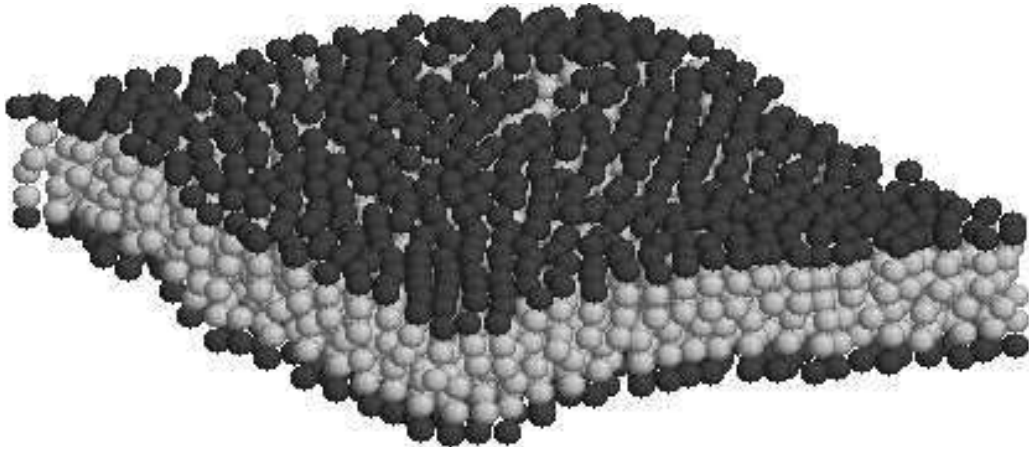
COARSE–GRAINED MODELS
and
SIMULATIONS
of BILAYER MEMBRANES



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Outline

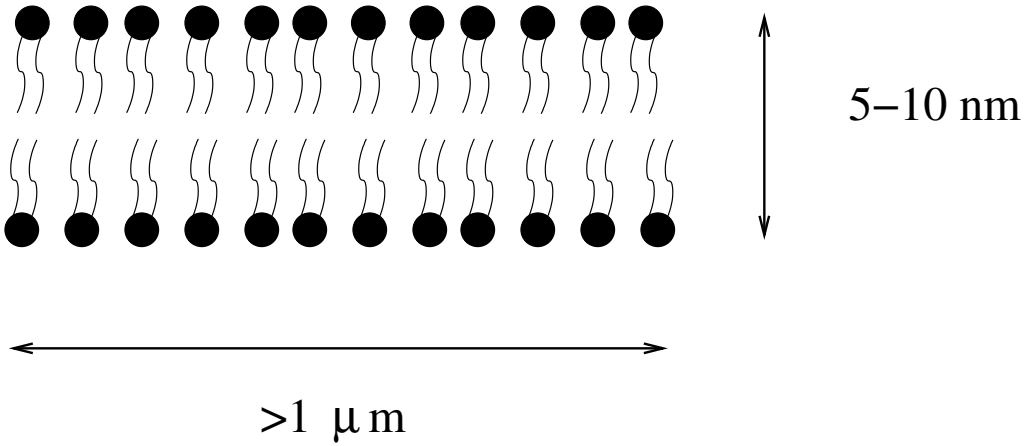
Membranes – some (well known) facts:

hydrophilic head

hydrophobic tail

* Created by self–assembly of amphiphilic molecules

* Quasi two–dimensional objects



* Soft (but strong) materials

– Resist lateral (in plane) stretching or compression $B \sim 100$ erg/cm^2

– May fluctuate strongly in the normal direction (out–of–plane)

$\kappa \sim 10^{-12}$ erg

Why are membranes interesting ?

* Statistical mechanics at reduced dimensionality

– Variety of phases [solid, fluid, gel (=hexatic?)]

– Large normal fluctuations

* Soft Matter

– 2D generalizations of linear polymer chains

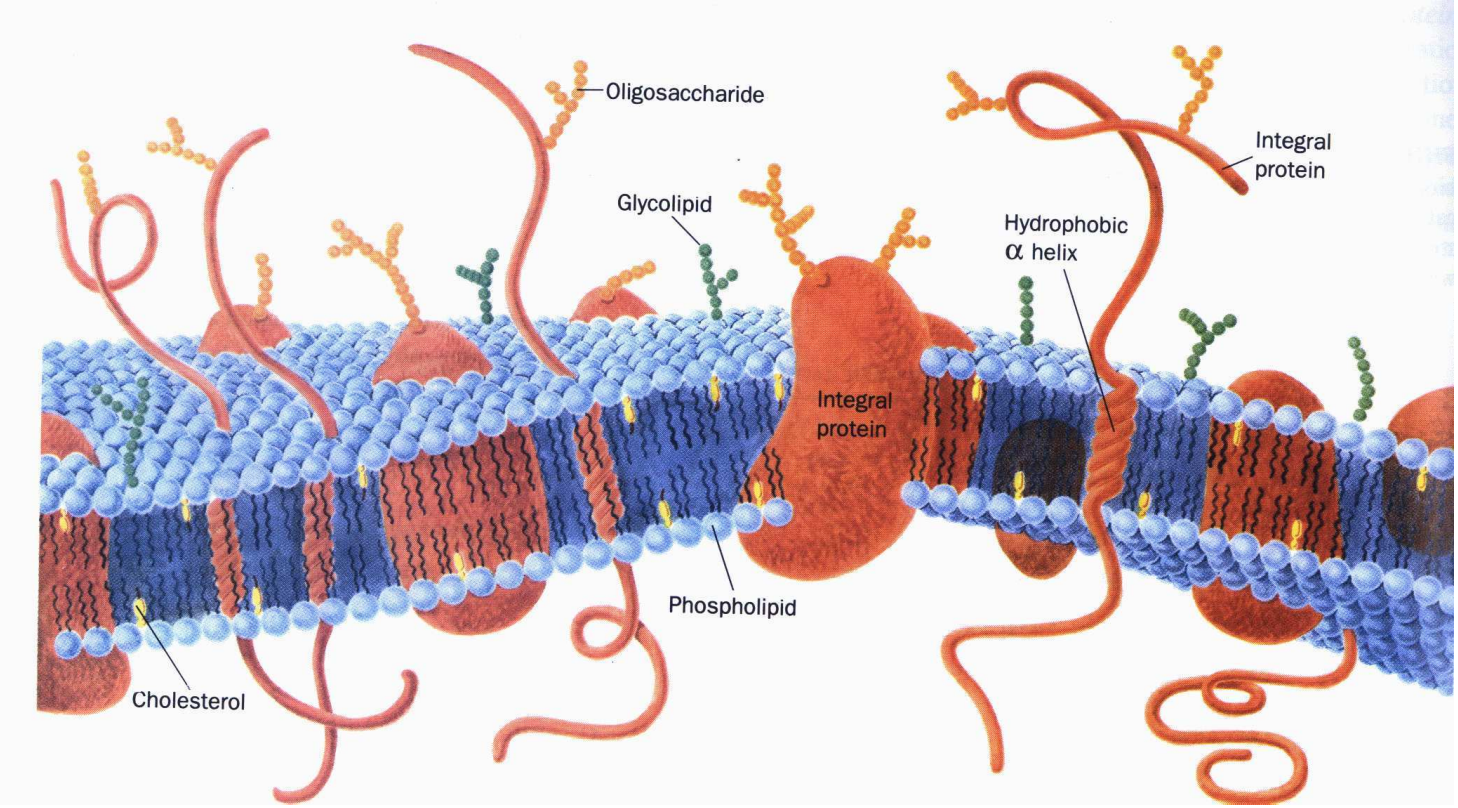
– Surface tension, bending elasticity and the interplay between them.

* Nano–biotechnology

– Liposome based drug delivery

– Gene therapy systems

Why are membranes interesting ?

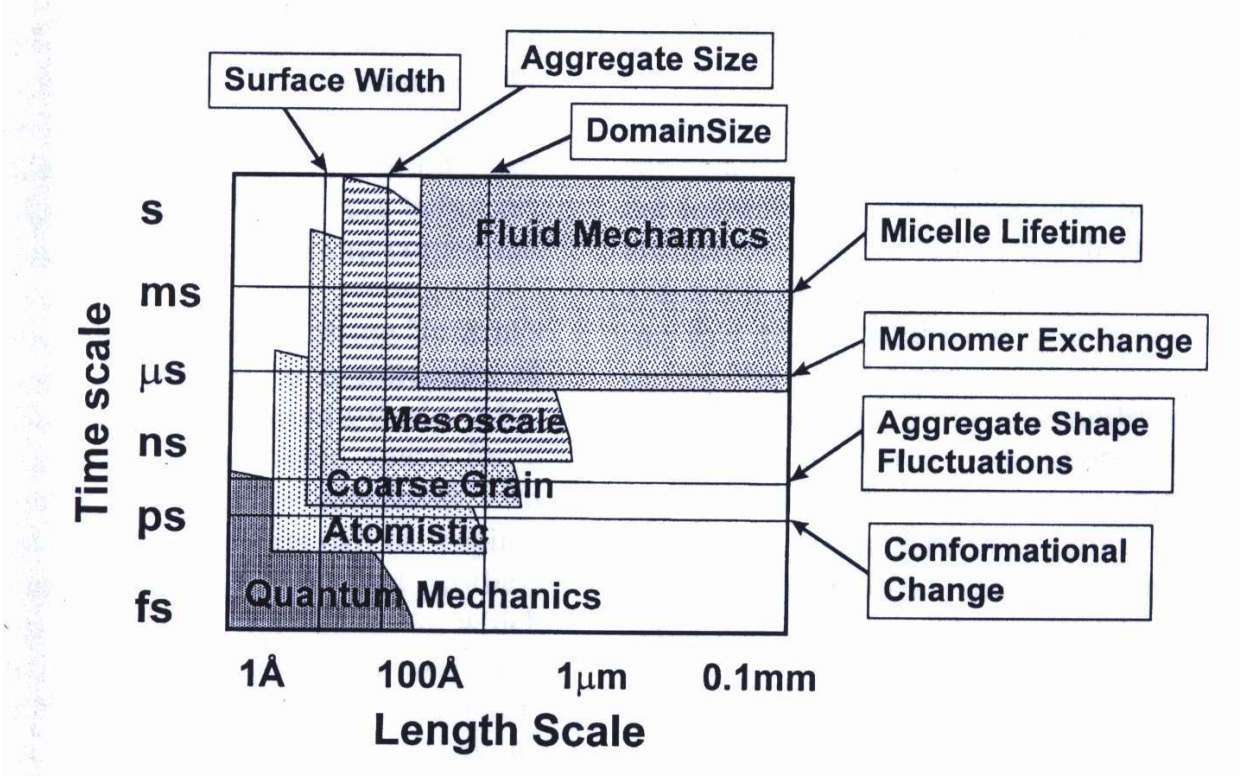


Simple model for biomembranes.

a. Understanding the relation between the physical properties of the lipid matrix and its biological functions.

b. Developing computational models which will serve as platforms for more complicated systems including mixtures of lipids and membranes proteins.

Length and time scales in membranes



Molecular level

Structure: area per lipid, bilayer thickness, chain tilt, fraction of gauche bonds, penetration of water.

Dynamics: motion of a single molecule, reorganization of small patches, aggregation (micelles).

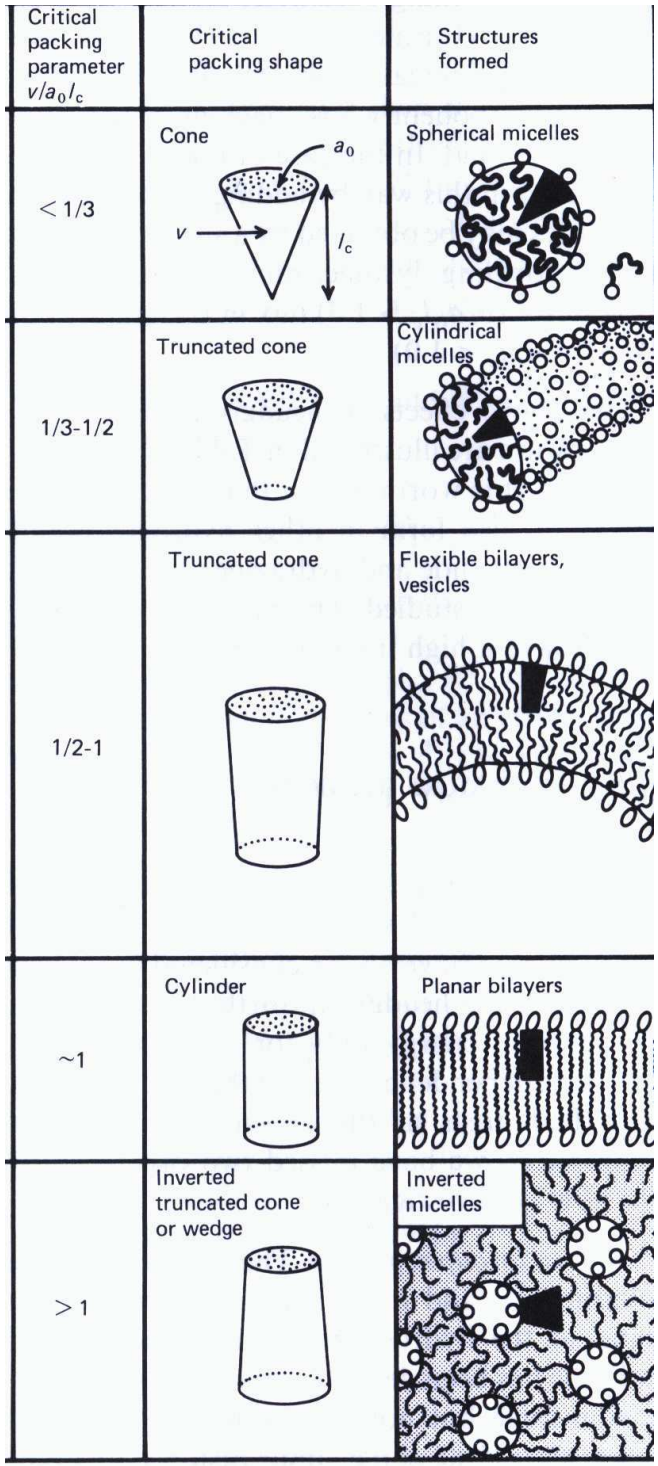
Membrane level

thermal fluctuations, shape transitions, phase diagram (solid–gel –fluid), domain formation (mixtures), self–assembly, elasticity, lateral diffusion, flip–flops, pores.

Atomistic computer models → microscopic properties

Coarse−grained models → how the macroscopic properties emerge from the microscopic entities and the interactions between them?

Continuum theories → macroscopic behavior



Example: the theory relating the the shape of the lipid molecules and morphology of the aggregate.

$$p \equiv \frac{v}{al}$$

p – packing parameter

v – molecule volume

l – tail length

a – head group surface area

Phenomenological continuum models

Helfrich Hamiltonian (Landau expansion in small curvature)

$$\mathcal{H} = \int_S dA \left[\sigma + \frac{1}{2}\kappa (c_1 + c_2 - 2c_0)^2 + \kappa_G c_1 c_2 \right]$$

surface tension

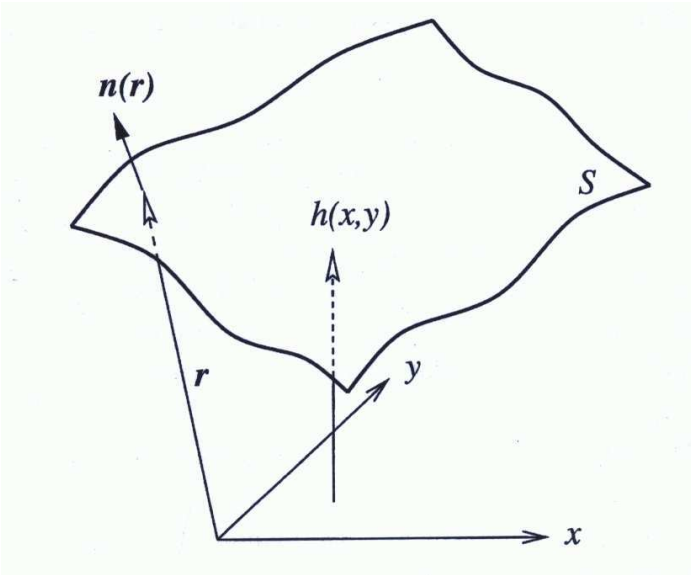
bending modulus

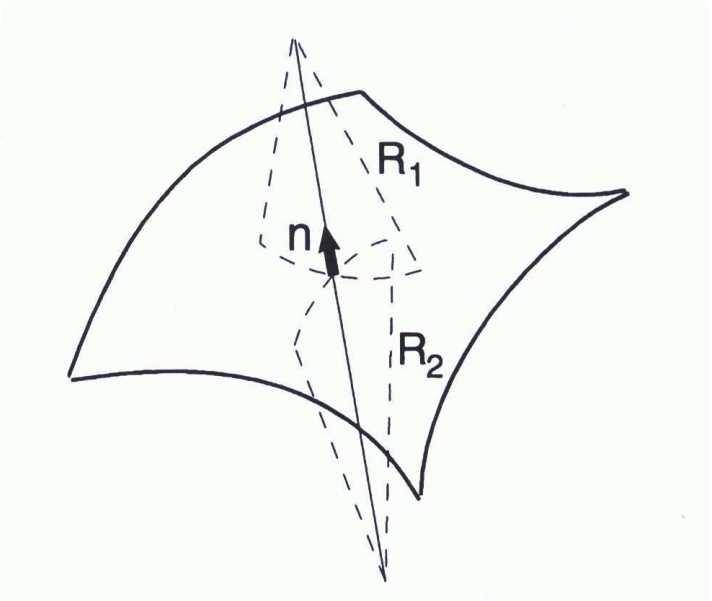
local curvatures

spontaneous curvature

saddle–splay modulus

Monge gauge





Helfrich Hamiltonian (cont.)

$h(x,y)$ – Monge gauge

$$\mathcal{H} \simeq \frac{1}{2}\int \left[\sigma\left(\vec{\nabla}h\right)^2 + \kappa\left(\nabla^2 h\right)^2\right] dxdy$$

Note:

* We assume that $c_0 = 0$ (flat reference surface)
* The Gaussian curvature contributes a constant term.

In Fourier space:

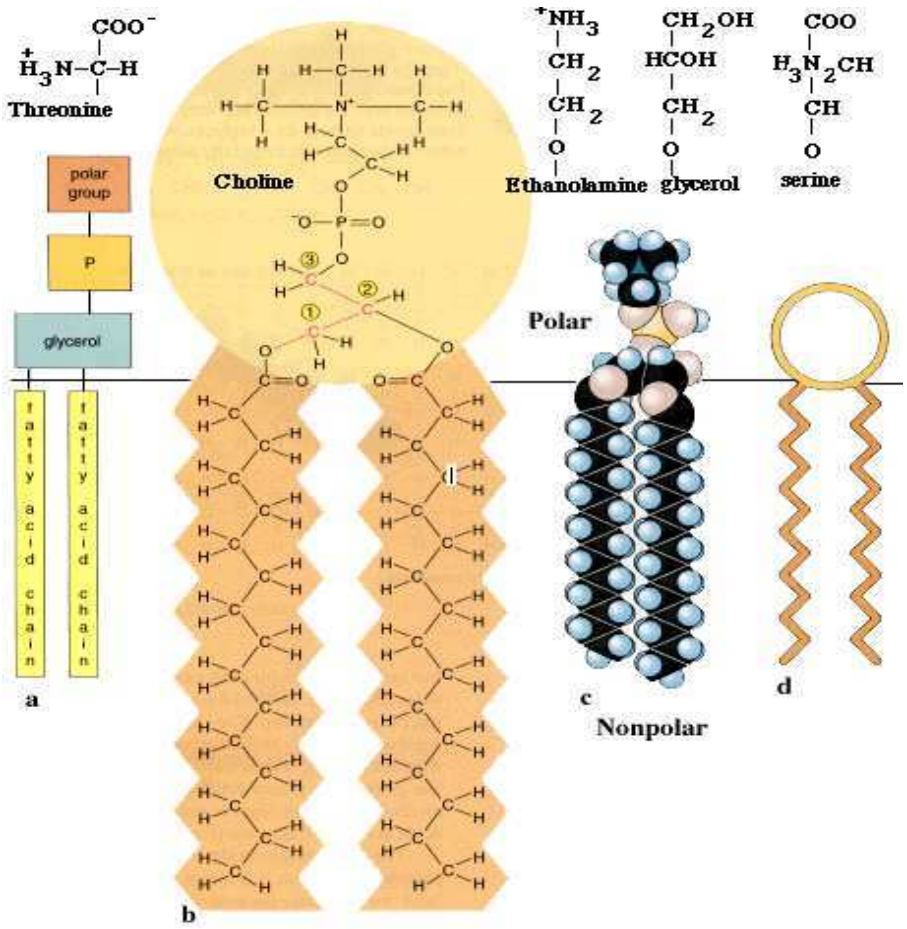
$$\mathcal{H} \simeq \frac{1}{2}\sum_{\vec{q}} \left[\sigma q^2 + \kappa q^4\right] |h_{\vec{q}}|^2 \qquad \frac{2\pi}{L} \leq |\vec{q}| \leq \frac{2\pi}{a}$$

Equipartition theorem:

$$\langle |h_{\vec{q}}|^2 \rangle = \frac{kT}{\sigma q^2 + \kappa q^4}$$

Spectral Intensity

Atomistic computer models



+ WATER MOLECULES
(20–50 Molecules per lipid)

+ INTERACTIONS:

covalent bonds

bond angles

non–bonded interactions (LJ)

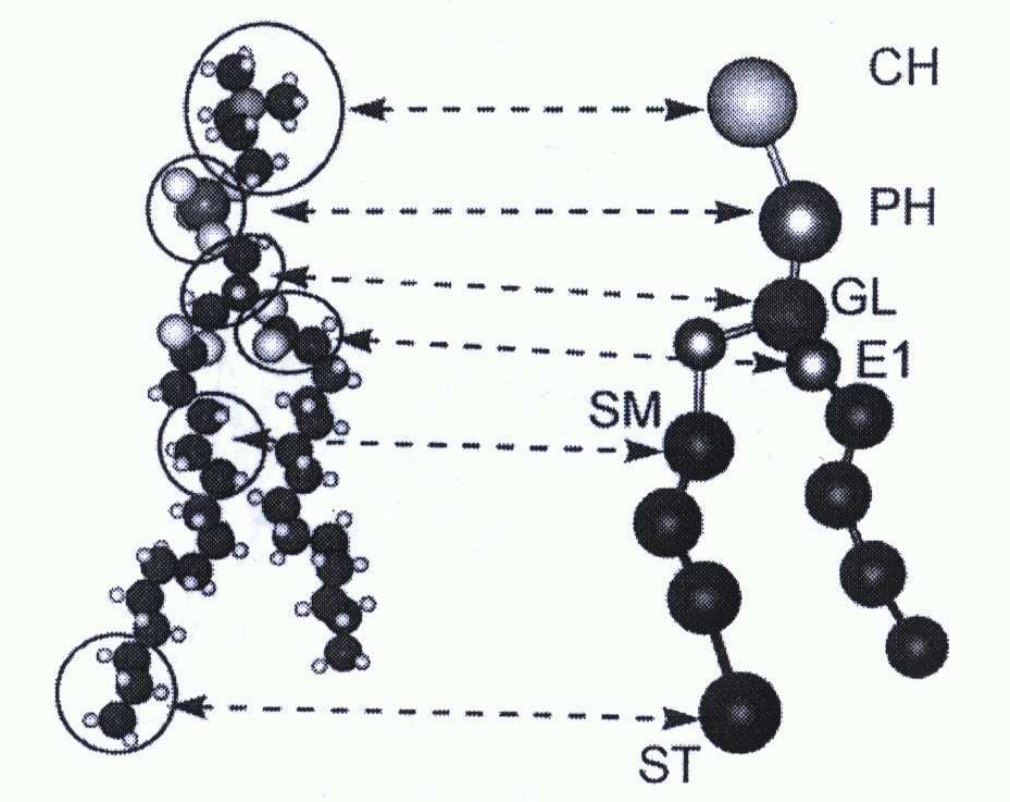
electrostatics

* Computationally very expensive (we need >150 atoms to simulate one lipid molecule).

* Restricted to small patches of 50–200 lipids and time scales of a few nanoseconds.

Coarse–grained computational models I

(coarse–description of specific systems)



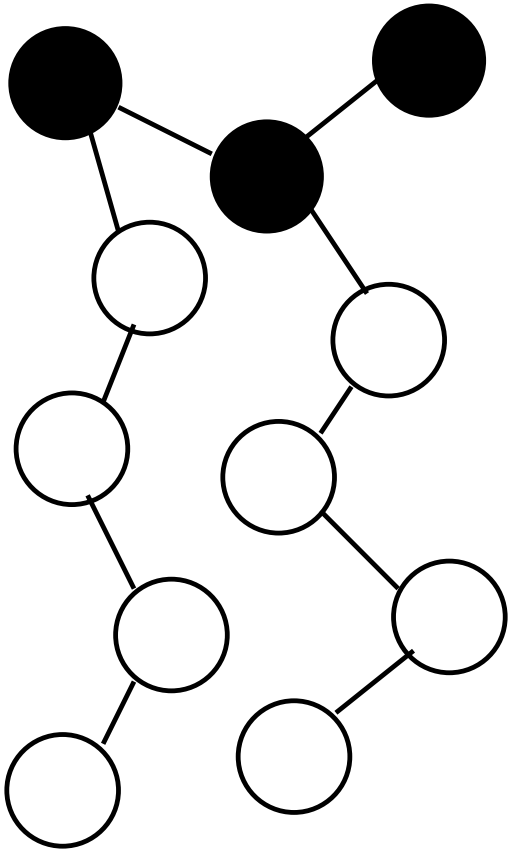
Coarse–grained model of a phospholipid molecule (DMPC)

[Shelley et al., J. Phys. Chem. B **105**,4464 (2001)]

The major challenge:

Finding effective potentials that reproduce microscopic features of the system.

Coarse–grained computational models II
(simplified models of amphiphilic molecules)



+ WATER PARTICLES (10–30 Molecules per Lipid)

SIMPLIFIED INTERACTIONS

Lennard–Jones

springs

many–body

no electrostatics!

[R. Goetz and R. Lipowsky, J. Chem. Phys. **108** ,7397 (1998)]

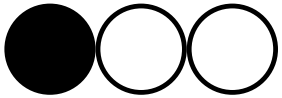
* Larger membranes, Larger time scales

* No specific lipid systems, only general properties

* Still computationally expensive (15–40 particles per "lipid")

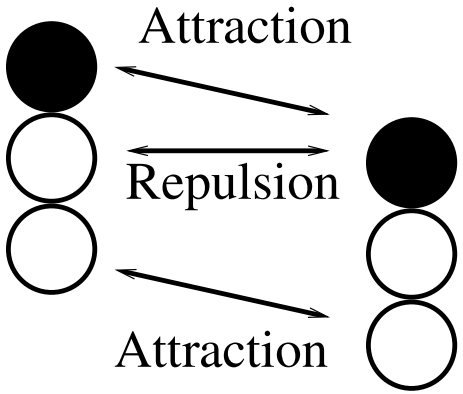
Even more simplified model (Minimal ?)

Principles of the model:

* lipids are modeled as rigid trimers 

* NO WATER !!!

* only Lennard–Jones pair interactions



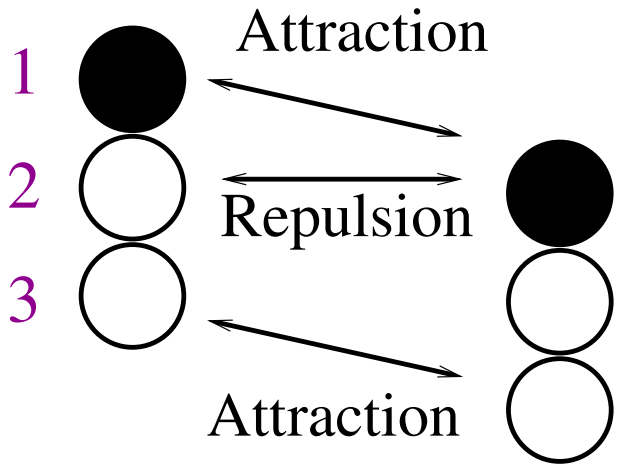
OF, J. Chem. Phys.**119**, 596 (2003)

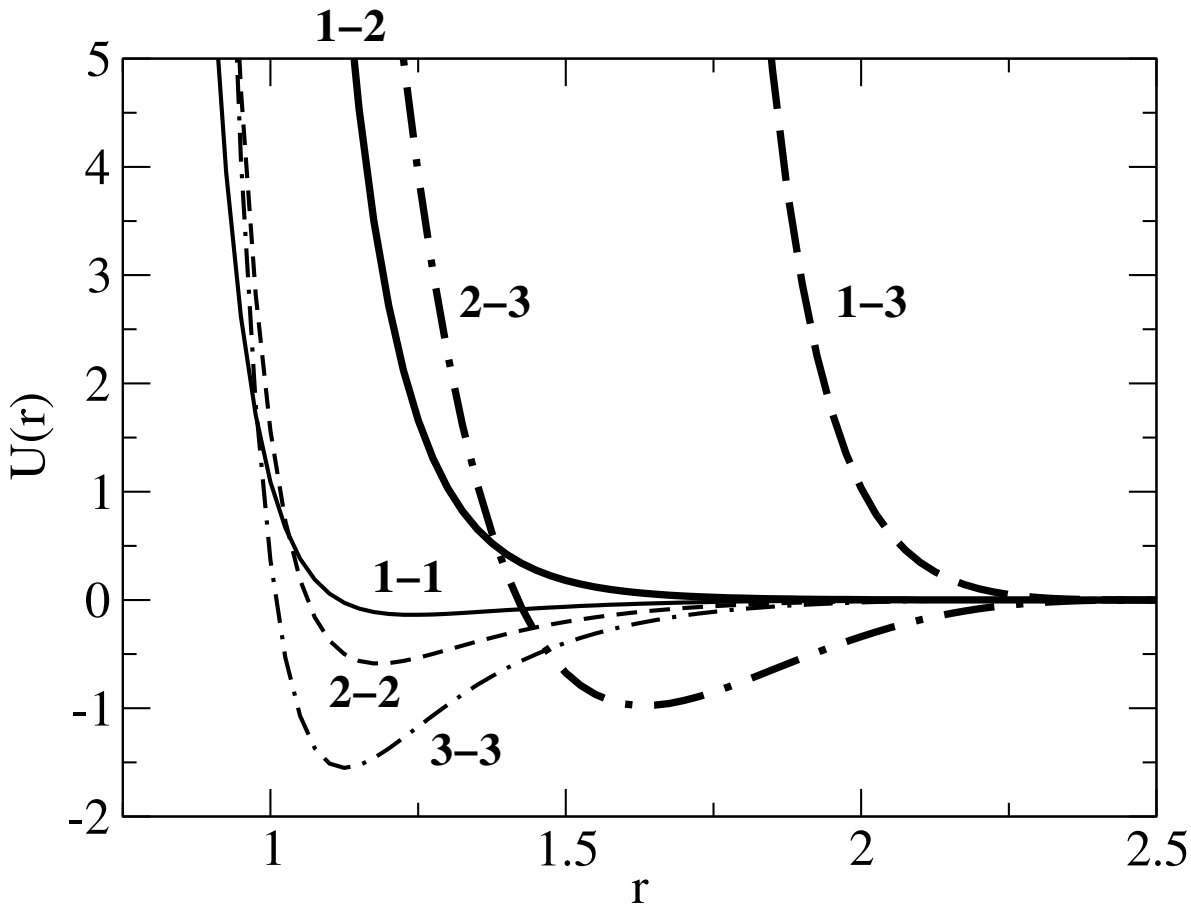
Problem: Water (via the hydrophobic interactions) confines the lipids to the membrane

Incorrect solution: strong attraction between lipids (solid membrane)

Correct solution: shallow potentials – smooth energy landscape

non–additive pair potentials – mimics hydrophobicity



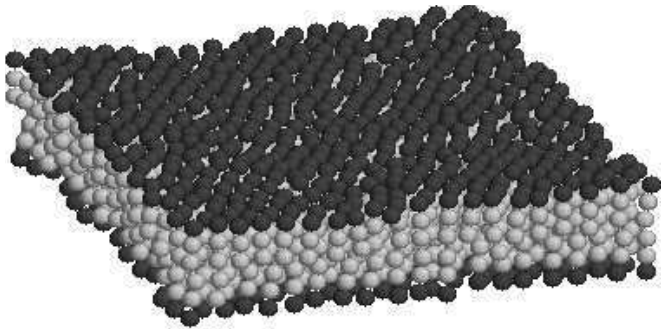


Phase diagram

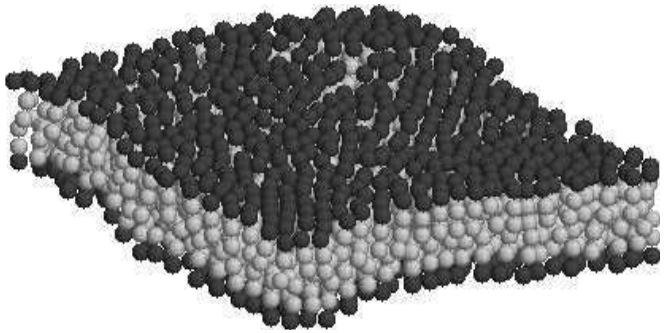
Small projected area (high density)

Large projected area (low density)

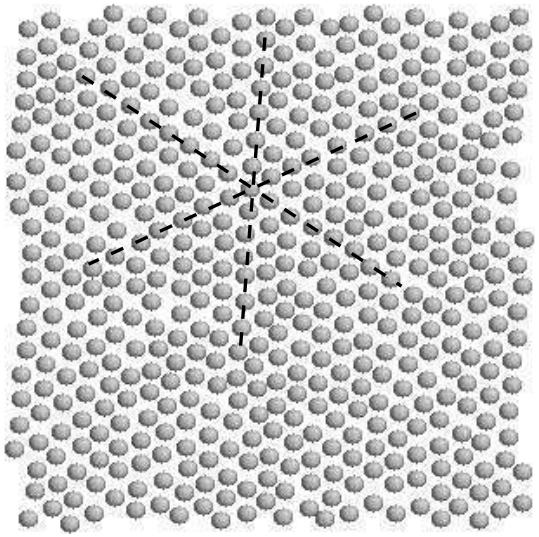
solid membrane

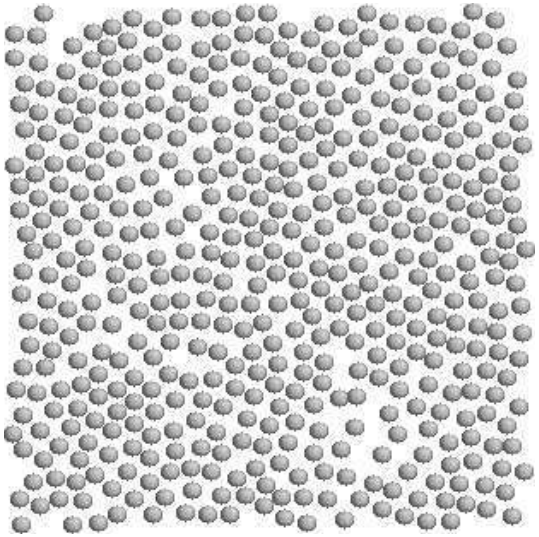


fluid membrane



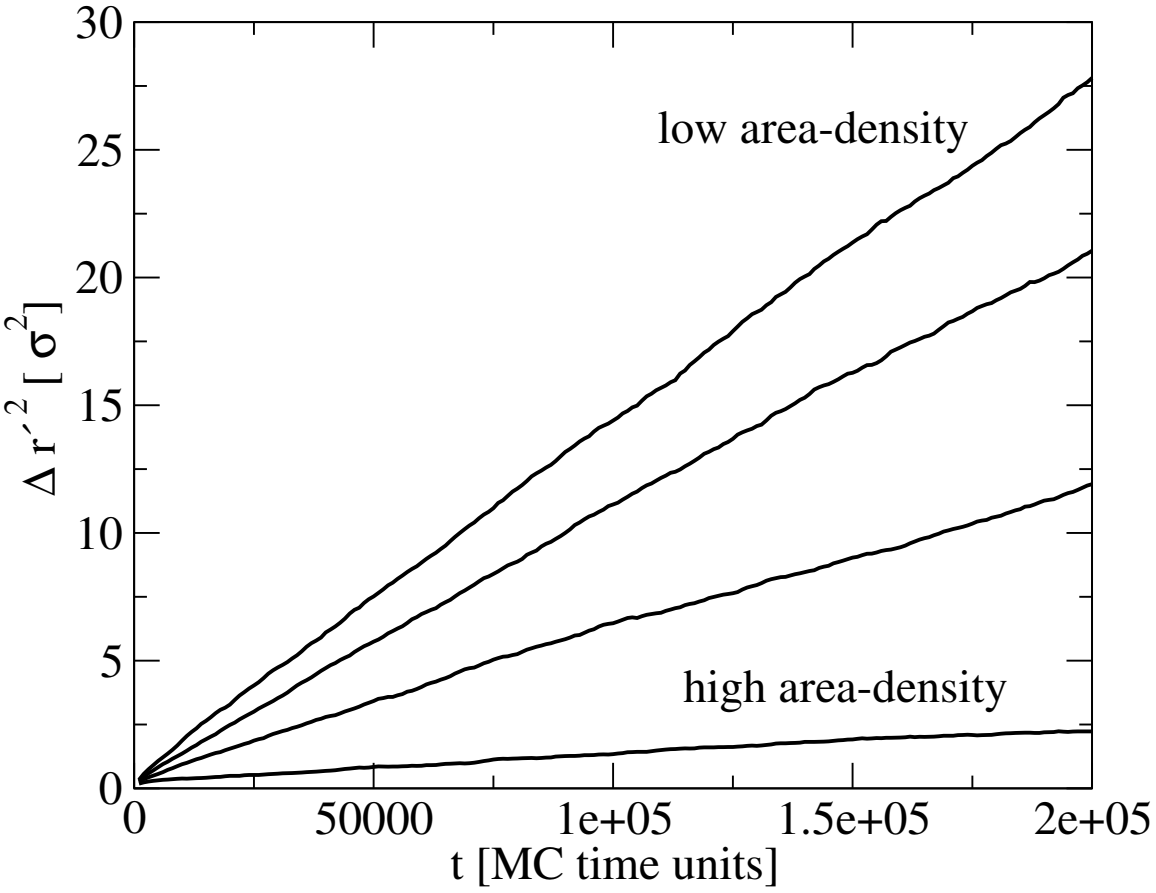
1000 Molecules





Fluid membranes

in–plane diffusion

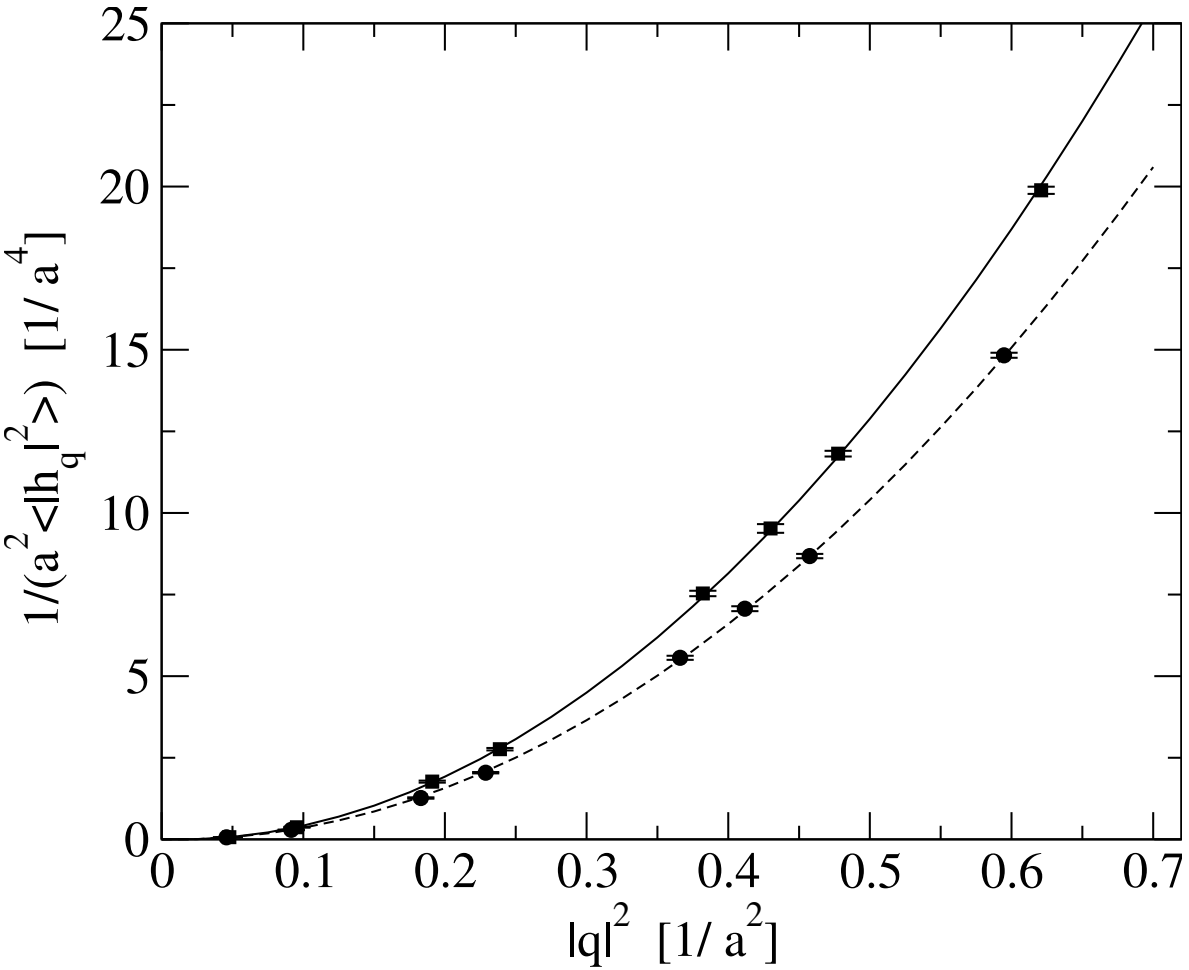


self–diffusion coefficient

$$D \equiv \lim_{t\to\infty} \frac{\Delta r'(t)^2}{4t} \equiv \lim_{t\to\infty} \frac{1}{4Nt} \sum_{i=1}^{N} \left[(\vec{r}_i(t) - \vec{r}_{\mathrm{CM}}(t)) - (\vec{r}_i(0) - \vec{r}_{\mathrm{CM}}(0)) \right]^2$$

Fluid membranes

out–of–plane fluctuations



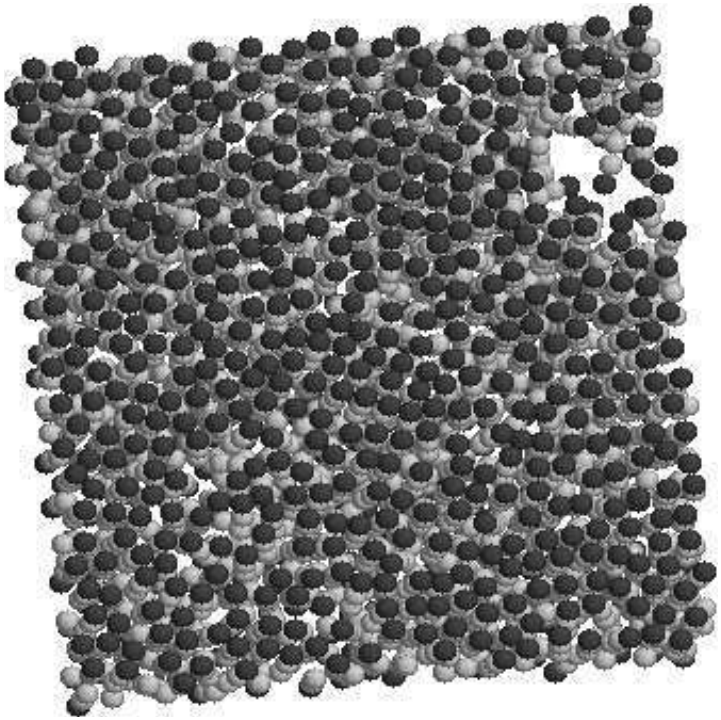
spectral intensity

$$\langle |h_q|^2 \rangle \propto \frac{kT}{\sigma q^2 + \kappa q^4}$$

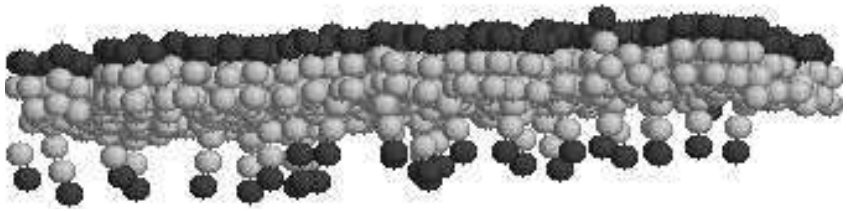
The bending modulus $\kappa \sim 40kT$

Pores and flip–flops

pore formation reduces the elastic energy ...



... and allows the trans–bilayer diffusion (flip–flops) of lipids



Pores – mechanism for reducing the membrane area

Surface tension $\sigma = K_A \dfrac{(A - A_s)}{A_s}$ > 0 – stretching

< 0 – compression

K_A – area compressibility

A – membrane area $\qquad$ A_s – tensionless (Schulman) area

Pore nucleation energy (Litster, 1975)

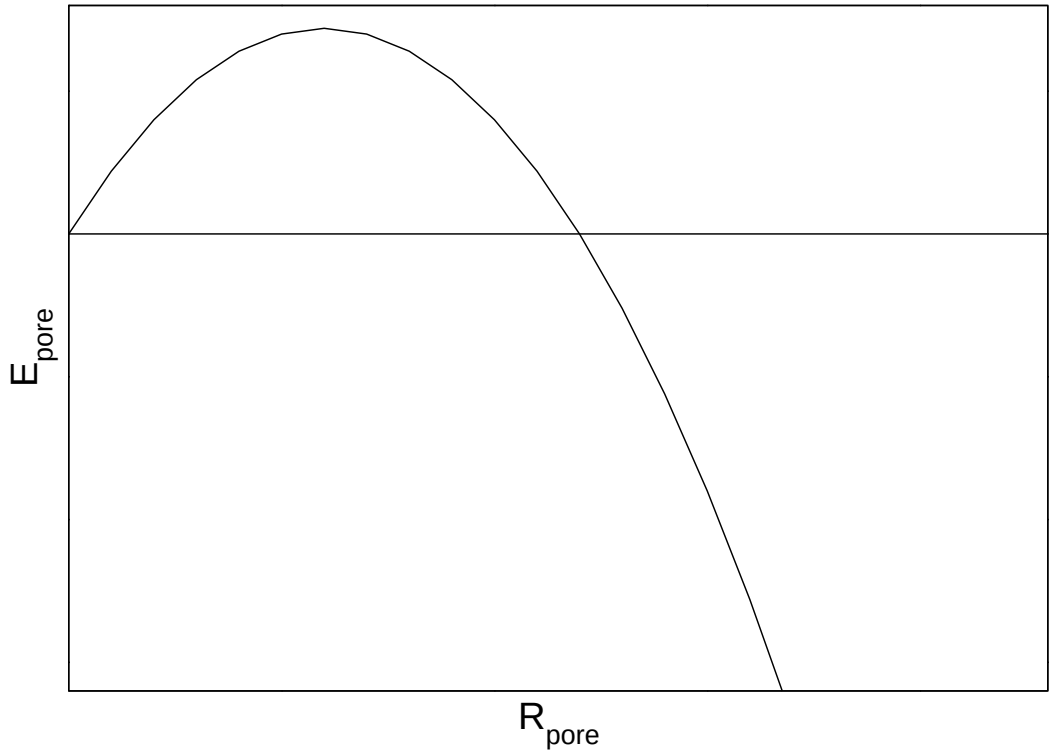
$$E_{\text{pore}}(R) = \lambda\, 2\pi R - \sigma\, \pi R^2$$

$$R_{\max} = \frac{\gamma}{\sigma}$$

$$E_{\max} = \frac{\pi \gamma^2}{\sigma}$$

$$\lambda \sim 10^{-11}\ N$$

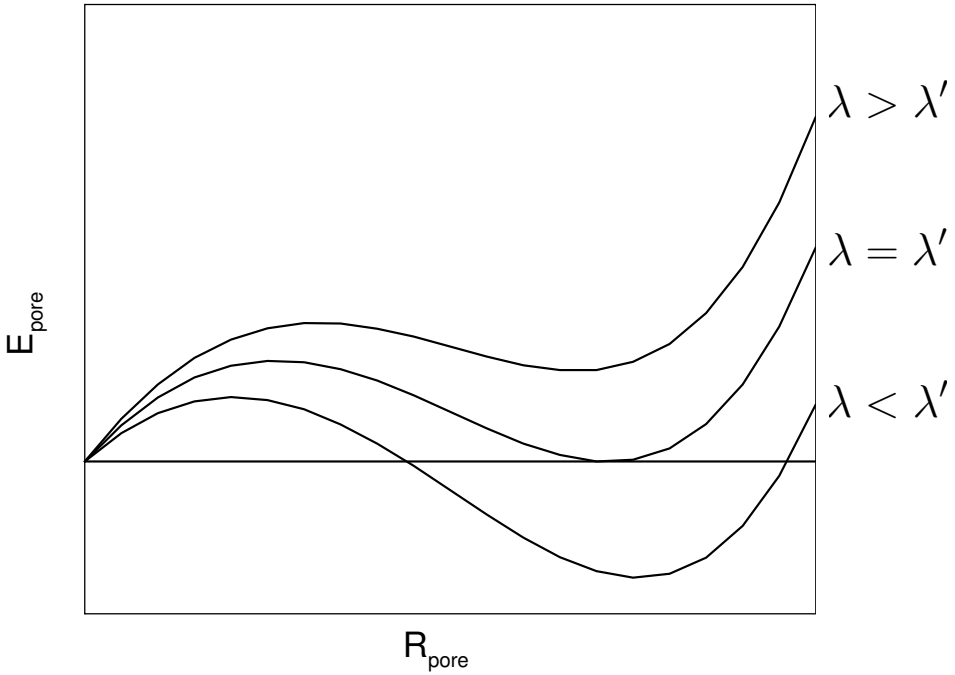
$$\sigma_{\text{rapture}} \leq 10^{-1}\ \frac{N}{m}$$

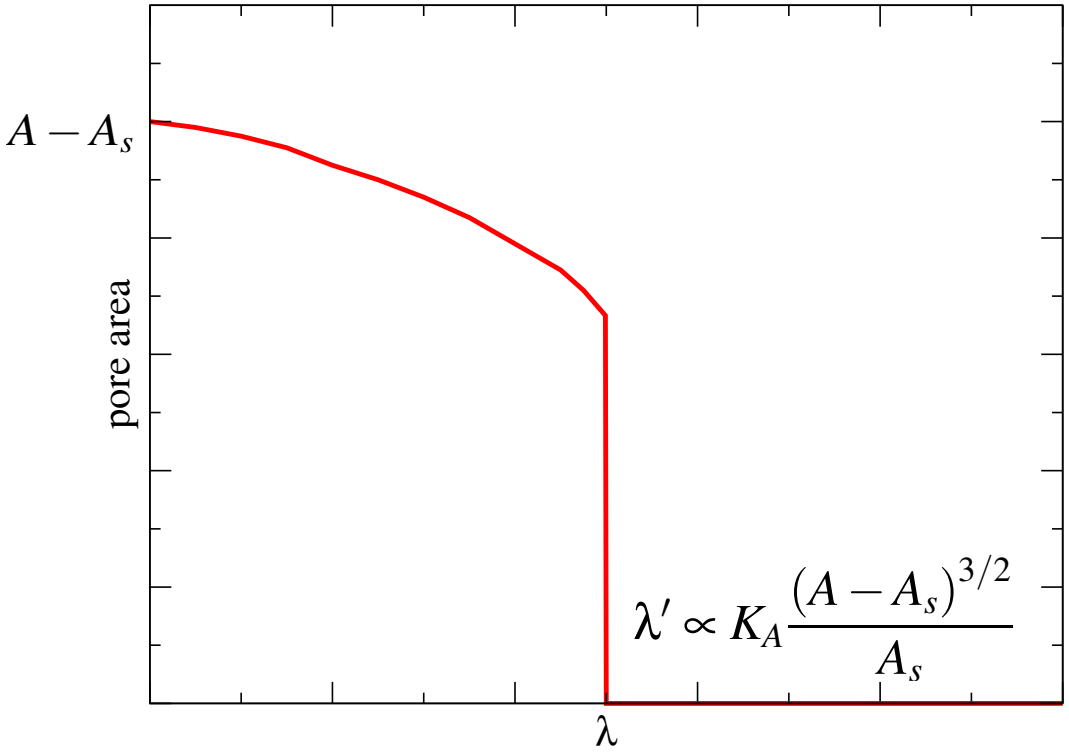


Pore formation – finite size dependence

Pore energy: $E_{\rm pore}\left(A, A_{\rm pore}\right) = K_A \dfrac{\left(A - A_{\rm pore} - A_s\right)^2}{2A_s} - K_A \dfrac{\left(A - A_s\right)^2}{2A_s} + \lambda L_{\rm pore}$

First order transition (circular pore)

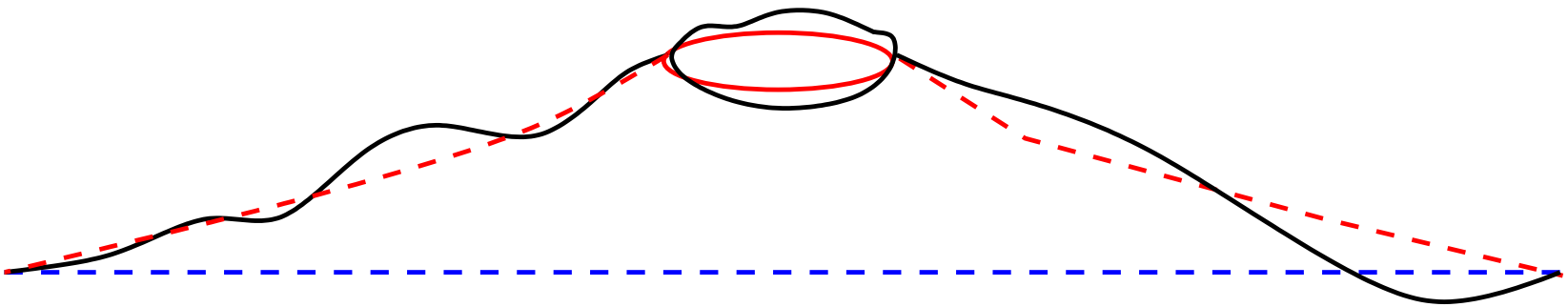




$\lambda > \lambda'$ – metastable pores

$\lambda = \lambda' \longrightarrow \Delta E \sim \dfrac{\lambda^{4/3}}{K_A^{1/3}} \left(A_s\right)^{1/3}$ – size dependence

Pore formation – role of thermal fluctuations

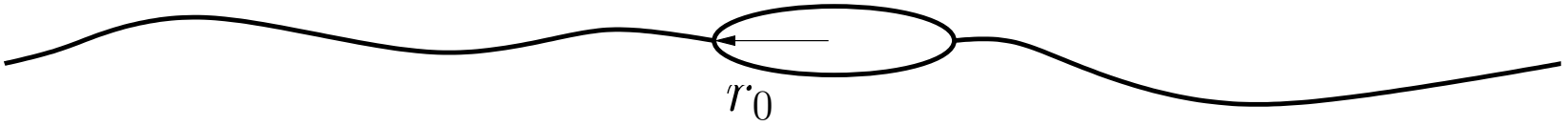


Small fluctuations of a membrane with quasi–spherical hole

1. pore height fluctuations (equilibrium profile)
2. membrane fluctuations around equlibrium height
3. fluctuations of pore shape

For small fluctuations (harmonic approximation)
these three contributions decouple!

* Membrane fluctuations and the surface tension



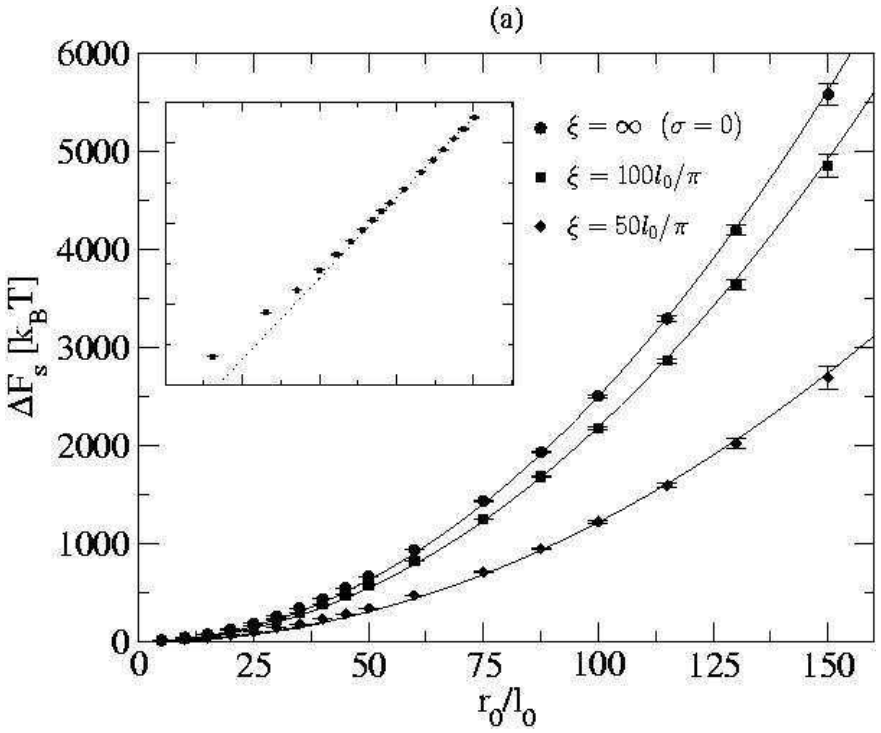
$$F_{\text{fluct}} \equiv F\left(r_0\right) - F(0)$$

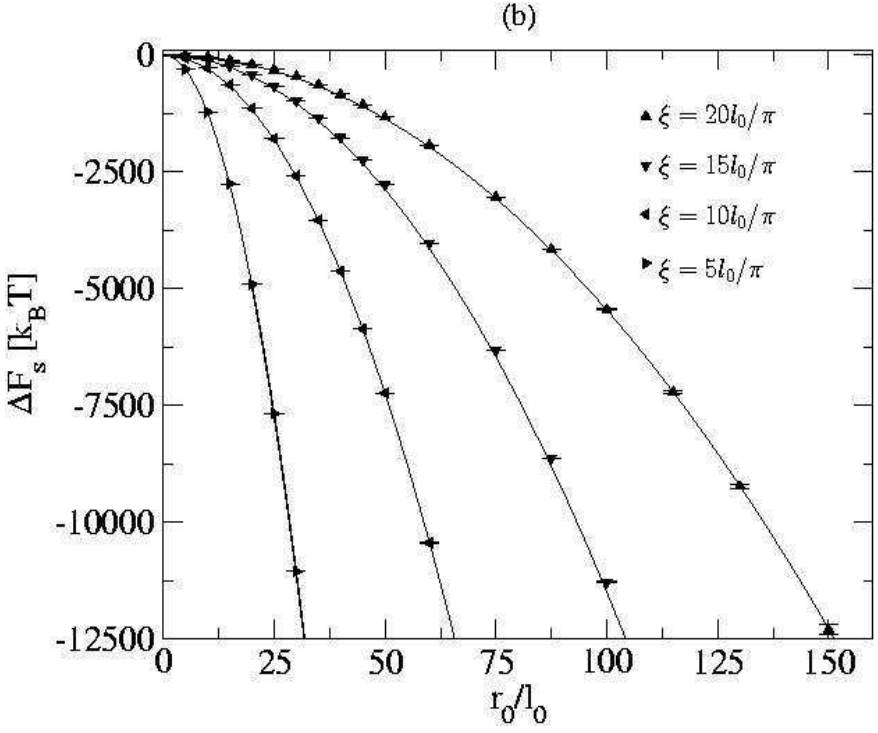
$$F_{\text{fluct}} \approx -\pi\sigma r_0^2 + \frac{k_B T}{2} \sum_{m,n} \ln \left[\frac{\sigma(\lambda_1^{m,n})^2 + \kappa(\lambda_1^{m,n})^4}{\sigma(\lambda_{1,(0)}^{m,n})^2 + \kappa(\lambda_{1,(0)}^{m,n})^4} \frac{L^2 - r_0^2}{L^2} \right]$$

elastic energy (smaller projected area)

entropy (change in the spectrum of thermal undulations)

OF and CD Santangelo, J. Chem. Phys. **122** , 044901 (2005).





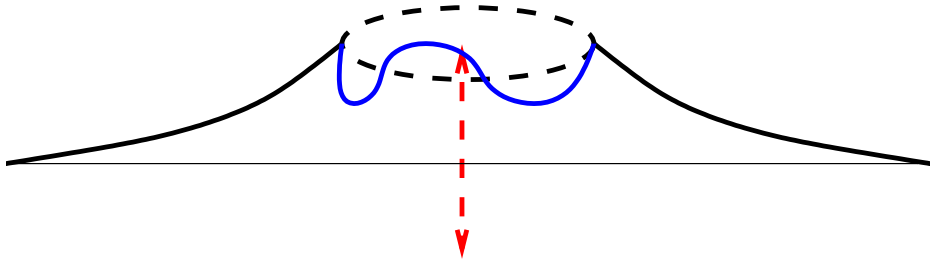
Eigenvalue equation:

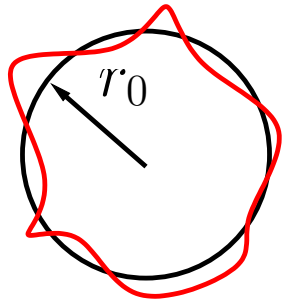
$$J_m(\lambda_1^{m,n} r_0) Y_m(\lambda_1^{m,n} L) - J_m(\lambda_1^{m,n} L) Y_m(\lambda_1^{m,n} r_0) = 0 \xrightarrow{r_0 = 0} J_m(\lambda_{1,(0)}^{m,n} L) = 0$$

$$F_{\text{fluct}} = -\pi r_0^2 \sigma + \frac{k_B T r_0^2}{\alpha l_0^2} \left\{ 2 - \alpha - \left(\frac{l_0}{\pi \xi} \right)^2 \ln \left[\left(\frac{\pi \xi}{l_0} \right)^2 + 1 \right] \right\} \qquad \xi = \sqrt{\kappa/\sigma}$$

$$\equiv \boxed{-\pi r_0^2 (\sigma - \Delta\sigma) \equiv -\pi r_0^2 \sigma_{\text{eff}}} \qquad (\alpha \sim 1.7)$$

Hole fluctuations and the line tension





$$F_{\text{fluct}} \equiv F\left(r_0\right) - F(0)$$

line tension energy

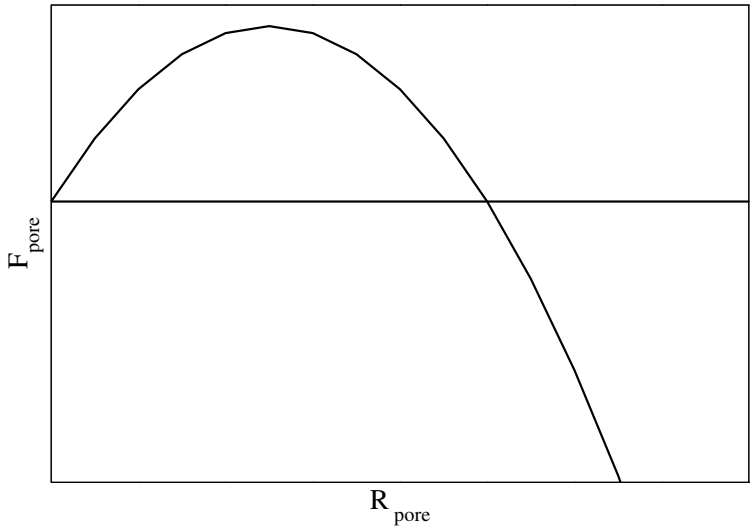
entropy (thermal fluctuations)

$$\begin{aligned}\Delta F &\simeq 2\pi r_0 \left\{\lambda + \frac{bk_BT}{\pi l_0}\left[\ln\left(\frac{bd_{\text{dB}}^2\lambda}{k_BTl_0}\right) - 2\right]\right\} \\ &\equiv 2\pi r_0(\lambda - \Delta\lambda) \equiv 2\pi r_0\lambda_{\text{eff}}\end{aligned}$$

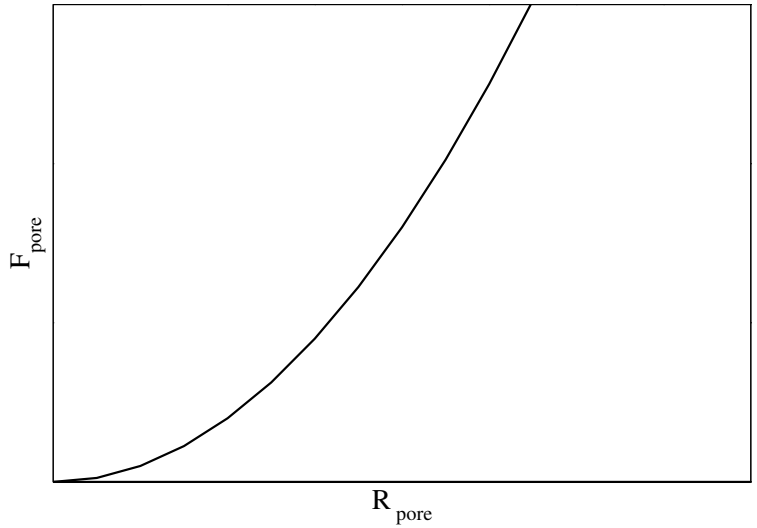
Entopically induced pores

$$F_{\text{pore}}(R) = \lambda_{\text{eff}}\, 2\pi R - \sigma_{\text{eff}}\, \pi R^2$$

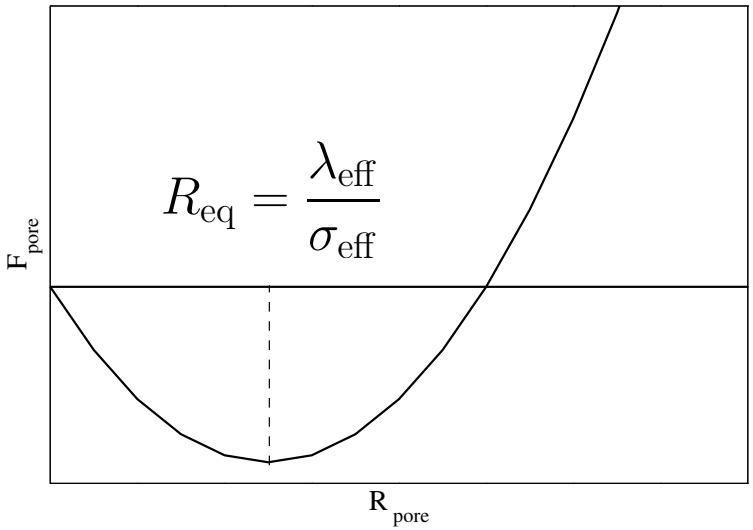
$$\lambda_{\text{eff}} < \lambda \; ; \; \sigma_{\text{eff}} < \sigma$$



$$\lambda_{\text{eff}} > 0 \; ; \; \sigma_{\text{eff}} > 0$$



$$\lambda_{\text{eff}} > 0 \; ; \; \sigma_{\text{eff}} < 0$$



$$\lambda_{\text{eff}} < 0 \; ; \; \sigma_{\text{eff}} < 0$$

Summary

1. We present a simple and efficient computer model of bilayer membranes. The absence of water from the simulation cell greatly reduces the computational effort.

2. Computer simulations reveal a variety of phenomena commonly observed in real bilayer systems.

3. Pore formation is a mechanism for reducing the membrane area. The energy barrier for this process increases with the size of the system.

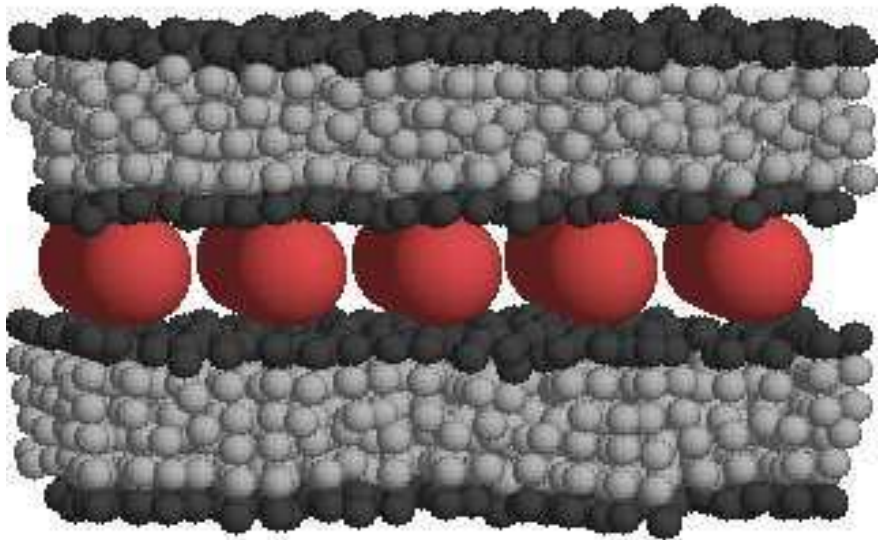
4. Thermal fluctuations renormalize the surface and line tension, making their effective values smaller than their bare ones. Depending on the sign of the effective coefficients, the opening of a pore may be:

A) thermodynamically unfavorable

B) a thermally activated process

C) occur spontaneously

More complex Systems – DNA–lipid complexes



* The new generation of gene–therapy vectors

* Form spontaneously

* Their phase behavior is dominated by electrostatic, bending, and stretching energies.

Thanks to ...

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Cyrus R. Safinya and his group

Niels G. Jensen