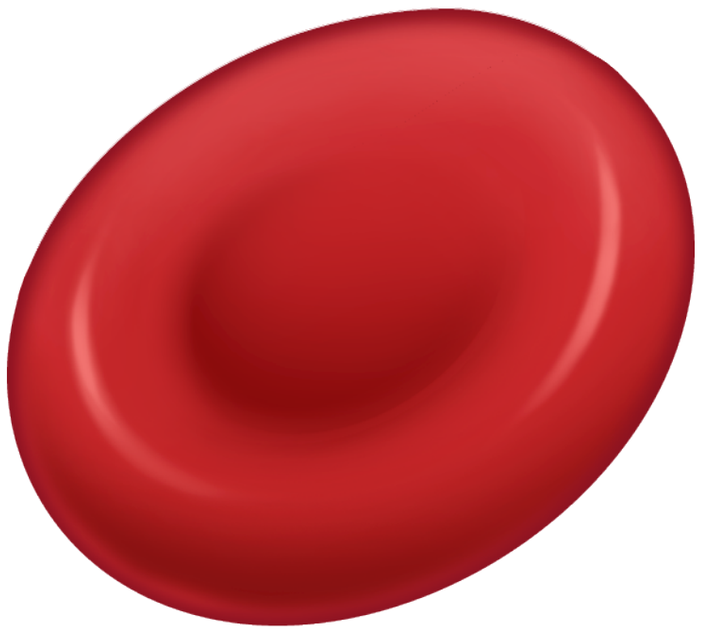
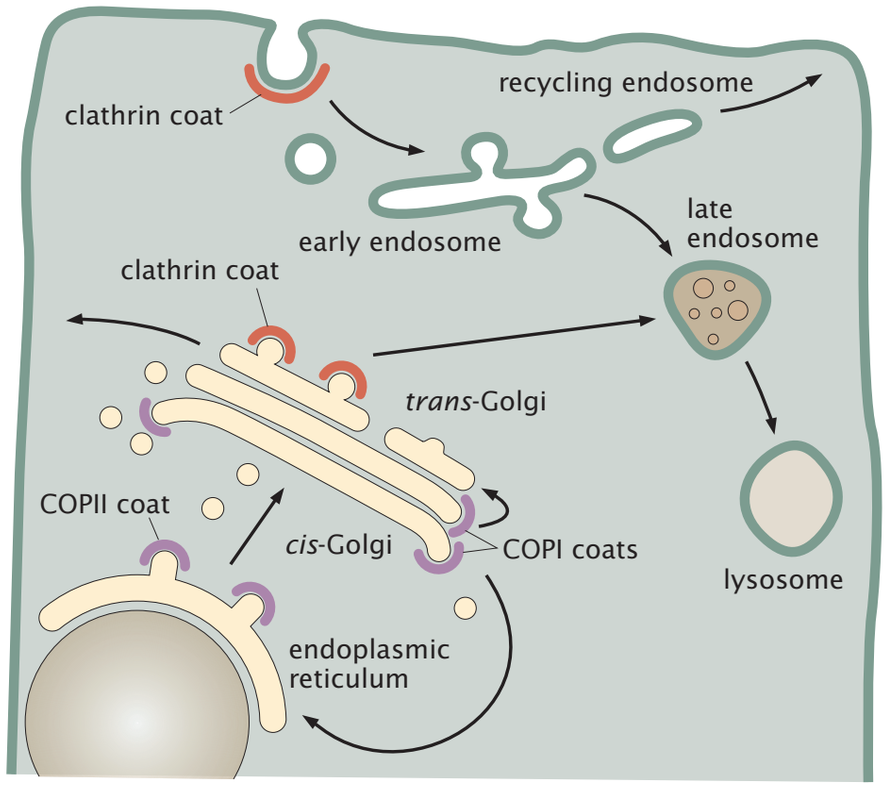
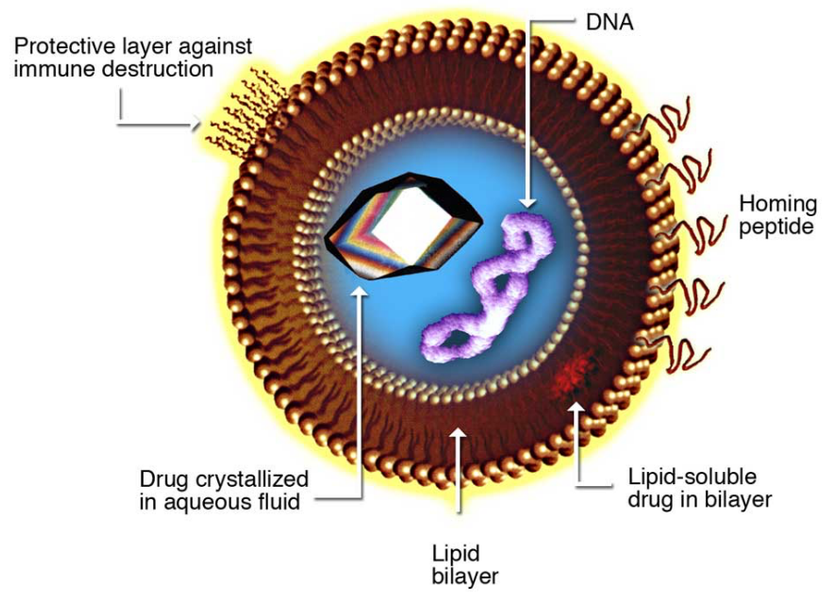
MAE 545: Lecture 15,16 (4/13, 4/18)

Shapes of cells, cellular transport via vesicles and drug delivery

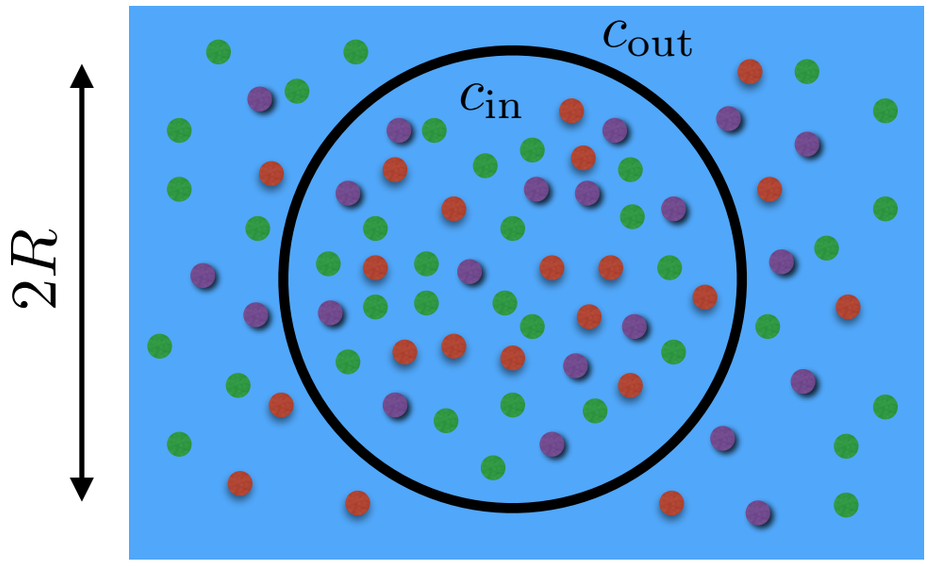






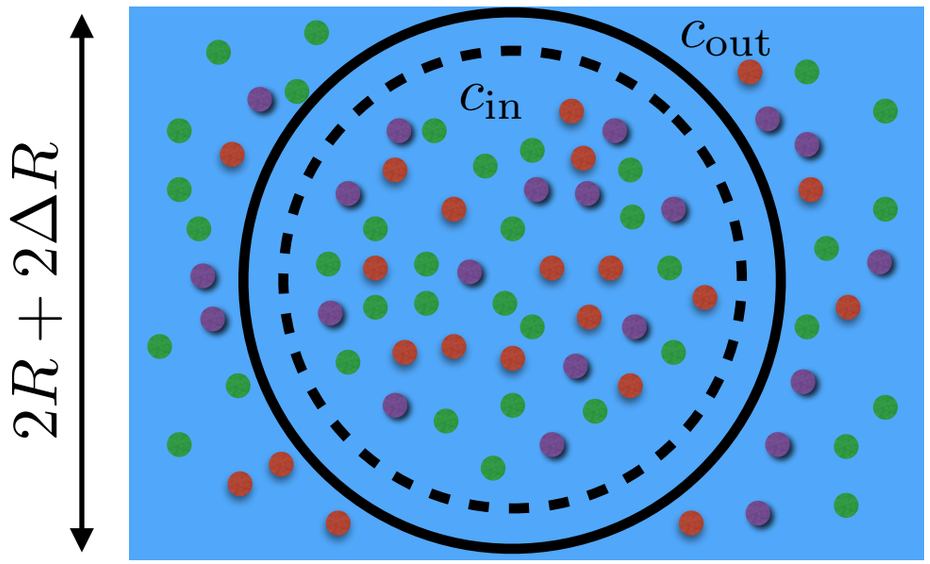
Cells in hypotonic and hypertonic solutions

$c_{\text{in}} > c_{\text{out}}$ **hypotonic solution**



Water flows in the cell until the mechanical equilibrium is reached.

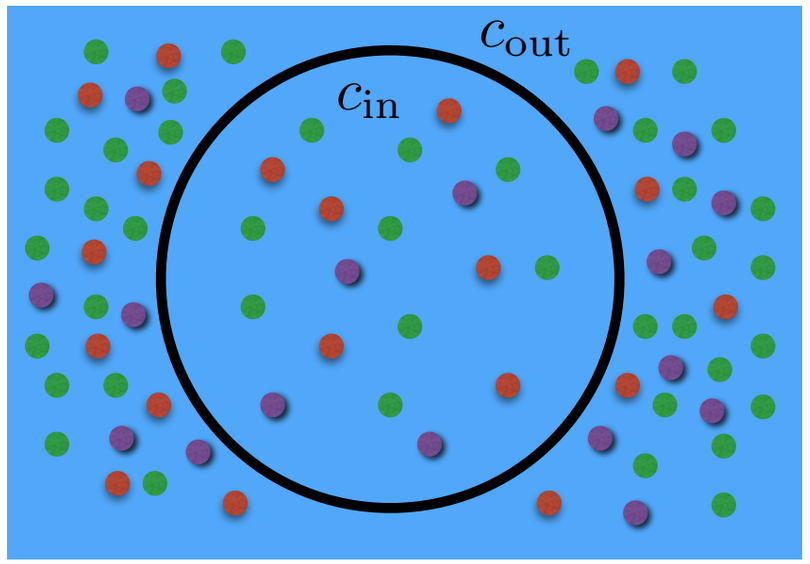
$c_{\text{in}} > c_{\text{out}}$



$$\frac{\Delta R}{R} = \frac{R\Delta p}{4B} = \frac{R}{4B} k_B T \left(c_{\text{in}} - c_{\text{out}}\right)$$

2

$c_{\text{in}} < c_{\text{out}}$ **hypertonic solution**

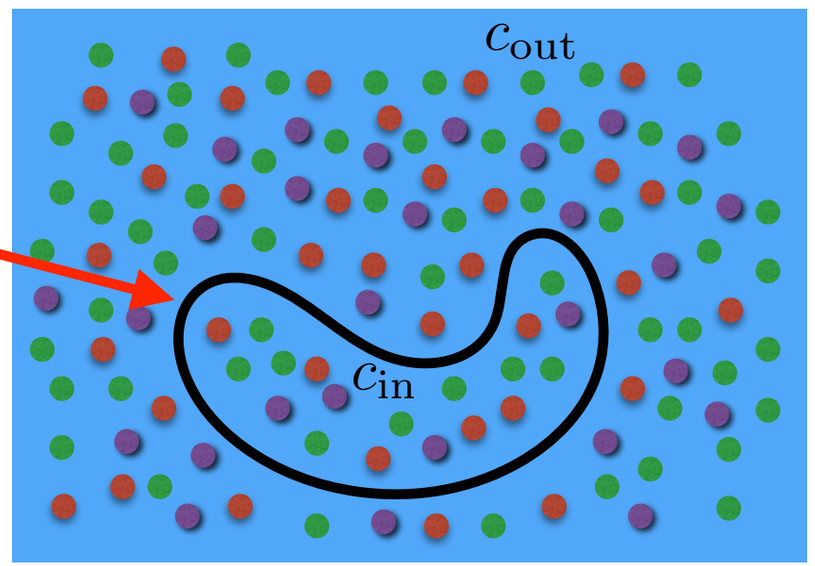


Water flows out of the cell until concentrations become equal.

$c_{\text{in}} = c_{\text{out}}$

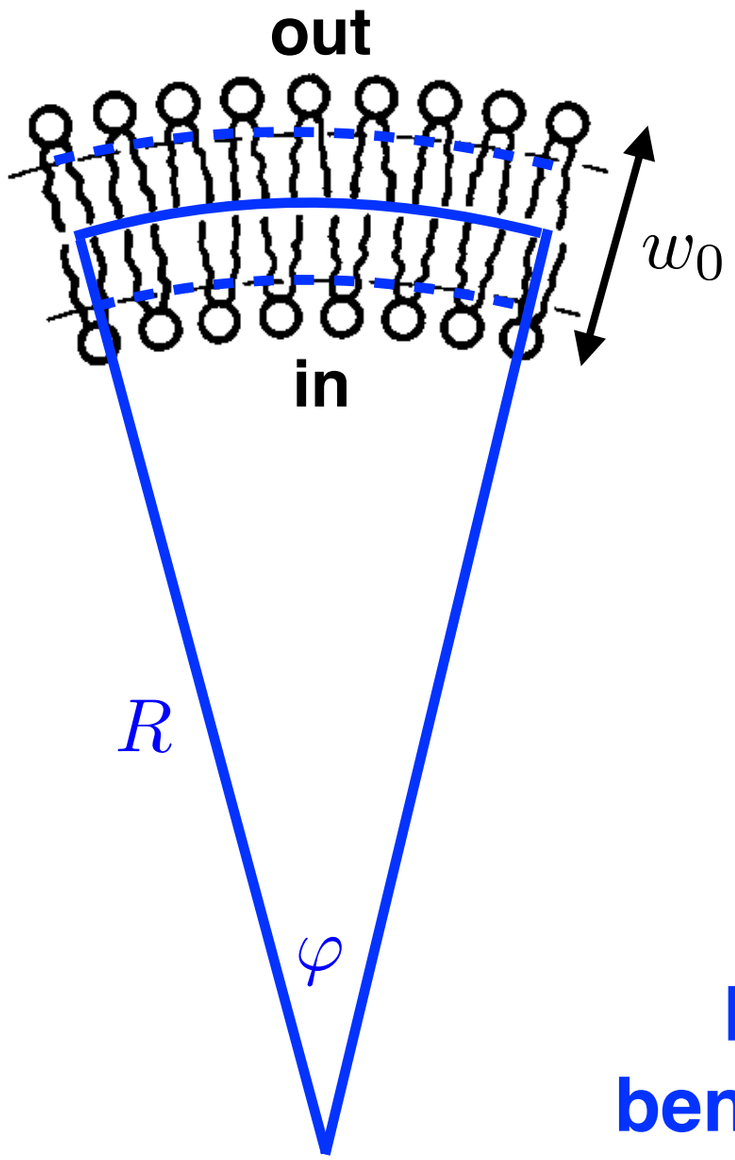
Thin cell membrane prefers to bend rather than compress

How can we estimate the shape of "deflated" cells?



$$V_0 = \frac{N}{c_{\text{out}}}$$

Area difference between lipid layers



Length difference for 2D example on the left

$$\Delta\ell = \ell_{\text{out}} - \ell_{\text{in}} = (R + w_0/2)\varphi - (R - w_0/2)\varphi$$

$$\Delta\ell = w_0\varphi = \frac{w_0\ell}{R}$$

Area difference between lipid layers in 3D

$$\Delta A = A_{\text{out}} - A_{\text{in}} = w_0 \int dA \left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

Lipids can move within a given layer, but flipping between layers is unlikely. This sets a preferred area difference ΔA_0 .

Non-local bending energy

$$E = \frac{k_r}{2Aw_0^2}\left(\Delta A - \Delta A_0\right)^2$$

$$k_r \approx 3\kappa \approx 60 k_B T$$

Total elastic energy for cells (vesicles)

Shape of cells (vesicles) can be obtained by minimizing the total elastic energy

this term is constant for a given topology

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

$$+\frac{k_r}{2A_0 w_0^2}\left(\Delta A - \Delta A_0\right)^2 + \frac{1}{2}k_B T c_{\text{out}} V_0 \left(\frac{V-V_0}{V_0}\right)^2$$

Energetically it is very costly to change the cell volume V_0 and the membrane area A_0 (large bulk modulus B)!

Introduce dimensionless quantities that would be equal to 1 for sphere

definition for sphere radius	dimensionless area	dimensionless volume	dimensionless curvature	dimensionless area difference between layers	dimensionless energy
$R_0 = \sqrt{\frac{A_0}{4\pi}}$	$a = \frac{A_0}{4\pi R_0^2} = 1$	$v = \frac{V_0}{4\pi R_0^3/3}$	$c_0 = C_0 R_0$	$\Delta a = \frac{\Delta A}{8\pi w_0 R_0}$	$e = \frac{E}{8\pi\kappa}$

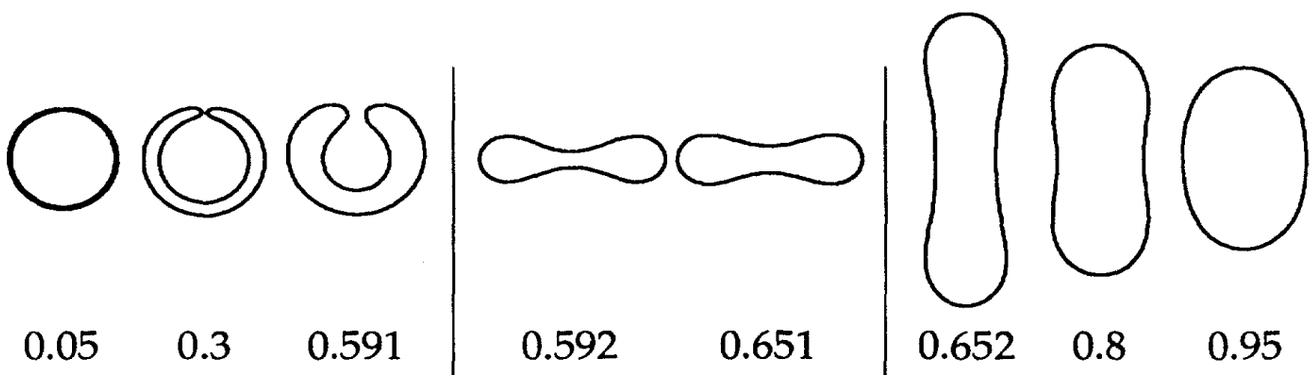
Minimal model: minimization of bending energy for lipid vesicles

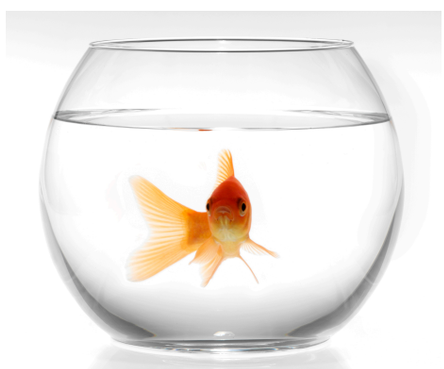
Find the shape of vesicles that minimize bending energy by constraining the volume to *v*<1.

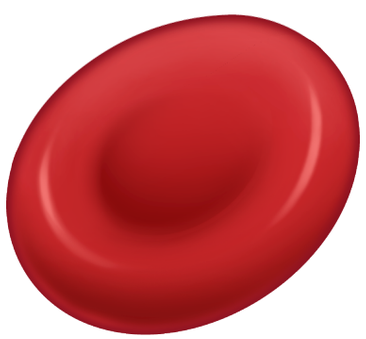
$$e = \int \frac{da}{4} \left(\frac{1}{r_1} + \frac{1}{r_2} \right)^2$$

Minimum energy configurations

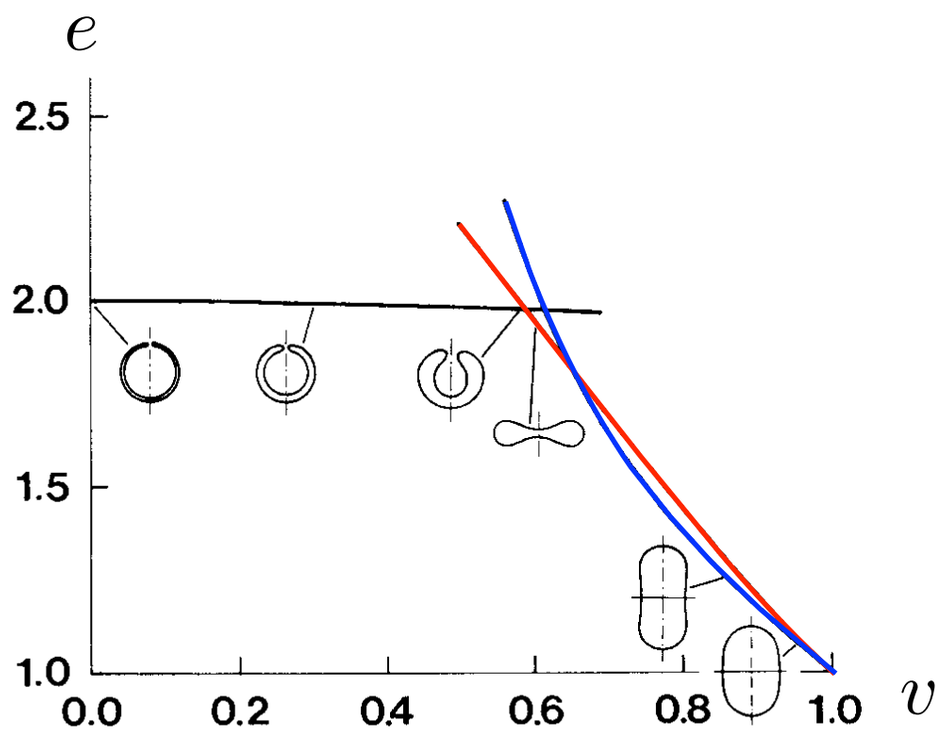
stomatocytes **oblates** **prolates**







U. Seifert *et al.*, PRA 44, 1182 (1991)

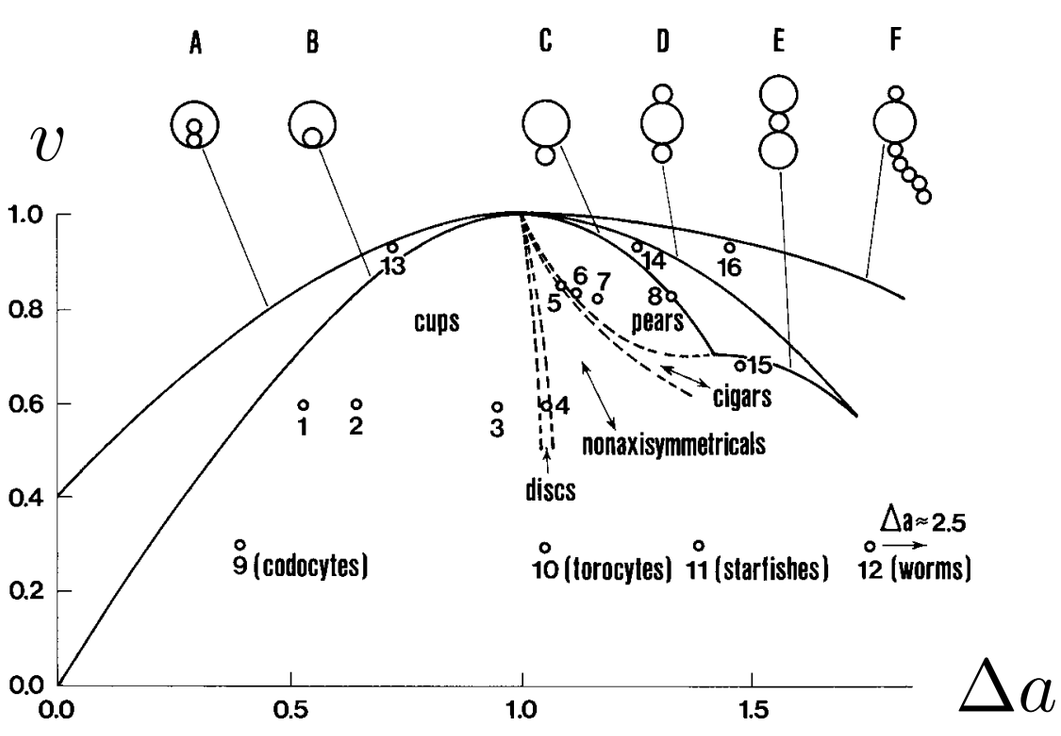


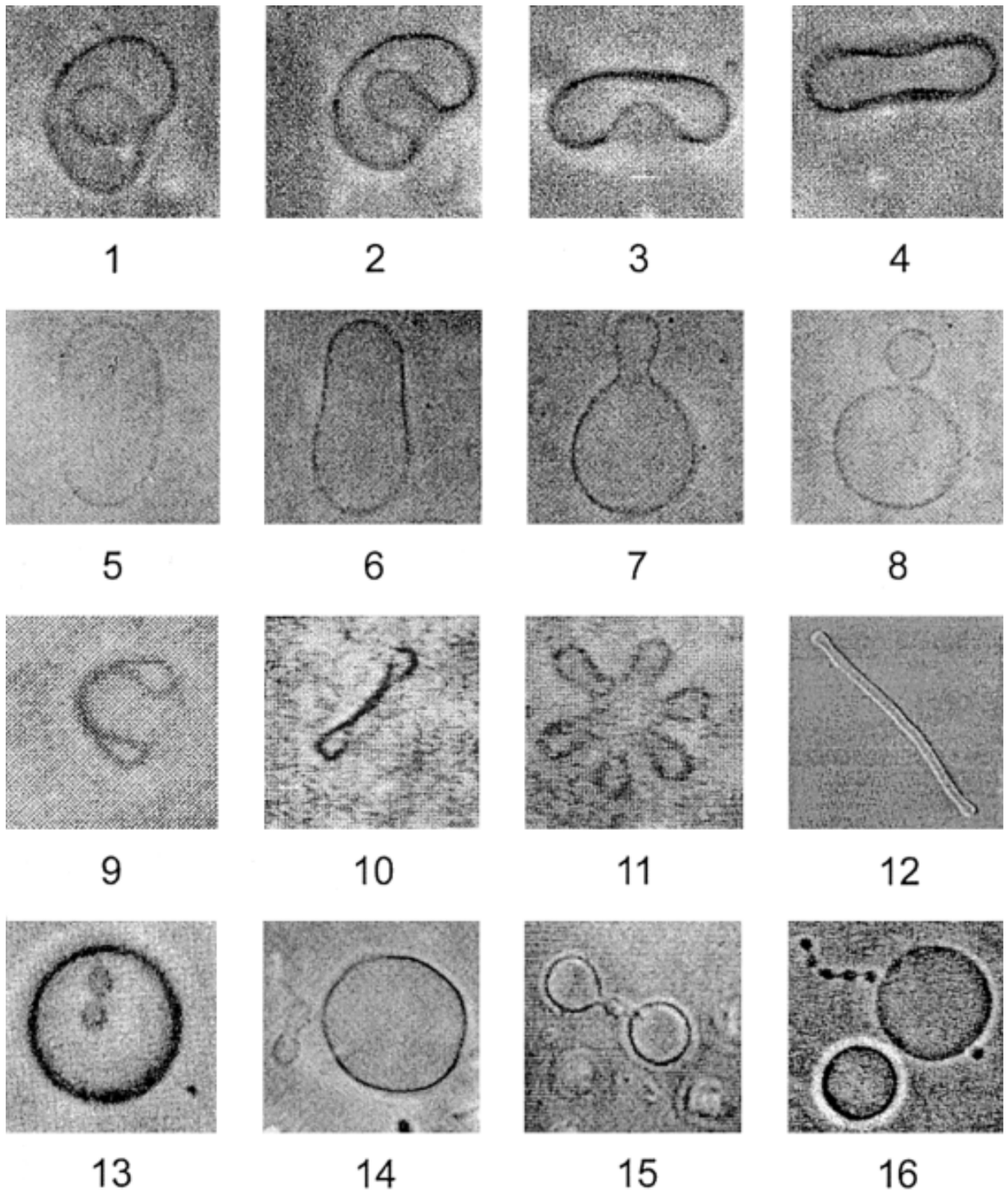
S. Svetina and B. Zeks,
Anat. Rec. 268, 215 (2002)

Bilayer couple model of vesicles

$$e = \int \frac{da}{4} \left(\frac{1}{r_1} + \frac{1}{r_2} - c_0 \right)^2 + \frac{k_r}{\kappa} \left(\Delta a - \Delta a_0 \right)^2$$

Phase diagram of vesicle shapes that minimize the free energy for $c_0 = 0,\ k_r/\kappa \to \infty$ **.**

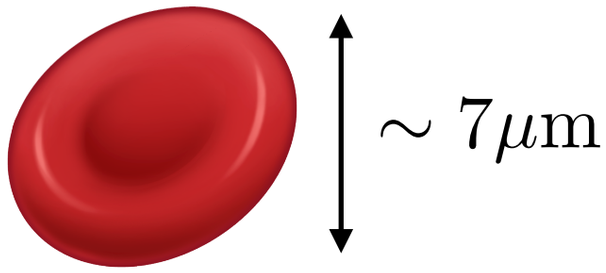




S. Svetina and B. Zeks,
Anat. Rec. 268, 215 (2002)

Shape of red blood cells

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

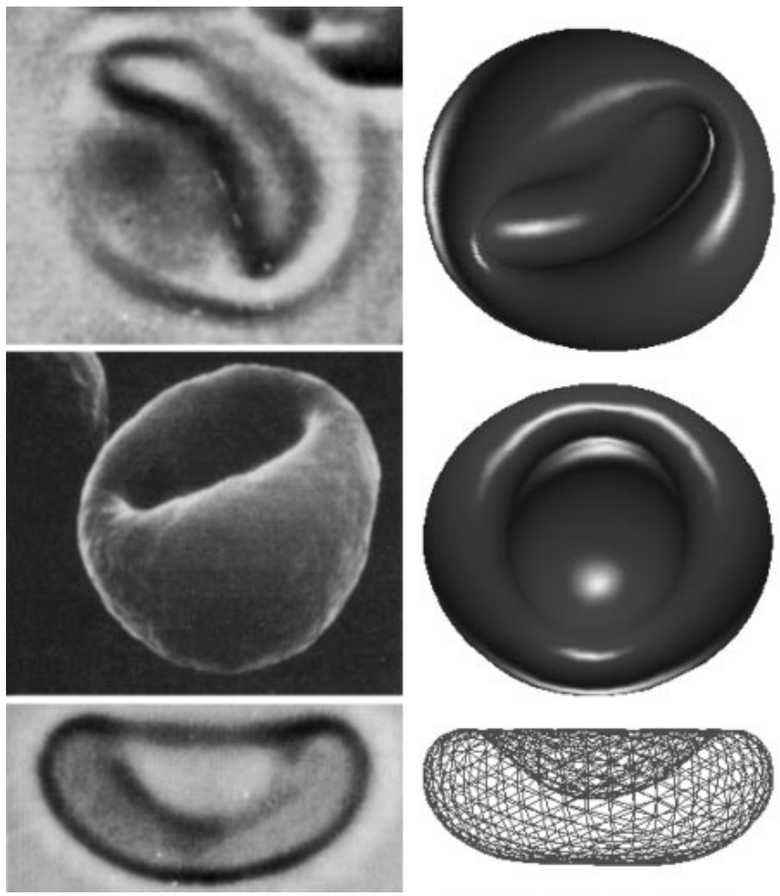


cationic amphipaths, low salt, low pH, cholesterol depletion

anionic amphipaths, high salt, high pH, cholesterol enrichment

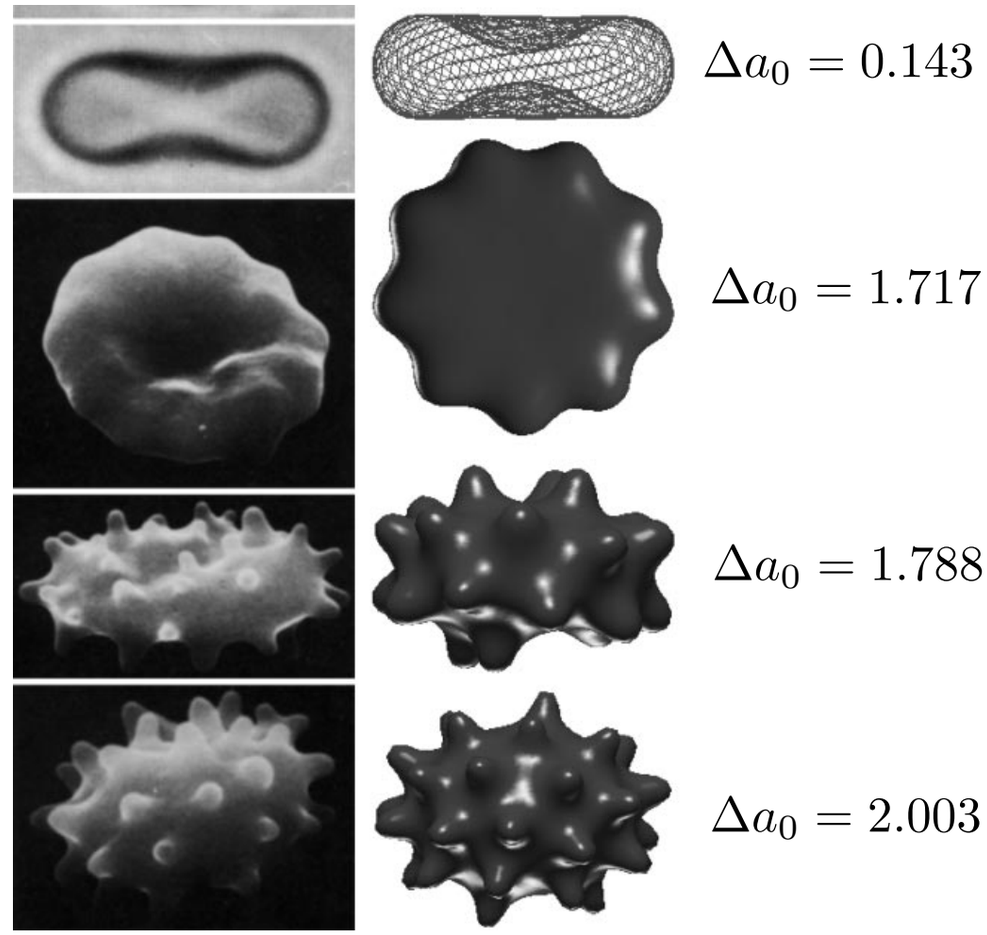
experiments **simulations** $v = 0.950$

stomatocytes



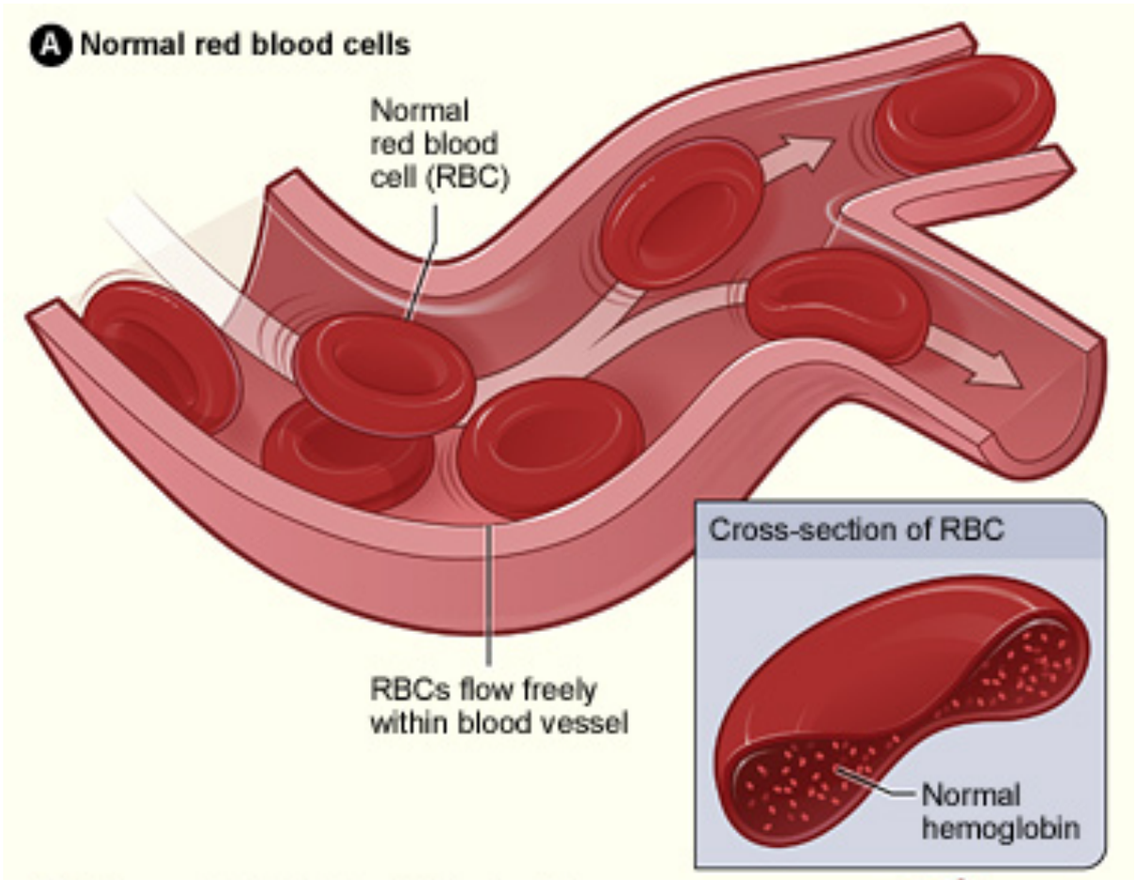
experiments **simulations** $v = 0.950$

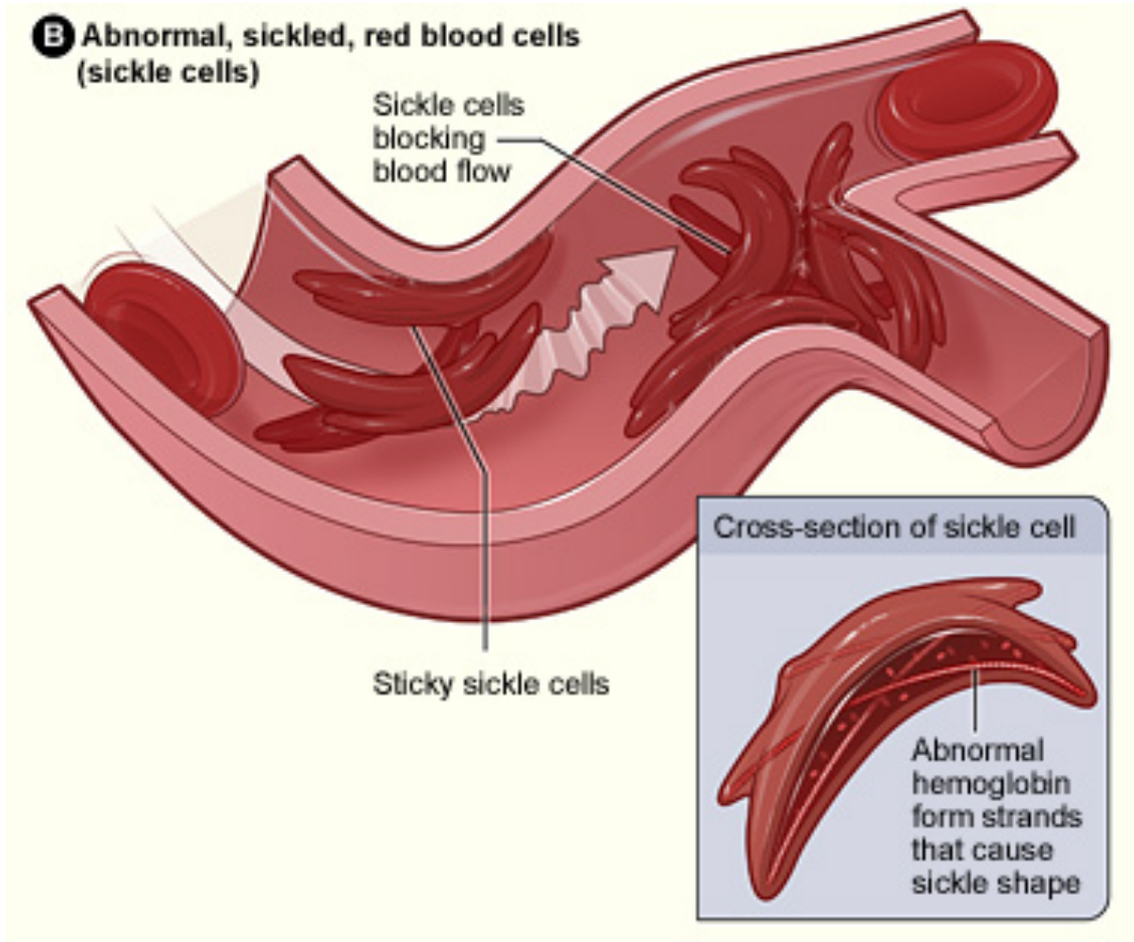
echinocytes



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

Sickle-cell disease (anaemia)





In low oxygen environment hemoglobin proteins inside sickle cells polymerize and form long strands.

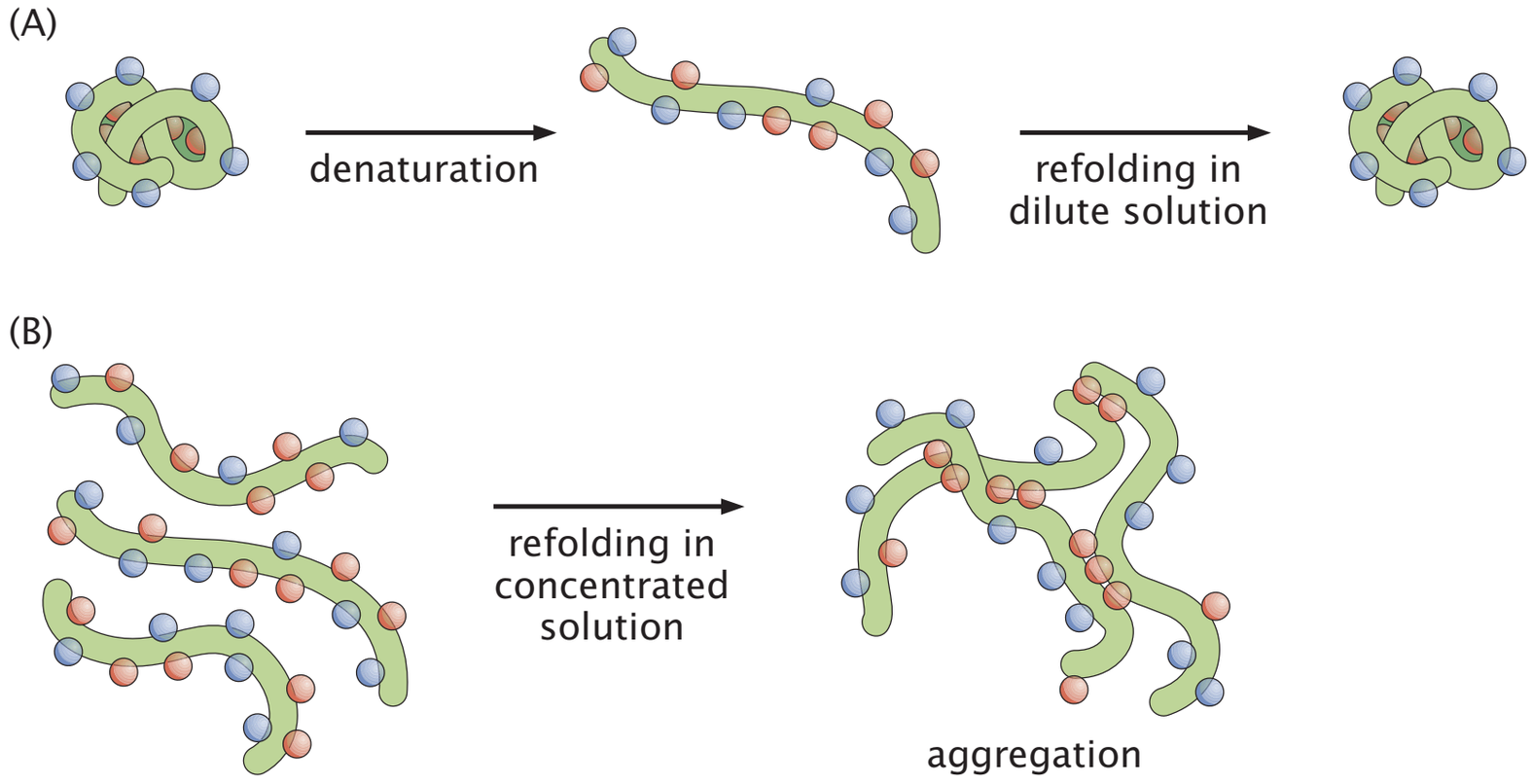
Sickle cells are much stiffer and cannot deform in order to pass through small capillaries.

Wikipedia

Protein aggregation and diseases

(A) In dilute solution misfolded proteins refold back into their native state.

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



hydrophilic amino acids

hydrophobic amino acids

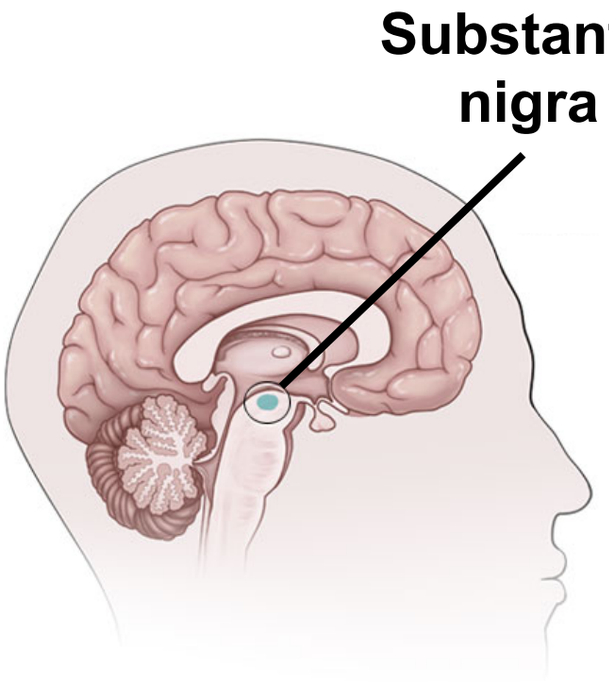
(B) In concentrated solution misfolded proteins tend to form aggregates.

Cells have special proteins called chaperons, which assist proteins folding into their native state and thus prevent aggregation.

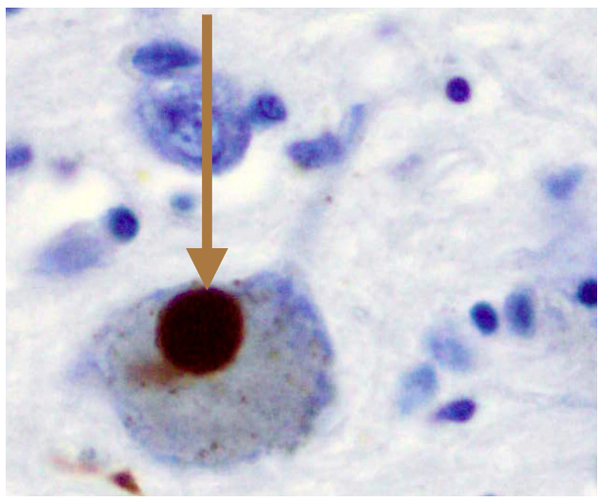
Protein aggregation is a cause of many diseases (Alzheimer's, Parkinson's, …)

Protein aggregates are associated with diseases

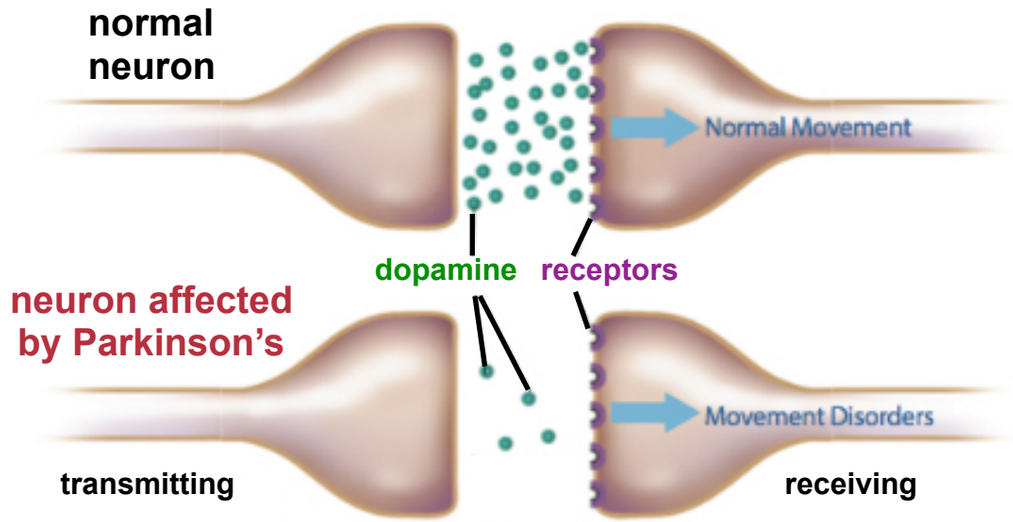
Parkinson's disease



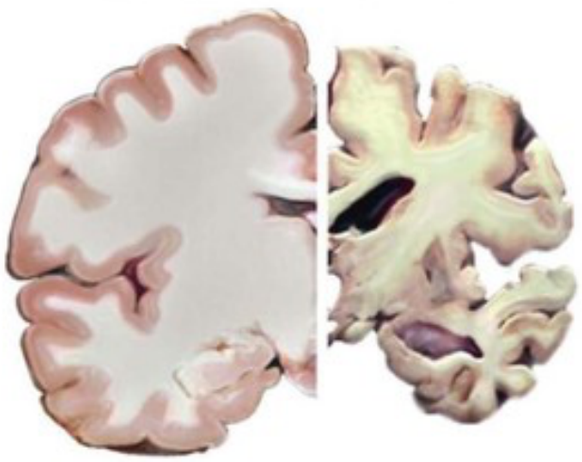
α-synuclein aggregates in dopamine producing nerve cells

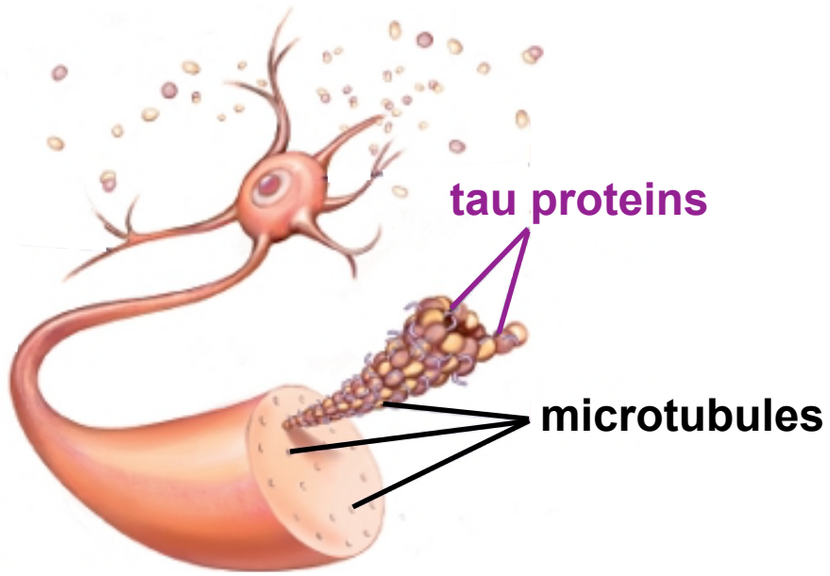


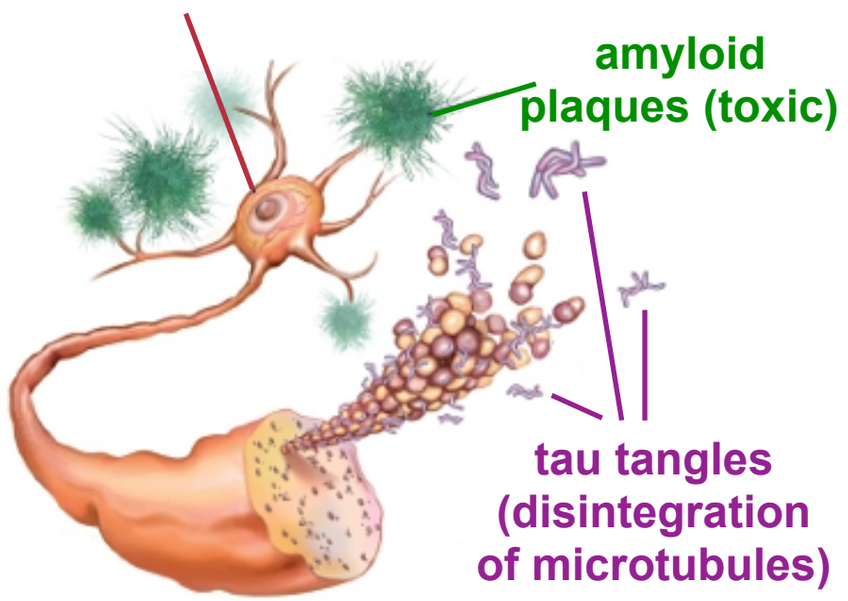
Loss of dopamine neurotransmitters results in movement disorders



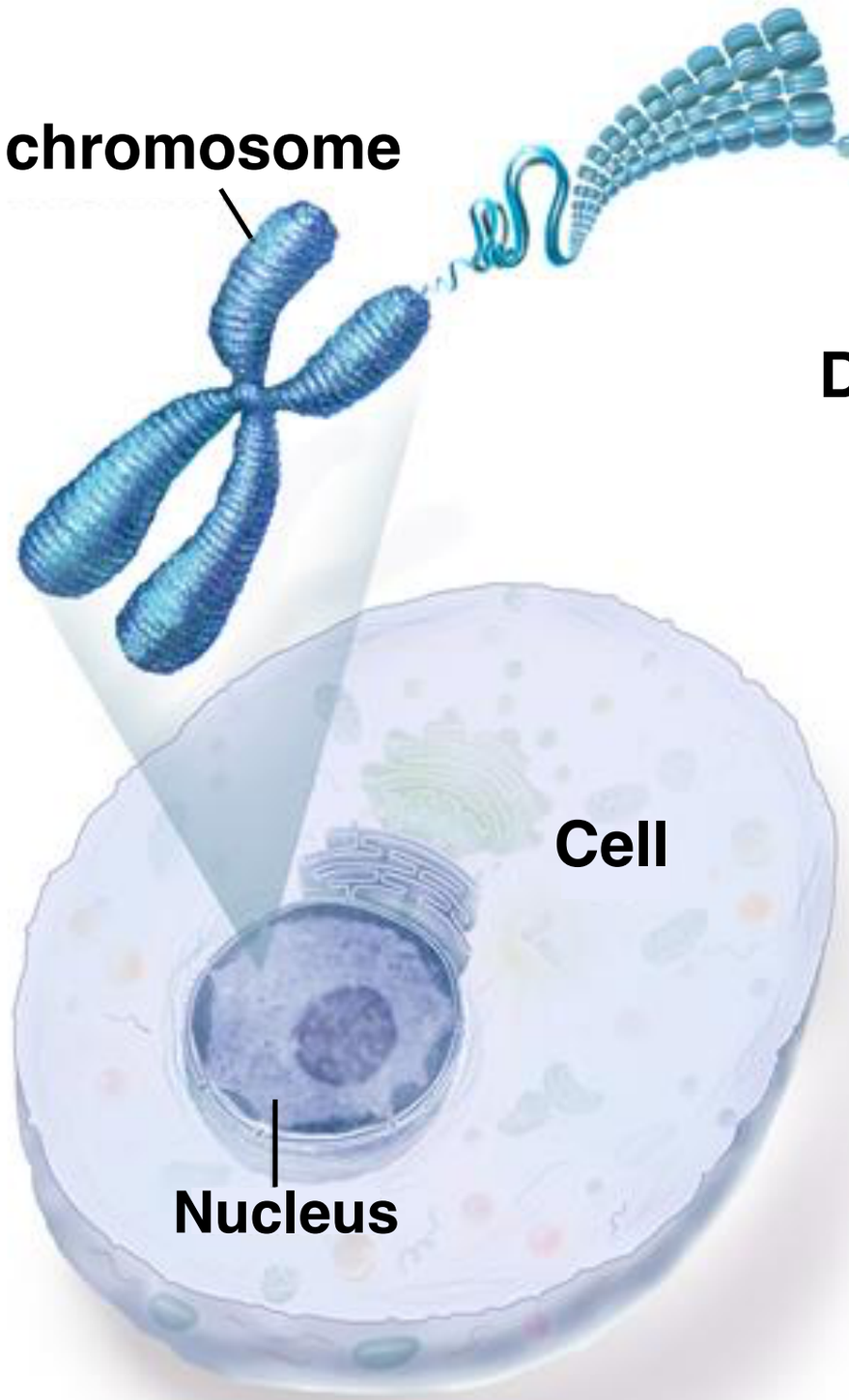
Alzheimer's disease

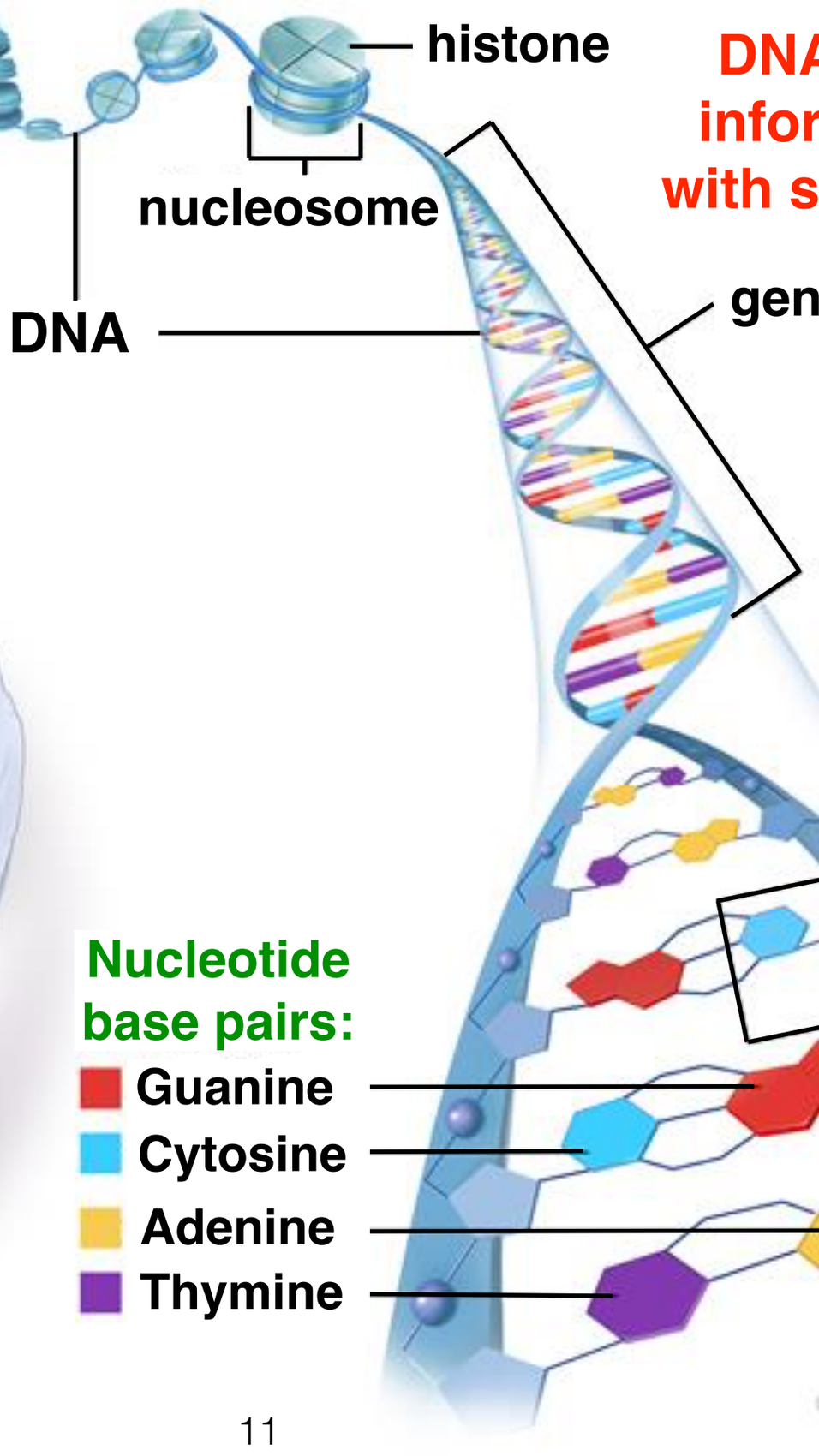






DNA structure





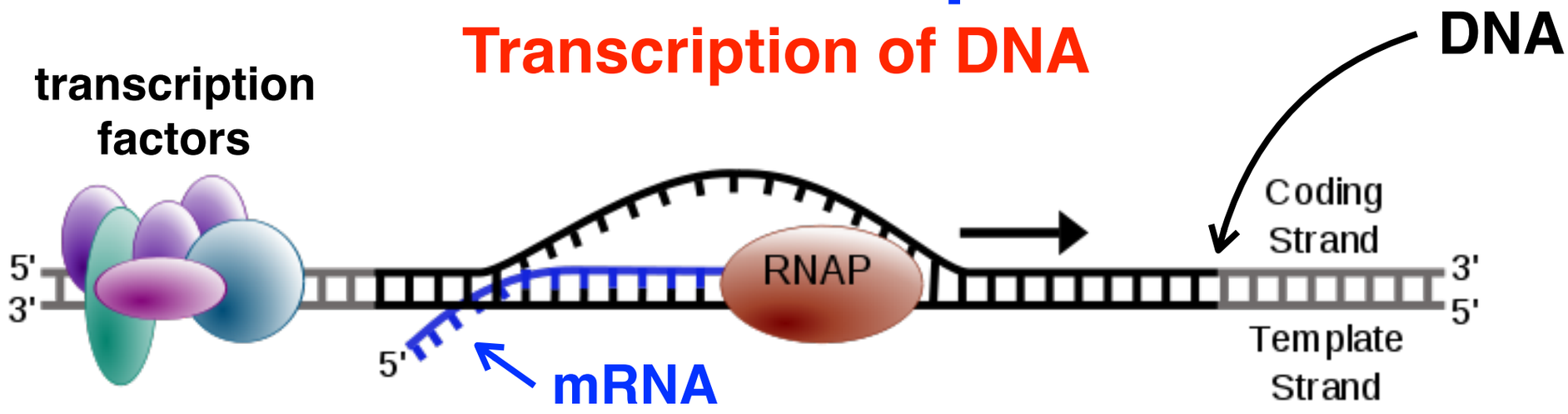
DNA stores genetic information encoded with sequence of bases

Nucleotide base pairs:

- Guanine
- Cytosine
- Adenine
- Thymine

Production of new proteins

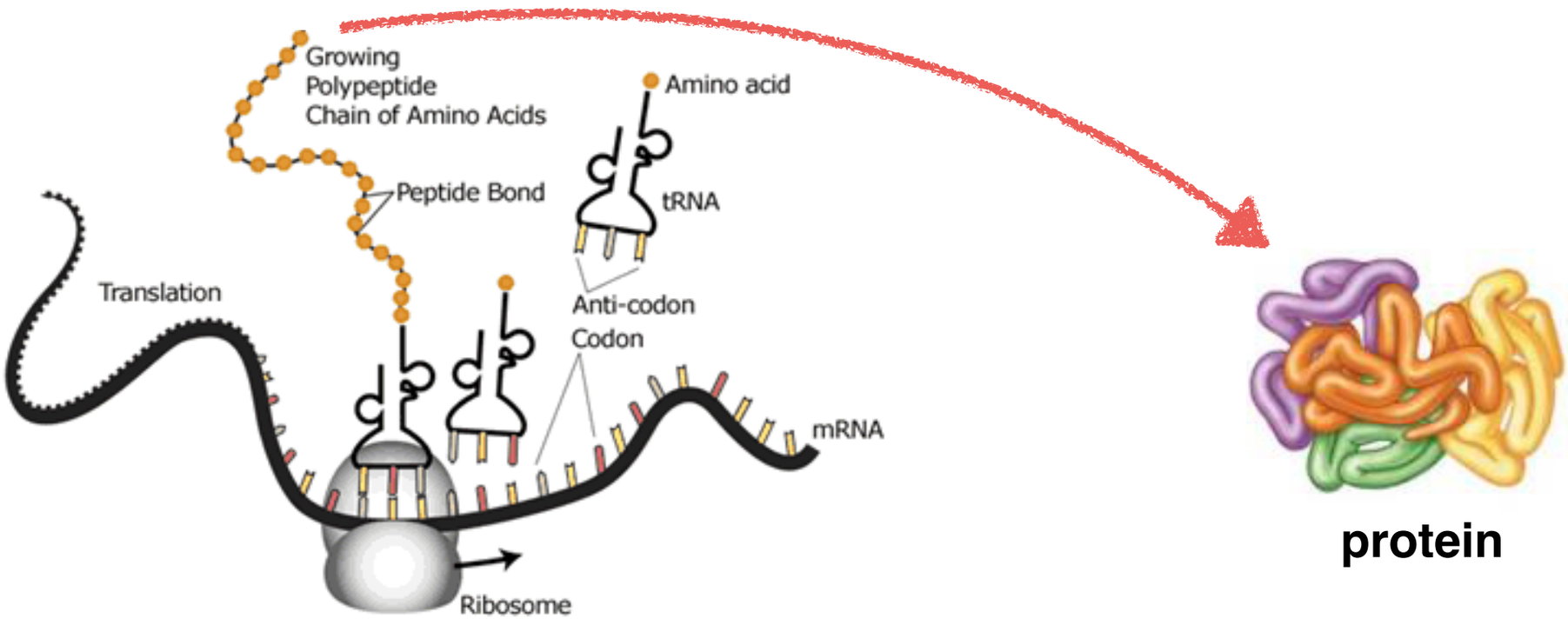
Transcription of DNA



Transcription factors are proteins, which bind to specific locations on DNA, and they help recruiting RNA polymerase (RNAP) that makes a messenger RNA (mRNA) copy of certain DNA segment.

Note: some transcription factors (repressors) also prevent transcription.

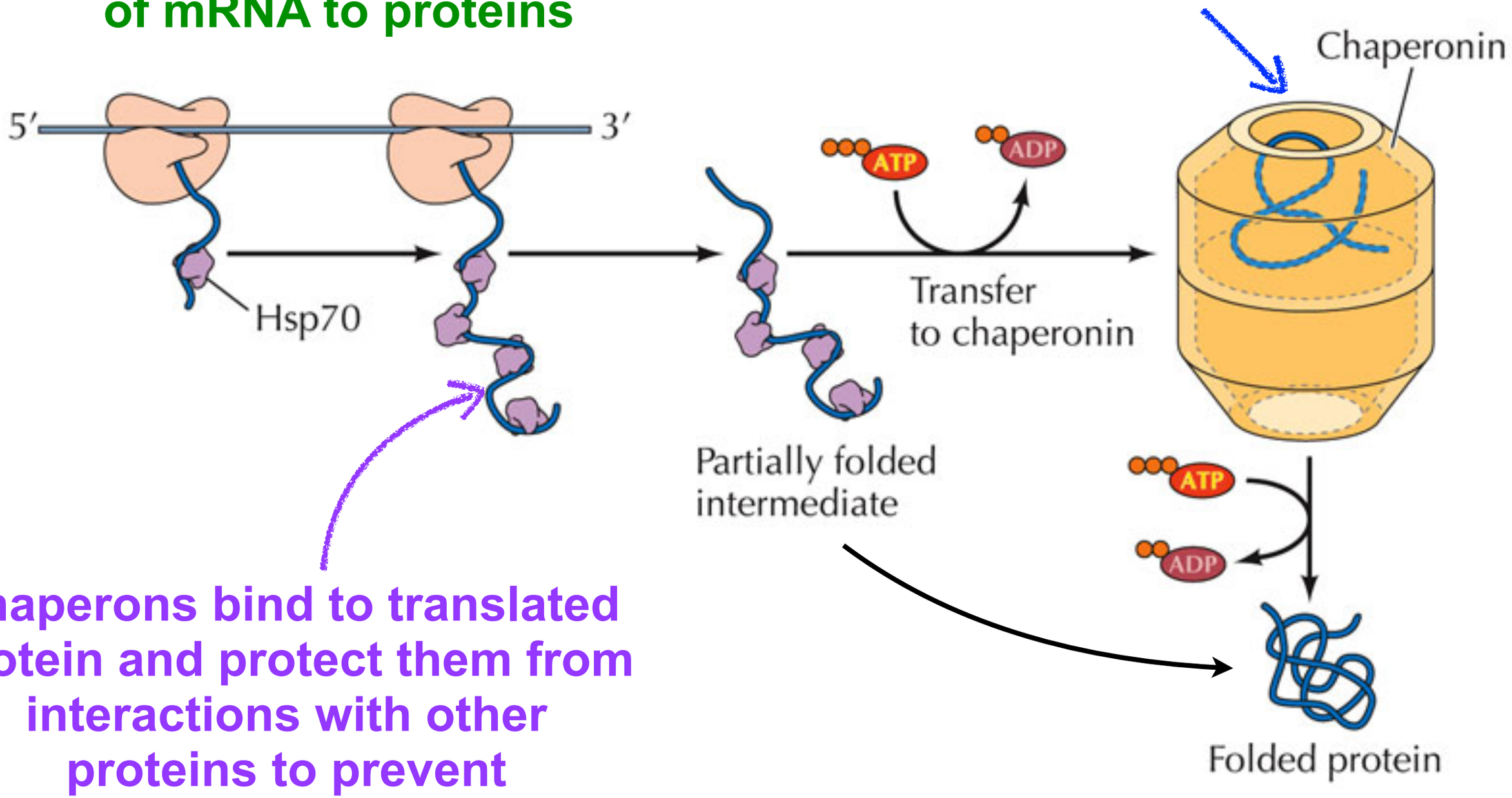
Translation of mRNA



Chaperons assist with protein folding and prevent protein aggregation

ribosome translation of mRNA to proteins

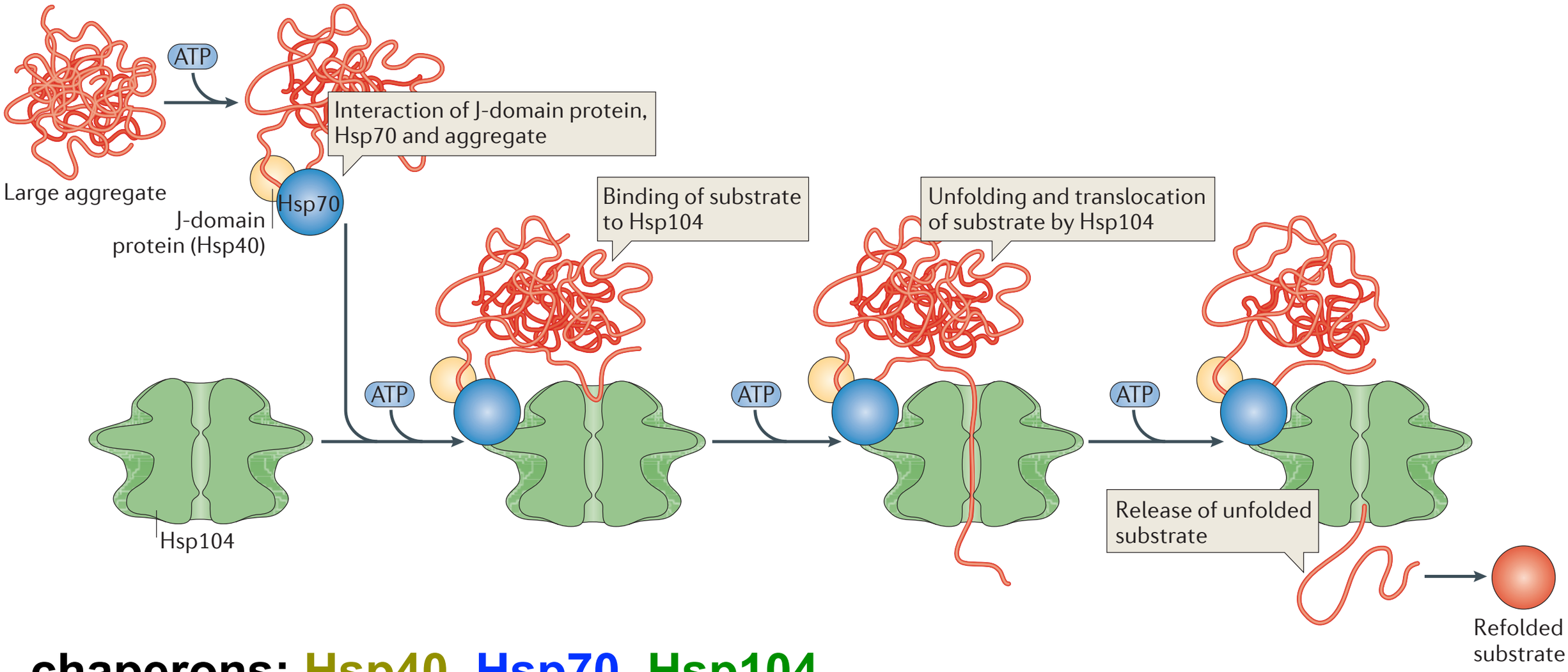
isolated proteins in chaperonin chambers fold into their compact native state



chaperons bind to translated protein and protect them from interactions with other proteins to prevent aggregation of proteins

B. Alberts et al., Molecular Biology of the Cell

Chaperons assist with disassembly of protein aggregates

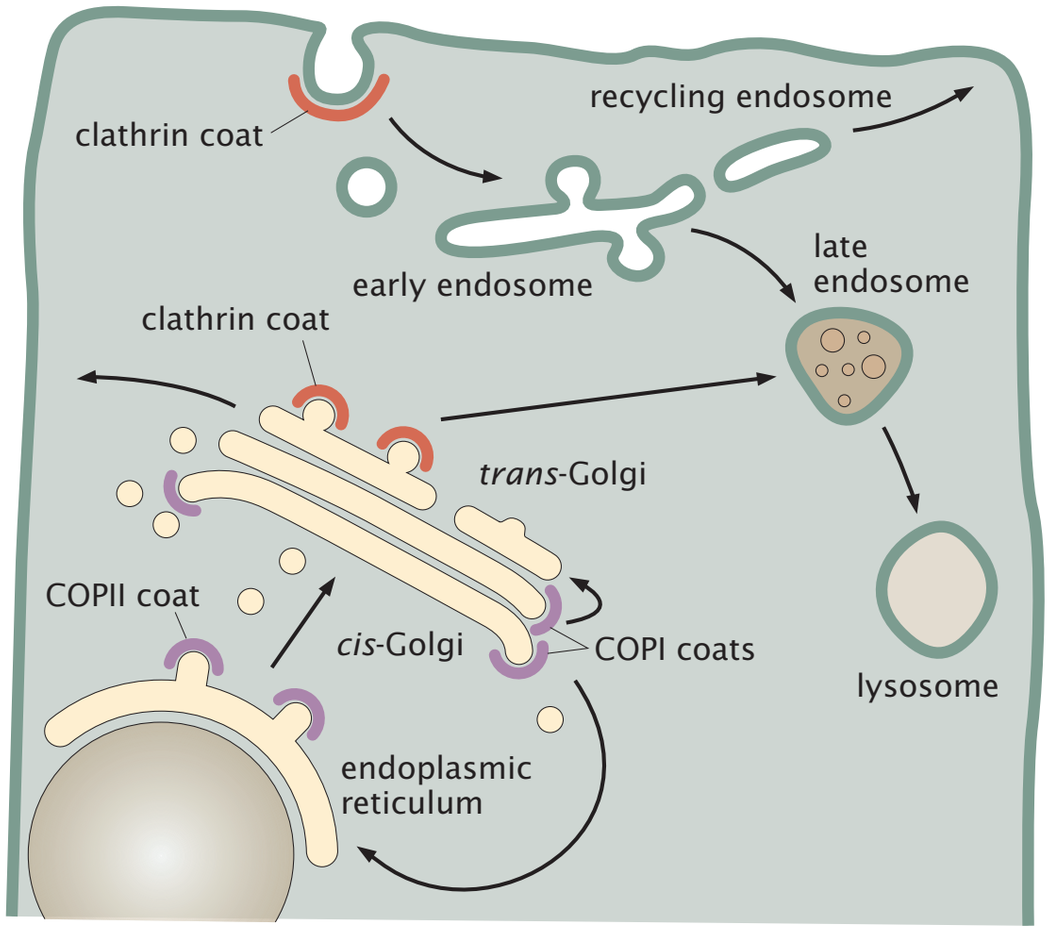


chaperons: Hsp40, Hsp70, Hsp104

Under normal cell conditions, protein aggregates are small and short lived!

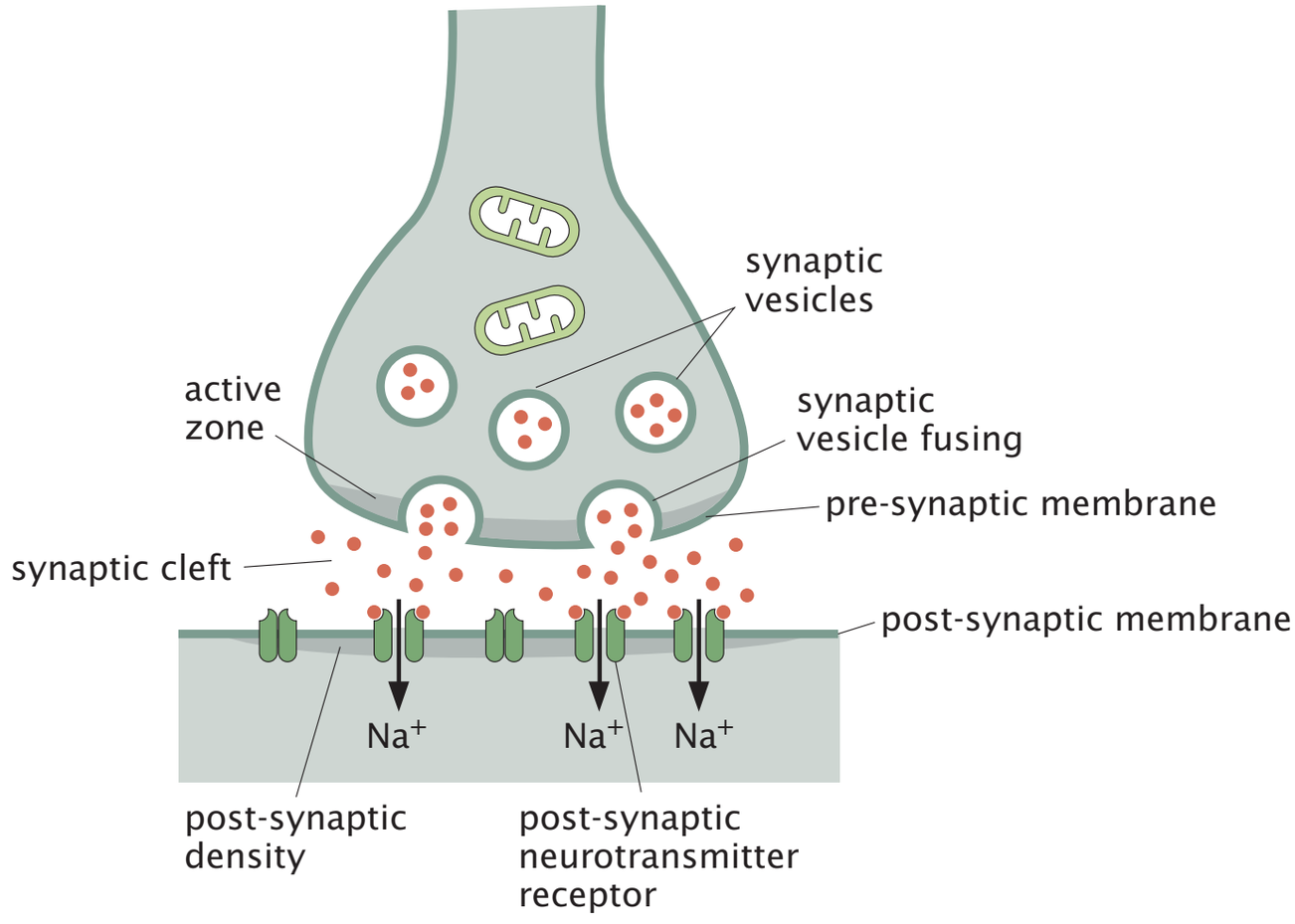
S. M. Doyle *et al.*, Nat. Rev. Mol. Cell Biol. **14**, 617 (2013)

Small vesicles are used for cellular transport of molecules



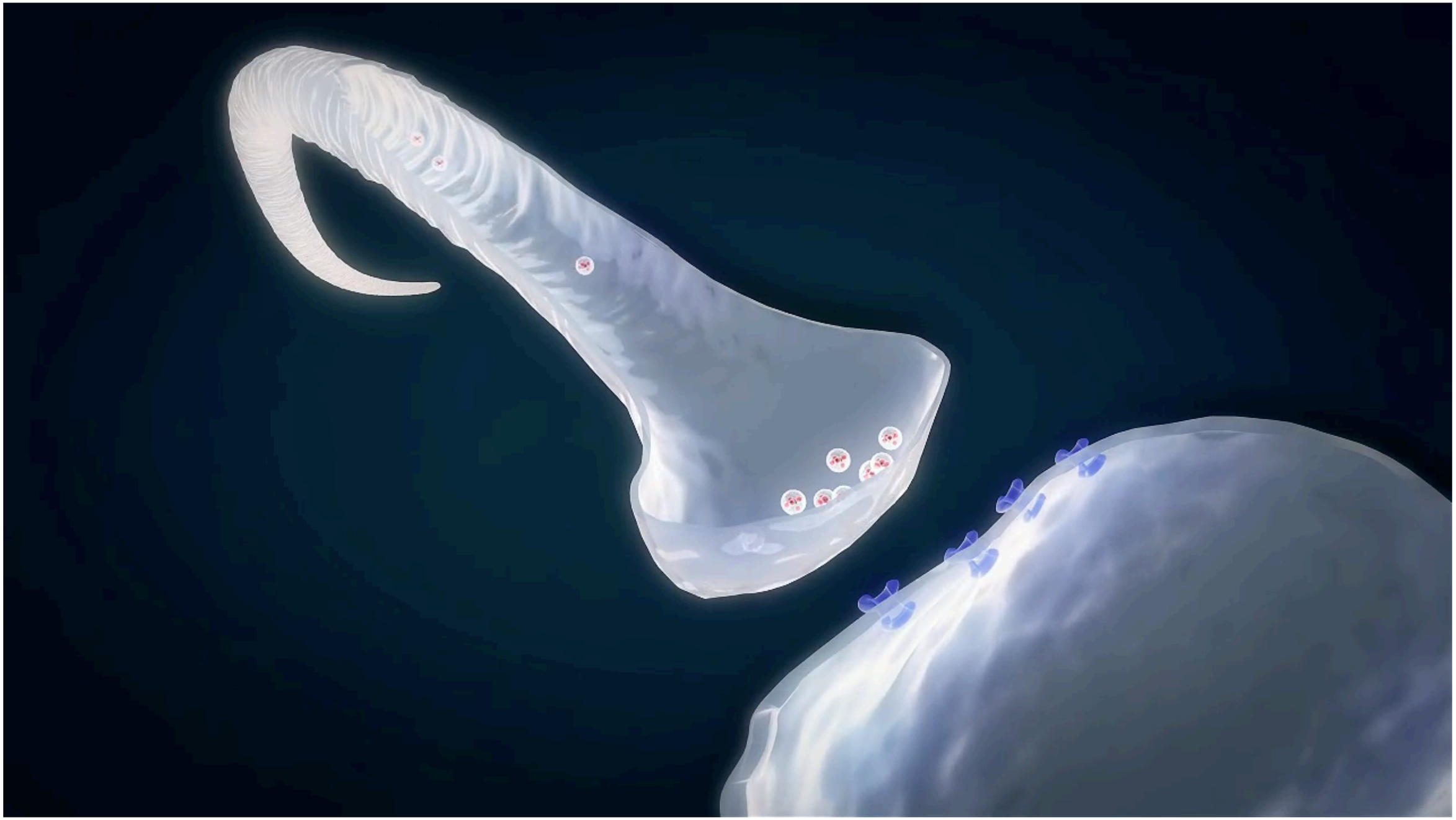
Vesicles are changing membrane topology!

transport of neurotransmitters in neuron cells



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

Transport of neurotransmitters in neuron cells



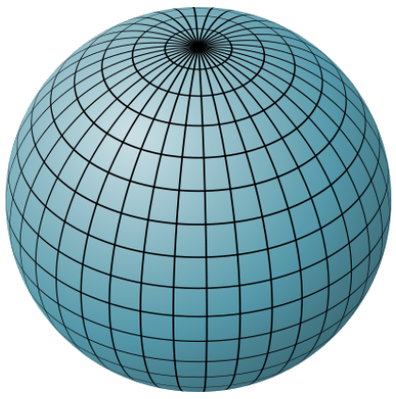
https://www.youtube.com/watch?v=FqTSYHtyHWE

Gauss-Bonet theorem

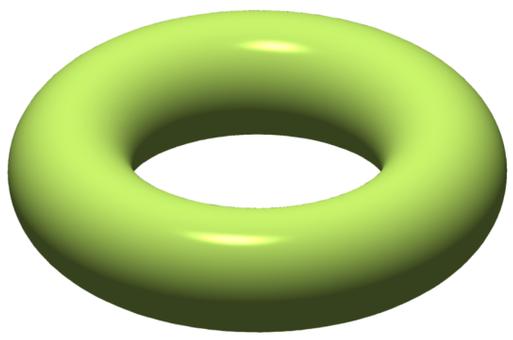
For closed surfaces the integral over Gaussian curvature only depends on the surface topology!

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

$g = 0$

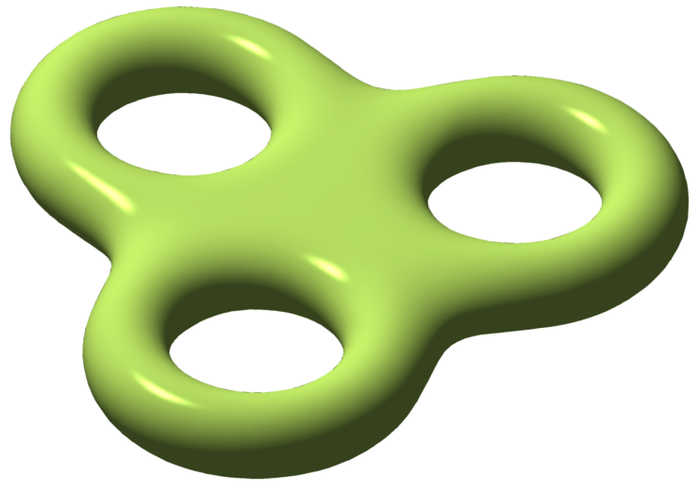


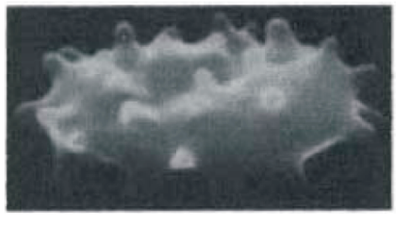
$g = 1$



$g = 2$

$g = 3$

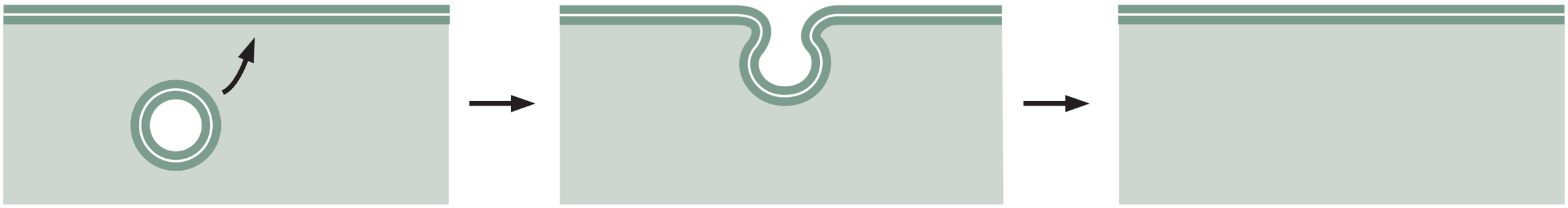




Creation of new vesicles or fusion of vesicles modifies the genus *g!*

Vesicle fusion with membrane

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



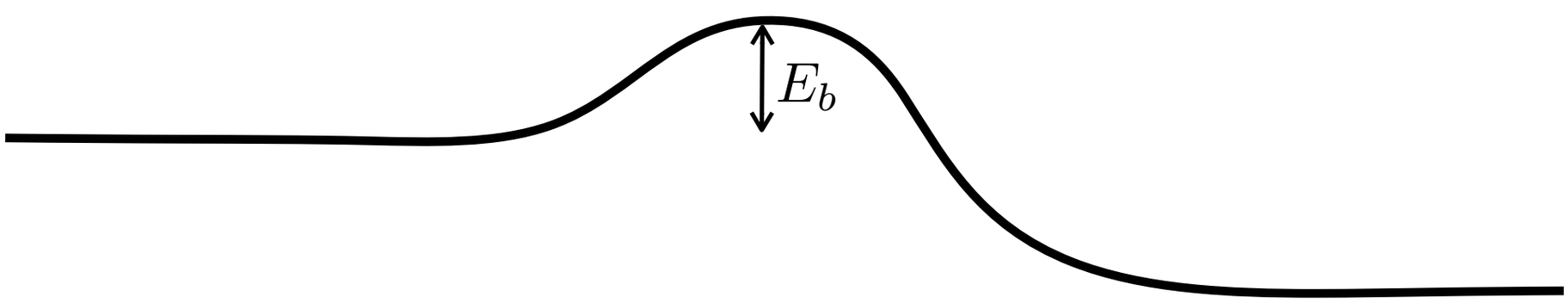
$E = 4\pi (2\kappa + \kappa_G)$

$E \sim +300 k_B T$

$E \approx 8\pi\kappa$

$E \sim +500 k_B T$

$E = 0$



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:

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

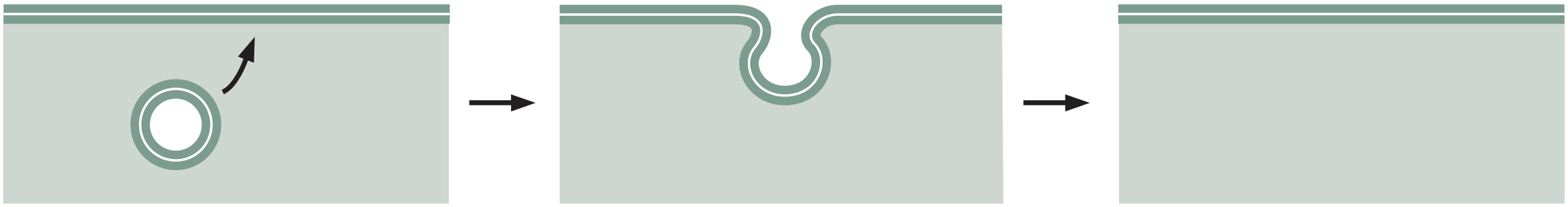
E_b **height of energy barrier**

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

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

Vesicle fusion with membrane

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



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

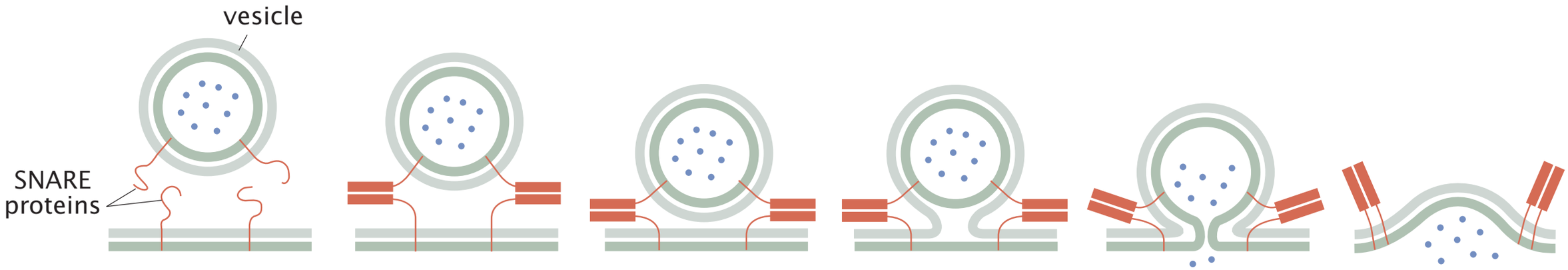
$$E \sim +300 k_B T$$

$$E \approx 8\pi\kappa$$

$$E \sim +500 k_B T$$

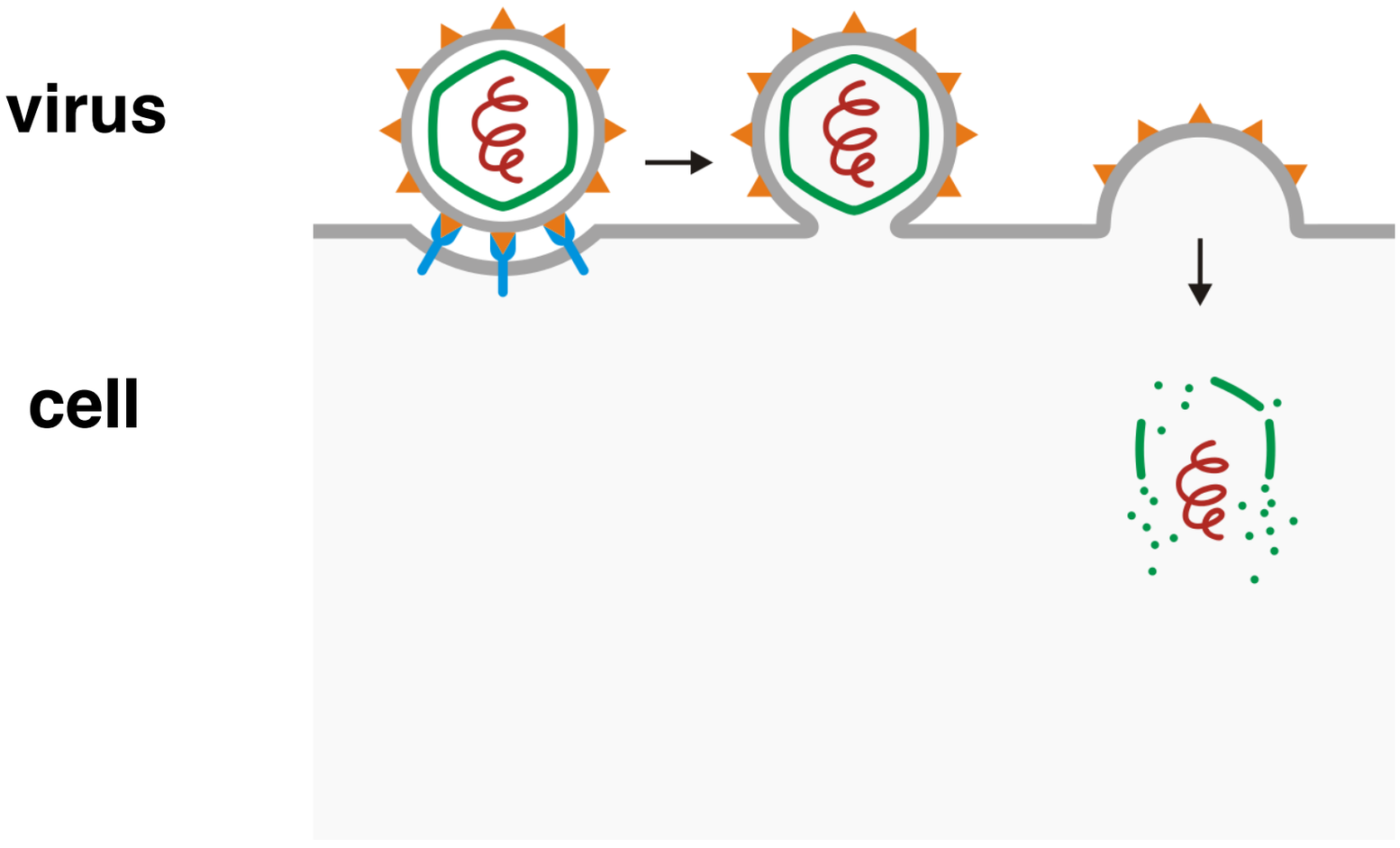
$$E = 0$$

In eukaryotic cells SNARE proteins accelerate membrane fusion by bringing vesicles closer to the membrane!



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

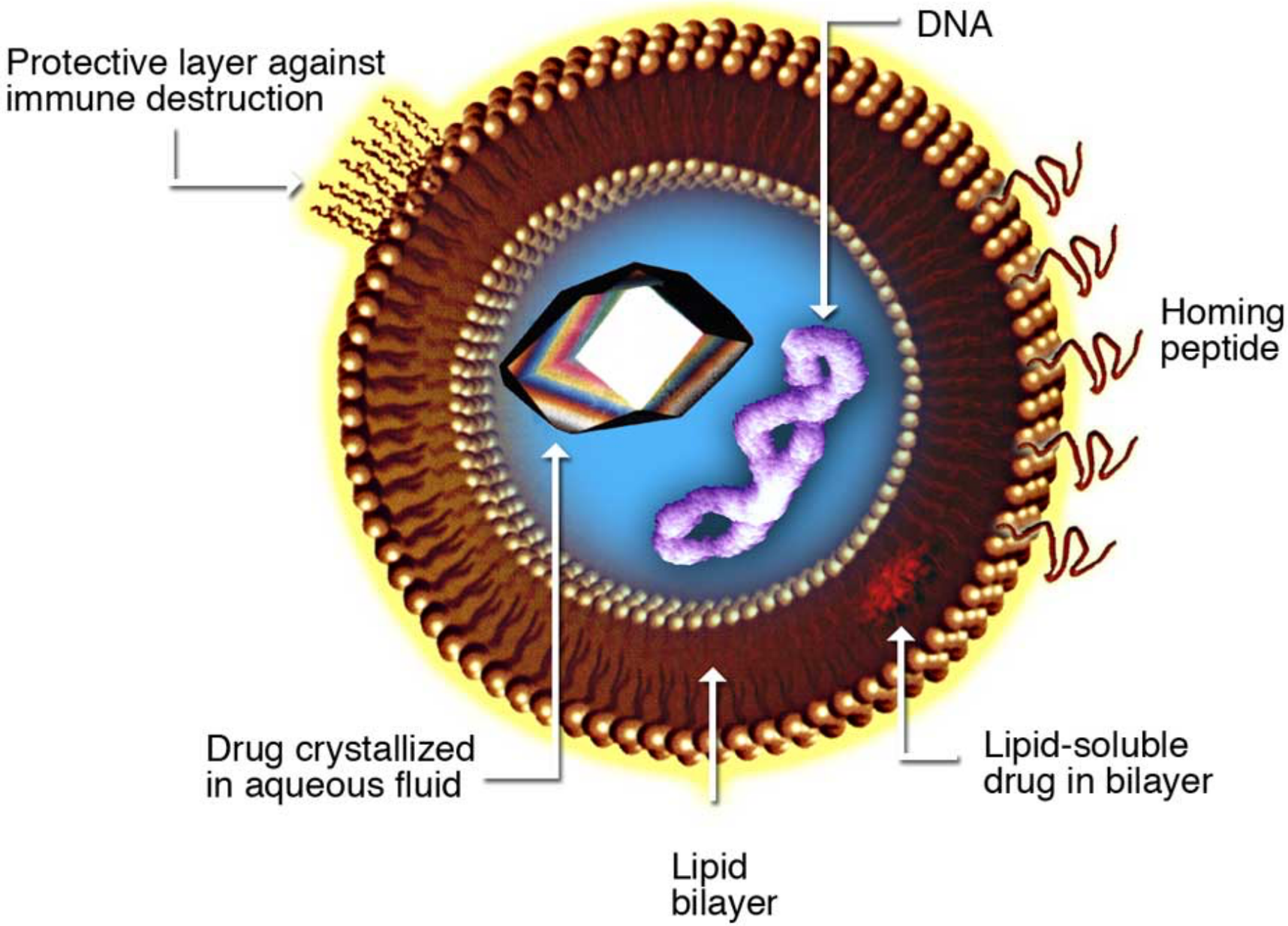
Viral entry to cell via receptor mediated membrane fusion



Example of viruses with viral envelope (lipid bilayer): HIV, influenza, hepatitis B virus, herpes viruses, …

Wikipedia

Lipid vesicles can be used for administration of drugs and nutrients

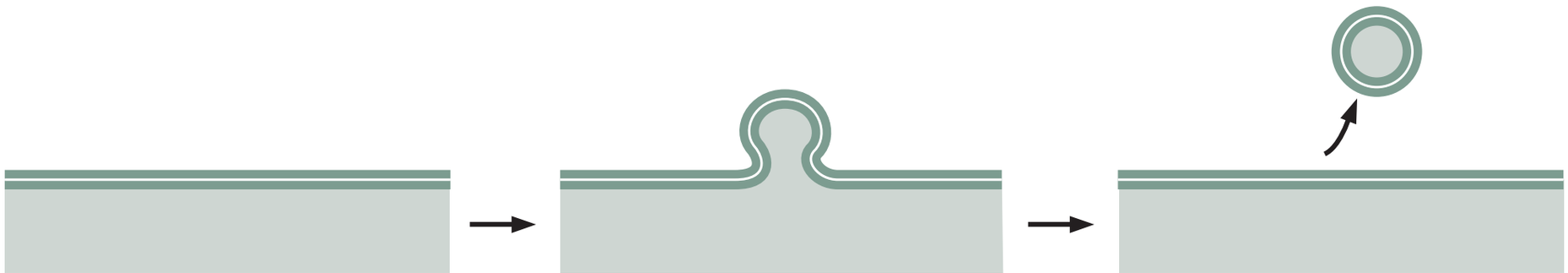


Targeted delivery to specific cells is achieved via binding of peptides to receptors expressed on the surface of target cells.

Wikipedia

Membrane budding

Creation of new vesicles costs energy!



$E = 0$

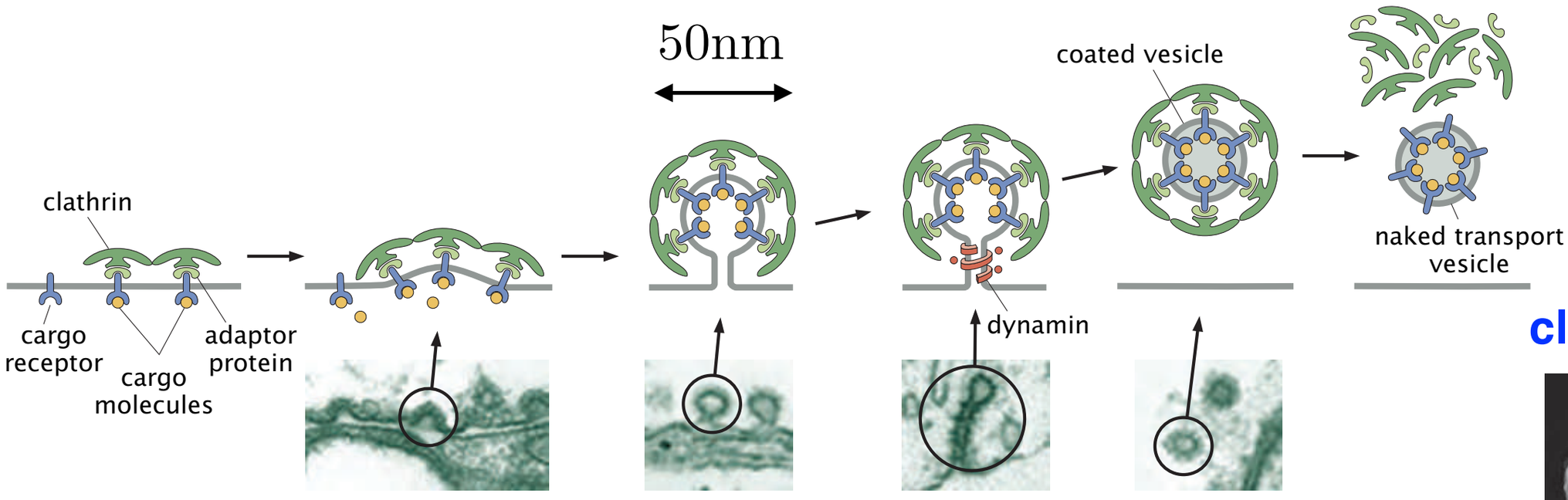
$E \approx 8\pi\kappa$

$E \sim +500 k_B T$

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

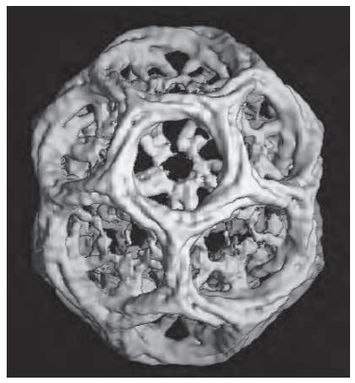
$E \sim +300 k_B T$

Creation of new cargo vesicles is assisted with receptor mediated coating of proteins (clathrin, COPI)

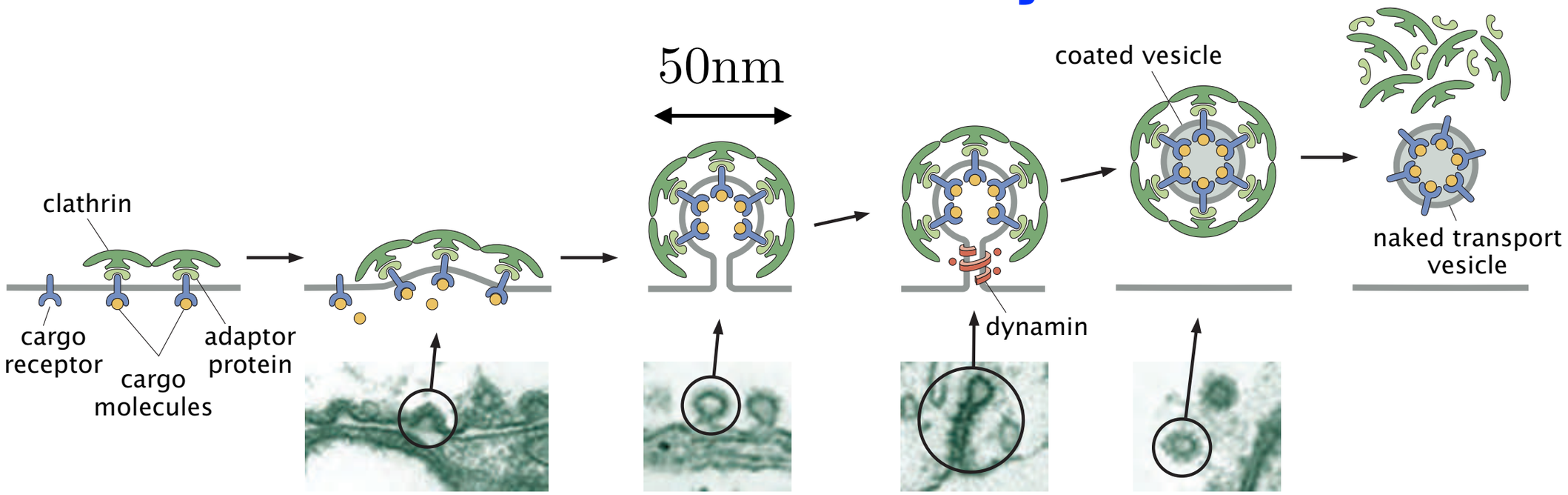


R. Phillips et al., Physical Biology of the Cell

clathrin cage

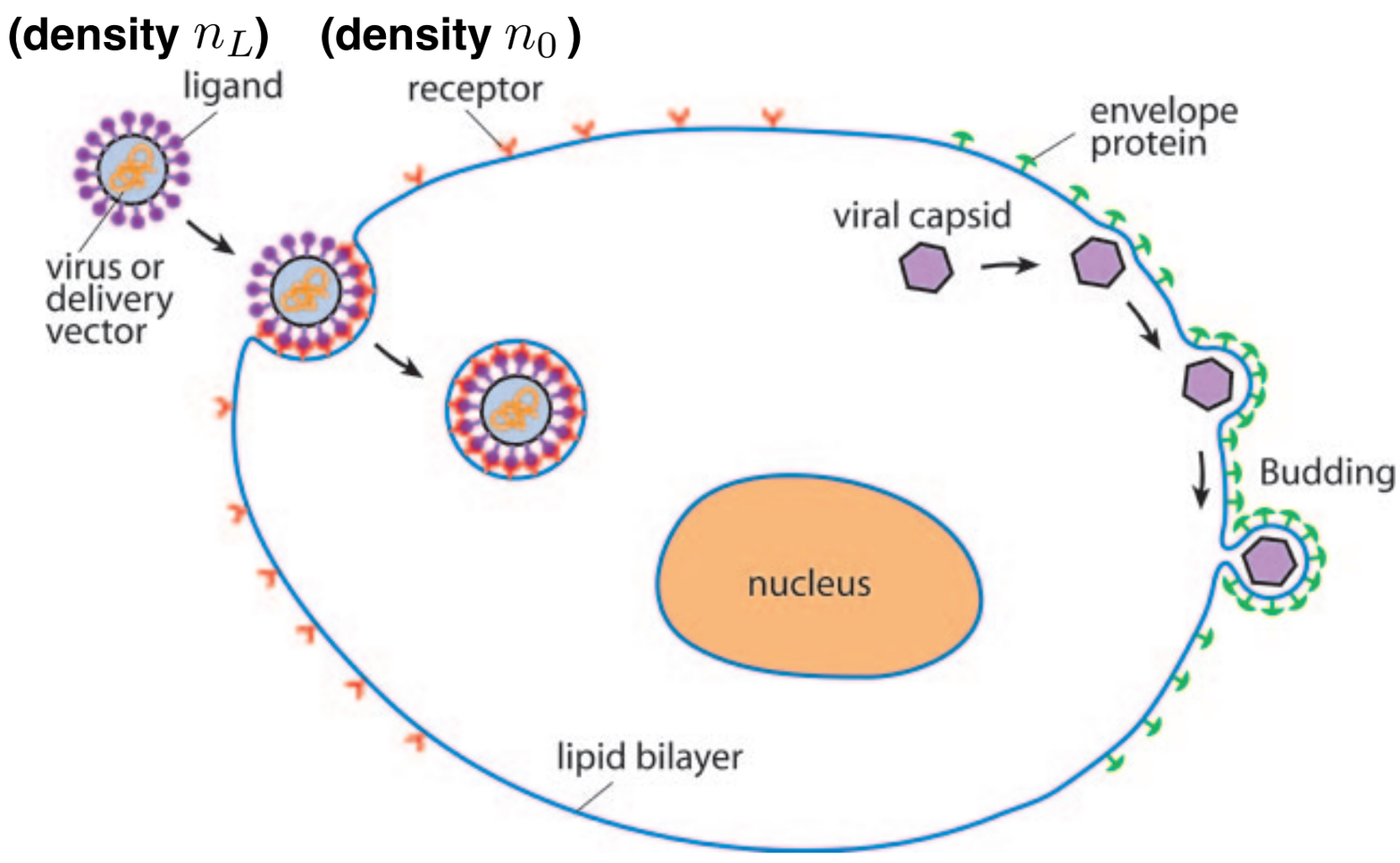


Clathrin-mediated endocytosis



http://
biochem.web.utah.edu/
iwasa/projects/
clathrin.html

Viral entry to cell via receptor mediated endocytosis



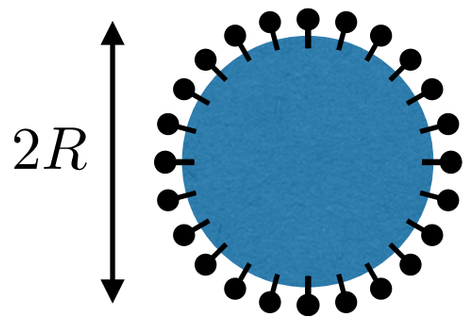
(similar process may help during budding of enveloped viruses)

Bending energy cost and loss of entropy for receptors is compensated by the binding energy between cell receptors and ligands on the surface of viral capsid.

G. Bao and X.R. Bao,
PNAS 102, 9997 (2005)

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

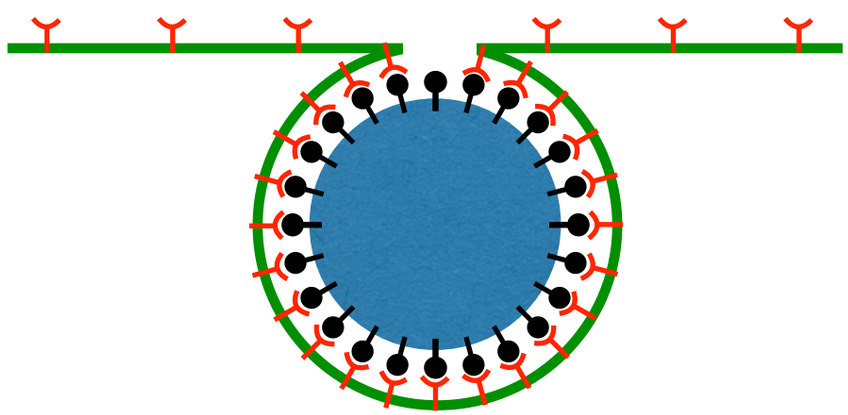
$U_b \sim 15k_BT$

bending rigidity

$\kappa \sim 20k_BT$

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 $\Delta E < 0$ **:**

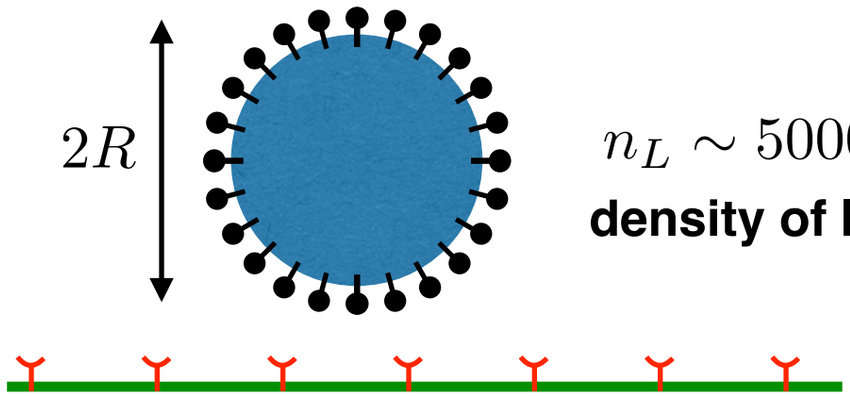
$$R > \sqrt{\frac{2\kappa}{n_L\left(U_B - k_BT\ln(n_L/n_0)\right)}} \sim 30\mathrm{nm}$$

How fast is this process?

Viral entry to cell via receptor mediated endocytosis

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

Side view:



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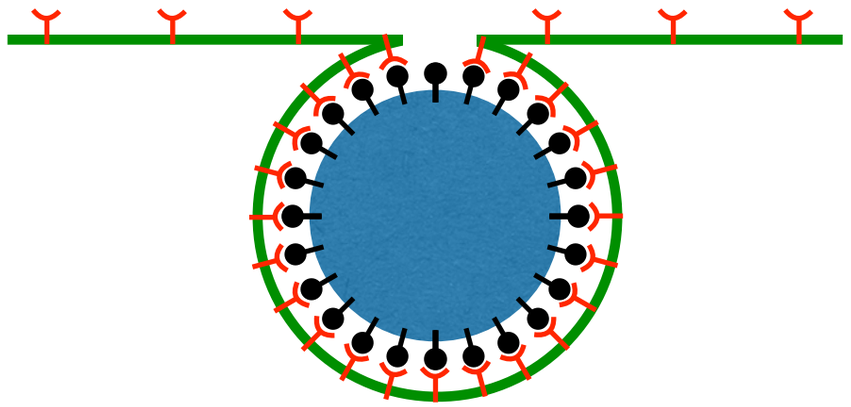
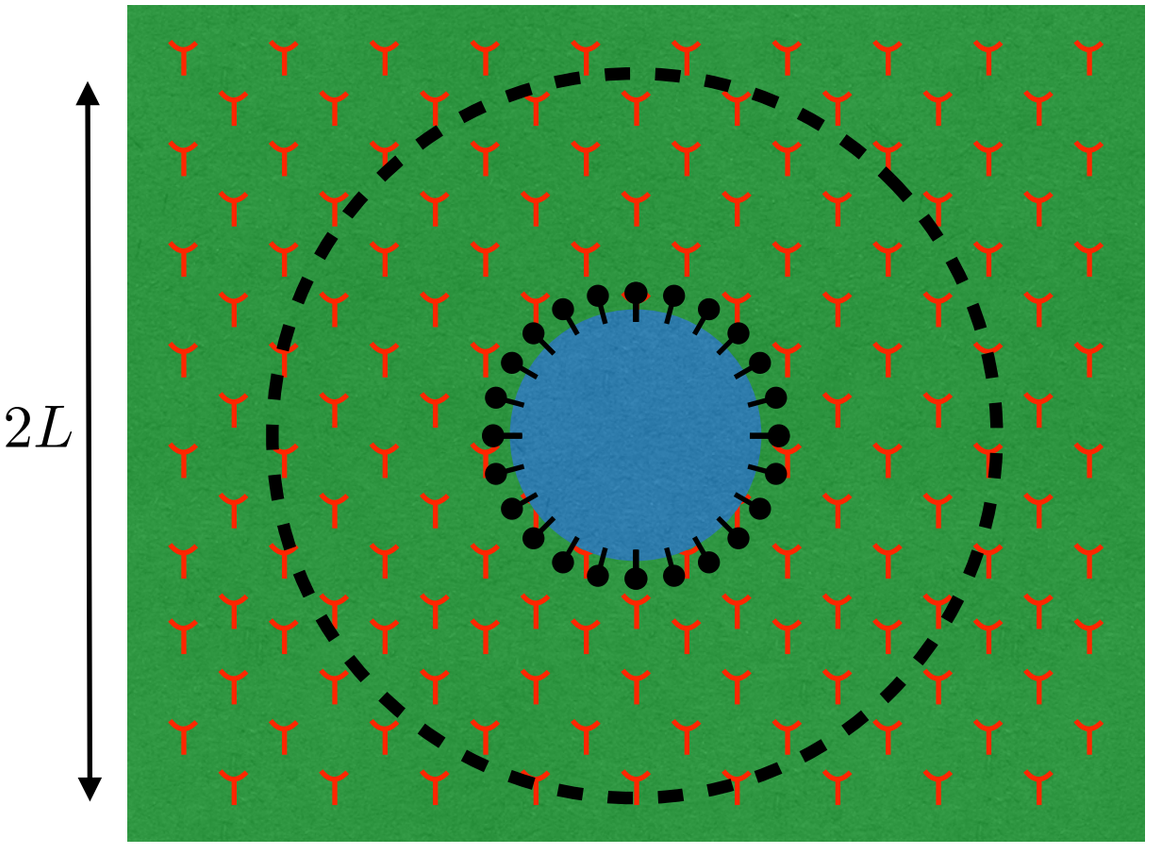


Top view:



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

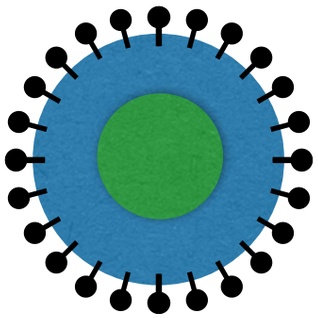
Need to recruit N_L receptors from circular region of radius L via diffusion

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

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

Use of magnetic nanoparticles for diagnostic and treatment of tumors

Receptors for LHRH hormone are over-expressed in breast, ovarian, and prostate cancer cells



LHRH hormone

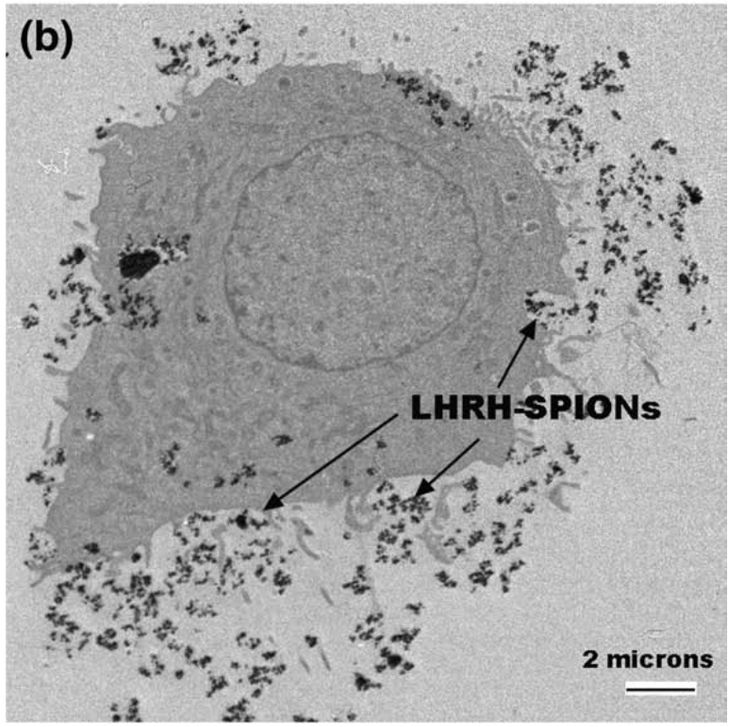
PEG coating

magnetic core

Magnetic particles enter only cancer cells via LHRH-receptor mediated endocytosis

PEG coating shields nanoparticles from immune system and prevents macro-clustering of nanoparticles.

Cancer cells containing magnetic nanoparticles can be detected with MRI (magnetic resonance imaging). Then magnetic particles can be heated via magnetic field to destroys cancer cells.



J. Meng *et al.,* Mater. Sci. Eng. C **29,** 1467 (2009)