Mesoscopic Simulations of Lipid Membranes

Patrick Diggins, Mingyang Hu and Markus Deserno

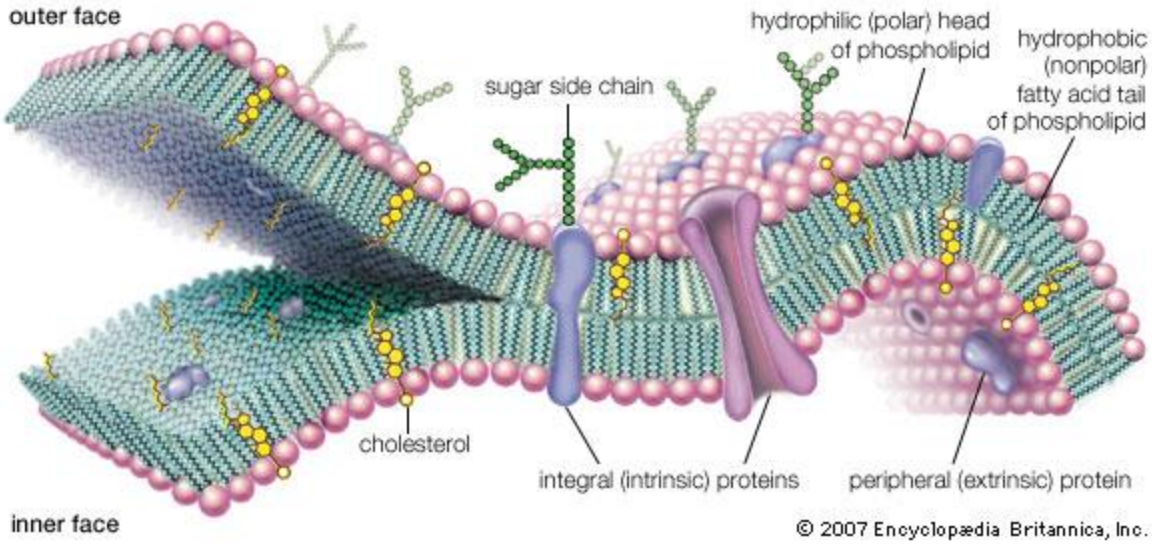
Department of Physics, Carnegie Mellon University, Pittsburgh PA, USA

October 8, 2013

Outline

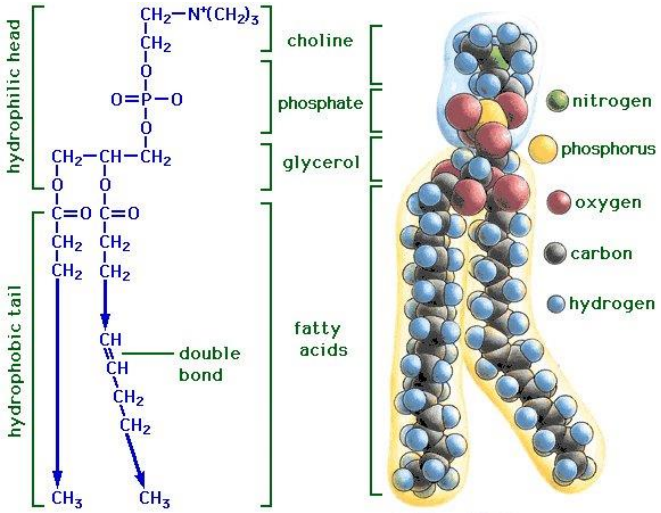
- Introduction
  - Lipid Membranes
  - Why coarse-graining
- Solvent-free CG Model
  - Why Solvent-free
  - Model
- Properties
  - Membrane Elasticity
  - Bending
  - Line Tension
- Code Implementation
- Applications
  - Vesicles
  - Protein-induced Budding
  - Lipid A-B Mixtures

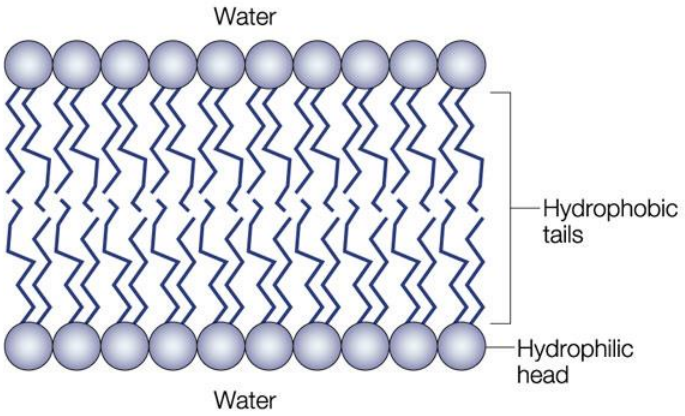
Lipid Membranes



- Lipid membranes form continuous barriers around cells and cellular organelles.
- They are formed by two layers of lipid molecules.

Lipid molecules: Building Blocks

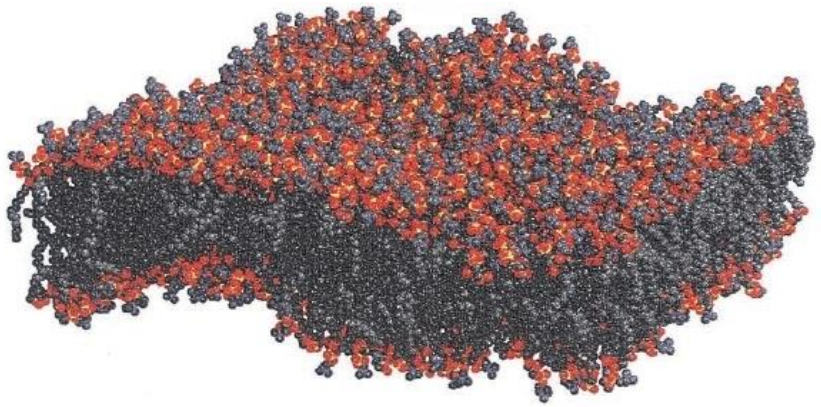




- Lipids are amphiphilic molecules
  - Hydrophilic head (soluble in water)
  - Hydrophobic tail (insoluble in water)
- Membranes form by spontaneous aggregation (self-assemble)

Scaling of Membrane Simulations

- Example simulation[1]
  - All-atom lipid bilayer
  - 20 nm X 20 nm
  - 1024 lipids
  - Simulation time: 10 ns



[1]Lindahl, E. and Edholm, O. *Mesoscopic undulations and thickness fluctuations in lipid bilayers from molecular dynamics simulations.* Biophys. J. 79, 426-433 (2000)

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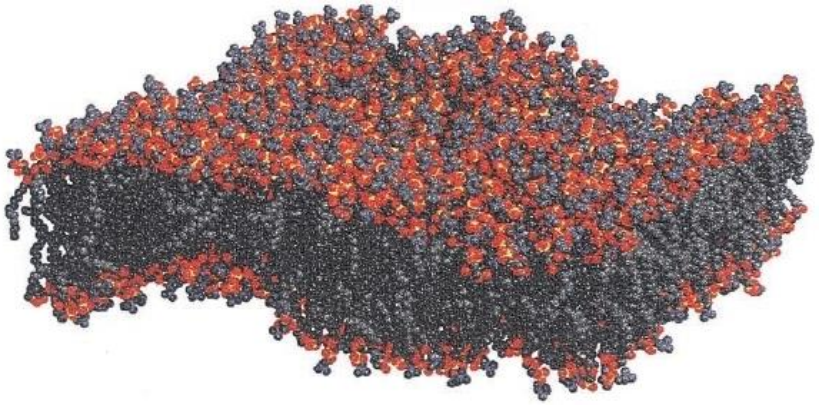

What if we want a box length of L = 200 nm?
How does computing effect scale with L?

$$\text{effort} \sim L^2$$

Amount of material

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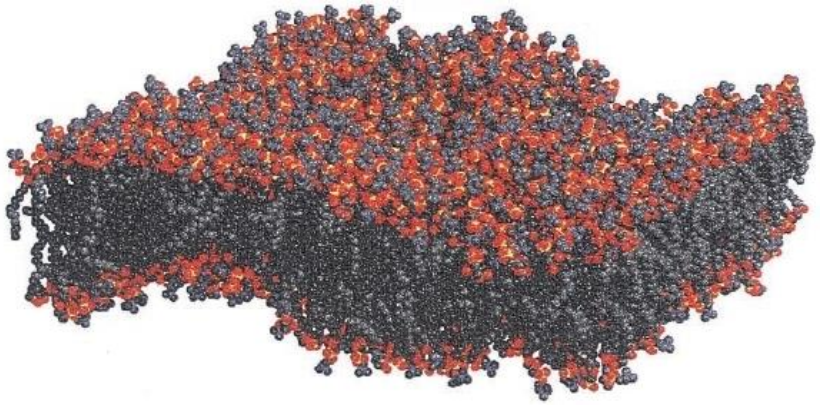


What if we want a box length of L = 200 nm?
How does computing effect scale with L?

$$\text{effort} \sim L^2 \times L^4 \sim L^6$$

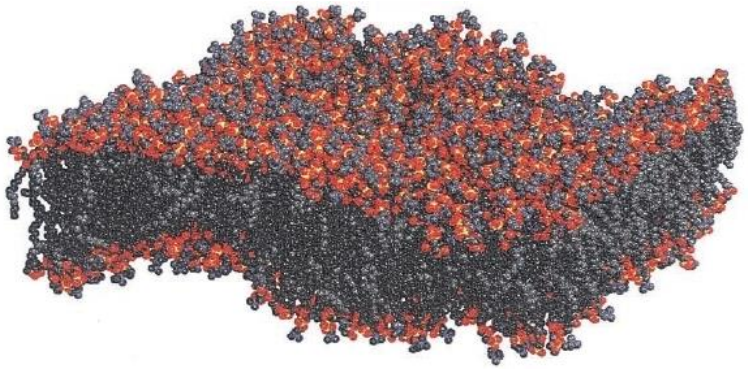
Amount of material

Equilibration time

[1]Lindahl, E. and Edholm, O. *Mesoscopic undulations and thickness fluctuations in lipid bilayers from molecular dynamics simulations.* Biophys. J. 79, 426-433 (2000)

Reason for Coarse-graining

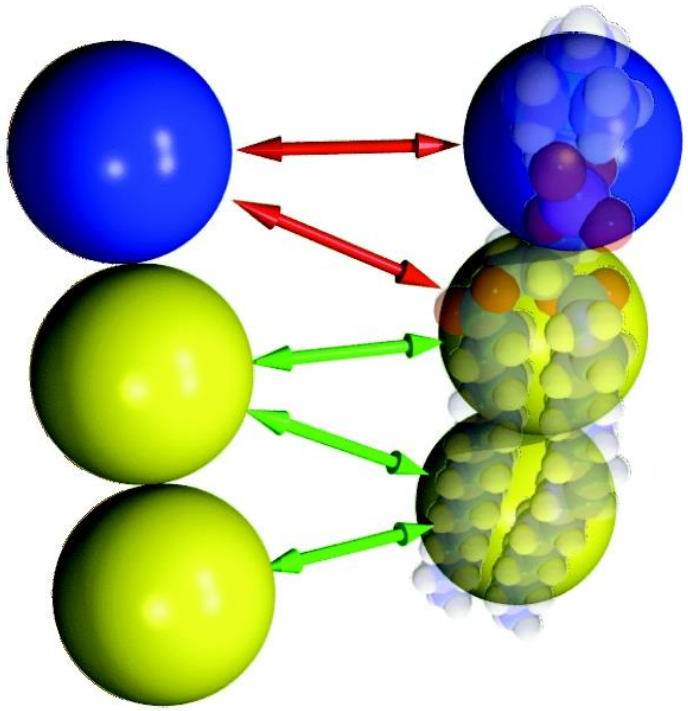
- Going from 20 nm to 200 nm is a million times more expensive.
- Can parallelization compensate?
- Size of membrane: $A = L^2$
- Domain decomposition scheme: increase in CPUs $\sim L^2$
- Simulation time $\sim L^6$
  - uncompensated by a factor of L^4



Parallelization alone does not compensate for increased size.

Reason for Coarse Graining: Efficiency

- Coarse graining gives better sampling.
  - Reduces the number of degrees of freedom
  - Allows larger time steps
  - Smooths the free energy landscape



Reason: Insight

- Coarse graining is the *art* of throwing away unnecessary details.
  - It helps show the important physics of the problem.
  - If the results are not physical, then you know that your theory is missing some important physics.
- Simplify the problem so that we may understand what is happening.

Top-Down approach to CG Lipids

- Goal is to create model that represents physical properties.
- The goal is not to mimic a specific higher resolution model.
- Top-down modeling is an art
  - No systematic way to approach problem

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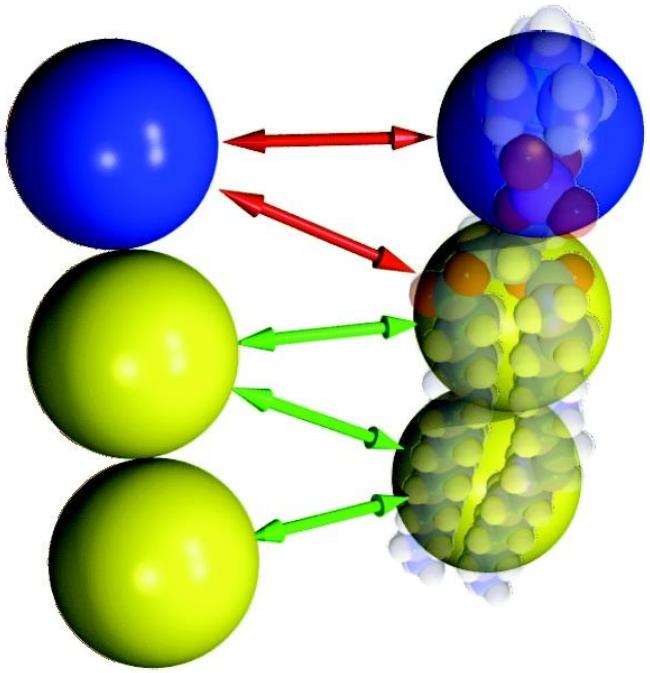
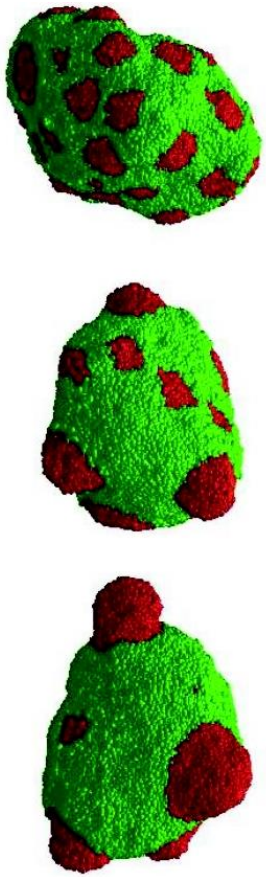
The CG Model[1]

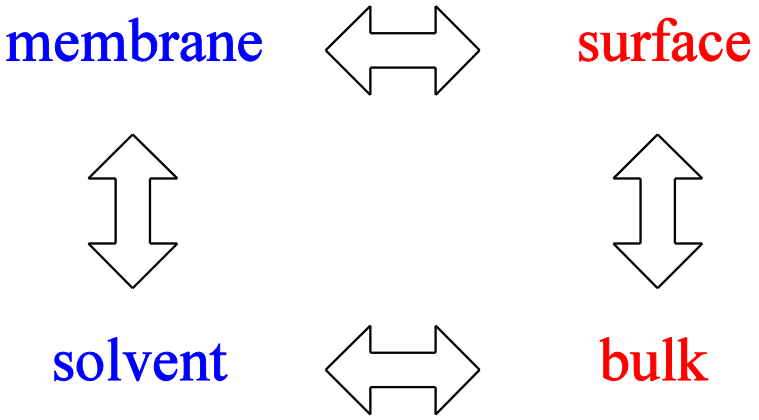


- Coarse-grained lipid designed to probe mesoscopic regime of lipid bilayers.
- 3 beads: reasonable aspect ratio
- Generic bead-spring
- Only pair forces
- Solvent free

[1]I.R. Cooke, K. Kremer, M Deserno, Phys. Rev. E 72, 011506 (2005)
I.R. Cooke and M. Deserno, J. Chem. Phys. 123, 224710 (2005)

Why Solvent Free?



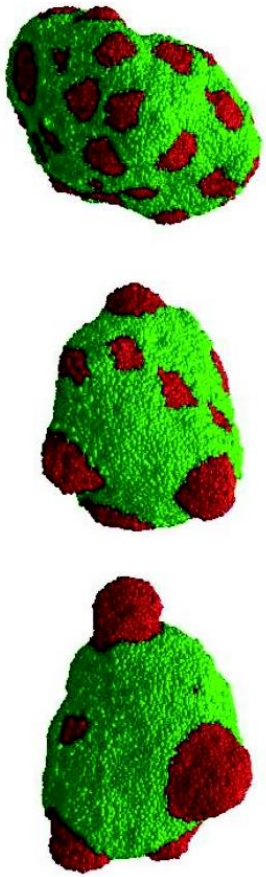


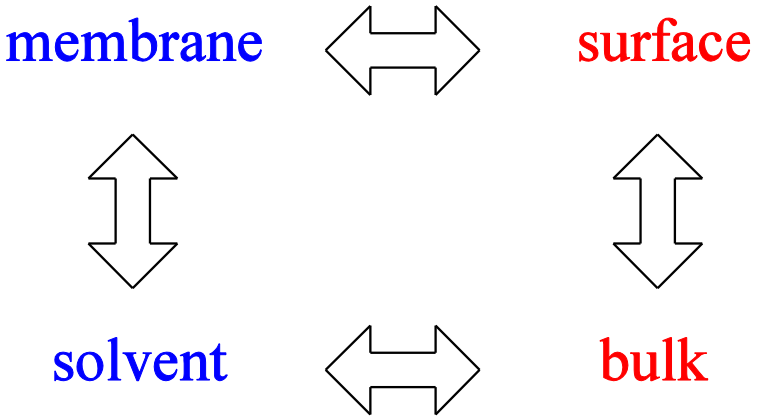
Example[1]:

- 16000 DPD lipids, 4 beads per lipid
- 64000 particles for lipids.
- How many total particles in the box?

[1]M. Laradji and P.B. Sunil Kumar, Phys. Rev. Lett. 93, 198105 (2004)

Why Solvent Free?





Example[1]:

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  - 1 536 000 particles
  - 96% of simulation time spent simulating the solvent.

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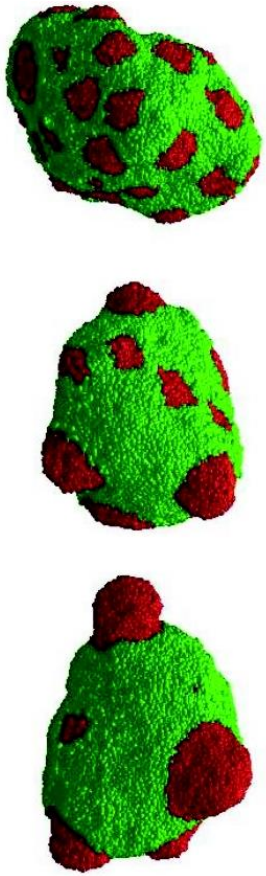
Why Solvent Free?



They wanted to study the dynamics of domain growth which depends on hydrodynamics.

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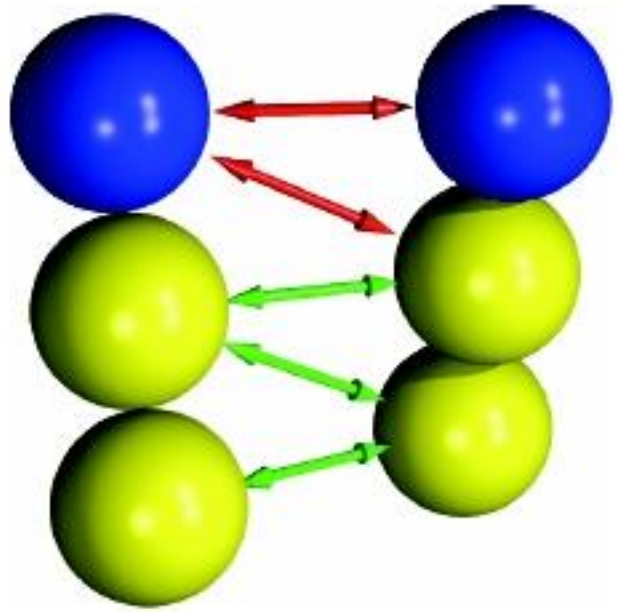
Difficulties with Solvent Free Models

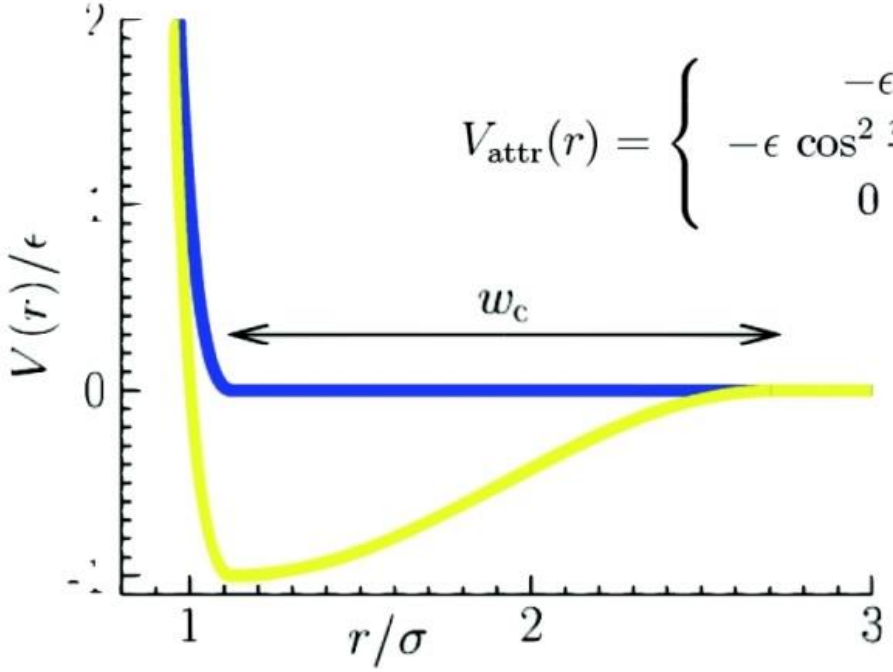
- Implicit solvent models are common and very useful in polymer physics.
- The need for self-assembly and fluidity makes lipid membrane models more difficult.



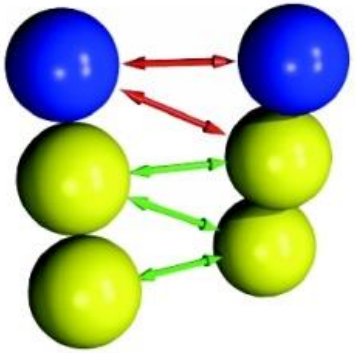
- Cannot use Lennard-Jones interactions:
  - Weak attraction leads to a gas phase
  - Strong attraction leads to a solid (gel) phase
  - No fluid phase

Interactions in the Model

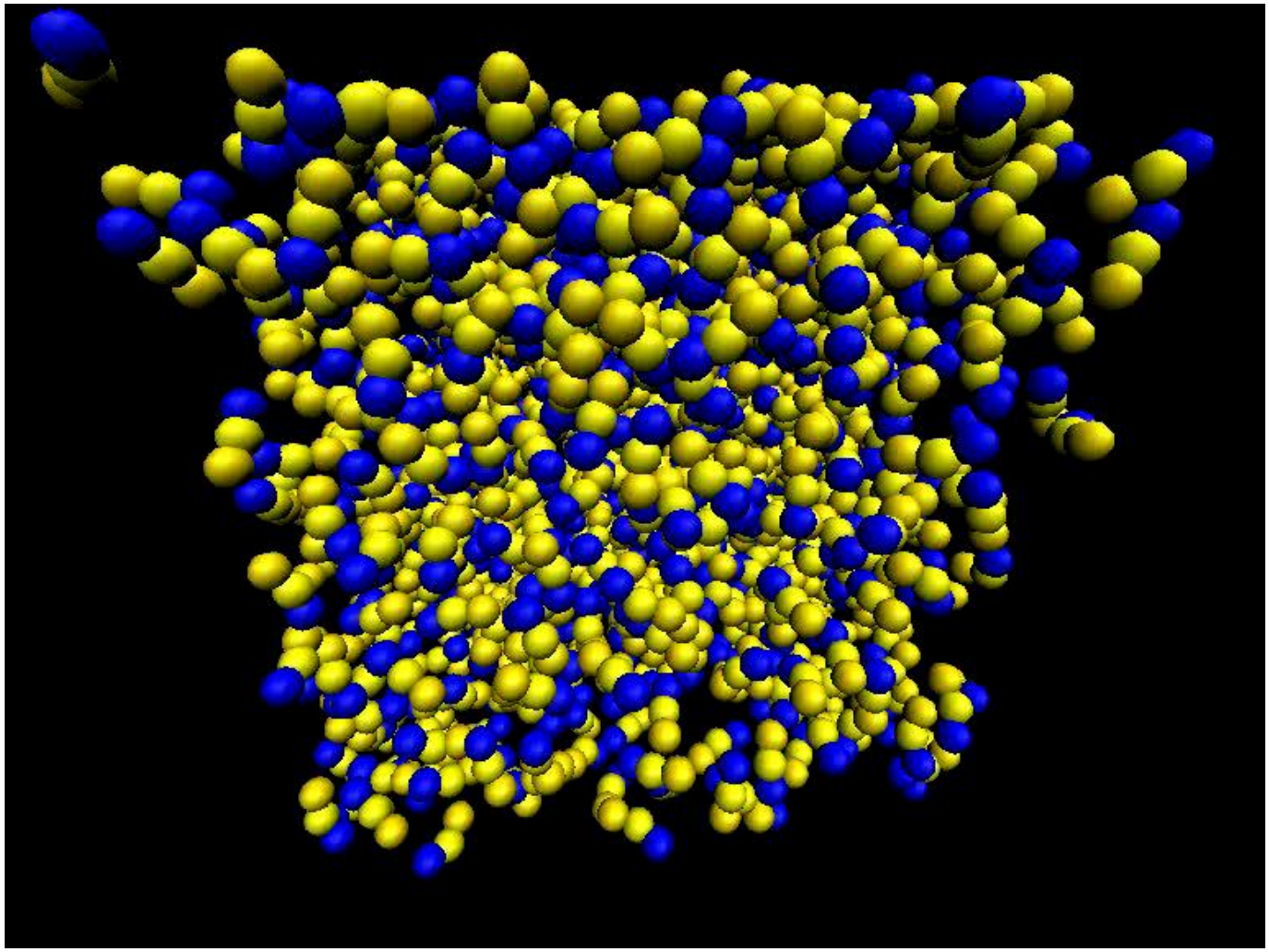
- Need potentials to:
  - Link the beads: $V_{bond}(r) = -\frac{1}{2}k_{bond}{r_\infty}^2 \ln[1-(r/{r_\infty}^2)]$
  - Control the stiffness of the lipid: $V_{bend}(r_{13}) = \frac{1}{2}k_{bend}(r_{13}-4\sigma)^2$
  - Nonbonded : $V_{rep}(r) = 4\epsilon[(r_c/r)^{12} - (r_c/r)^6 + 1/4]\Theta(r_c - r)$



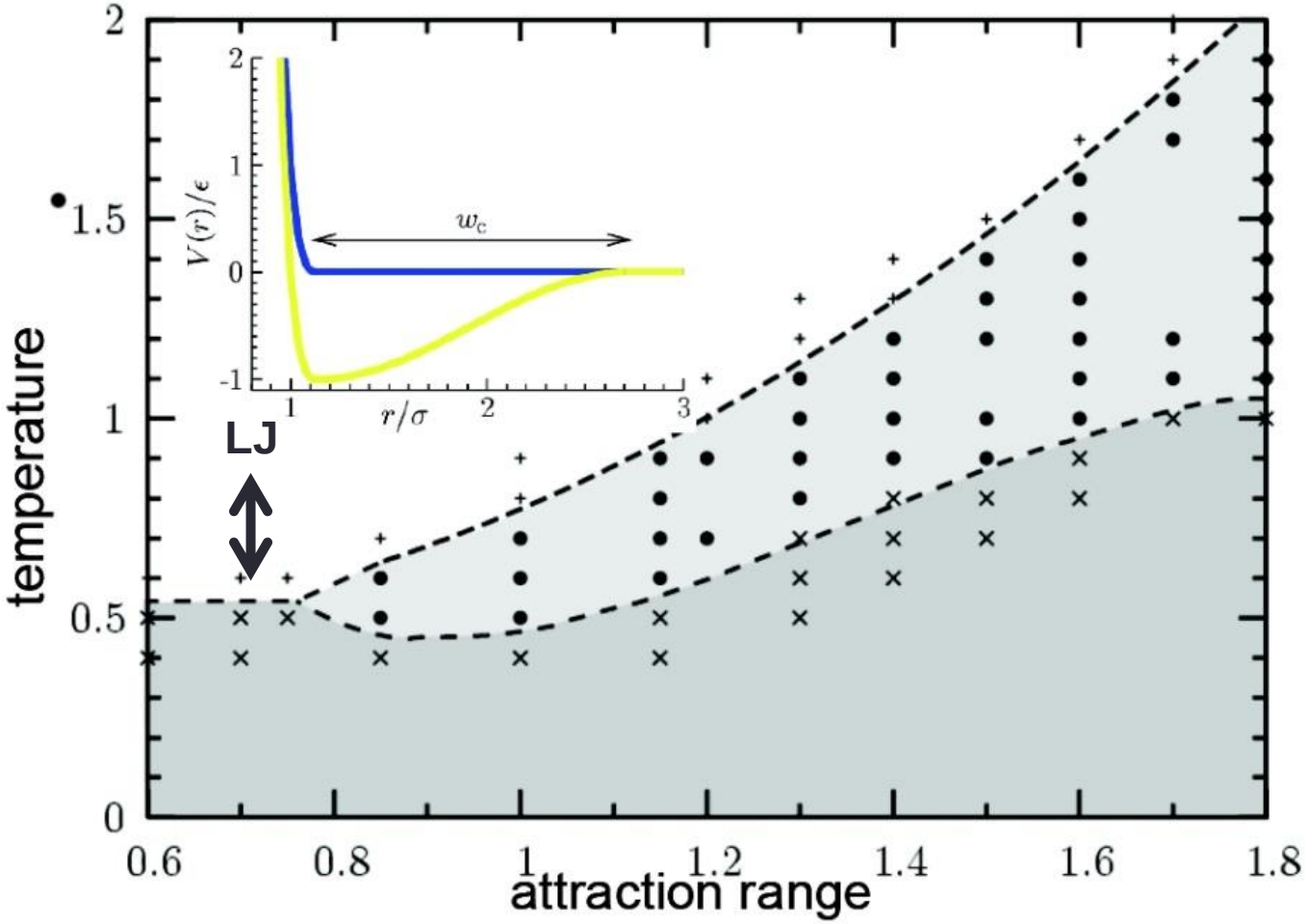
$$V_{\text{attr}}(r) = \begin{cases} -\epsilon & , \quad r < r_c \\ -\epsilon \cos^2 \frac{\pi(r-r_c)}{2w_c} & , \quad r_c \le r \le r_c + w_c \\ 0 & , \quad r > r_c + w_c \end{cases} ,$$



Self-assembly



Phase behavior of the model



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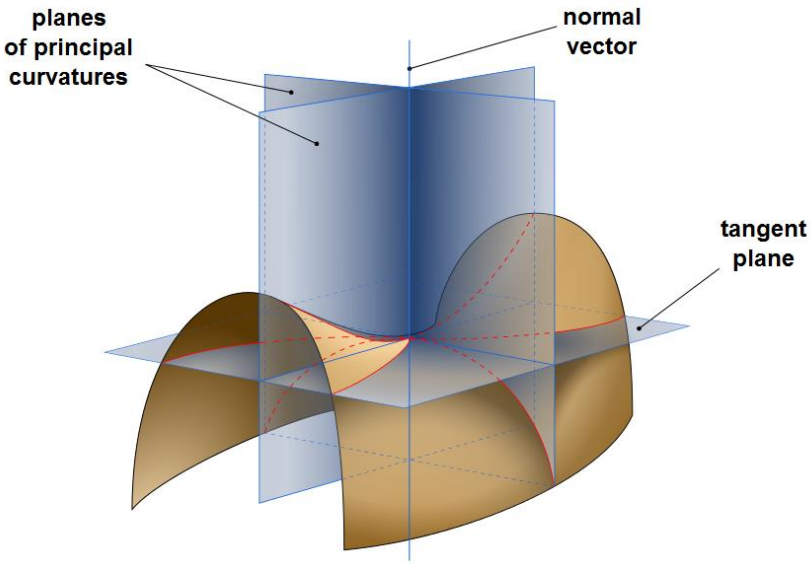
Membrane Elasticity

- Model the membrane as a 2D elastic sheet (continuum theory):

$$\mathrm{E}[S] = \int_S dA \left\{ \frac{1}{2}\kappa(K - K_0)^2 + \bar{\kappa} K_G + \sigma \right\}$$

  - κ: Bending modulus
  - $\bar{\kappa}$: Gaussian curvature modulus
  - $K = c_1 + c_2$: Total curvature
  - K_0: Intrinsic curvature
  - $K_G = c_1 c_2$: Gaussian curvature
  - σ: Surface tension



en.widipedia.org/wiki/Curvature

Bending Modulus from Fluctuation Spectrum

- $\mathrm{E}[S] = \int_S dA \left\{ \frac{1}{2}\kappa(K - K_0)^2 + \sigma \right\} \simeq$

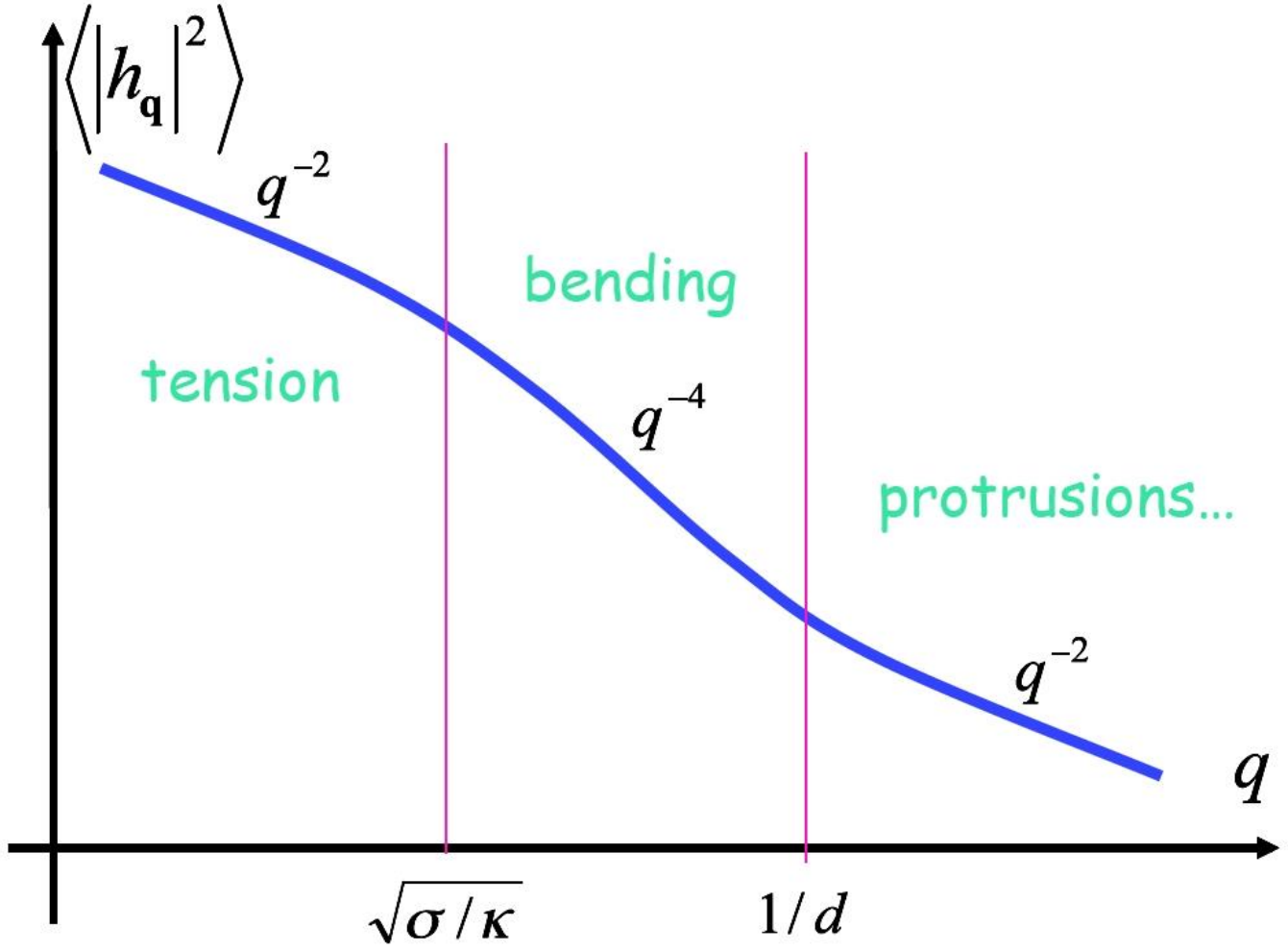
  $\int dx\, dy \left\{ \frac{1}{2}\kappa(\nabla^2 h)^2 + \frac{1}{2}\sigma(\nabla h)^2 \right\}$

  - $h(x, y)$: height function (Monge gauge)

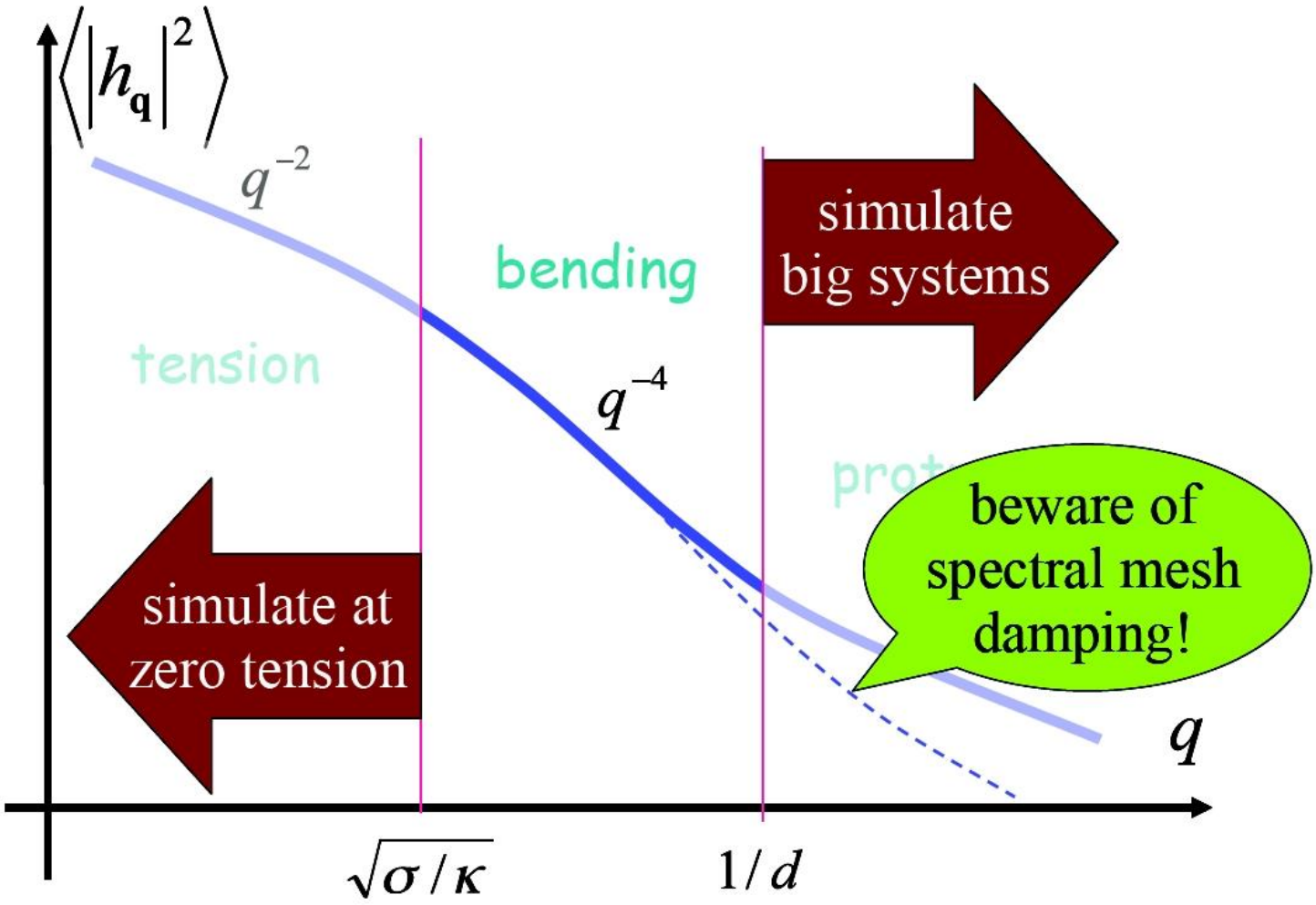
- Fourier expansion and equipartition theorem

$$\left\langle |h_q|^2 \right\rangle = \frac{k_b T}{L^2[\kappa q^4 + \sigma q^2]} \xrightarrow[\sigma \to 0]{} \frac{k_b T}{L^2 \kappa q^4}$$

Fluctuation spectrum from continuum theory



Fluctuation spectrum from continuum theory



Problems with Fluctuation Spectrum

- Equilibration time of Fourier modes scale like q^{-4}
- Measuring large bending modulus κ ($20\ k_bT$) from small perturbation ($1\ k_bT$).
- Result relevant for strong bending?

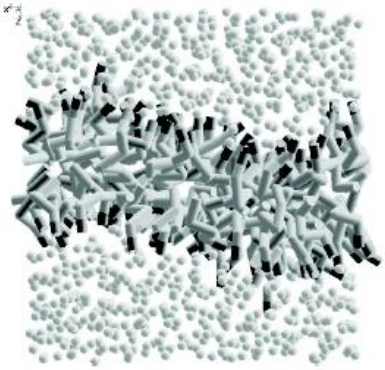
$$h(x) = h_q e^{iqx} \rightarrow K = -h''(x) = h_q q^2 e^{iqx}$$

$$\langle K^2 \rangle = q^4 \left\langle \left| h_q \right|^2 \right\rangle = \frac{k_bT}{L^2\kappa}$$

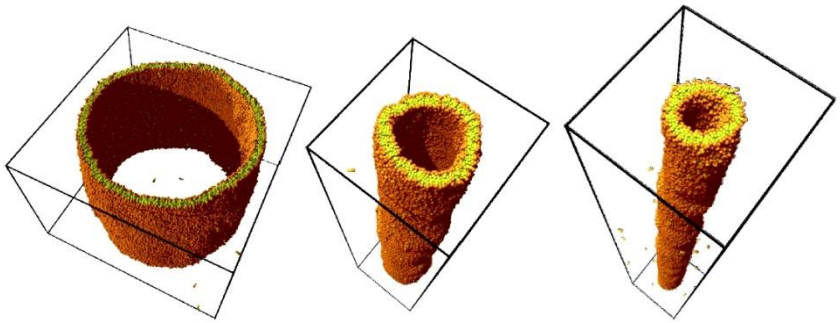
$$\bar{R} = \frac{1}{\langle K^2 \rangle^{1/2}} = \sqrt{\frac{\kappa}{k_bT}} L \sim 5L$$

κ from Actively Bent Membranes

- First implementation[1]:
  - Enforce large undulation mode
  - Measure the constraining force.



- Better way[2]:
  - Stretch a membrane tether



[1]W. K. den Otter and W. J. Briels, J. Chem. Phys. 118, 4712 (2003)
[2]V. A. Harmandaris and M. Deserno, J. Chem. Phys. 125, 204905 (2006)

Cylindrical tethers

- Energy:

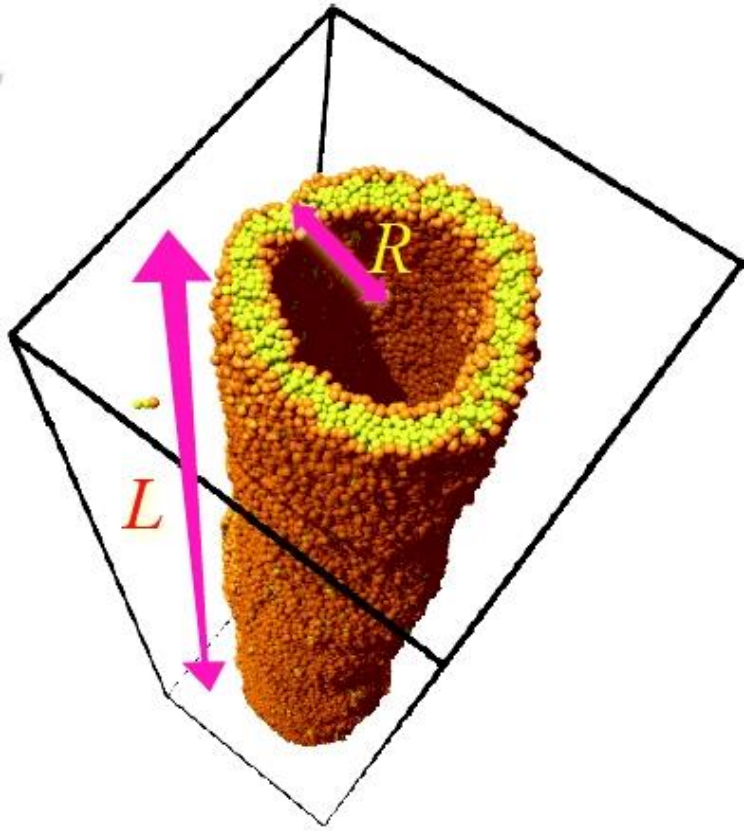
$$E = \frac{1}{2}\kappa\left(\frac{A}{R^2}\right)$$

- Force:

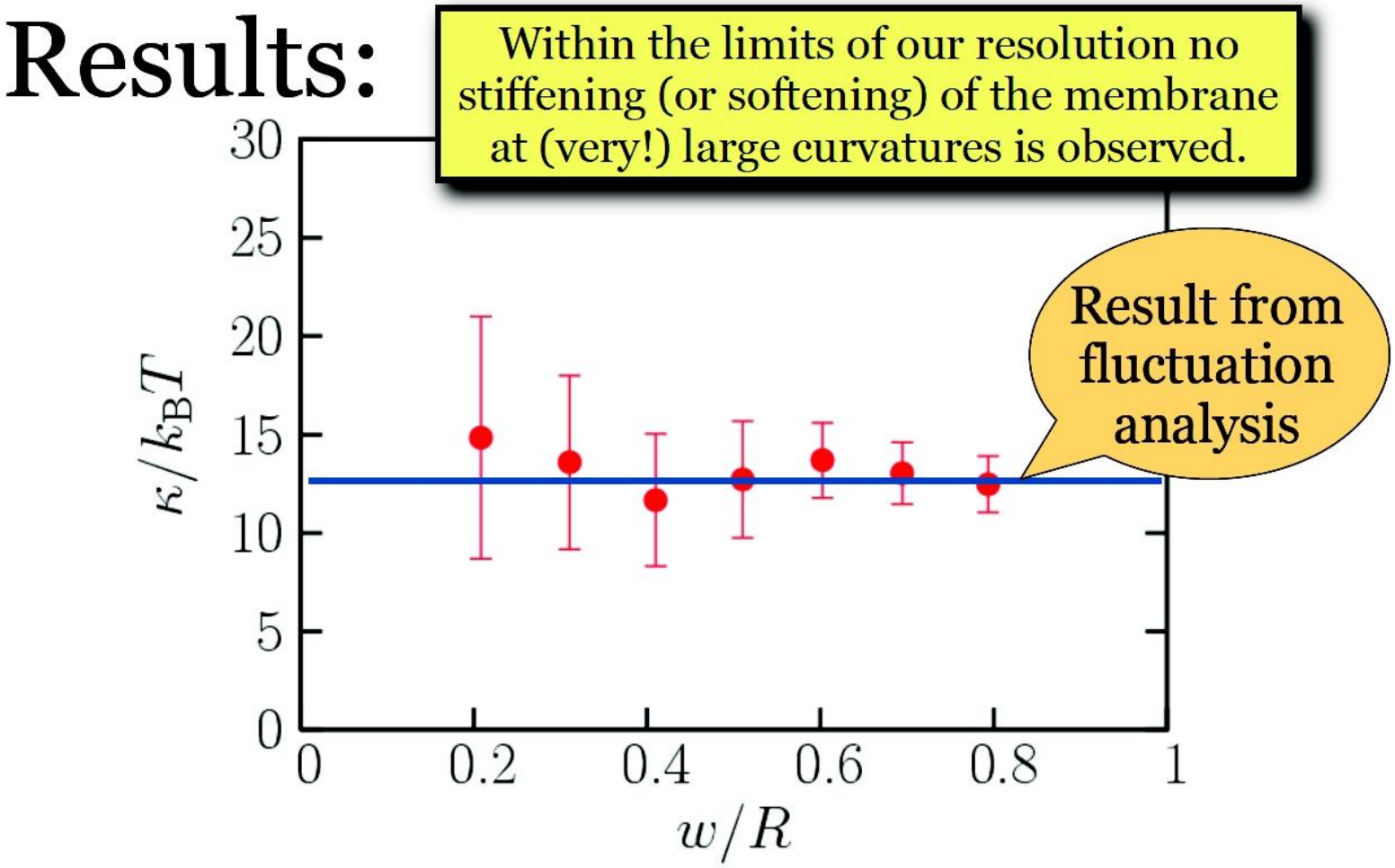
$$F = \left(\frac{\partial E}{\partial L}\right)_A = \frac{2\pi\kappa}{R}$$

- Bending modulus:

$$\kappa = \frac{FR}{2\pi}$$



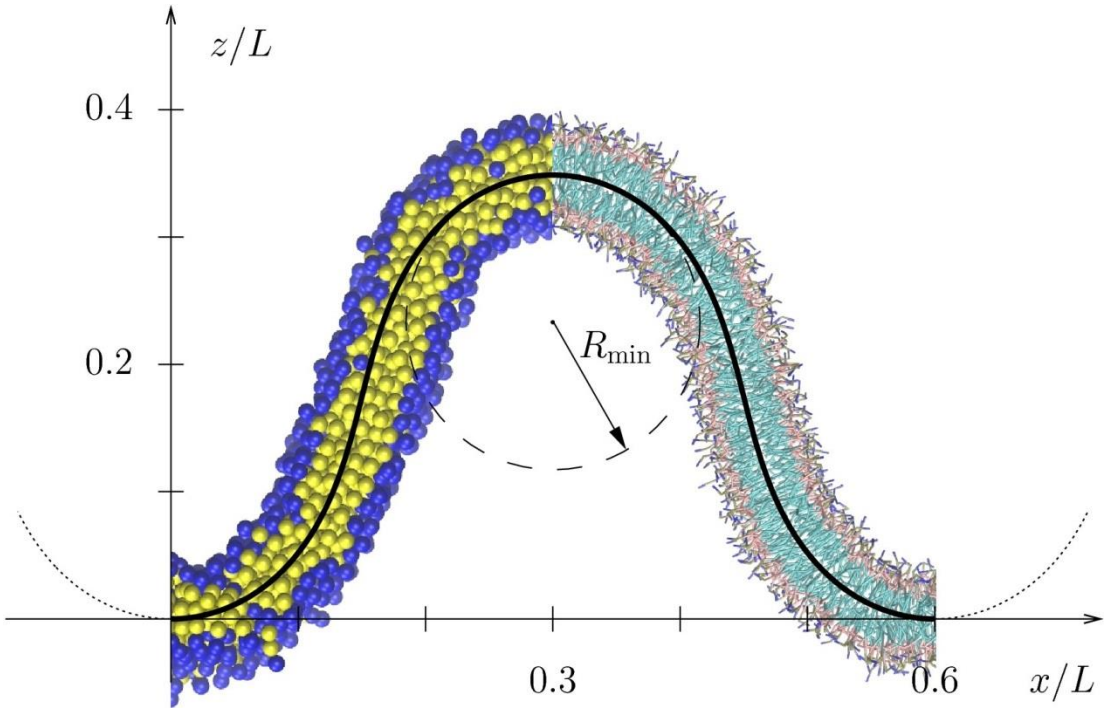
Actively Bent Membranes (Results)



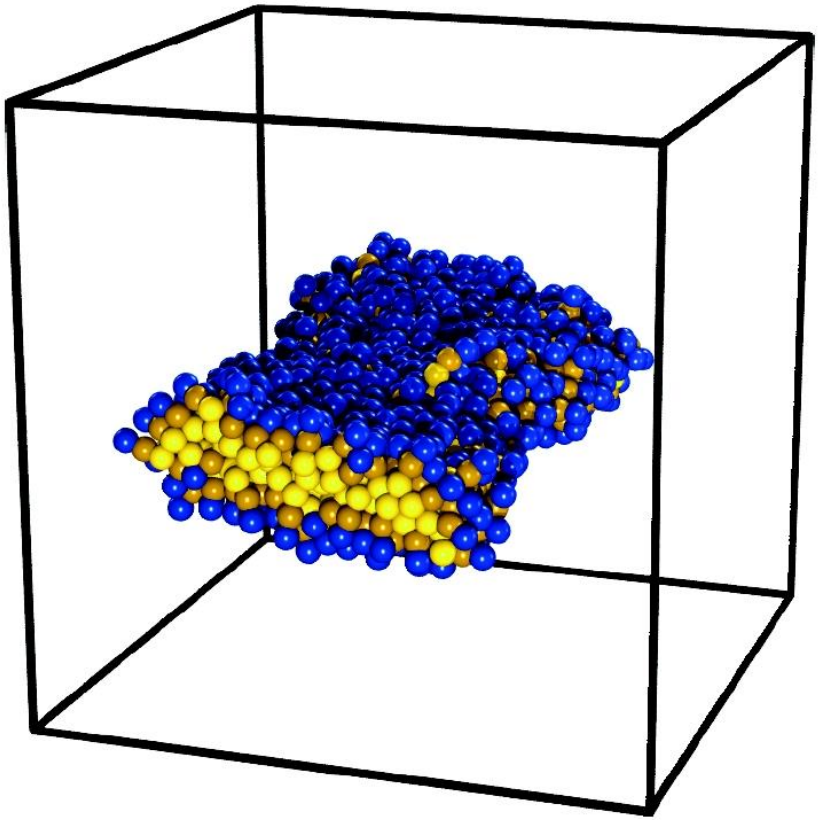
V. A. Harmandaris and M. Deserno, J. Chem. Phys. 125, 204905 (2006)

κ from buckled membrane

- New method to determine κ from a buckled membrane.
- Subject of talk on Friday.

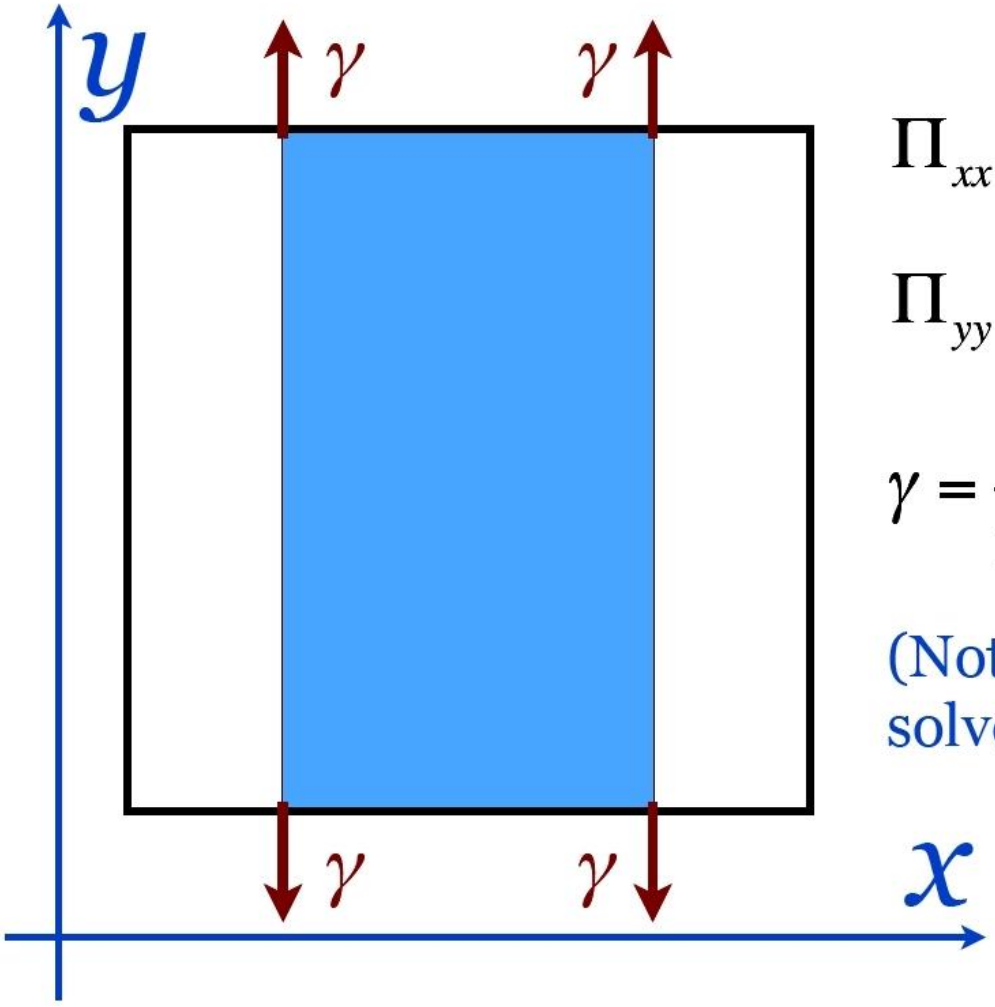


Simple way to extract line tension



- Simulate a periodically half-connected bilayer
- Stress tensor is imbalanced by twice the line tension.

Extracting line tension



$$\Pi_{xx} = P$$

$$\Pi_{yy} = P - 2\gamma / L_x L_z$$

$$\gamma = \frac{1}{2} L_x L_z \left(\Pi_{xx} - \Pi_{yy} \right)$$

(Notice that $P = 0$ in the solvent free case!)

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Implementation

- `mbtools` architecture:
  - Engine (`C`)
    - Interactions (lj-cos^2 interaction implemented as a feature)
    - Several analysis routines (e.g. modes, stress tensor)
  - User-interface (`Tcl`)
    - System generation (e.g. initial particle positions)
    - Parameters (configuration files)
    - Register particles in ESPResSo (e.g. topology, interactions
    - Call to `integrate` command
    - Analysis/output
- Program structure located in:

  `ESPRESSO/packages/mbtools`

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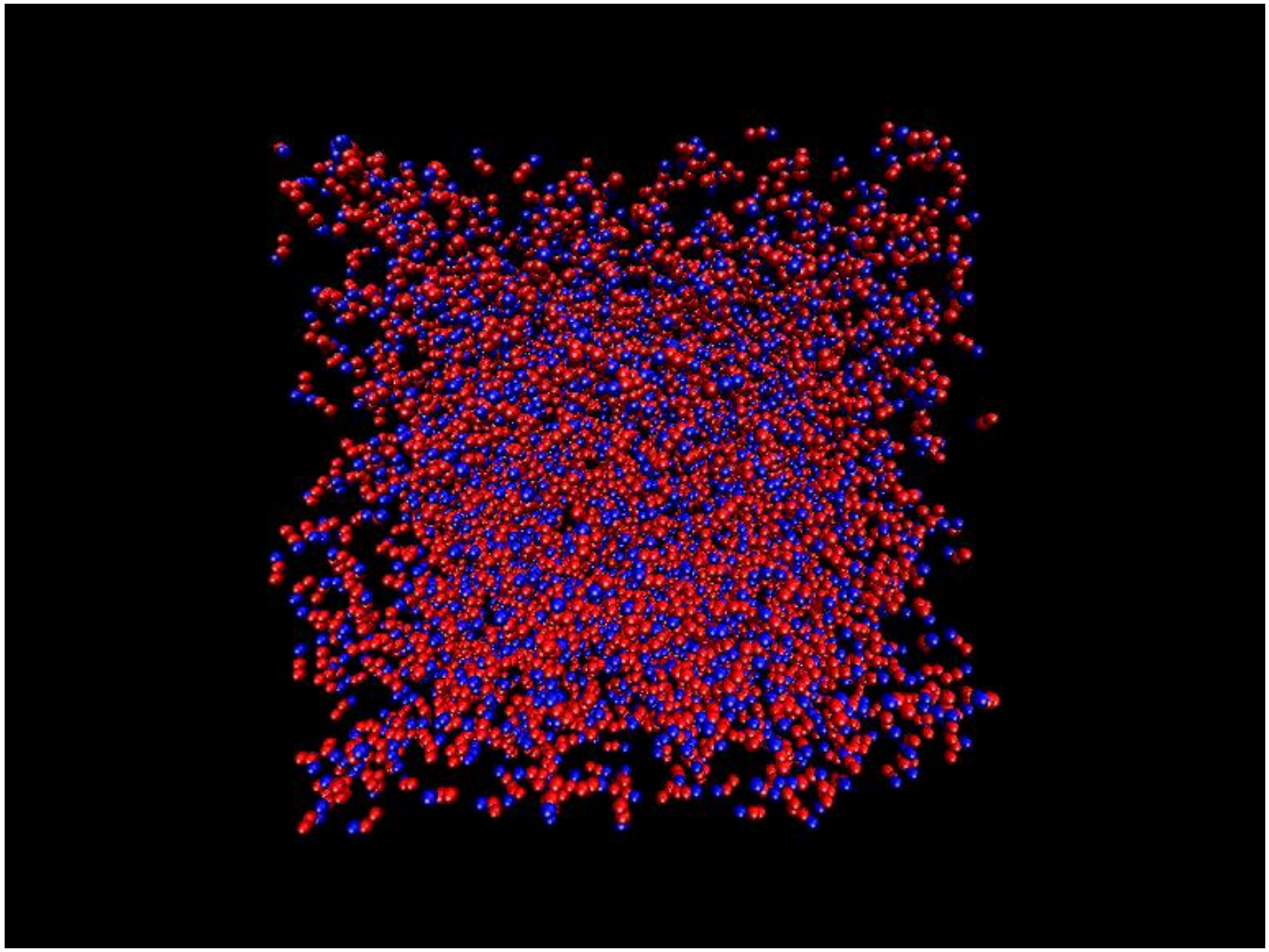
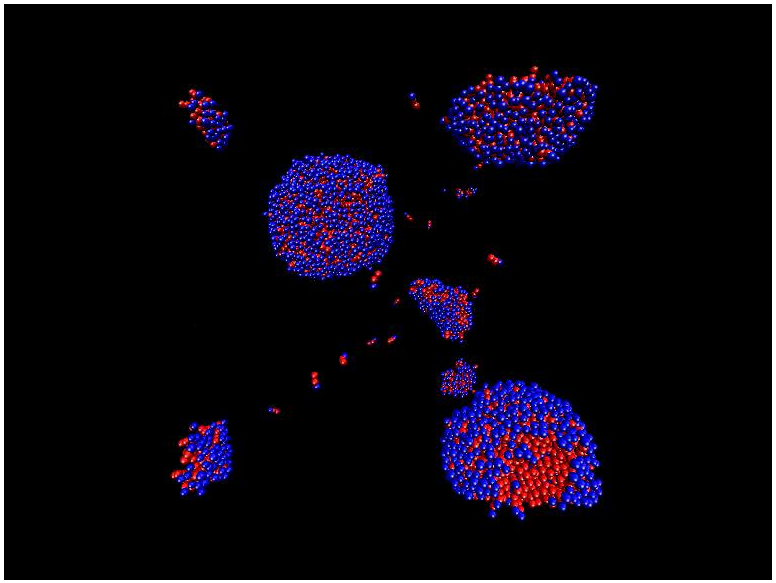
Vesicles

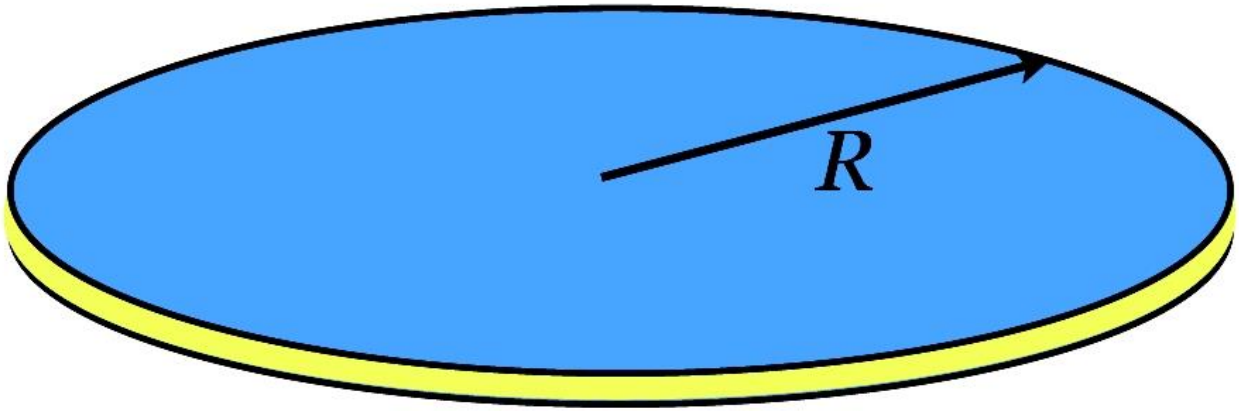


Vesicles

- Sonicate vesicle solution:
  - Rip membranes into small pieces
- The (flat) pieces merge and become bigger
- At some point, they close up to form vesicles.
- Competition between bending rigidity and line tension.



Energetics



$$E_{\text{pancake}} = 2\pi R\,\gamma$$

$$E_{\text{vesicle}} = 4\pi\left(2\kappa + \bar{\kappa}\right)$$

Energies are equal, if

$$R_{\text{pancake}} = \frac{2\left(2\kappa + \bar{\kappa}\right)}{\gamma}$$

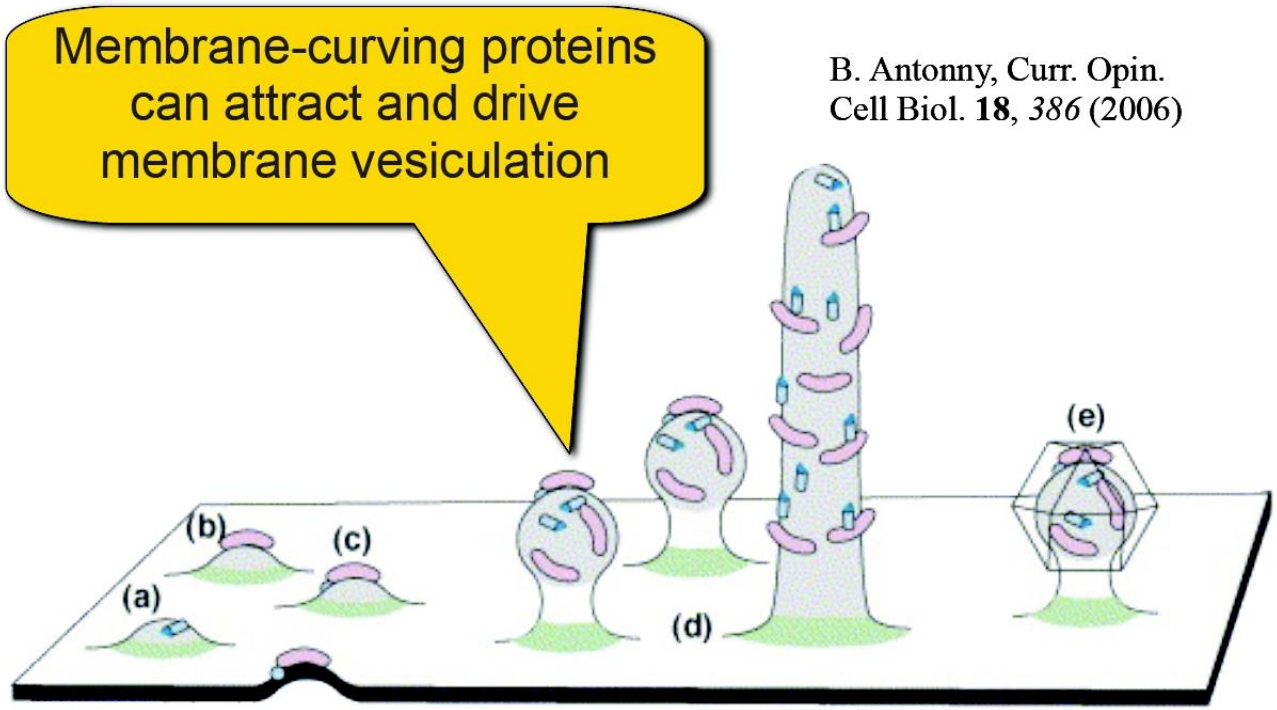
(real stability analysis: 2 → 4)

Diameter of Vesicles

- What do we expect:
  - $\kappa = 20 k_b T \approx 80$ pN nm
  - $\bar{\kappa} \approx -\kappa$
    - For more information of $\bar{\kappa}$, see Hu *et. al.*[1]
  - $\gamma \approx 10$pN
  - $R_{pancake} = \frac{4(2\kappa+\bar{\kappa})}{\gamma} \approx \frac{4\kappa}{\gamma} \approx \frac{320\ \mathrm{pNnm}}{10\ \mathrm{pN}} = 32\ \mathrm{nm}$

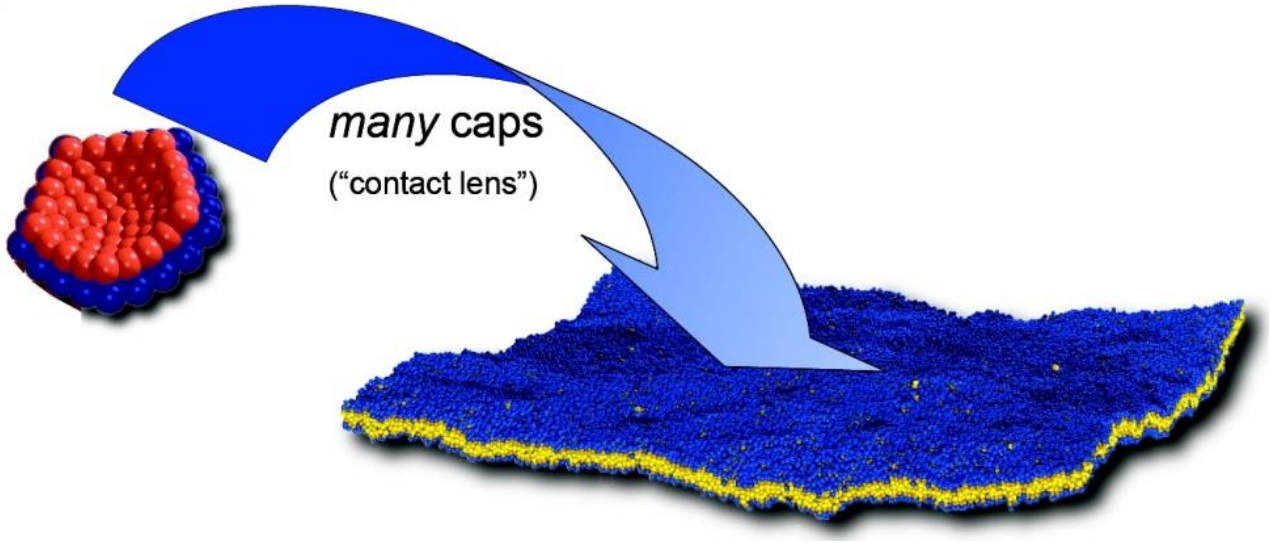
[1]M Hu, J. J. Briguglio, and M. Deserno. Biophys. J. **102**, 1403-1410 (2012)

Protein-induced budding



Intuitive model, but physically justified?

Protein-induced budding



- 36 curved caps, ~50 000 lipids
- 160 nm side-length
- Total time ~1ms
- No lateral tension
- No explicit interaction between caps

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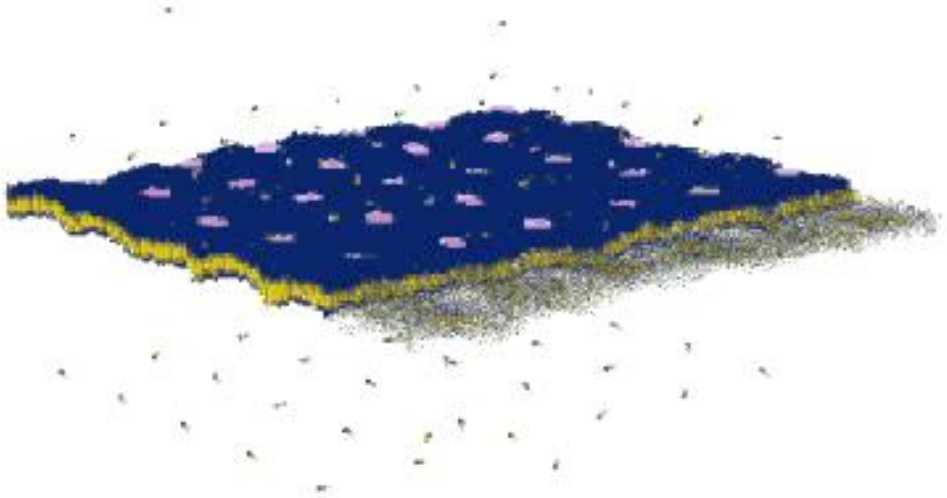
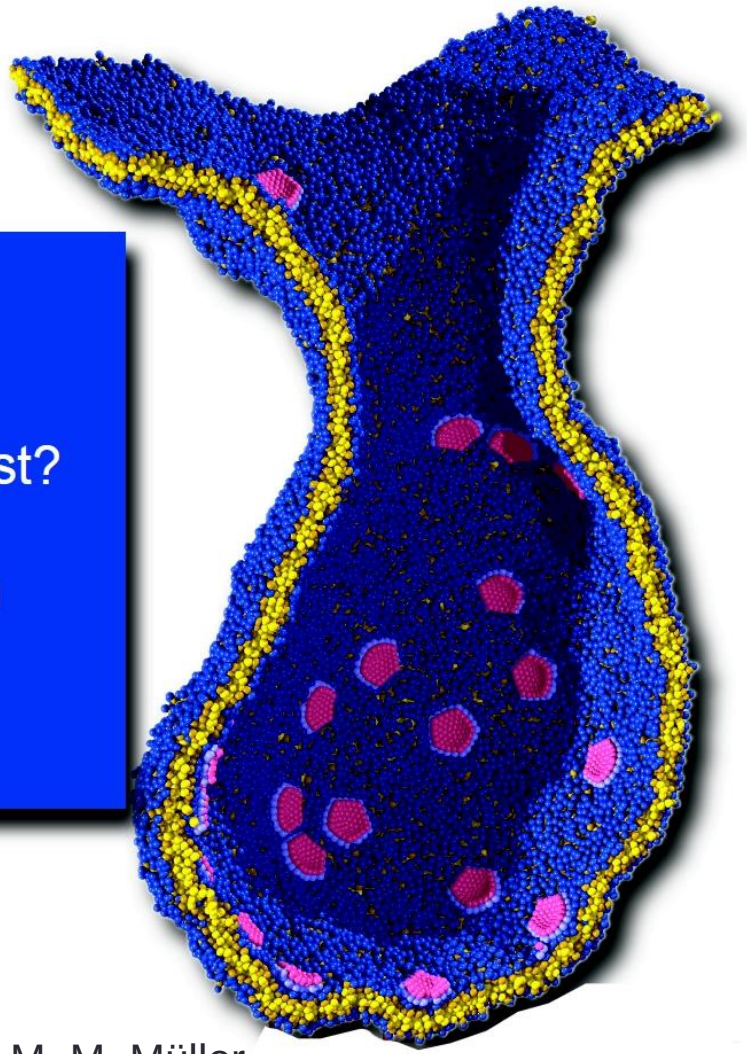
Protein-induced budding



B. J. Reynwar, G. Illya, V. A. Harmandaris, M. M. Müller, K. Kremer and M. Deserno. Nature 447, 461 (2007)

Protein-induced budding

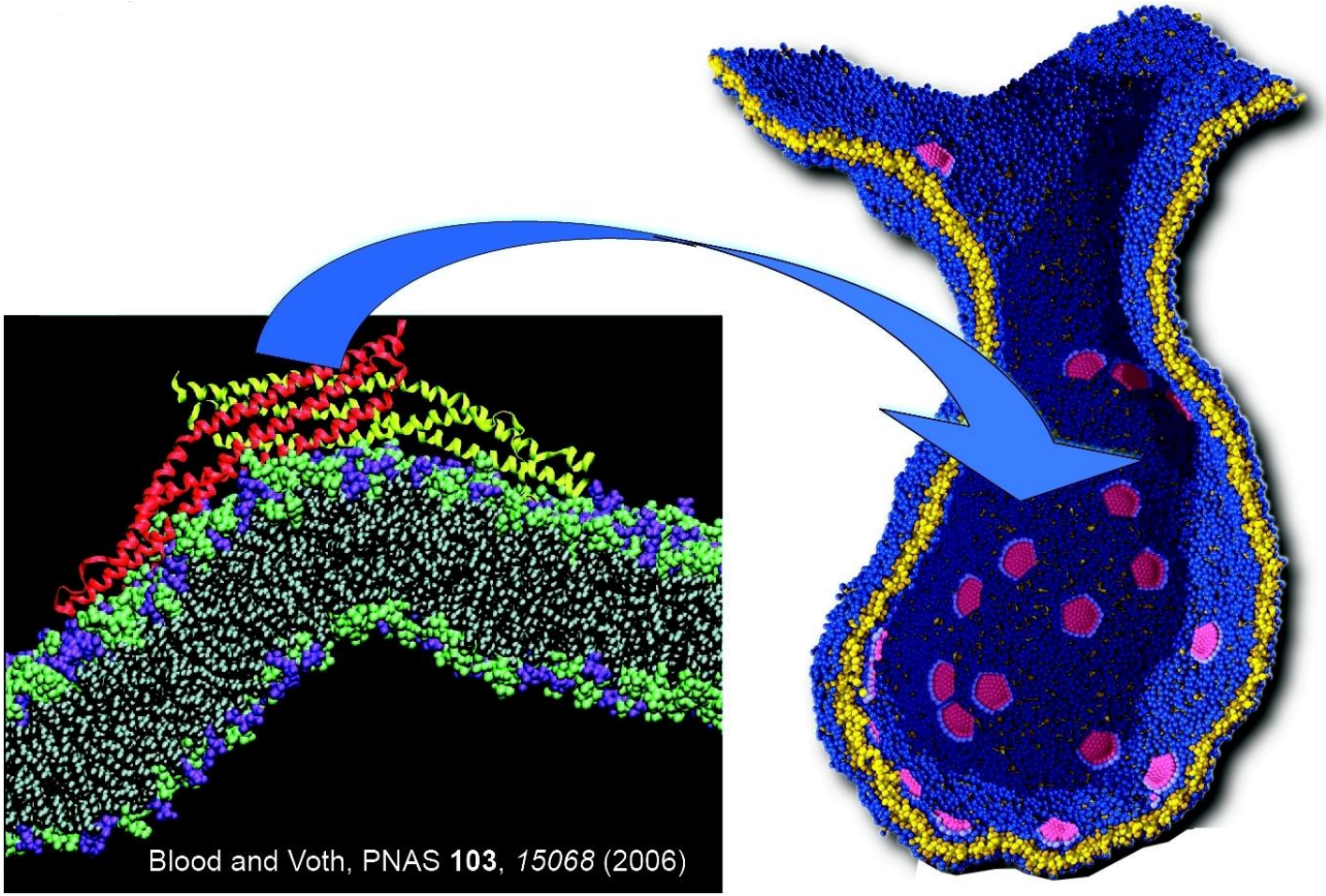


Some observations:

- Caps **attract** collectively
- Attractive pair-forces exist?
- No crystalline structure
- Cooperative vesiculation
- No “scaffolding”
- 50-100nm length scales
- several milliseconds

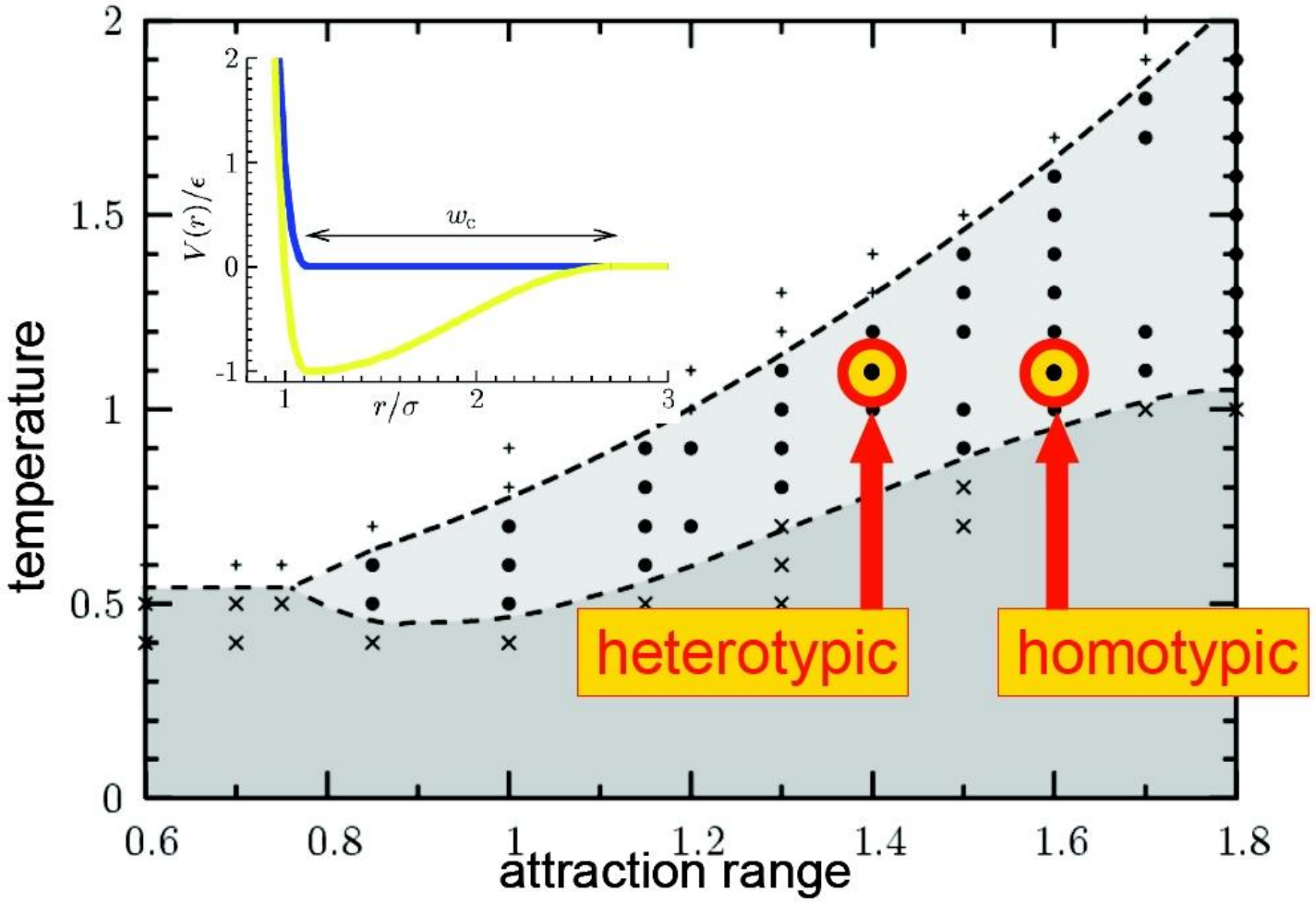
B. J. Reynwar, G. Illya, V. A. Harmandaris, M. M. Müller, K. Kremer and M. Deserno. Nature 447, 461 (2007)

Protein Induced budding

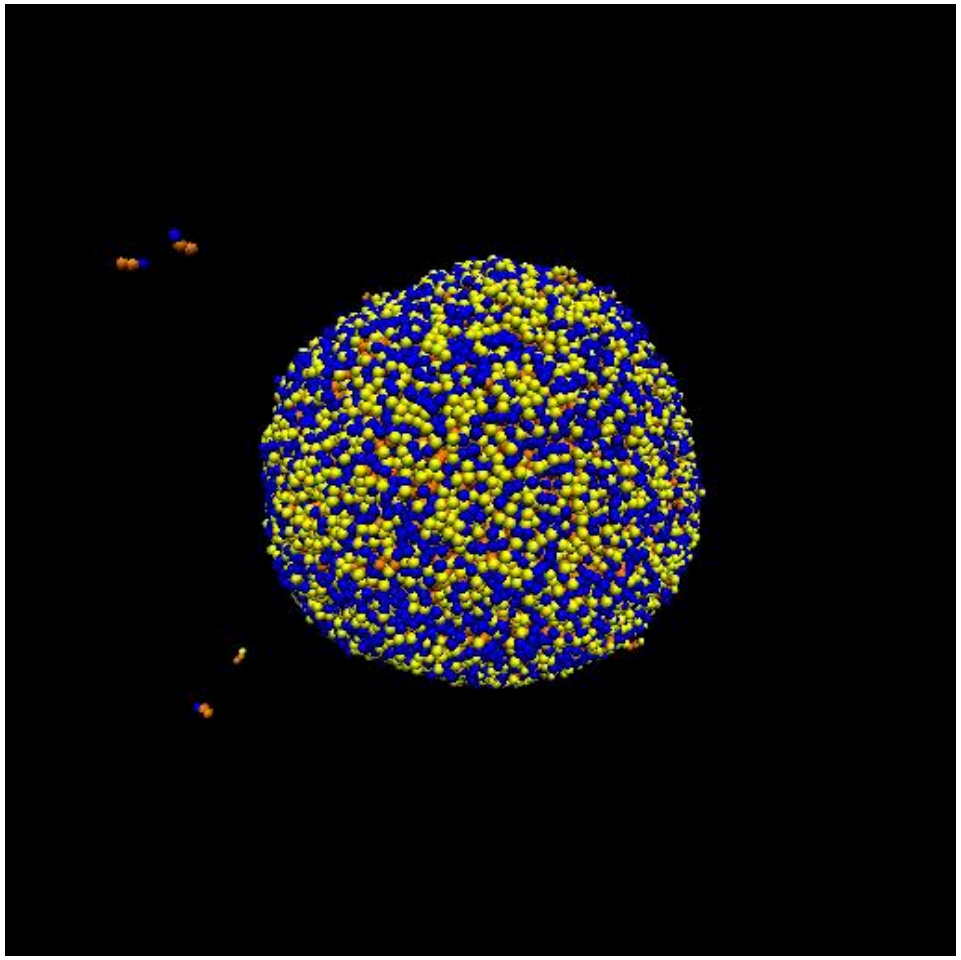


B. J. Reynwar, G. Illya, V. A. Harmandaris, M. M. Müller, K. Kremer and M. Deserno. Nature 447, 461 (2007)

Lipid A-B Mixtures

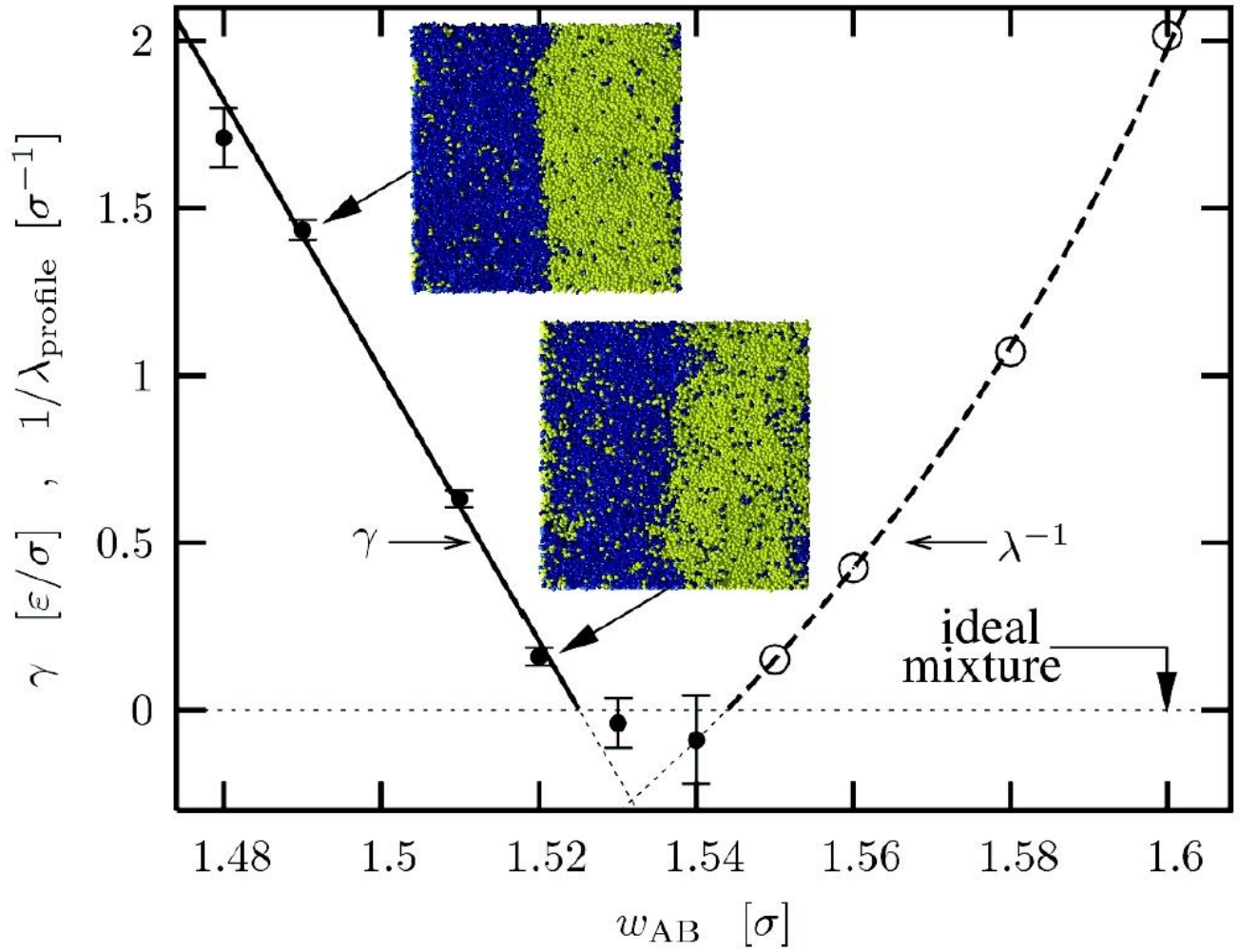


Movies

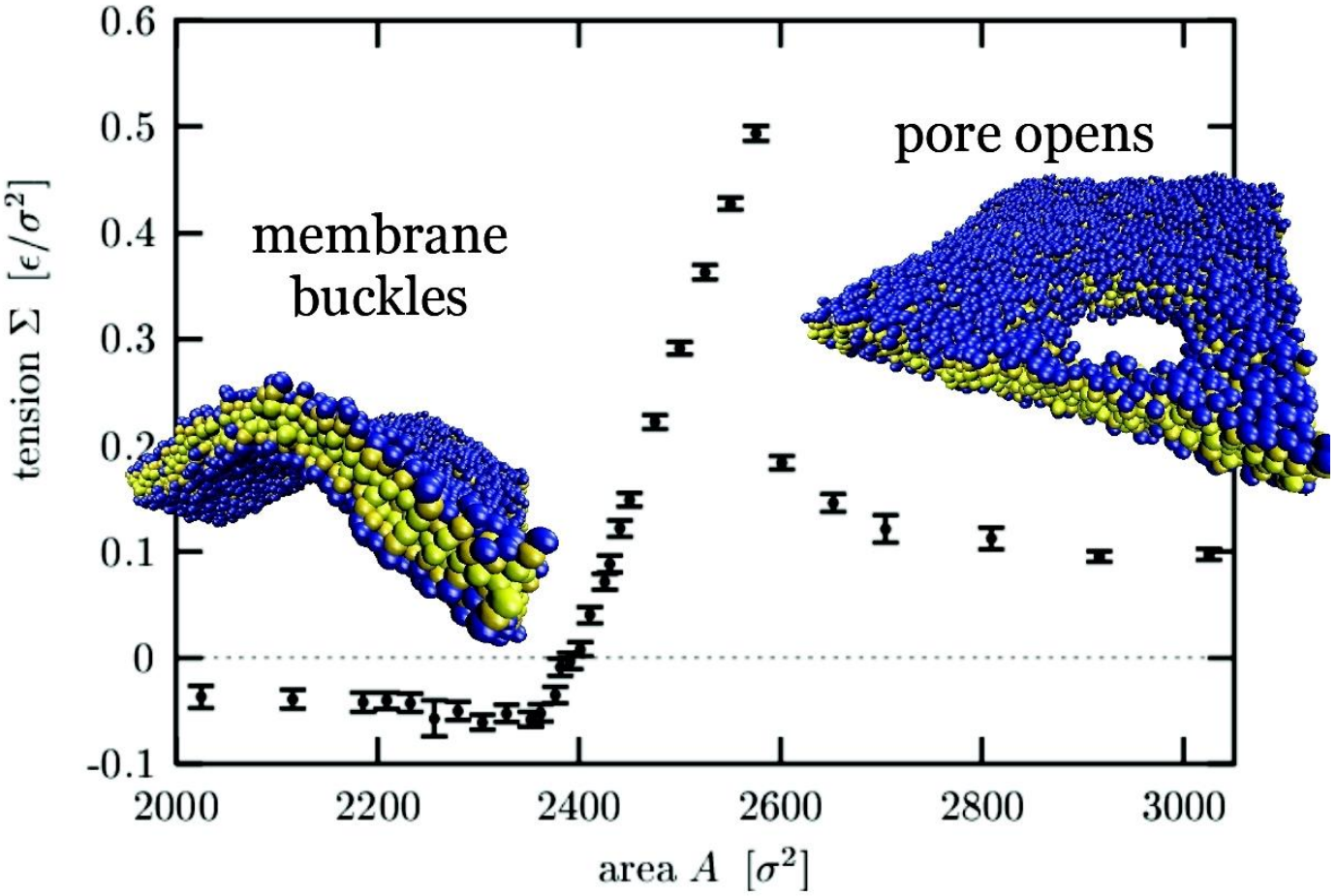


B.J. Reynwar and M. Deserno, Biointerphases **3**, FA118 (2009)

Mixtures


2
1.5
1
0.5
0
γ [ε/σ] , $1/\lambda_{\mathrm{profile}}$ [σ^{-1}]
γ
λ^{-1}
ideal
mixture
1.48
1.5
1.52
1.54
1.56
1.58
1.6
w_{AB} [σ]

Stretching Modulus



I. R. Cooke and M. Deserno, J. Chem. Phys. **123**, 224710 (2005)