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Summer 2007

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# Coarse-Grained Modeling of Cytoskeletal Dynamics

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Courtesy of Ju Li. Used with permission.



2<sup>nd</sup> GEM<sup>4</sup> Summer School  
Cell and Molecular Mechanics in BioMedicine  
with a focus on Cancer  
June 25– July 6, 2007  
National University of Singapore

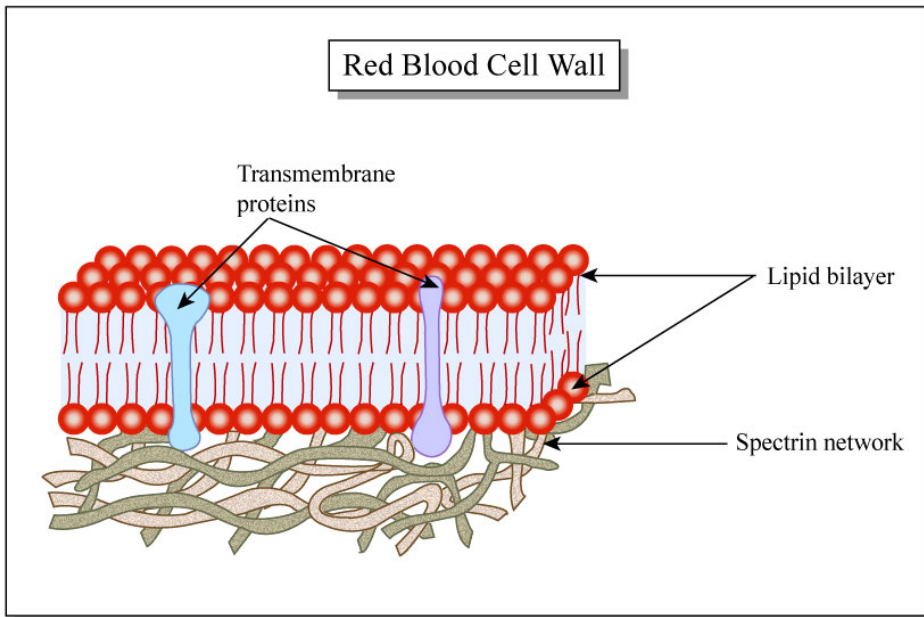


Figure by MIT OpenCourseWare.

One spectrin tetramer has 39 segments,  
 contour length  $\sim 200$  nm.  
 Room-temperature length  $\sim 80$  nm  
 due to thermal fluctuations.

← one segment  $\sim 5$  nm →

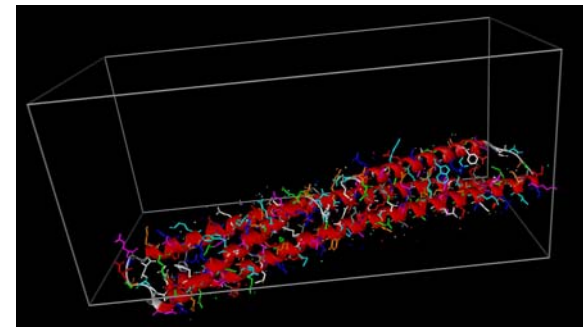
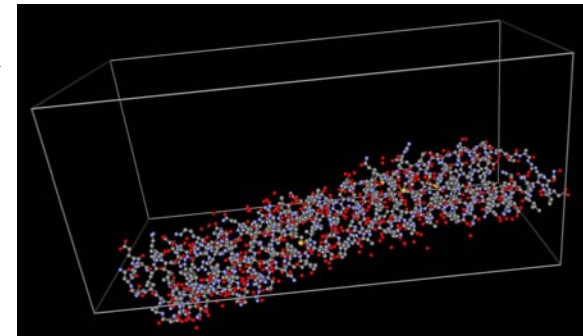
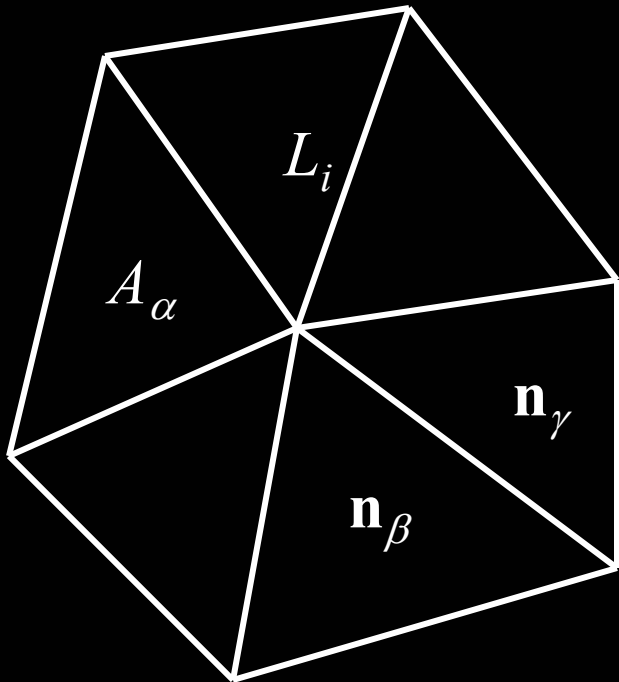


Image removed due to copyright restrictions.  
 See Fig. 2 in Takeuchi et al. "Structure of the  
 Erythrocyte Membrane Skeleton as Observed by  
 Atomic Force Microscopy." *Biophys J* 74  
 (1998): 2171-2183.

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# Spectrin-Net Level, Whole Red Blood Cell model (Discher, Boal, Boey, 1998)



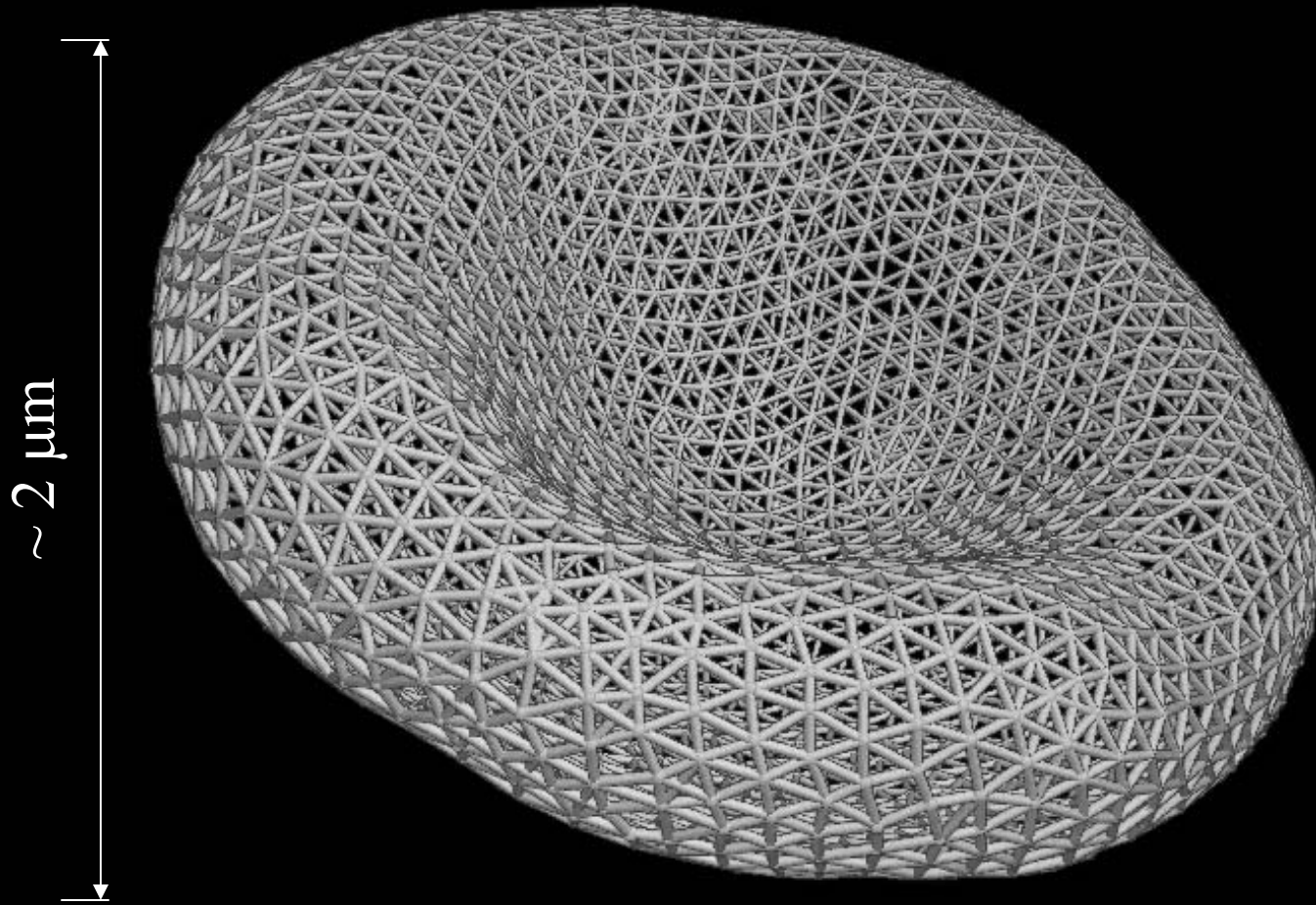
$$V_{\text{total}} = \sum_{i \in \text{spectrin link}} V_{\text{WLC}}(L_i) +$$

$$\sum_{\alpha \in \text{triangle}} \frac{C}{A_\alpha} +$$

$$\sum_{\beta, \gamma \in \text{triangle}} K_{\text{bend}} (1 - \mathbf{n}_\beta \cdot \mathbf{n}_\gamma)$$

+ total volume constraint + total area constraint

# Small Cell Simulation of Volume Deflation



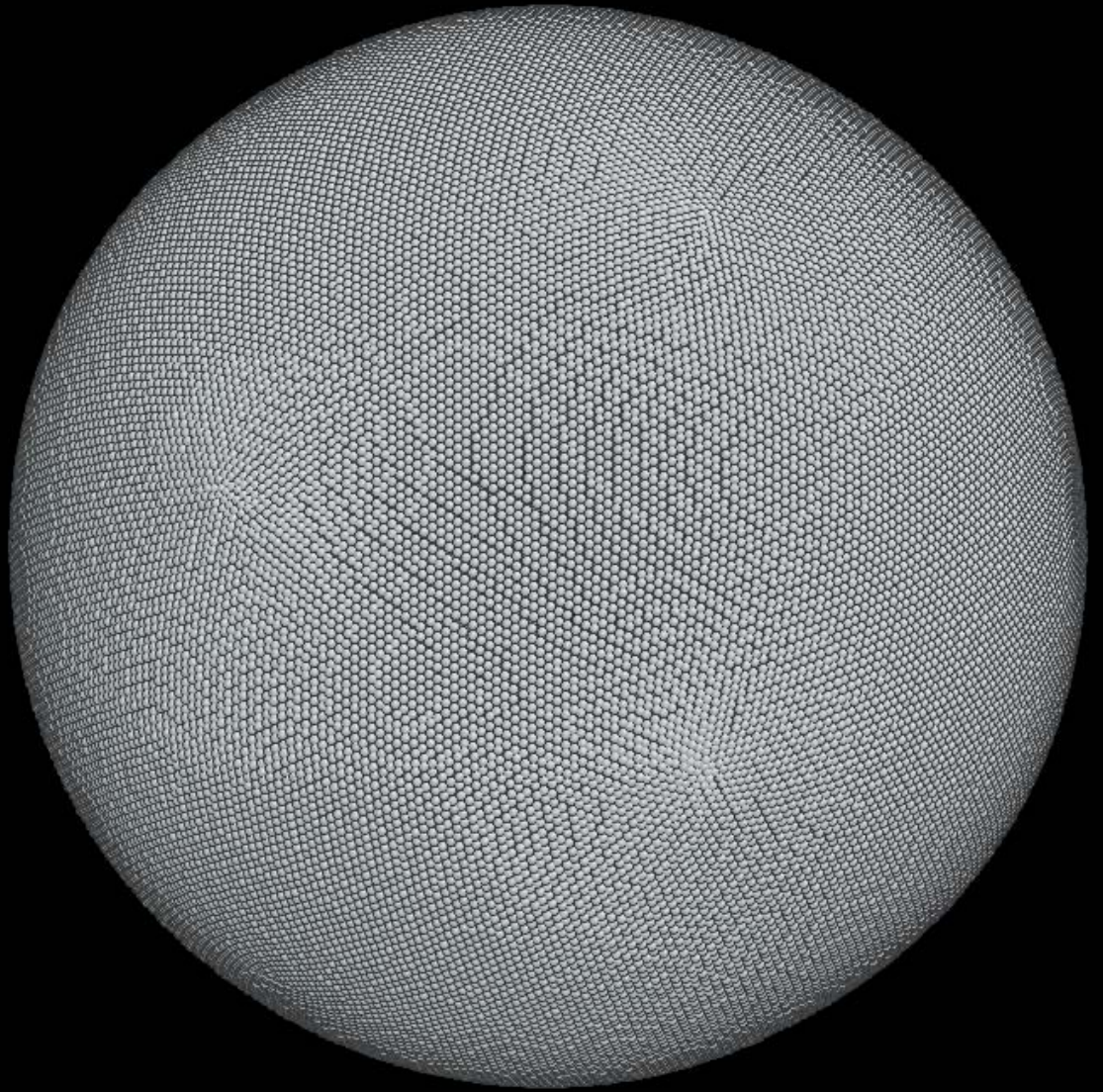
2562 vertices

Full-sized cell  
with bending  
energy

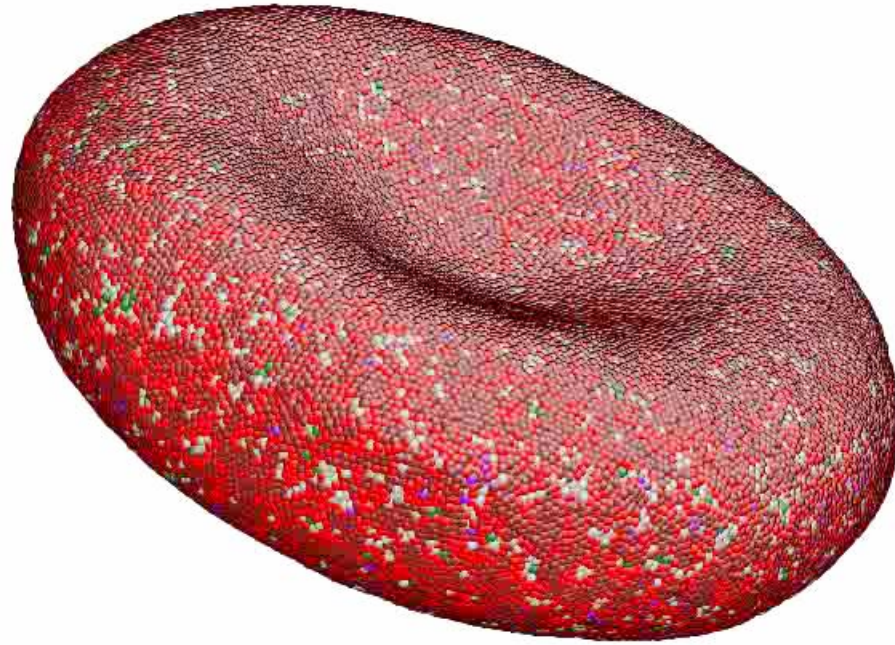
$E_{\text{bend}}$  only

Canham (1970)

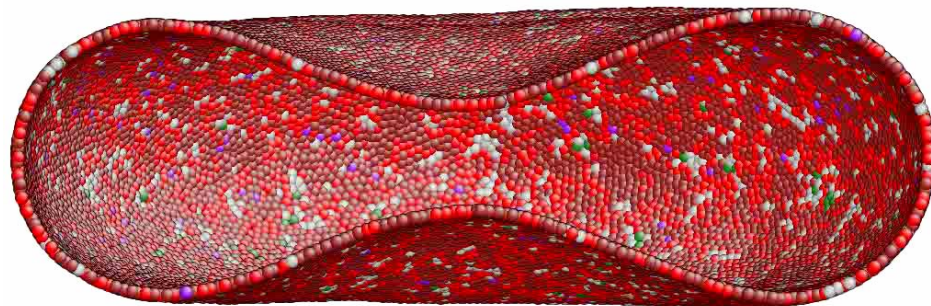
Helfrich (1973)



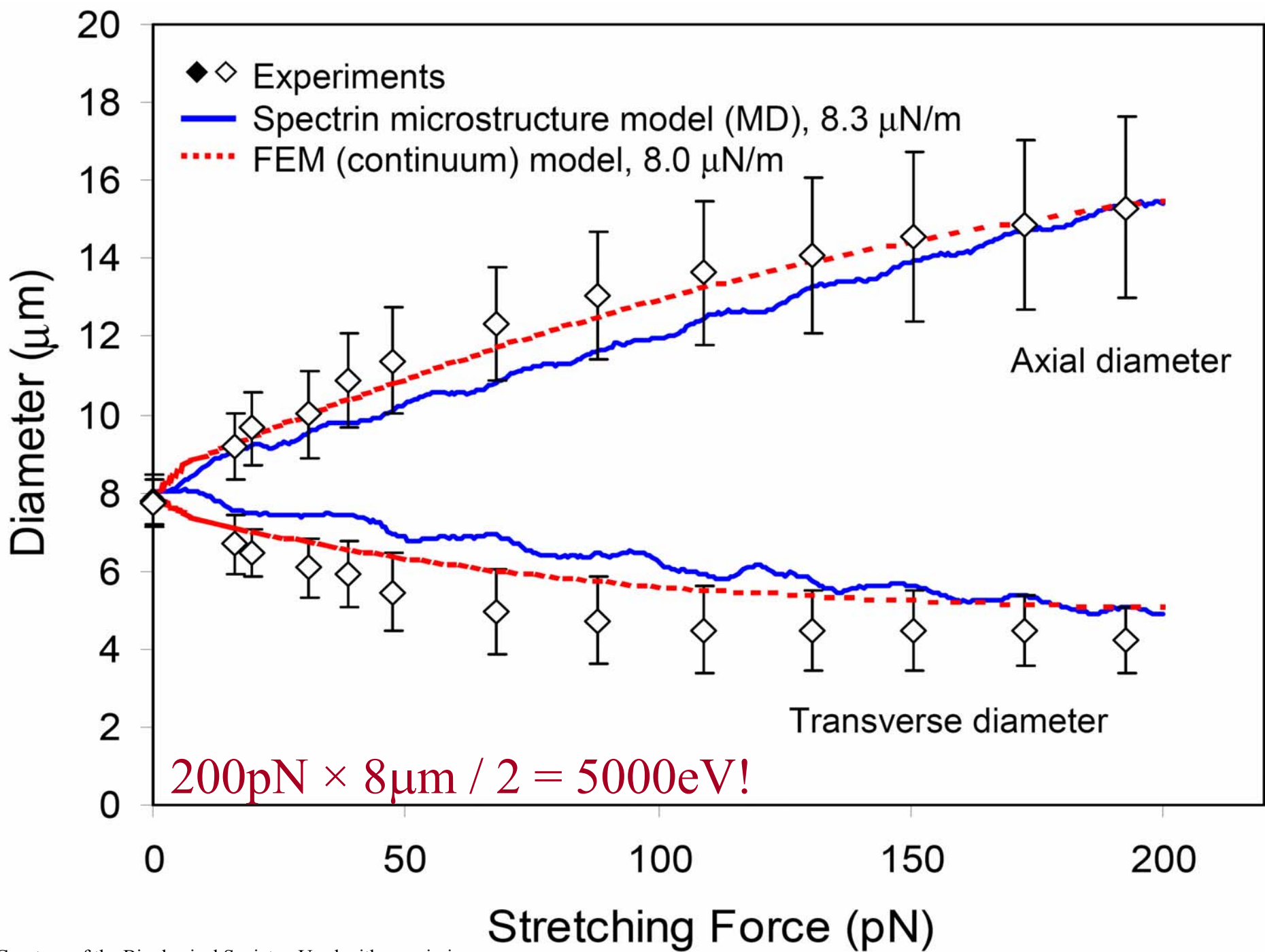
# OT stretching simulation with bending + in-plane energies



Courtesy of the Biophysical Society. Used with permission.

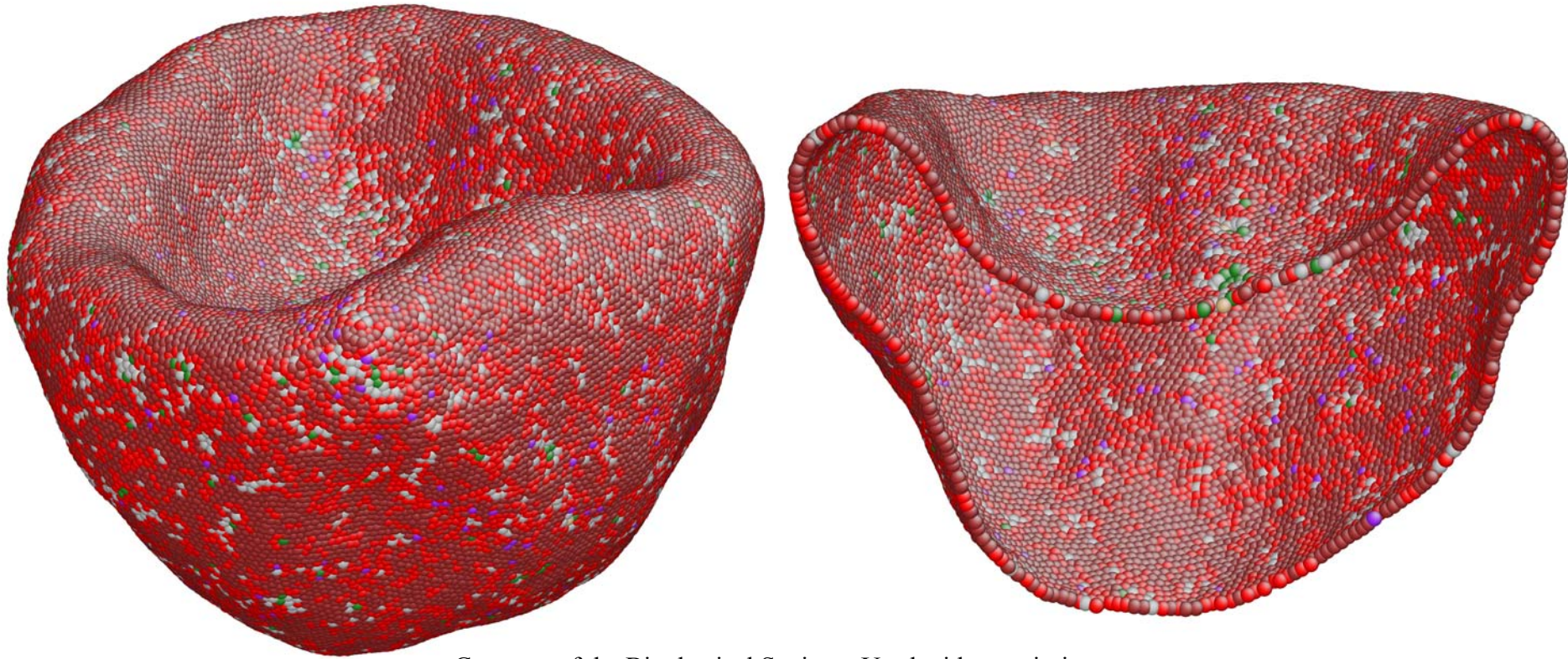


Li, Dao, Lim &  
Suresh, *Biophys.*  
*J.* **88** (2005) 3707.





# Why is biconcave the stable equilibrium shape?



Courtesy of the Biophysical Society. Used with permission.

$$E_{\text{bend}} \sim 8\pi\kappa: \kappa \sim 2 \times 10^{-19} \text{ J} \rightarrow E_{\text{bend}} \sim 30 \text{ eV}$$

$$E_{\text{shear}} \sim \mu\varepsilon^2 A: \mu \sim 8\mu\text{N/m}, \varepsilon \sim 0.1, A \sim 140\mu\text{m}^2 \\ \rightarrow E_{\text{shear}} \sim 70 \text{ eV}$$

# Material Concept Hypothesis

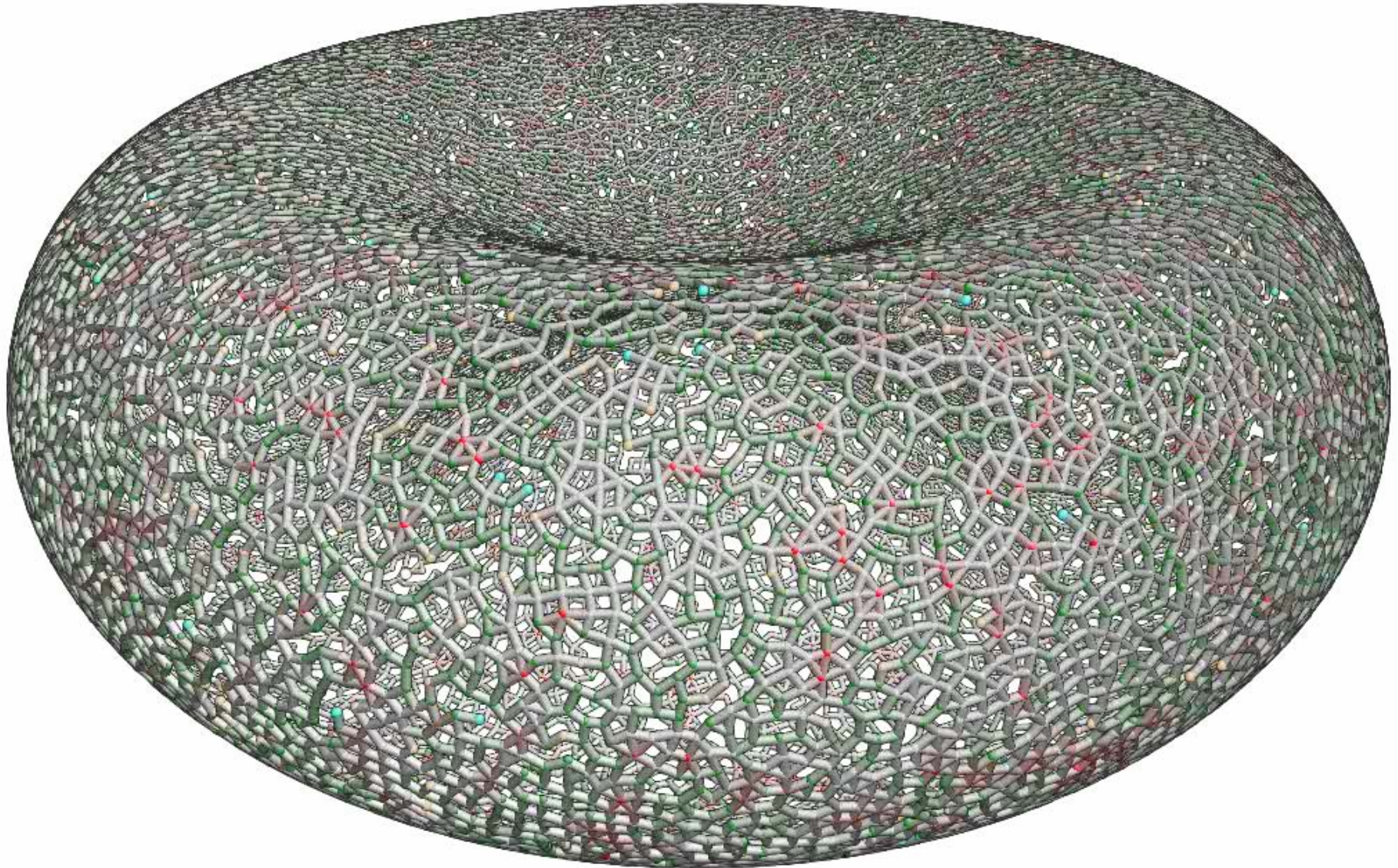
Li, Dao, Lim & Suresh, *Biophys. J.* **88** (2005) 3707.

- In an ideal limit, for any RBC shape, the cytoskeleton will always undergo remodeling in topological connectivity at a slow rate to relax its in-plane *shear* elastic energy to *zero*.

“liquefaction”, “slow-flowing glass”

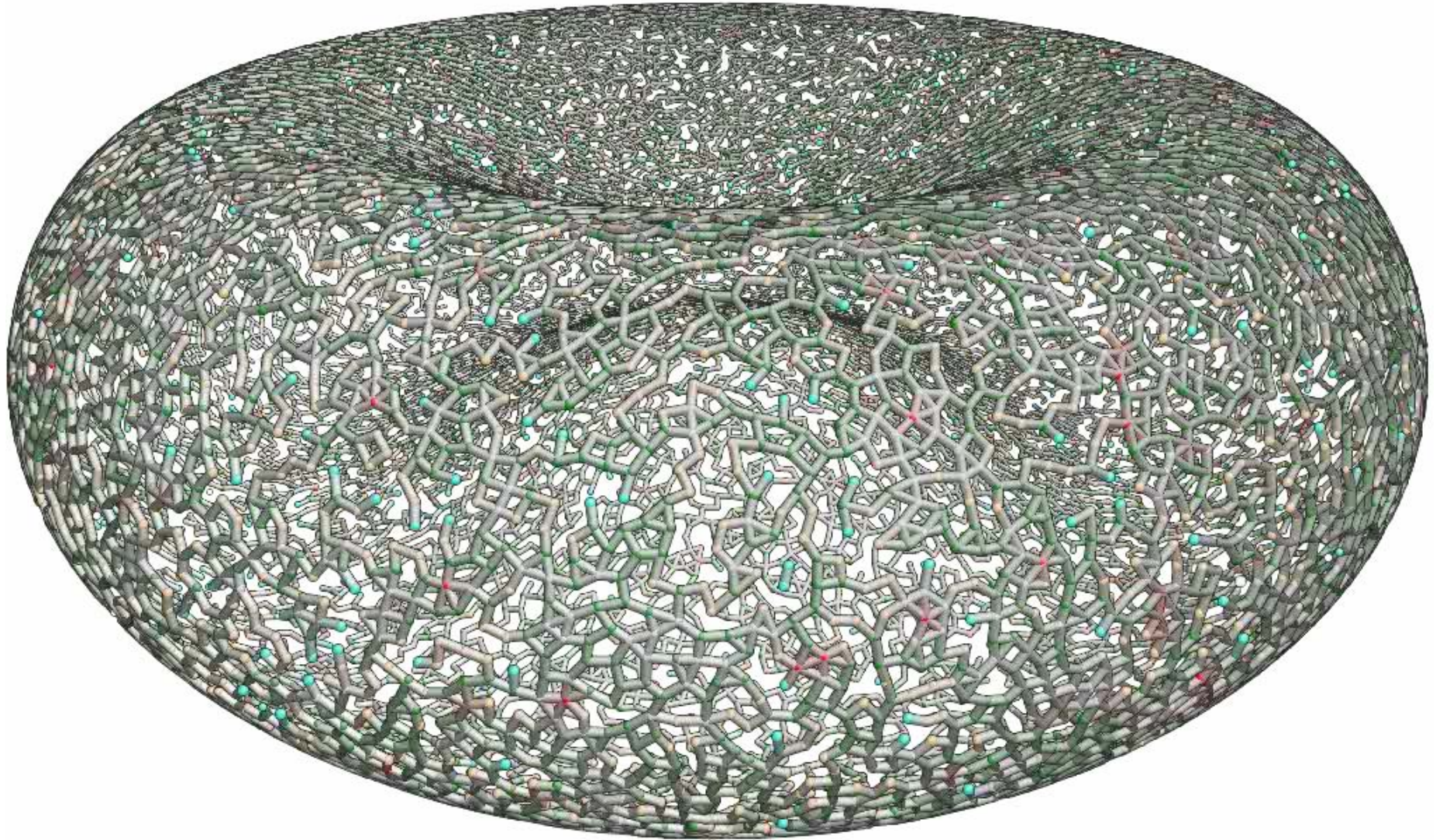
- At the timescale of optical tweezers stretching, the above relaxation is not significant, so large shear energy can be injected temporarily.

# Stillinger-Weber liquid on curved surface:



**no shear energy can survive long!**

# RBC cytoskeleton at reduced spectrin density



very large holes start to percolate ...

# Extreme Statistics of Cytoskeletal Defects in RBC

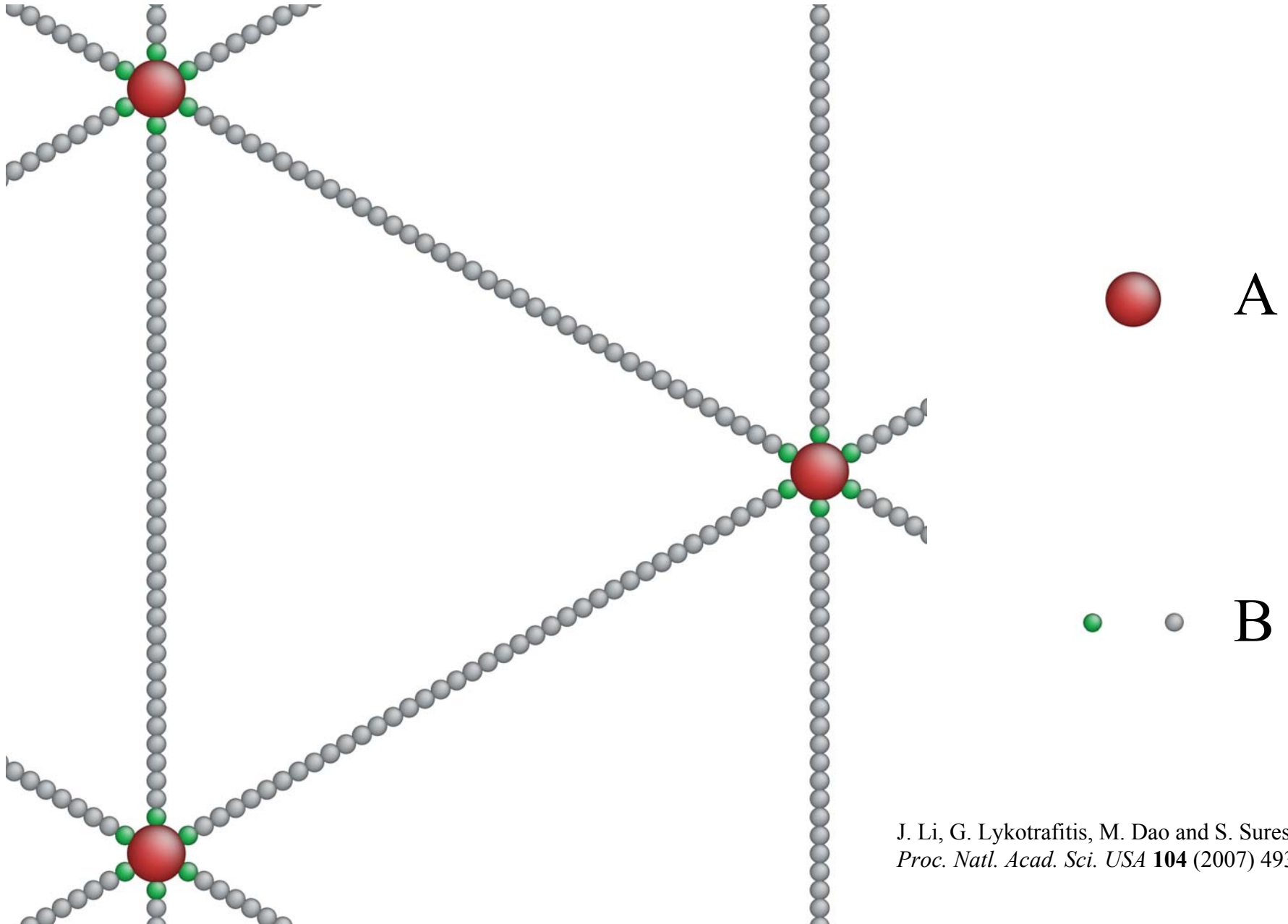
	actin#	spectrin#	largest polygon hole
normal	28673	81718	6
degree-4.5	26880	57523	8
degree-4	24372	48012	11
degree-3.5	21504	37416	22
degree-3	18637	26837	35

But this is basically from a “geometrical” simulation.  
No biophysical basis yet.

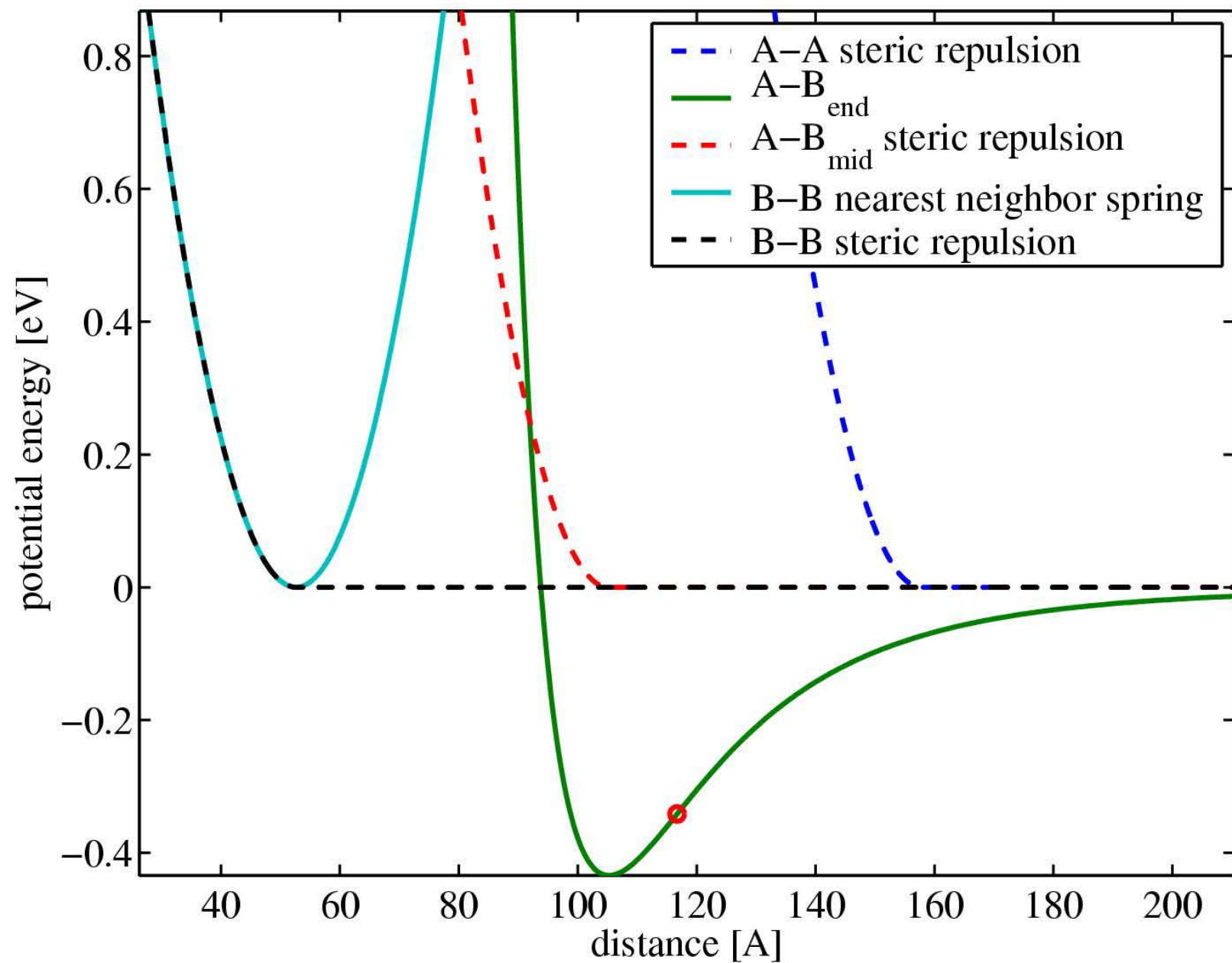
# Intermediate Summary

- Spectrin-level and continuum FEM analyses indicate our optical tweezers experiments give approximately the same in-plane shear modulus as micropipette aspiration experiments:  $\mu = 5 \text{ to } 10 \times 10^{-6} \text{ N/m}$ .
- Stabilization of biconcave equilibrium shape strongly suggests the cytoskeleton undergoes slow but constant remodeling topologically to always relax the in-plane shear elastic energy to zero.
- Connection to single-molecule stretching experiments (“intermolecular potential development”).

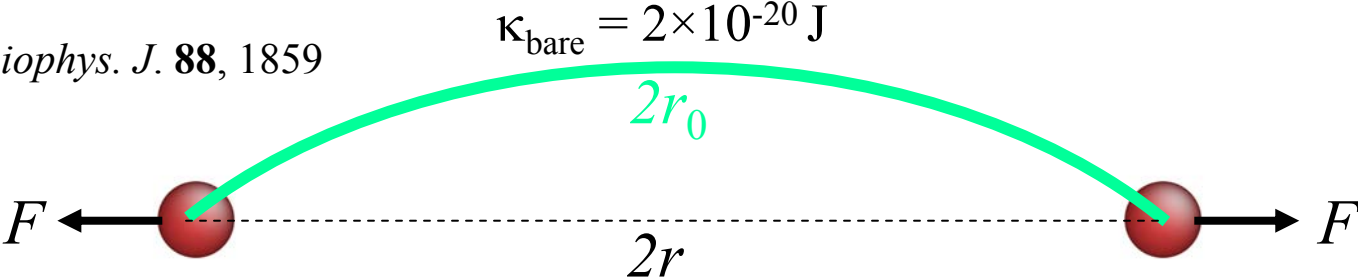
# CGMD model with *breakable* actin-spectrin junction



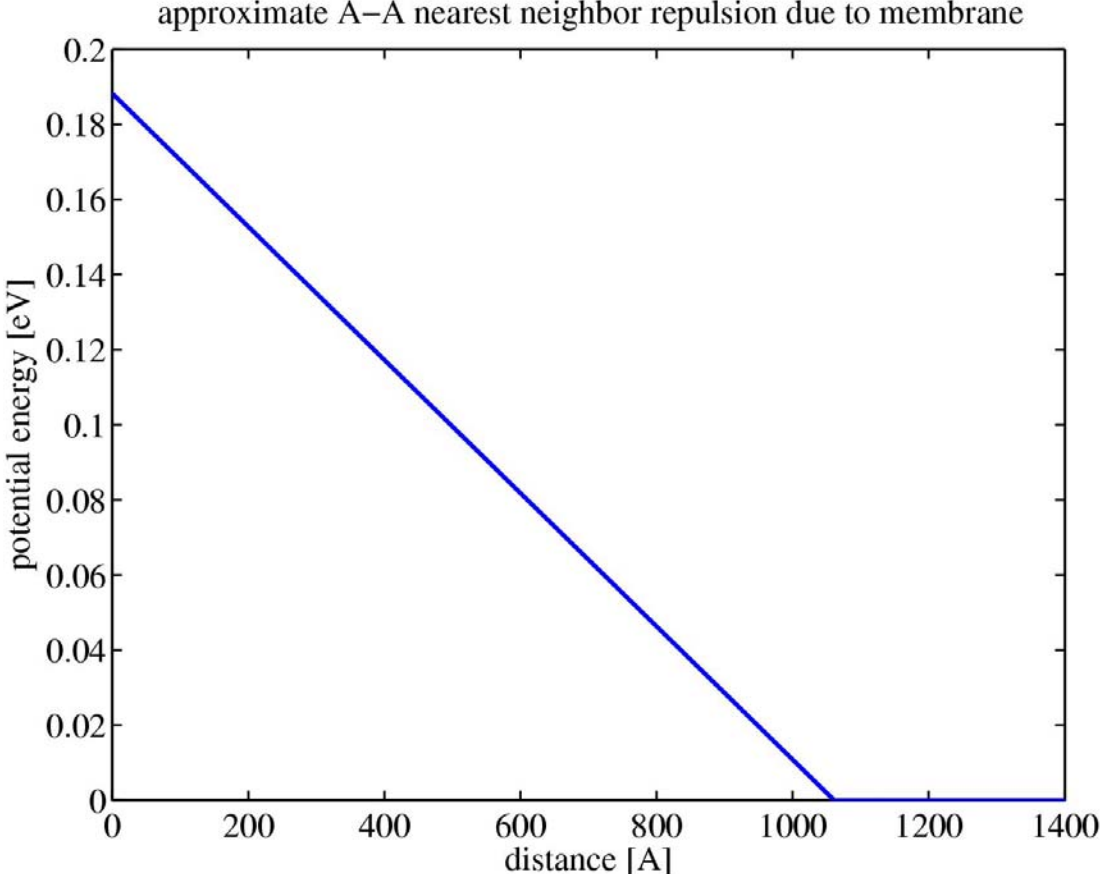
J. Li, G. Lykotrafitis, M. Dao and S. Suresh,  
*Proc. Natl. Acad. Sci. USA* **104** (2007) 4937.



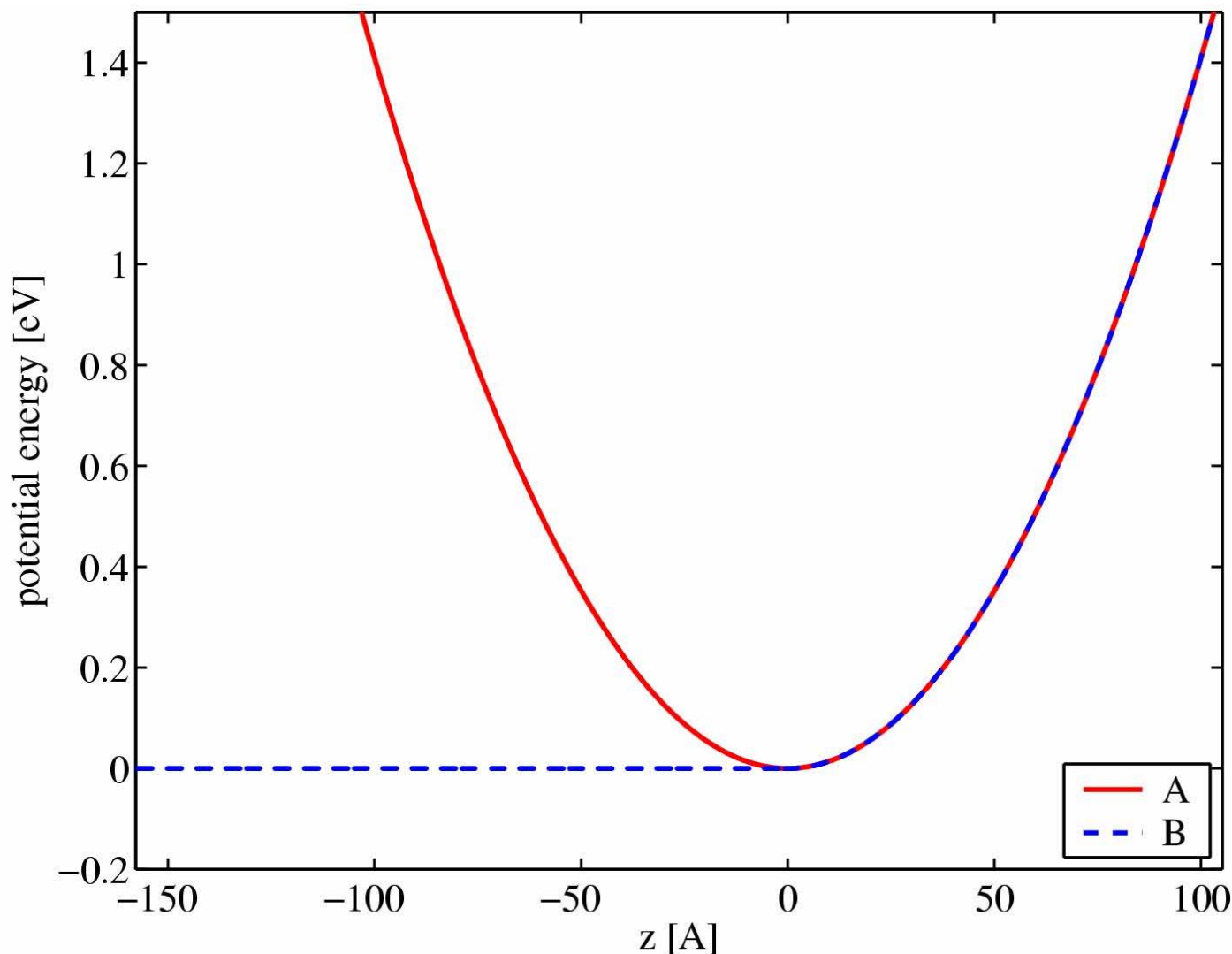


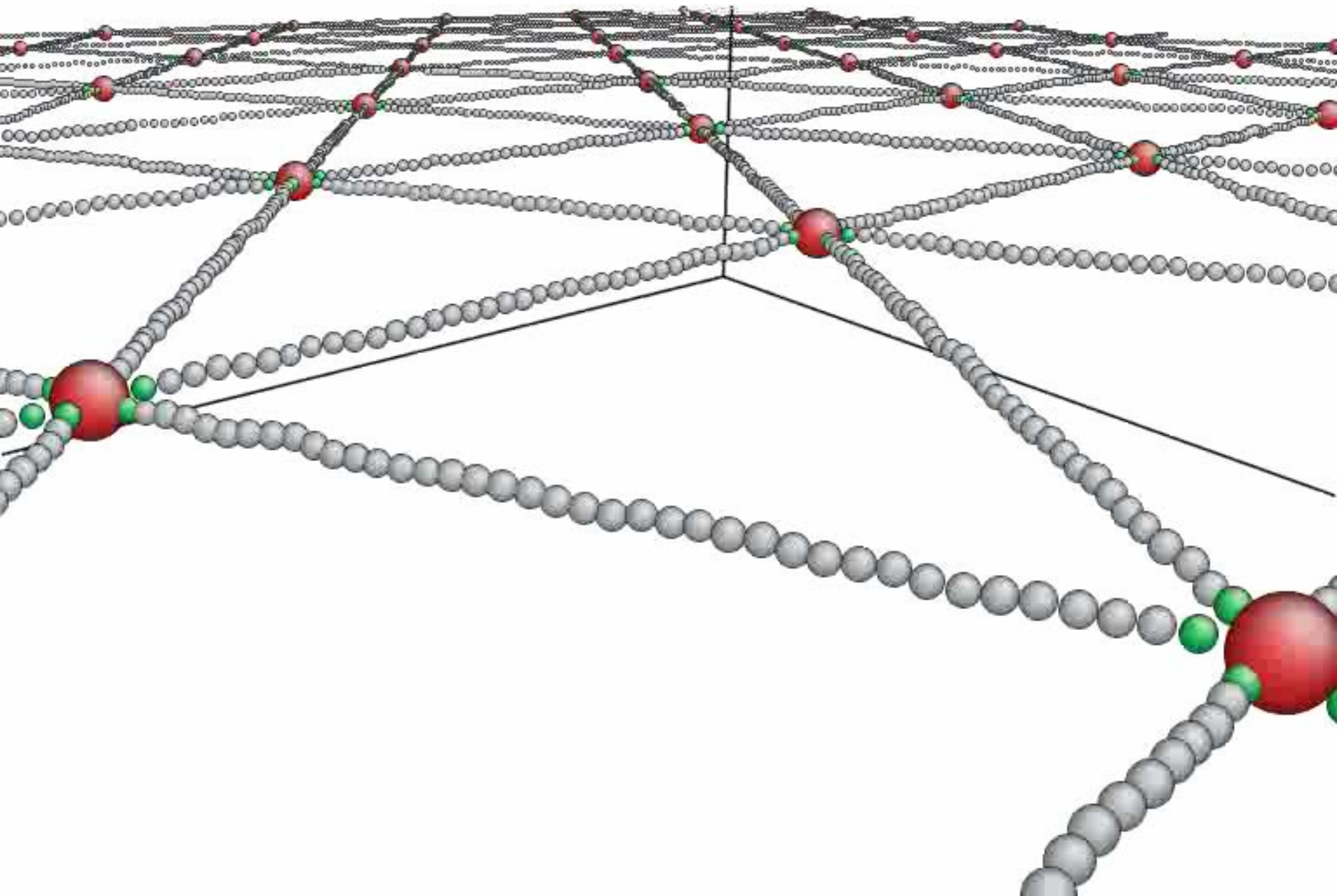


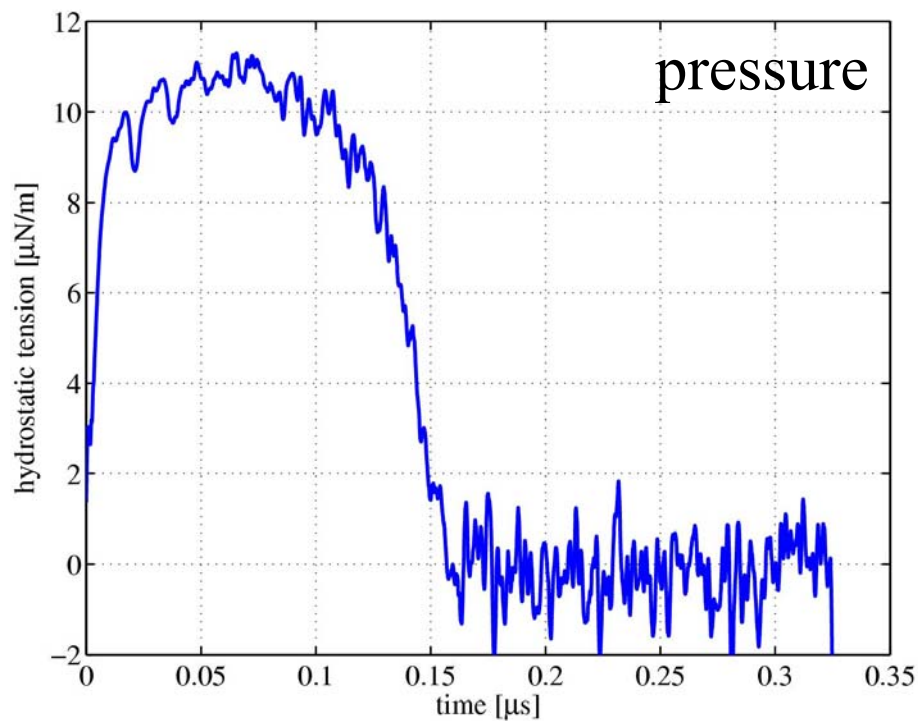
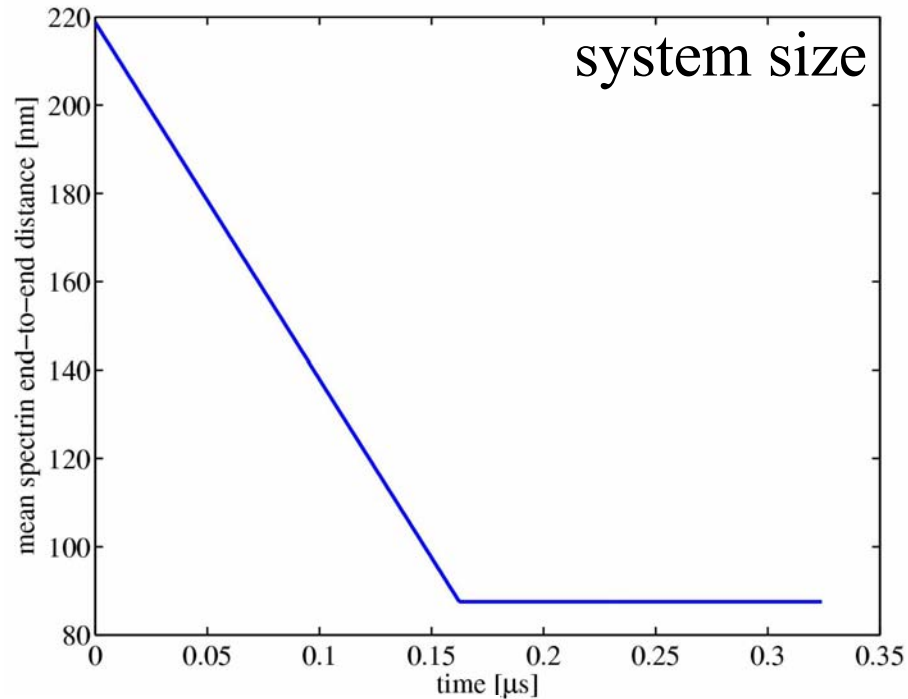
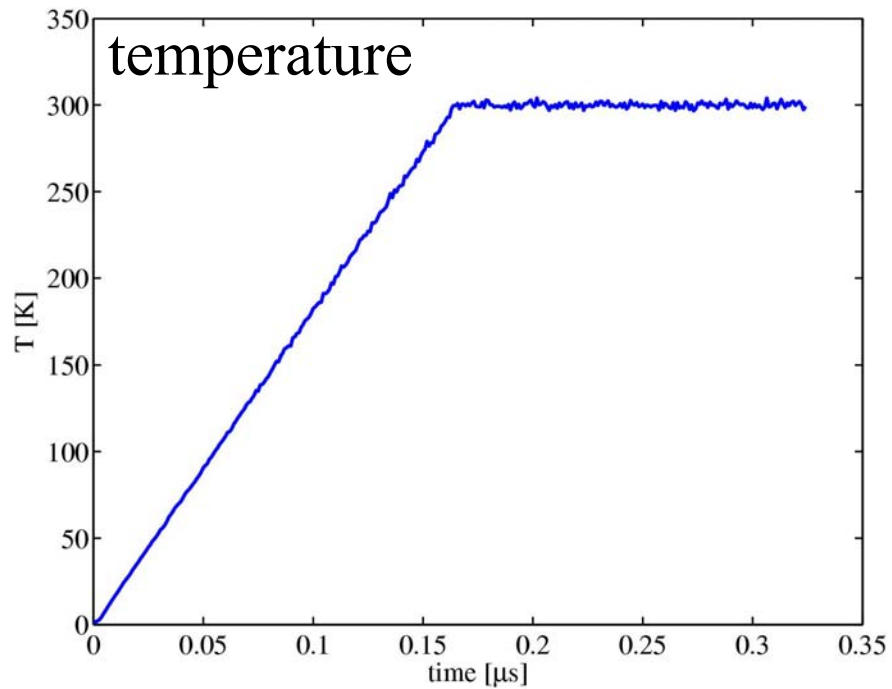
$$F = \alpha \frac{4\pi\kappa_{\text{bare}}}{3r_0}, \quad \alpha \text{ chosen to be } 0.36$$



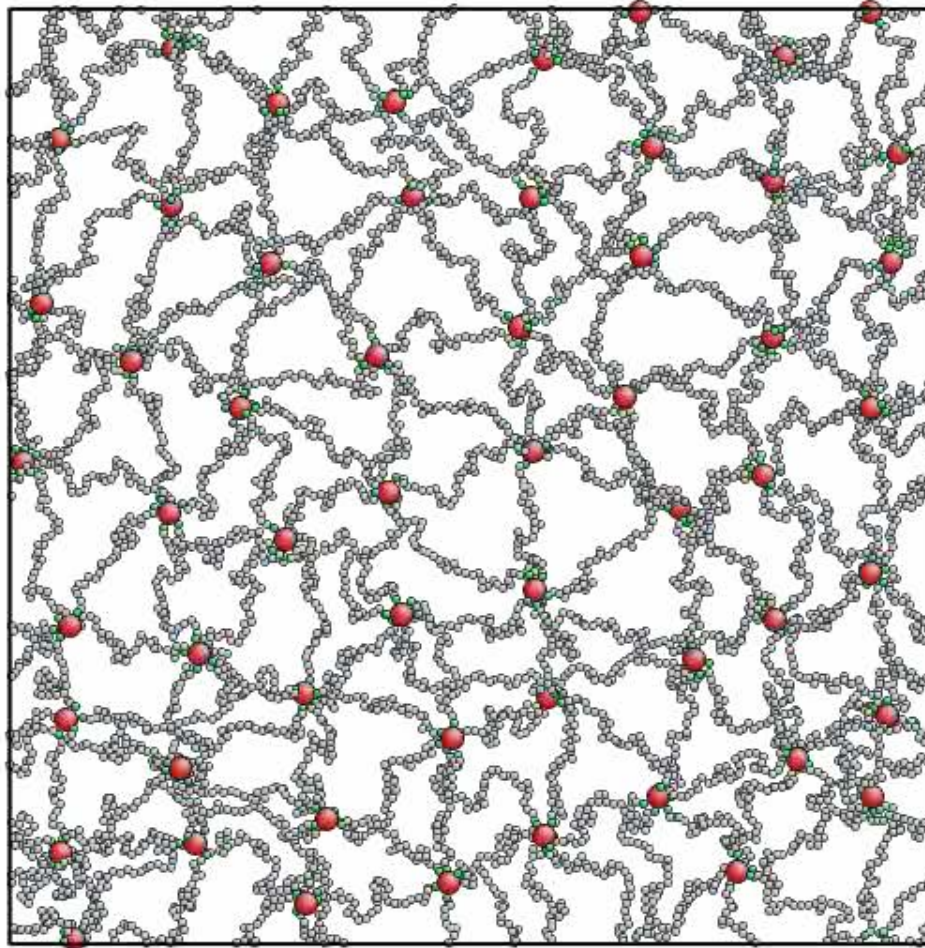
We also put soft ( $0.1k_{\text{BB}}$ ) confinement potential on A and B in  $z$  to mimic interaction with the membrane without actually simulating the membrane.



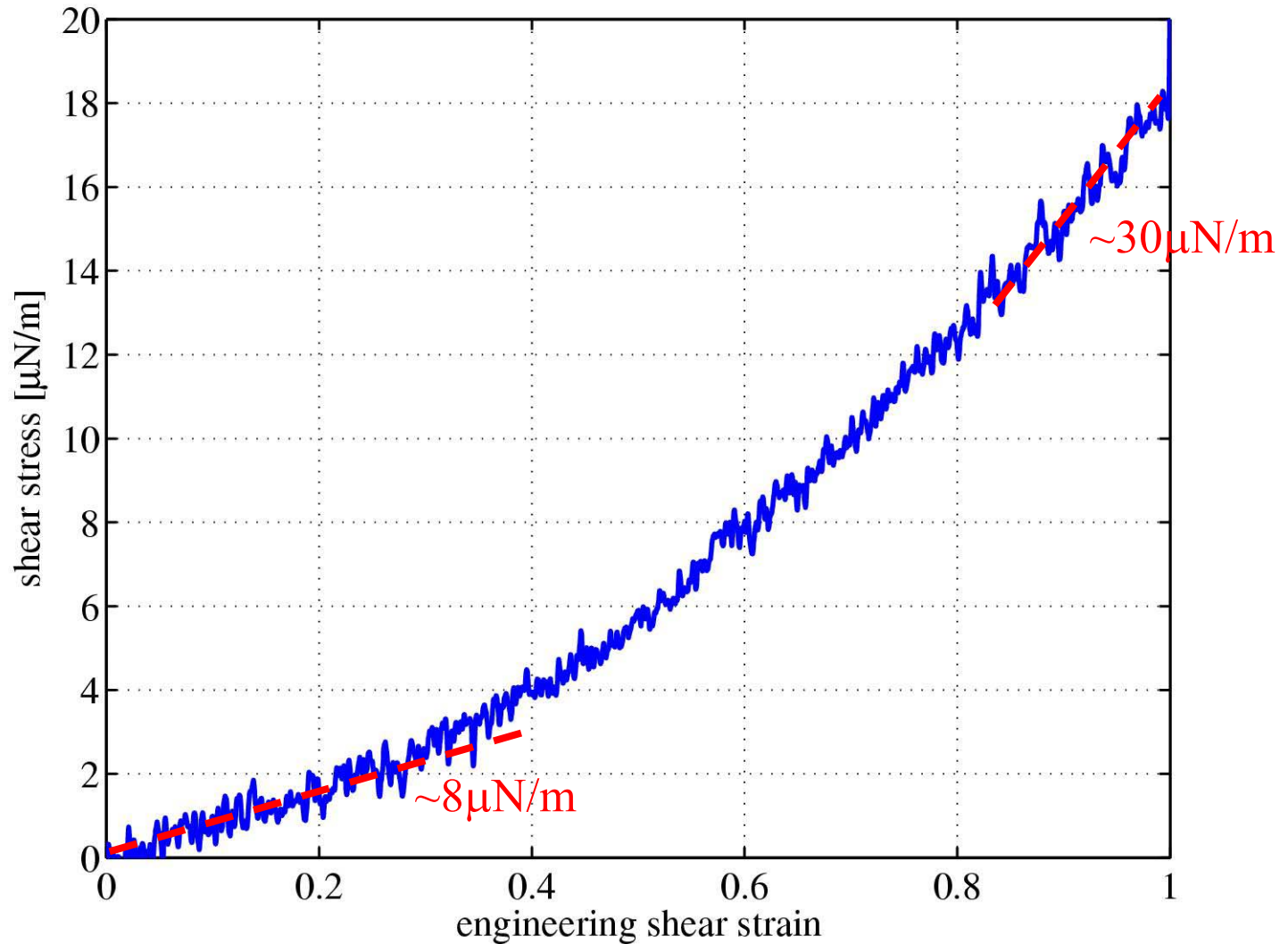




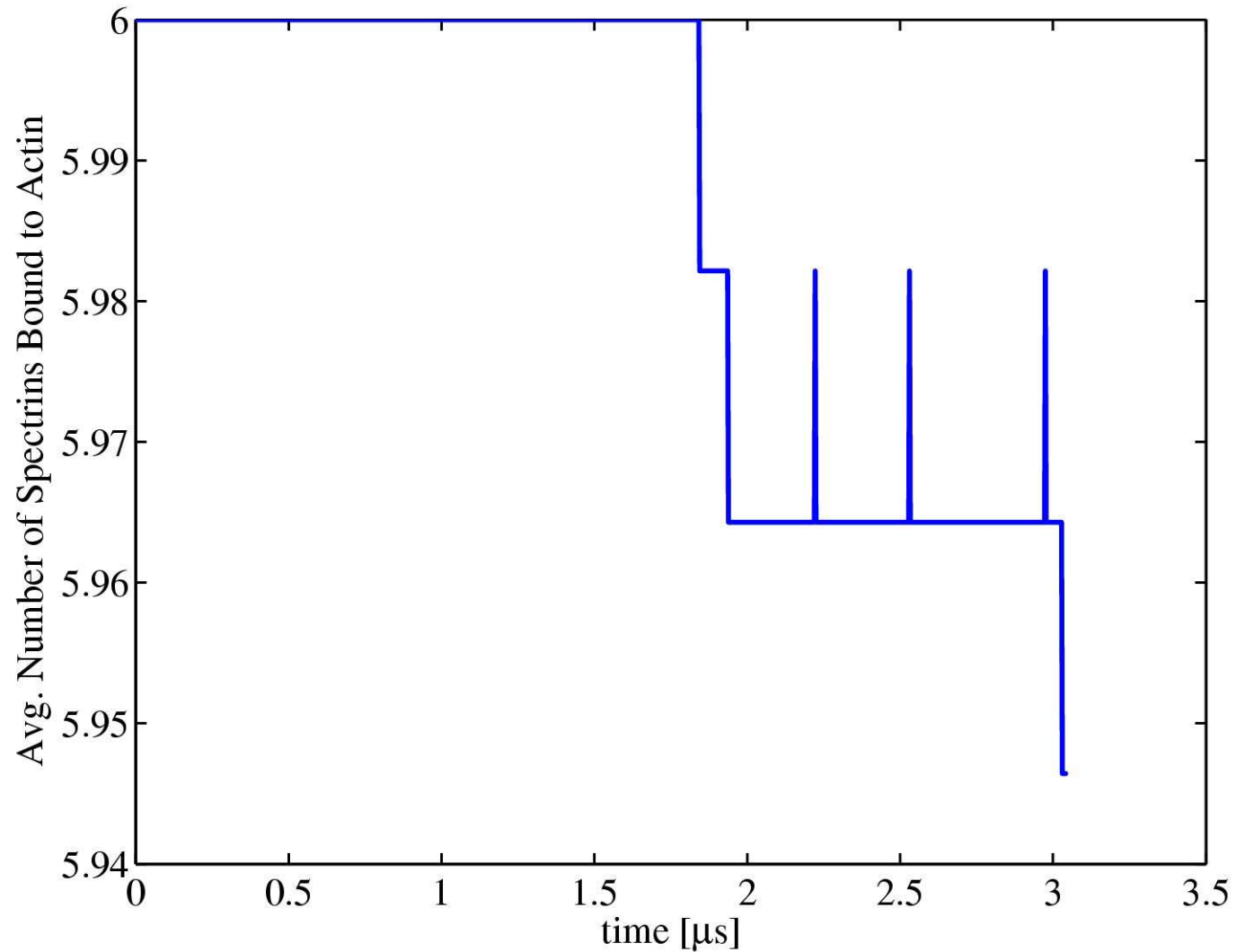
Pure shear deformation  
at 300K and strain rate  $3 \times 10^5/s$



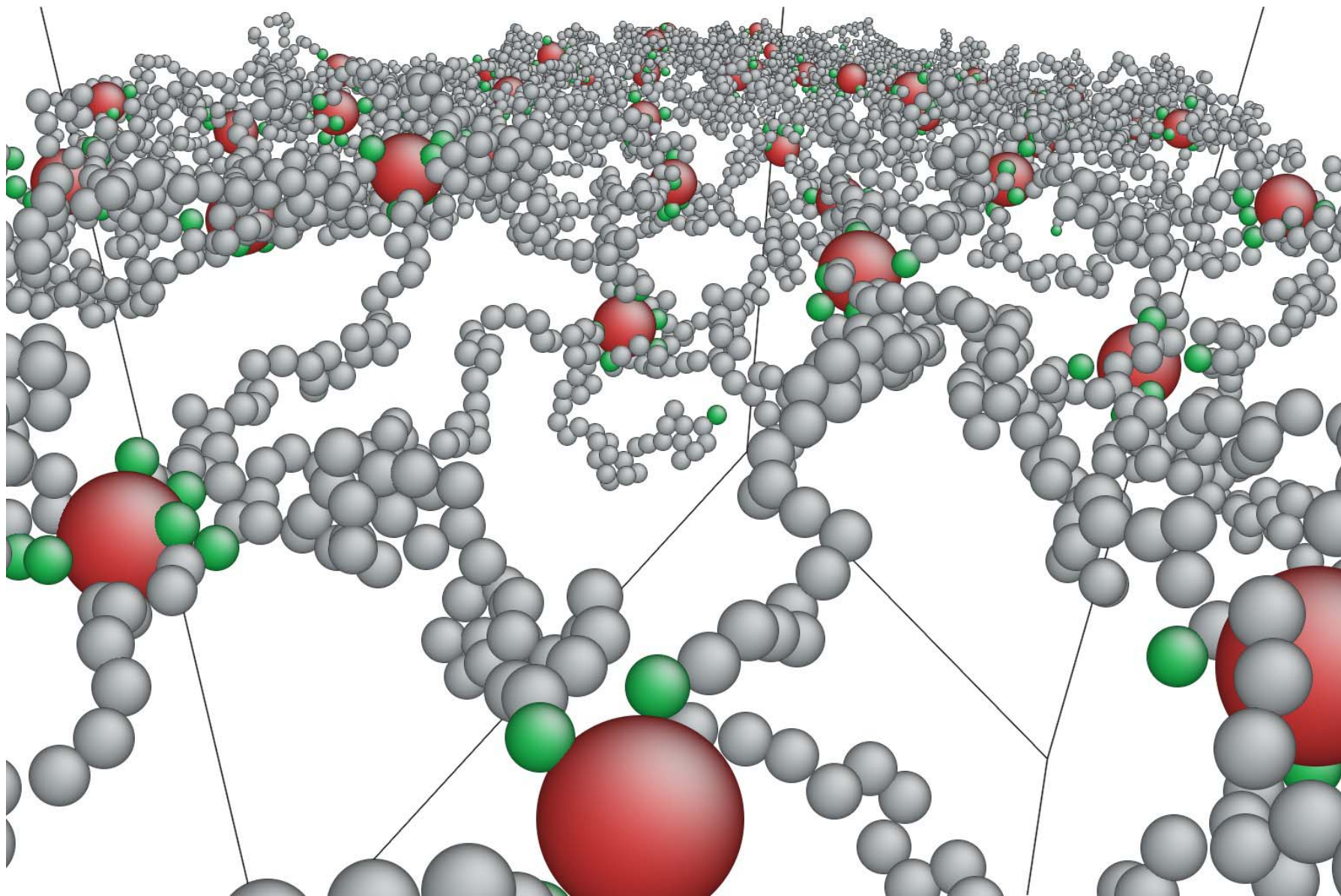
# Stress-strain curve at 300K and no ATP



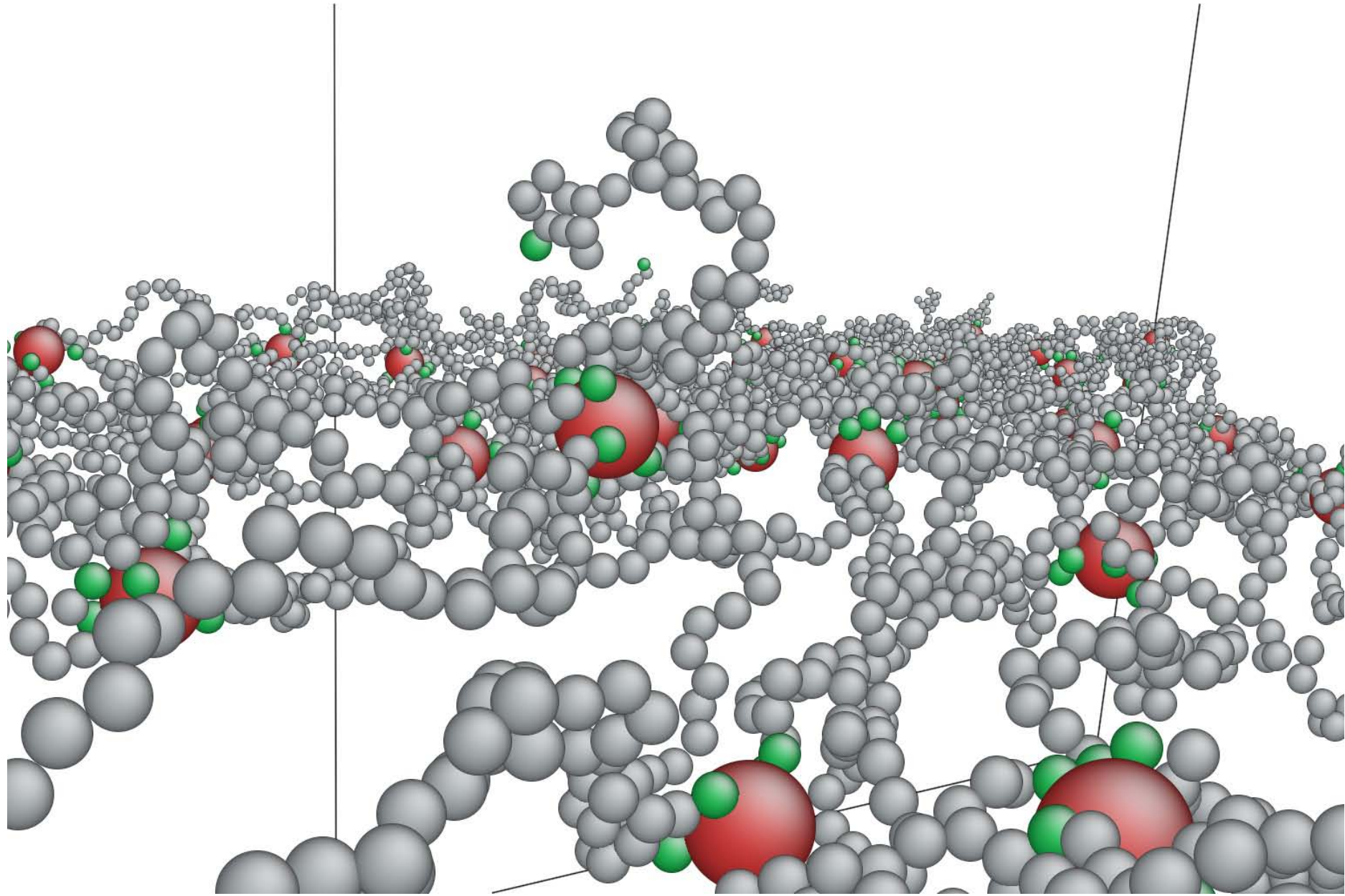
# Defect statistics at 300K with no ATP



# A broken link 5-fold defect

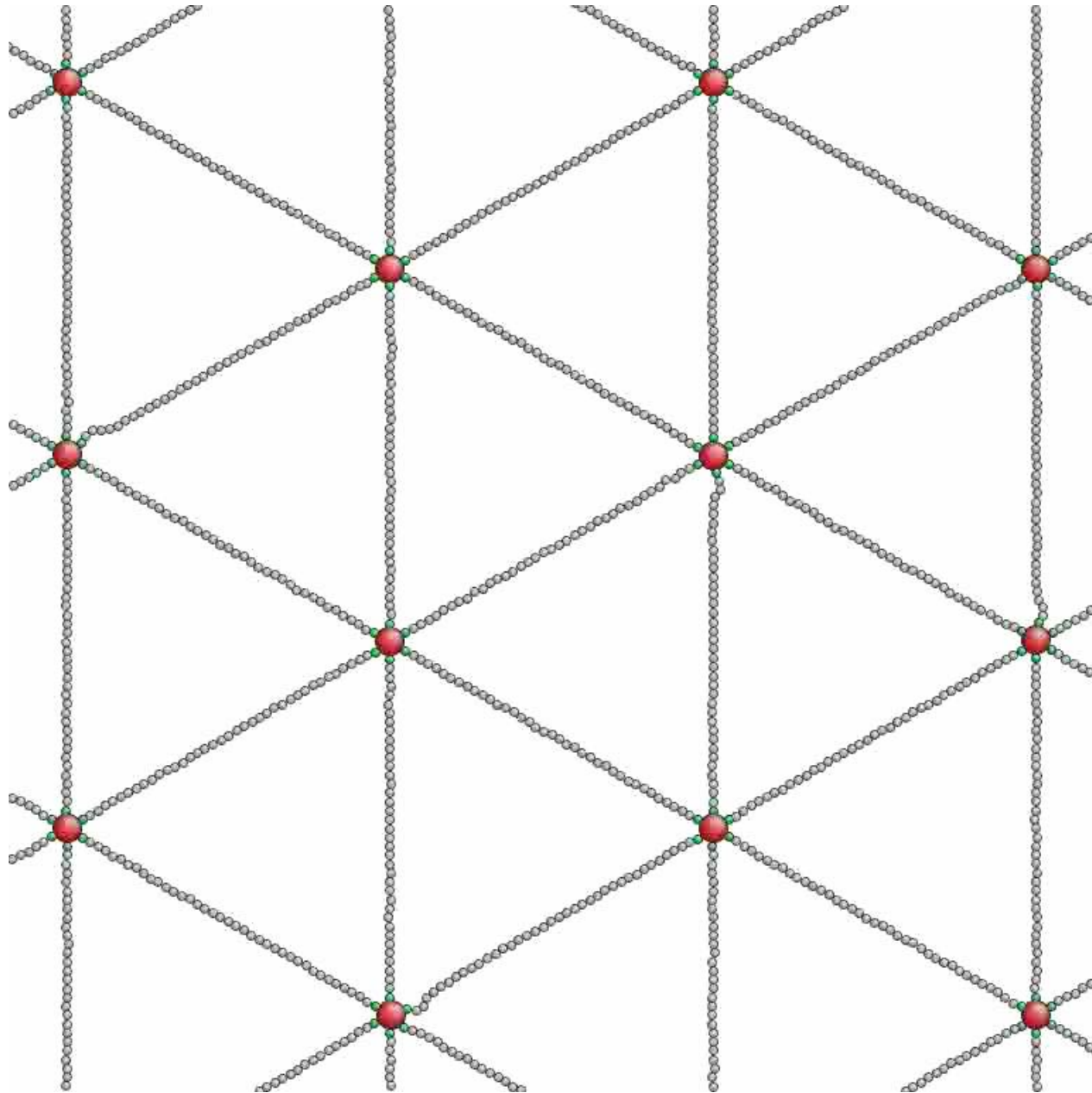




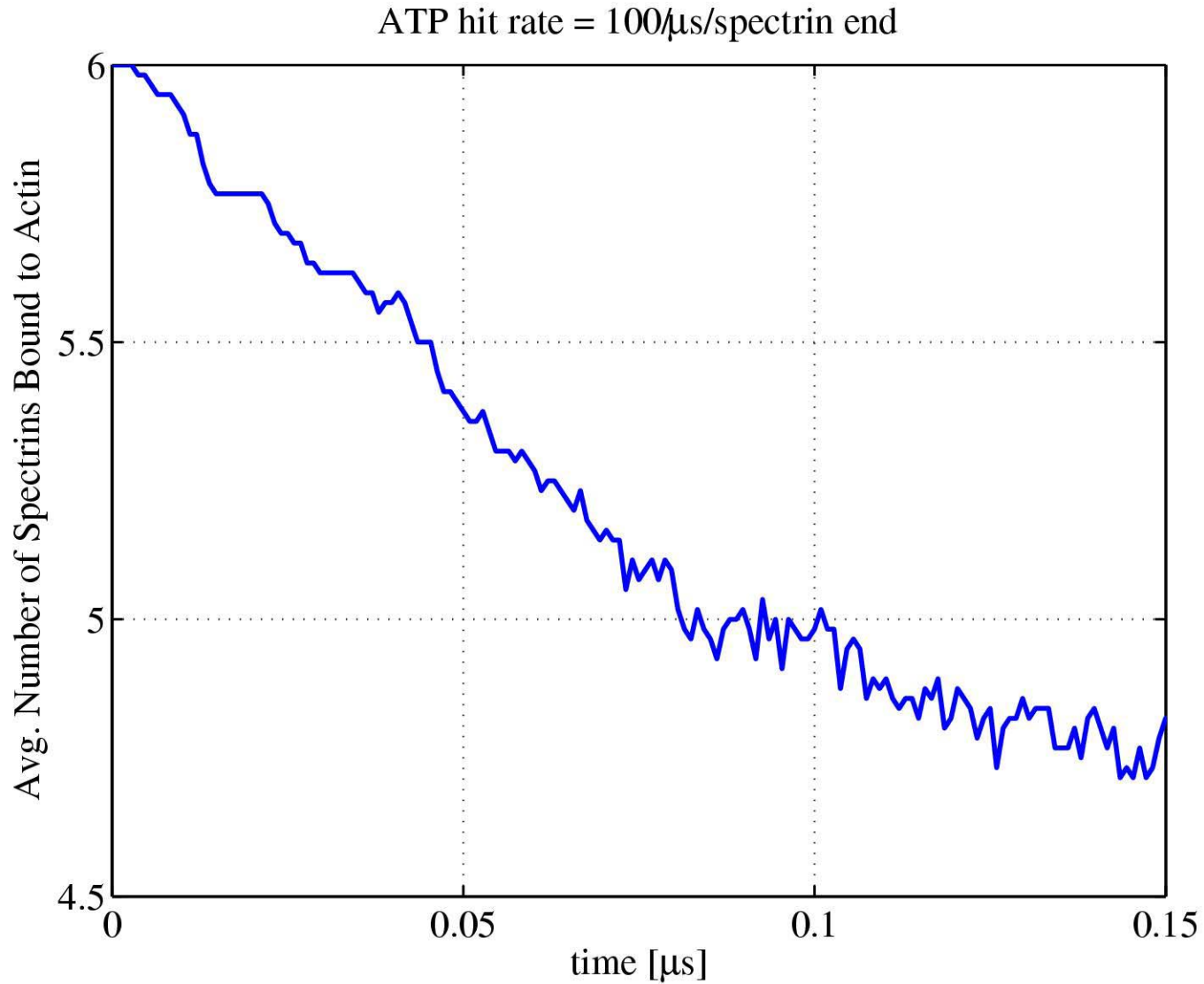


**Corrugation due to buckling: elevated / depressed in height**

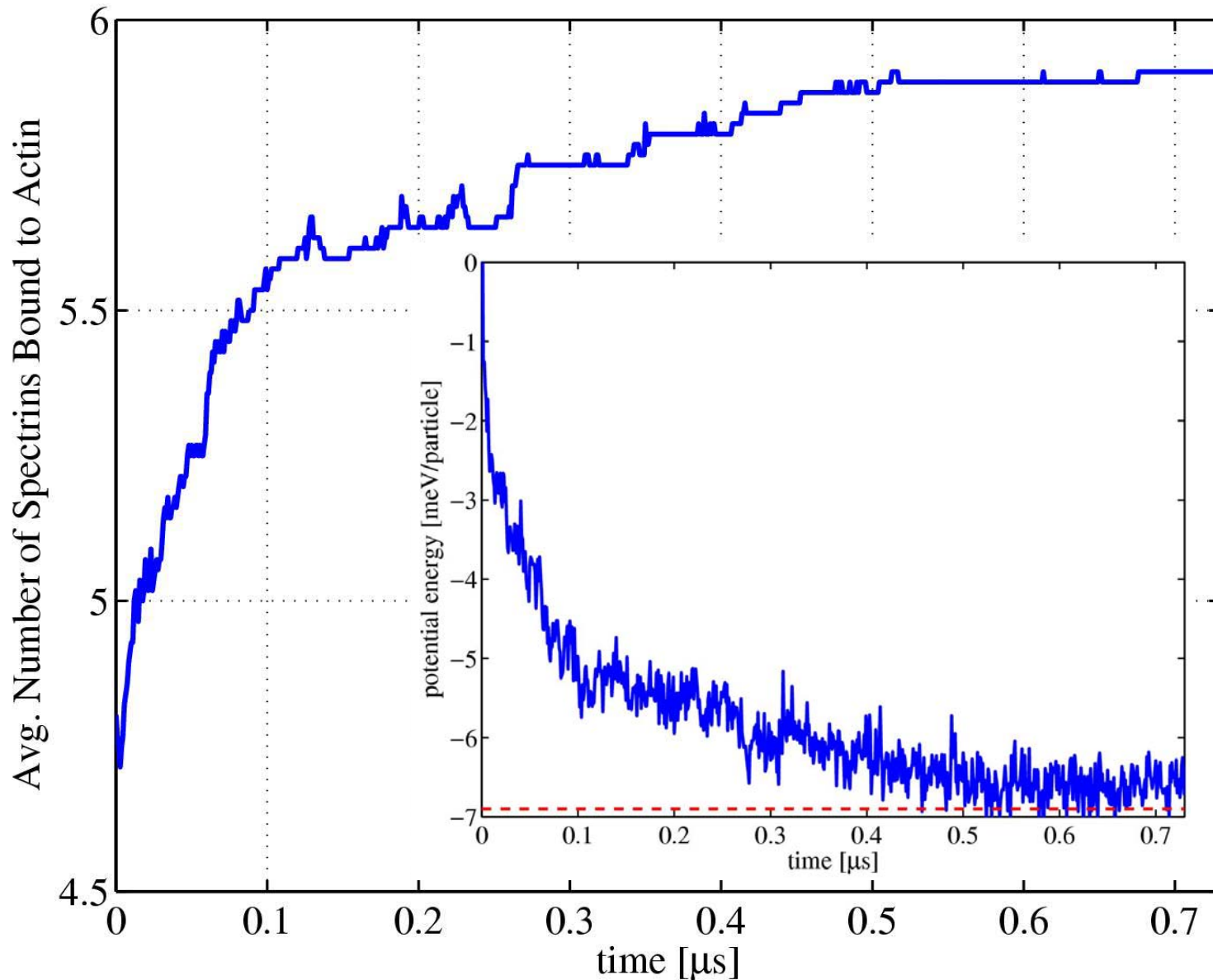
**Now add ATP (0.5eV random kinetic energy to green ball):**  
**hit rate = 100/ $\mu$ s per spectrin end**



# Defect statistics at 300K, ATP hit rate $100/\mu\text{s}$



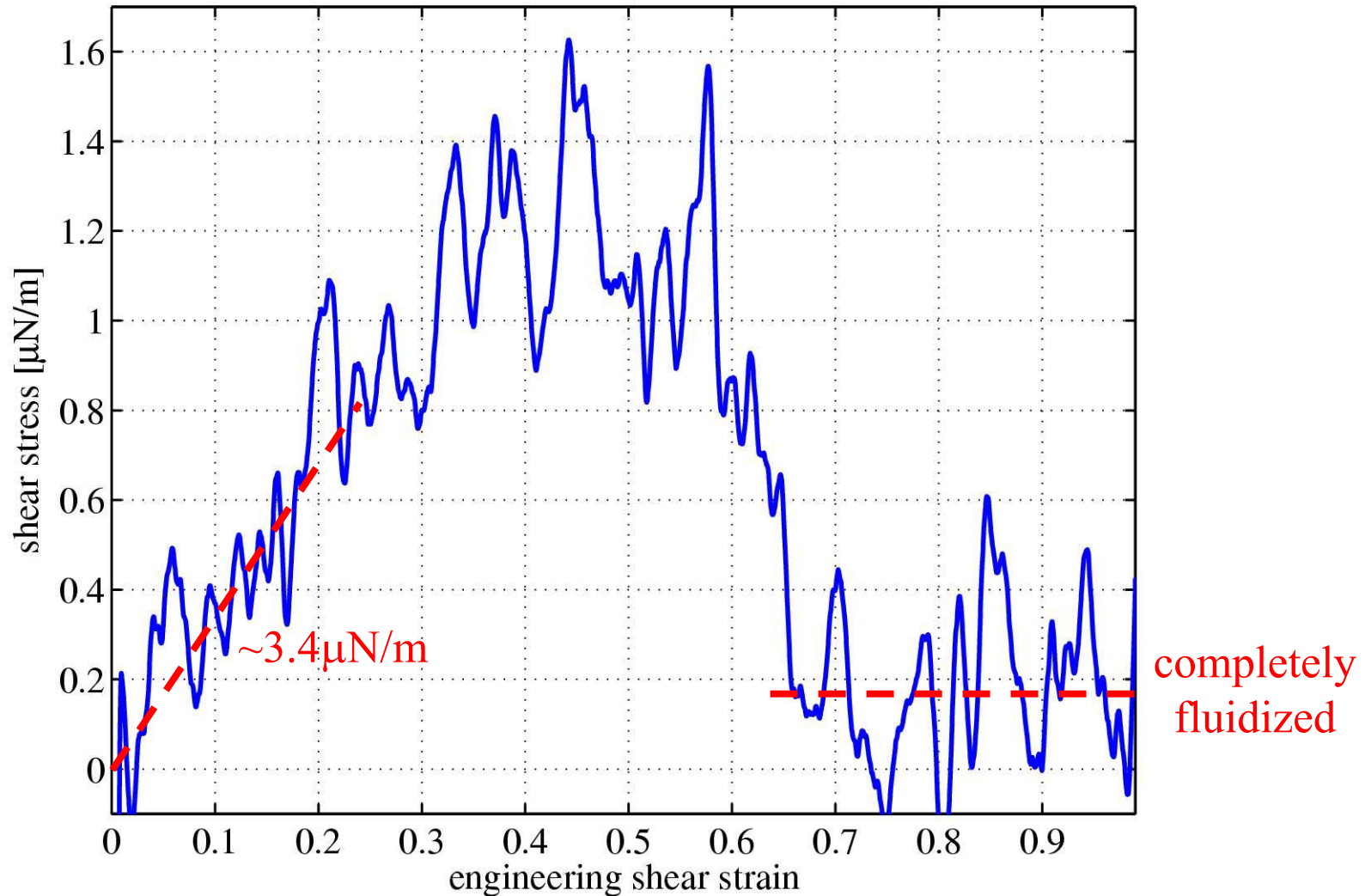
Now turn off ATP hits, “anneal” at 300K...



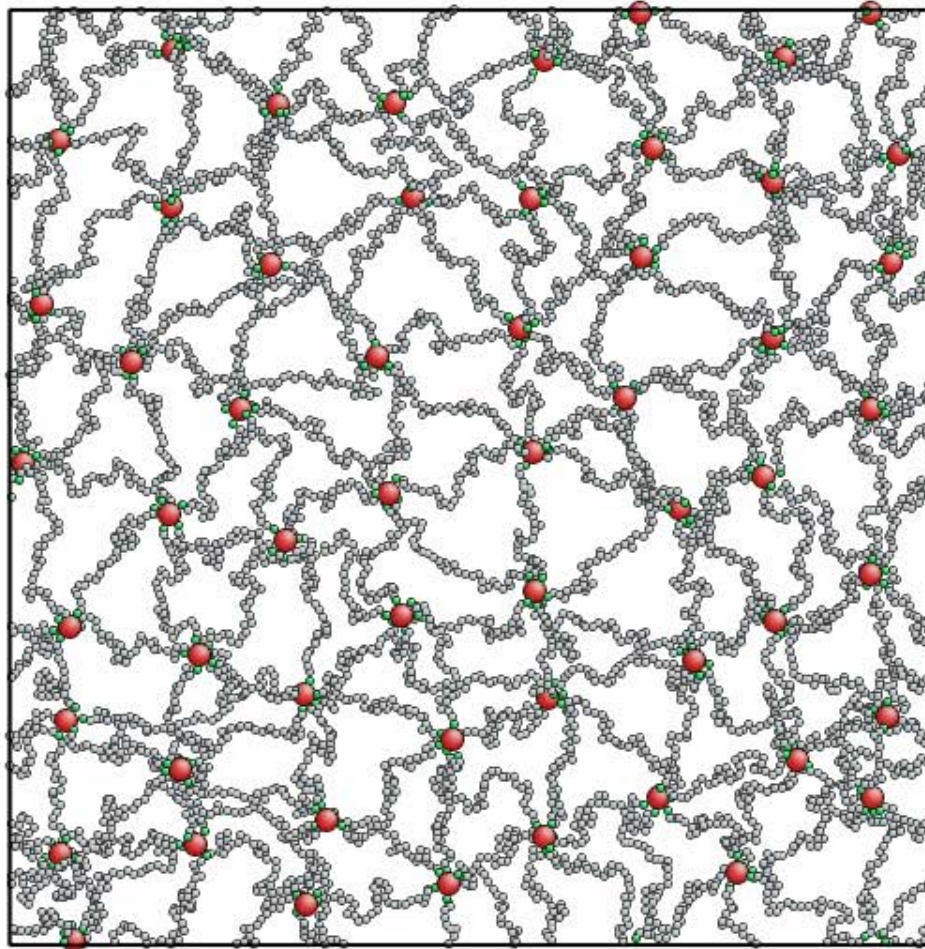
Miraculously, the system recovers, within CGMD simulation timescale.

A more reasonable ATP hit rate:  $10/\mu\text{s}$ .  
Simultaneously, also shear deform.

ATP hit rate =  $10/\mu\text{s}$ /spectrin, strain rate =  $3 \times 10^5/\text{s}$

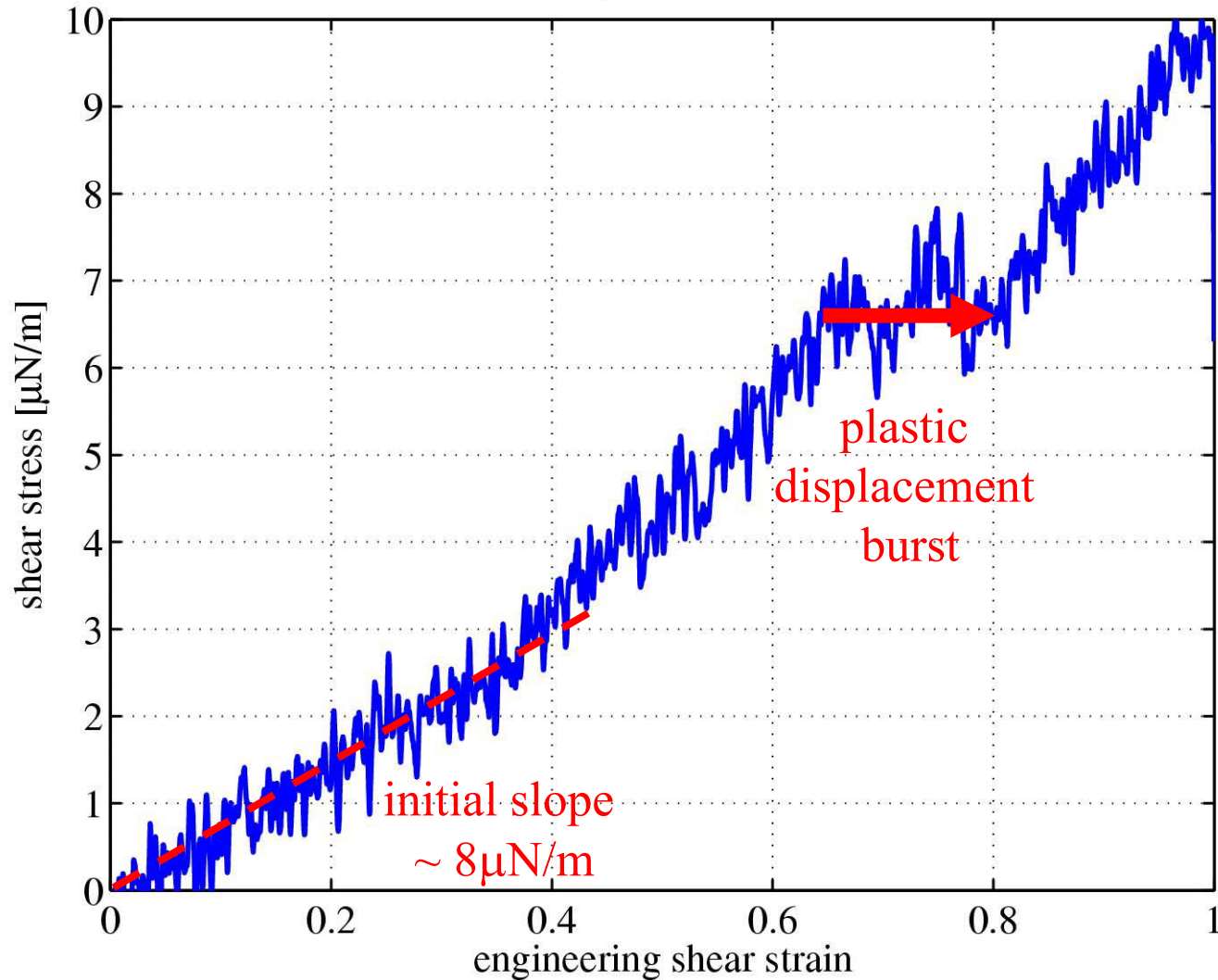


ATP hit rate =  $10/\mu\text{s}$

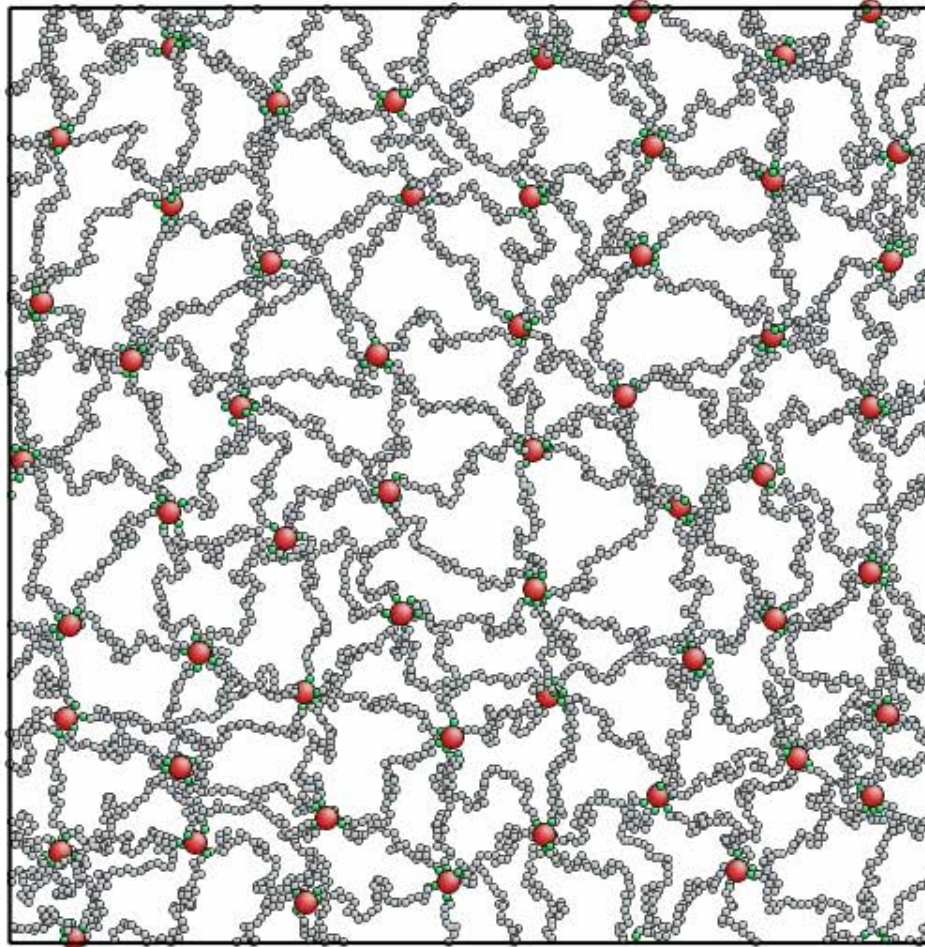


ATP hit rate =  $1/\mu\text{s}$ :

ATP hit rate =  $1/\mu\text{s}$ , strain rate =  $3 \times 10^5/\text{s}$



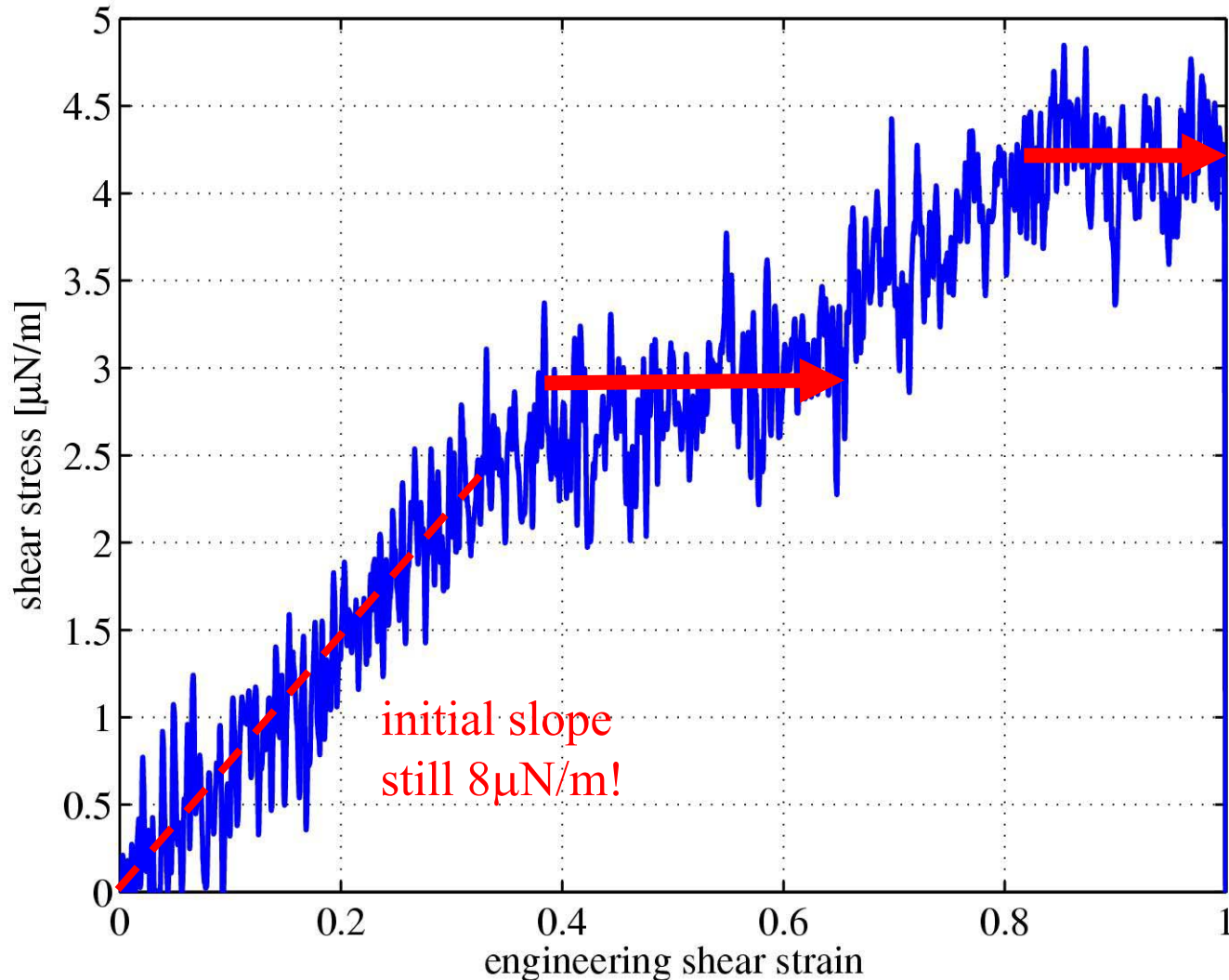
ATP hit rate =  $1/\mu s$



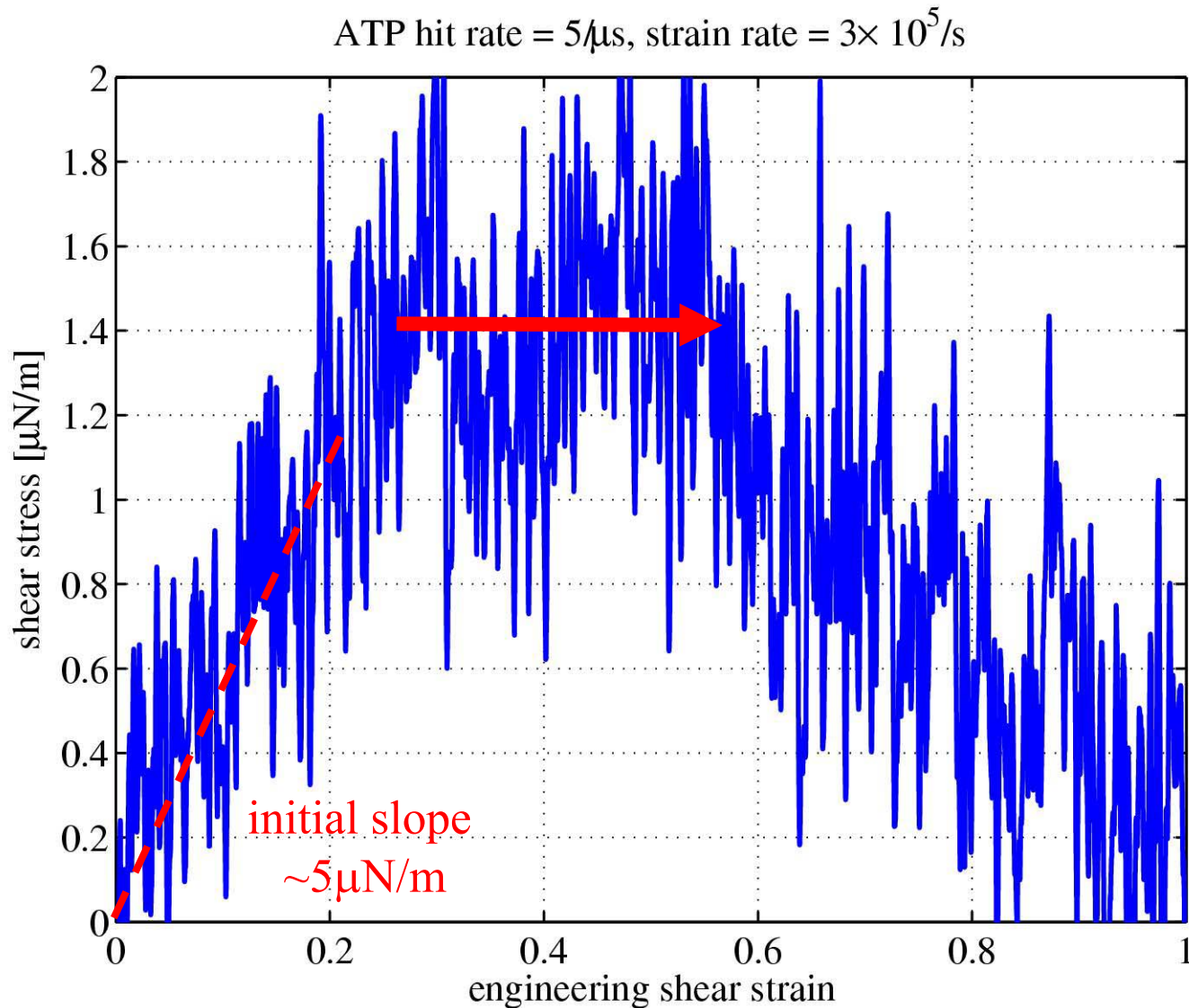


ATP hit rate =  $2/\mu\text{s}$ :  
two plastic displacements... also longer

ATP hit rate =  $2/\mu\text{s}$ , strain rate =  $3 \times 10^5/\text{s}$



# ATP hit rate = $5/\mu\text{s}$ : large-strain resistance collapses, manifest global yield



# Summary

- A minimal CGMD model with *breakable* actin-spectrin junction has been developed, with physically reasonable parameters and behavior.
- ATP hydrolysis is modeled as stochastic kinetic energy transfer. As ATP hit rate rises, we see initiation of plastic displacement excursions, followed by macroscopic yield, and eventually, complete fluidization.
- Practical timescale of CGMD able to simulate **recovery**. J. Li, G. Lykotrafitis, M. Dao and S. Suresh, *Proc. Natl. Acad. Sci. USA* **104** (2007) 4937.

A preview:

## **Vector Fluids: A Coarse-Grained 2D Fluid Membrane Model**

The simplest potential that allows discrete agents to self-assemble into a 2D monolayer, and diffuse around as a 2D fluid.

Each agent has five degrees of freedom  $\{\mathbf{x}_i, \mathbf{n}_i\}$ , with constraint  $|\mathbf{n}_i| = 1$ . Define

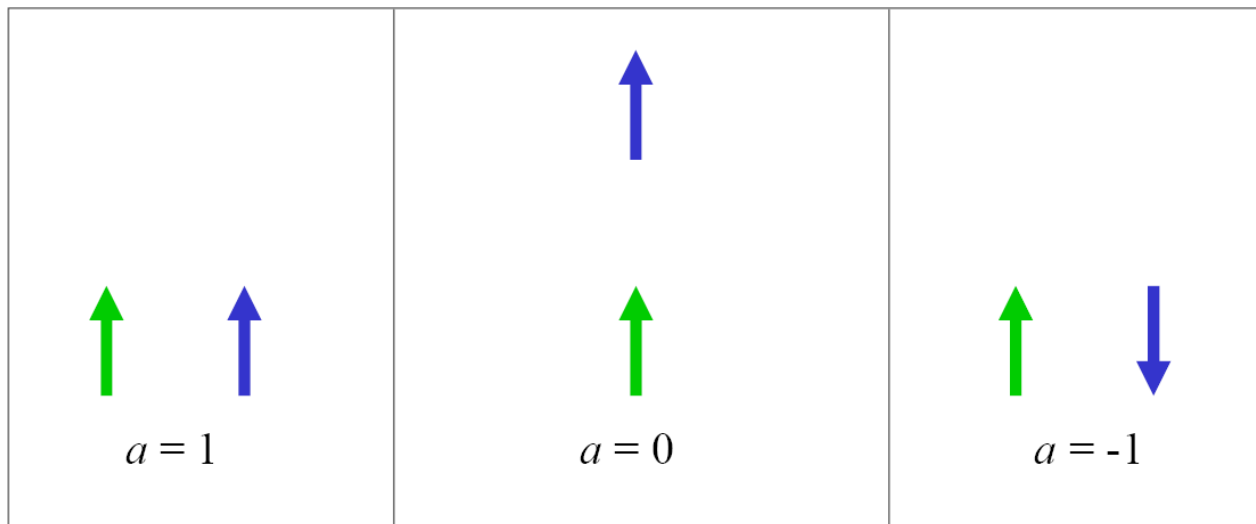
$$\mathbf{x}_{ji} \equiv \mathbf{x}_j - \mathbf{x}_i, \quad r_{ji} \equiv |\mathbf{x}_{ji}|, \quad \hat{\mathbf{x}}_{ji} \equiv \frac{\mathbf{x}_{ji}}{r_{ji}}$$

The total potential is pairwise additive

$$V = \sum_{i < j} v_{ij}$$

with

$$v_{ij}(\mathbf{x}_i, \mathbf{n}_i, \mathbf{x}_j, \mathbf{n}_j) = v_{\text{repulsive}}(r_{ji}) + v_{\text{attractive}}(r_{ji})a(\mathbf{n}_i, \mathbf{n}_j, \hat{\mathbf{x}}_{ji})$$



$$a(\mathbf{n}_i, \mathbf{n}_j, \hat{\mathbf{x}}_{ji}) = (\mathbf{n}_i \times \hat{\mathbf{x}}_{ji}) \cdot (\mathbf{n}_j \times \hat{\mathbf{x}}_{ji}) = \mathbf{n}_i \cdot \mathbf{n}_j - (\mathbf{n}_i \cdot \hat{\mathbf{x}}_{ji})(\mathbf{n}_j \cdot \hat{\mathbf{x}}_{ji})$$

