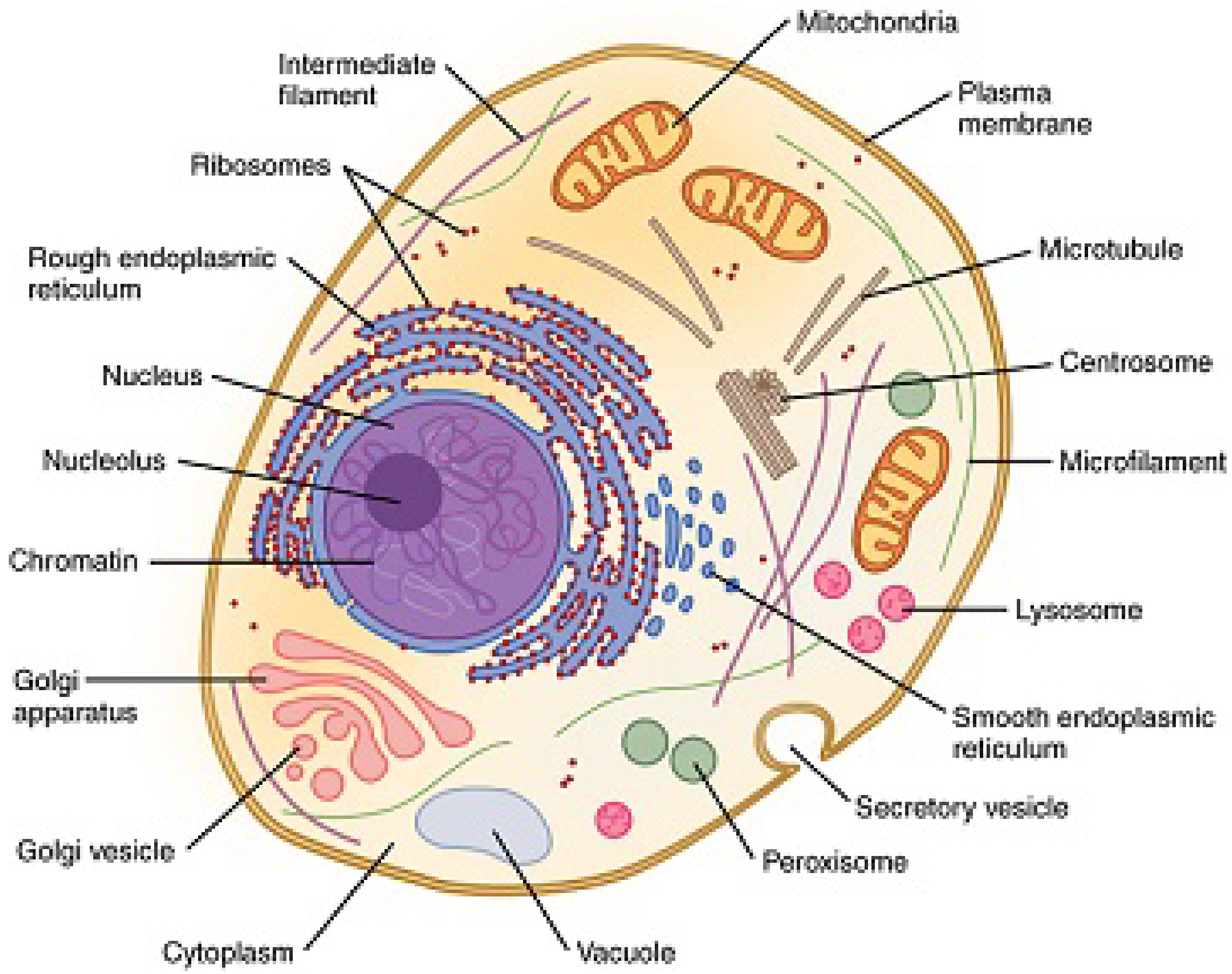
Lipid bilayers
The fats of life

Chem 163

15 Nov. 2022

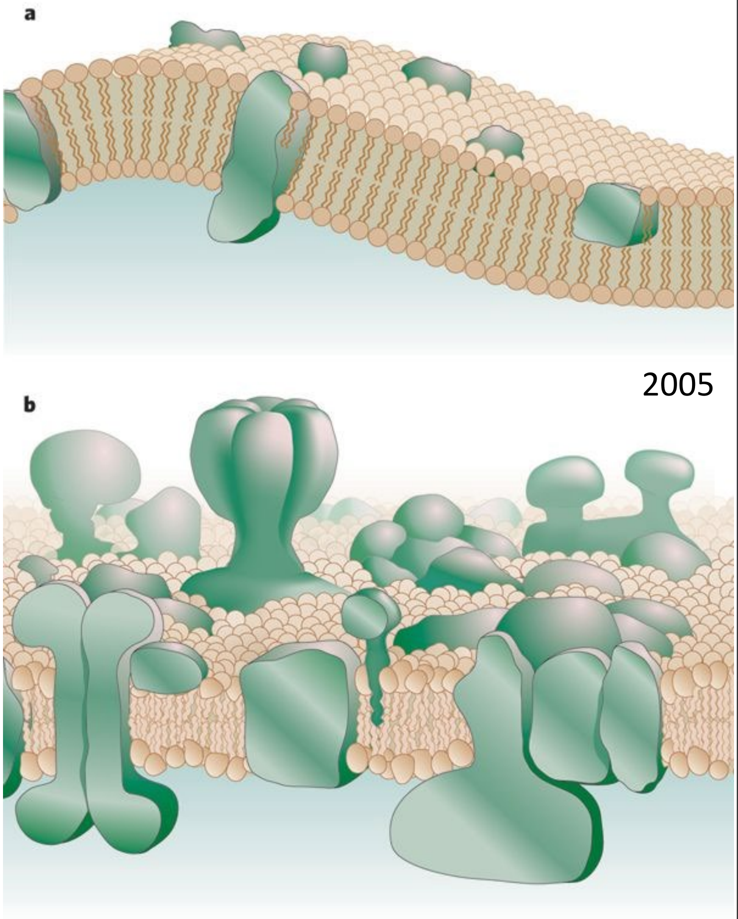
Adam E. Cohen

Membranes in a cell



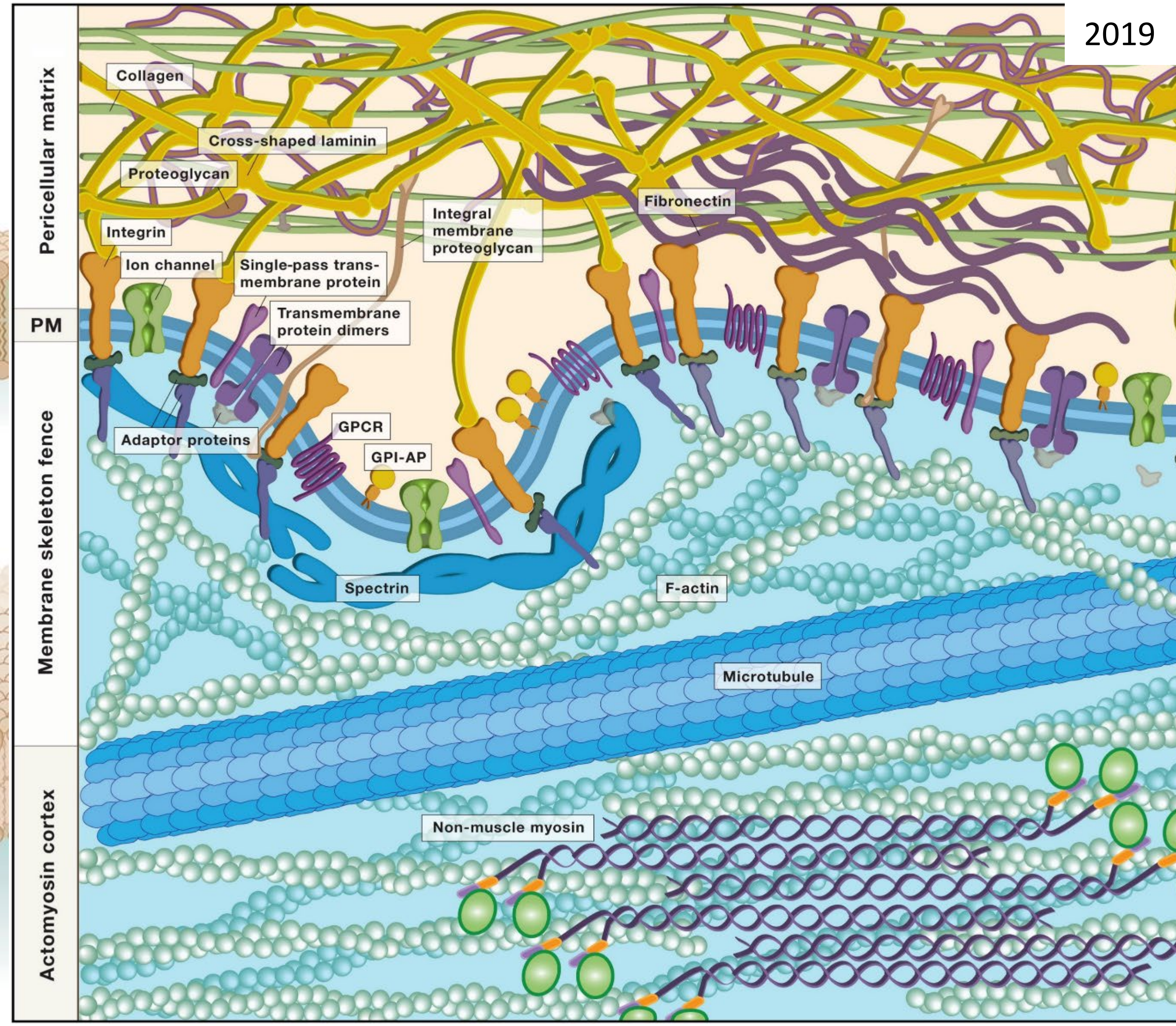
Evolving view of membrane structure

1972



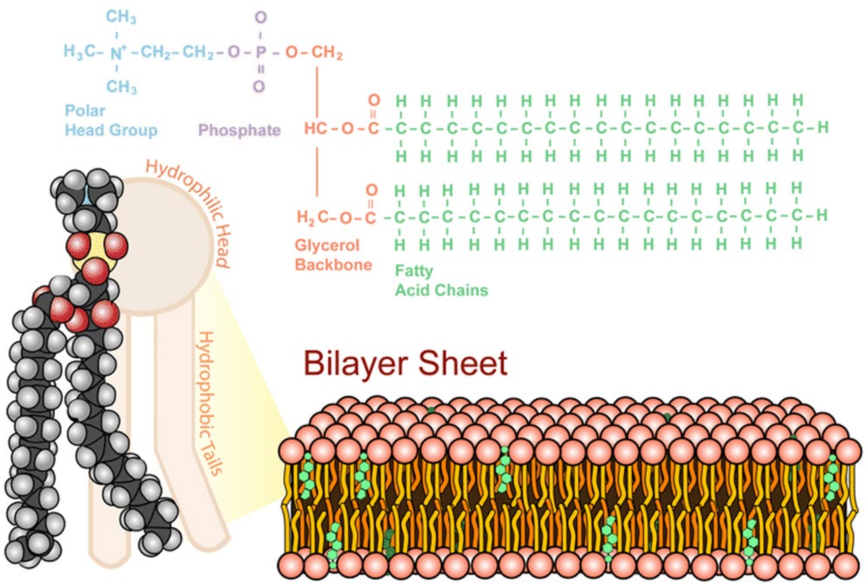
https://www.nature.com/articles/nature04394/figures/1

2019



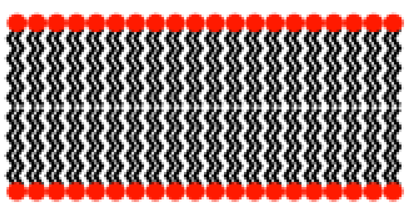
https://www.sciencedirect.com/science/article/pii/S0092867419304040#fig1

phosphatidylcholine

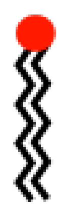


~3 nm

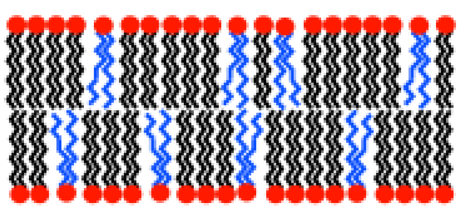
Depends on cholesterol



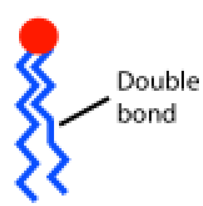
Saturated lipids only



Saturated

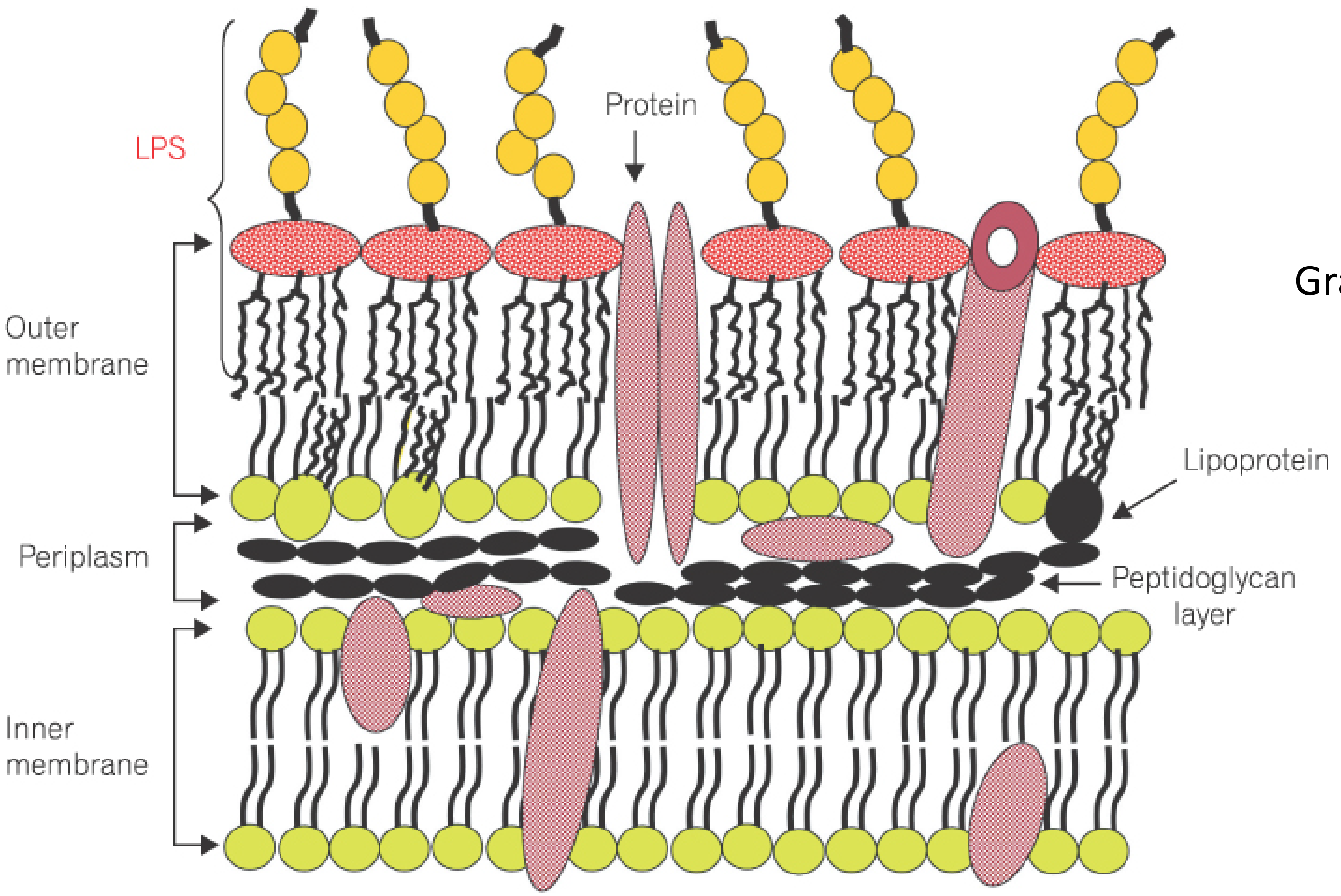


Mixed saturated and unsaturated



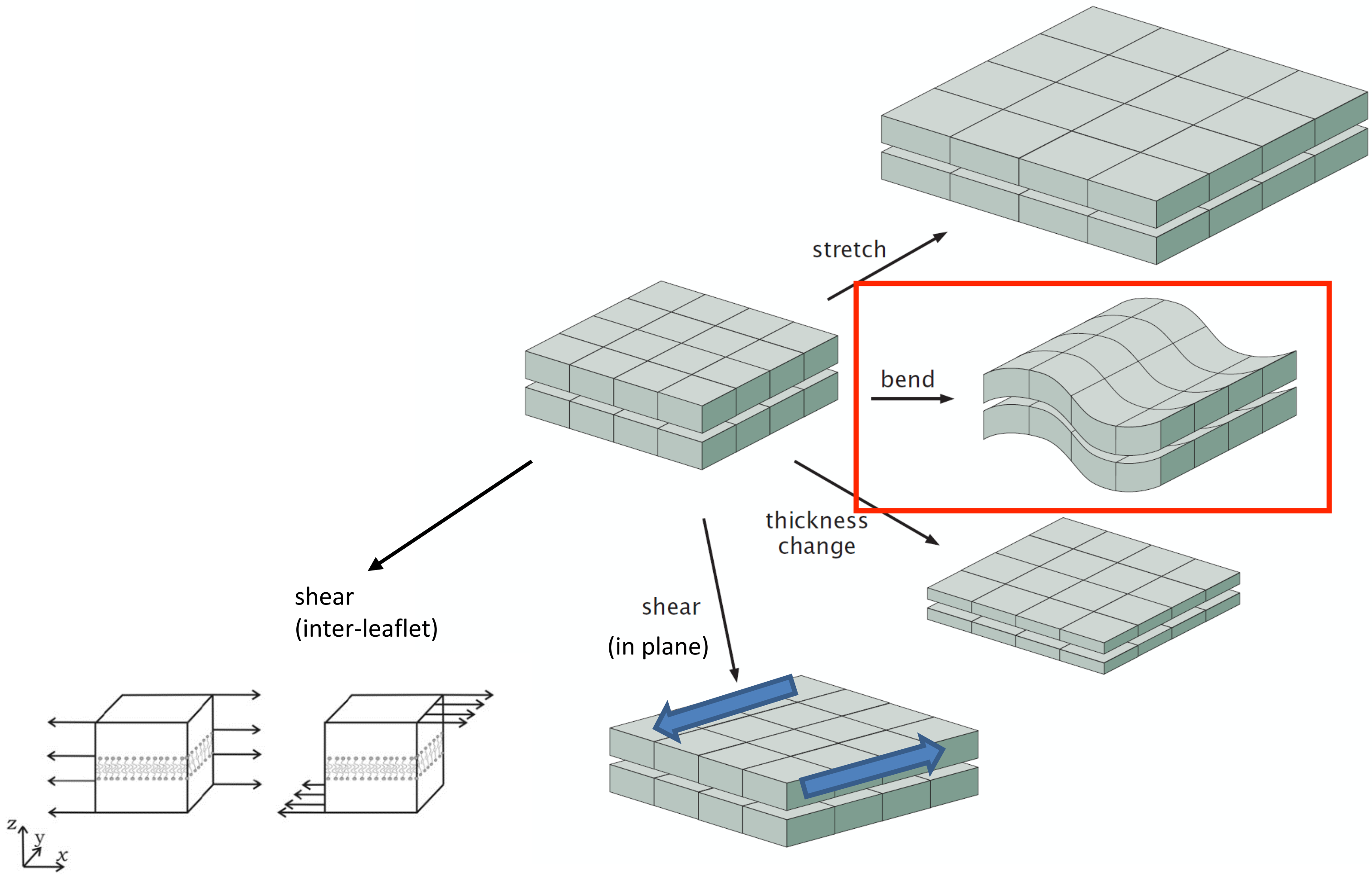
Monounsaturated

Bacteria



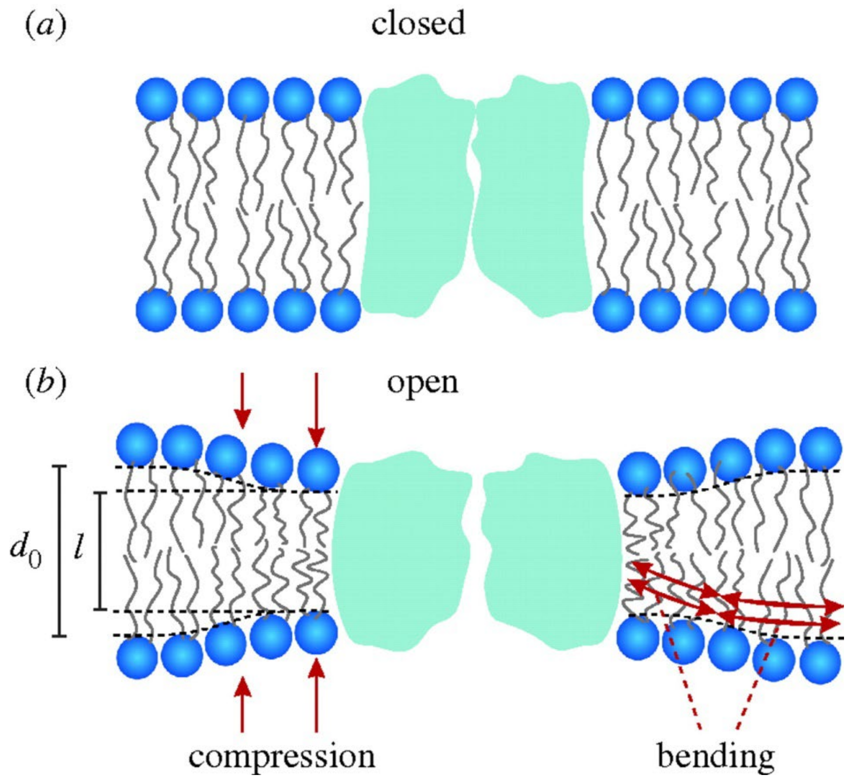
Gram negative

Mechanical deformations of membranes



Phillips, PBoC

In-plane compression



Bending energy

$$E = \int dA \left[\frac{\kappa}{2} \left(\frac{1}{R_1} + \frac{1}{R_2} - C_0 \right)^2 + \frac{\kappa_G}{R_1 R_2} \right]$$

Helfrich free energy

bending rigidity $\kappa \sim 20 k_B T$

Gaussian bending rigidity $\kappa_G \sim -0.8\kappa$

mean curvature $H = \frac{1}{2}\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$

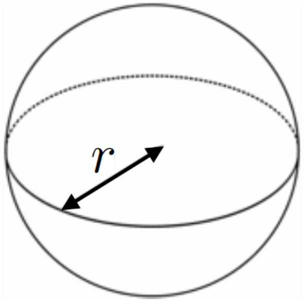
Gaussian curvature $G = \frac{1}{R_1 R_2}$

spontaneous curvature C_0

Example: bending energy for a sphere

$$\frac{1}{R_1} = \frac{1}{R_2} = \frac{1}{r}$$

$$C_0 = 0$$



$$E = 4\pi (2\kappa + \kappa_G) \sim 300 k_B T$$

bending energy is independent of the sphere radius!

Andrej Kosmrlj, Princeton, MAE545_S2018/lecture16_slides.pdf

Gauss-Bonet theorem

For closed surfaces the integral over Gaussian curvature only depends on the surface topology!

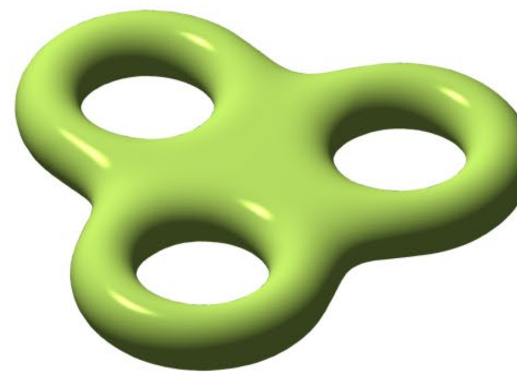
$$\int \frac{dA}{R_1 R_2} = 4\pi\,(1-g)$$

$g = 0$

$g = 1$

$g = 2$

$g = 3$



Creation of new vesicles or fusion of vesicles modifies the genus *g*!

Andrej Kosmrlj, Princeton, MAE545_S2018/lecture16_slides.pdf

Vesicle fusion with membrane

Bending energy:

$$E = \int dA \left[\frac{\kappa}{2} \left(\frac{1}{R_1} + \frac{1}{R_2} \right)^2 + \frac{\kappa_G}{R_1 R_2} \right]$$

$\kappa \sim 20 k_B T$

$\kappa_G \sim -0.8\kappa$

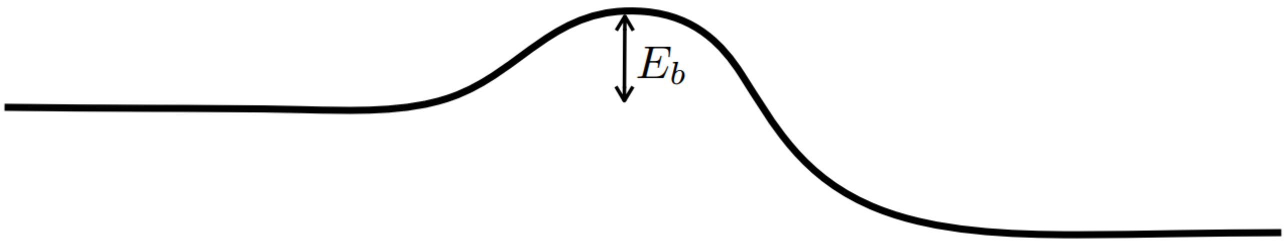
$E = 4\pi(2\kappa + \kappa_G)$

$E \sim +300 k_B T$

$E \approx 8\pi\kappa$

$E \sim +500 k_B T$

$E = 0$



Fusion of small vesicles with the membrane is energetically favorable, but the initial merging provides a large energy barrier!

Characteristic time to cross the barrier:

$$t \sim t_0 e^{E_b / k_B T}$$

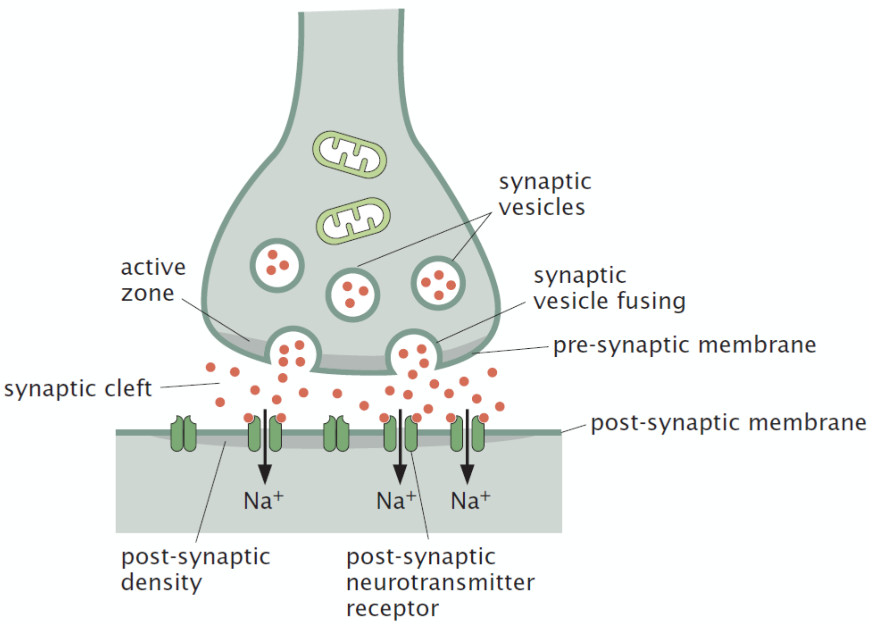
E_b **height of energy barrier**

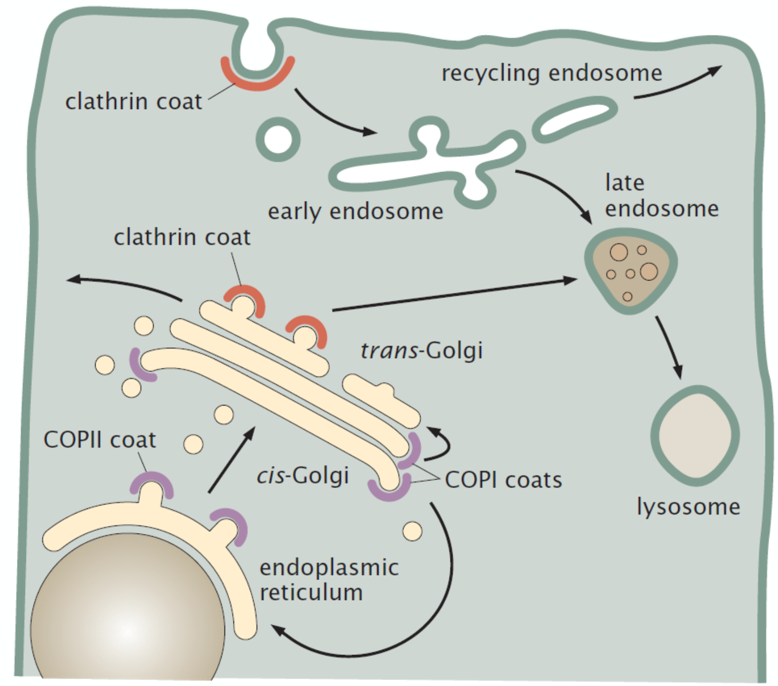
t_0 **time between successive attempts for crossing the barrier**

R. Phillips et al., Physical Biology of the Cell

Vesicle fusion and budding are common

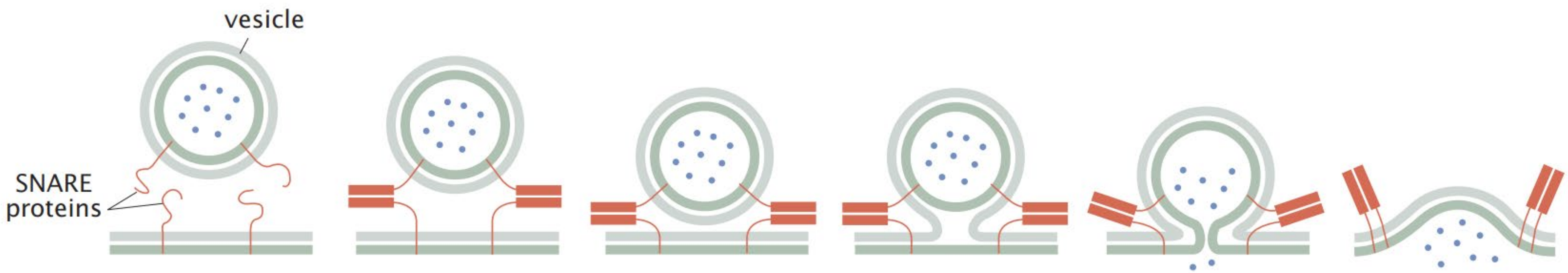
transport of neurotransmitters in neuron cells

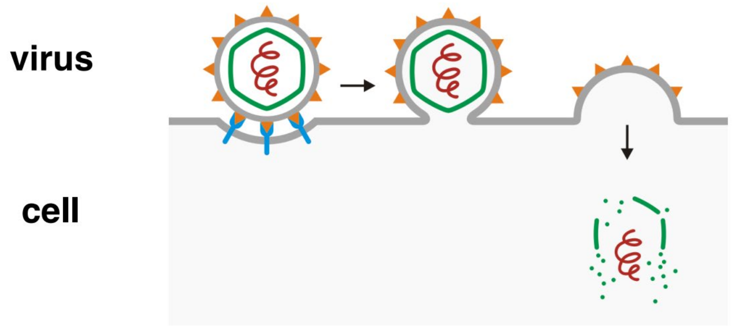




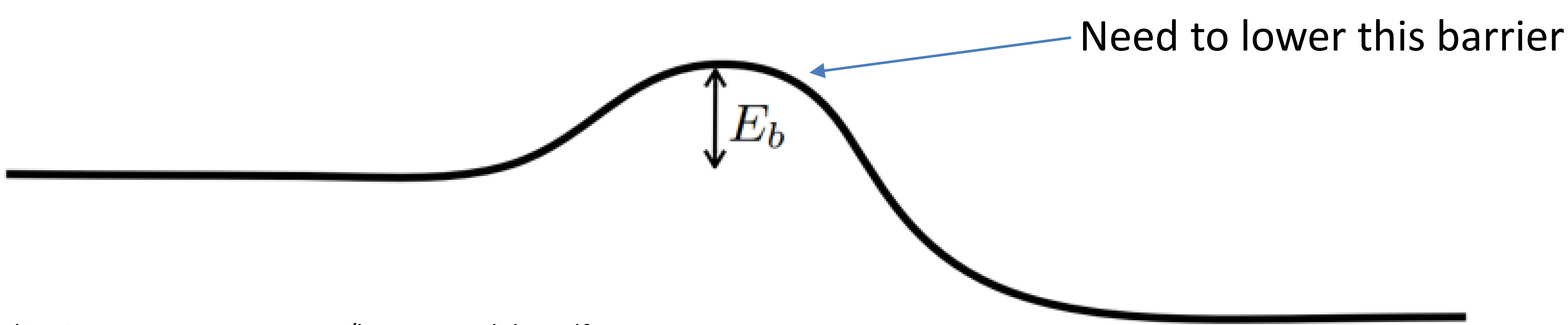
Andrej Kosmrlj, Princeton, MAE545_S2018/lecture16_slides.pdf

Need protein catalysts to facilitate vesicle fusion





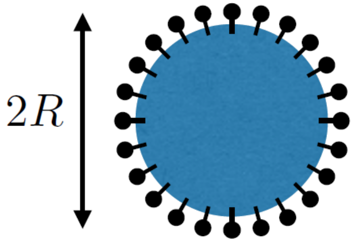
e.g. HIV, influenza, hepatitis B, herpes, sars-cov-2



Andrej Kosmrlj, Princeton, MAE545_S2018/lecture16_slides.pdf

Viral entry to cell via receptor mediated endocytosis

H. Gao *et al.*, PNAS 102, 9469 (2005)

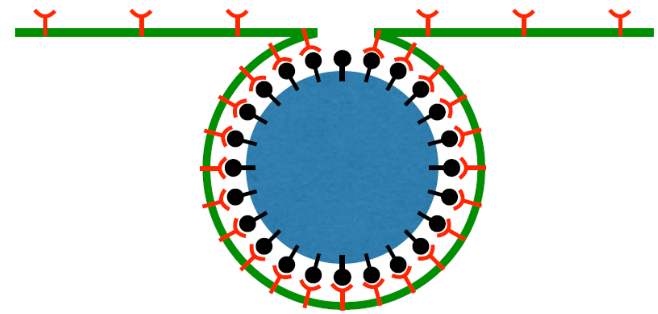


$n_L \sim 5000 \mu\mathrm{m}^{-2}$

density of ligands

$n_0 \sim 50\text{-}500 \mu\mathrm{m}^{-2}$

density of receptors



receptor-ligand binding energy

$U_b \sim 15 k_B T$

bending rigidity

$\kappa \sim 20 k_B T$

total number of ligands

$N_L = 4\pi R^2 n_L$

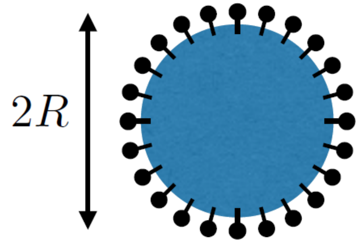
$$\Delta E \approx 8\pi\kappa - 4\pi R^2 n_L U_B + 4\pi R^2 k_B T n_L \ln(n_L/n_0)$$

membrane bending energy | **binding energy of receptors** | **loss of entropy for receptors**

Endocytosis occurs when $\Delta E < 0$: →

$$R > \sqrt{\frac{2\kappa}{n_L \left(U_B - k_B T \ln(n_L/n_0)\right)}} \sim 30\mathrm{nm}$$

Viral entry to cell via receptor mediated endocytosis



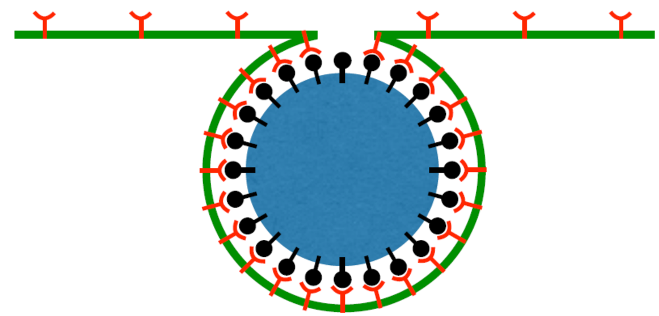
$n_L \sim 5000\mu\text{m}^{-2}$

density of ligands

H. Gao *et al.*, PNAS 102, 9469 (2005)

$n_0 \sim 50\text{-}500\mu\text{m}^{-2}$

density of receptors



receptor-ligand binding energy

$U_b \sim 15k_BT$

bending rigidity

$\kappa \sim 20k_BT$

total number of ligands

$N_L = 4\pi R^2 n_L$

diffusion of receptors

$D \sim 10^4\text{nm}^2/\text{s}$

$$R > \sqrt{\frac{2\kappa}{n_L\left(U_B - k_BT\ln(n_L/n_0)\right)}} \sim 30\text{nm}$$

Need to recruit N_L receptors from circular region of radius L via diffusion

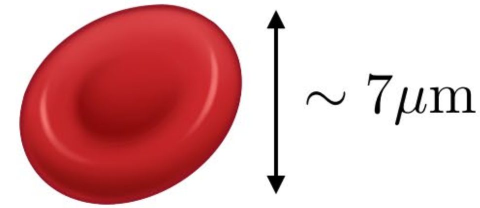
$$N_L = \pi L^2 n_0 = 4\pi R^2 n_L$$

$$t \sim \frac{L^2}{D} \sim \frac{R^2 n_L}{D n_0} \gtrsim 10\text{s}$$

Andrej Kosmrlj, Princeton, MAE545_S2018/lecture16_slides.pdf

Shape of red blood cells

In the usual environment red blood cells have discocyte shape. Modifying cell environment can induce different shapes.



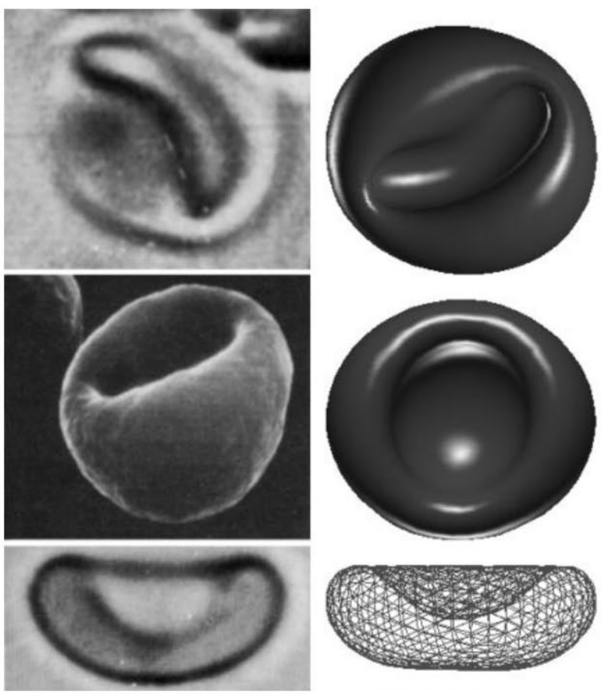
cationic amphipaths, low salt, low pH, cholesterol depletion

stomatocytes

experiments **simulations**

Volume fill fraction

$v = 0.950$



Area difference between inner and outer leaflet

$\Delta a_0 = -0.858$

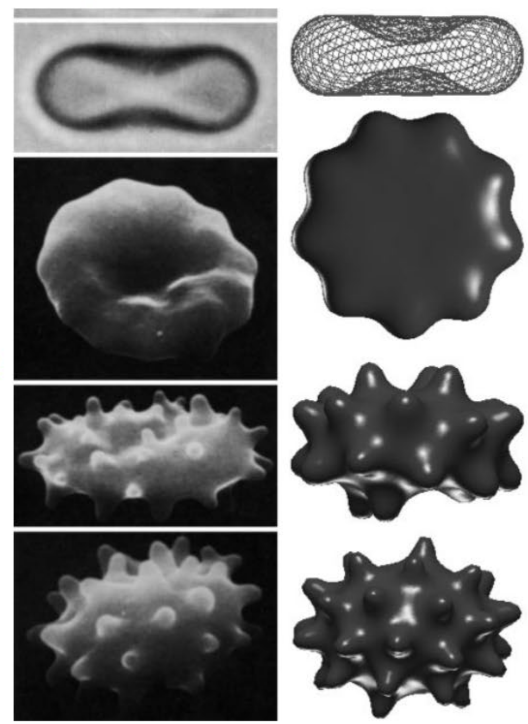
$\Delta a_0 = -0.358$

$\Delta a_0 = 0.072$

anionic amphipaths, high salt, high pH, cholesterol enrichment

echinocytes

experiments **simulations** $v = 0.950$



$\Delta a_0 = 0.143$

$\Delta a_0 = 1.717$

$\Delta a_0 = 1.788$

$\Delta a_0 = 2.003$

G. Lim *et al.*, PNAS 99, 16766 (2002)

Andrej Kosmrlj, Princeton, MAE545_S2018/lecture15_slides.pdf

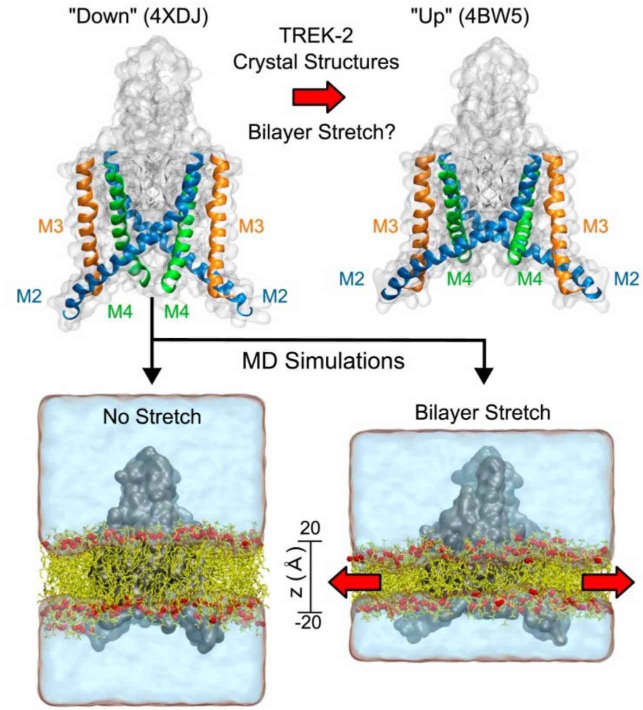
Stretching

- Membrane tension

$1\ k_BT = 4\ (nm^2 \cdot mN/m)$

Membrane tension: σ ~ 0.02 mN/m
(water: σ = 72 mN/m)

$$U_{tension} = \sigma \int da$$
$= \sigma A$



Aryal,... Tucker, Structure, 2017

- Stretching modulus

$$U_{stretch} = \frac{K_a}{2} \int \left(\frac{\Delta a}{a_0}\right)^2 da$$

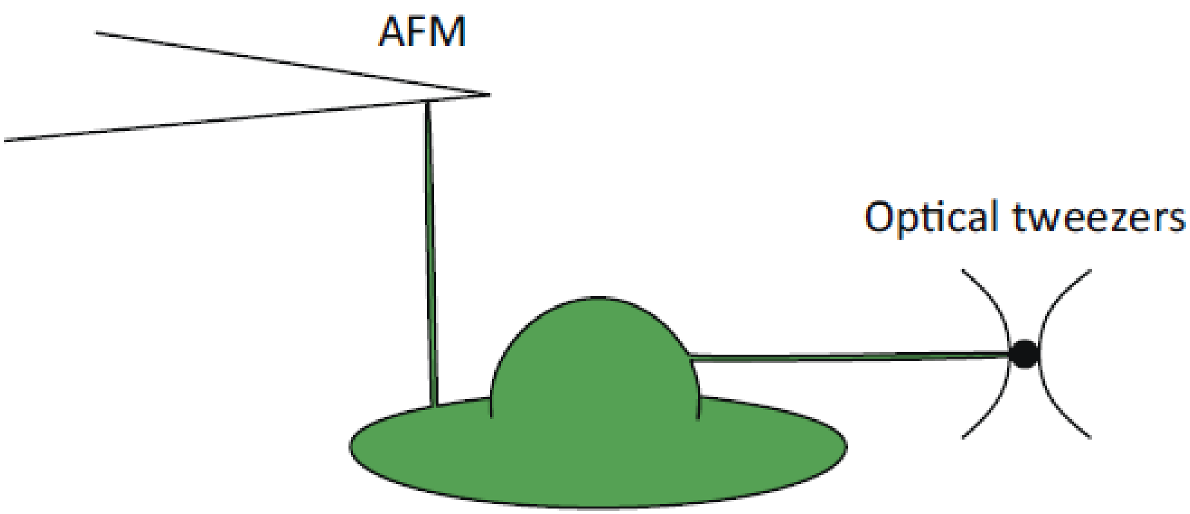
K_a ~ 55 – 70 k_BT/nm^2 , 230 – 290 mN/m

Increase in cross-sectional area: **4~5 *nm^2***

Membrane tension to activate the channels: **1~10 *mN/m***

Membrane tension < 1 mN/m is not going to make a difference to mechanosensitive channels.

Tube extrusion



Munoz, Fletcher, and Weiner, Trends in Cell Biology, 2013

Membrane tension: σ ~ 0.02 mN/m
(water: σ = 72 mN/m)

Bending modulus: k_c ~ 0.2 pN μm
(compare to $k_B T$!)

Mechanical energy of a tube

$$U = \left(\frac{1}{2} k_c \frac{1}{r^2} + \sigma\right) 2\,\pi r\, L \; - fL$$

$$\frac{\partial U}{\partial r} = 0 \qquad \frac{\partial U}{\partial L} = 0$$

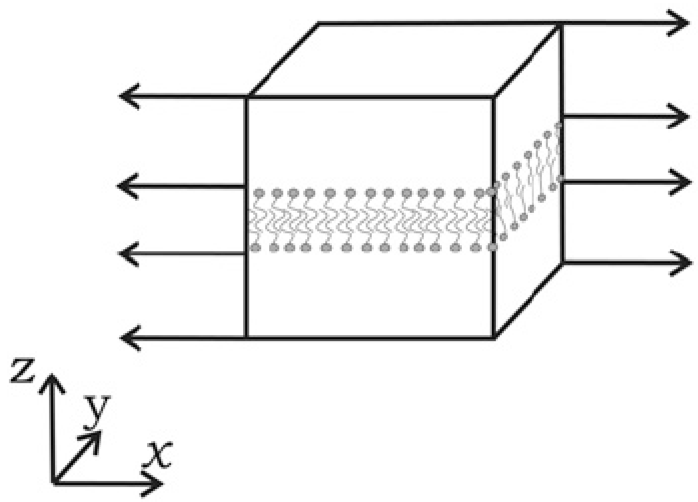
$$r = \sqrt{\frac{k_c}{2\sigma}} \qquad F = 2\,\pi\sqrt{2 k_c \sigma}$$

Shear flow

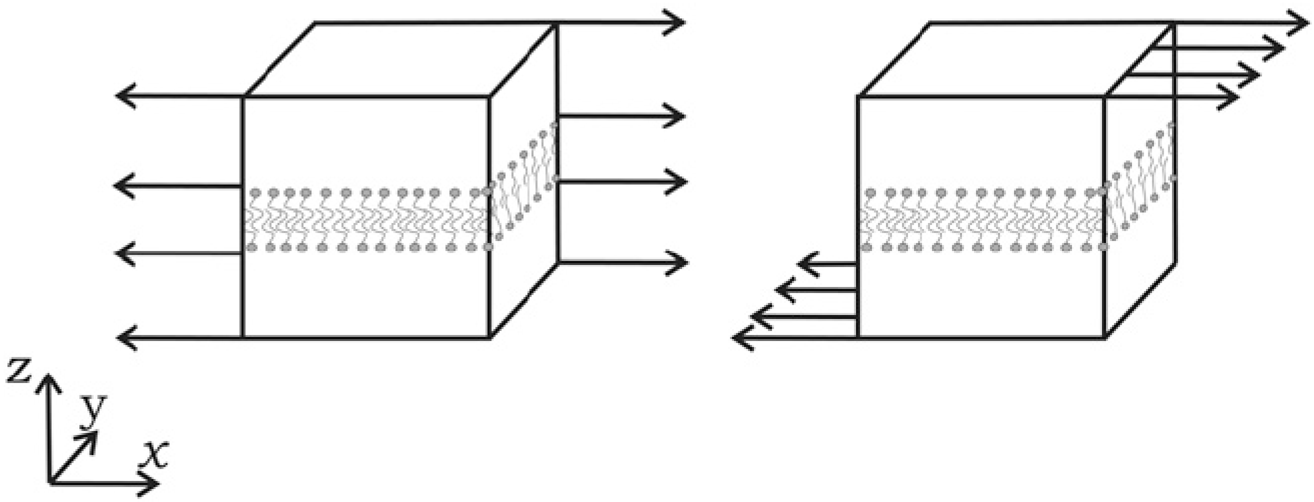
Stokes-Brinkman equation governs the flow field ($\vec{v}$) of lipids:

$$\nabla\sigma = \eta\nabla^2\vec{v} + \frac{\eta}{k}\vec{v}$$ → *Drag by fixed proteins*

σ: membrane tension;
η: in-plane membrane viscosity (μ h);
k: Darcy permeability coefficient ([k] = m^2). Measure of spacing between obstacles



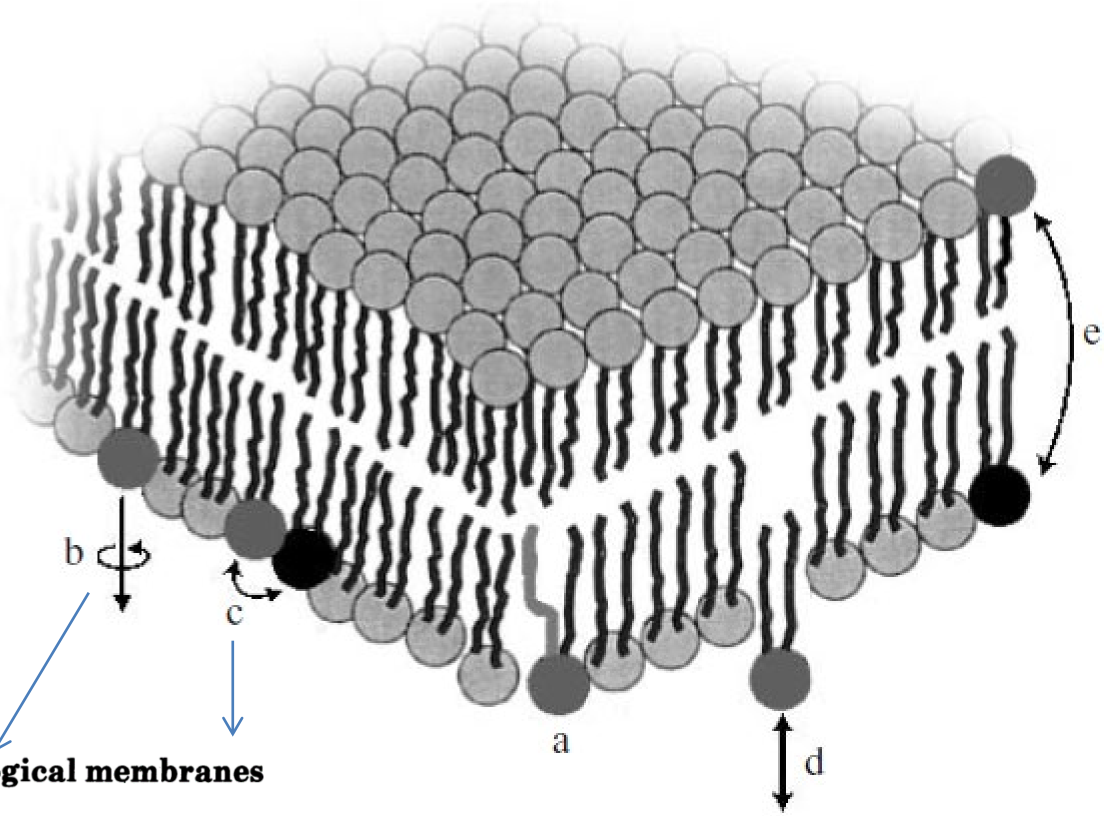
Inter-leaflet shear



Important in membrane tether extrusion

Diffusion

4 types of motions:



Hours – days spontaneously

Flippases accelerate

Proc. Nat. Acad. Sci. USA
Vol. 72, No. 8, pp. 3111–3113, August 1975
Biophysics

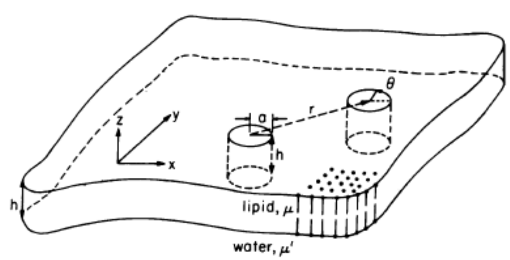
Brownian motion in biological membranes

(diffusion)

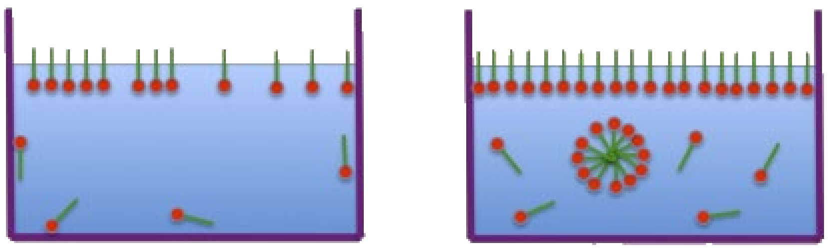
P. G. SAFFMAN AND M. DELBRÜCK

$$b_T^{(ii)} = \frac{1}{4\pi\mu h}\left(\log \frac{\mu h}{\mu' a} - \gamma\right)$$

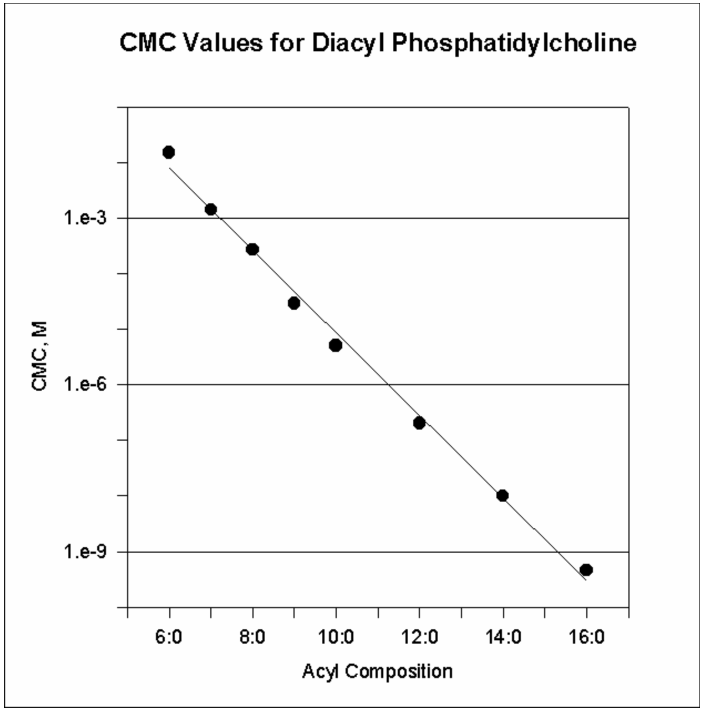
μ – in-plane viscosity
h – thickness
a – radius
γ – Euler's constant 0.5772…



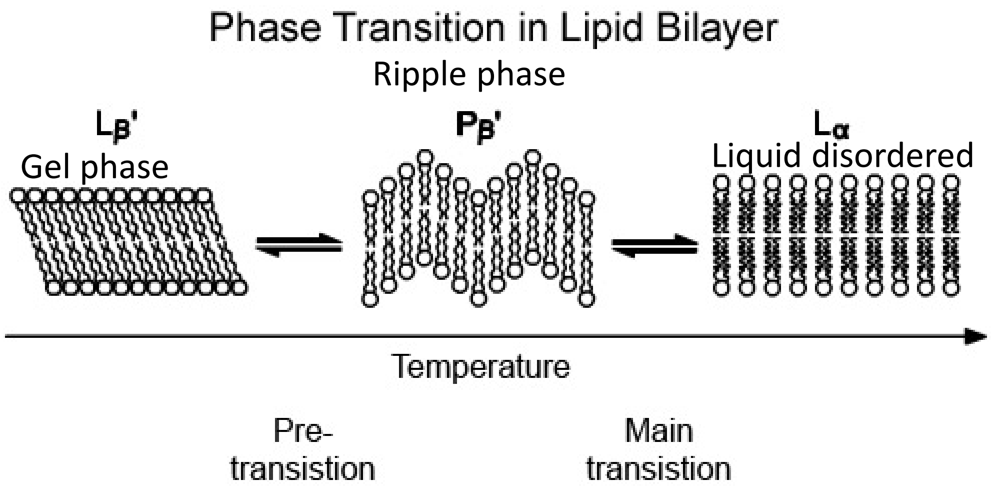
Lipid solubility

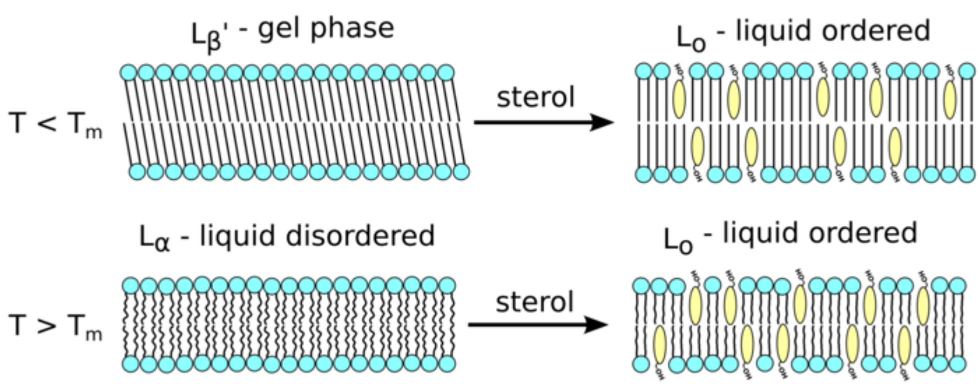


CMC = critical micellar concentration

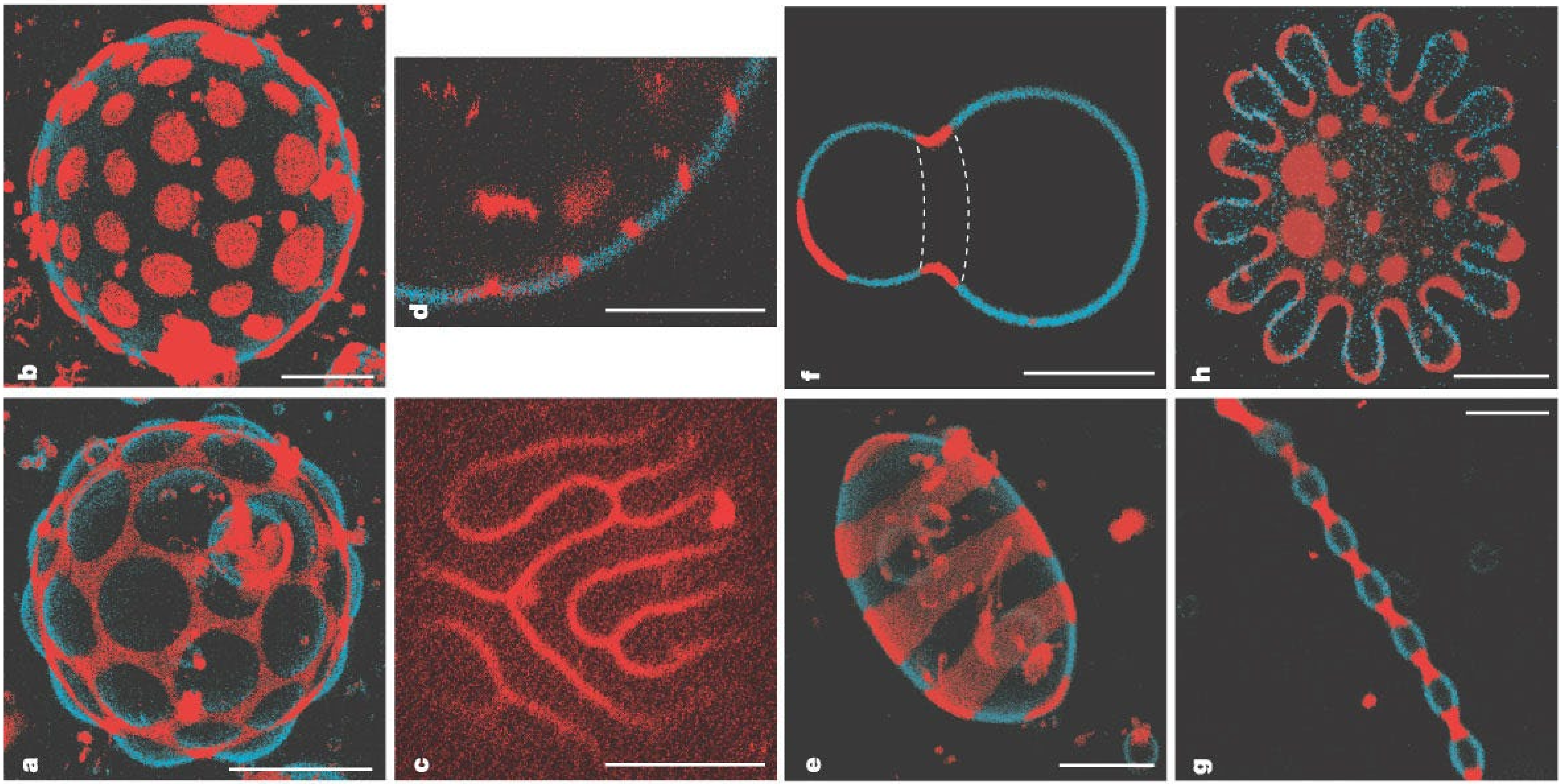


Phase transitions





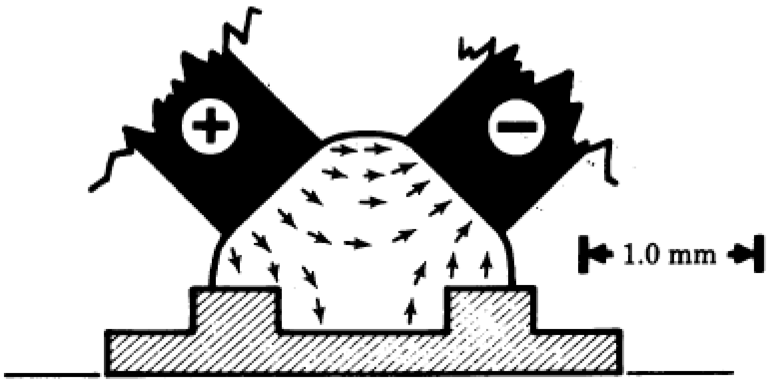
Binary phase transitions

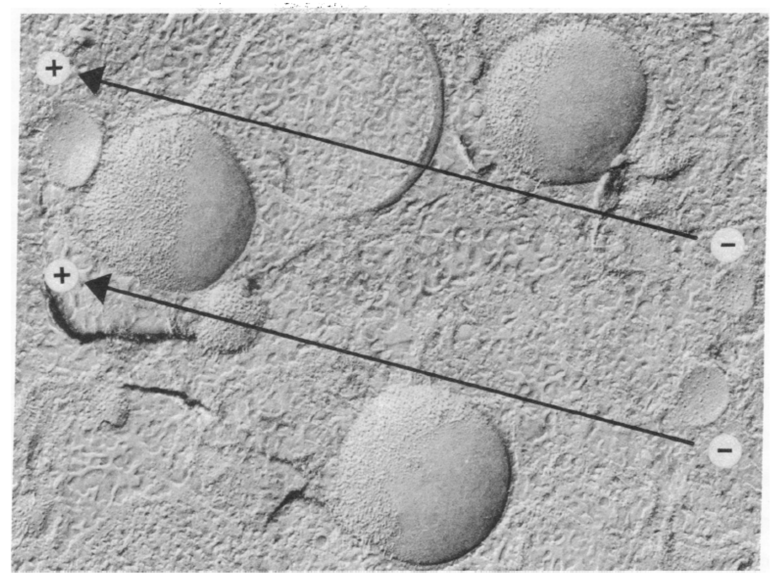


[Imaging coexisting fluid domains in biomembrane models coupling curvature and line tension]
Tobias Baumgart, Samuel T. Hess and Watt W. Webb
Nature 425, 821-824(23 October 2003)
doi:10.1038/nature02013

sphingomyelin,
dioleoylphosphatidylcholine (DOPC)
cholesterol

Proteins in membranes





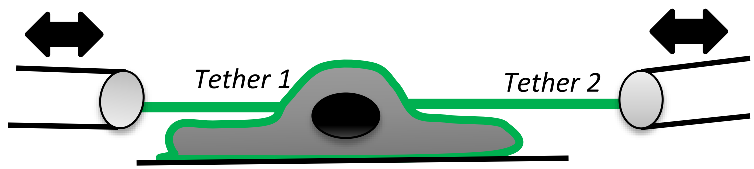
Proc. Natl. Acad. Sci. USA
Vol. 78, No. 10, pp. 6246–6250, October 1981
Cell Biology

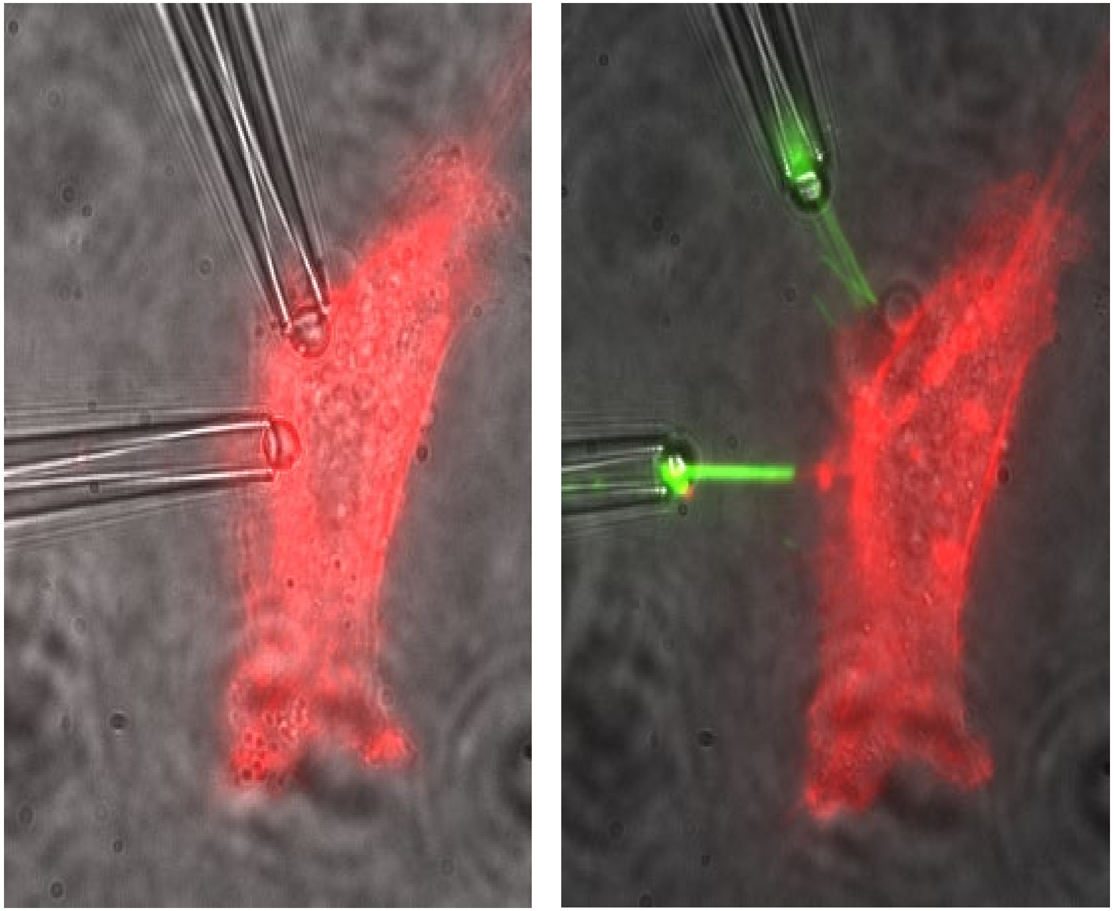
Rate of lateral diffusion of intramembrane particles: Measurement by electrophoretic displacement and rerandomization

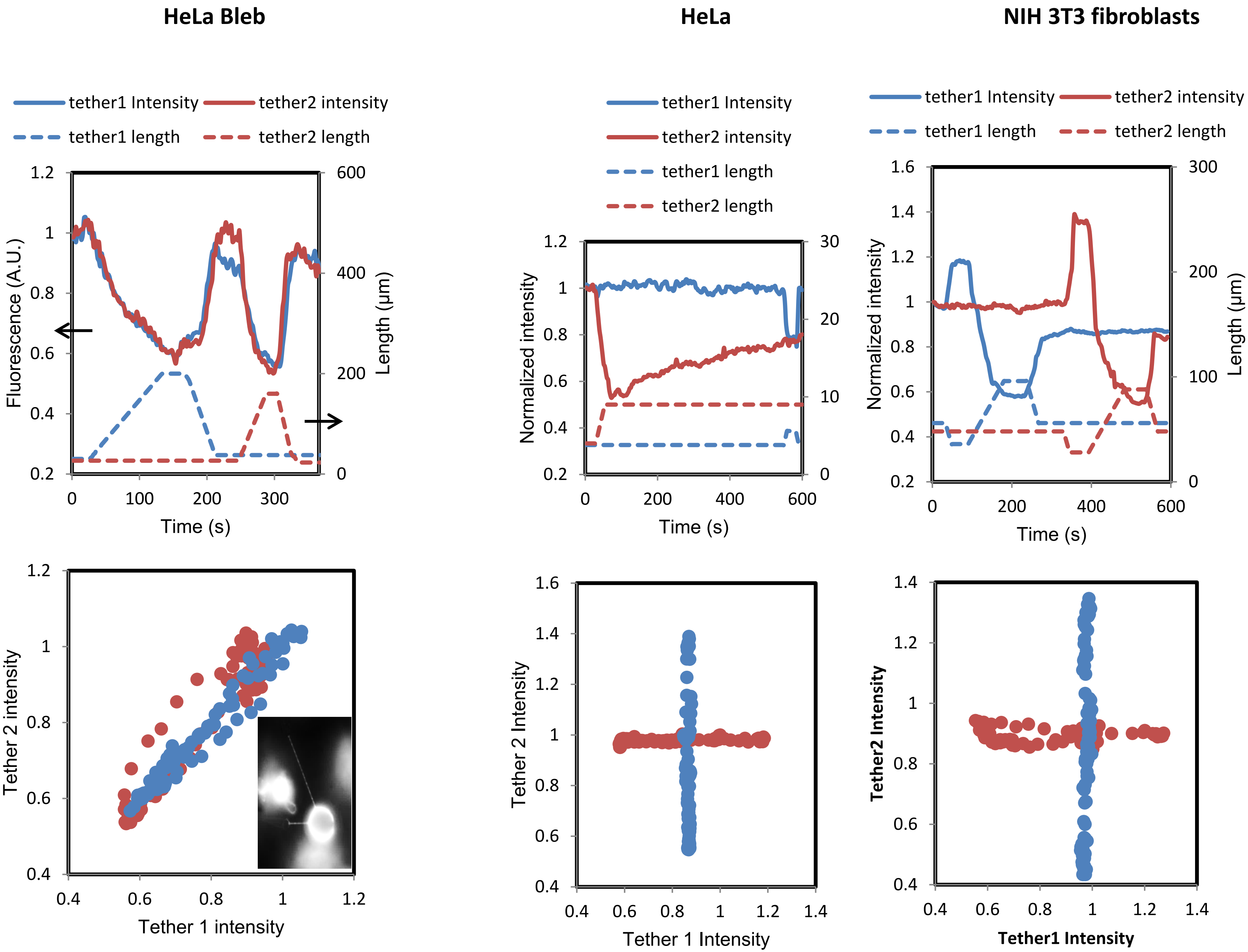
(lateral diffusion coefficient/integral proteins/freeze-fracture electron microscopy)

ARTHUR E. SOWERS AND CHARLES R. HACKENBROCK

Double tether experiment to measure propagation of tension within cells







HeLa Bleb
HeLa
NIH 3T3 fibroblasts
tether1 Intensity
tether2 intensity
tether1 length
tether2 length
Fluorescence (A.U.)
Length (µm)
Time (s)
Normalized intensity
Tether 2 intensity
Tether 1 intensity
Tether 2 Intensity
Tether 1 Intensity
Tether2 Intensity
Tether1 Intensity