Multi-scale Simulations of Soft Contact and Adhesion of Stem Cells with Extra-cellular Matrix

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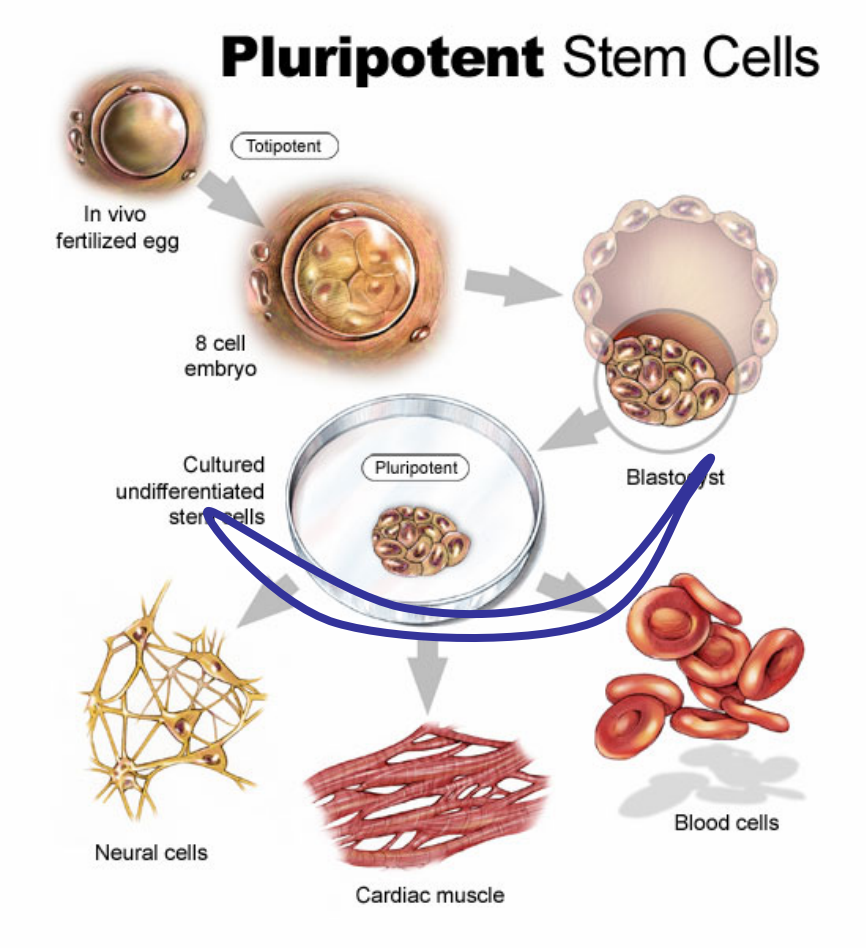
I. Introduction



How ?

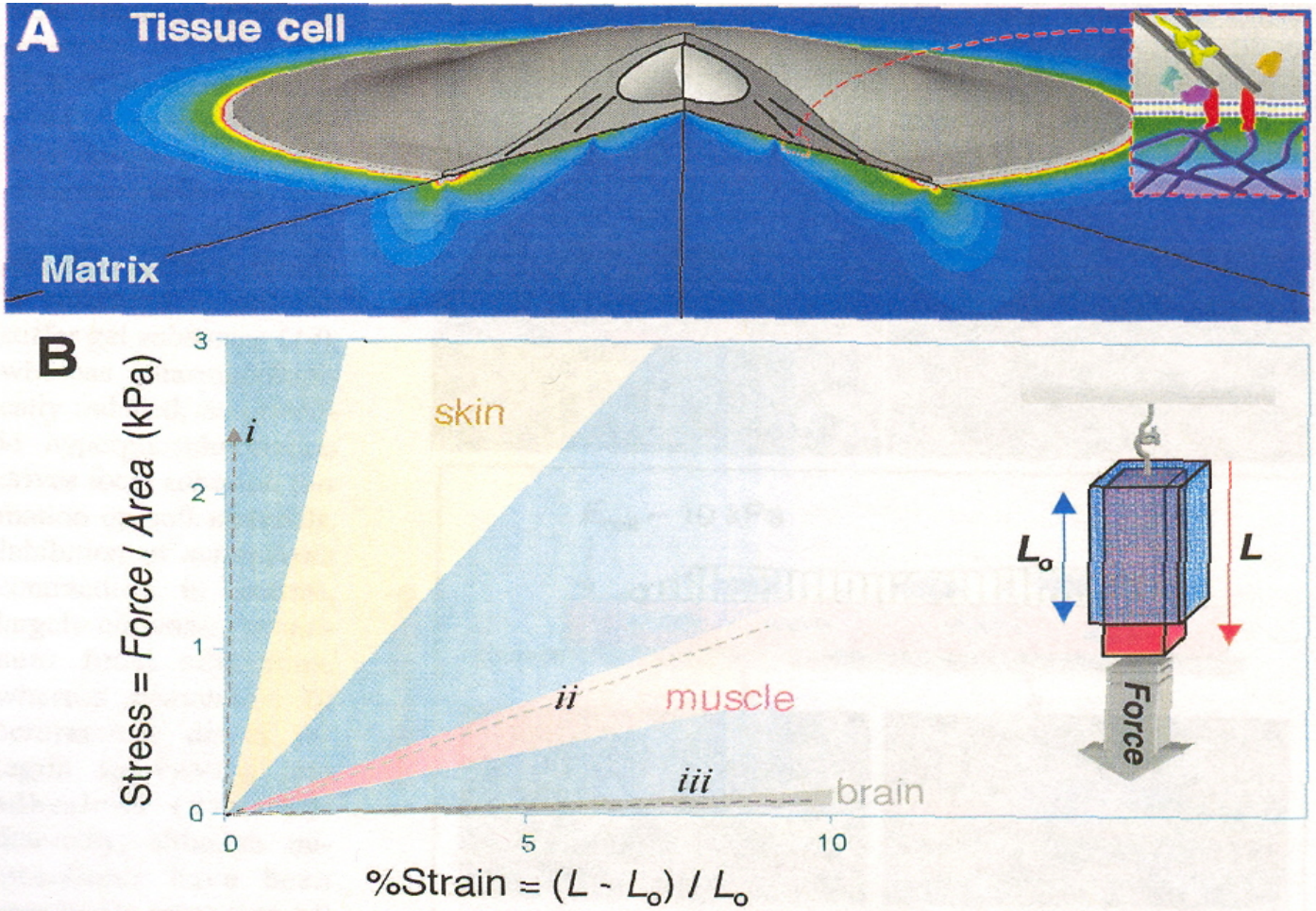


Fig. 1. Substrate strain and tissue stiffness. (**A**) Strain distribution computed in a soft matrix beneath a cell. The circular cell has a uniform and sustained contractile prestress from the edge to *near the nucleus* (*81*). (**B**) *Stress versus strain illustrated for several soft tissues extended by a force* (per cross-sectional area). The range of slopes for these soft tissues subjected to a small strain gives the range of Young's elastic modulus, *E*, for each tissue (*24*, *28*, *30*). Measurements are typically made on time scales of seconds to minutes and are in SI units of Pascal (Pa). The dashed lines (- - -) are those for (i) PLA, a common tissue-engineering polymer (*89*); (ii) artery-derived acellularized matrix (*90*); and (iii) matrigel (*42*).

Dennis E. Discher et al [2005] *Science*

A.J. Engler et al (2006) *Cell*

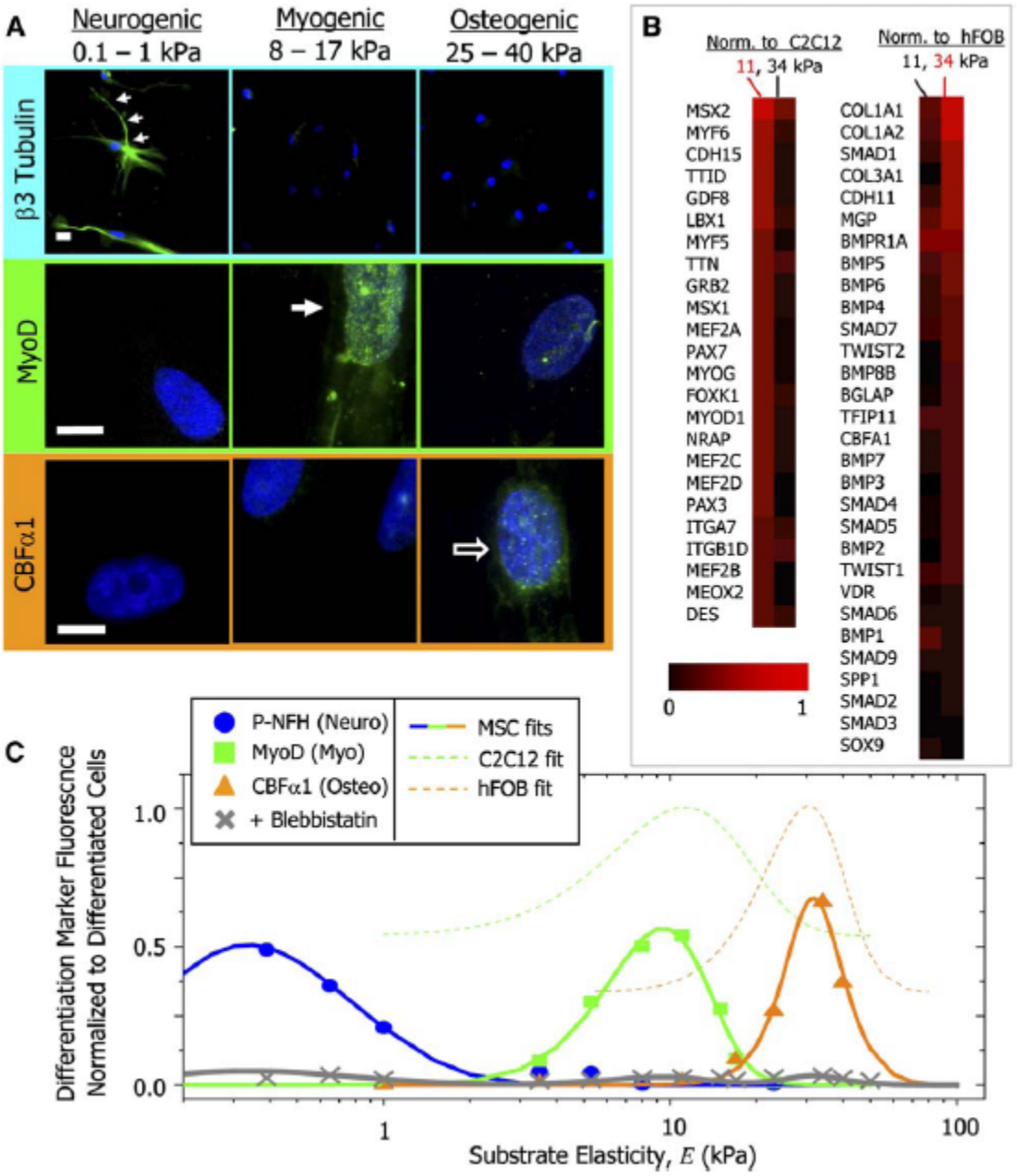
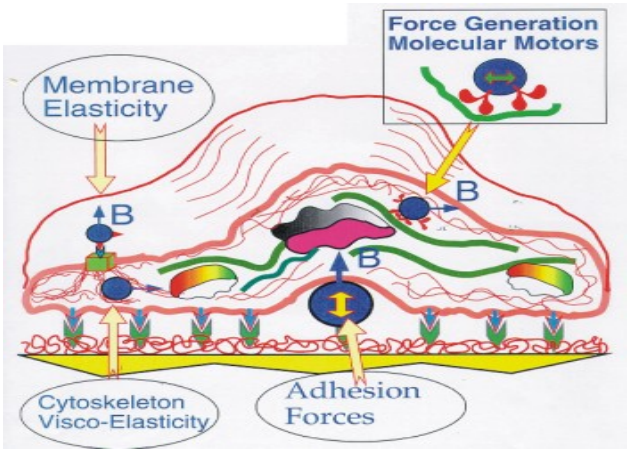


Figure 3. Protein and Transcript Profiles Are Elasticity Dependent under Identical Media Conditions

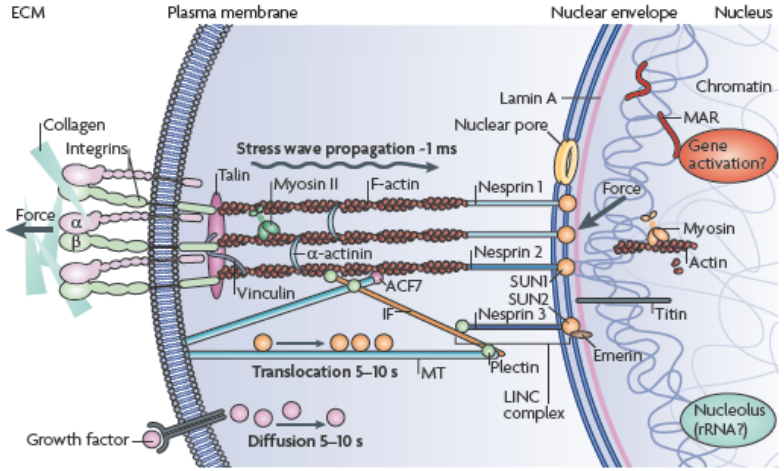
II. How do model mechanotransduction ?

(1) What is the suitable constitutive model for cells?

(2) How to model the cell contact and adhesion ?

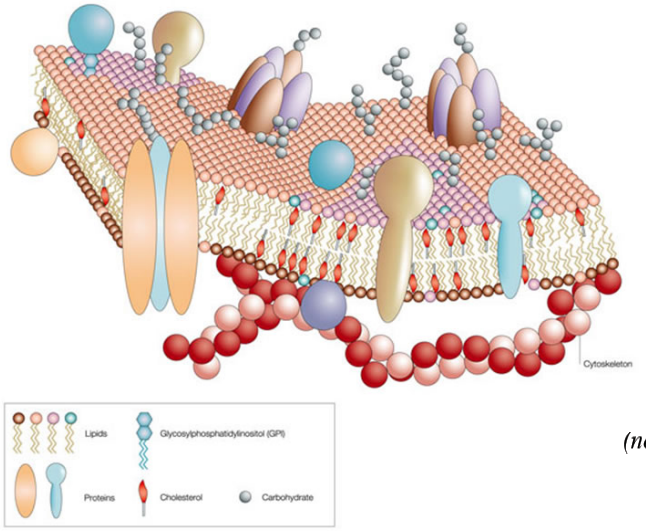


Ligand-receptor interactions



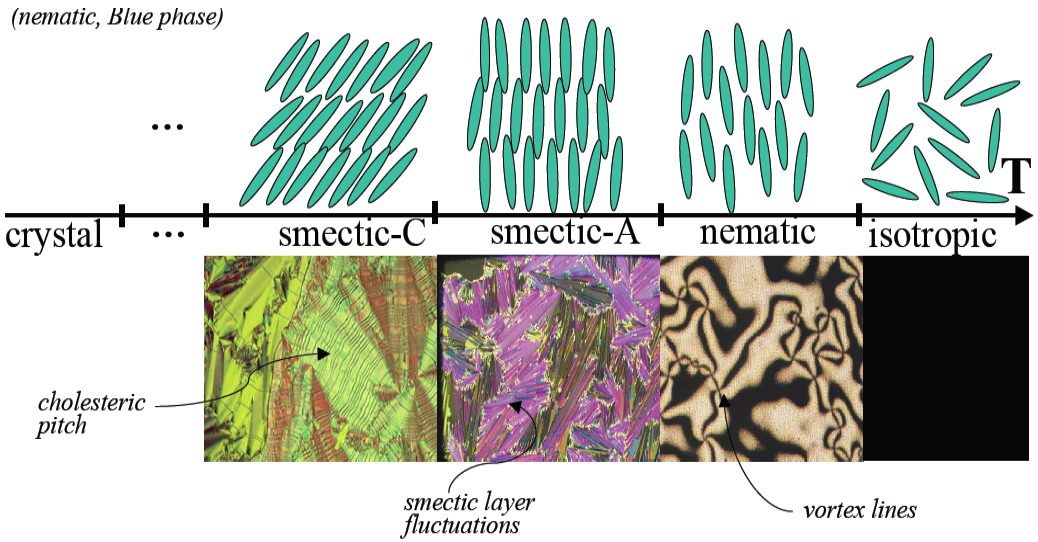
Ning Wang et al. Natural Reviews Molecular Cell Biology [2009]

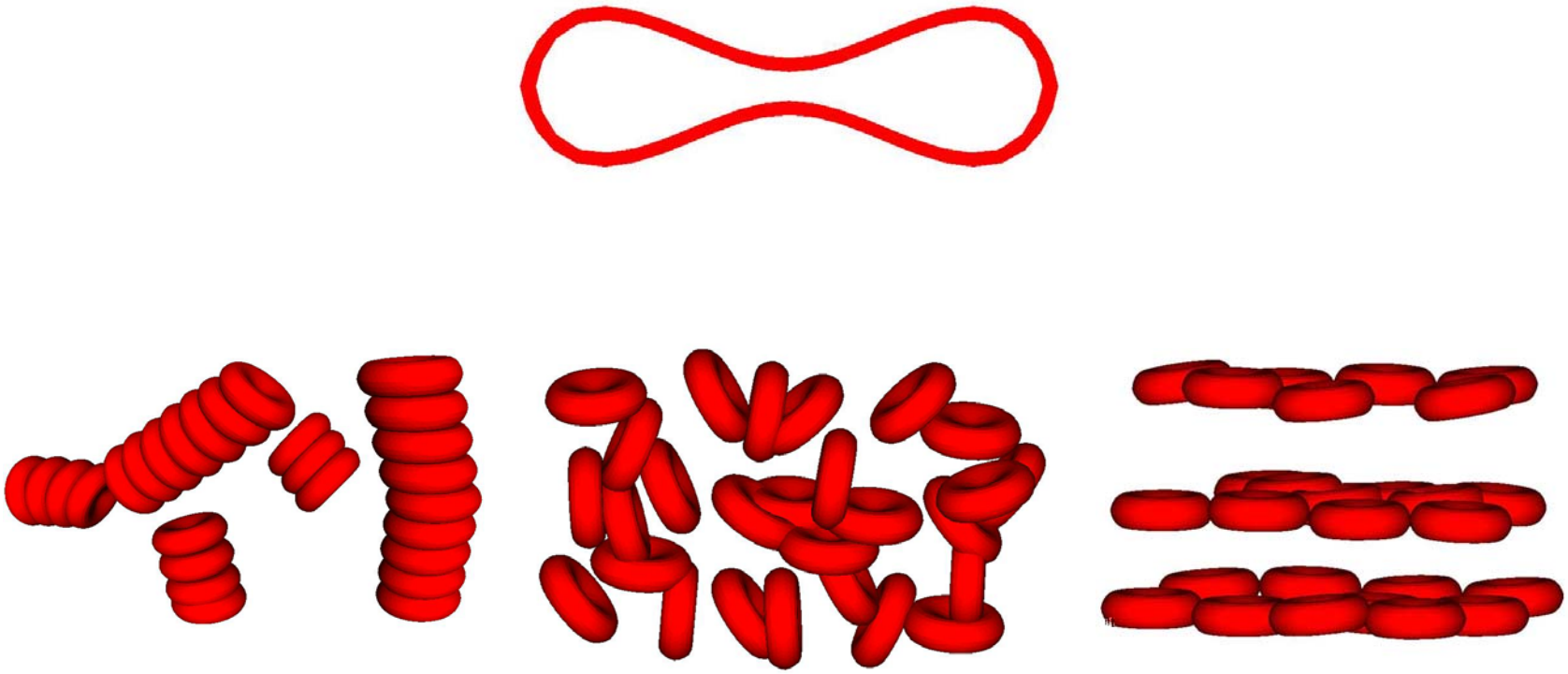
A. How to model cell membrane ?



Fluid Mosaic Model
(Singer and Nicolson[1972])

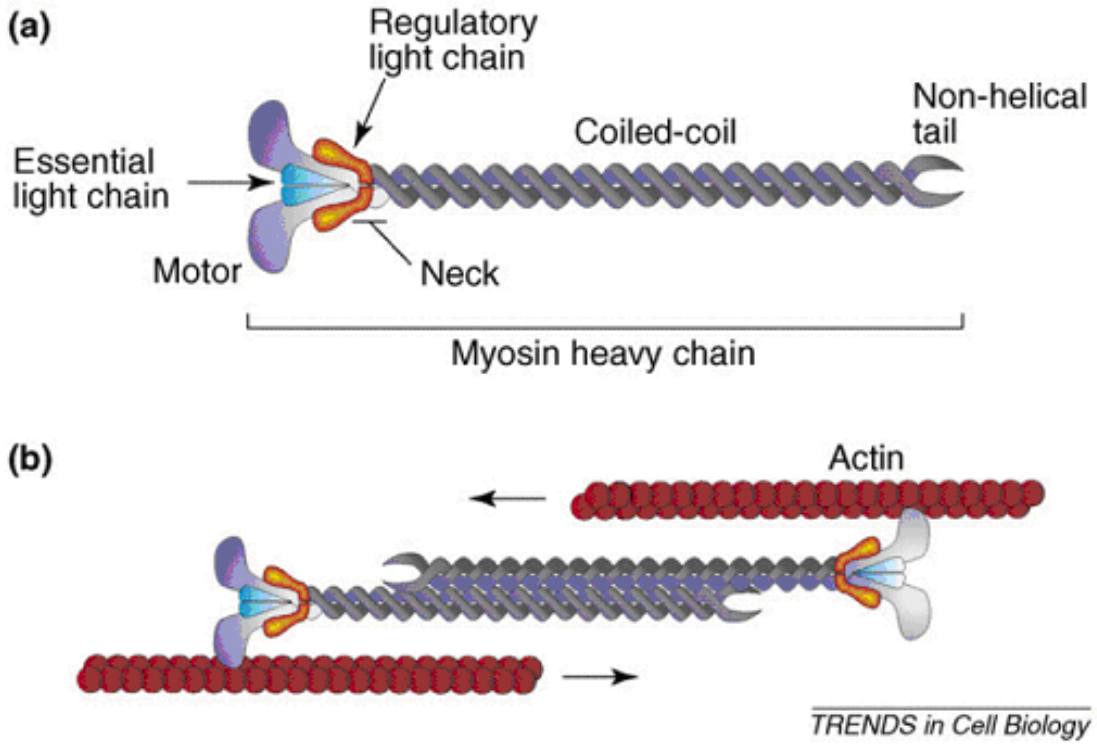
Liquid Crystals





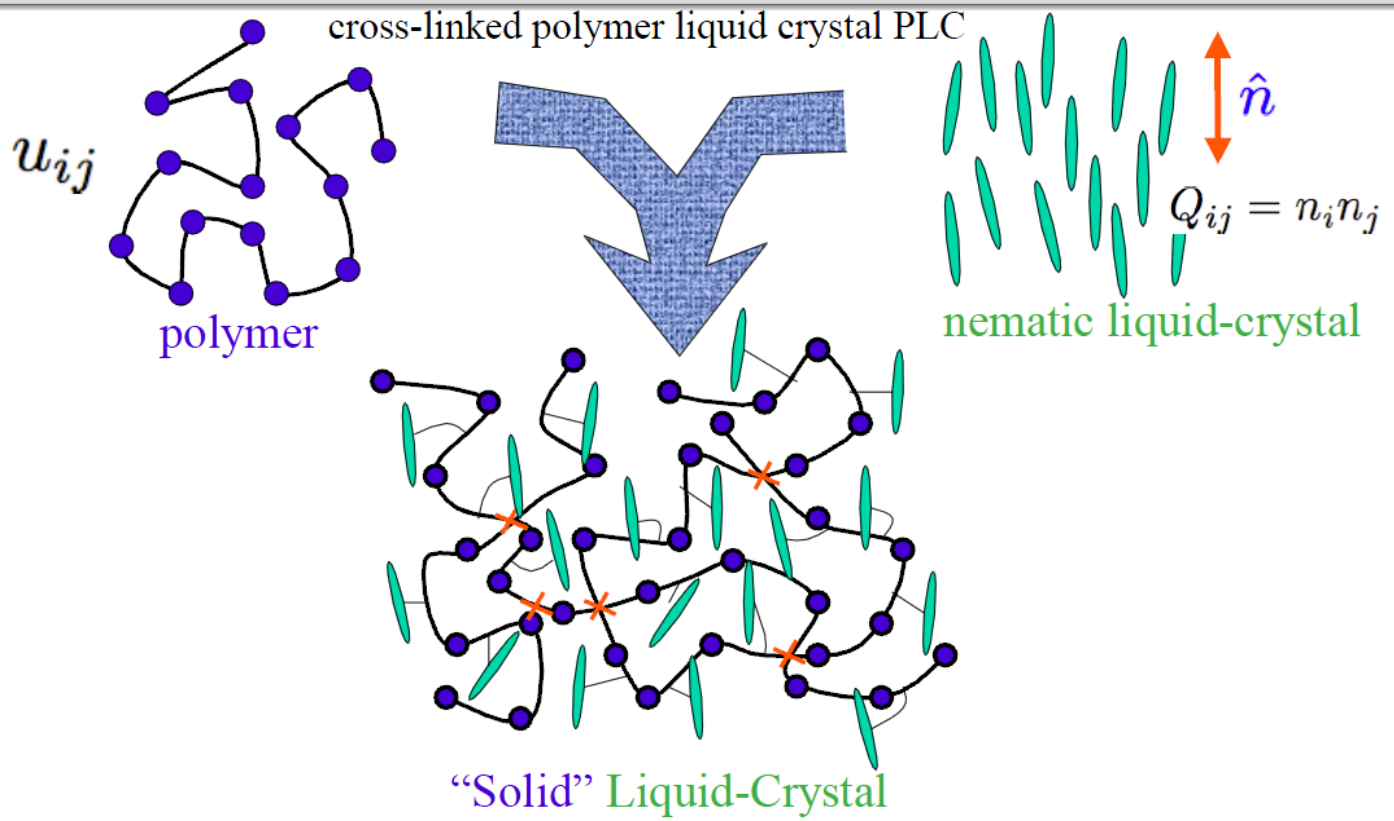
Inspired by the fluid mosaic model, Helfrich [1973] developed a Liquid Crystal Membrane model that has successfully predicted the bi-concave shape of red blood cells.

B. How to model interior of the cell e.g. the acto-myosin interaction ?



The actomyosin cytoskeleton. (a) Schematic diagram of a myosin II monomer, depicting the light and heavy chains. The different parts of the heavy chain, including the motor, neck, coiled-coil and nonhelical domains, are indicated. (b) Myosin II self-assembles into bipolar filaments through interactions of the C-terminus; the N-terminus binds to actin filaments. Activation of the myosin II motor domain leads to the pulling of actin filaments (in the direction of the arrows) to induce cortical tension (Clark et al [2007]).

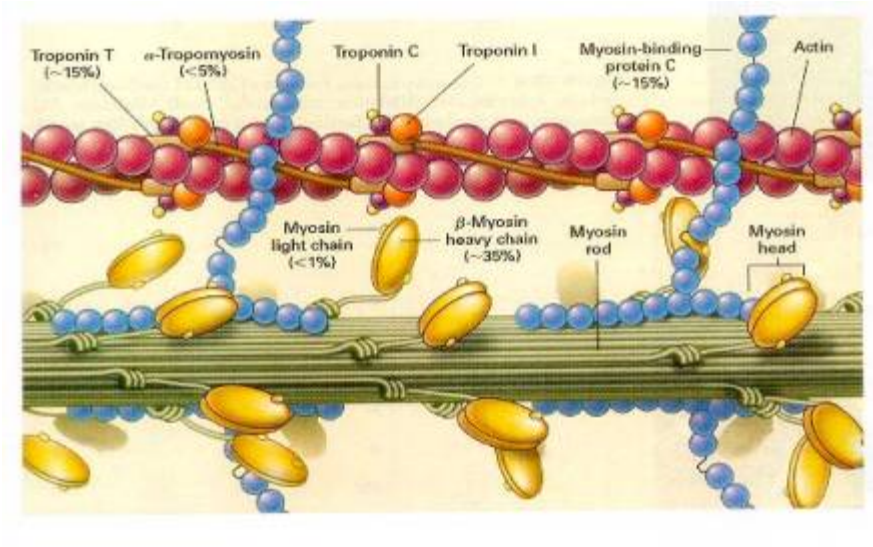
Liquid Crystal Elastomers



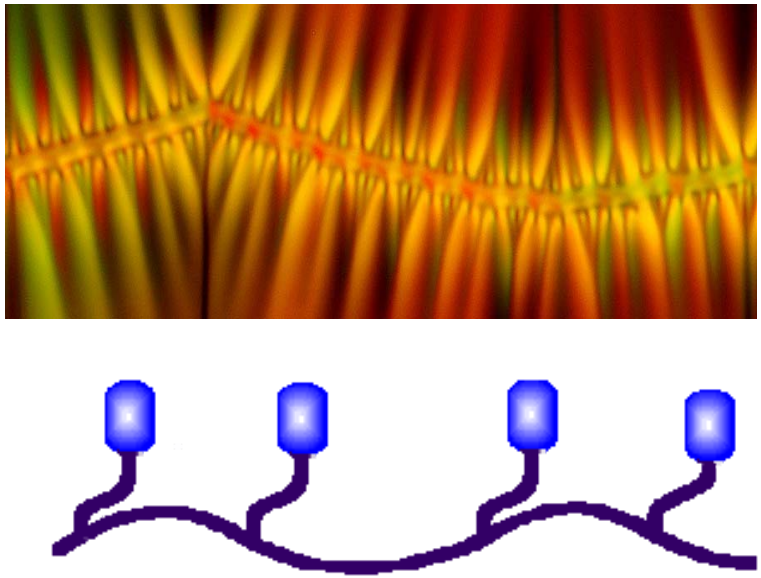
exhibits most conventional liquid-crystal phases (I, N, Sm-A, Sm-C,…)

How to model a cell ?

We model cytoskeleton of cells as a liquid crystal elastomer, and we hypothesize that the stem cell cytoskeleton is a special type of liquid crystal elastomer.



Actomyosin molecules in a cell



Mesogen in nematic liquid crystal elastomer

ARTICLES

Crosslinked actin networks show liquid crystal elastomer behaviour, including soft-mode elasticity

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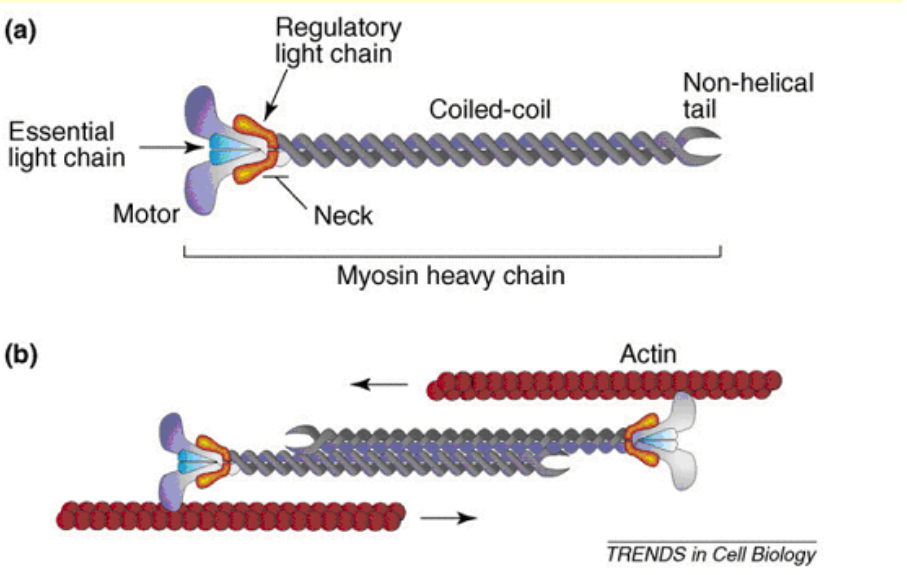
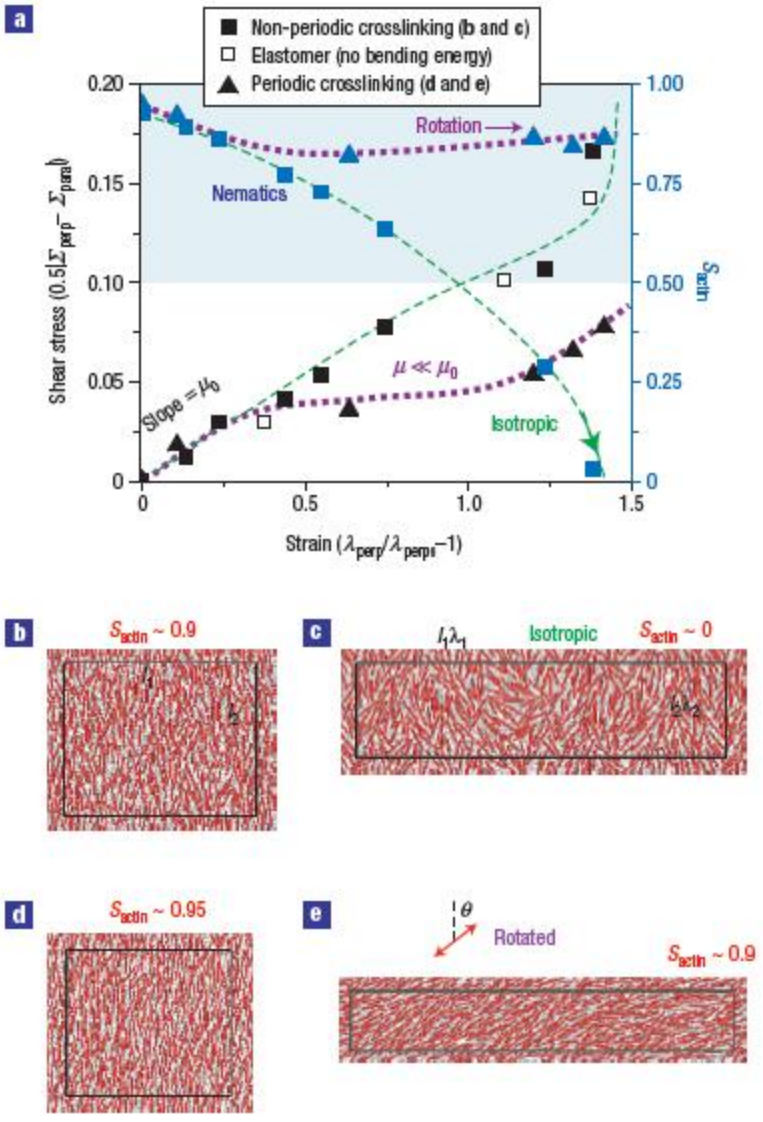
Actin filament networks with protein crosslinks of distinct length a
filament systems with flexible crosslinkers of varying length and



Nature Physics, [2007] Vol. 3



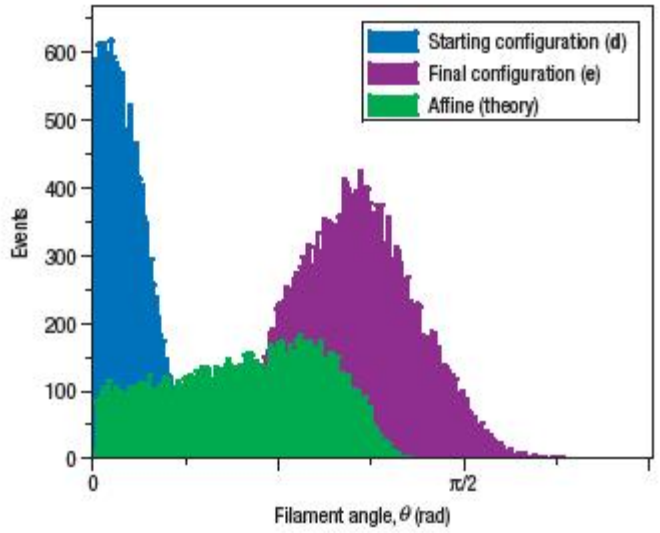


Figure 5 The nature of network crosslinking plays a key role in response to shear. a, Shear stress and S_{actin} (blue) of three different loose networks subjected to extension perpendicular to the direction of initial alignment ($L_{actin}/D_{actin} \approx 9$). Networks with random crosslinking (b,c) show no net rotation of their director and also show the same stress–strain response as a network lacking filaments (filled squares versus open squares). In contrast, networks with periodic crosslinking (d,e) show a soft plateau in stress (filled triangles). **f**, Affine predictions (green) underestimate the simulation's filament rotations (purple) after stretching from $r = 1$ (blue) → 6.

From Dalhaimer et al. [2007]
Nature Physics, 3, 345-360

Constitutive Modeling for Cells

1. **We adopt a modified Ericksen-Leslie Theory (Lin and Liu [2000]) as the constitutive model for Nematic Liquid Crystal;**
2. **We are developing a hydrodynamics theory for Liquid Crystal Elastomer;**
3. **We use Mooney-Rivlin material as the hyperelastic model;**
4. **We use Newtonian Fluid model as the constitutive model of cell plasma;**

Nematic Liquid Crystal

The strong forms of the simplified Ericksen-Leslie theory are

$$\begin{aligned} \rho_f \frac{D\mathbf{v}}{Dt} &= \nabla \cdot \boldsymbol{\sigma} + \mathbf{b}, \quad \forall\, \mathbf{x} \in V(t) \\ \rho_d \frac{D\tilde{\mathbf{h}}}{Dt} &= \gamma \left\{ \nabla \cdot \boldsymbol{\nabla} \otimes \mathbf{h} - \mathbf{f}(\mathbf{h}) \right\}, \quad \forall\, \mathbf{x} \in V(t) \end{aligned}$$

where the Cauchy stress is given as

$$\boldsymbol{\sigma} = -p\mathbf{I} + 2\mu\mathbf{d} - \lambda \nabla \cdot (\nabla \otimes \mathbf{h} \odot \nabla \otimes \mathbf{h}) - \mathbf{G}$$

and $\mathbf{h}(\mathbf{X}, t)$ is the director field, and $\mathbf{G}$ is the contribution from the contact boundary condition,

$$\mathbf{G} = \begin{cases} A(\mathbf{h} \cdot \nabla\varphi_s)\mathbf{h} \otimes \nabla\varphi_s & \text{planar anchoring} \\ A[(\mathbf{h} \cdot \mathbf{h})\nabla\varphi_s - (\mathbf{h} \cdot \nabla\varphi_s)\mathbf{h}] \otimes \nabla\varphi_s & \text{homeotropic anchoring} \end{cases}$$

Yue et al [2000]

Here φ_s is a phase field of level set function such that

$$\begin{array}{lcll} \varphi_s & = & 1, & \forall\ \mathbf{x} \in V_s(t) \\ 0 & < & \varphi_s < 1 & \forall \mathbf{x} \text{ between the contact interface} \\ \varphi_s & = & 0, & \forall\ \mathbf{x} \in V_c(t) \end{array}$$

The Lagangian level-set phase field, φ_s, is chosen as the determinant of the moment matrix of meshfree interpolant of the substrate,

$$\varphi_s(\mathbf{x}, t) = \sum_I N_I(\mathbf{x}), \quad \forall\ \mathbf{x} \in V_s$$

Note that we may construct another Lagrangian level-set phase field by using the moment matrix of meshfree interpolant of the cell, and we use it to replace the director elastic constant γ as

$$\gamma \quad \rightarrow \quad \gamma\varphi_c, \quad \text{and} \quad \varphi_c = \sum_I N_I(\mathbf{x}),\ \forall \mathbf{x} \in V_c$$

Note that we can also use φ_c to calculate curvature for other type of surface tension calculation,

$$\kappa = \nabla_x \cdot \mathbf{n} = \mathbf{F}^{-T} \nabla_{\mathbf{X}} \cdot \Big(\frac{\mathbf{F}^{-T} \cdot \nabla_X \varphi_c}{\|\mathbf{F}^{-T} \cdot \nabla_X \varphi_c\|} \Big)$$

Remarks:

1. $\frac{D\tilde{\mathbf{h}}}{Dt}$ is the objective rate, and it can be

1. The convected rate : $\overset{\circ}{\mathbf{h}} = \frac{D\mathbf{h}}{Dt} + \mathbf{l}^T\mathbf{h};$

2. The corotational rate : $\overset{\triangle}{\mathbf{h}} = \frac{D\mathbf{h}}{Dt} - \mathbf{wh};$

and $\mathbf{l}$ is the velocity gradient, and $\mathbf{w}$ is the spin tensor,

$$\begin{aligned} \mathbf{l} &= \dot{\mathbf{F}}\mathbf{F}^{-1} \\ \mathbf{w} &= \frac{1}{2}(\mathbf{l} - \mathbf{l}^T) \end{aligned}$$

2.A Ginzburg-Landau type potential is used in calculate director field evolution,

$$\begin{aligned} F(\mathbf{h}) &= \frac{1}{4\epsilon^2}(|\mathbf{h}|^2 - 1)^2 \\ \mathbf{f}(\mathbf{h}) &= F'(\mathbf{h}) = \frac{\mathbf{h}}{\epsilon^2}(|\mathbf{h}|^2 - 1) \end{aligned}$$

Liquid Crystal Elastomer

A typical entropic free-energy expression for a liquid crystal elastomer is (Warner and Terentjev [2007]),

$$\Psi_{bulk} = \frac{1}{2} k_B T T_r \Big(\boldsymbol{\ell}_0 \cdot \mathbf{F}^T \cdot \boldsymbol{\ell}^{-1} \cdot \boldsymbol{F} \Big) + \frac{1}{2} k_B T \ln \Big(\frac{Det(\boldsymbol{\ell})}{a^3} \Big)$$

where k_B is the Boltzmann constant, T is temperature, $\boldsymbol{\ell}_0$ and $\boldsymbol{\ell}$ are polymer's step length tensors at referential configuration and current configuration respectively. They are related to the director field $\mathbf{h}$ as

$$\boldsymbol{\ell} = \ell_\perp \mathbf{I}^{(2)} + (\ell_\parallel - \ell_\perp) \mathbf{h} \otimes \mathbf{h},$$

and the first Piola-Kirchhoff stress is

$$\mathbf{P} = \frac{\partial \Psi}{\partial \mathbf{F}}.$$

Define the step length anisotropy as

$$s := \ell_\parallel / \ell_\perp$$

Liquid Crystal Elastomer (cont'd)

To regularize the potential, we add the Oseen-Frank potential

$$\Psi_{grad} = \frac{\kappa(s-1)^2}{2s}|\mathbf{F}^{-T}\nabla \otimes \mathbf{h}|^2$$

and let

$$\mathbf{G} = \nabla \otimes \mathbf{h}$$

the total liquid-crystal elastomer potential is (Fried & Korchagin [2002])

$$\begin{aligned}\Psi_t &= \frac{\mu}{2}\Big(|\mathbf{F}|^2 - \frac{s-1}{s}\,\Big|\,\mathbf{F}^T\mathbf{h}\,\Big|^2 + (s-1)|\mathbf{F}\mathbf{h}_0|^2 - \frac{(s-1)^2}{s}(\mathbf{F}^T\mathbf{h}\cdot\mathbf{h}_0)^2 - 3\Big)\\ &\quad + \frac{\kappa(s-1)^2}{2s}|\mathbf{F}^{-T}\mathbf{G}|^2\end{aligned}$$

Define the order parameter tensor,

$$\mathbf{Q} = Q_c(\mathbf{h}\otimes\mathbf{h} - \frac{1}{3}\mathbf{I}^{(2)}) \text{ and } \boldsymbol{\ell} = \frac{(\ell_\parallel - \ell_\perp)}{Q_c}\mathbf{Q} + \frac{(\ell_\parallel + 2\ell_\perp)}{3}\mathbf{I}^{(2)}$$

Liquid Crystal Elastomer (cont'd)

We pastulate the following Hydrodynamics of Liquid-Crystal Elastmors:

$$\rho\frac{\partial^2\mathbf{u}}{\partial t^2} = -\mathbf{F}^{-T}\nabla p + \mathrm{Div}\frac{\partial\Psi_t}{\partial\mathbf{F}} + \mathbf{b}$$

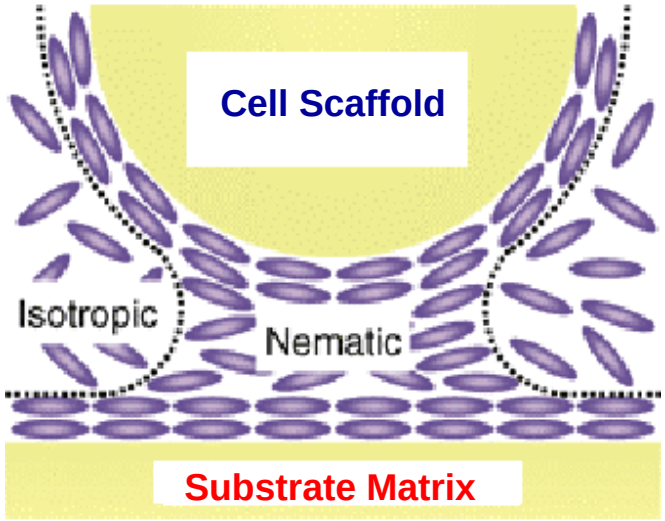
and (Allen & Cahn)

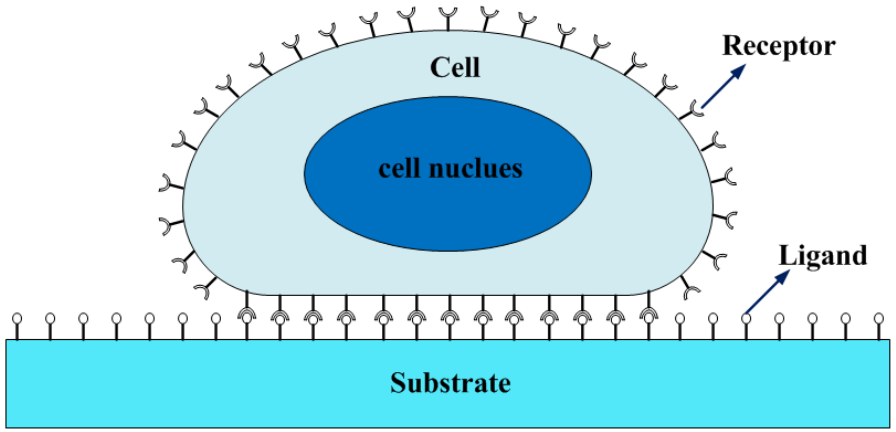
$$\frac{D\tilde{\mathbf{h}}}{Dt} = -\mathbf{L}\frac{\delta\Psi_t}{\delta\mathbf{h}}$$

For $\mathbf{L} = \mathcal{L}\mathbf{I}^{(2)} \otimes \mathbf{I}^{(2)}$,

$$\begin{aligned}\frac{D\tilde{\mathbf{h}}}{Dt} &= \mathcal{L}\frac{\kappa(s-1)^2}{s}\nabla_X\left\{\mathbf{F}^{-1}J\mathbf{F}^{-T}\nabla_X\mathbf{G}\right\} \\ &- \mathcal{L}\mu\left\{\frac{s-1}{s}(\mathbf{F}^T\mathbf{h})\cdot\mathbf{F}^T + \frac{(s-1)^2}{s}(\mathbf{F}^T\mathbf{h}\cdot\mathbf{h}^0)(\mathbf{F}^T\mathbf{h}^0)\right\}\end{aligned}$$

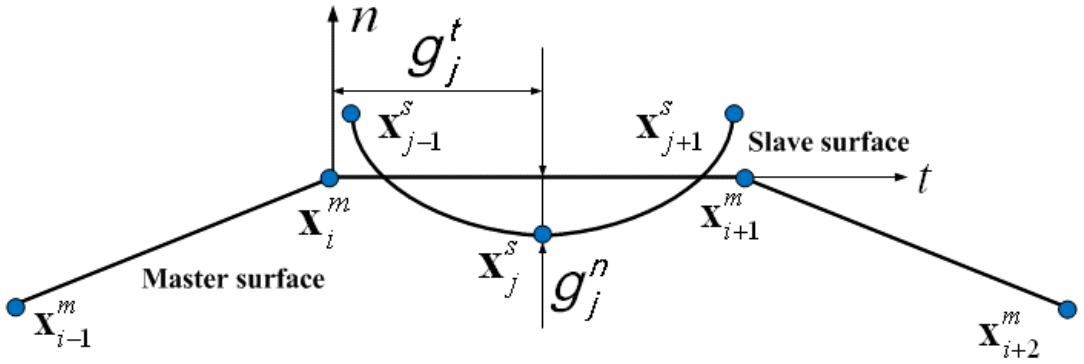
Use liquid crystal to model lipid bilayer and more

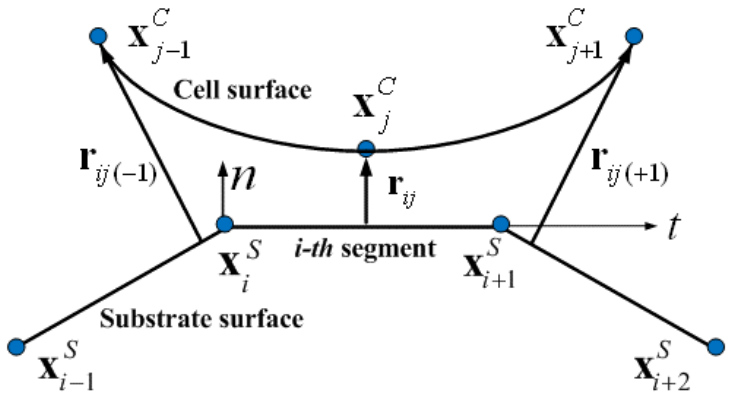




The Contact and Adhesion Model

Classical Contact vs. Cohesive Contact





$$g_j^n = (\mathbf{x}_j^s - \mathbf{x}_i^m)\cdot\mathbf{n}_i \qquad g_j^t = (\mathbf{x}_j^s - \mathbf{x}_i^m)\cdot\mathbf{t}_i$$

$$\mathbf{f}_j^n = \frac{2M_j^s g_j}{\Delta t^2}\mathbf{n}_i = f_j^n \mathbf{n}_i$$

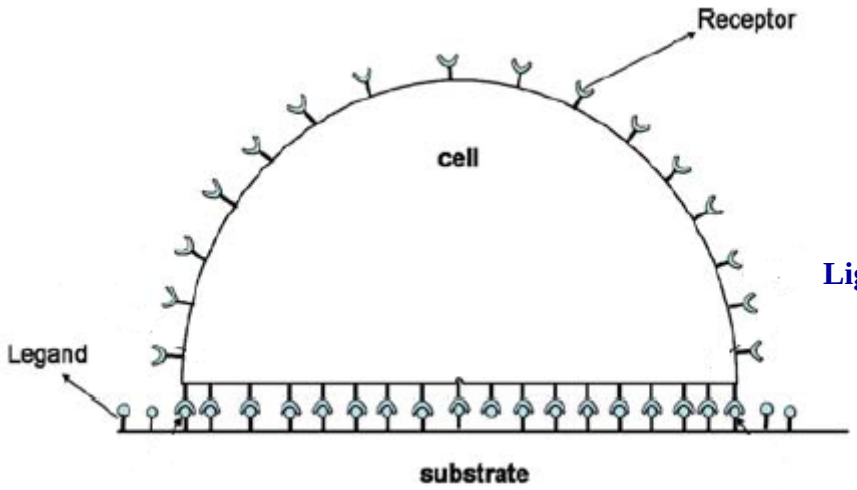
$$\mathbf{f}_j^{stick} = -\frac{M_j^s}{\Delta t}\mathbf{v}_j^t \qquad \mathbf{f}_j^{slip} = -|\mu_k f_j^n|\frac{\mathbf{v}_j^t}{\|\mathbf{v}_j^t\|}$$

$$\mathbf{f}_j^t = -min(|\mu_k f_j^n|, \|\mathbf{f}_j^{stick}\|)\frac{\mathbf{v}_j^t}{\|\mathbf{v}_j^t\|}$$

$$\Phi(r) = \sigma\left[\left(\frac{\varepsilon}{r}\right)^4 - 2\left(\frac{\varepsilon}{r}\right)^2\right]$$

$$\mathbf{F}(r) = -\frac{\partial\Phi}{\partial\mathbf{r}} = \phi'(r)\frac{\mathbf{r}}{r}$$

$$\phi'(r) = \frac{4\sigma}{\varepsilon}\left\{\left(\frac{\varepsilon}{r}\right)^5 - \left(\frac{\varepsilon}{r}\right)^3\right\}$$

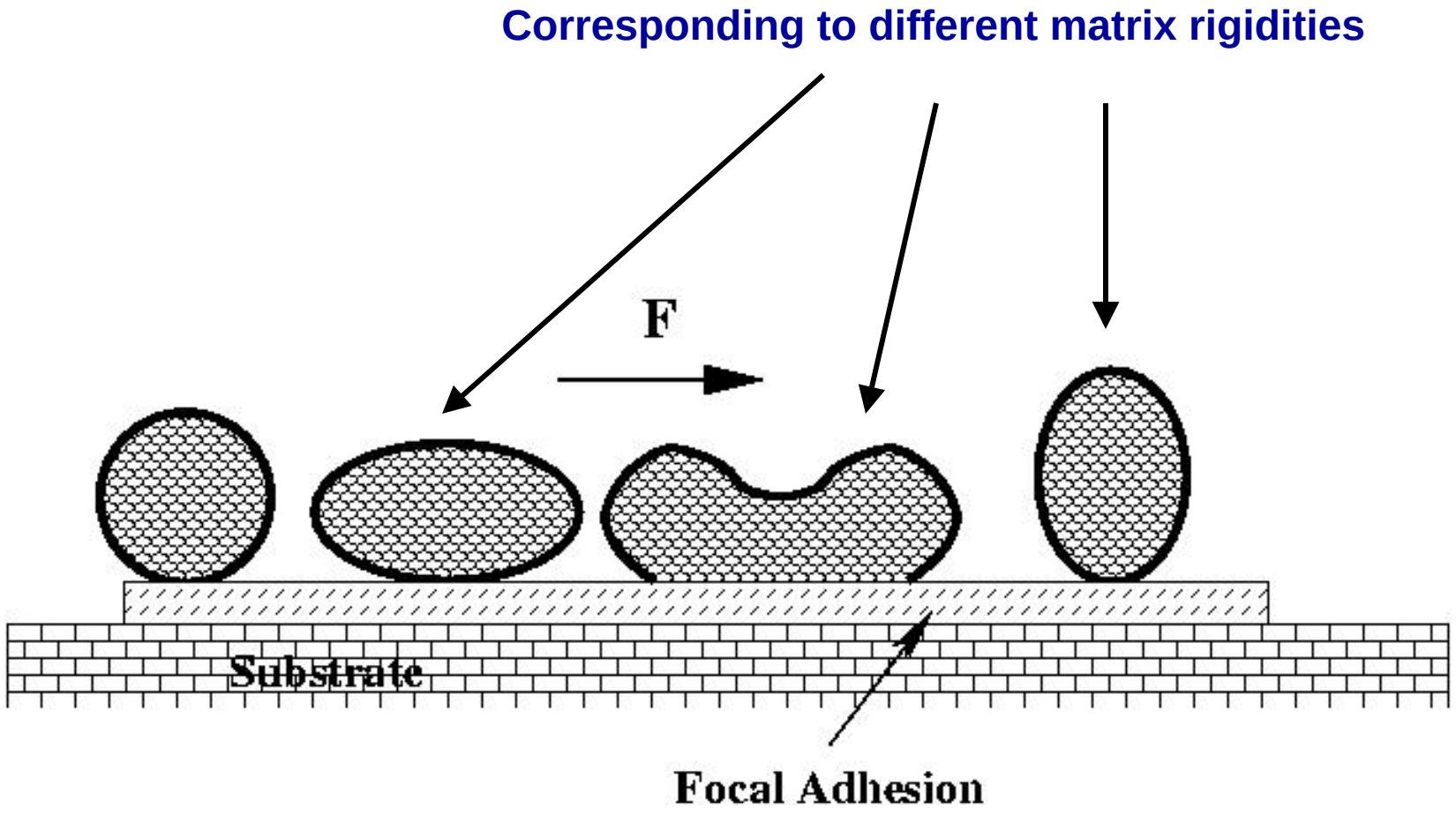


Ligand-receptor formation

Q.H. Cheng, P. Liu, H.J. Gao, Y.W. Zhang, JMPS 57, 2009

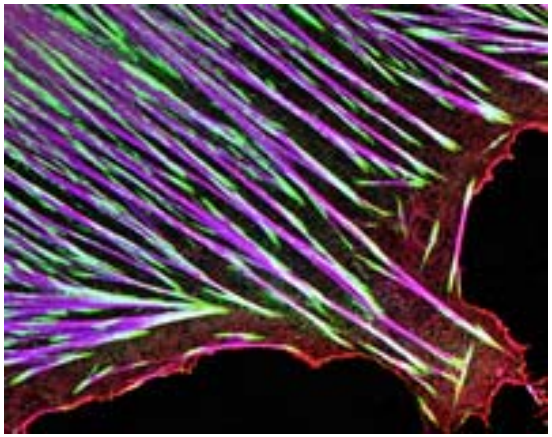
Roy and Qi, Biomech. Model Mechanobio, 2010

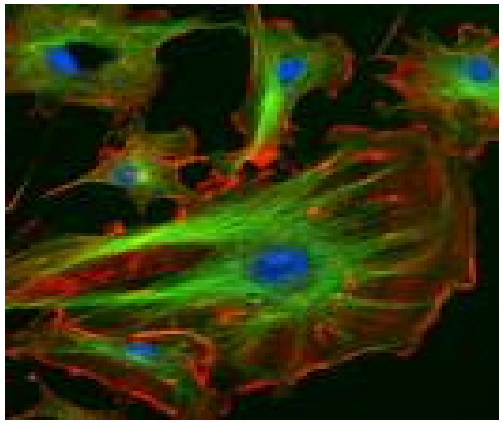
Hypothesis I: **Substrates with different stiffness may result different cell shapes and internal conformations**



Hypothesis II:

Focal adhesion and its self-assembly may be modeled as the soft elastic mode of the liquid crystal elastomer.





III. Computational Algorithms and Formulations

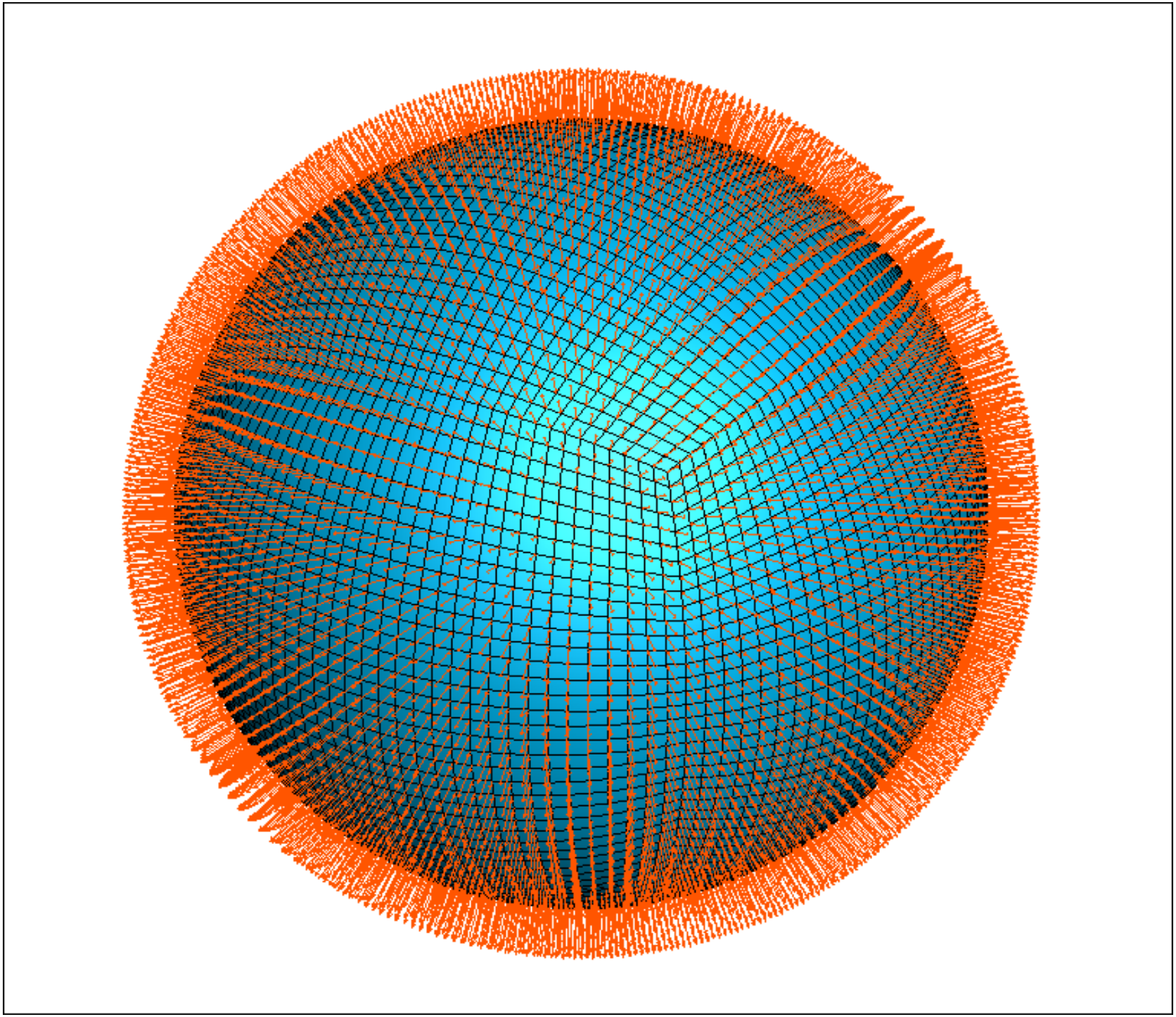
- Explicit Lagrangian Meshfree Formulation;
- Frank energy as penalty to stabilize the computation;

IV. Simulation Results

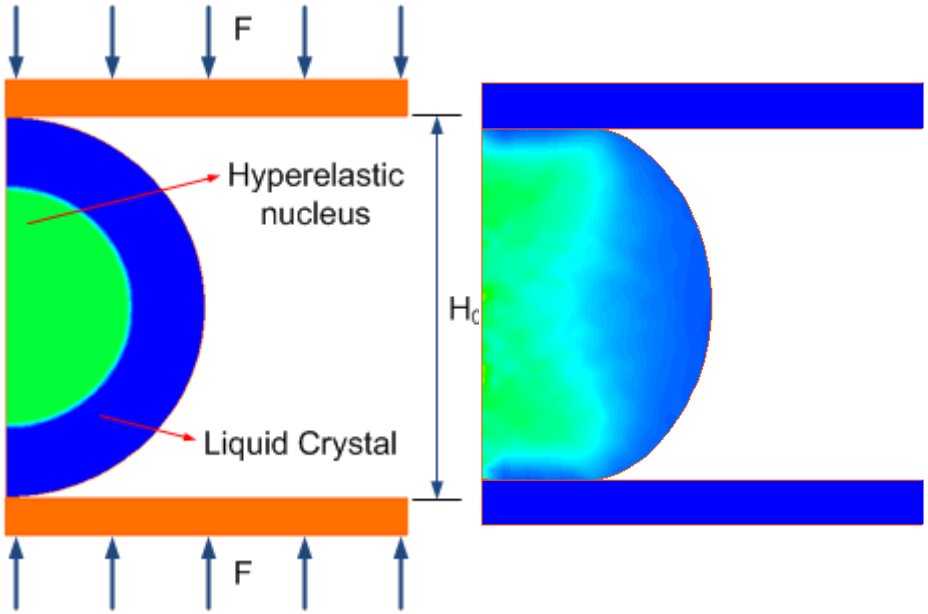
(A) Verification of Model;

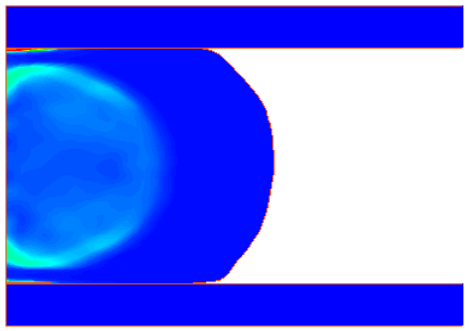
(B) Simulation of cell spreading;

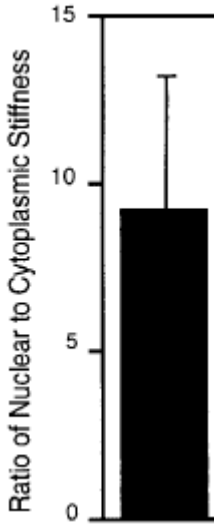
(C) Simulation based on different cell models;



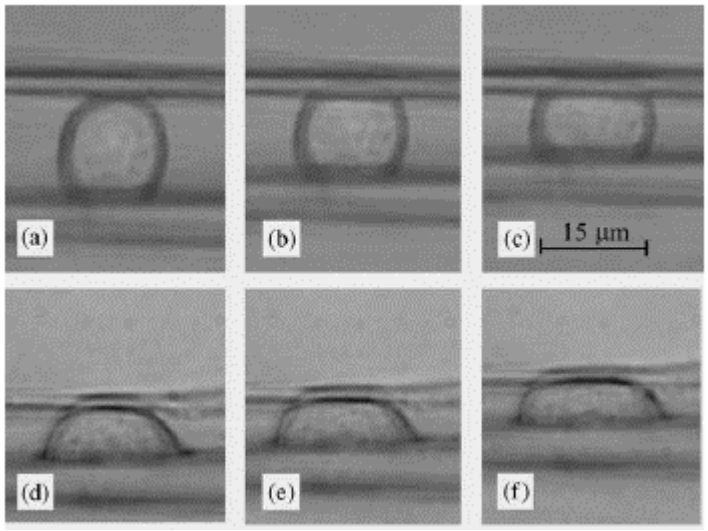
Model Verification



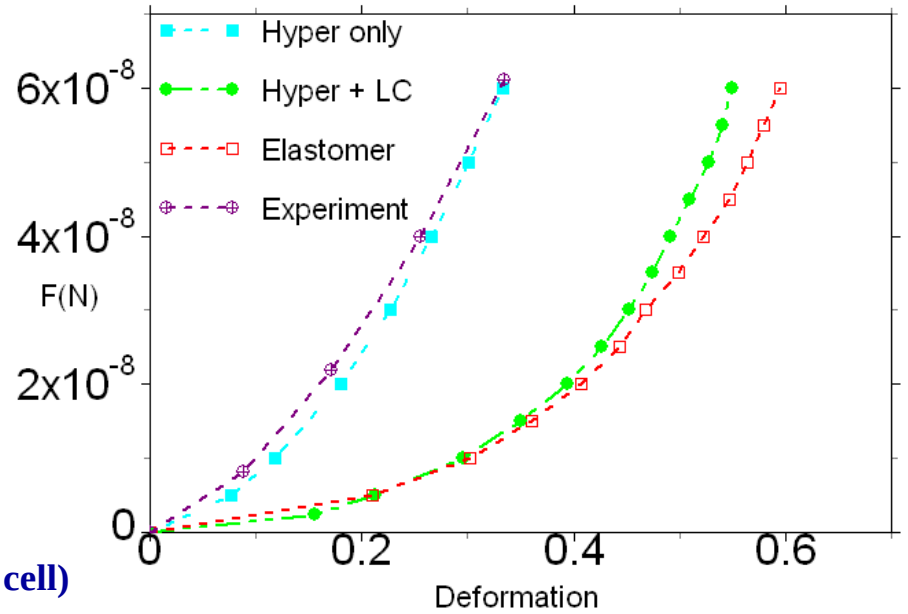


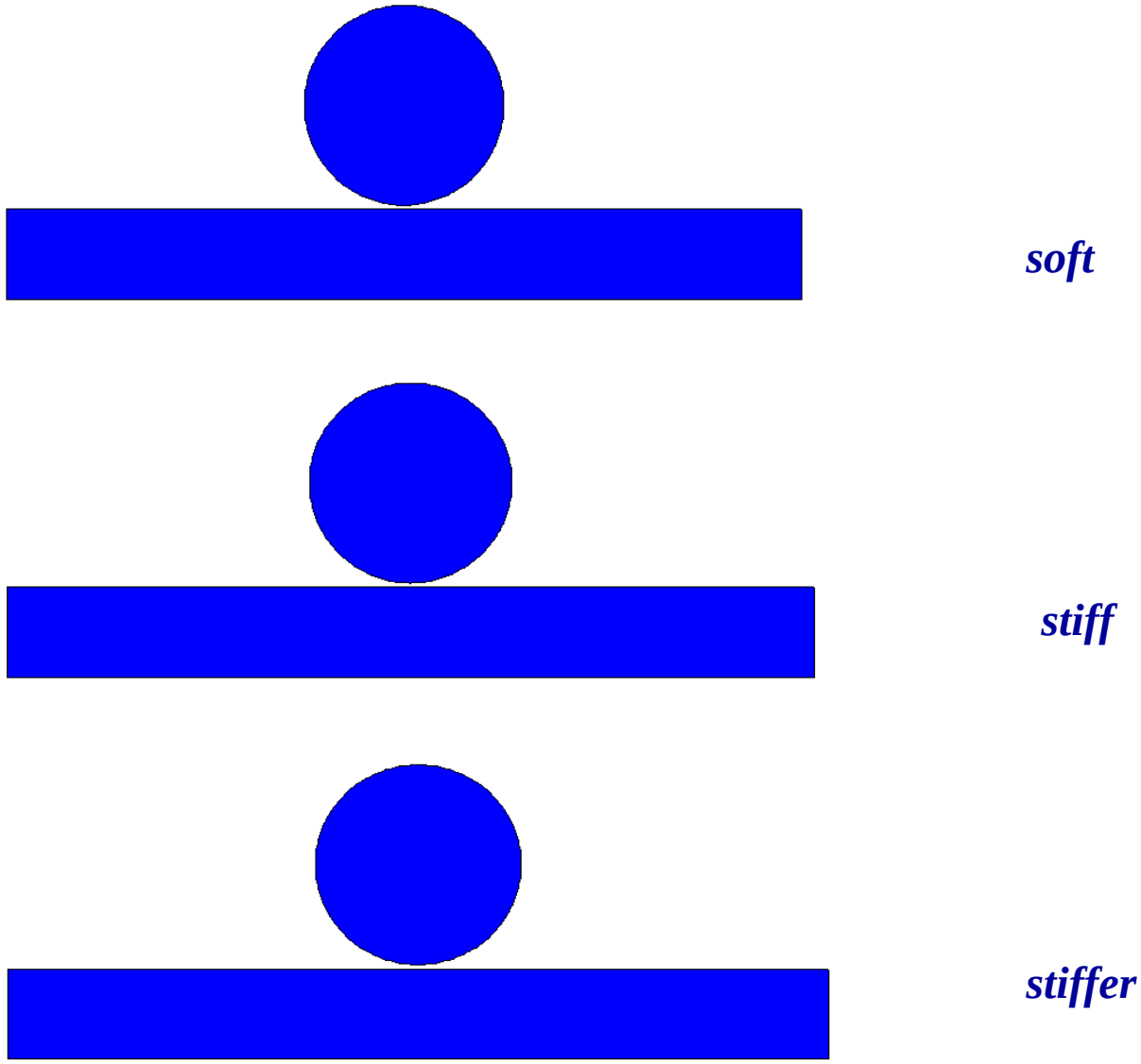


Maniotis et al. PNAS, 1997

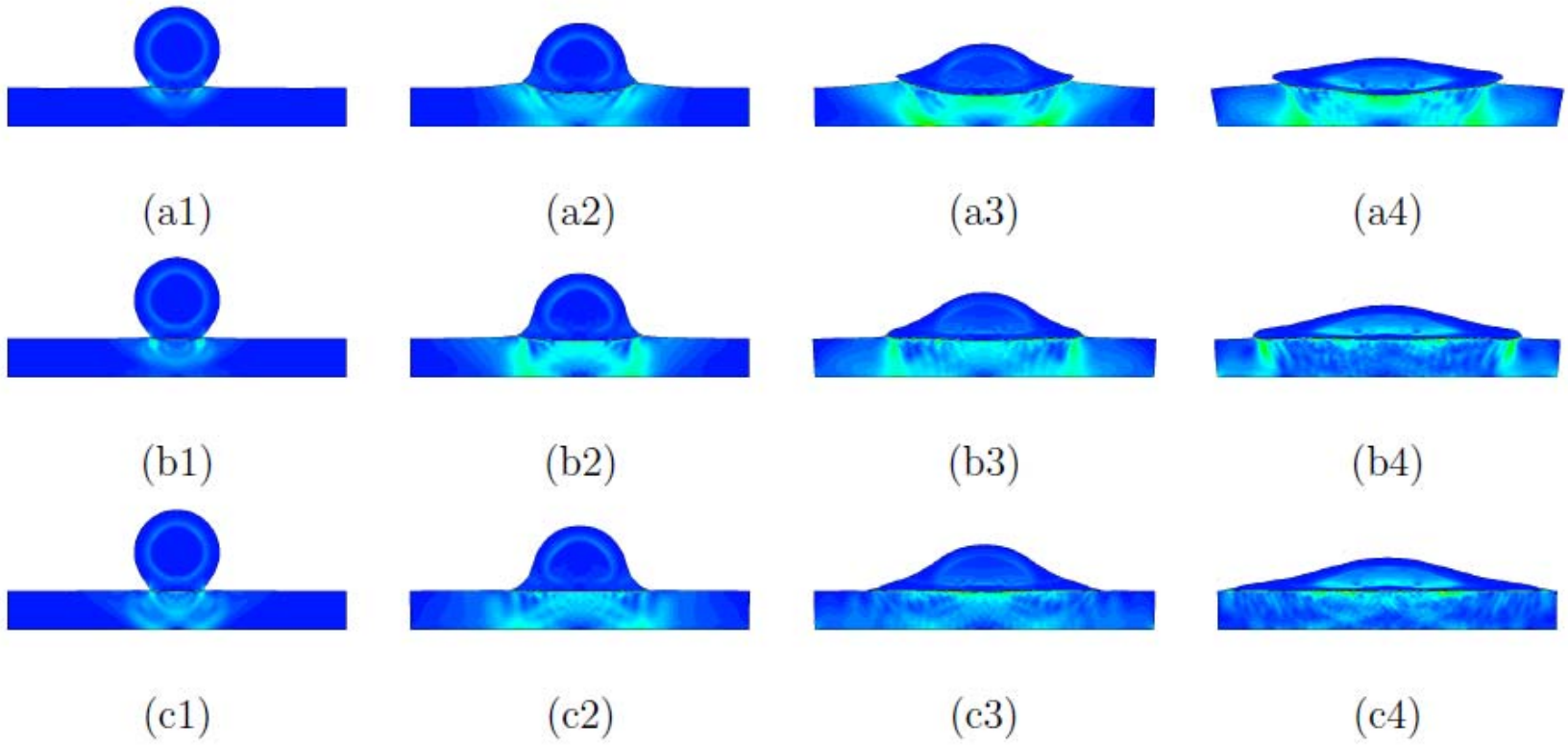


Caille et al. J. of Biomechanics, 2002 (endothelial cell)

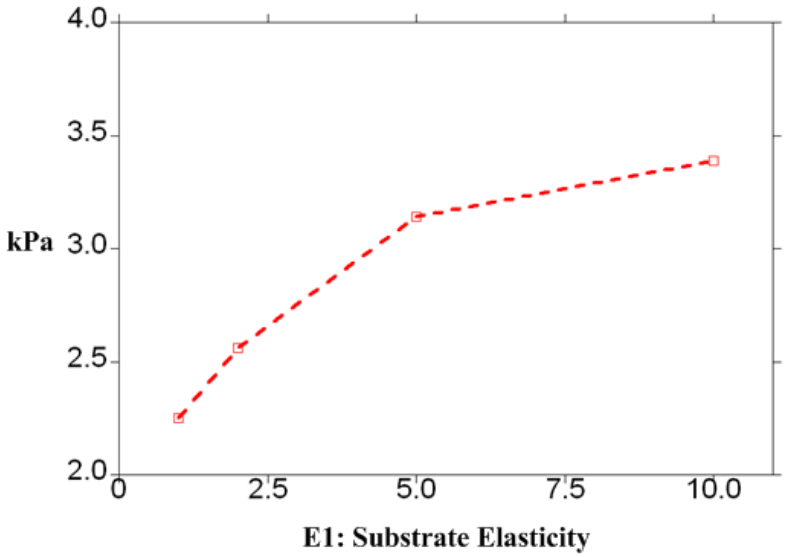


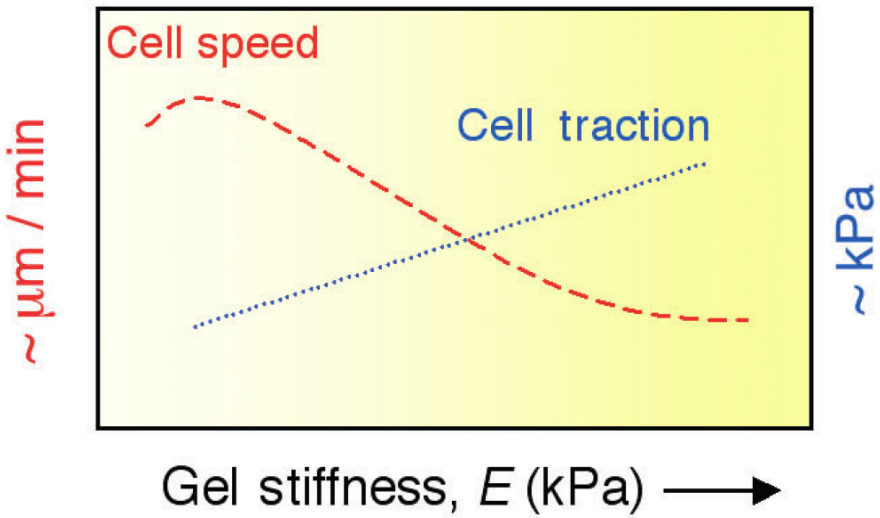


Cell response to stiffness of different substrates



Cell spreading over substrates with different stiffness: (a)Substrate-I, (b) Substrate-II, and (c) Substrate-III (*Zeng and Li, JMBBM, 2010*)

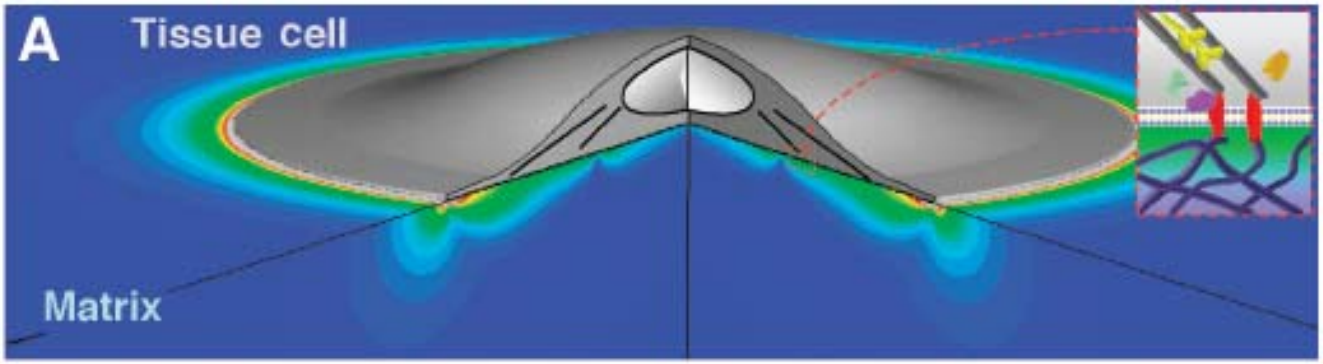




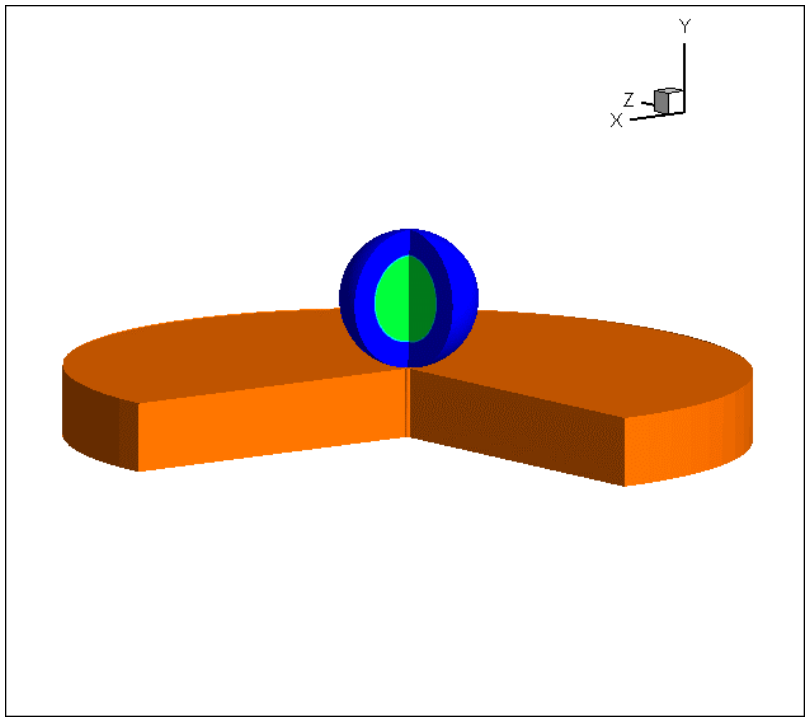
Traction force versus the stiffness of substrate

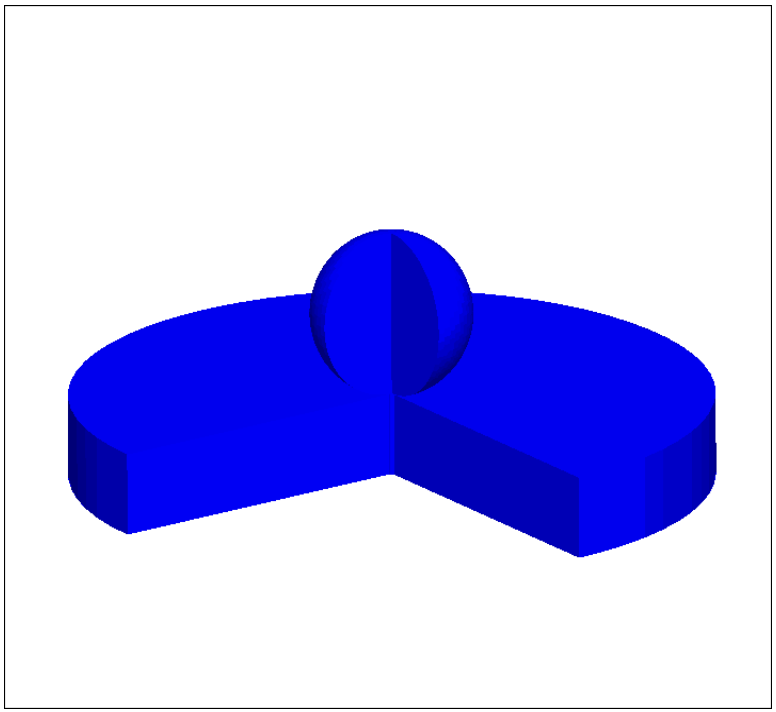
Experimental Measurements (Dennis E. Discher, et al Science [2005])

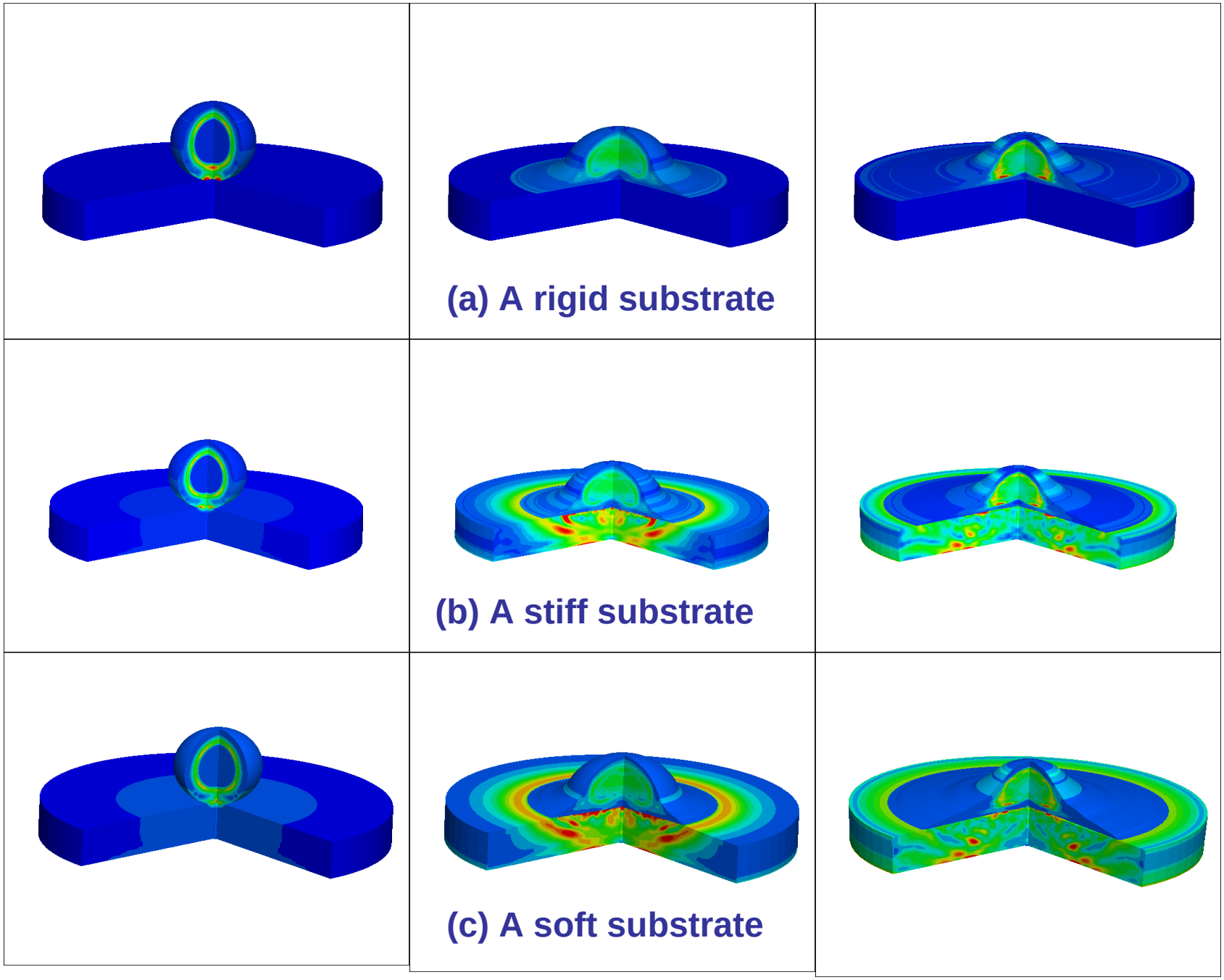
Cell Spreading Simulation

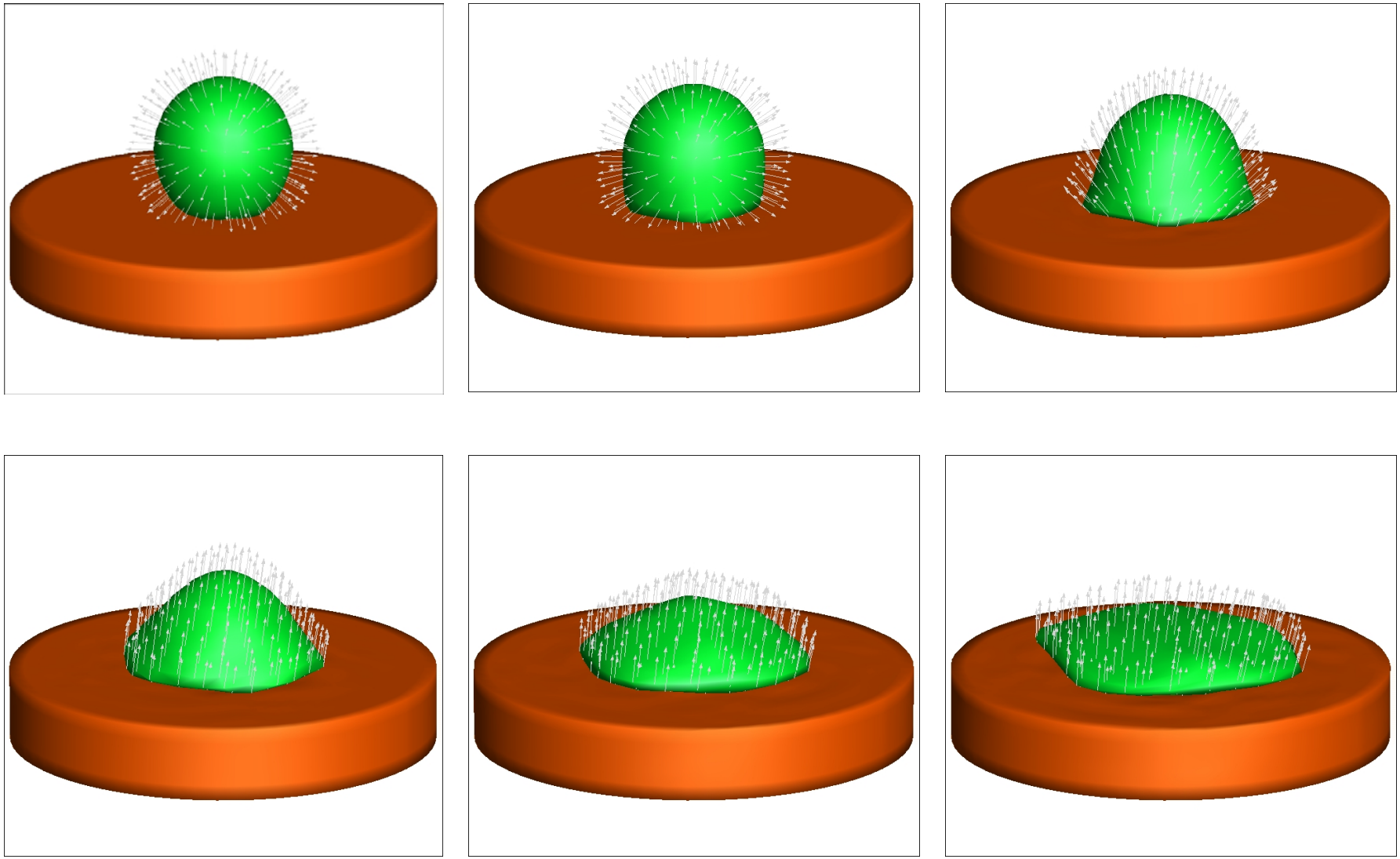


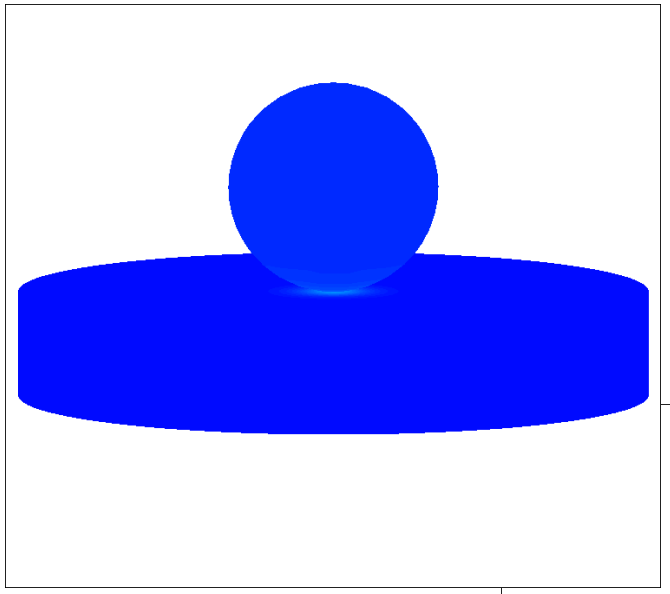
Dennis E. Discher et al. Science [2005]

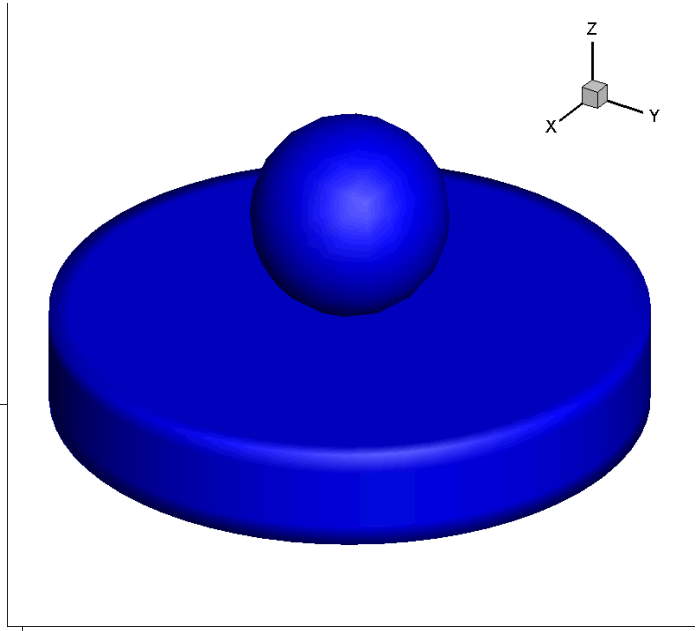





(a) A rigid substrate
(b) A stiff substrate
(c) A soft substrate



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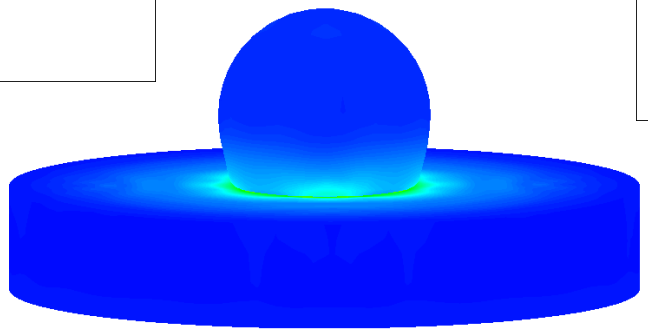

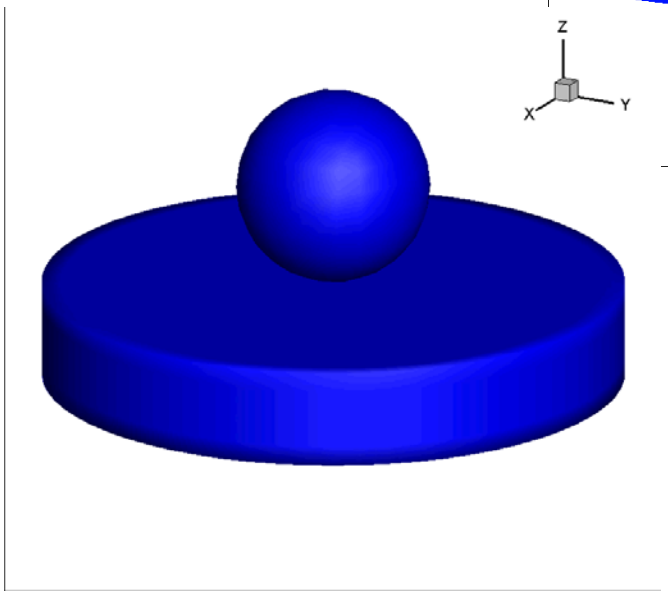
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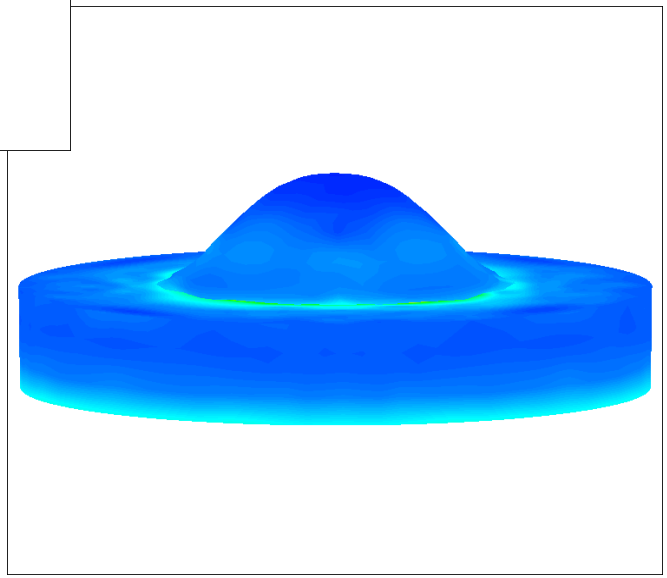
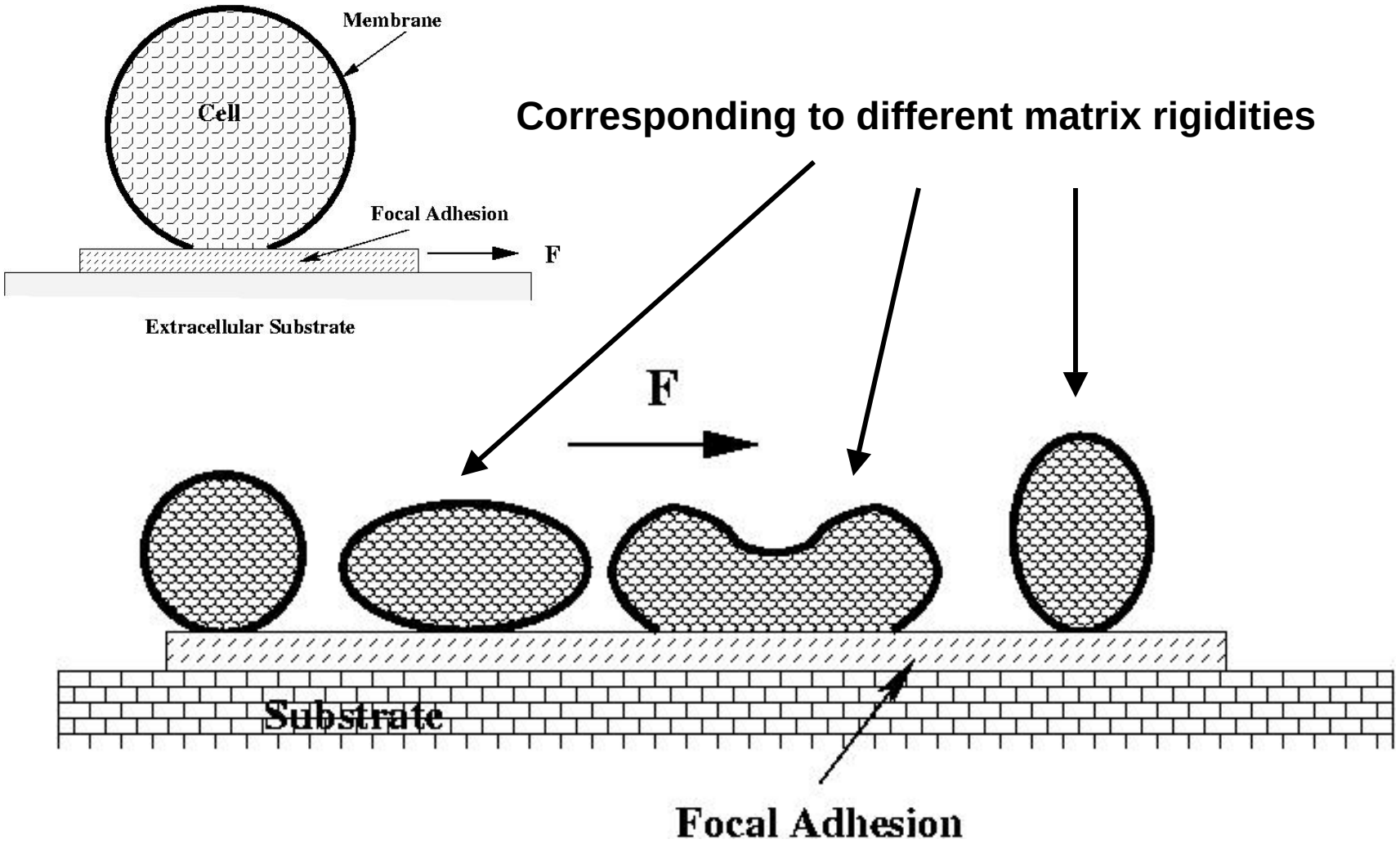
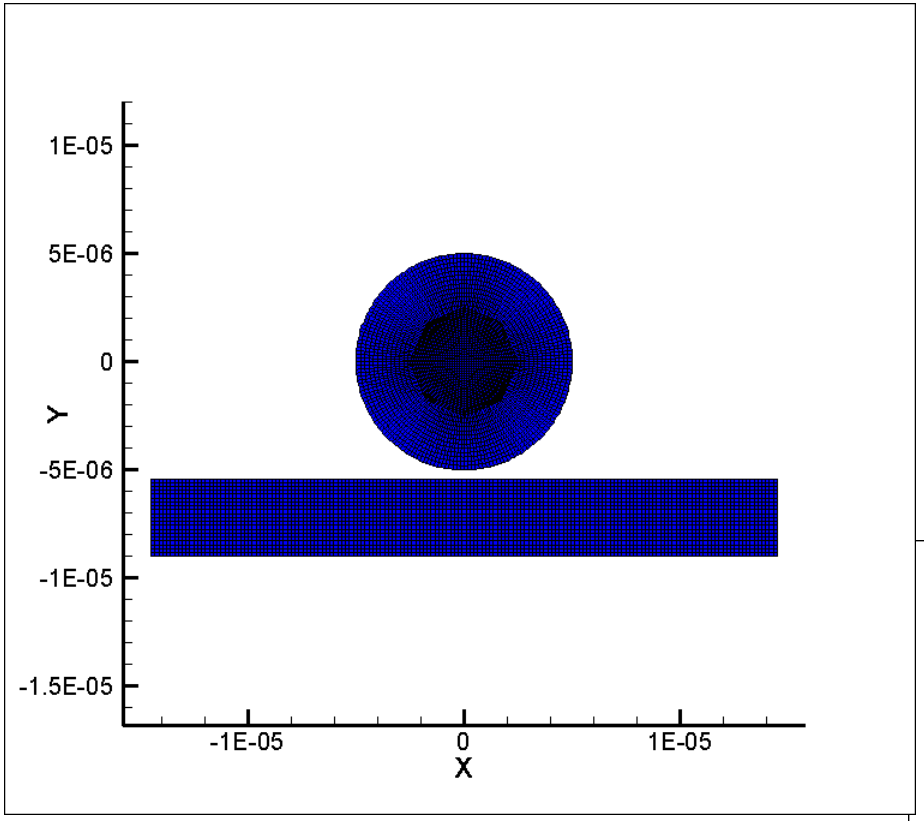


V. Some Interesting Findings

A. Mechanotransduction at distance;
B. Order parameter dependence on mechanical property of substrates;
C. Cell motility dependence on mechanical property of substrates;
D. Why is Liquid Crystal Elastomer Cell Model so interesting and exciting ?

Hypothesis I. Substrates with different stiffness will result different cell shapes and internal conformations

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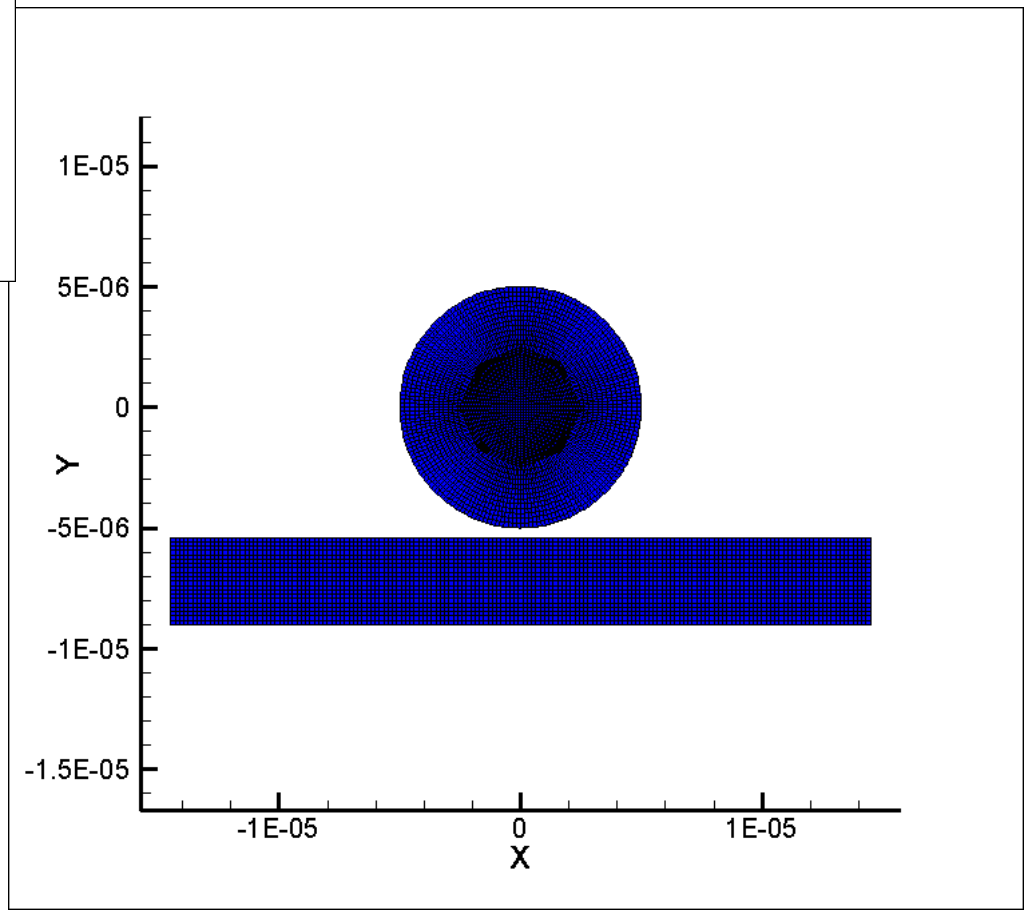
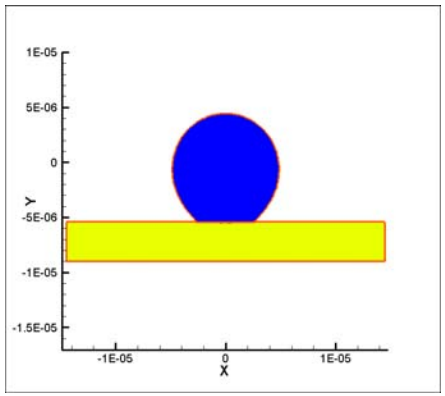
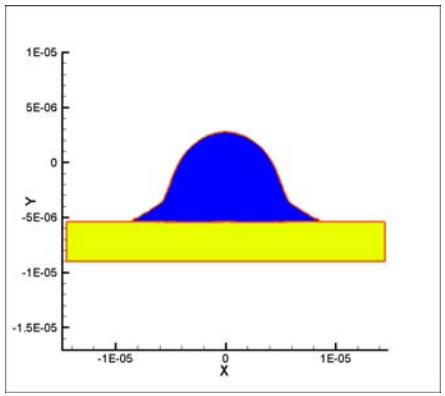
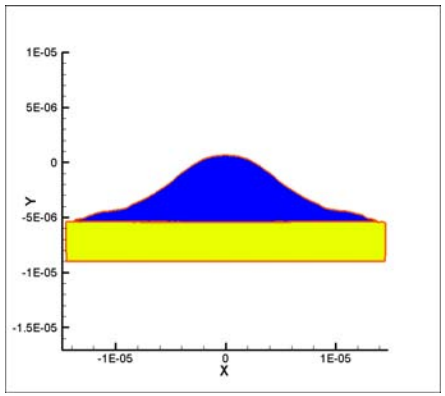
5E-06
0
-5E-06
-1E-05
-1.5E-05
Y
-1E-05
0
1E-05
X


1E-05
5E-06
0
-5E-06
-1E-05
-1.5E-05
Y
-1E-05
0
1E-05
X

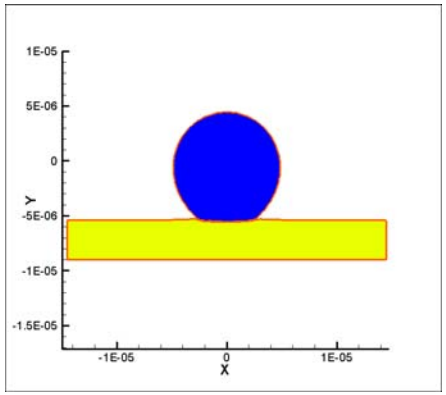
Cell spreading in three different substrates:

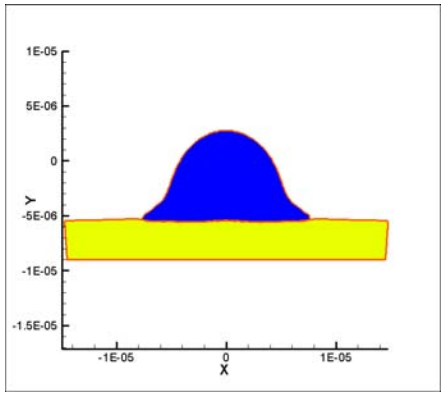


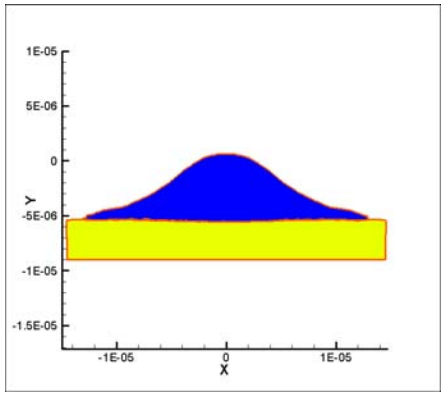




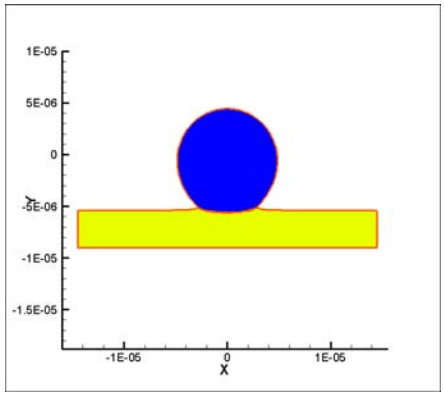
Stiff

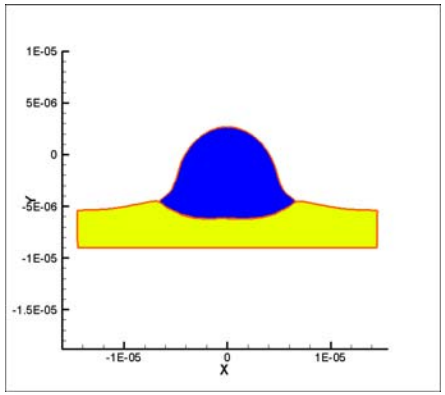


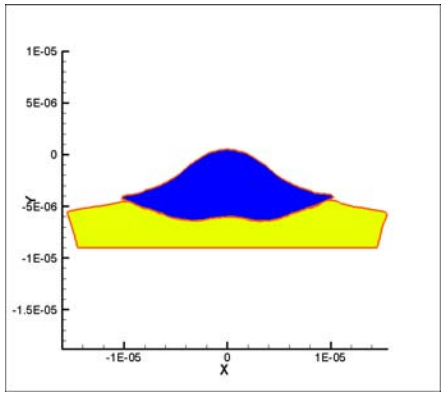




Soft

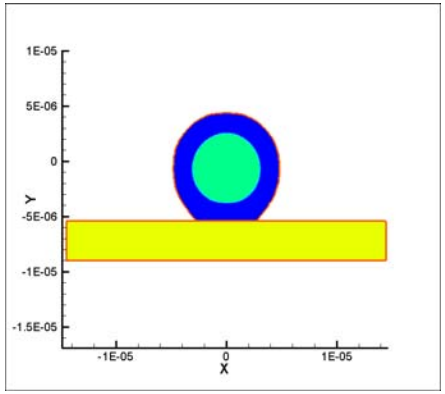


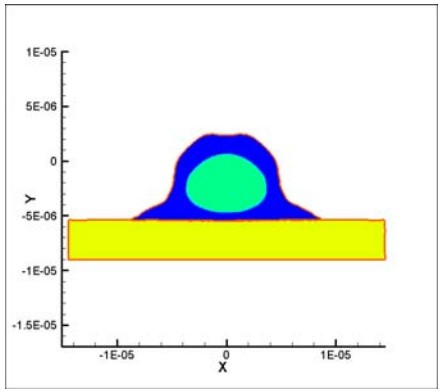


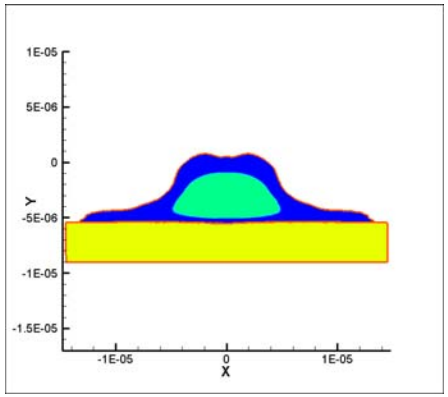


Softer

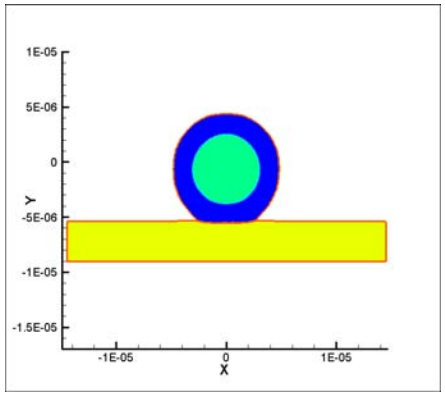
Cell spreading in three different substrates:

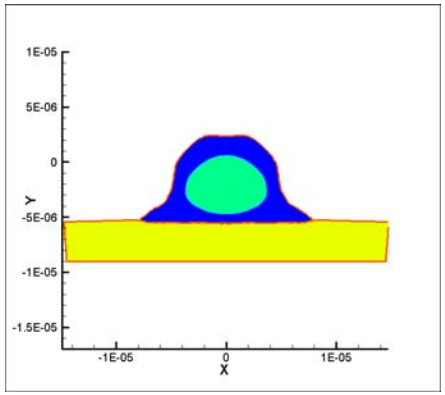


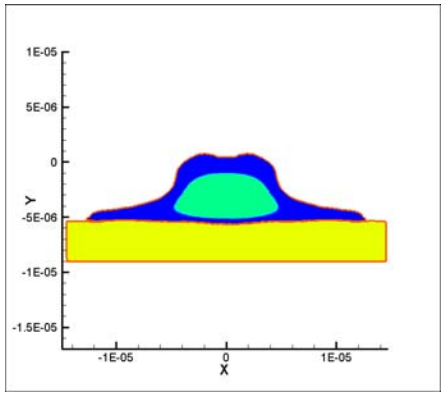




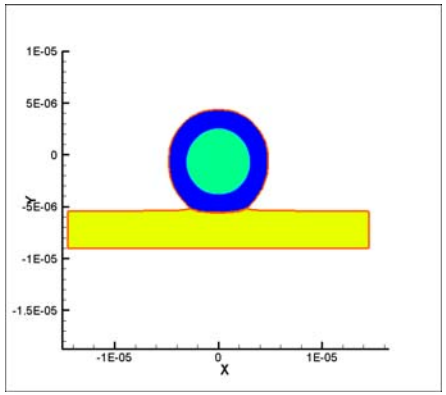
Rigid

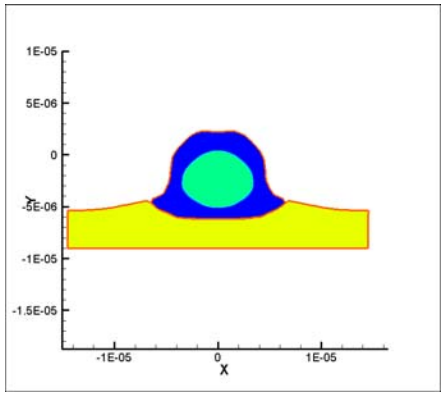


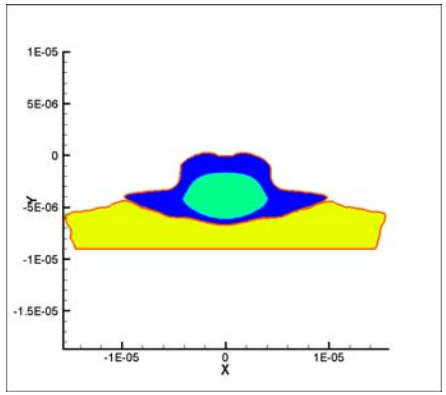




Soft

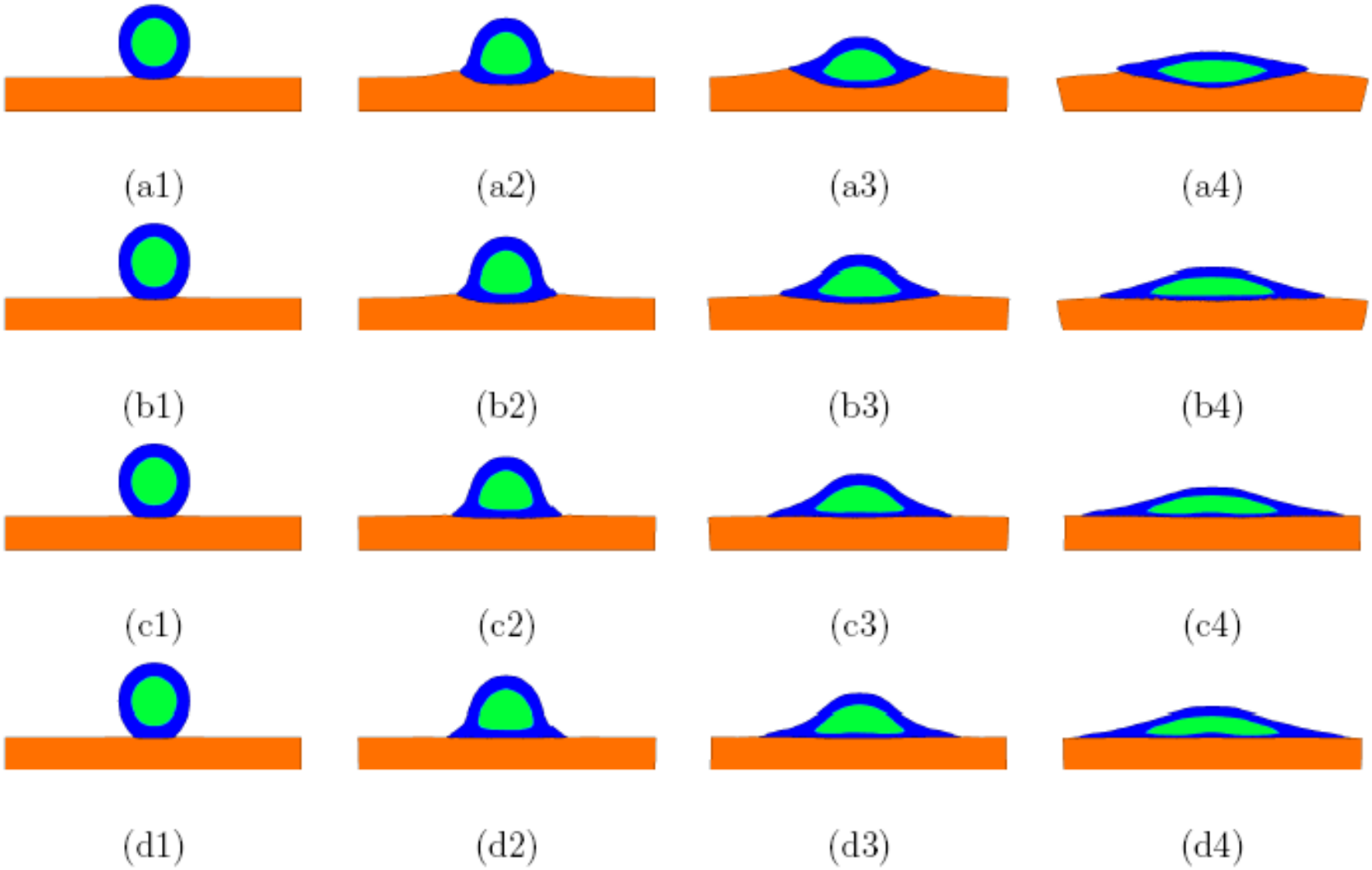


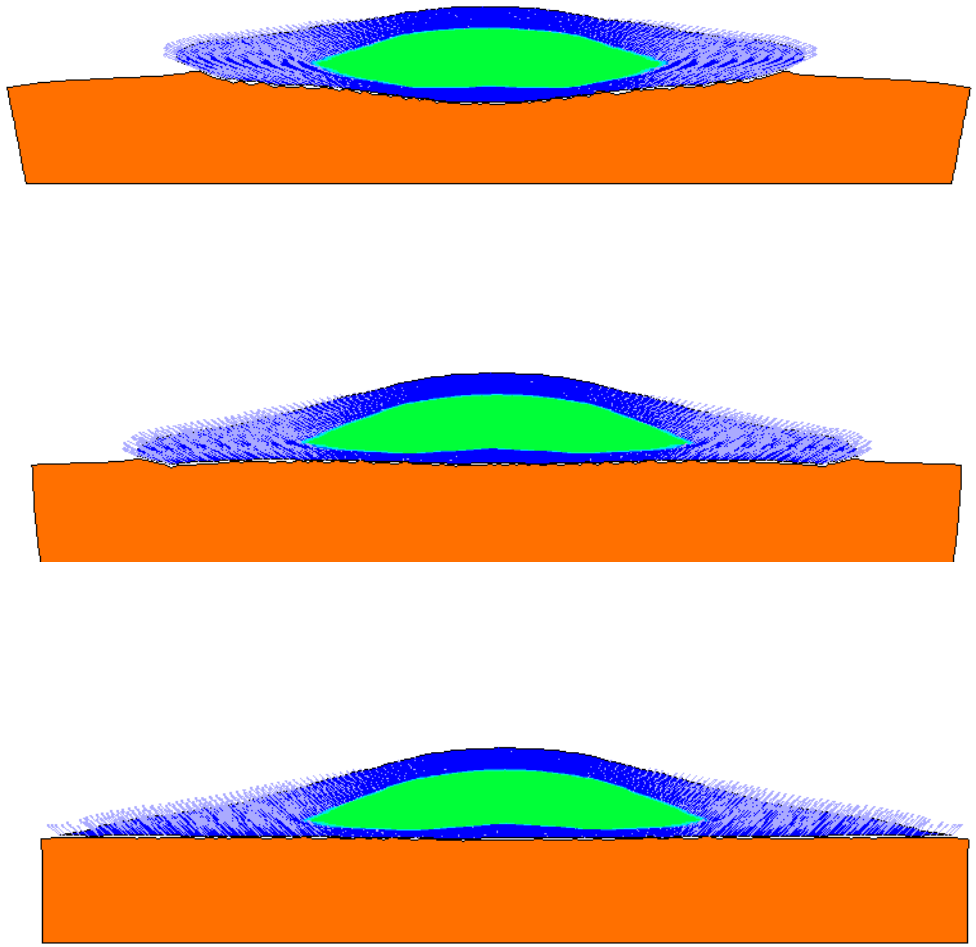




Softer

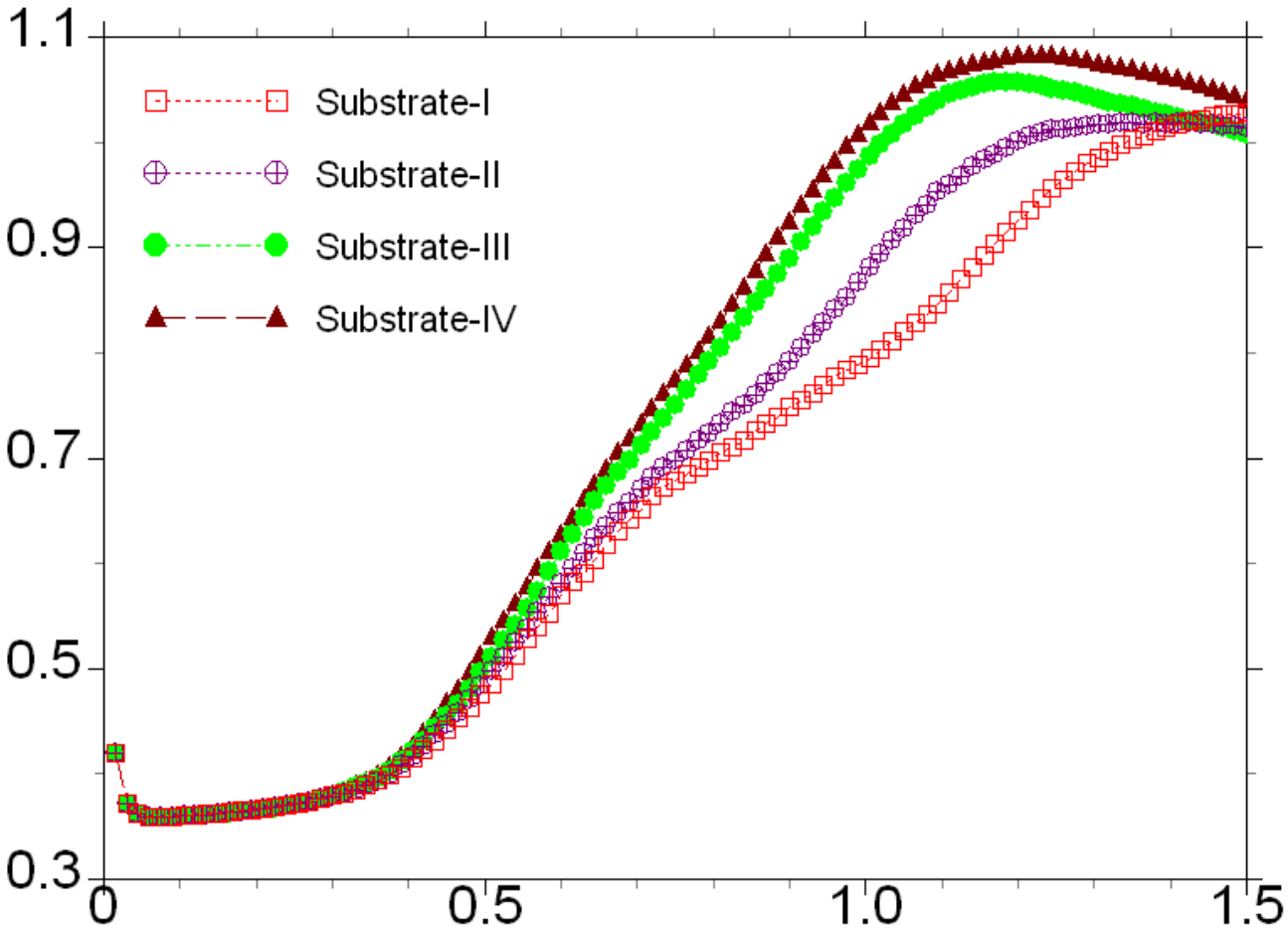
Cell Response to Stiffness of Different Substrates (*Zeng and Li, JMBBM, 2010*)





Mechanotransduction at distance

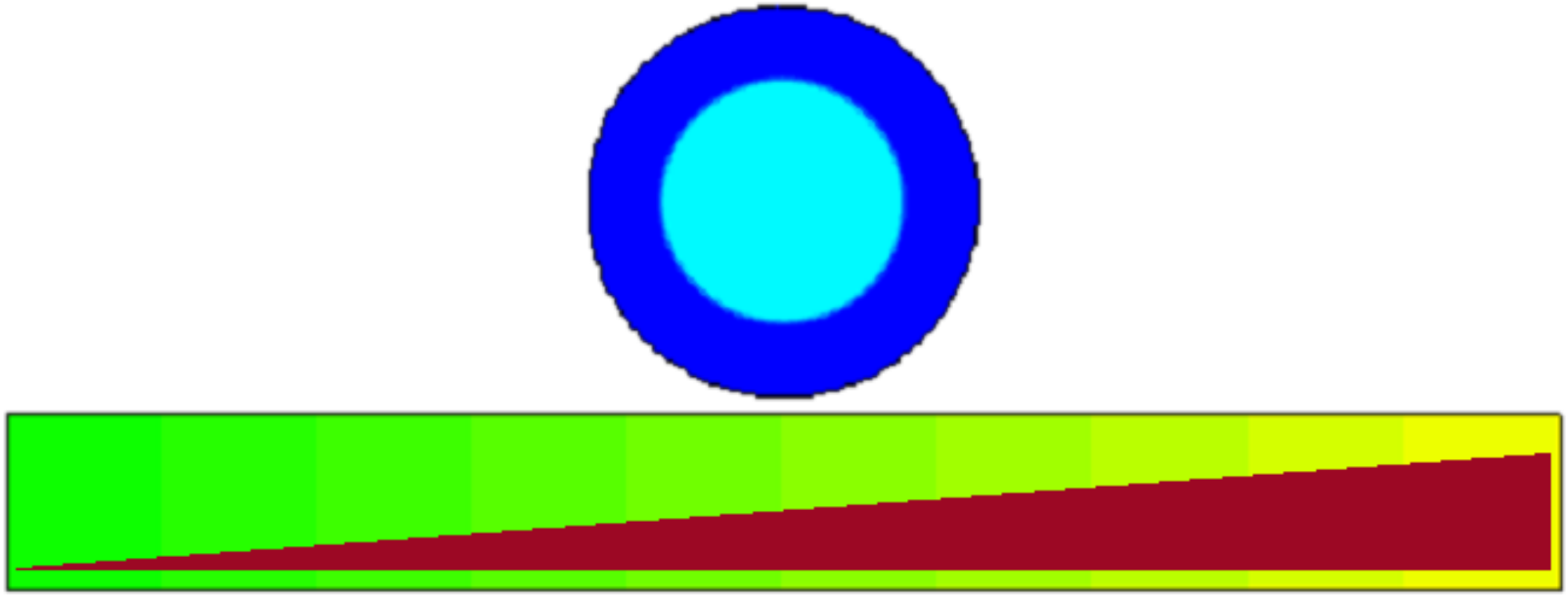
B. Order parameter dependence on substrate stiffness



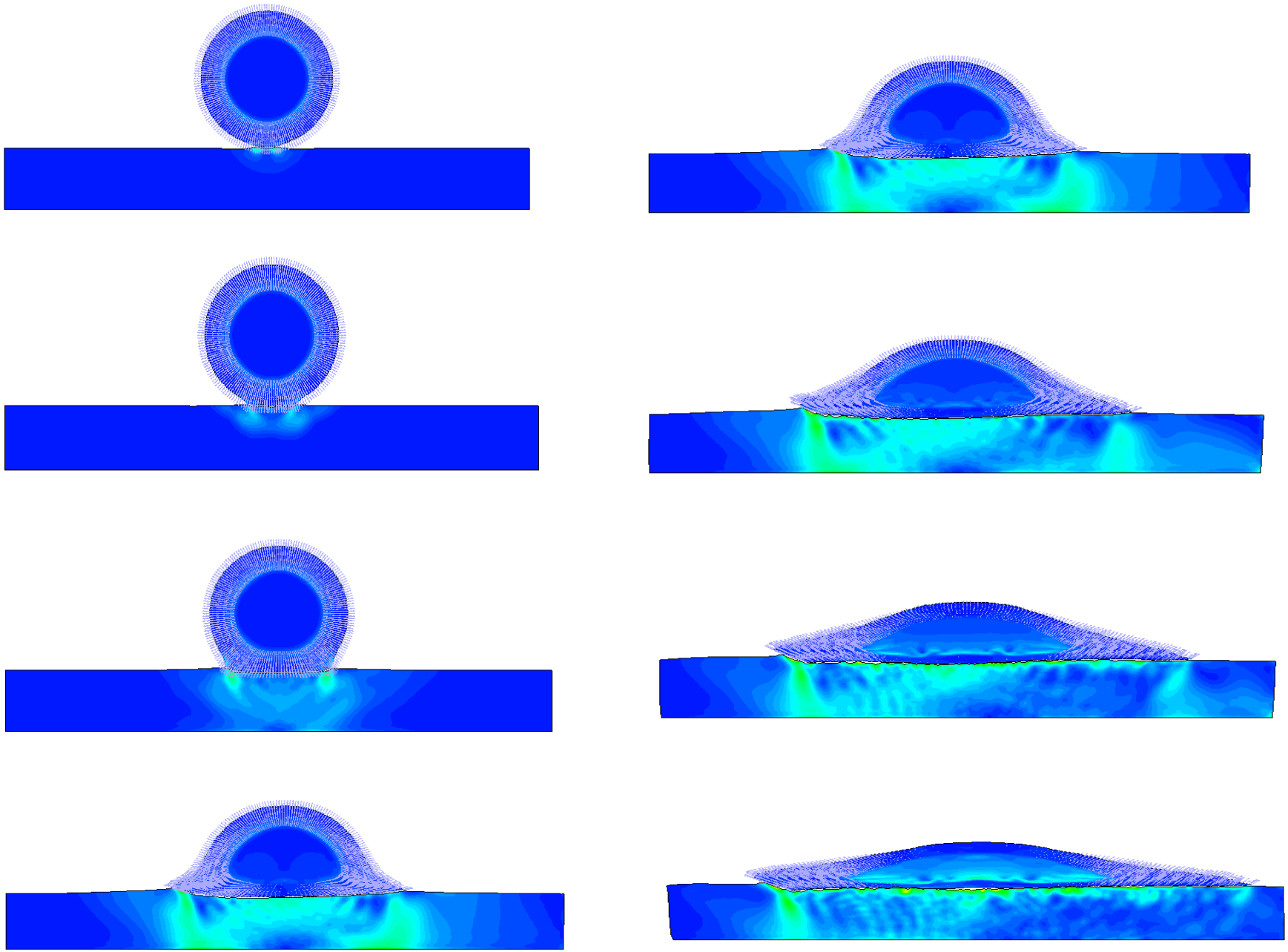
Effective order parameter, $\mathbf{Q} = \frac{2}{3}\mathbf{h} \otimes \mathbf{h} - \frac{1}{3}\mathbf{I}$, and $Q = \sqrt{\mathbf{Q} : \mathbf{Q}}$ vs. time.

This implies the dependence of molecular conformation on elasticity of the substrate !

C. Cell motility dependence on mechanical property of substrates;



Direction of the Substrate Stiffness Increase



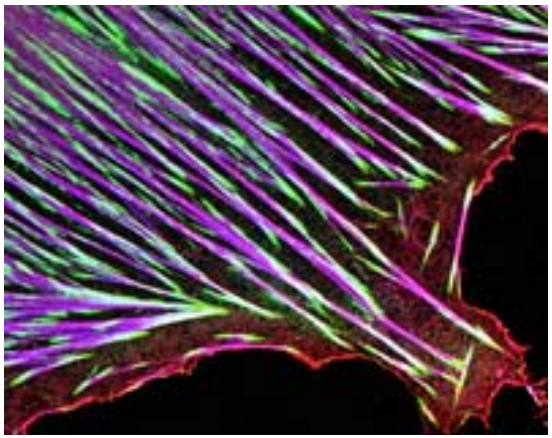
D. Why is Liquid Crystal Elastomer Cell Model so interesting and exciting ?

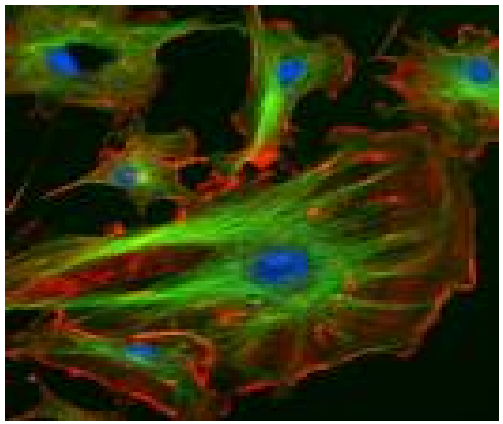
It is because that it exhibits a so-called soft elastic mode ----
(solid-liquid phase `transformation')
that is: LCE cannot sustain shear stress under certain deformation
(Golubovic & Lubensky [1989], Kundler and Finkelmann [1995],
And Warner and Terentjev [2006])

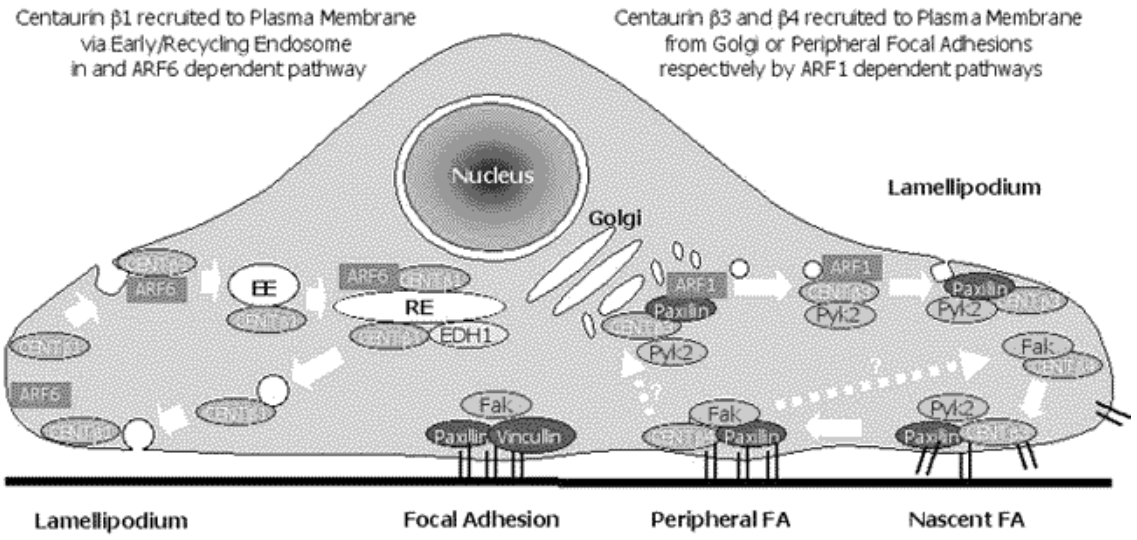
Hypothesis:
The elastic soft mode transition may provide an model to explain the mystery of focal adhesion !

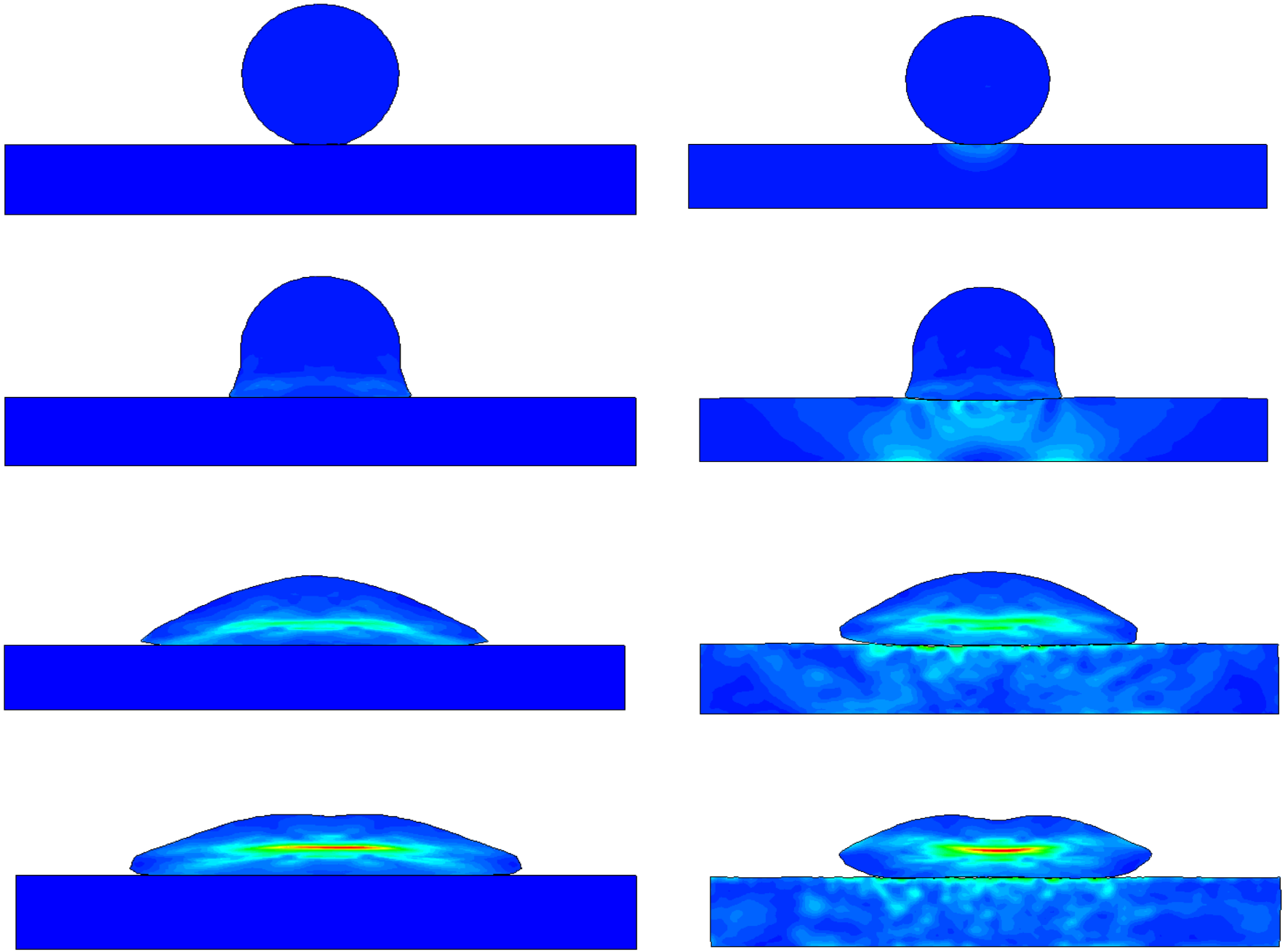
Hypothesis II:

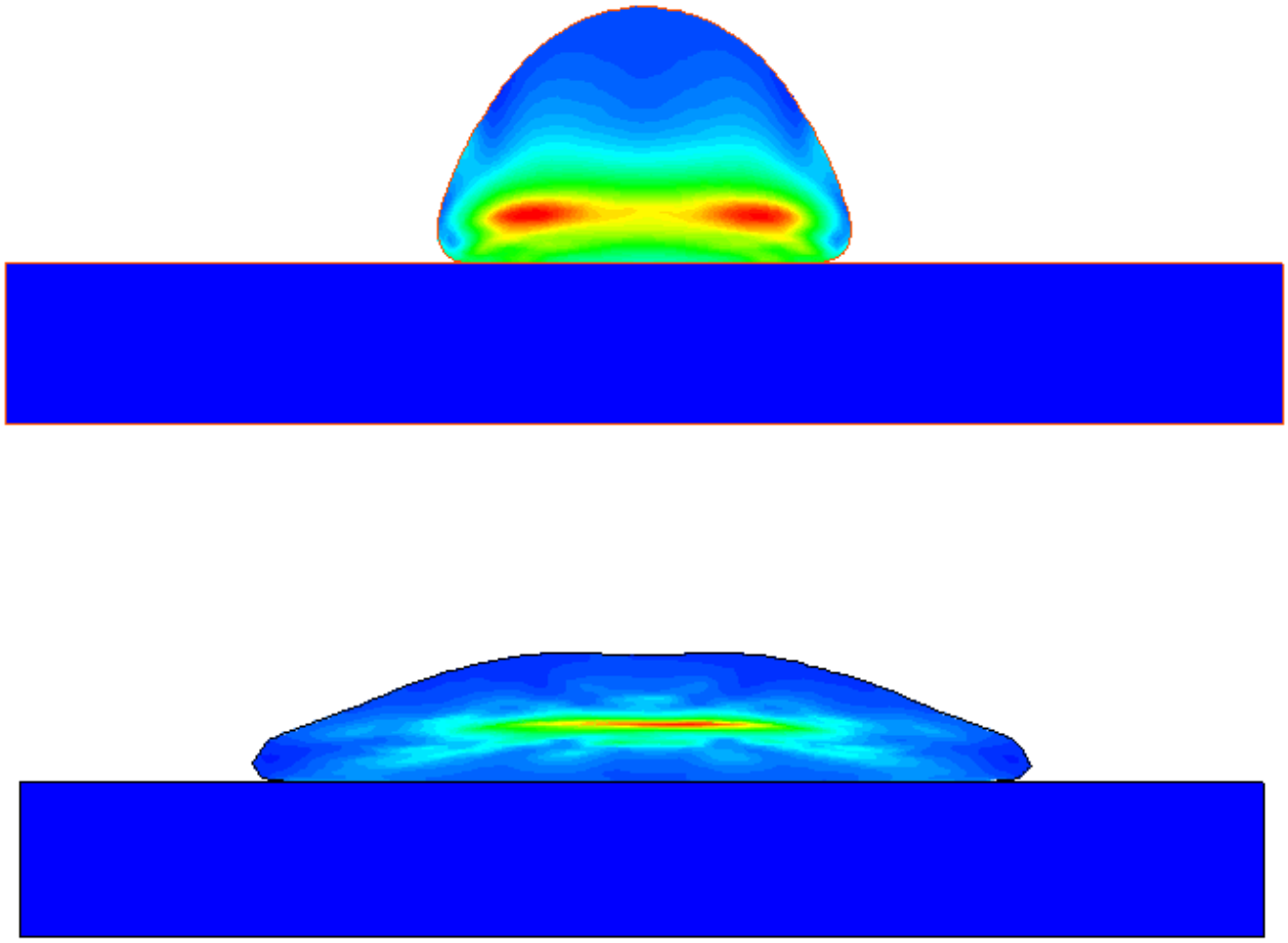
Focal adhesion and its self-assembly may be modeled as the soft elastic mode of the liquid crystal elastomer.



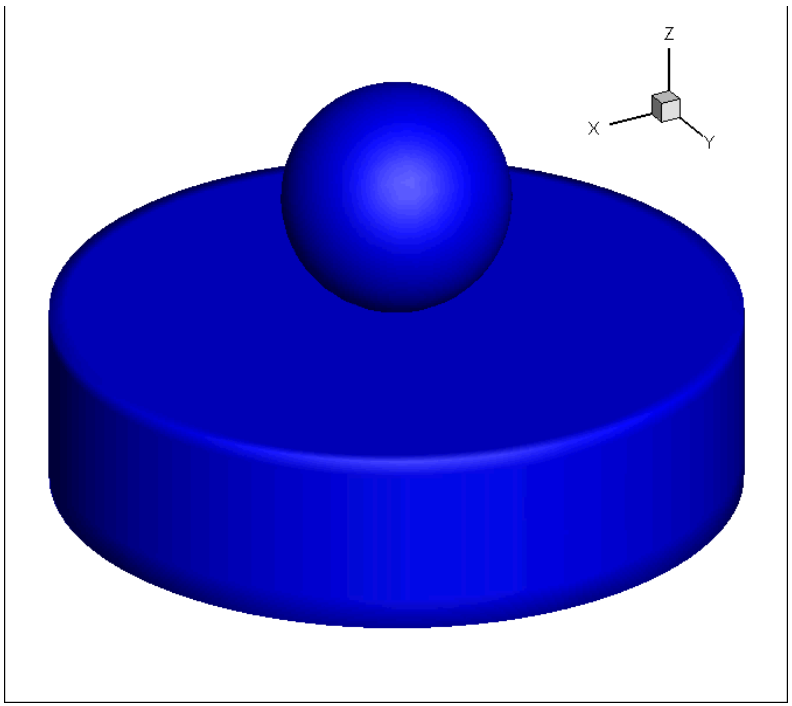








Hyperelastic cell vs. Liquid crystal elastomer cell


Z
X
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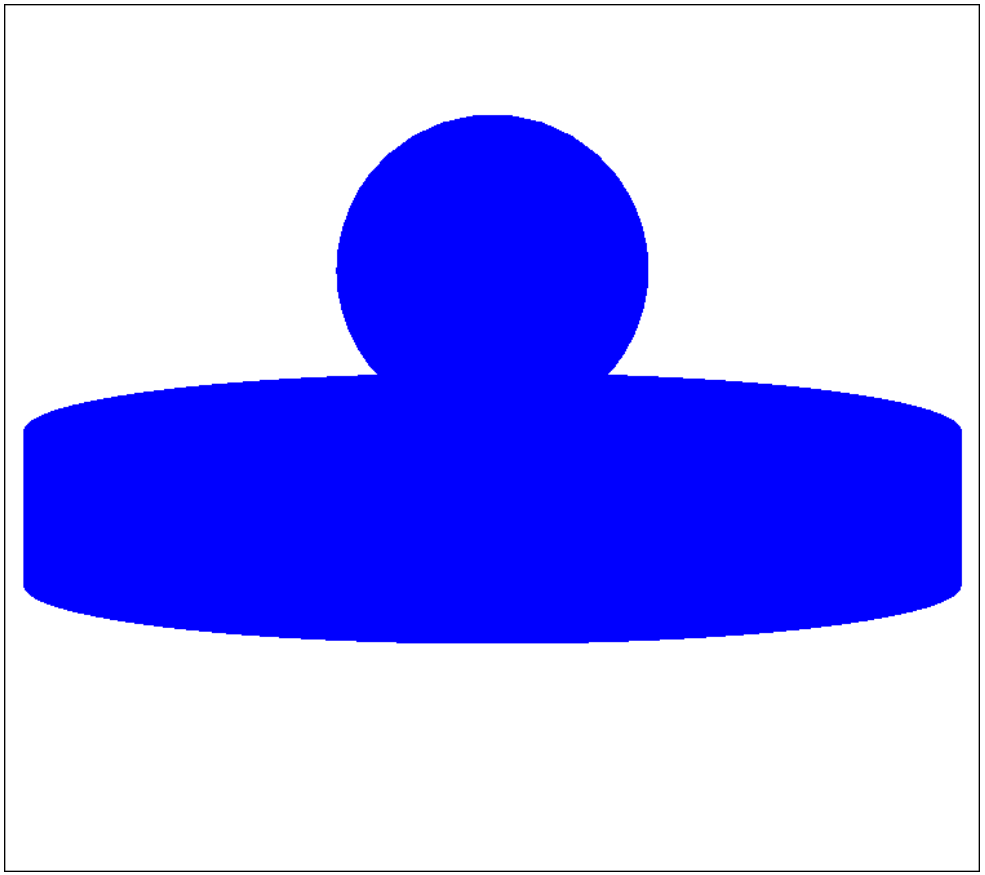

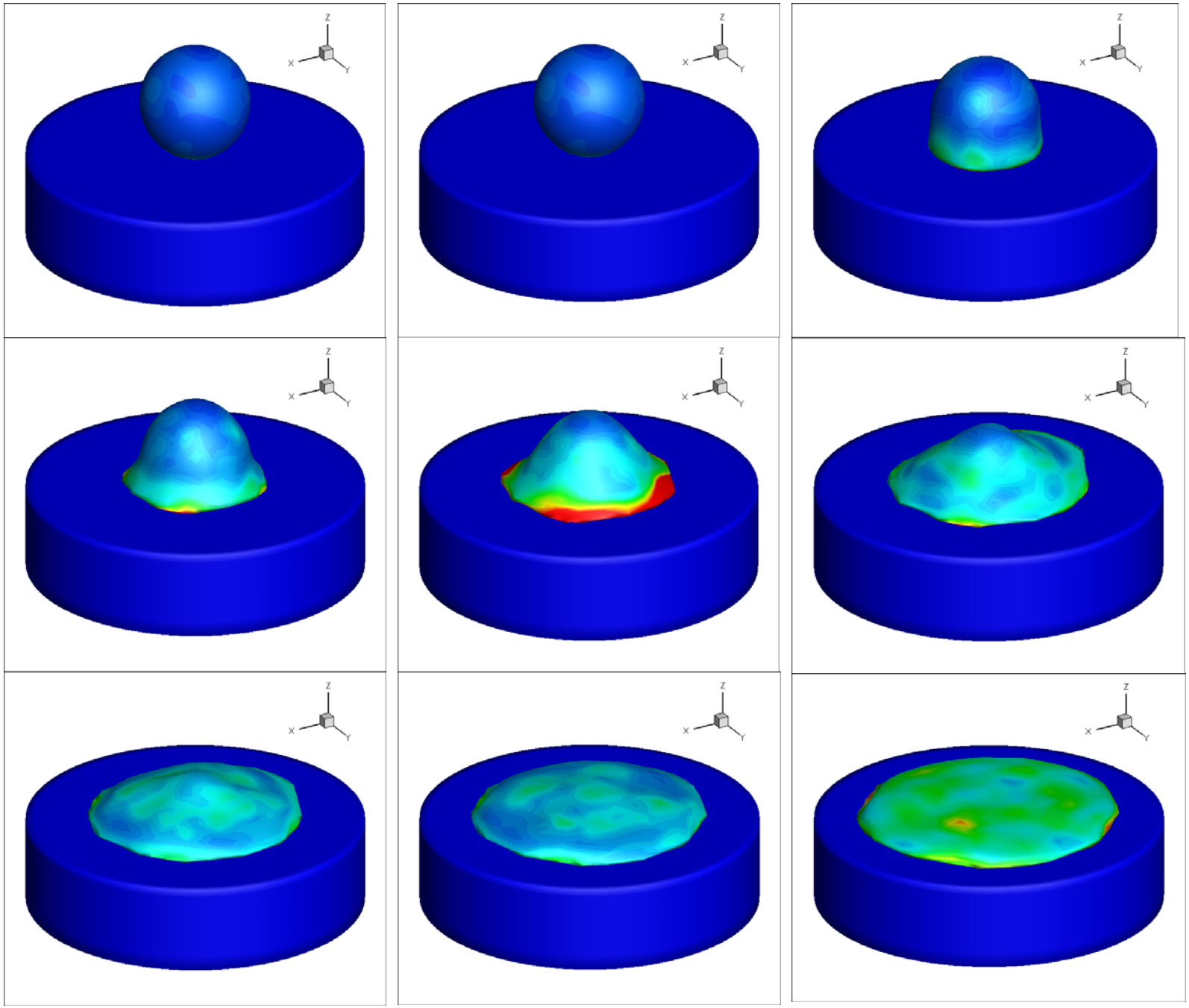

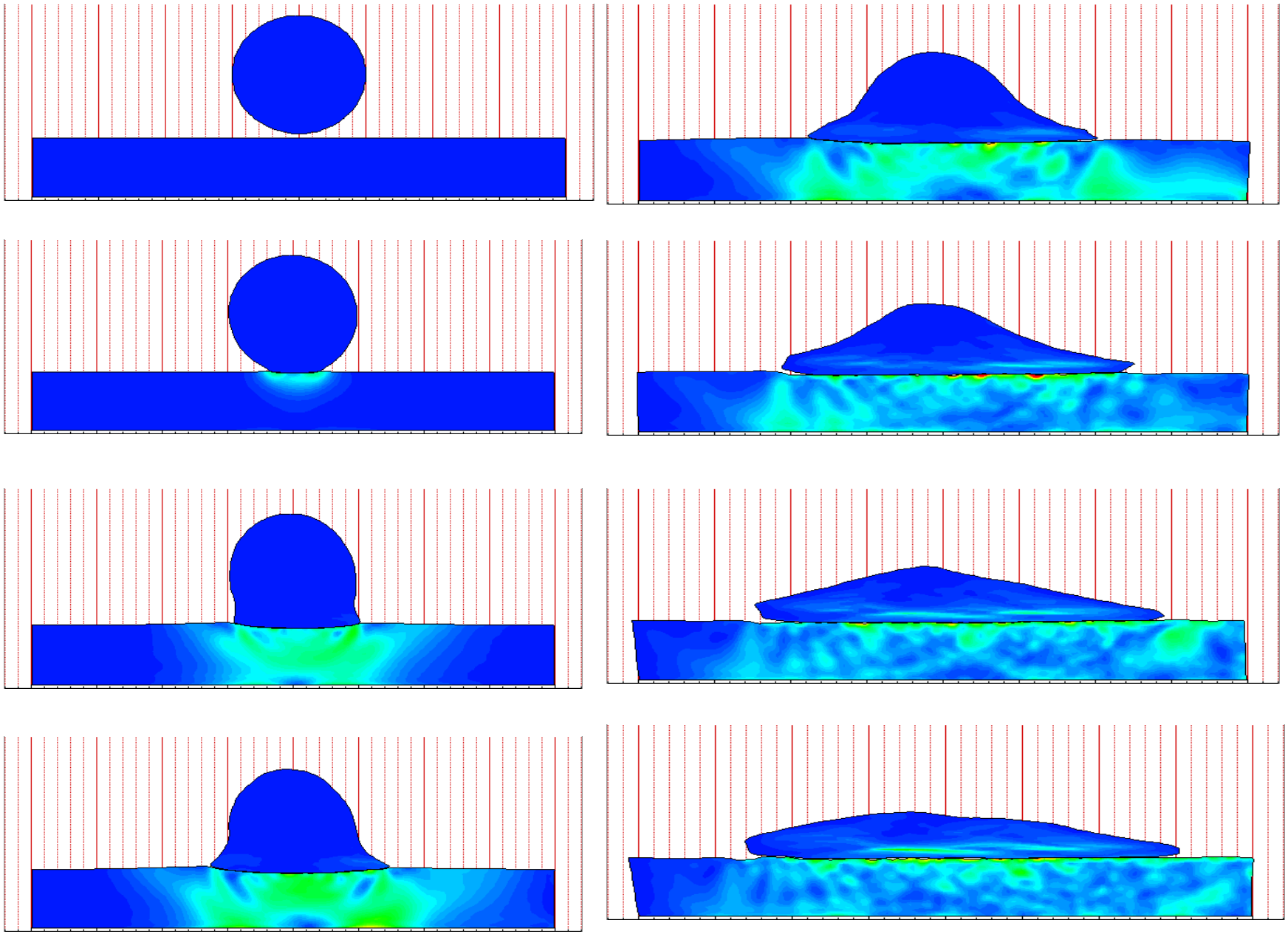

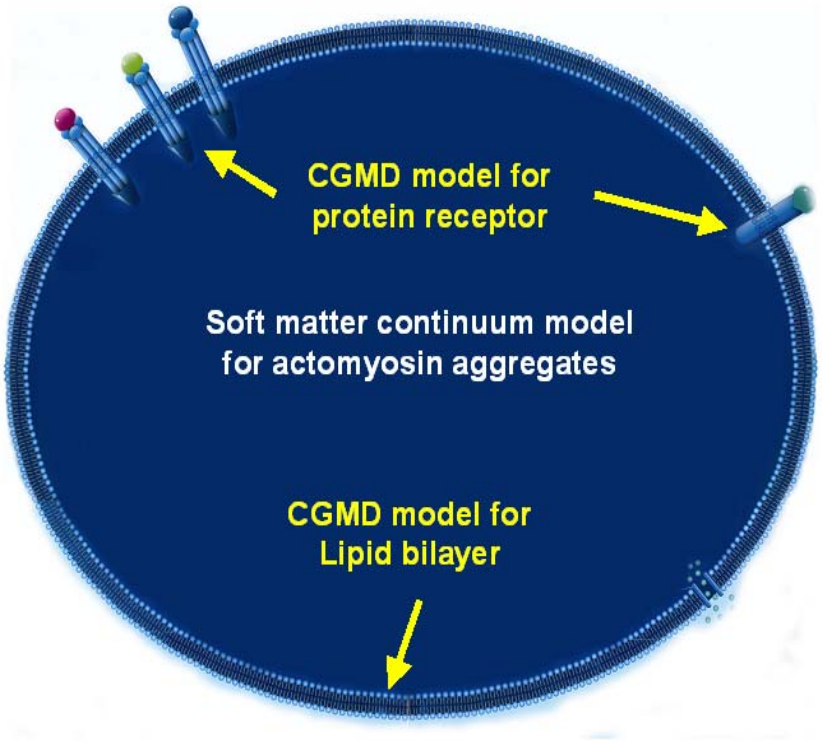

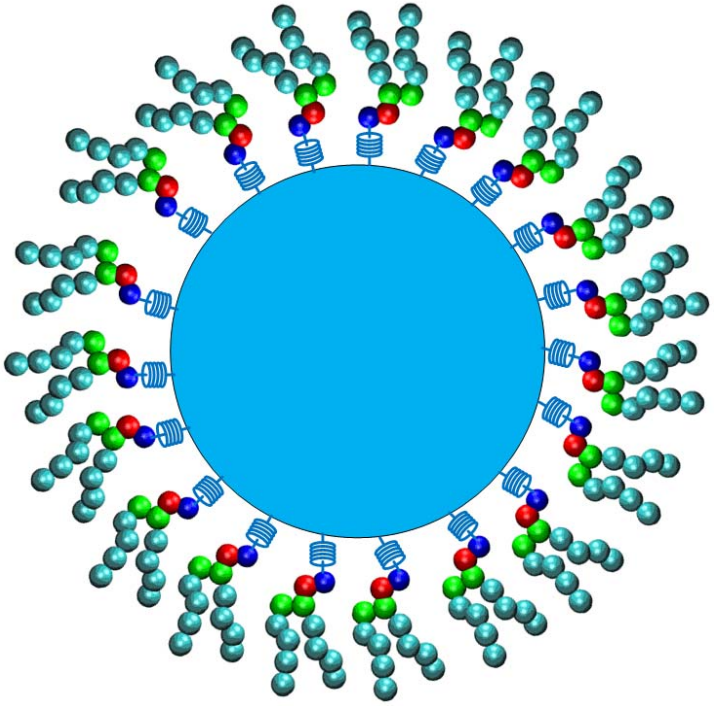

Work in Progress

VI. Conclusions

Our Simulations have shown that the stem cell has sensitive mechano-transduction abilities:

(1) When a stem cell is in contact with a substrate, its contractile traction force will change depending on stiffness of the substrate;

(2) with substrates of different stiffness, the cell shape configuration and micro-structure conformation differ;

(3) the size of spreading area of the cell also depends on stiffness of the substrate;

(4) Order parameter evolution history depends on the stiffness of the substrate.