Mesoscopic simulations of lipid membranes

Mingyang Hu, Patrick Diggins, and Markus Deserno

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

October 11, 2012

Mingyang Hu
mingyang@cmu.edu

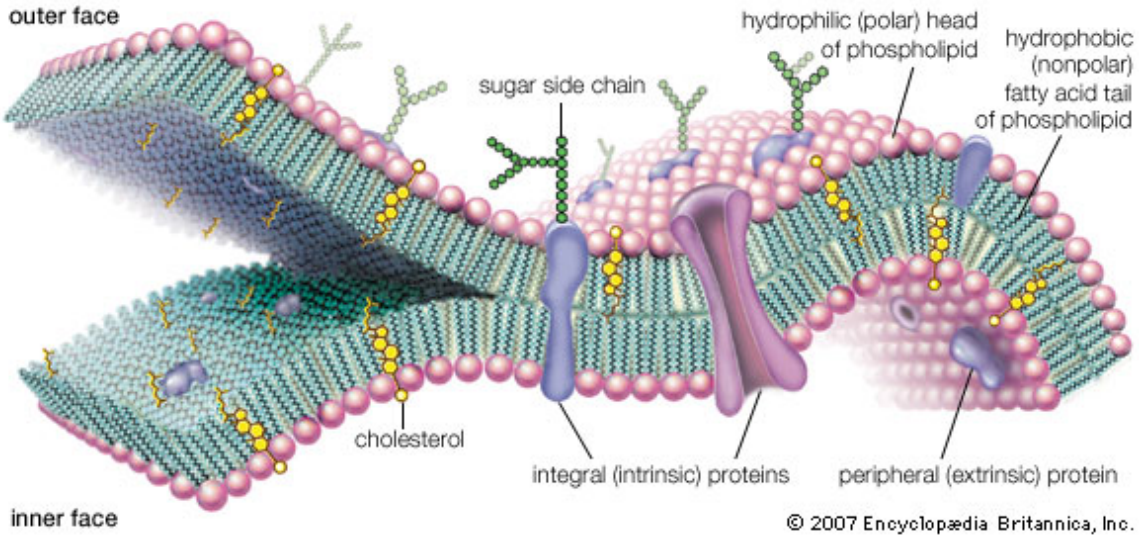
Introduction
Lipid Membrane
Why coarse-graining?
Solvent-free CG Model
Solvent-free
Model
Code Implementation
Properties
Membrane elasticity
Bending
Line tension
Applications
Vesicles
Protein-induced budding
Lipid A-B–mixtures
stretching

Outline

Mingyang Hu
mingyang@cmu.edu

Introduction
Lipid Membrane
Why coarse-graining?
Solvent-free CG Model
Solvent-free
Model
Code Implementation
Properties
Membrane elasticity
Bending
Line tension
Applications
Vesicles
Protein-induced budding
Lipid A-B–mixtures
stretching

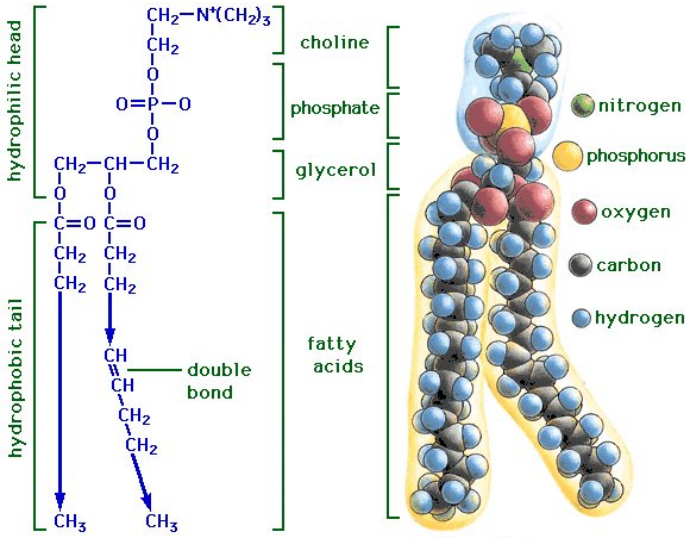
What's a lipid membrane?

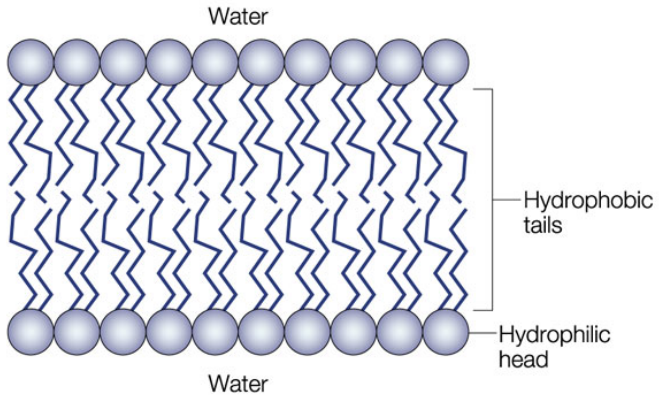


- forms continuous barriers around cells, cell nuclei
- made of two layers of lipid molecules
- controls the diffusion of molecules in and out of the cell

Mingyang Hu
mingyang@cmu.edu

Building blocks: Lipid molecules

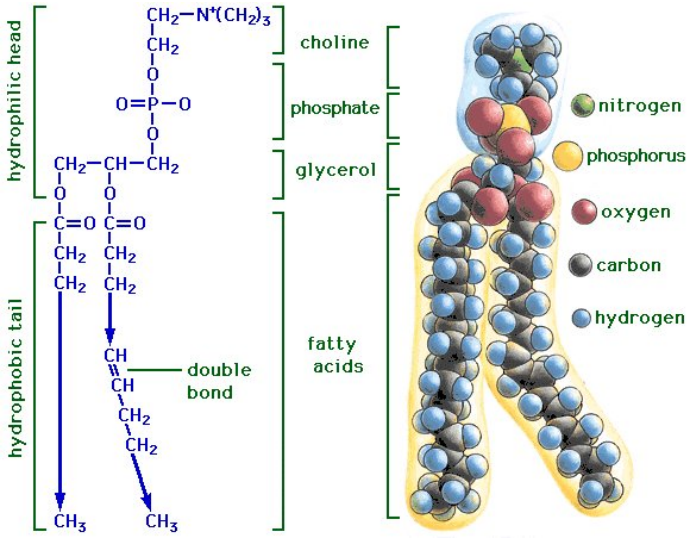


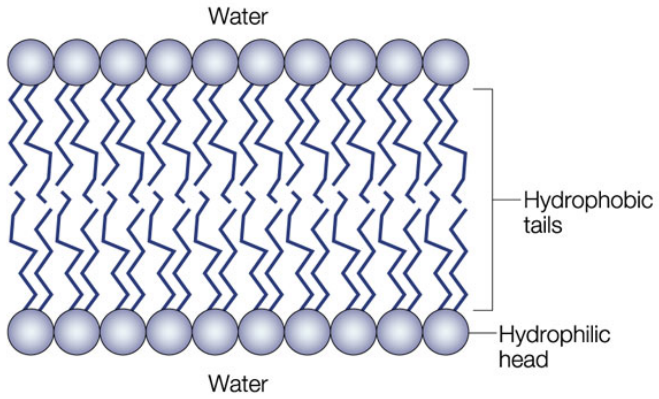


- amphiphilic molecule
  - hydrophilic head (polar: “attracted” by water)
  - hydrophobic tails (apolar: “repelled” by water)

Mingyang Hu
mingyang@cmu.edu

Building blocks: Lipid molecules



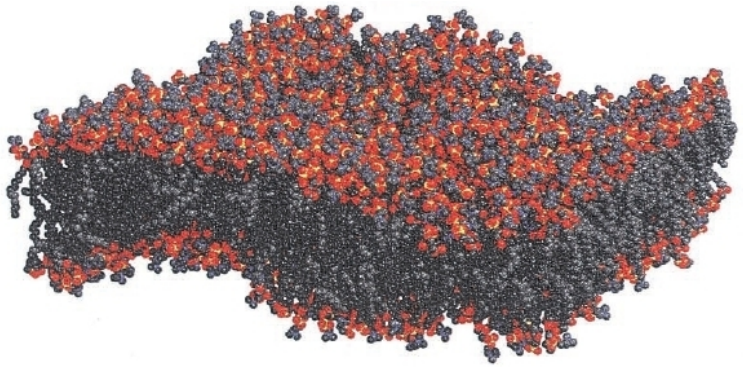


- amphiphilic molecule
  - hydrophilic head (polar: “attracted” by water)
  - hydrophobic tails (apolar: “repelled” by water)
- membranes form by spontaneous aggregation of lipids
  - *self-assembly* process

Why coarse-graining?

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

All-atom lipid bilayer
$20\,\mathrm{nm} \times 20\,\mathrm{nm}$, 1024 lipids
simulation time: $10\,\mathrm{ns}$

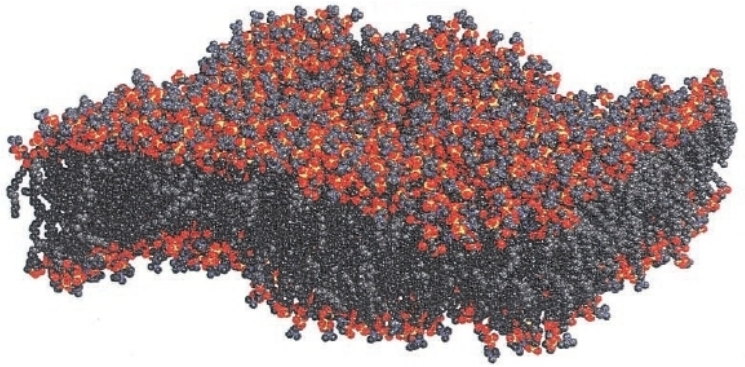


Mingyang Hu
mingyang@cmu.edu

Why coarse-graining?

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

All-atom lipid bilayer
$20\,\mathrm{nm} \times 20\,\mathrm{nm}$, 1024 lipids
simulation time: $10\,\mathrm{ns}$



What if we want a boxlength of $L = 200\mathrm{nm}$?

How does computing effort scale with L?

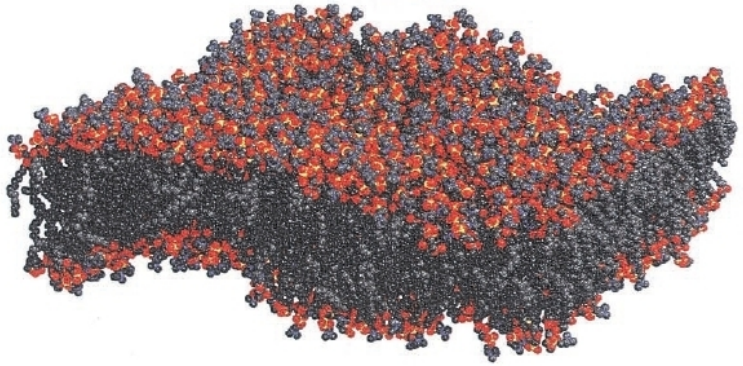
$$\text{effort} \sim \underbrace{L^2}_{\text{geometry}}$$

Mingyang Hu
mingyang@cmu.edu

Why coarse-graining?

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

All-atom lipid bilayer
$20\,\mathrm{nm} \times 20\,\mathrm{nm}$, 1024 lipids
simulation time: $10\,\mathrm{ns}$



What if we want a boxlength of $L = 200\mathrm{nm}$?

How does computing effort scale with L?

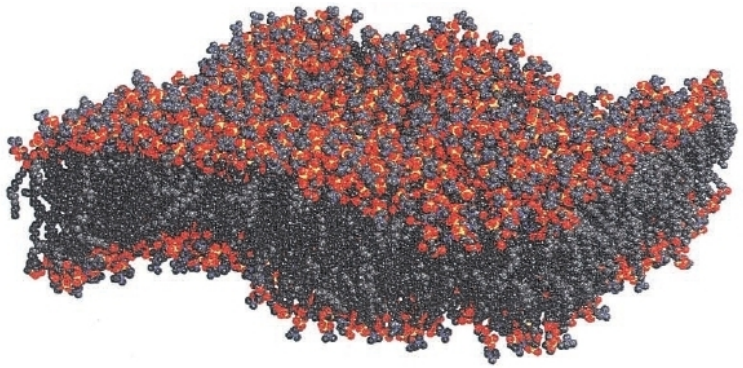
$$\text{effort} \sim \underbrace{L^2}_{\text{geometry}} \times \underbrace{L^4}_{\text{equilibration}} \sim L^6$$

Mingyang Hu
mingyang@cmu.edu

Efficiency

$\boxed{20\,\text{nm}} \longrightarrow \boxed{200\,\text{nm}}$

Million times more computationally expensive!



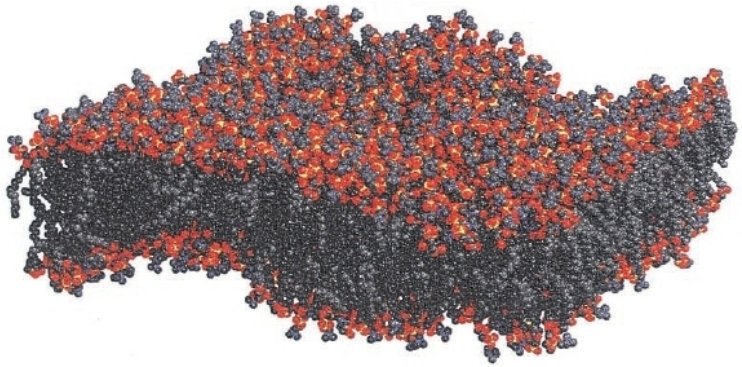
- amount of material $\sim$ membrane area $A = L^2$.
- domain decomposition scheme:
  - increase # CPUs $\sim A$
- but simulation time $\sim A^3$
  - uncompensated factor of A^2

Mingyang Hu
mingyang@cmu.edu

Efficiency

$$\boxed{20\,\text{nm}} \longrightarrow \boxed{200\,\text{nm}}$$

Million times more computationally expensive!



- CG helps to understand the essence of the problems
- CG reduces the number of DOF
- CG allows larger time steps
- CG smoothens the free energy surface

  $\Rightarrow$ Better sampling

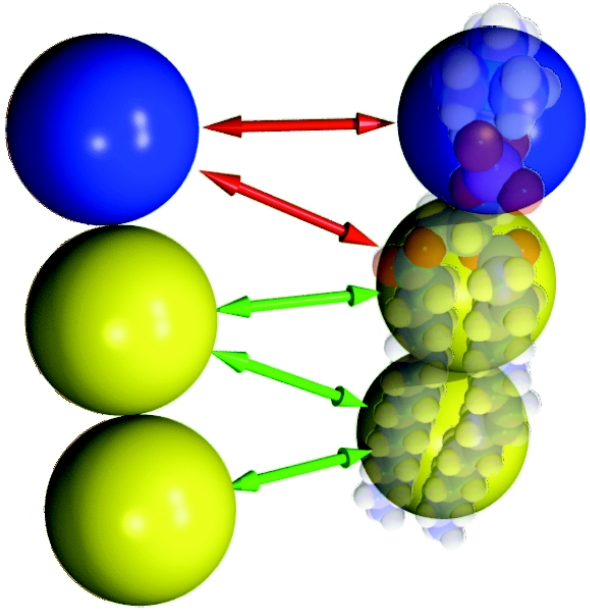
Mingyang Hu
mingyang@cmu.edu

Outline

Mingyang Hu
mingyang@cmu.edu

Introduction
Lipid Membrane
Why coarse-graining?
Solvent-free CG Model
Solvent-free
Model
Code Implementation
Properties
Membrane elasticity
Bending
Line tension
Applications
Vesicles
Protein-induced budding
Lipid A-B–mixtures
stretching

The CG model[1]



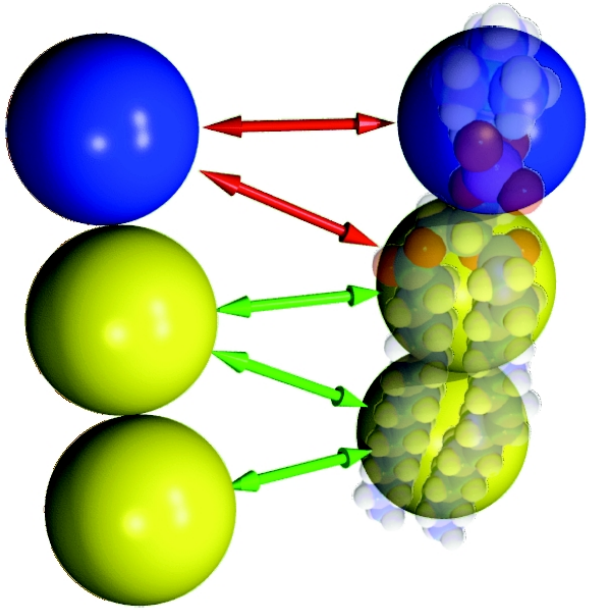
Coarse-grain in order to probe the mesoscopic regime of lipid bilayers

- generic top-down bead-spring
- 3 beads: reasonable aspect ratio
- 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).

Mingyang Hu
mingyang@cmu.edu

The CG model[1]



Coarse-grain in order to probe the mesoscopic regime of lipid bilayers

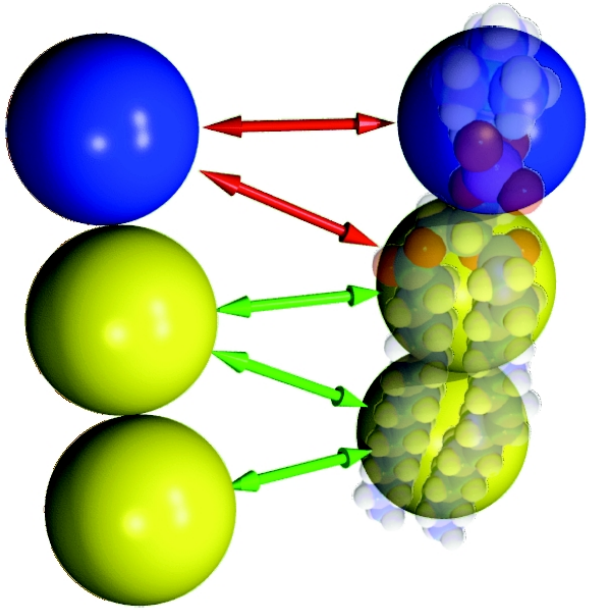
- generic top-down bead-spring
- 3 beads: reasonable aspect ratio
- only pair forces
- solvent free

- Note: several other similar models exist.
- Here I'll talk about the one used in our group
- It has been implemented in ESPResSo.

[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).

Mingyang Hu
mingyang@cmu.edu

The CG model[1]



Coarse-grain in order to probe the mesoscopic regime of lipid bilayers

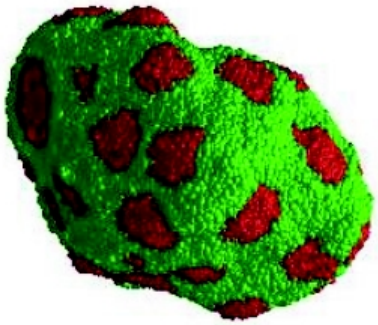
- generic top-down bead-spring
- 3 beads: reasonable aspect ratio
- only pair forces
- solvent free

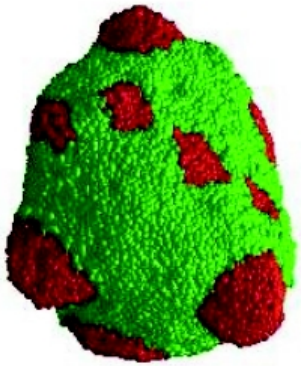
- Note: several other similar models exist.
- Here I'll talk about the one used in our group
- It has been implemented in ESPResSo.

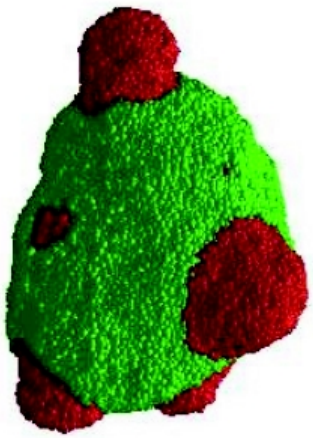
[1] I.R. Cooke, K. Kremer, M. Deserno, Phys. Rev. E **72**, 011506 (2005) I.R. Cooke and M. Deserno, J. Chem. Phys. **123**, 224710 (2005).

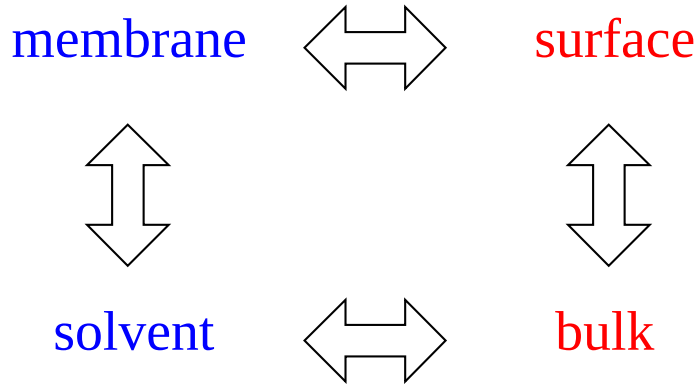
Mingyang Hu
mingyang@cmu.edu

Why is “solvent free” good?









Example[a]

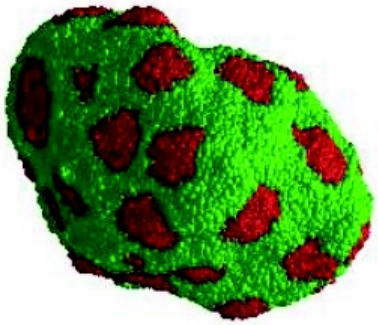
- 16,000 DPD lipids, 4 beads per lipid.
- 64,000 particles for lipids.
- But in total 1,536,000 particles in box!

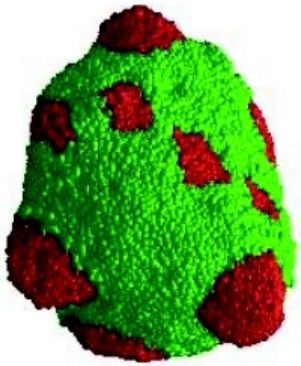
96% simulation time spent with solvent.

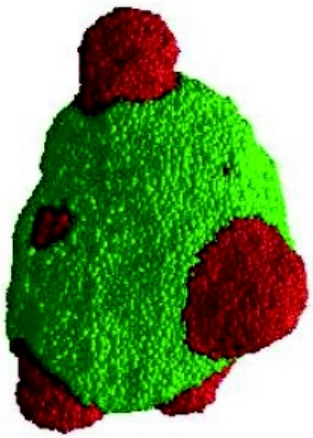
[a] M. Laradji & P.B. Sunil Kumar, Phys. Rev. Lett. **93**, 198105 (2004).

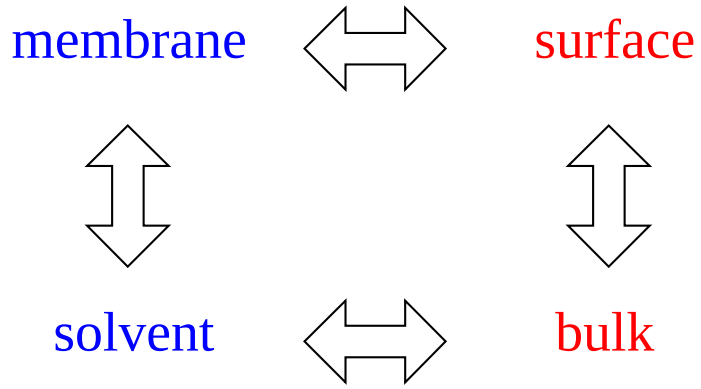
Mingyang Hu
mingyang@cmu.edu

Why is “solvent free” good?









Example[a]

- 16,000 DPD lipids, 4 beads per lipid.
- 64,000 particles for lipids.
- But in total 1,536,000 particles in box!

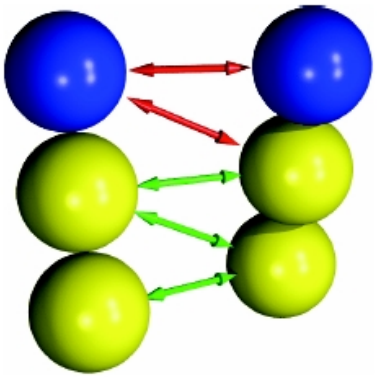
They had a good reason for doing this:
study of the *dynamics* of domain growth,
where hydrodynamics is an important factor.

[a] M. Laradji & P.B. Sunil Kumar, Phys. Rev. Lett. **93**, 198105 (2004).

Mingyang Hu
mingyang@cmu.edu

Difficulties

- Implicit solvent models are incredibly common and useful in polymer physics.
- Why has it taken so long for them to appear in the field of membrane research?
  - Polymers don't first have to self assemble!
- One needs additional cohesion to make the lipids come together.
- Fluidity has proven to be the major challenge.



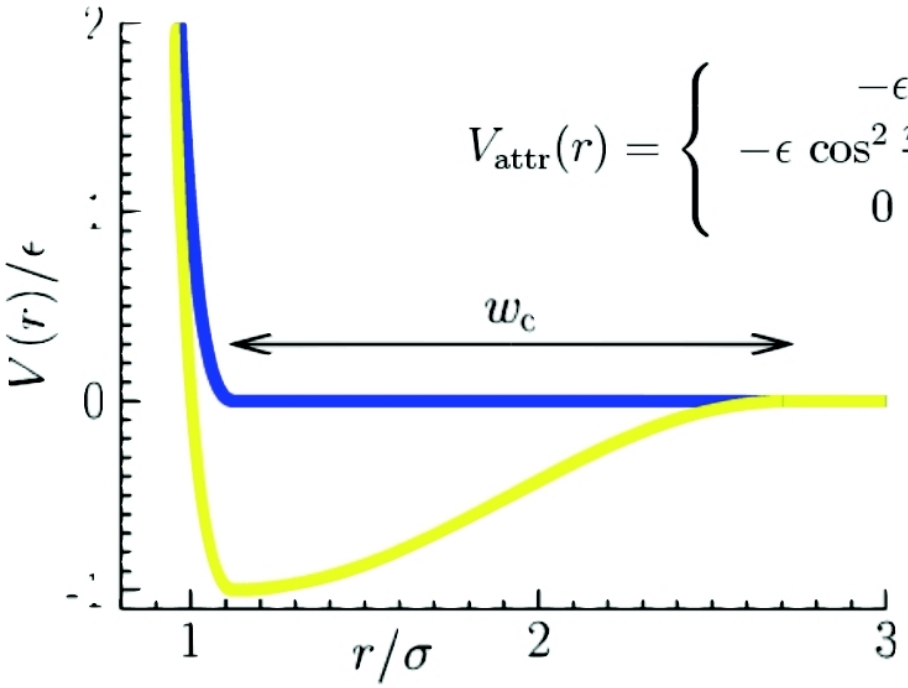
Lennard-Jones interactions:

- weak attraction $\rightarrow$ gas phase
- no fluid phase in between?!
- strong attraction $\rightarrow$ solid (gel) phase

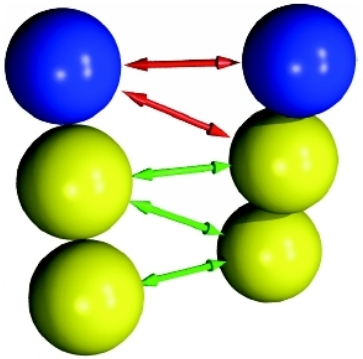
Mingyang Hu
mingyang@cmu.edu

Model

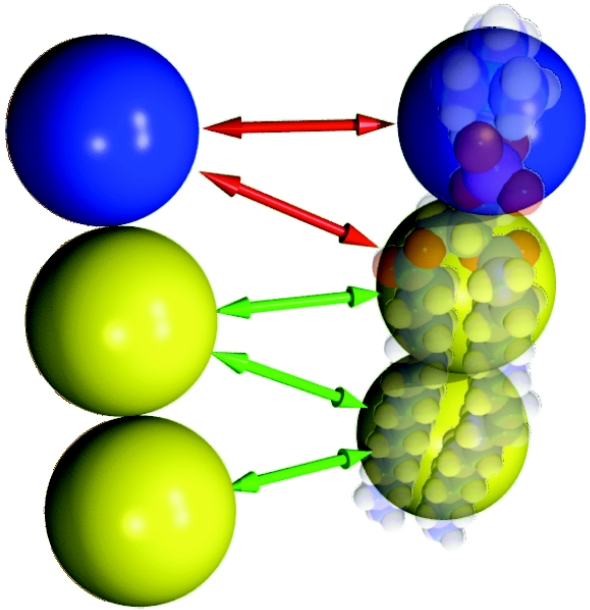
- link three beads $V_{\text{bond}}(r) = -\frac{1}{2}k_{\text{bond}}r_{\infty}^2 \ln\left[1-(r/r_{\infty}^2)\right]$
- make lipid stiff $V_{\text{bend}}(r_{13}) = \frac{1}{2}k_{\text{bend}}(r_{13}-4\sigma)^2$
- nonbonded $V_{\text{rep}}(r) = 4\epsilon\left[\left(\frac{r_c}{r}\right)^{12} - \left(\frac{r_c}{r}\right)^{6} + \frac{1}{4}\right]\Theta(r_{c-r})$

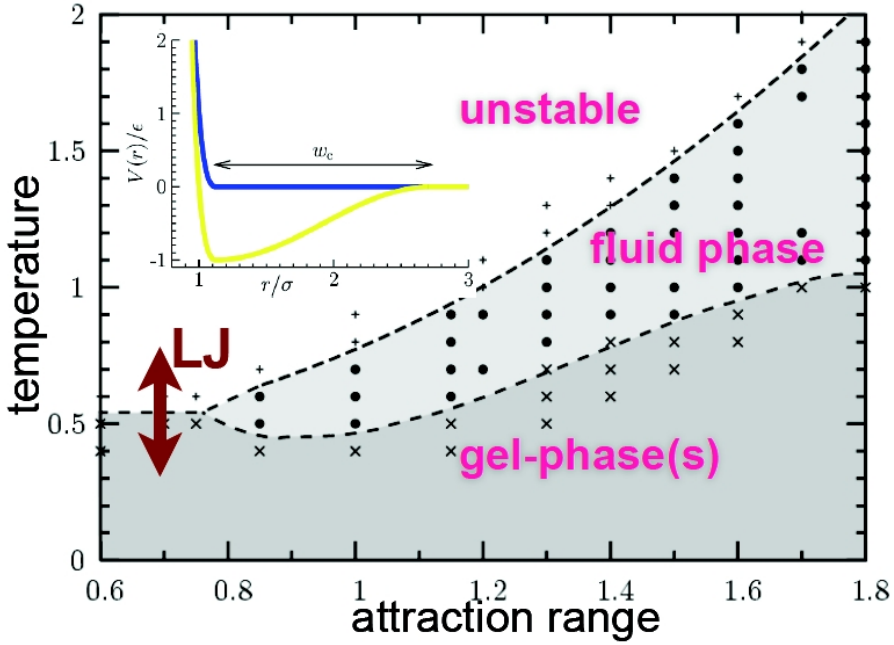


$$V_{\text{attr}}(r) = \begin{cases} -\epsilon & , \quad r < r_c \\ -\epsilon \cos^2 \frac{\pi(r-r_c)}{2w_c} & , \quad r_c \le r \le r_c + w_c \\ 0 & , \quad r > r_c + w_c \end{cases},$$



Overall phase behavior





- long-range attractions “save” the system some entropy!

Mingyang Hu
mingyang@cmu.edu

Self-assembly

movies/self_assembly_1.mpg

Mingyang Hu
mingyang@cmu.edu

Outline

Mingyang Hu
mingyang@cmu.edu

Introduction
Lipid Membrane
Why coarse-graining?
Solvent-free CG Model
Solvent-free
Model
Code Implementation
Properties
Membrane elasticity
Bending
Line tension
Applications
Vesicles
Protein-induced budding
Lipid A-B–mixtures
stretching

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`

Program structure

- `mbtools` is a Tcl *package*.
  - set of Tcl functions
  - (crude) version control
- load package to get access to enclosed functions

```
package require mbtools [1.0.0]
```

- ESPResSo loads `mbtools` during initialization (file `ESPRESSO/scripts/init.tcl`)

```
lappend auto_path "[pwd]/packages/mbtools/"
```

- `auto_path` contains the list of (sub)directories checked by the package loader
- use *namespaces* to avoid defining two functions with the same name

Mingyang Hu
mingyang@cmu.edu

Program structure

```
# Espresso/packages/mbtools/mbtools.tcl
#

package require ::mbtools::utils
package require ::mbtools::system_generation
package require ::mbtools::analysis

package provide mbtools 1.0.0

namespace eval mbtools {

}

# Espresso/packages/mbtools/utils/setup.tcl
#

proc ::mbtools::utils::readcheckpoint { dir }
```

Config file example (incomplete...)

```
# .../mbtools/examples/simplebilayer.tcl
#

# define geometry
set geometry { geometry "flat -fixz" }
# time step
set main_time_step 0.01
# analysis
lappend analysis_flags pressure
```

From command line:

```
Espresso scripts/main.tcl simplebilayer.tcl
```


Mingyang Hu
mingyang@cmu.edu

Outline

Mingyang Hu
mingyang@cmu.edu

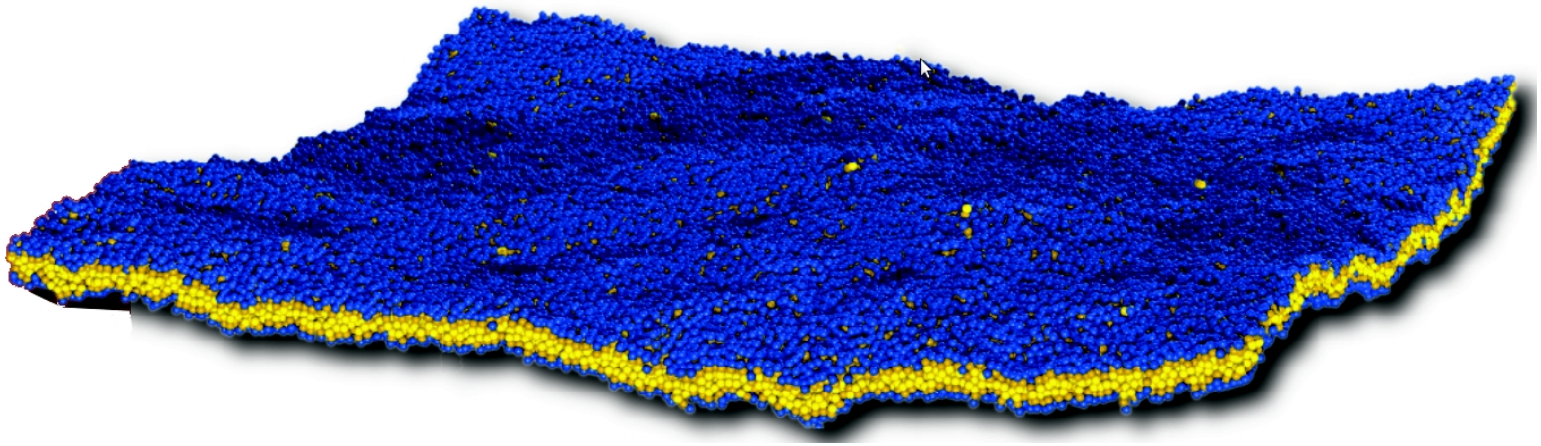
Introduction
Lipid Membrane
Why coarse-graining?
Solvent-free CG Model
Solvent-free
Model
Code Implementation
Properties
Membrane elasticity
Bending
Line tension
Applications
Vesicles
Protein-induced budding
Lipid A-B–mixtures
stretching

Membrane elasticity

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

$$E = \int \mathrm{d}A \left\{ \frac{1}{2}\kappa K^2 + \sigma \right\} \simeq \frac{1}{2} \int \mathrm{d}x\mathrm{d}y \left\{ \kappa(\nabla^2 h)^2 + \sigma(\nabla h)^2 \right\}$$

  - κ: bending modulus
  - K: total curvature
  - σ: surface tension
  - $h(x, y)$: height function (Monge gauge)



Mingyang Hu
mingyang@cmu.edu

Bending modulus

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

$$E = \int \mathrm{d}A \left\{ \frac{1}{2}\kappa K^2 + \sigma \right\} \simeq \frac{1}{2} \int \mathrm{d}x\mathrm{d}y \left\{ \kappa(\nabla^2 h)^2 + \sigma(\nabla h)^2 \right\}$$

  - κ: bending modulus
  - K: total curvature
  - σ: surface tension
  - $h(x, y)$: height function (Monge gauge)

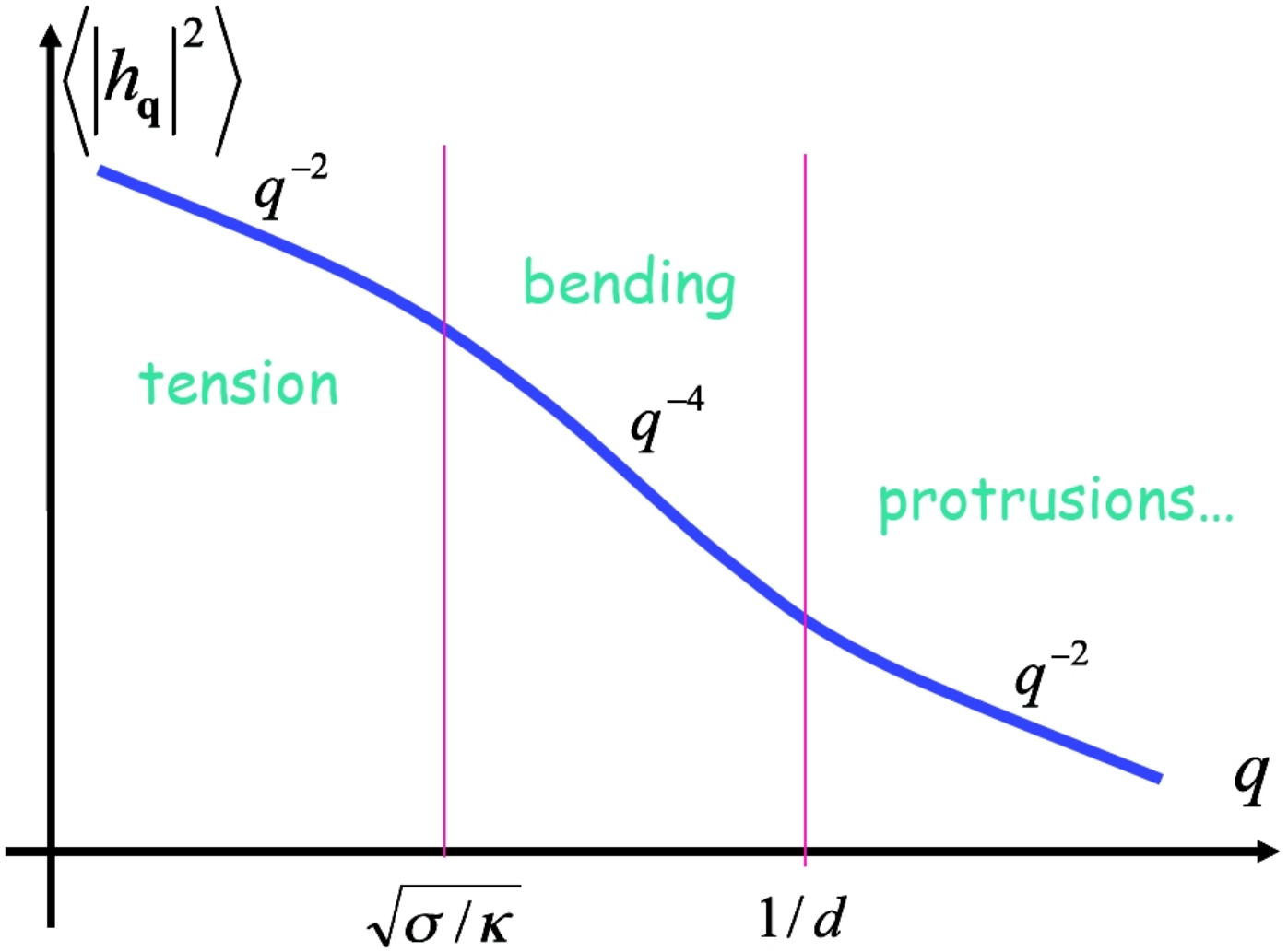
- Fourier expansion and equipartition theorem

$$\langle |h_{\mathbf{q}}|^2 \rangle = \frac{k_{\mathrm{B}}T}{L^2[\kappa q^4 + \underbrace{\sigma q^2}_{\text{set to 0}}]} = \frac{k_{\mathrm{B}}T}{L^2\kappa} q^{-4}$$

  - determine bending modulus κ

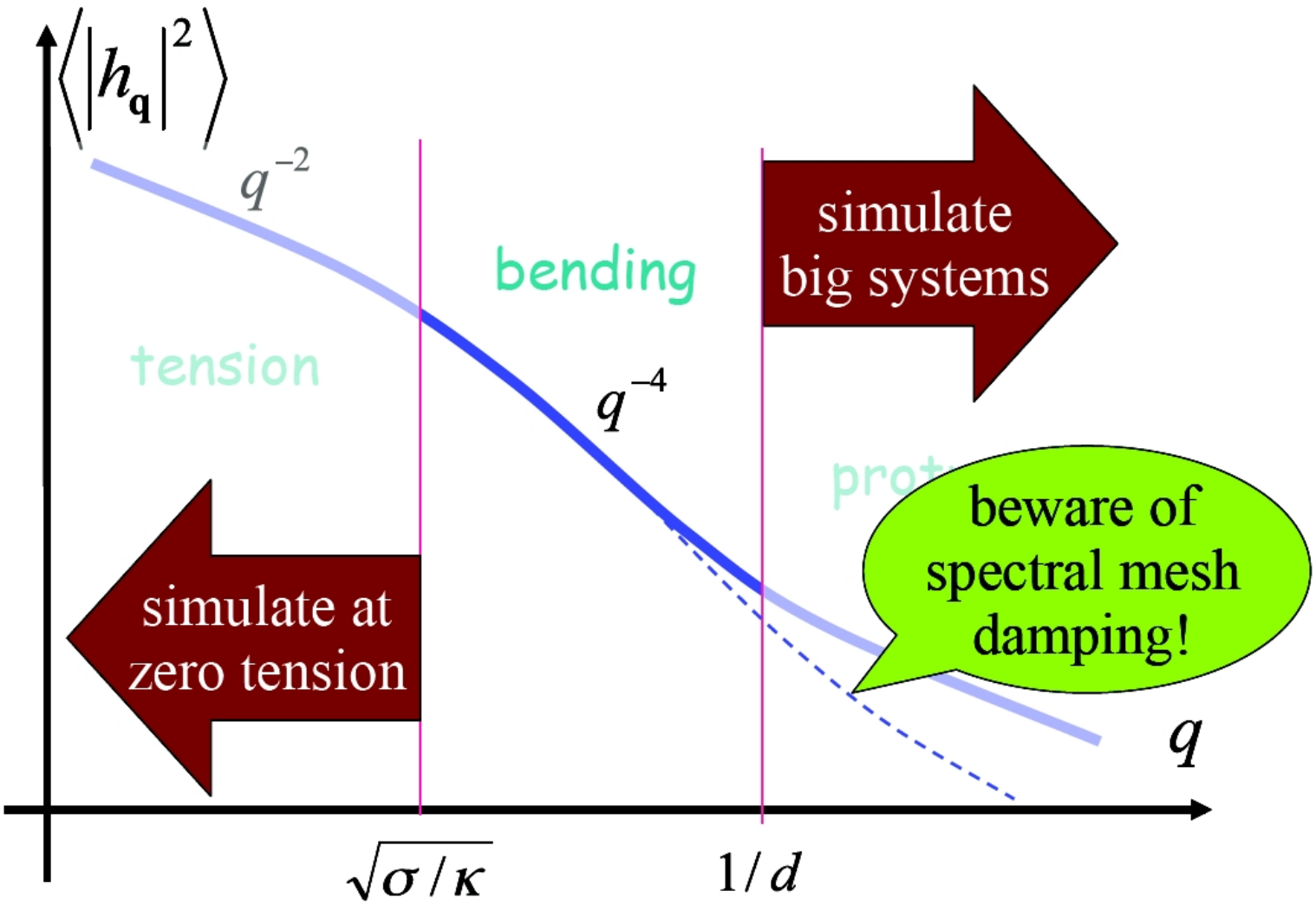
Mingyang Hu
mingyang@cmu.edu

Fluctuation spectrum from continuum theory



Mingyang Hu
mingyang@cmu.edu

Fluctuation spectrum from continuum theory



Mingyang Hu
mingyang@cmu.edu

However...

- Equilibration time of Fourier modes scales like q^{-4}
- Large bending modulus κ from small perturbation ($k_\mathrm{B}T$) $\rightarrow$ small signal!

$$h(x) = h_\mathbf{q} \mathrm{e}^{\mathrm{i}qx} \qquad \rightarrow \qquad K = -h''(x) = h_\mathbf{q} q^2 \mathrm{e}^{\mathrm{i}qx}$$

$$\langle K^2 \rangle = \langle |h''(x)|^2 \rangle = q^4 \langle |h_\mathbf{q}|^2 \rangle = \frac{k_\mathrm{B}T}{L^2 \kappa}$$

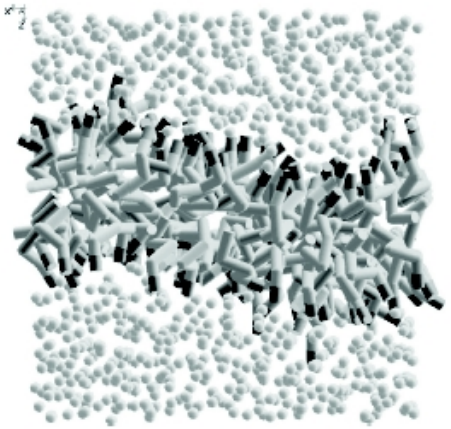
$$\bar{R} = \frac{1}{\langle K^2 \rangle^{1/2}} = \sqrt{\frac{\kappa}{k_\mathrm{B}T}} L \simeq 3 \ldots 5L$$

- Result relevant for strong bending?

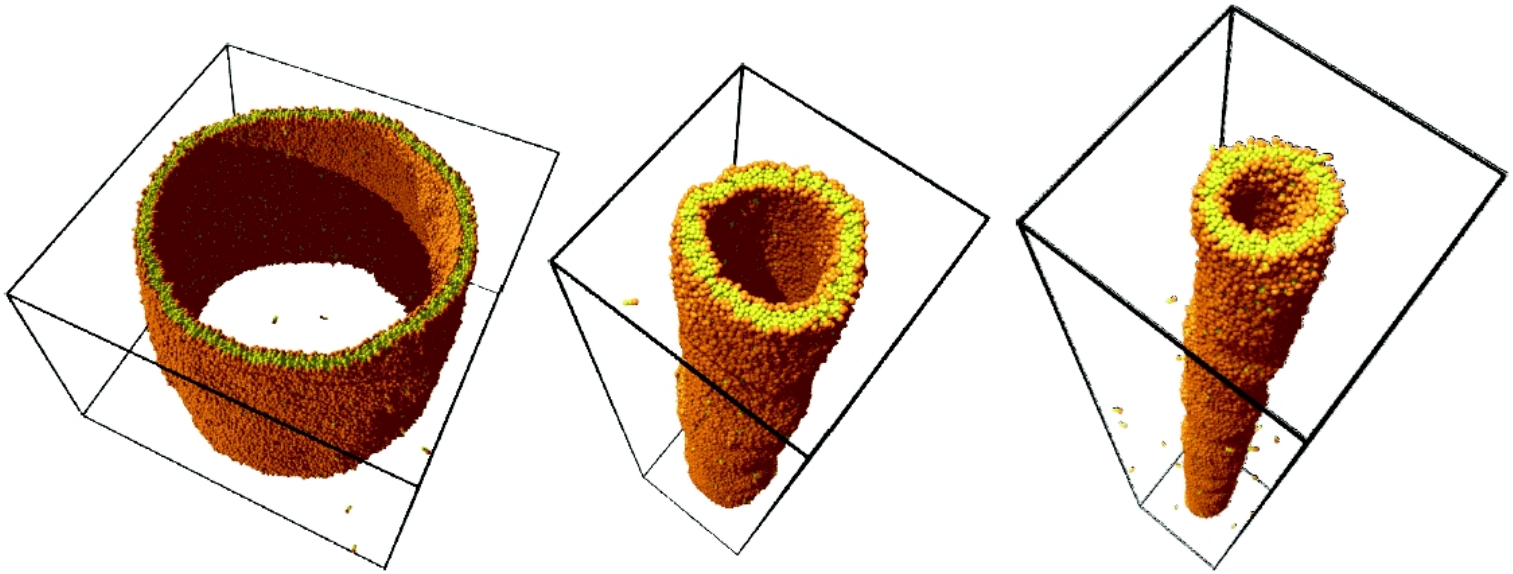
Mingyang Hu
mingyang@cmu.edu

κ from actively bent membranes

- first implementation:
  W.K. den Otter and W.J. Briels, J. Chem. Phys. **118**, 4712 (2003)
- Enforce large undulation mode, measure constraining force.



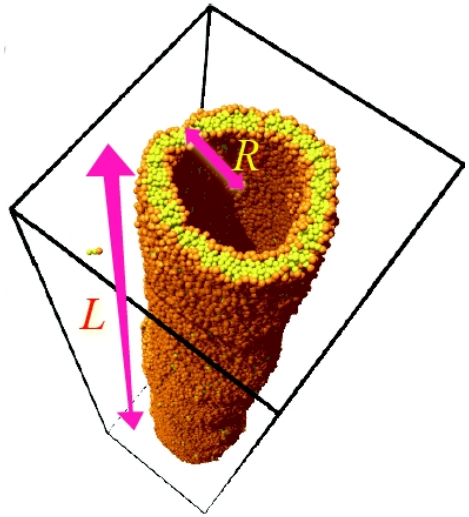
Simpler way: stretch a membrane tether![2]



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

κ from actively bent membranes[3]

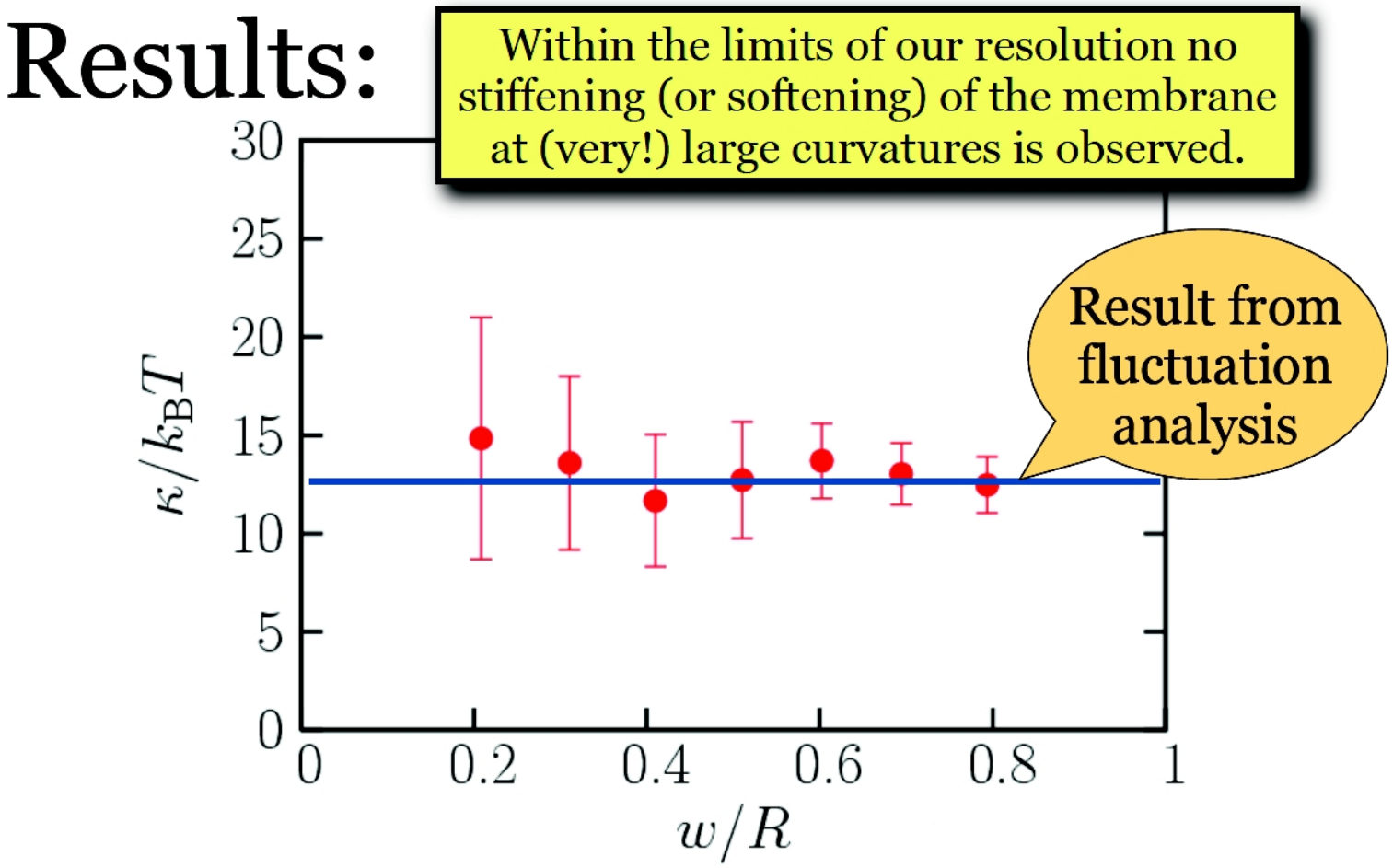
- Area:
$$A = 2\pi RL$$
- Energy:
$$E = \frac{\kappa}{2} \times \frac{1}{R^2} \times A$$
- Force:
$$F = \left(\frac{\partial E}{\partial L}\right)_A = \cdots = \frac{2\pi\kappa}{R}$$
- Bending modulus:
$$\kappa = \frac{FR}{2\pi} \simeq \frac{\overline{F}\,\overline{R}}{2\pi}$$



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

Mingyang Hu
mingyang@cmu.edu

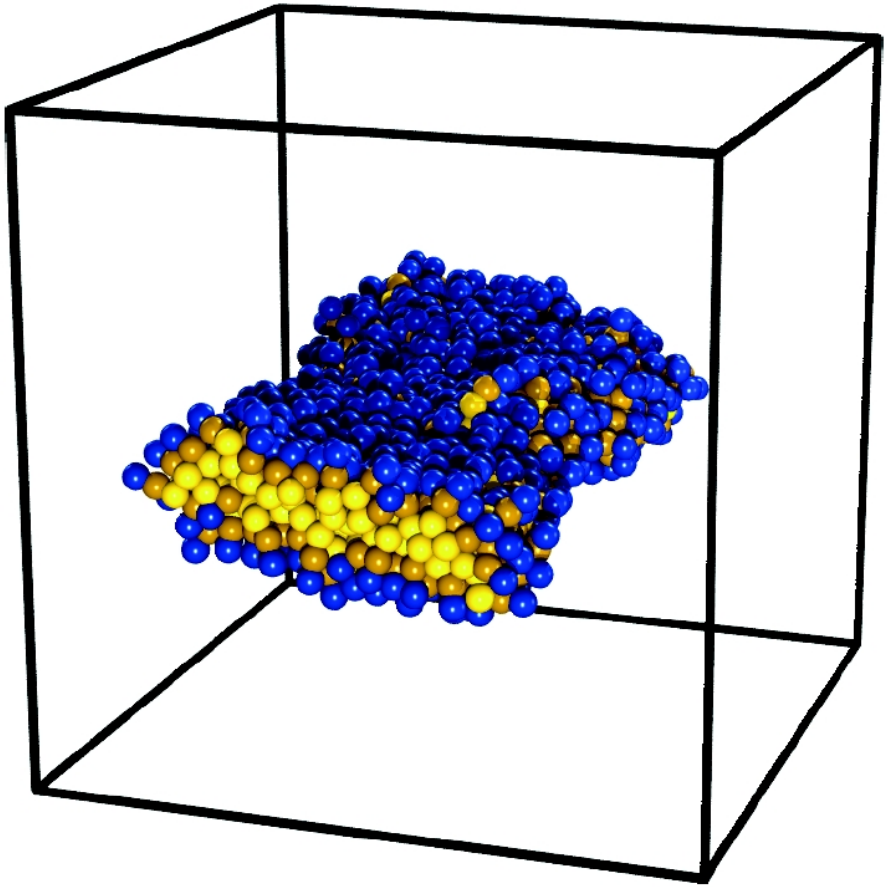
κ from actively bent membranes[4]



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

Mingyang Hu
mingyang@cmu.edu

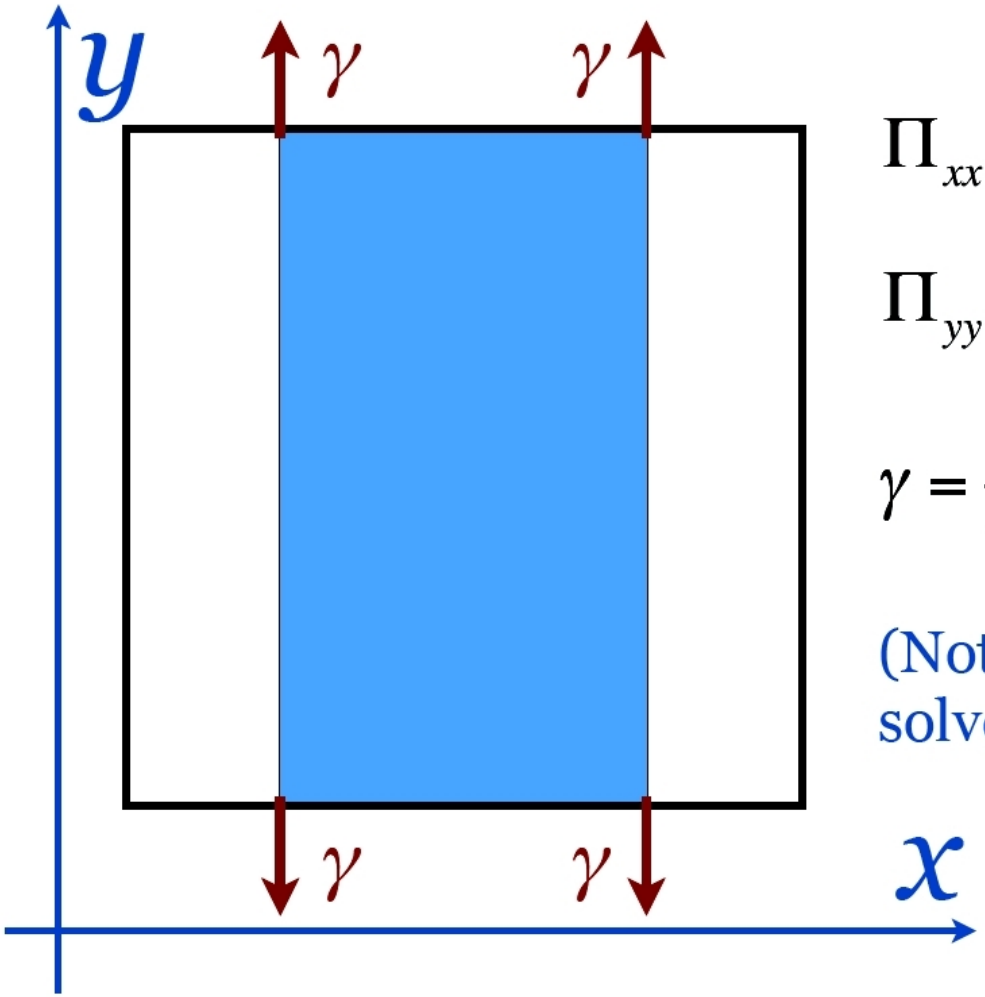
Simpler way of extracting the line tension



- simulate a periodically half-connected bilayer in a box
- stress tensor will be imbalanced precisely by twice the line tension!

Mingyang Hu
mingyang@cmu.edu

Simpler way of extracting the 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!)

Mingyang Hu
mingyang@cmu.edu

Outline

Mingyang Hu
mingyang@cmu.edu

Introduction
Lipid Membrane
Why coarse-graining?
Solvent-free CG Model
Solvent-free
Model
Code Implementation
Properties
Membrane elasticity
Bending
Line tension
Applications
Vesicles
Protein-induced budding
Lipid A-B–mixtures
stretching

Vesicles

- competition between bending rigidity and line tension [5]
- sonicate vesicle solution: rip vesicles into bits and pieces!
- these (flat) pieces will merge and grow bigger
- at what point will they again close up and form vesicles?

[5] "The size of bilayer vesicles generated by sonication", W. Helfrich, Physics Letters A, Vol 50, Issue 2, p. 115-116

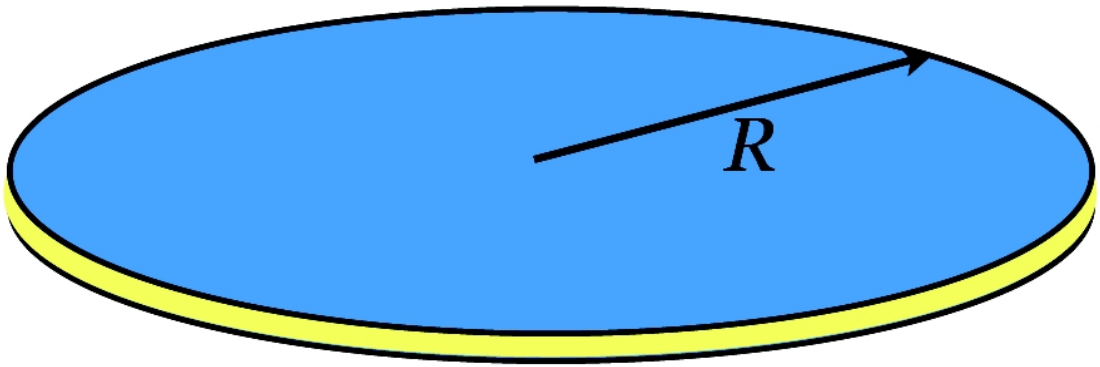
Mingyang Hu
mingyang@cmu.edu

Vesicles

movies/c16sa.mpg

Mingyang Hu
mingyang@cmu.edu

Vesicles



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

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

Energies are equal, if

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

(real stability analysis: 2 → 4)

$$\begin{aligned} E_{\text{vesicle}} &= 4\pi R^2 \cdot \left[\frac{1}{2}\kappa\left(\frac{1}{R}+\frac{1}{R}\right)^2 + \bar{\kappa}\frac{1}{R}\cdot\frac{1}{R}\right] \\ &= 4\pi(2\kappa + \bar{\kappa}) \end{aligned}$$

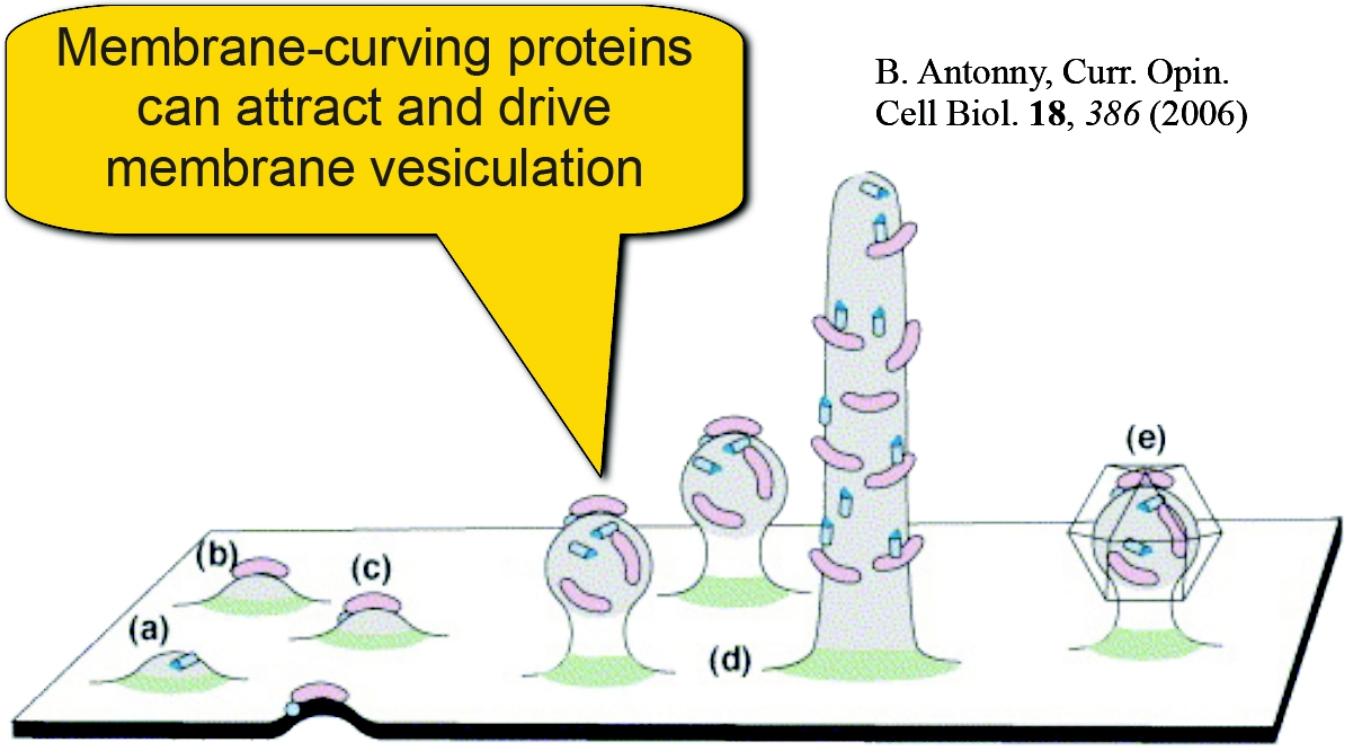
Vesicles

What values do we expect?

- $\kappa = 20\, k_{\mathrm{B}} T \simeq 80\,\mathrm{pN}\cdot\mathrm{nm}$
- $\overline{\kappa} \simeq -\kappa$ (very little is known about $\overline{\kappa}$, come back tomorrow!)
- $\gamma \simeq 10\,\mathrm{pN}$
- $R_{\mathrm{pancake}} = \frac{4(2\kappa+\overline{\kappa})}{\gamma} \simeq \frac{4\kappa}{\gamma} \simeq \frac{320\,\mathrm{pNnm}}{10\,\mathrm{pN}} = 32\,\mathrm{nm}$
- This is then also the diameter of vesicles we expect to find!

Mingyang Hu
mingyang@cmu.edu

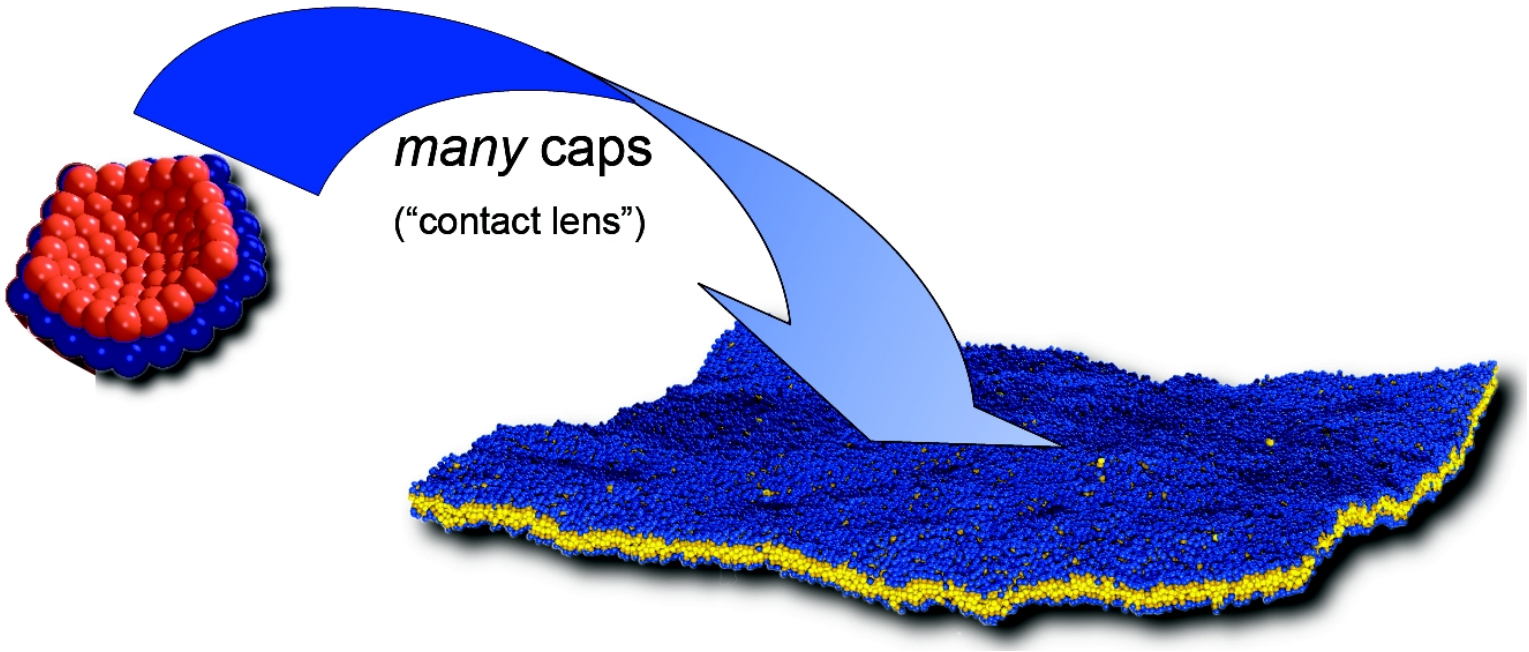
Protein-induced budding



Intuitive, but no physical justification!

Mingyang Hu
mingyang@cmu.edu

Protein-induced budding[6]



- 36 curved caps, ∼50,000 lipids
- 160nm side-length, total time ∼1ms
- no lateral tension
- no explicit interaction between caps

[6] B.J. Reynwar et al., Nature **447**, 461 (2007)

Mingyang Hu
mingyang@cmu.edu

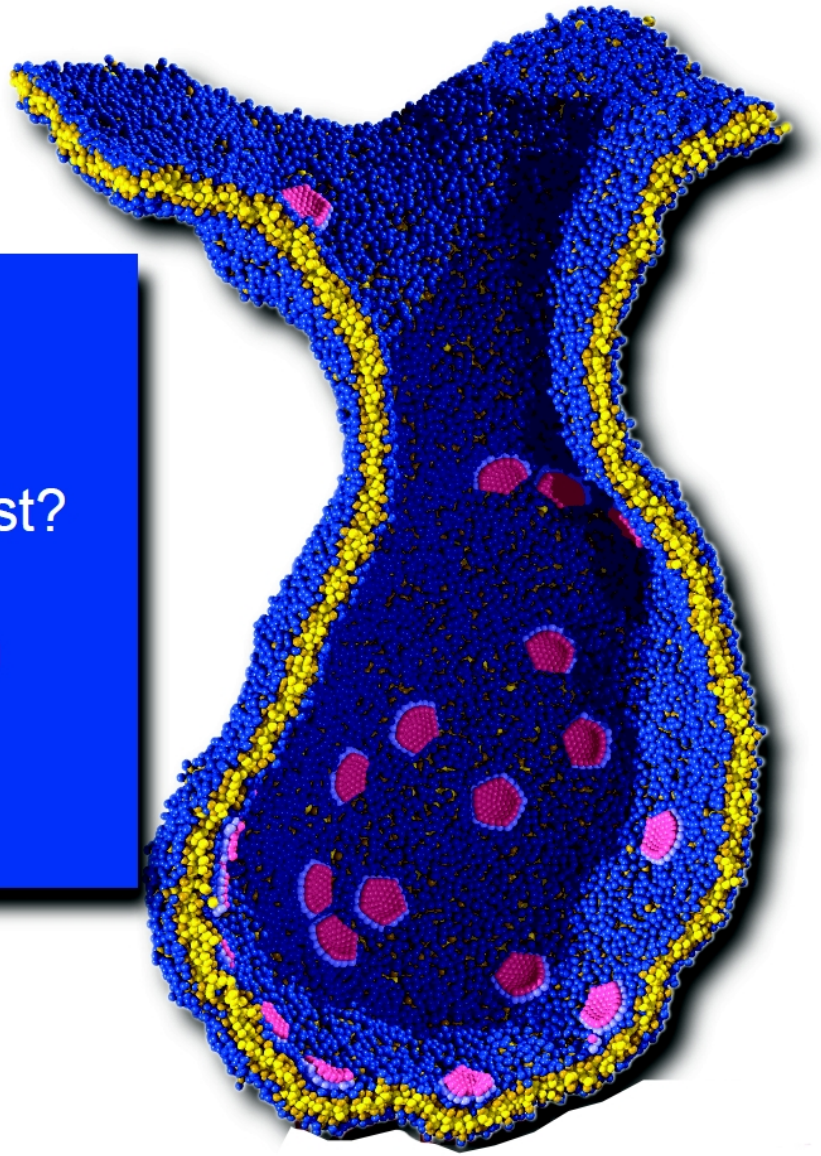
Protein-induced budding[7]

movies/caps.avi

[7] B.J. Reynwar et al., Nature **447**, 461 (2007)

Mingyang Hu
mingyang@cmu.edu

Protein-induced budding[8]



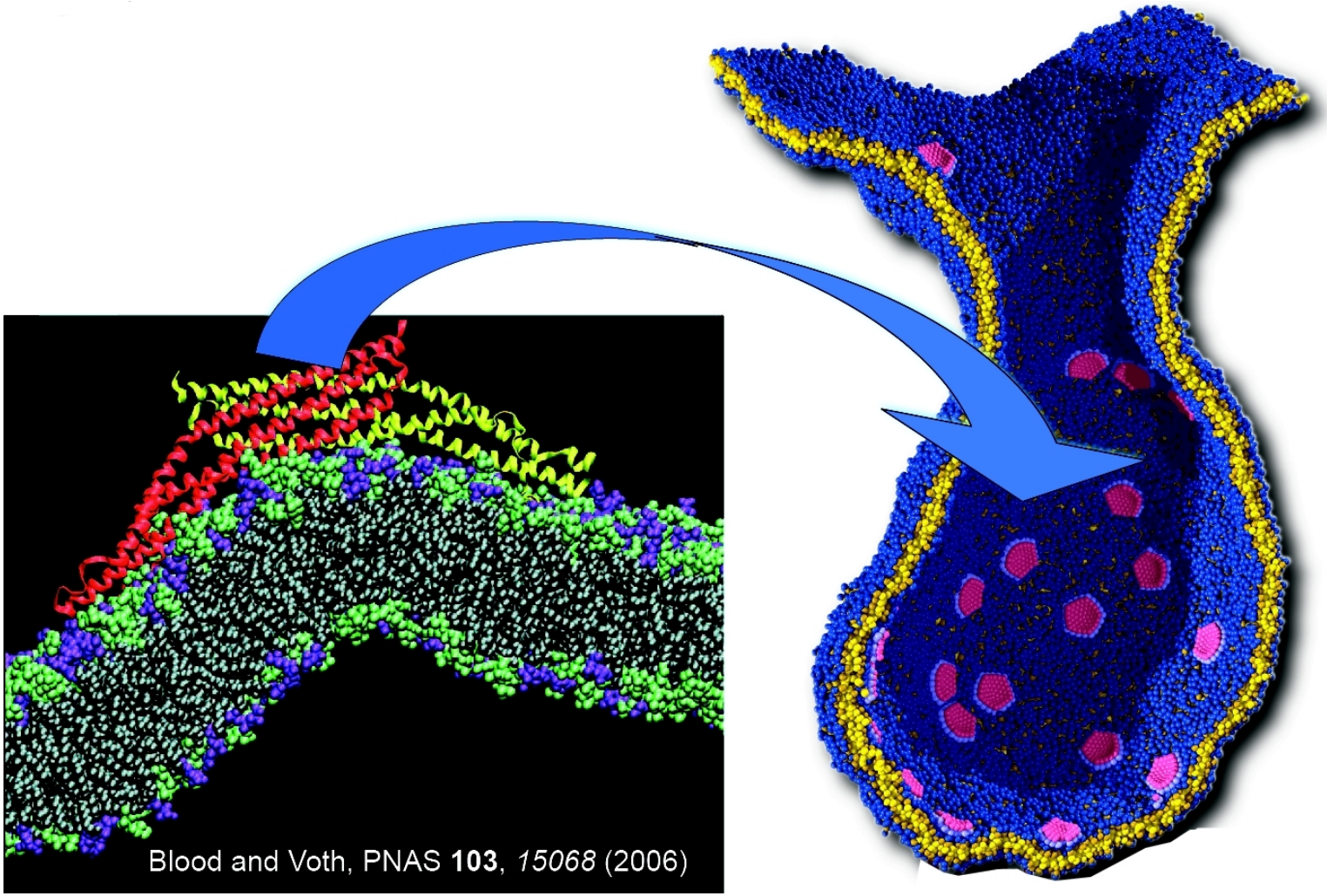
Some observations:

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

[8] B.J. Reynwar et al., Nature **447**, 461 (2007)

Mingyang Hu
mingyang@cmu.edu

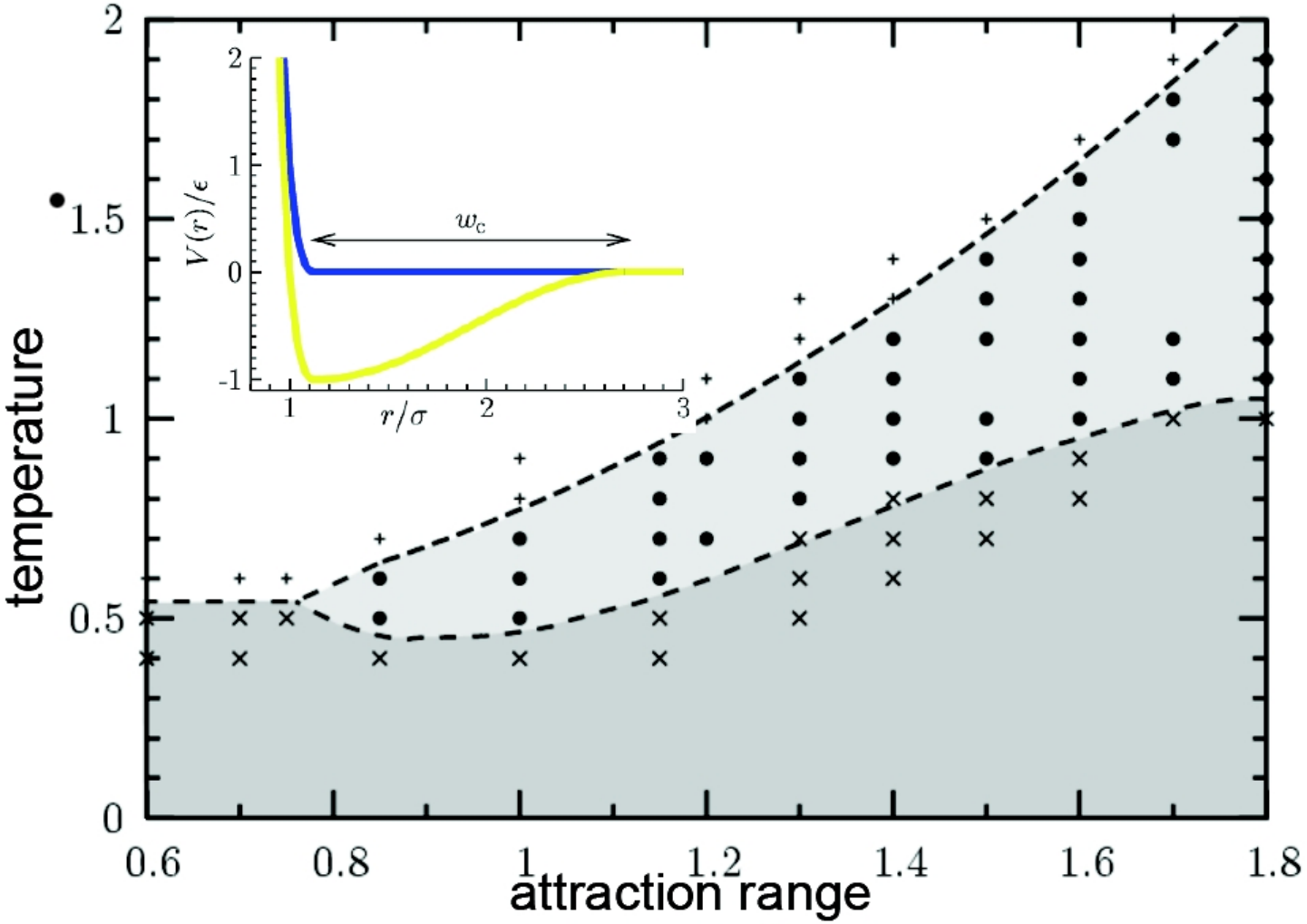
Protein-induced budding[9]



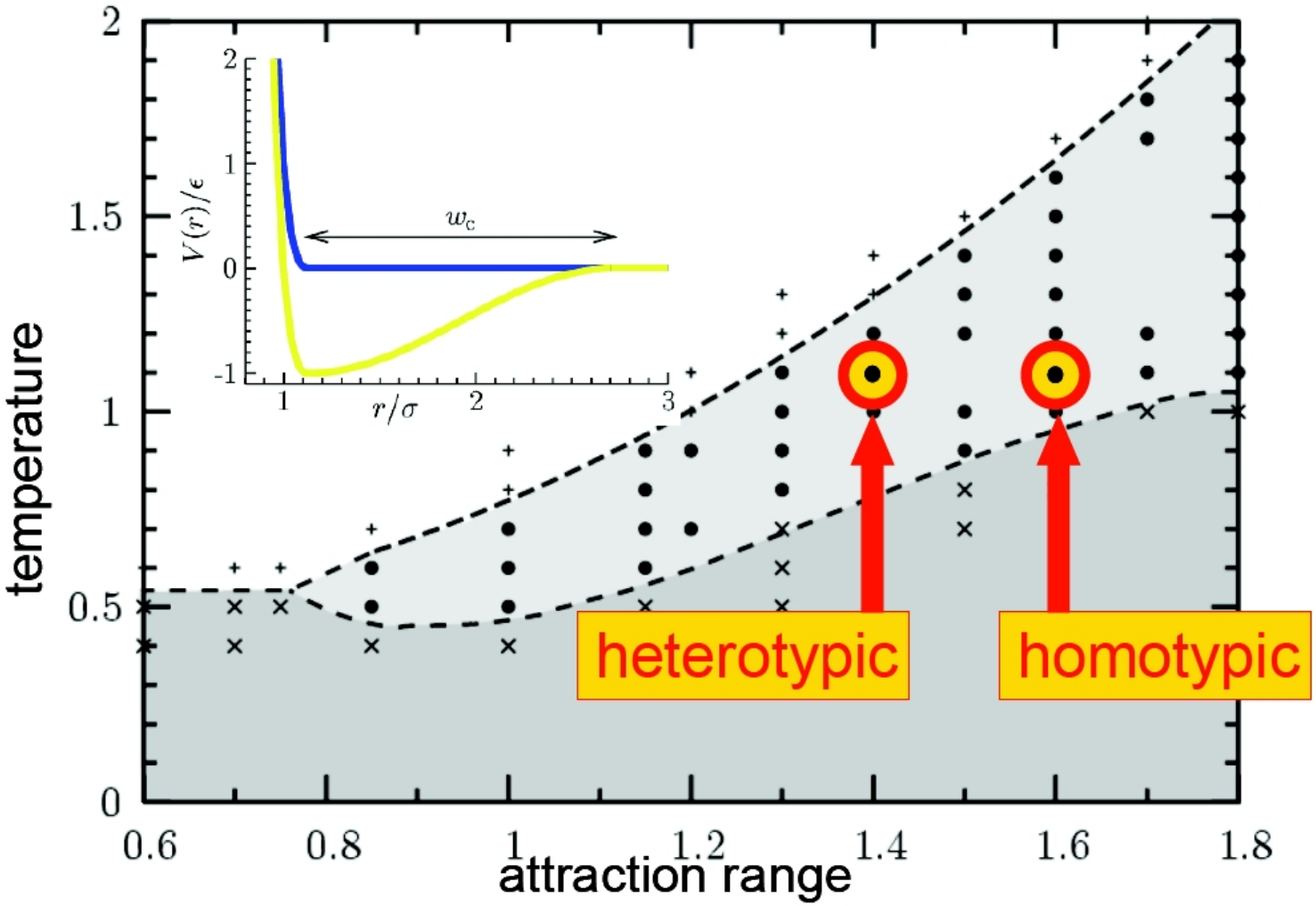
[9] B.J. Reynwar et al., Nature **447**, 461 (2007)

Mingyang Hu
mingyang@cmu.edu

Lipid A-B–mixtures



Lipid A-B–mixtures



$$w_{\mathrm{AB}} < w_{AA} = w_{BB}$$

Lipid A-B–mixtures[10]

movies/budding.mpg

[10] B.J. Reynwar & M. Deserno, Biointerphases **3**, FA118 (2009)

Mingyang Hu
mingyang@cmu.edu

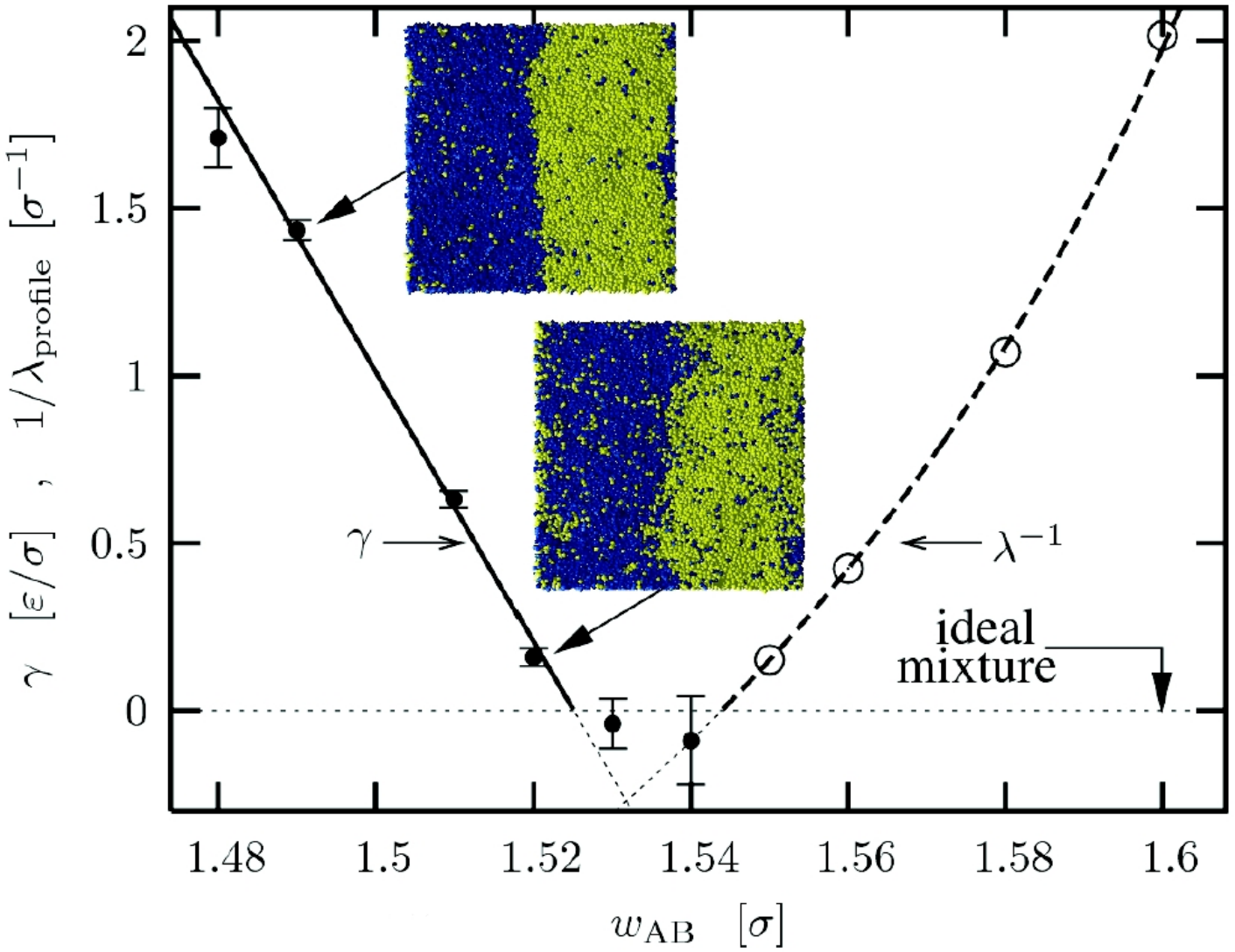
Lipid A-B–mixtures[11]

movies/spinodal.avi

[11] from Sarah Veatch

Mingyang Hu
mingyang@cmu.edu

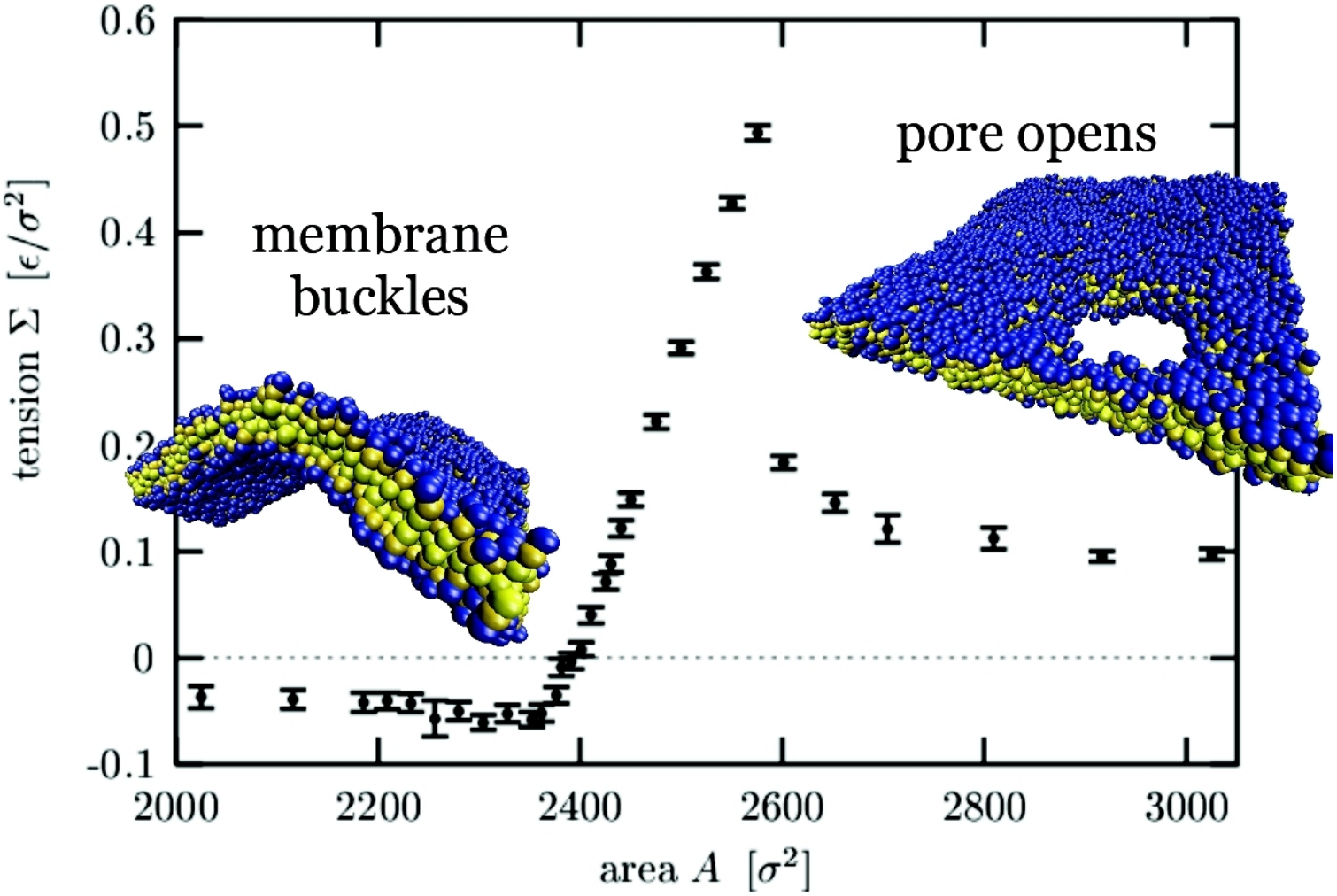
Lipid A-B–mixtures



$$w_{\mathrm{AB}} < w_{AA} = w_{BB}$$

Mingyang Hu
mingyang@cmu.edu

stretching modulus[12]



[12] i.r. cooke and m. deserno, j. chem. phys. **123**, 224710 (2005)

stretching modulus

simple theory:

farago, jcp, 2003; tolpekina/den otter/briels, jcp 2004; cooke/deserno, jcp 2005

membrane stretching plus line energy

$$e = \frac{1}{2} m \frac{(a - a_s - \pi r^2)^2}{a_s} + 2\pi\gamma r$$

rescaling of energy

$$\lambda^3 = \frac{\gamma a_s}{\pi m}, \quad \tilde{r} = \frac{r}{\lambda}, \quad b = \frac{a - a_s}{\pi \lambda^2}$$

equilibrium condition for pore radius

$$\tilde{r}^3 - b\tilde{r} + 1 = 0$$

Mingyang Hu
mingyang@cmu.edu