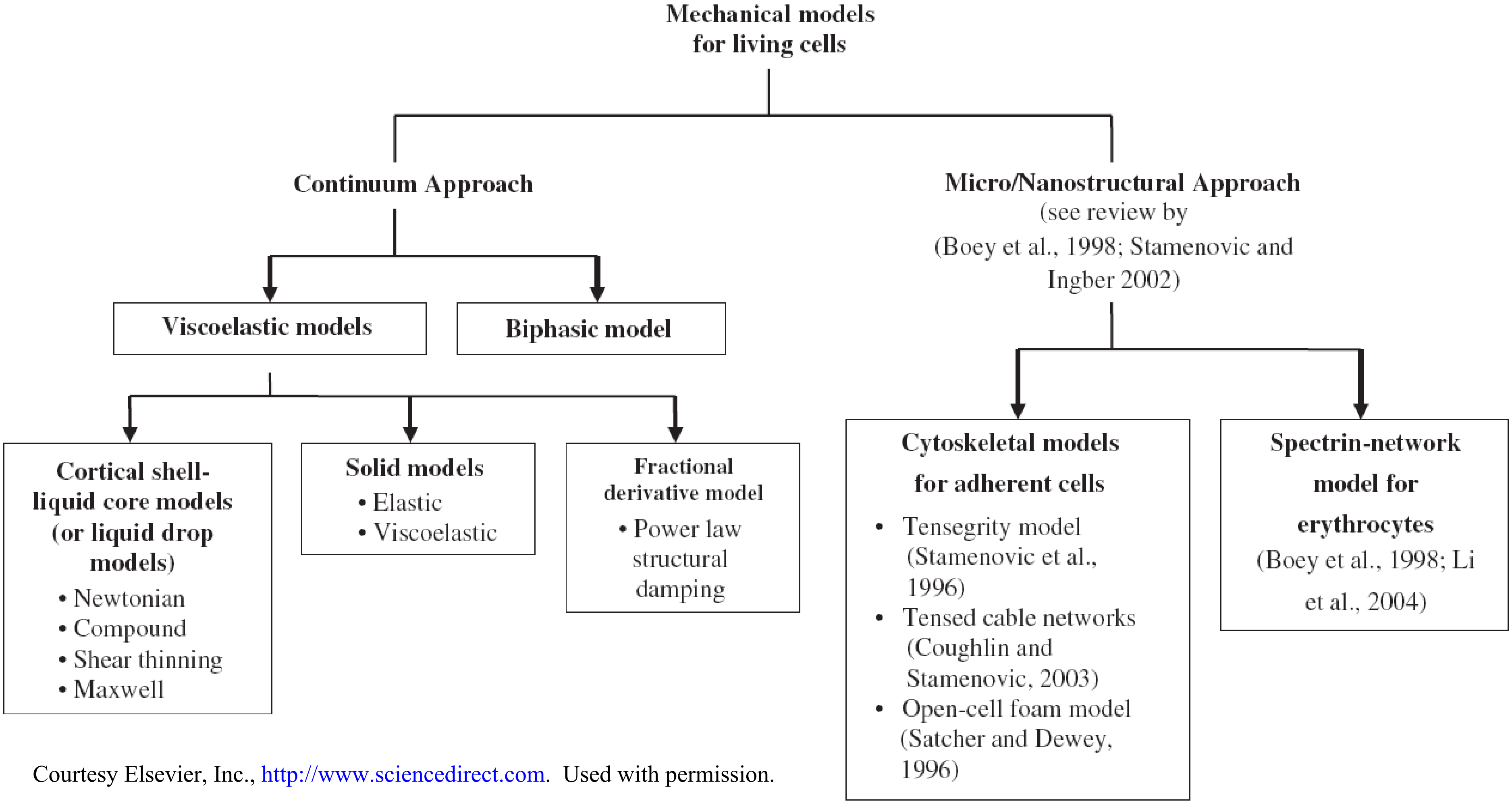
GEM4 Summer School
June 25 – July 6, 2007
NUS, Singapore

Motivation – Why Single-Cell Mechanics?

- Living cells and molecules sense mechanical forces, converting them into biological responses.
- Biological and biochemical signals are known to influence the ability of the cells to sense, generate and bear mechanical forces
- Red blood cell: Blood flow in microcirculation is influenced by the deformability of red blood cell

Mechanical Models for Living Cells



Mechanical models for living cells

- **Continuum Approach**
  - **Viscoelastic models**
    - **Cortical shell-liquid core models (or liquid drop models)**
      - Newtonian
      - Compound
      - Shear thinning
      - Maxwell
    - **Solid models**
      - Elastic
      - Viscoelastic
    - **Fractional derivative model**
      - Power law structural damping
  - **Biphasic model**
- **Micro/Nanostructural Approach** (see review by (Boey et al., 1998; Stamenovic and Ingber 2002)
  - **Cytoskeletal models for adherent cells**
    - Tensegrity model (Stamenovic et al., 1996)
    - Tensed cable networks (Coughlin and Stamenovic, 2003)
    - Open-cell foam model (Satcher and Dewey, 1996)
  - **Spectrin-network model for erythrocytes** (Boey et al., 1998; Li et al., 2004)

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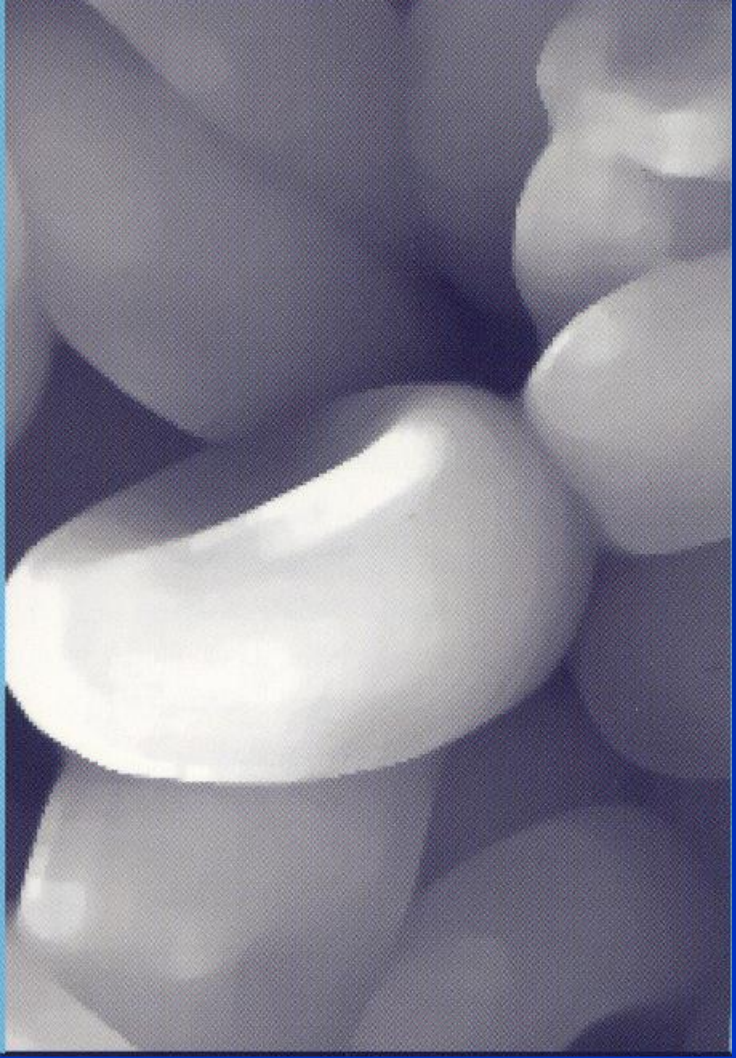
C.T. Lim *et al., J Biomech* , 39, 195–216, 2006

Continuum Modeling of Human Red Blood Cell

Studying the deformation characteristics of healthy & diseased red blood cell



red blood cell (erythrocyte)

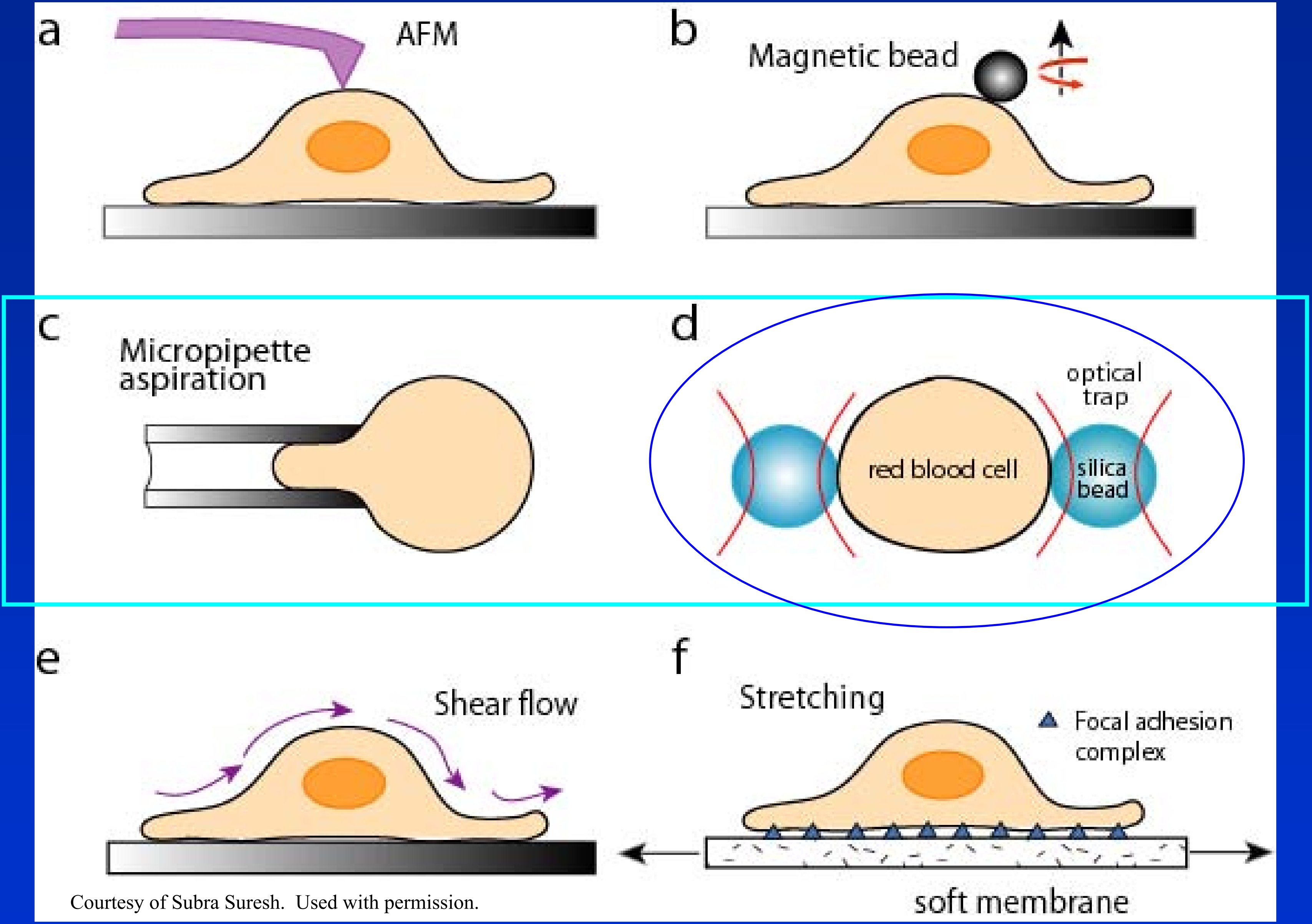
"Simple" model cell without nucleu

Undergoes severe, reversible, large elastic deformation

Approx. 0.5 million circulations over 120 days

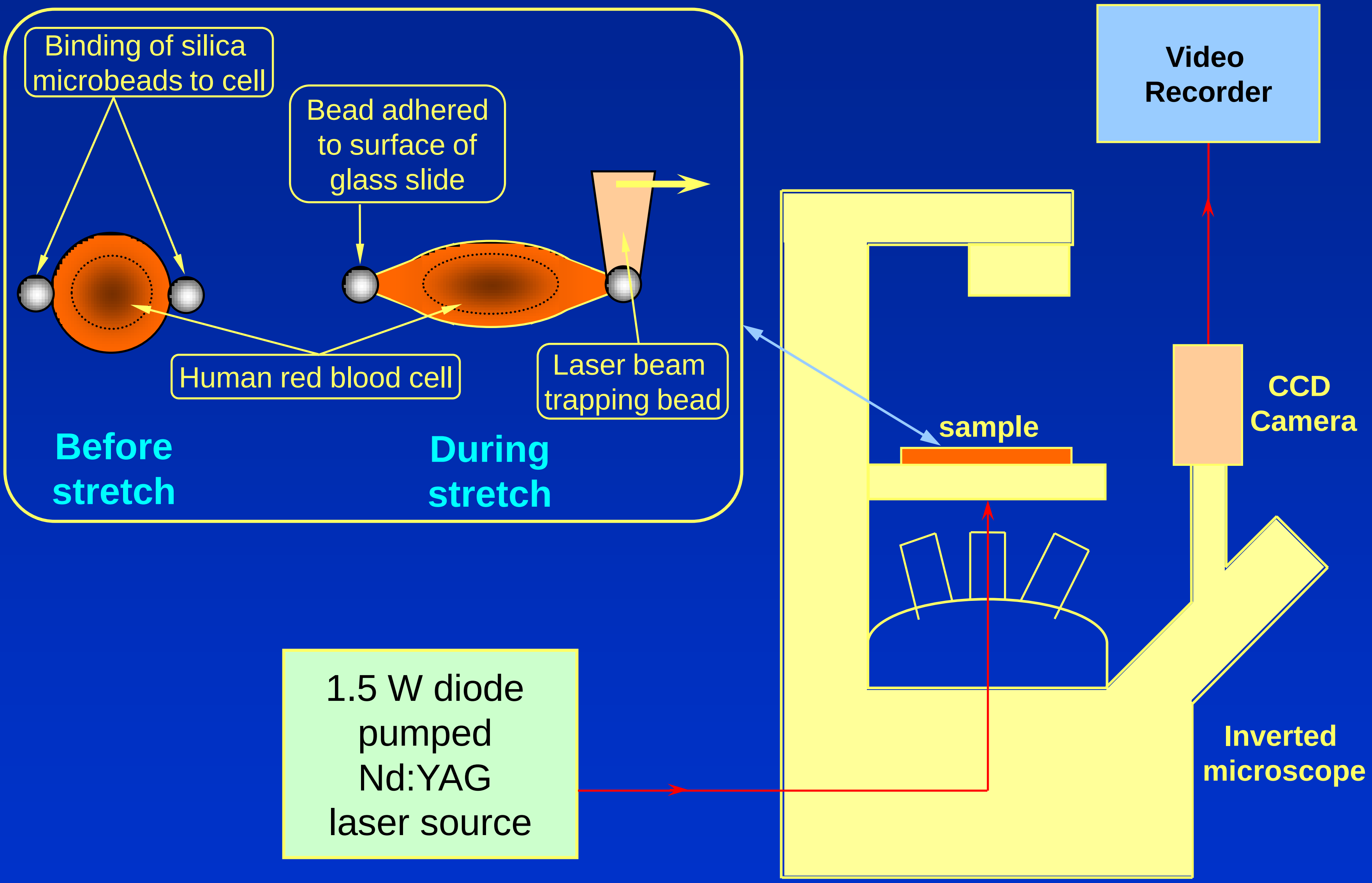
~ 3,000,000 red blood cells produced every second

Experimental Techniques



Courtesy of Subra Suresh. Used with permission.

G. Bao and S. Suresh, *Nature Materials* (2003)



Binding of silica microbeads to cell

Bead adhered to surface of glass slide

Human red blood cell

Laser beam trapping bead

Before stretch

During stretch

Video Recorder

CCD Camera

sample

Inverted microscope

1.5 W diode pumped Nd:YAG laser source

Dao, Lim and Suresh, *J. Mech. Phys. Solids* (2003)

Lim et al., *Acta Materialia* (2004)

Courtesy Elsevier, Inc., http://www.sciencedirect.com. Used with permission.

Courtesy Elsevier, Inc., http://www.sciencedirect.com. Used with permission.

Dao, Lim and Suresh, *J Mech Phys Solids*, 2003

Mills et al., *Mechanics and Chemistry of Biosystems*, 2004

Previous Efforts & Current Focus

- Micropipette Aspiration
  - E. A. Evans, Y.C. Fung, R. Skalak, …
- Optical Tweezers
  - S. Henon, J. Sleep, D.E. Discher, …
- Our Focus: Optical Tweezers Experiment
  - Larger force range: > 200 pN
  - Full 3-D Whole Cell Modeling
  - Spectrin-Level Modeling & Continuum Verification
  - Finite Deformation Formulations

Hereditary blood cell disorders:

Sickle-cell disease

Spectrin molecules

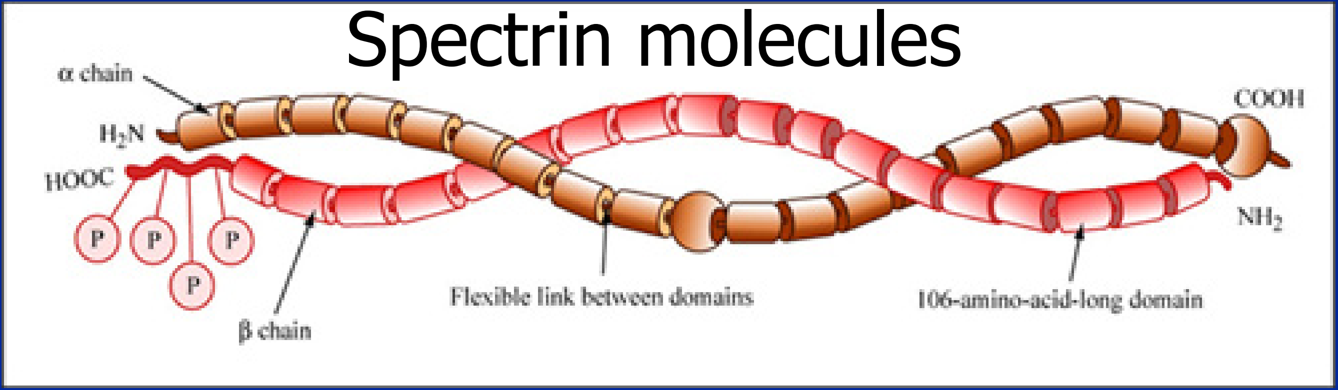
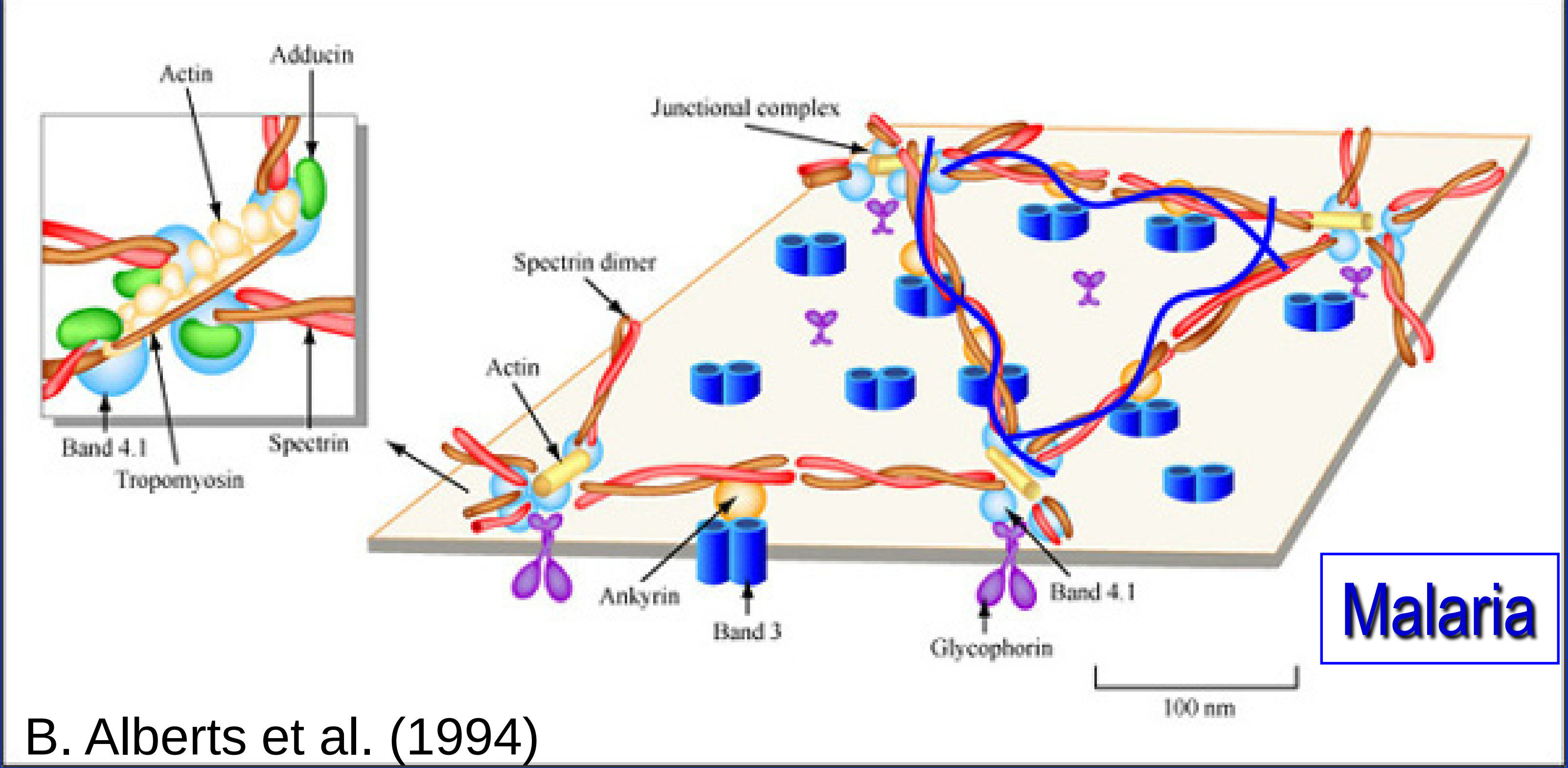


Figure by MIT OpenCourseWare.

Molecular structure of human RBC cytoskeleton



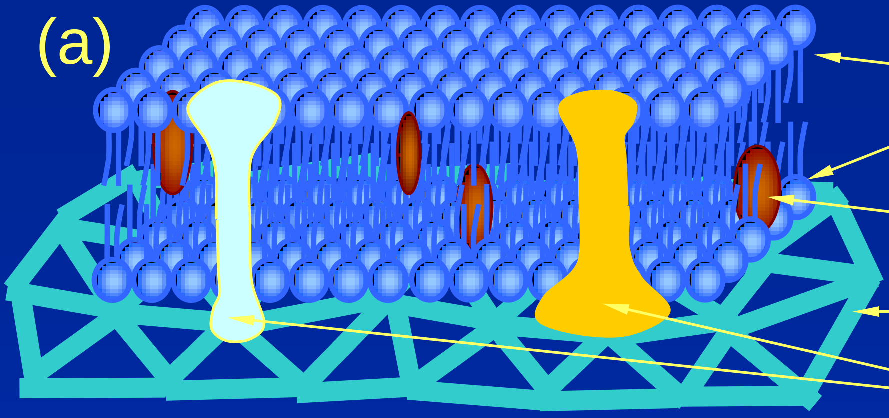
Malaria

B. Alberts et al. (1994)

Figure by MIT OpenCourseWare. After B. Alberts et al, 1994.

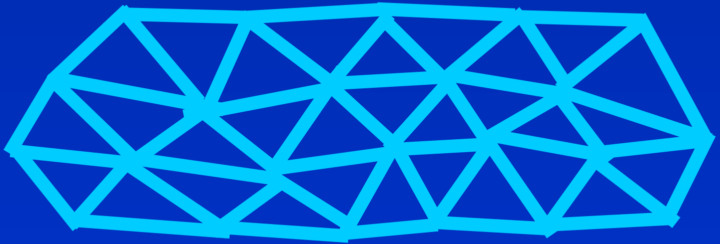
Spherocytosis, elliptocytosis, Asian ovalocytosis

(a)



Structure of the cell membrane

(b) Spectrin Network + Lipid Membrane



Worm-like chain (WLC) model

with surface & bending energies

(c)

In-plane shear modulus: μ

Bending stiffness: κ

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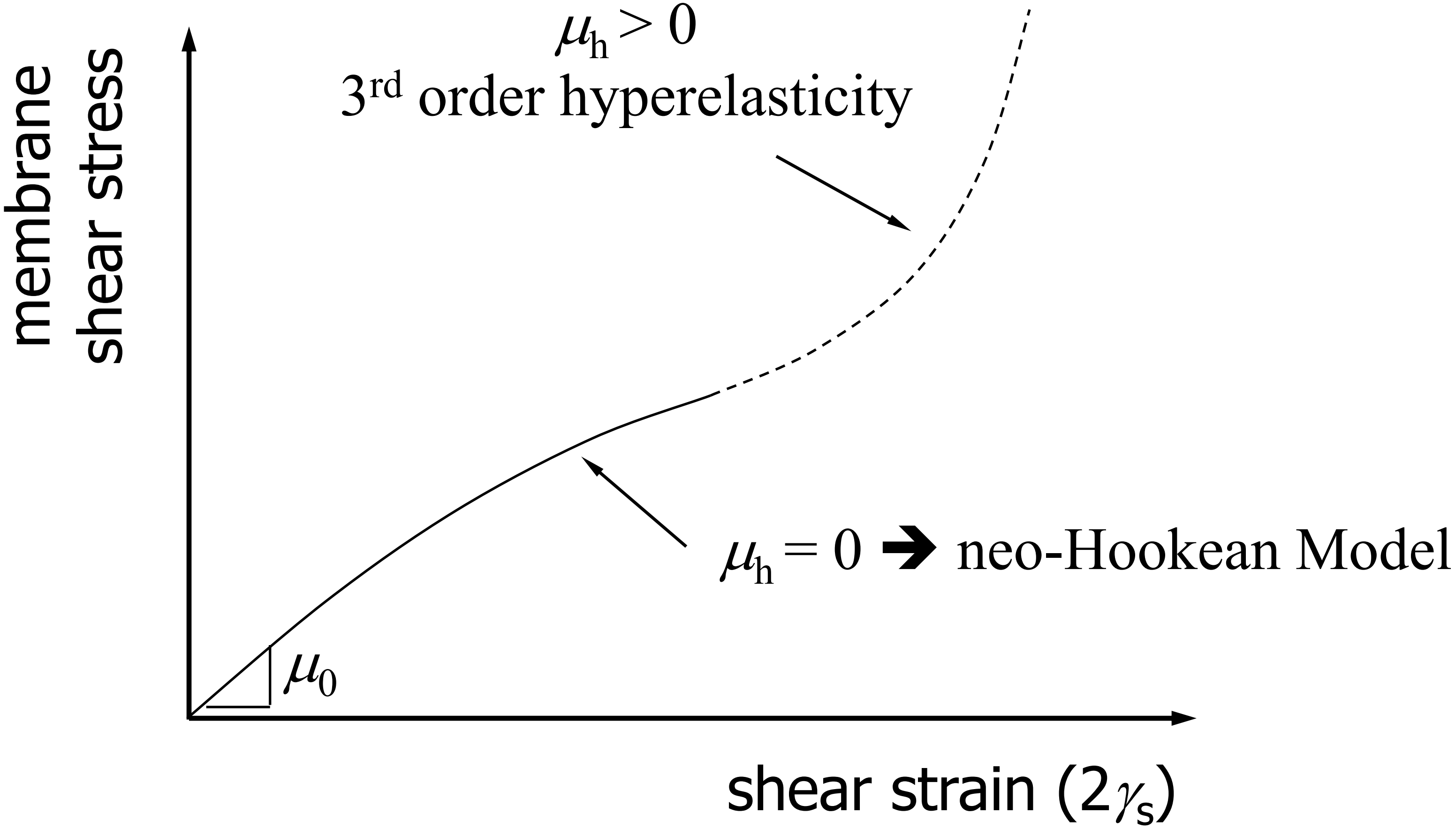
Dao, Lim & Suresh, *J. Mech. Phys. Solids* (2003)

Li, Dao, Lim & Suresh, *Biophys J* (2005)

Hyperelasticity Model

$$\Phi = \frac{\mu_0}{2}\left(\lambda_1^2+\lambda_2^2+\lambda_3^2-3\right)+\mu_h\left(\lambda_1^2+\lambda_2^2+\lambda_3^2-3\right)^3$$

$\lambda_1\lambda_2\lambda_3 = 1$



Hyperelasticity Model

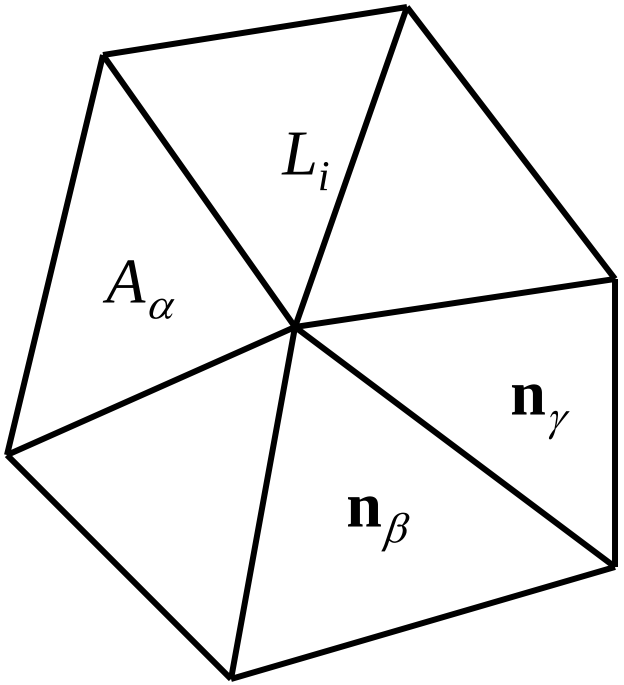
Neo-Hookean: $$\Phi = \frac{\mu_0}{2}\left(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3\right)$$

Incompressible Material: $\lambda_1\lambda_2\lambda_3 = 1$

Conserving Area: $\lambda_1\lambda_2 = 1$ so that $\lambda_3 = 1$

Classical RBC Membrane Model

Response of a perfect spectrin network



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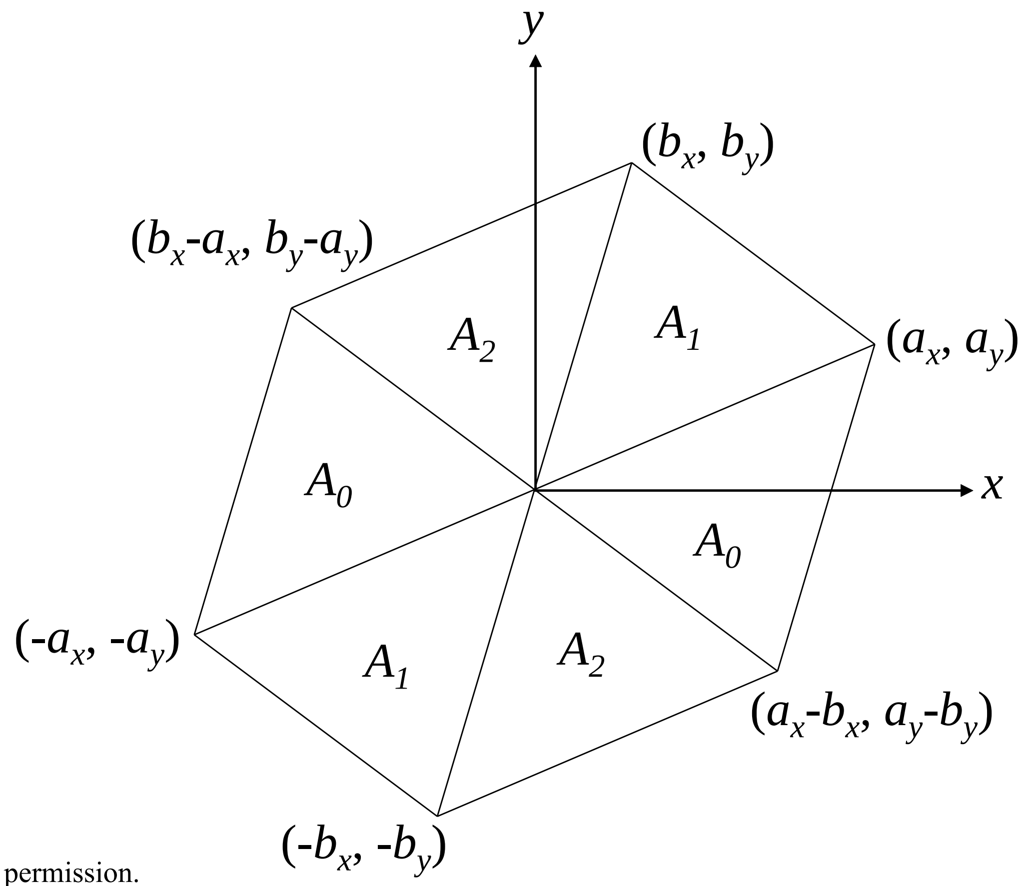
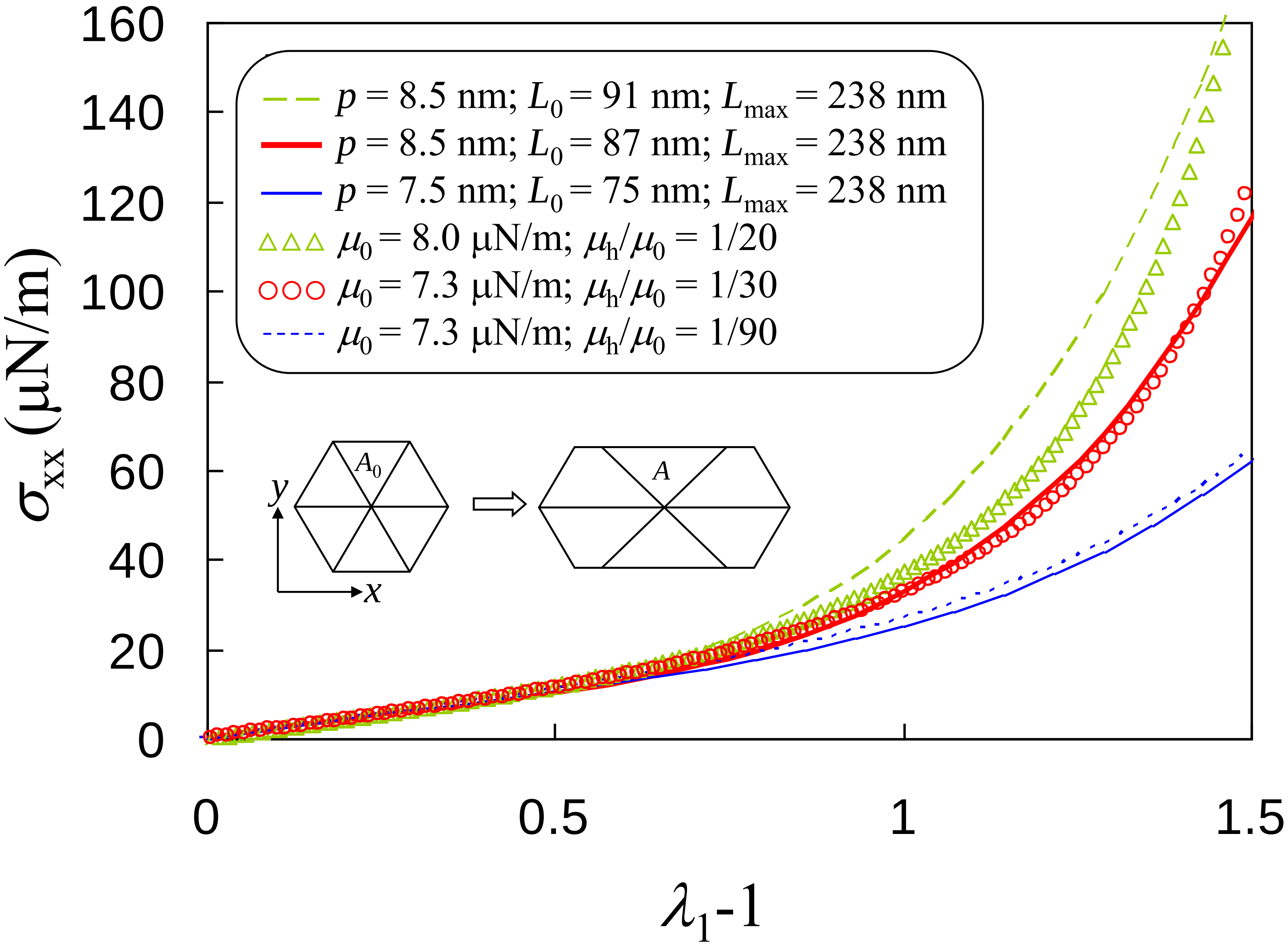
(a)



(b)

$$\tau_{\alpha\beta} = -\frac{1}{2A}\left[\frac{f_{\mathrm{WLC}}(a)}{a}a_\alpha a_\beta + \frac{f_{\mathrm{WLC}}(b)}{b}b_\alpha b_\beta + \frac{f_{\mathrm{WLC}}(c)}{c}c_\alpha c_\beta\right] - qC_q A^{-q-1}\delta_{\alpha\beta}.$$



Li, Dao, Lim & Suresh, *Biophys J* (2005); Dao, Li & Suresh, *Mat Sci Eng C* (2006)

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Please see Figure 4 in Dao, M., J. Li, and S. Suresh. "Molecularly Based Analysis of Deformation of Spectrin Network and Human Erythrocyte." *Mat Sci Eng C* (2006): 1232-1244.

Constitutive Model: Prior literature

Constant Area Assumption: $\lambda_1 \lambda_2 = 1$

$$\boxed{T_s = 2\mu\gamma_s = \frac{\mu}{2}\left(\lambda_1^2 - \lambda_2^2\right)}$$

μ – membrane shear modulus

λ_i – the principal stretches

T_s , γ_s – membrane shear stress (force/length), shear strain

$$T_s = \frac{1}{2}\left(T_1 - T_2\right) \qquad \gamma_s \equiv \frac{1}{2}\left(\varepsilon_1 - \varepsilon_2\right) = \frac{1}{4}\left(\lambda_1^2 - \lambda_2^2\right)$$

E. Evans, Biophys. J., 1973

Micropipette Aspiration

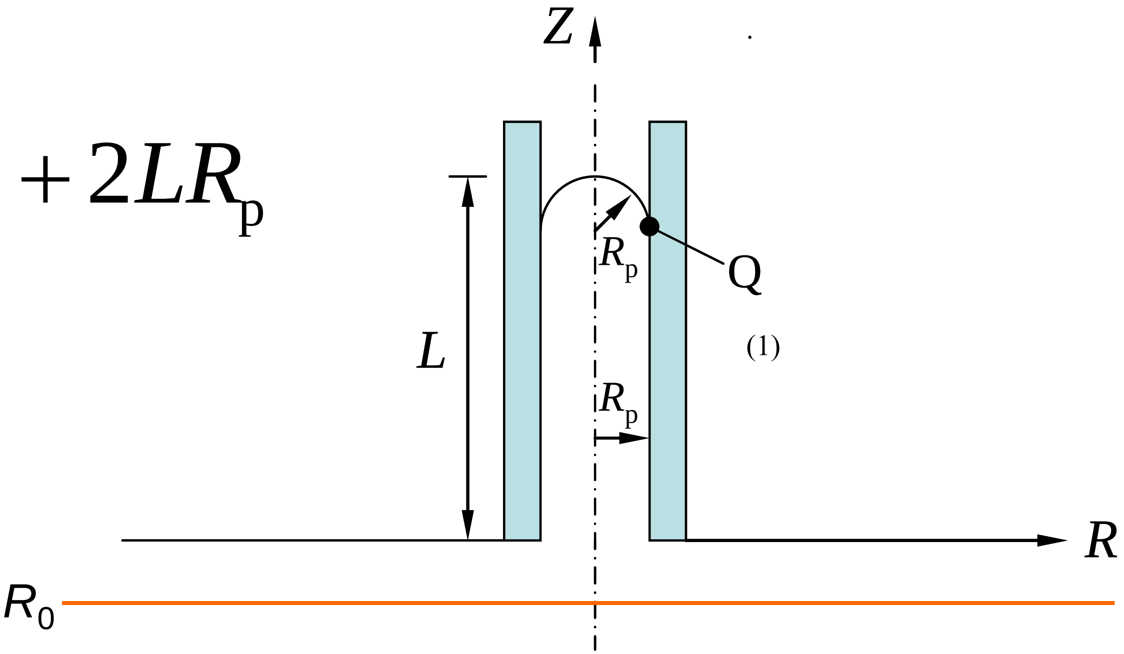
The total area in the deformed configuration would be divided in three parts: outside the pipette + in the pipette below the cap (L-R_p) + spherical cap, thus

$$\text{Deformed Area } = \left(\pi R^2 - \pi R_p^2\right) + \left(L - R_p\right) 2\pi R_p + 2\pi R_p^2 = \pi\left(R^2 - R_p^2 + 2LR_p\right)$$

$$\text{Unreformed (Original) Area = } \quad \pi R_0^2$$

Area Conservation gives

$$R_0^2 = R^2 - R_p^2 + 2LR_p$$



Micropipette Aspiration

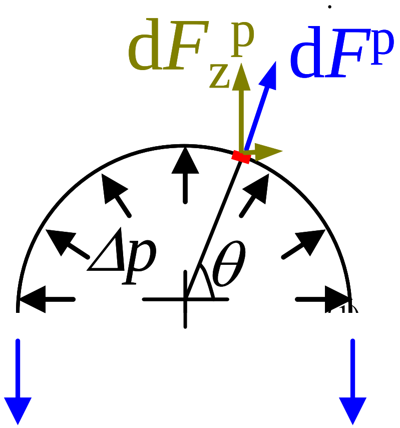
$$\lambda_R = \frac{\partial R}{\partial R_0} = \frac{R_0}{R} \qquad \lambda_\phi = \frac{1}{\lambda_R} = \frac{R}{R_0}$$

Constitutive Law:

$$T_s = \frac{\mu}{2}\left(\lambda_R^2 - \lambda_\phi^2\right) = \frac{\mu}{2}\left(\frac{R_0^2}{R^2} - \frac{R^2}{R_0^2}\right) = \frac{\mu}{2}\left(\frac{R^2 - R_p^2 + 2LR_p}{R^2} - \frac{R^2}{R^2 - R_p^2 + 2LR_p}\right)$$

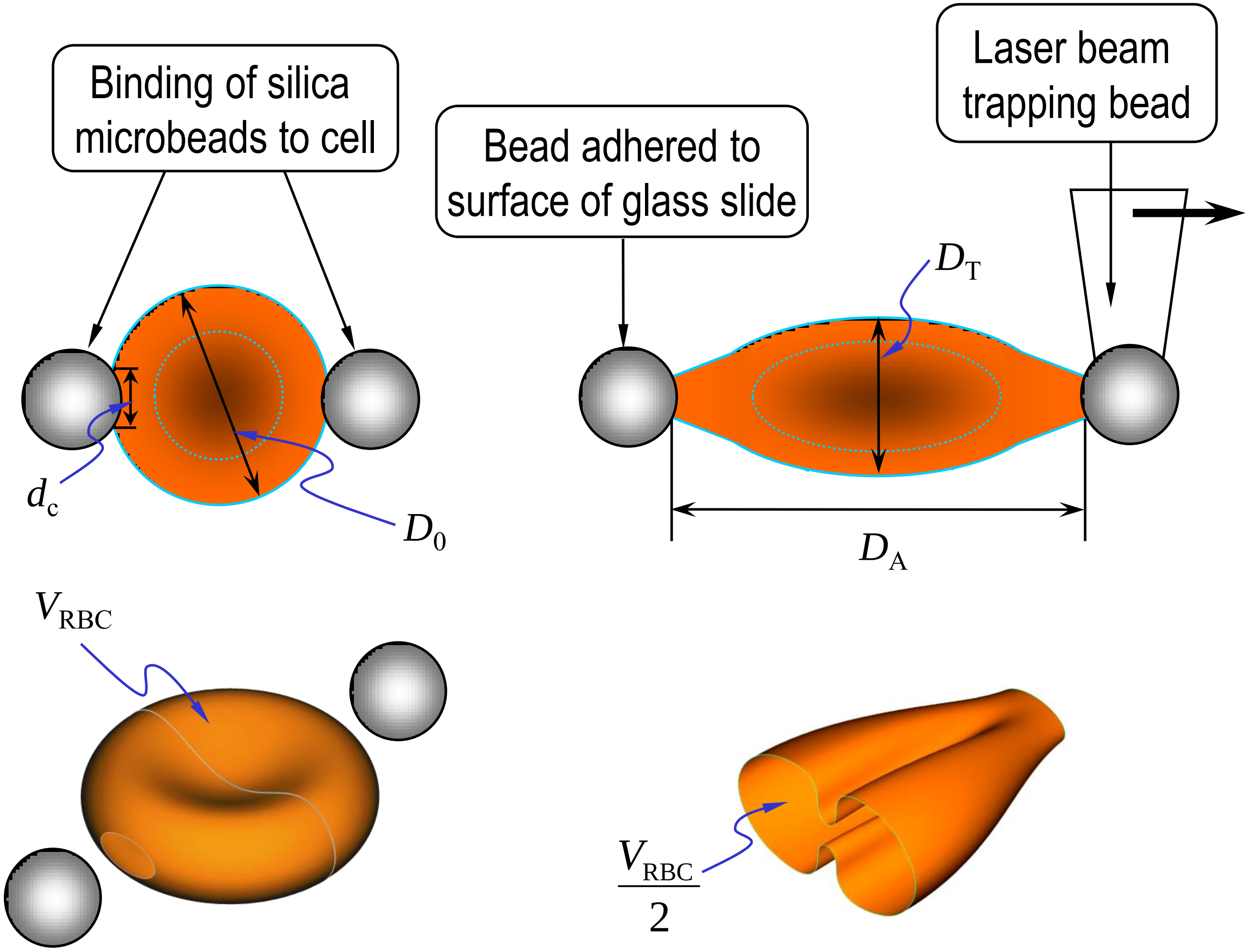
$$T_z = \Delta p R_p / 2 = T_R\Big|_{R=R_p}$$

$$\boxed{\frac{\Delta p R_p}{\mu} = \frac{2L}{R_p} - 1 + \ln\left(\frac{2L}{R_p}\right)}$$



$$F_z = 2\pi R_p T_z$$

Modeling Optical Tweezers Experiments



Binding of silica microbeads to cell

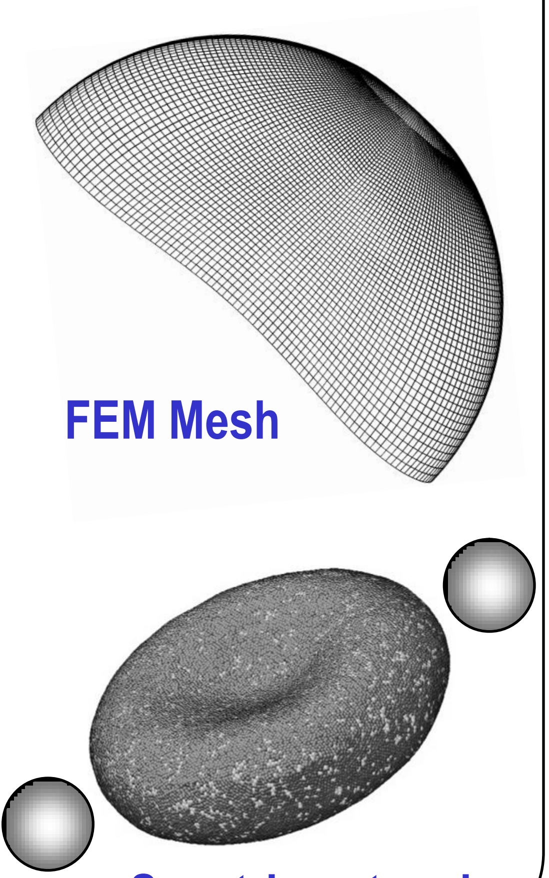
Bead adhered to surface of glass slide

Laser beam trapping bead

Before stretch

During stretch

Initial Model Setup



FEM Mesh

Spectrin network

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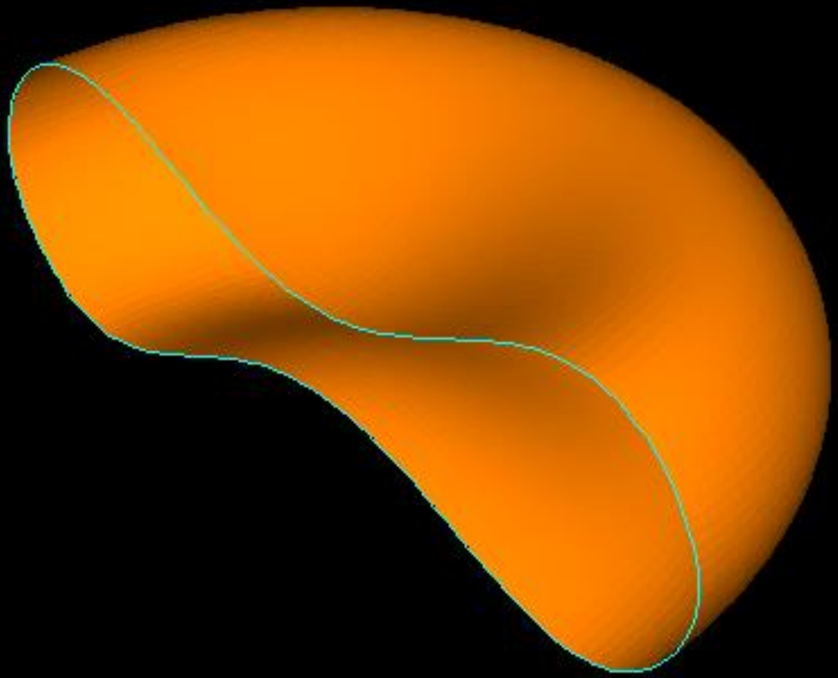
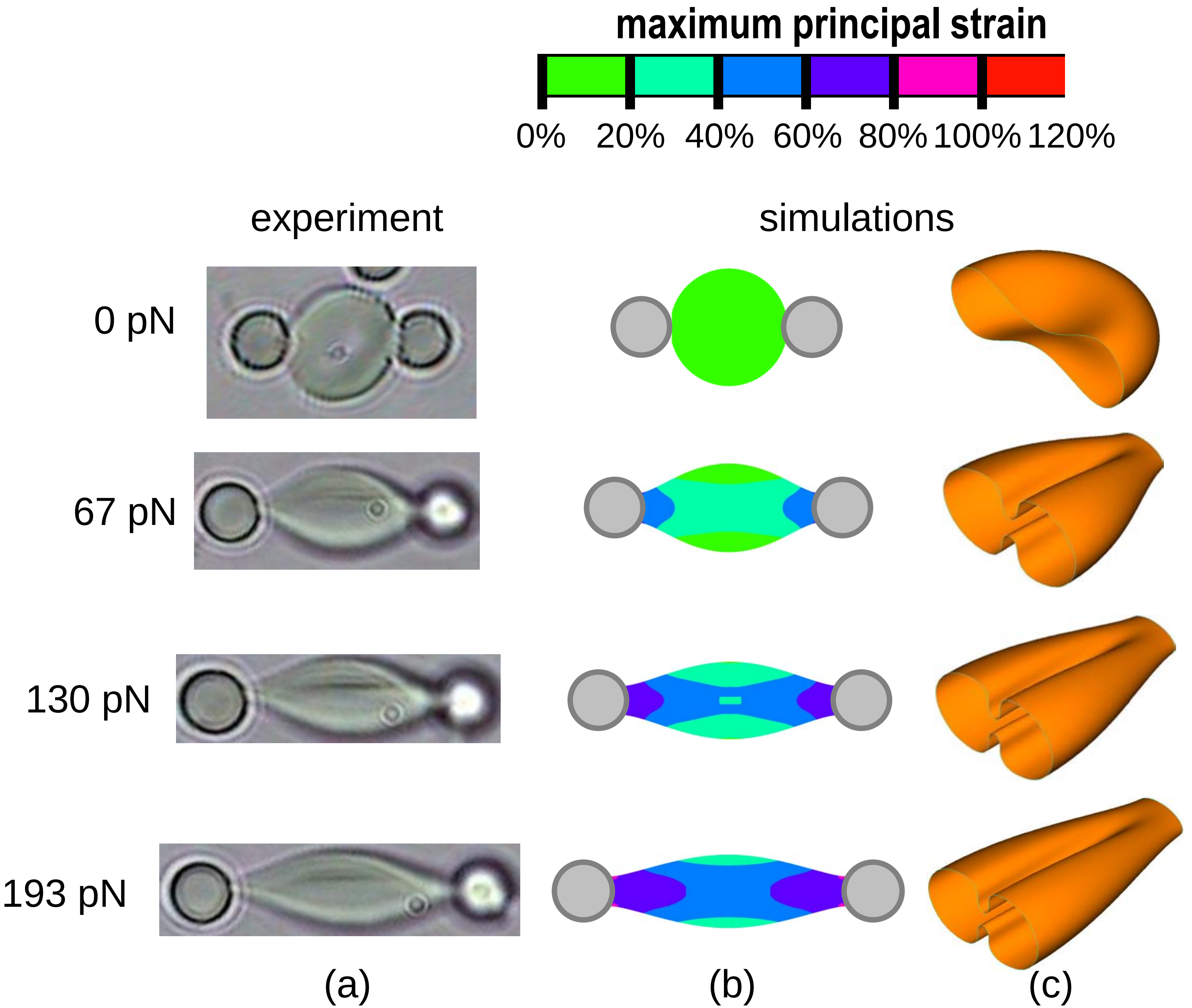
Computational Model

One half of the human red blood cell stretched by optical tweezers:

3-D computer simulation for comparison with experiment



Dao, Lim and Suresh, *J Mech Phys Solids*, 2003



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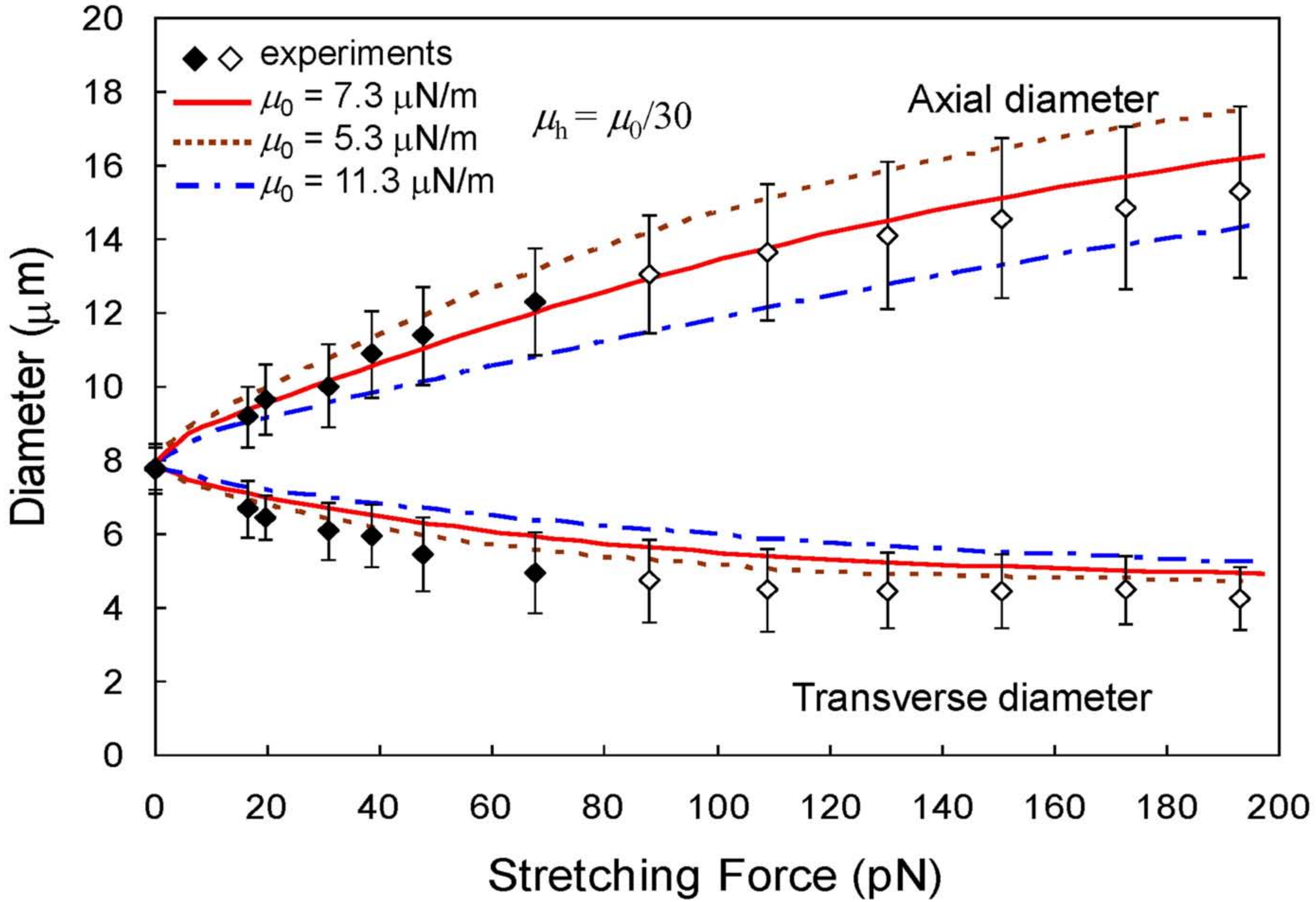
Source: Mills, J. P., L. Qie, M. Dao, C. T. Lim and S. Suresh. "Nonlinear Elastic and Viscoelastic Deformation of the Human Red Blood Cell with Optical Tweezers." *Mechanics and Chemistry of Biosystems* 1 (2004): 169-180.

Dao, Lim & Suresh, *J Mech Phys Solids* (2003)



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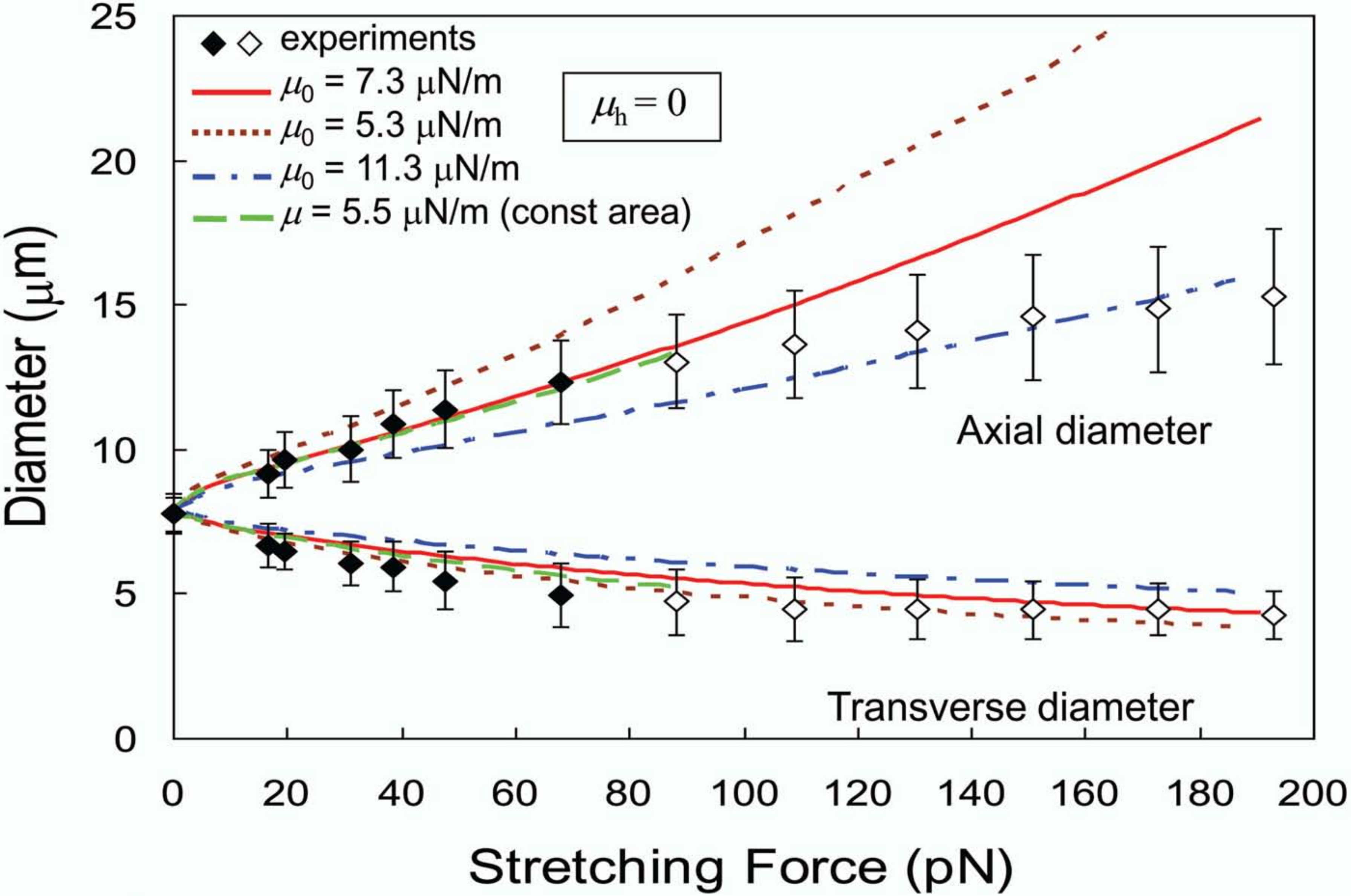

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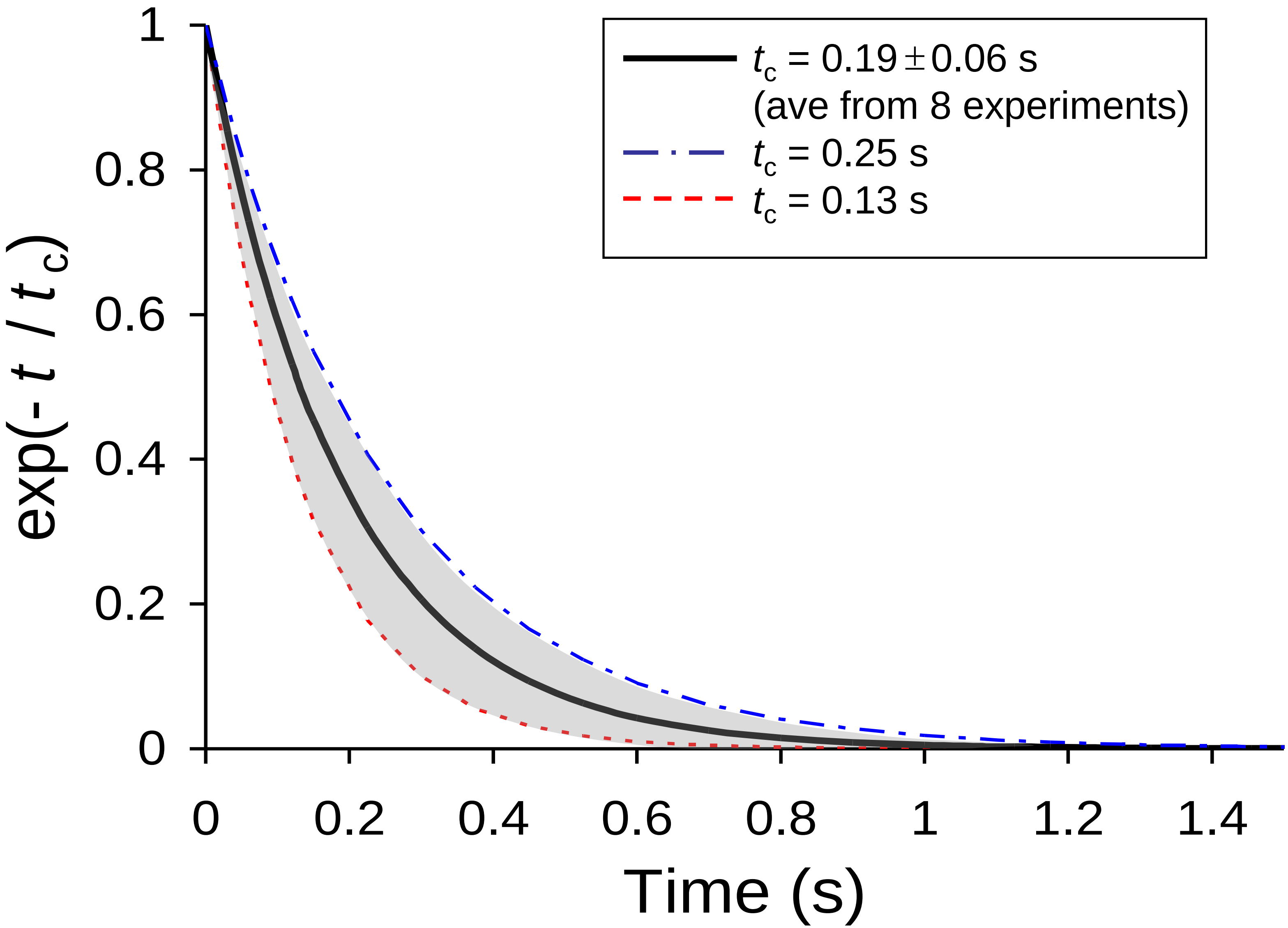

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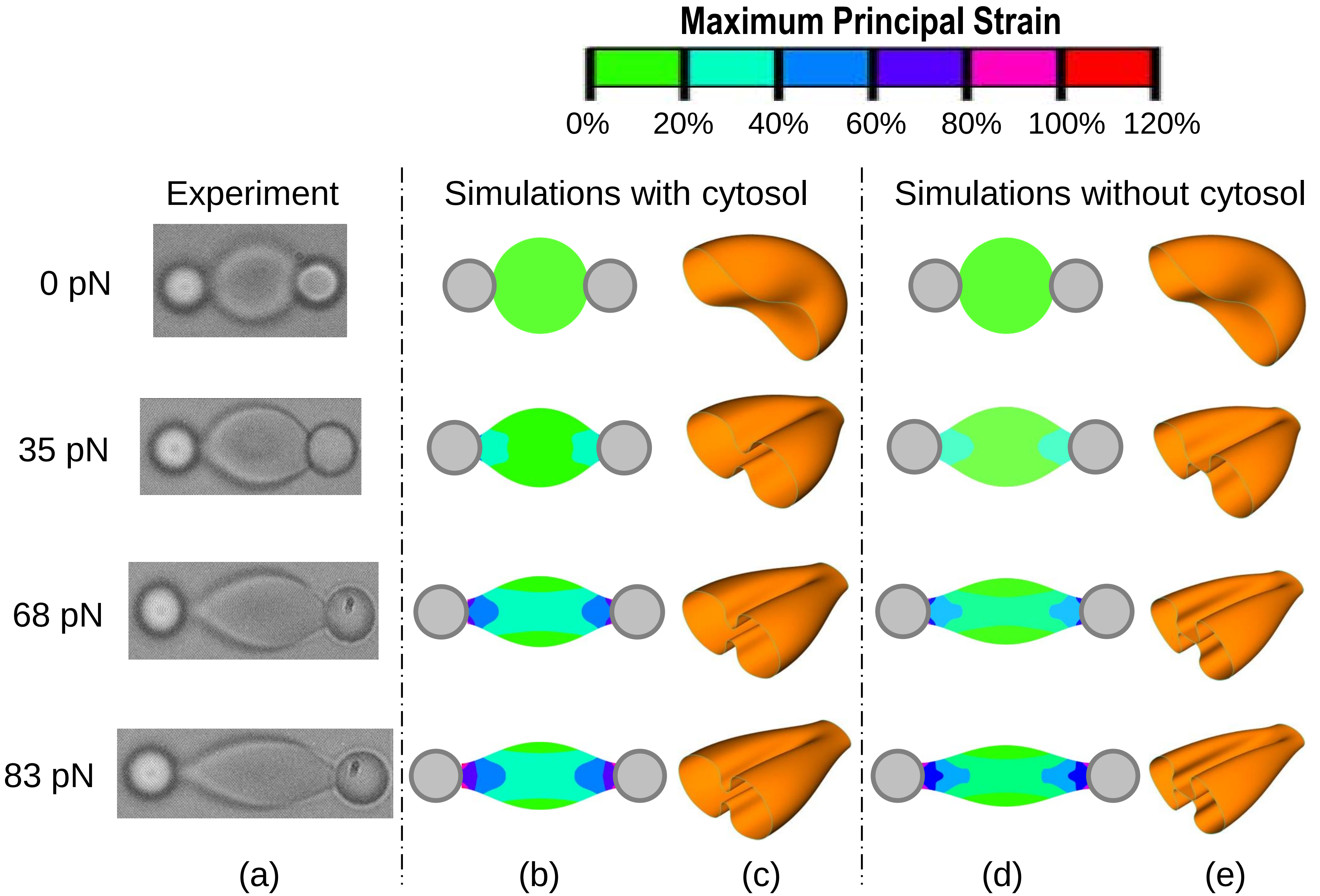

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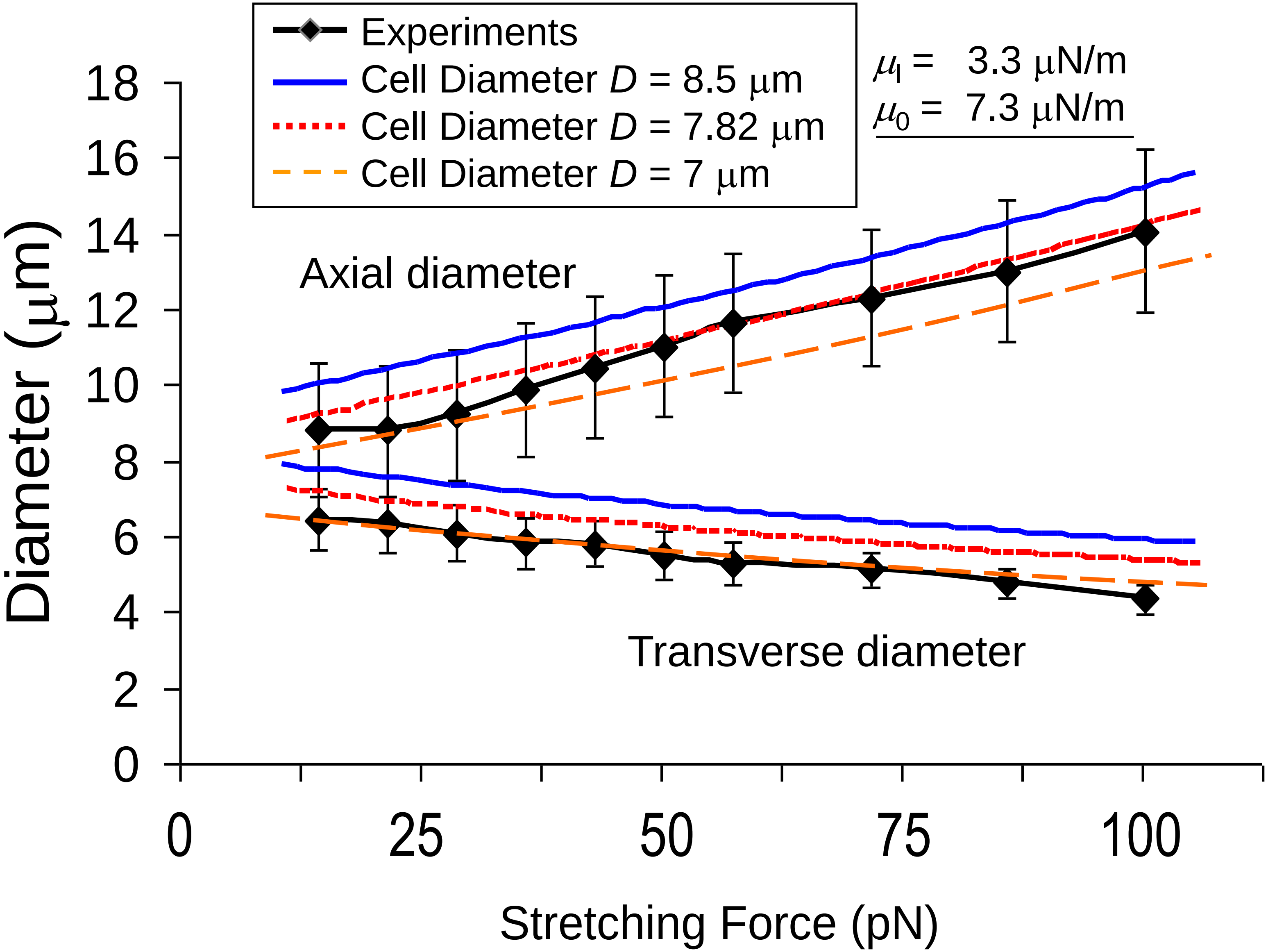

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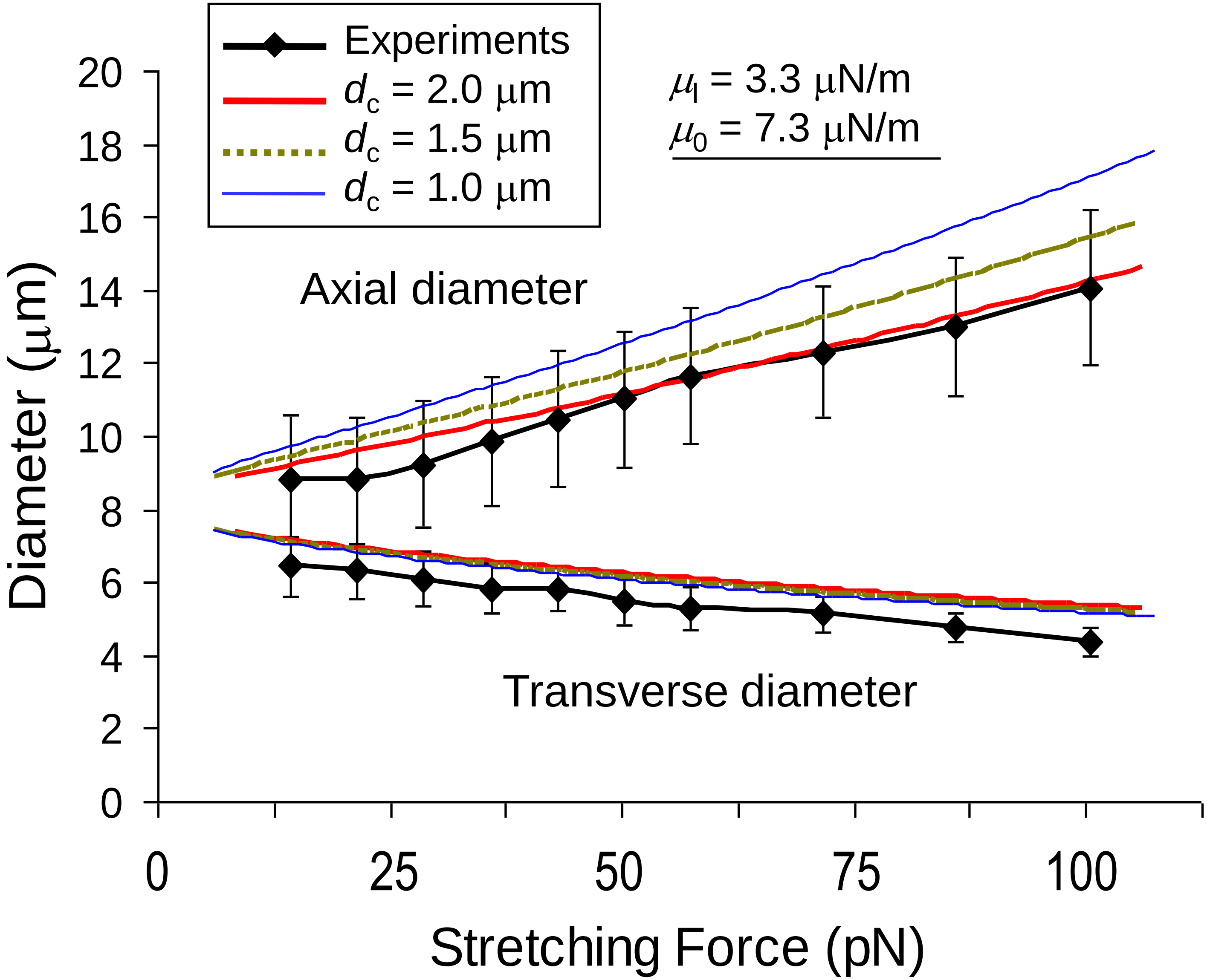

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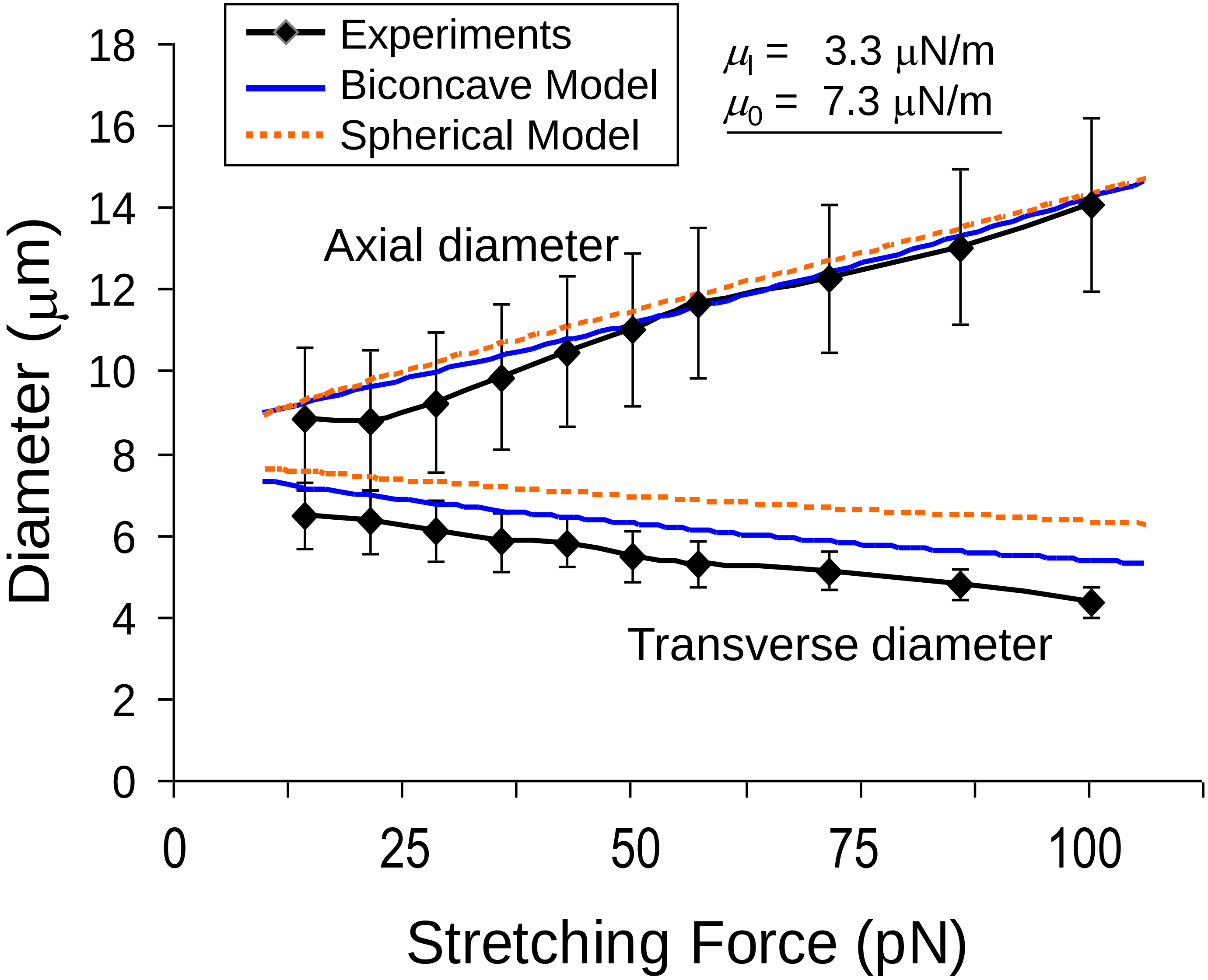
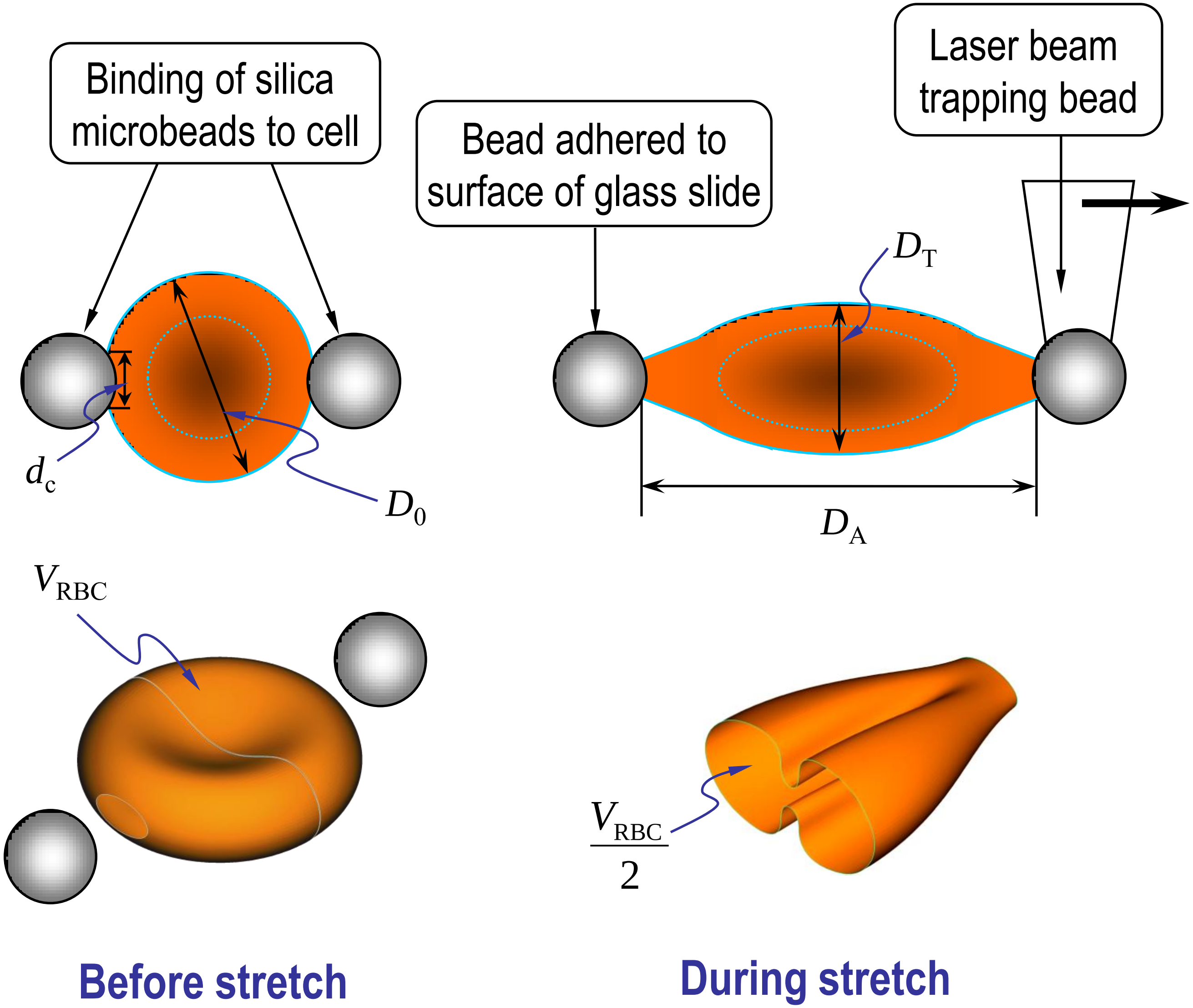


Dao, Lim and Suresh, *J Mech Phys Solids*, 2003

Scaling Functions of Optical Tweezers Expts



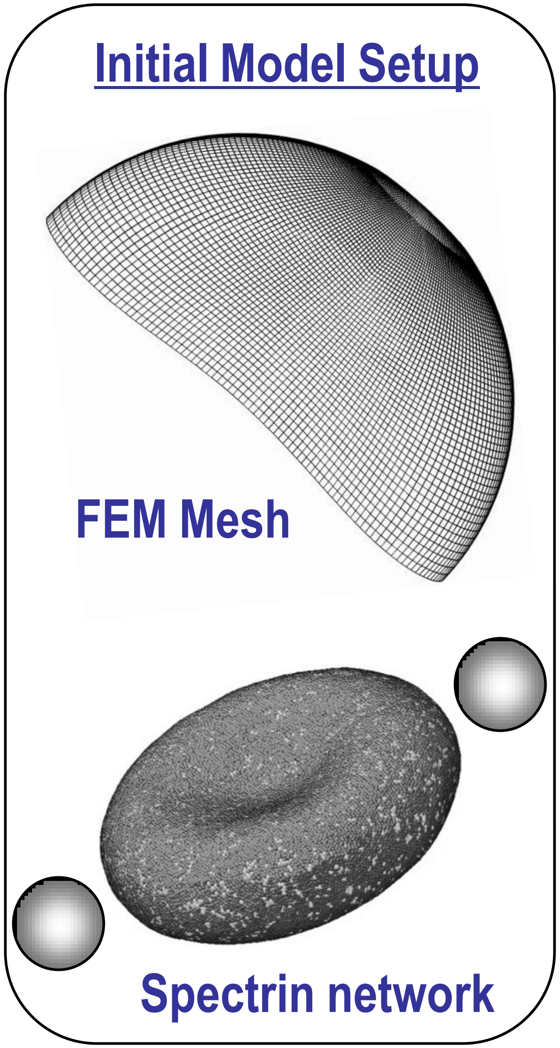
Binding of silica microbeads to cell

Bead adhered to surface of glass slide

Laser beam trapping bead

Before stretch

During stretch



Initial Model Setup

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Scaling Functions of Optical Tweezers Expts

Considering the small influence of bending modulus, OT force

$$F = F\left(D_{\mathrm{A}}, \mu_0, \mu_{\mathrm{h}}, d_{\mathrm{c}}, D_0\right)$$

Dimensional Analysis gives $\displaystyle \frac{F}{\mu_0 D_0} = \Pi\left(\frac{D_{\mathrm{A}}}{D_0}, \frac{D_0}{d_{\mathrm{c}}}, \frac{\mu_{\mathrm{h}}}{\mu_0}\right)$

$$\boxed{F \propto \mu_0 \qquad \mu_0 \propto p \qquad F \propto p}$$

$$f_{\mathrm{WLC}}(L) = -\frac{k_{\mathrm{B}}T}{p}\left\{\frac{1}{4(1-x)^2} - \frac{1}{4} + x\right\}, \qquad x \equiv \frac{L}{L_{\max}} \in [0,1)$$

Dao, Li & Suresh, *Mat Sci Eng C* (2006)

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Please see Fig. 10(a) in Dao, Li, Suresh. "Molecularly Based Analysis of Deformation of Spectrin Network and Human Erythrocyte." *Mat Sci Eng C* (2006): 1232-1244.

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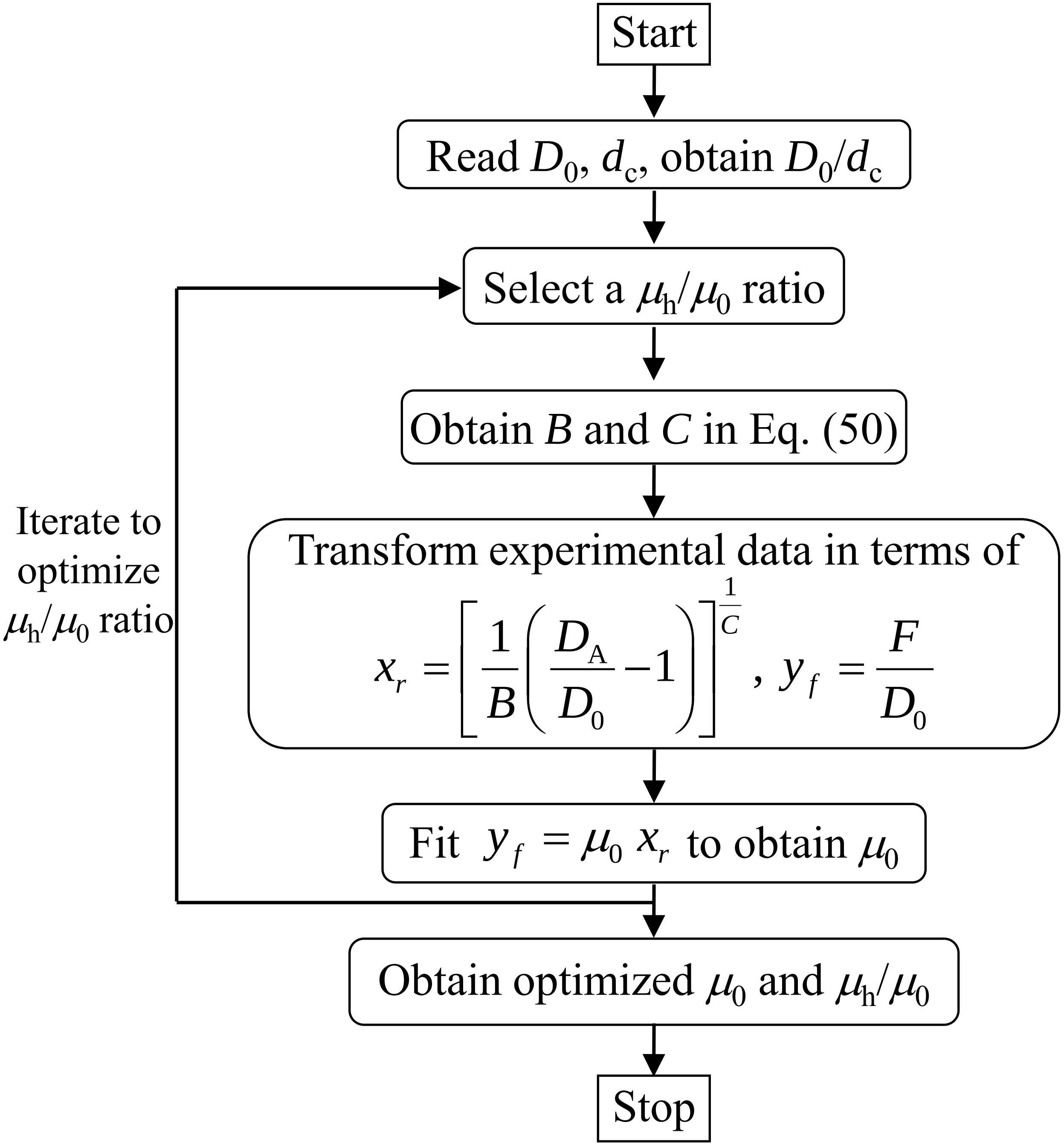
Please see Fig. 10(b) in Dao, Li, Suresh. "Molecularly Based Analysis of Deformation of Spectrin Network and Human Erythrocyte." *Mat Sci Eng C* (2006): 1232-1244.



Start

Read D_0, d_c, obtain D_0/d_c

Select a μ_h/μ_0 ratio

Obtain B and C in Eq. (50)

Transform experimental data in terms of

$$x_r = \left[\frac{1}{B}\left(\frac{D_A}{D_0} - 1\right)\right]^{\frac{1}{C}}, \; y_f = \frac{F}{D_0}$$

Fit $y_f = \mu_0 \, x_r$ to obtain μ_0

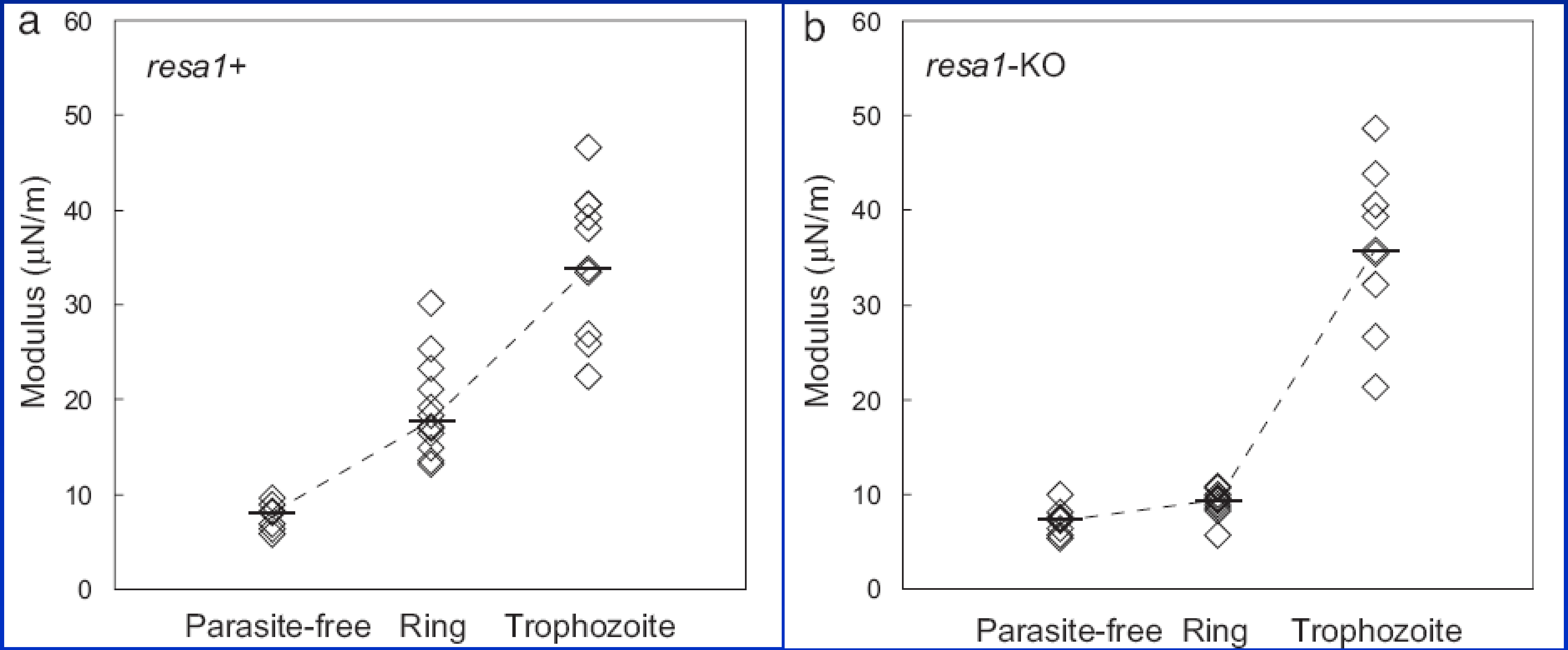
Iterate to optimize μ_h/μ_0 ratio

Obtain optimized μ_0 and μ_h/μ_0

Stop

Dao, Li & Suresh, *Mat Sci Eng C* (2006)

Critical experiments on single-protein effects



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Source: Mills, et al. "Effect of Plasmodial RESA Protein on Deformability of Human Red Blood Cells Harboring Plasmodium Falciparum." *PNAS* 104 (2007): 9213-9217. Copyright 2007 National Academy of Sciences, U.S.A.

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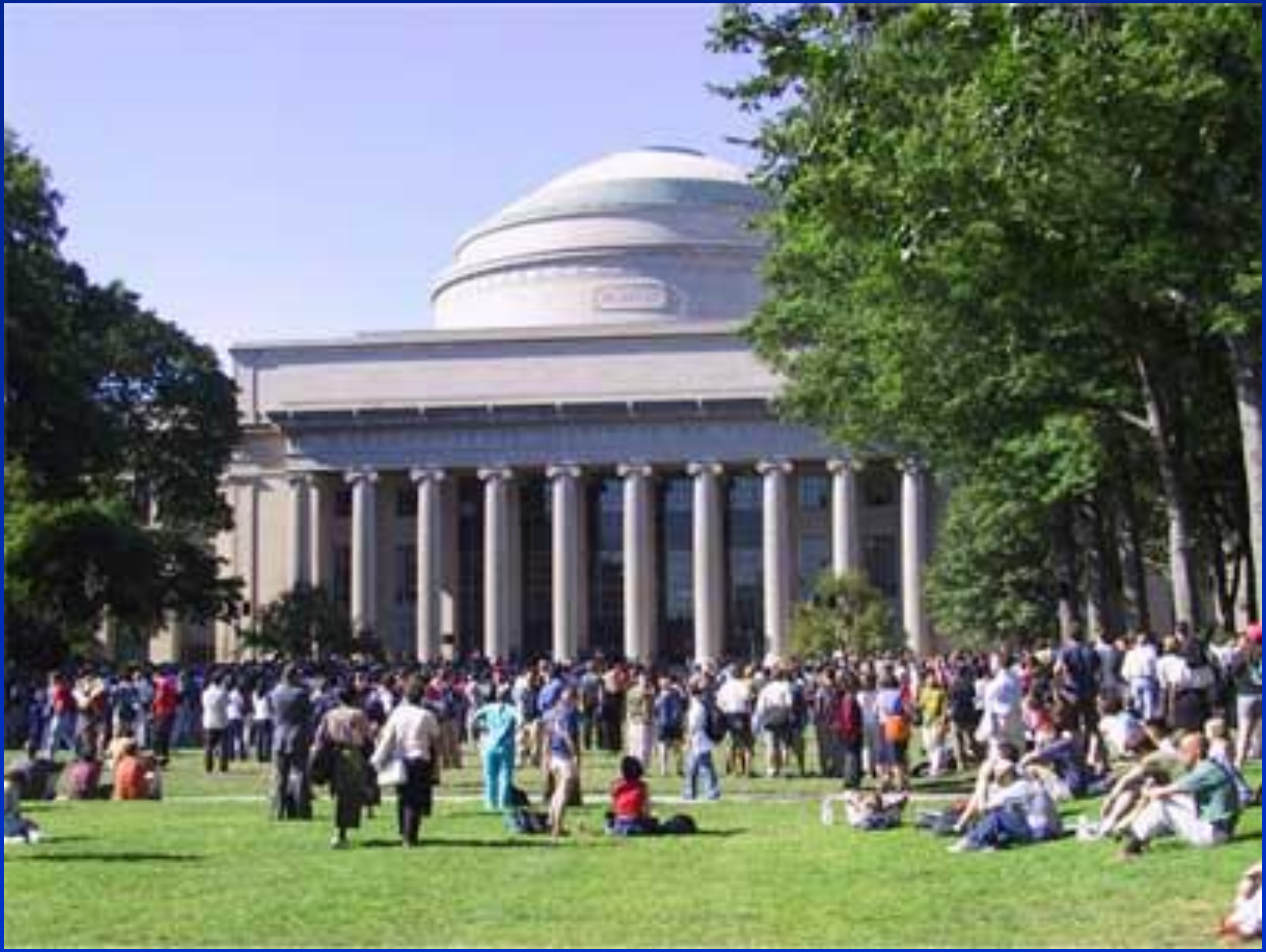
Please see Fig. 9 in Dao, Li, Suresh. "Molecularly Based Analysis of Deformation of Spectrin Network and Human Erythrocyte." *Mat Sci Eng C* (2006): 1232-1244.

Summary

- Continuum mechanics model is a useful tool in extracting mechanical properties of the cell (within certain limitations)
  - Geometry irregularity
  - Nonlinear deformation

  → Computational cell mechanics
- Continuum modeling framework of human RBC under optical tweezers stretching developed, which significantly facilitates mechanical property extraction in experiments



Thank you!