Continuum Modeling of the Cell

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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

Continuum Approach

Viscoelastic models

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)

Cortical shell-liquid core models
(or liquid drop models)
- Newtonian
- Compound
- Shear thinning
- Maxwell

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 nucleus

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.
Inverted microscope

Before stretch

Human red blood cell

Binding of silica microbeads to cell

Bead adhered to surface of glass slide

During stretch

Laser beam trapping bead

1.5 W diode pumped Nd:YAG laser source


Video Recorder

CCD Camera

Inverted microscope

sampling

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

Molecular structure of human RBC cytoskeleton

Spherocytosis, elliptocytosis, Asian ovalocytosis

B. Alberts et al. (1994)
**Structure of the cell membrane**

- (a) Lipid bilayer
- Cholesterol
- Spectrin network
- Transmembrane proteins

(b) Spectrin Network + Lipid Membrane

- Worm-like chain (WLC) model with surface & bending energies

(c) Effective Continuum Membrane

- In-plane shear modulus: $\mu$
- Bending stiffness: $\kappa$


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

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

\[\lambda_1 \lambda_2 \lambda_3 = 1\]

membrane shear stress

shear strain \((2\gamma_s)\)

\[\mu_h > 0\]

3rd order hyperelasticity

\[\mu_h = 0 \rightarrow \text{neo-Hookean Model}\]
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

\[ \tau_{\alpha\beta} = -\frac{1}{2A} \left[ \frac{f_{WLC}(a)}{a} a_{\alpha} a_{\beta} + \frac{f_{WLC}(b)}{b} b_{\alpha} b_{\beta} + \frac{f_{WLC}(c)}{c} c_{\alpha} c_{\beta} \right] - q C_q A^{-q-1} \delta_{\alpha\beta}. \]
$\sigma_{xx} (\mu N/m)$

$\kappa_{1-1}$

$p = 8.5 \text{ nm}; L_0 = 91 \text{ nm}; L_{\text{max}} = 238 \text{ nm}$

$p = 8.5 \text{ nm}; L_0 = 87 \text{ nm}; L_{\text{max}} = 238 \text{ nm}$

$p = 7.5 \text{ nm}; L_0 = 75 \text{ nm}; L_{\text{max}} = 238 \text{ nm}$

$\mu_0 = 8.0 \mu N/m; \mu_h/\mu_0 = 1/20$

$\mu_0 = 7.3 \mu N/m; \mu_h/\mu_0 = 1/30$

$\mu_0 = 7.3 \mu N/m; \mu_h/\mu_0 = 1/90$

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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: $\lambda_1 \lambda_2 = 1$

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

$\mu$ – membrane shear modulus

$\lambda_1$ – the principal stretches

$T_s$, $\gamma_s$ – membrane shear stress (force/length), shear strain

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

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

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

Unreformed (Original) Area = \(\pi R_0^2\)

Area Conservation gives

\[ R_0^2 = R^2 - R_p^2 + 2LR_p \]
Micropipette Aspiration

\[ \lambda_R = \frac{\partial R}{\partial R_0} = \frac{R_0}{R} \quad \lambda_\phi = \frac{1}{\lambda_R} = \frac{R}{R_0} \]

Constitutive Law:

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

\[ T_z = \Delta p R_p / 2 = T_R \bigg|_{R=R_p} \]

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

\[ F_z = 2\pi R_p T_z \]
Modeling Optical Tweezers Experiments

Binding of silica microbeads to cell

Before stretch

During stretch

Bead adhered to surface of glass slide

Laser beam trapping bead

\[ D_0 \]

\[ D_A \]

\[ D_T \]

\[ d_c \]

\[ V_{RBC} \]

\[ \frac{V_{RBC}}{2} \]

FEM Mesh

Spectrin network

Initial Model Setup

One half of the human red blood cell stretched by optical tweezers: 3-D computer simulation for comparison with experiment.

experiment

simulations

0 pN
67 pN
130 pN
193 pN

(a) (b) (c)

Courtesy of Tech Science Press. Used with permission.

\exp(-t/t_c)

- $t_c = 0.19 \pm 0.06$ s
  (ave from 8 experiments)
- $t_c = 0.25$ s
- $t_c = 0.13$ s


Maximum Principal Strain

Experiment

Simulations with cytosol

Simulations without cytosol


Axial diameter

Experiments

Cell Diameter $D = 8.5 \, \mu m$

$\mu_i = 3.3 \, \mu N/m$

Cell Diameter $D = 7.82 \, \mu m$

$\mu_0 = 7.3 \, \mu N/m$

Cell Diameter $D = 7 \, \mu m$

$\alpha = 3.3 \, \mu N/m$

Experiments

$\mu_1 = 3.3 \, \mu N/m$

$\mu_0 = 7.3 \, \mu N/m$


\[ \mu_i = 3.3 \, \mu\text{N/m} \]
\[ \mu_0 = 7.3 \, \mu\text{N/m} \]
Scaling Functions of Optical Tweezers Expts

Before stretch

During stretch

Binding of silica microbeads to cell

Bead adhered to surface of glass slide

Laser beam trapping bead

Initial Model Setup

FEM Mesh

Spectrin network

Scaling Functions of Optical Tweezers Expts

Considering the small influence of bending modulus, OT force

\[ F = F \left( D_A, \mu_0, \mu_h, d_c, D_0 \right) \]

Dimensional Analysis gives

\[ \frac{F}{\mu_0 D_0} = \Pi \left( \frac{D_A}{D_0}, \frac{D_0}{d_c}, \frac{\mu_h}{\mu_0} \right) \]

\[ F \propto \mu_0 \quad \mu_0 \propto p \quad F \propto p \]

\[ f_{WLC}(L) = -\frac{k_B T}{p} \left\{ \frac{1}{4(1-x)^2} - \frac{1}{4} + x \right\}, \quad x \equiv \frac{L}{L_{\text{max}}} \in [0,1) \]

Dao, Li & Suresh, Mat Sci Eng C (2006)
Image removed due to copyright restrictions.
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 $\mu_h/\mu_0$ 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 $\mu_0$

Obtain optimized $\mu_0$ and $\mu_h/\mu_0$

Stop

Dao, Li & Suresh, Mat Sci Eng C (2006)
Critical experiments on single-protein effects

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

• Continuum modeling framework of human RBC under optical tweezers stretching developed, which significantly facilitates mechanical property extraction in experiments
Thank you!