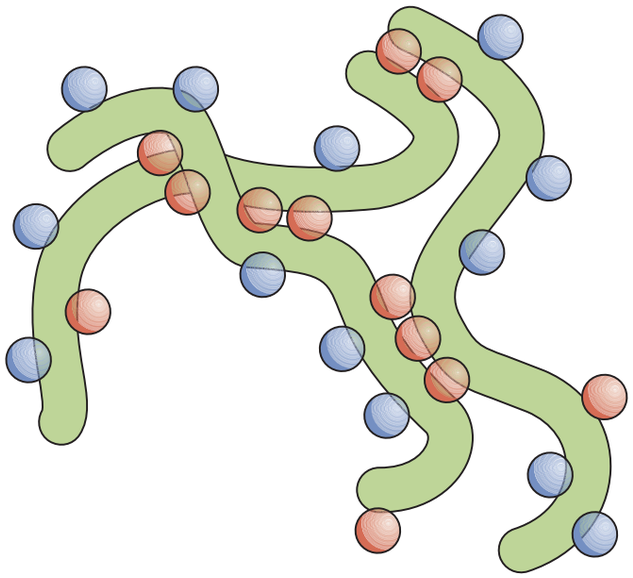
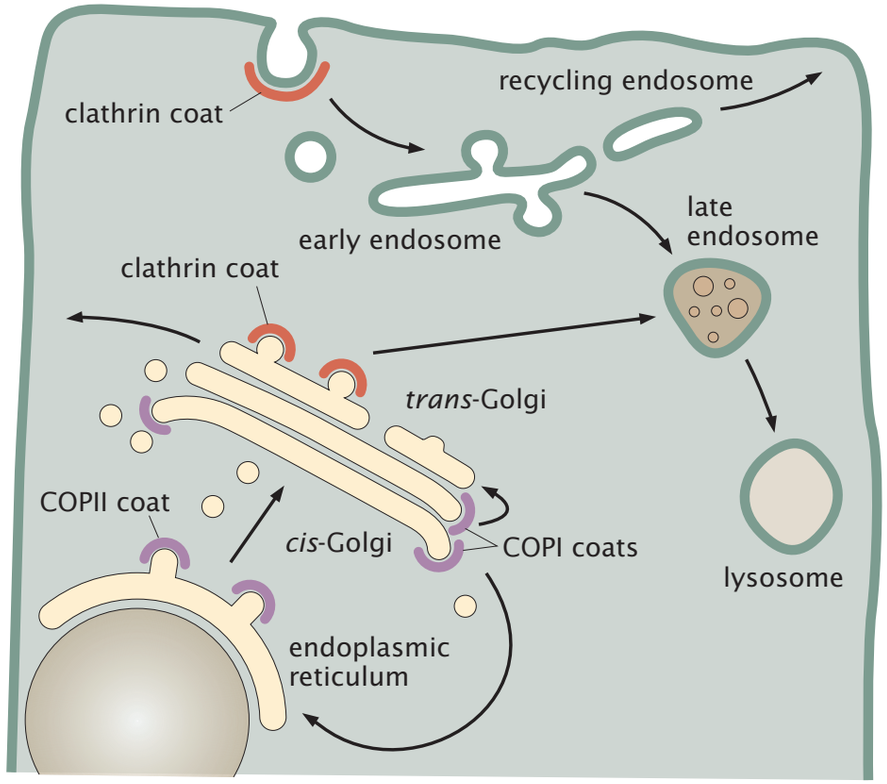
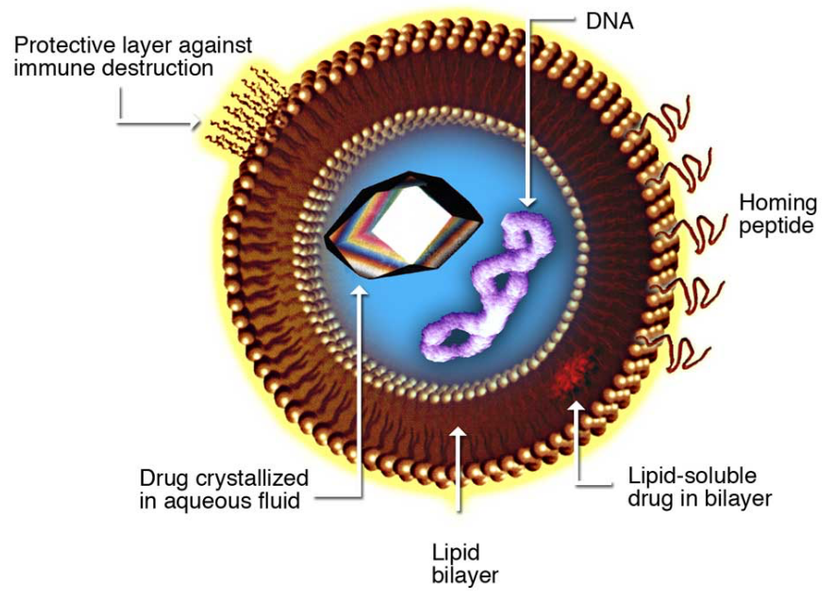
MAE 545: Lecture 15 (4/3)

Aggregation of proteins, cellular transport via vesicles and drug delivery

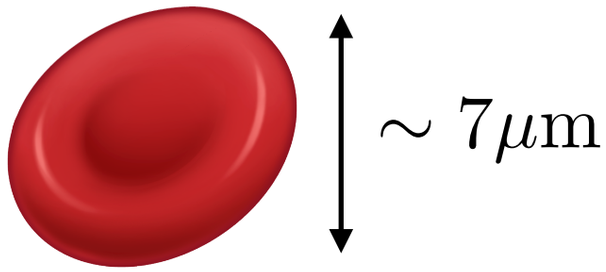






Shape of red blood cells

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

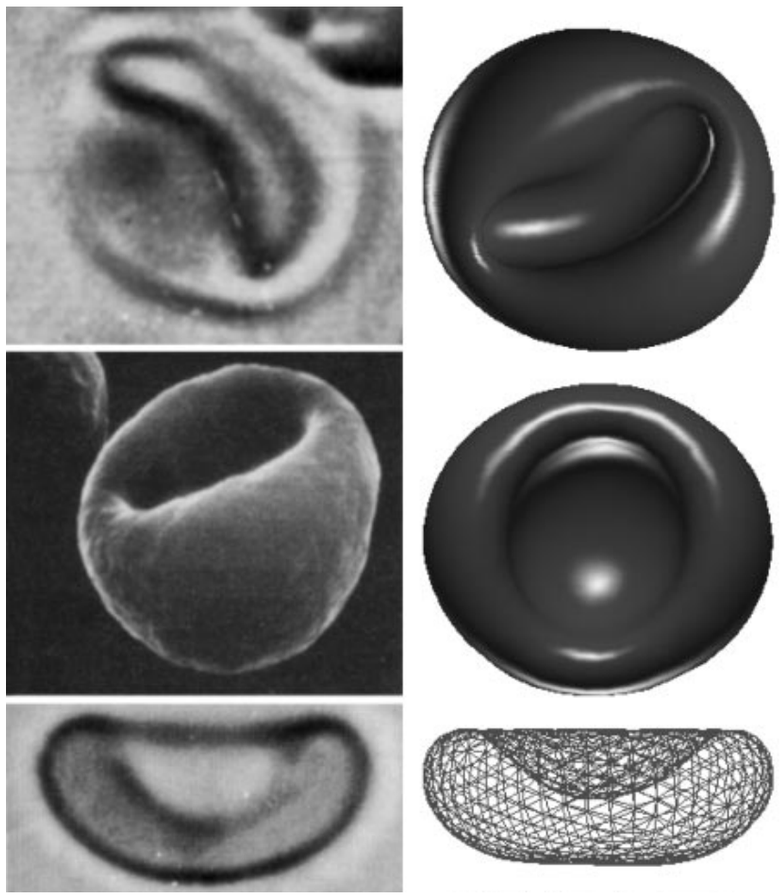


cationic amphipaths, low salt, low pH, cholesterol depletion

anionic amphipaths, high salt, high pH, cholesterol enrichment

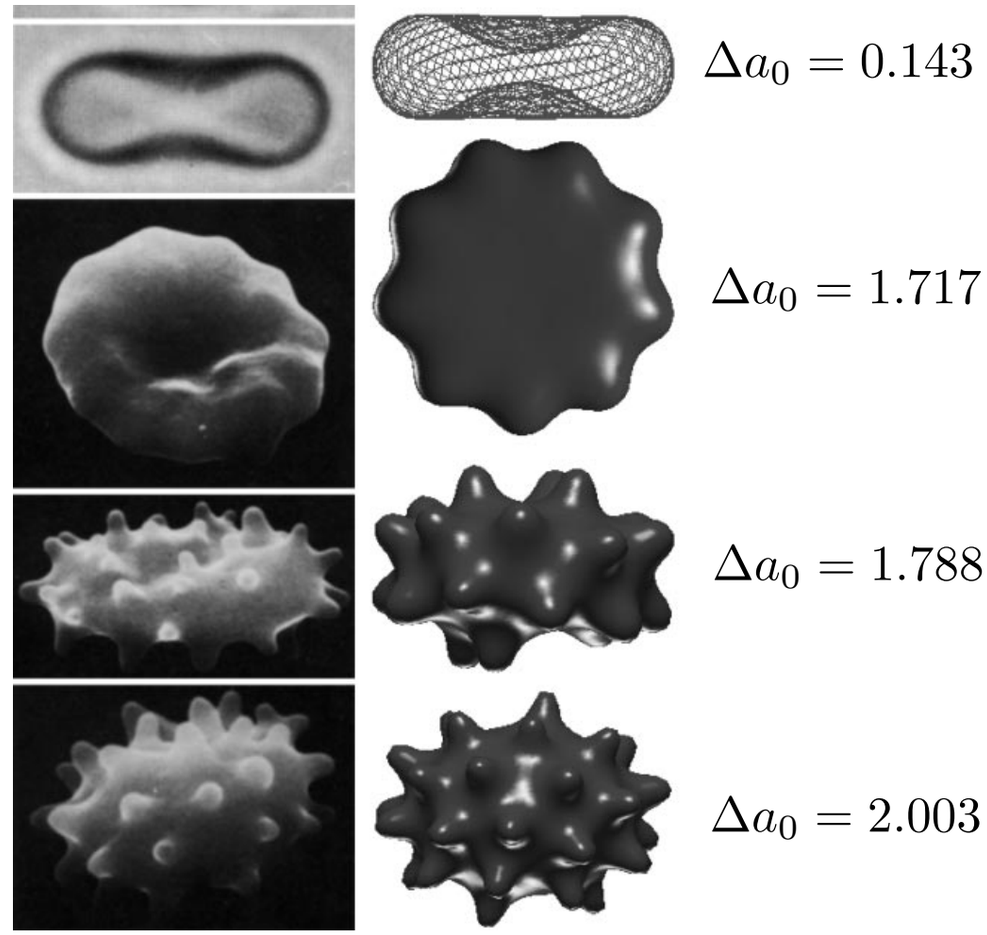
experiments **simulations** $v = 0.950$

stomatocytes



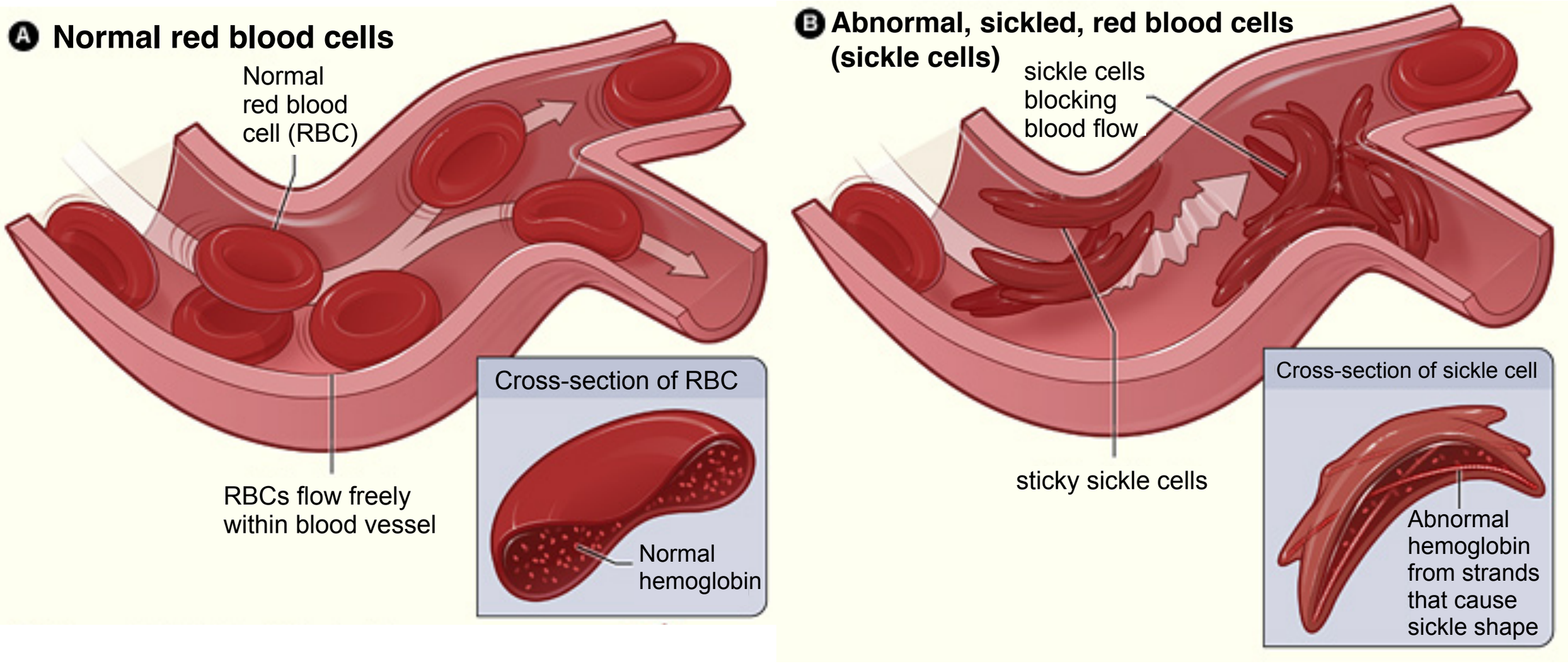
experiments **simulations** $v = 0.950$

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.

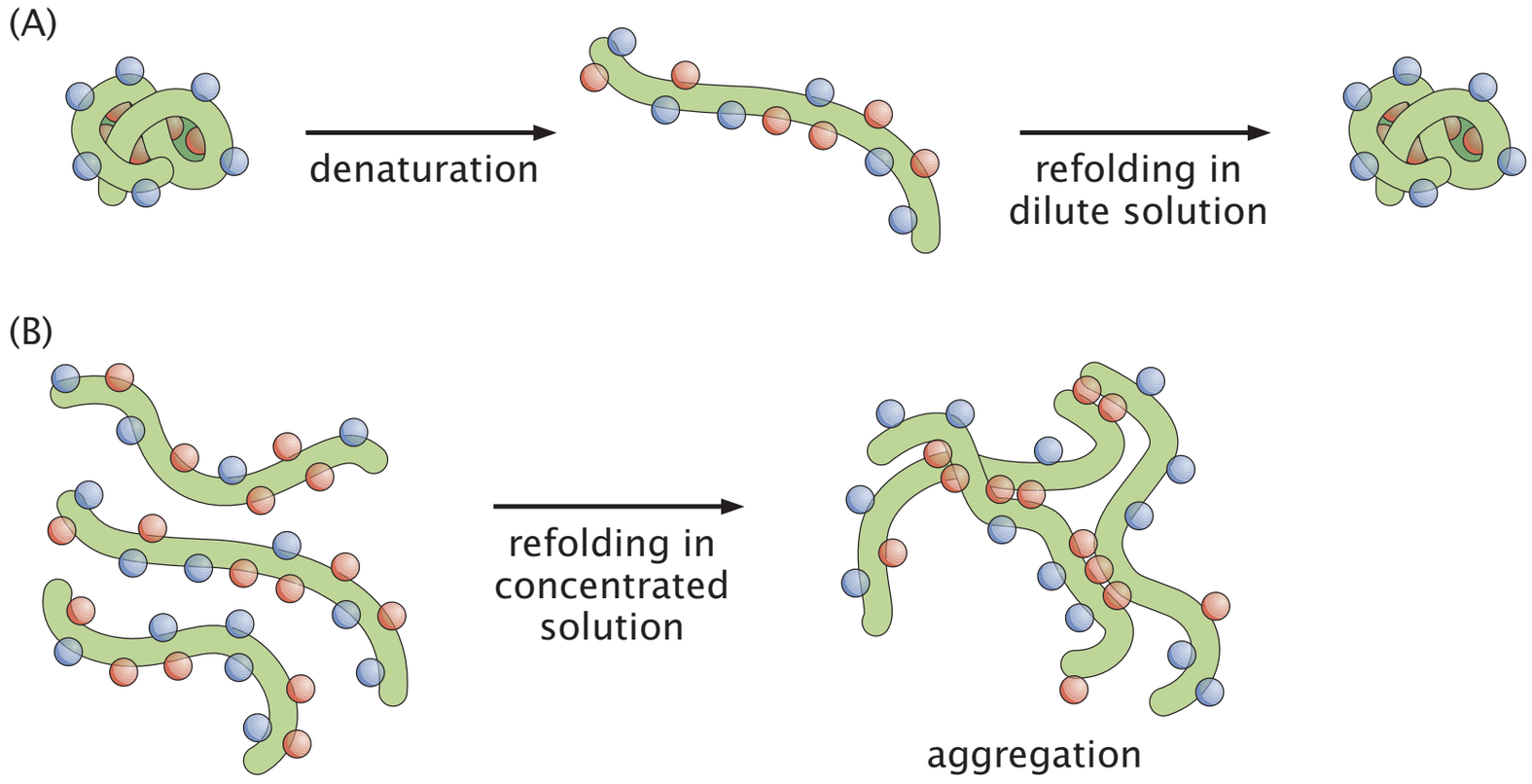
Sickle cells are much stiffer and cannot deform in order to pass through small capillaries.

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

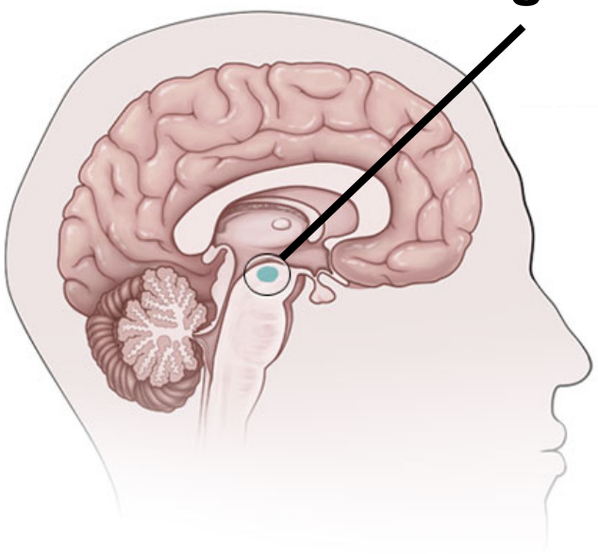
(B) In concentrated solution misfolded proteins tend to form aggregates.

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

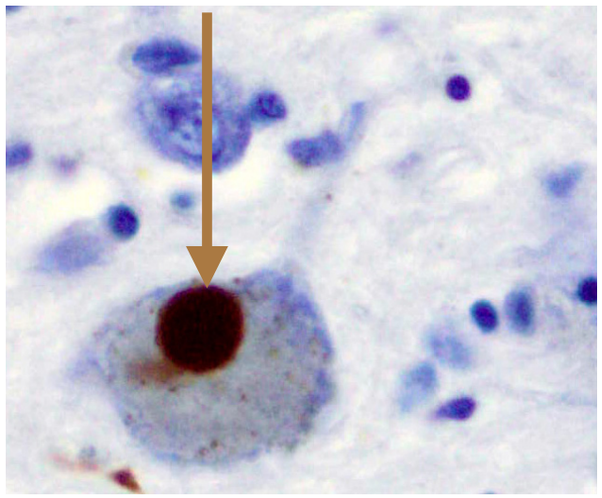
Protein aggregation is a cause of many diseases (Alzheimer's, Parkinson's, …)

Protein aggregates are associated with diseases

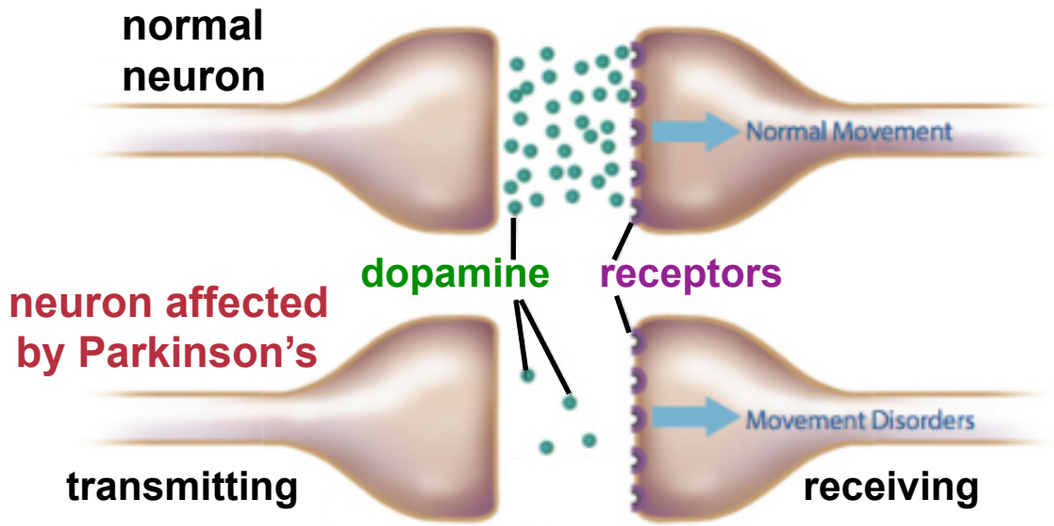
Parkinson's disease



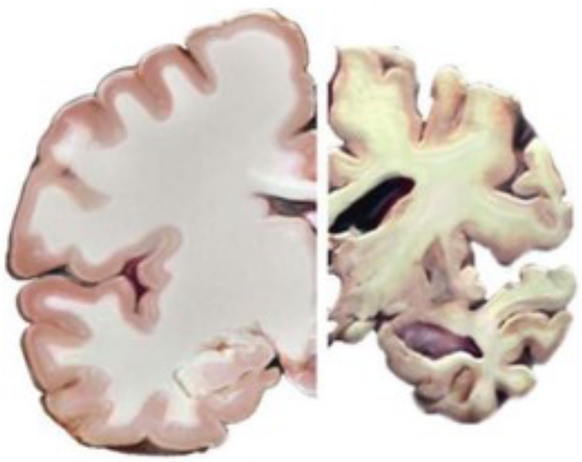
α-synuclein aggregates in dopamine producing nerve cells

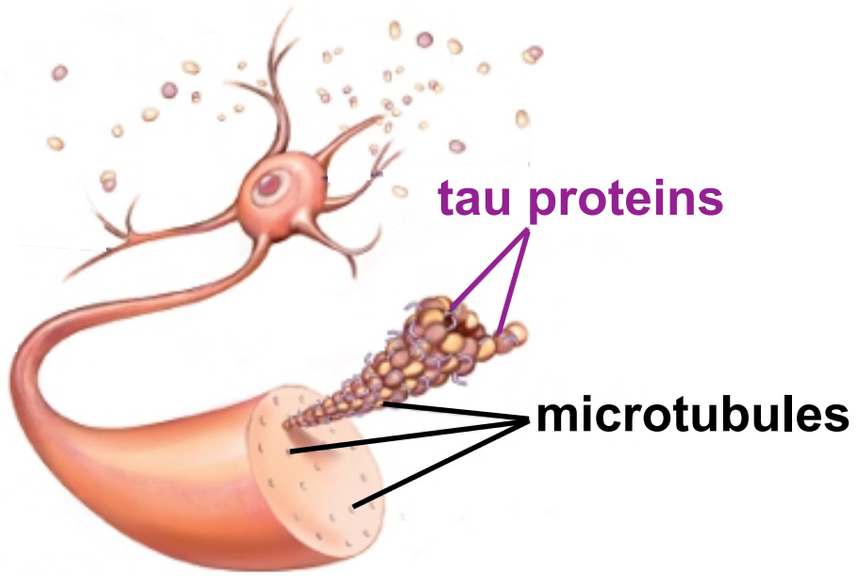


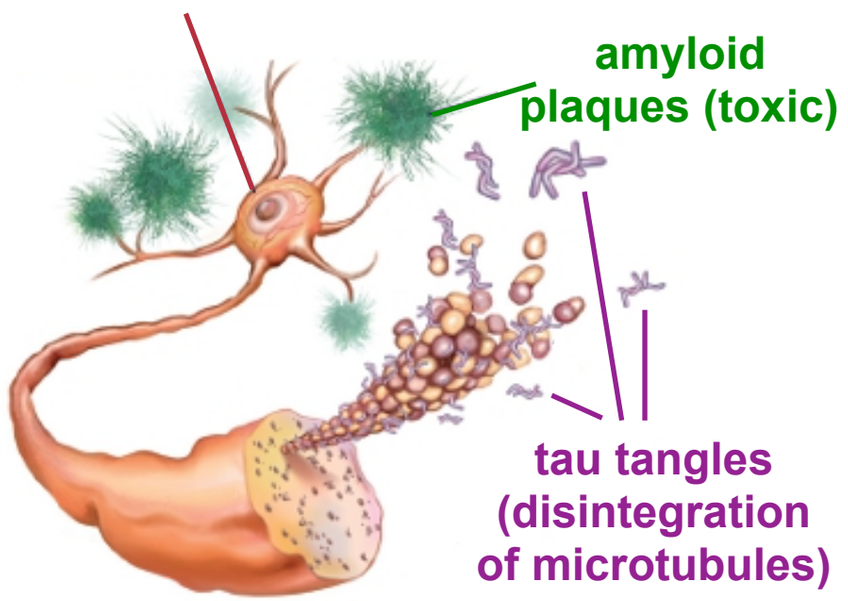
Loss of dopamine neurotransmitters results in movement disorders



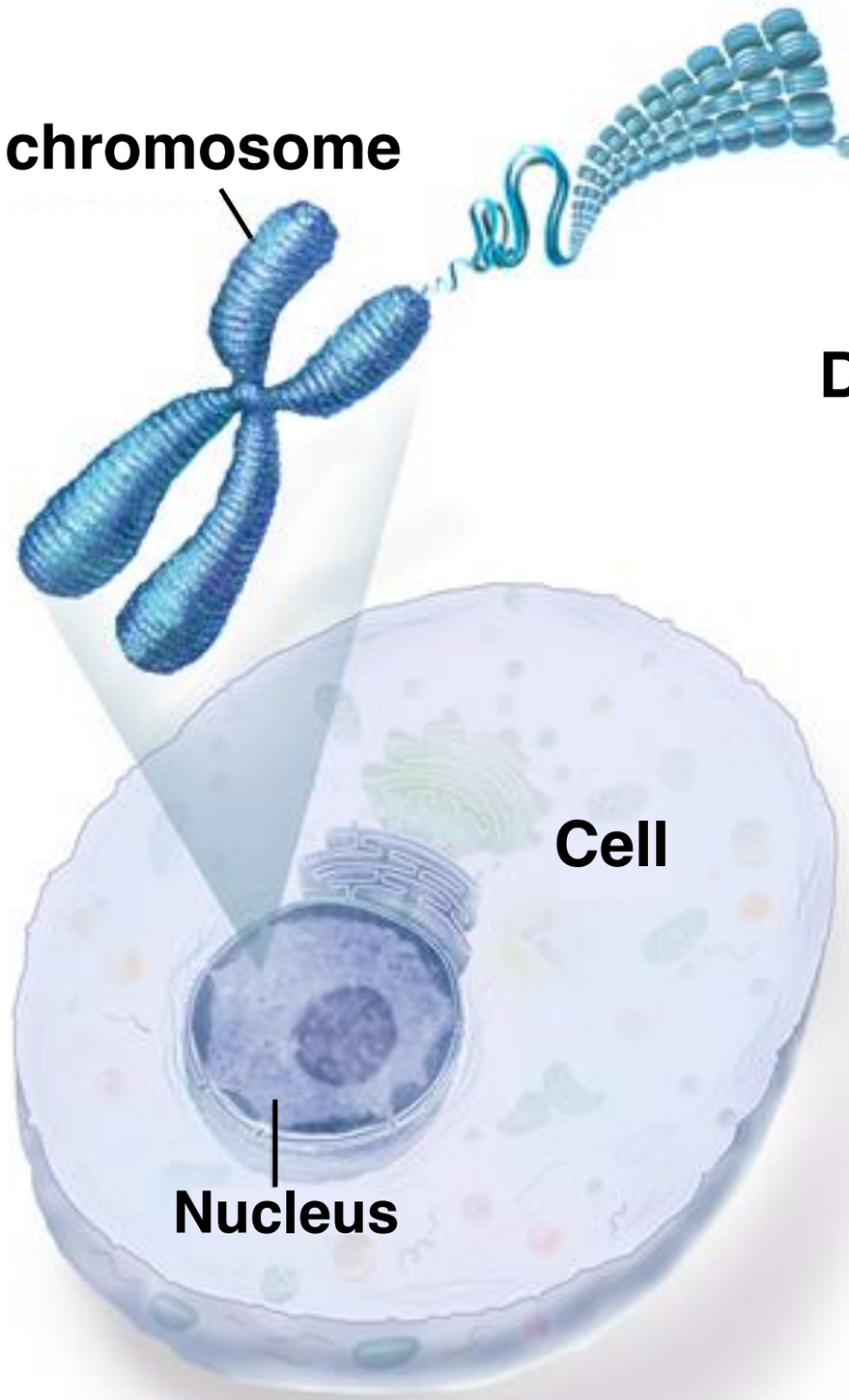
Alzheimer's disease

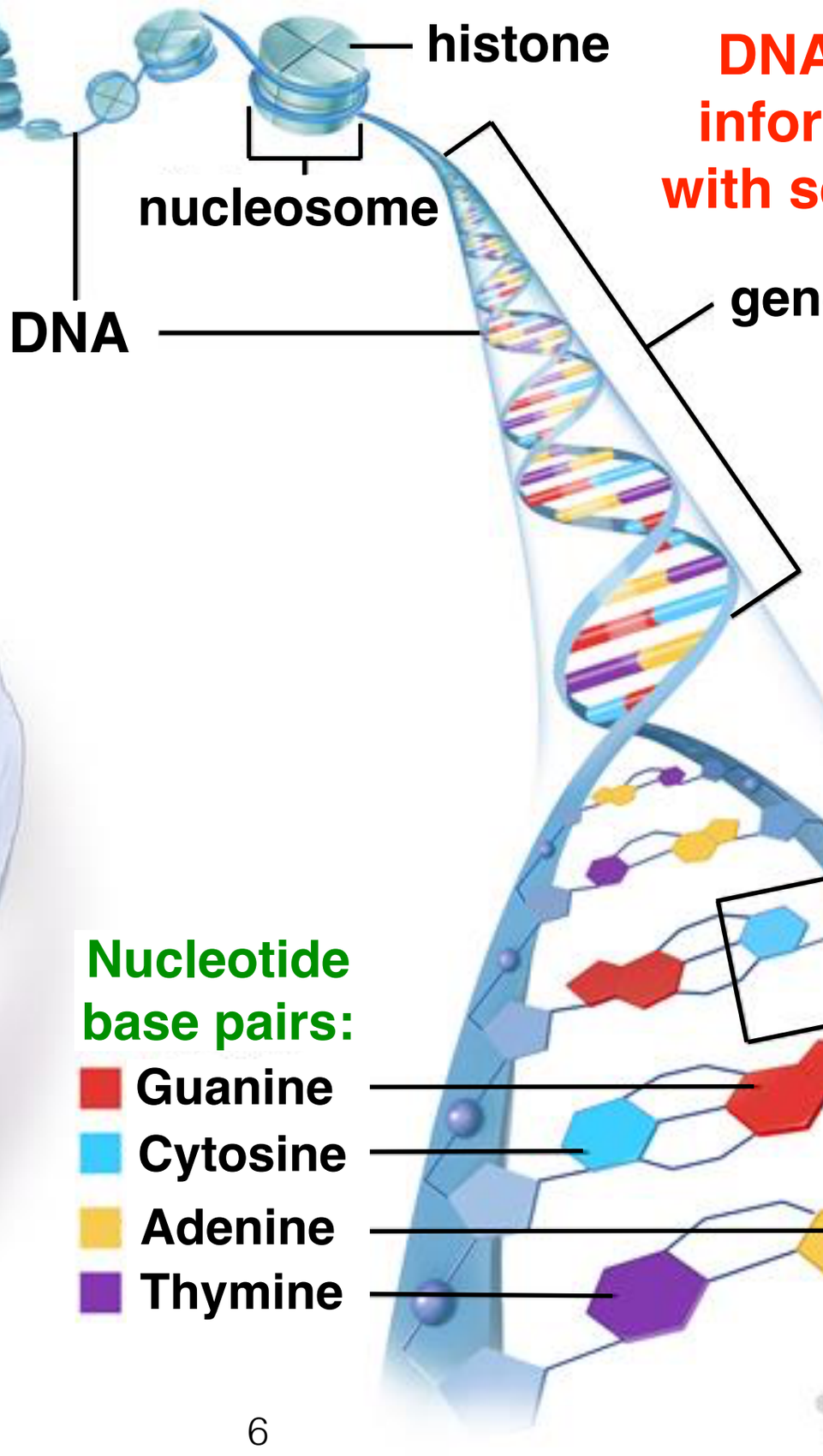






DNA structure





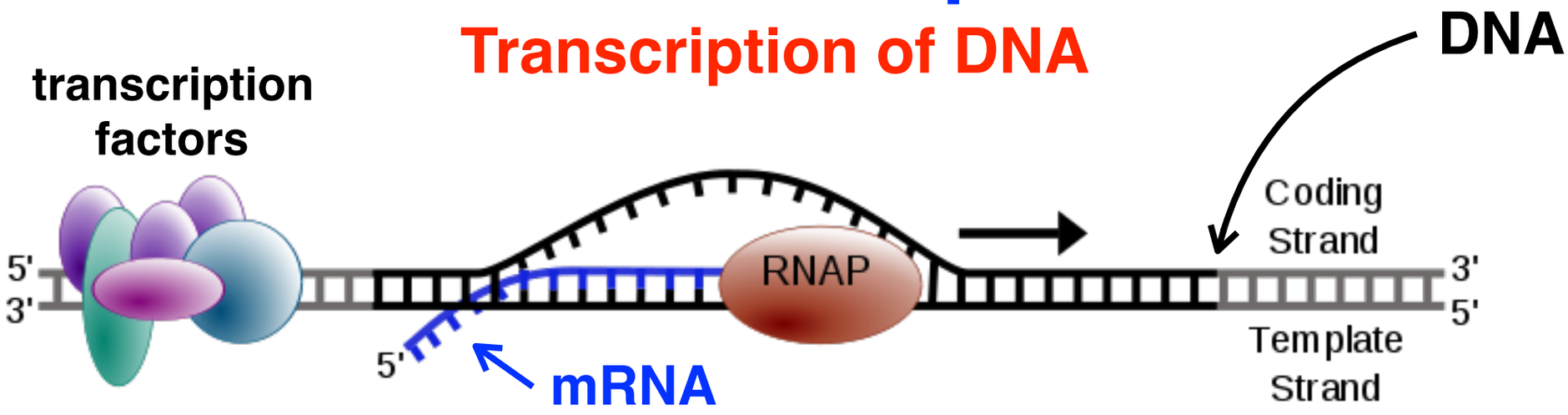
DNA stores genetic information encoded with sequence of bases

Nucleotide base pairs:

- Guanine
- Cytosine
- Adenine
- Thymine

Production of new proteins

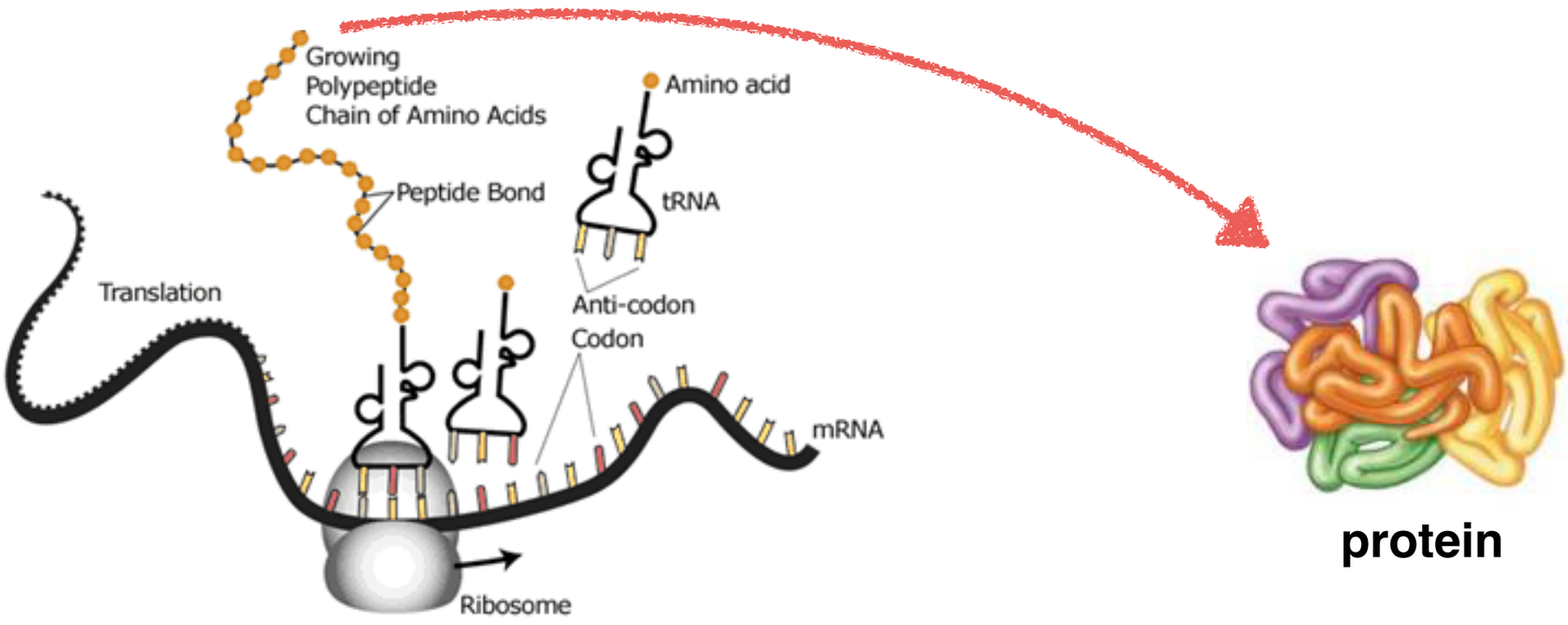
Transcription of DNA



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.

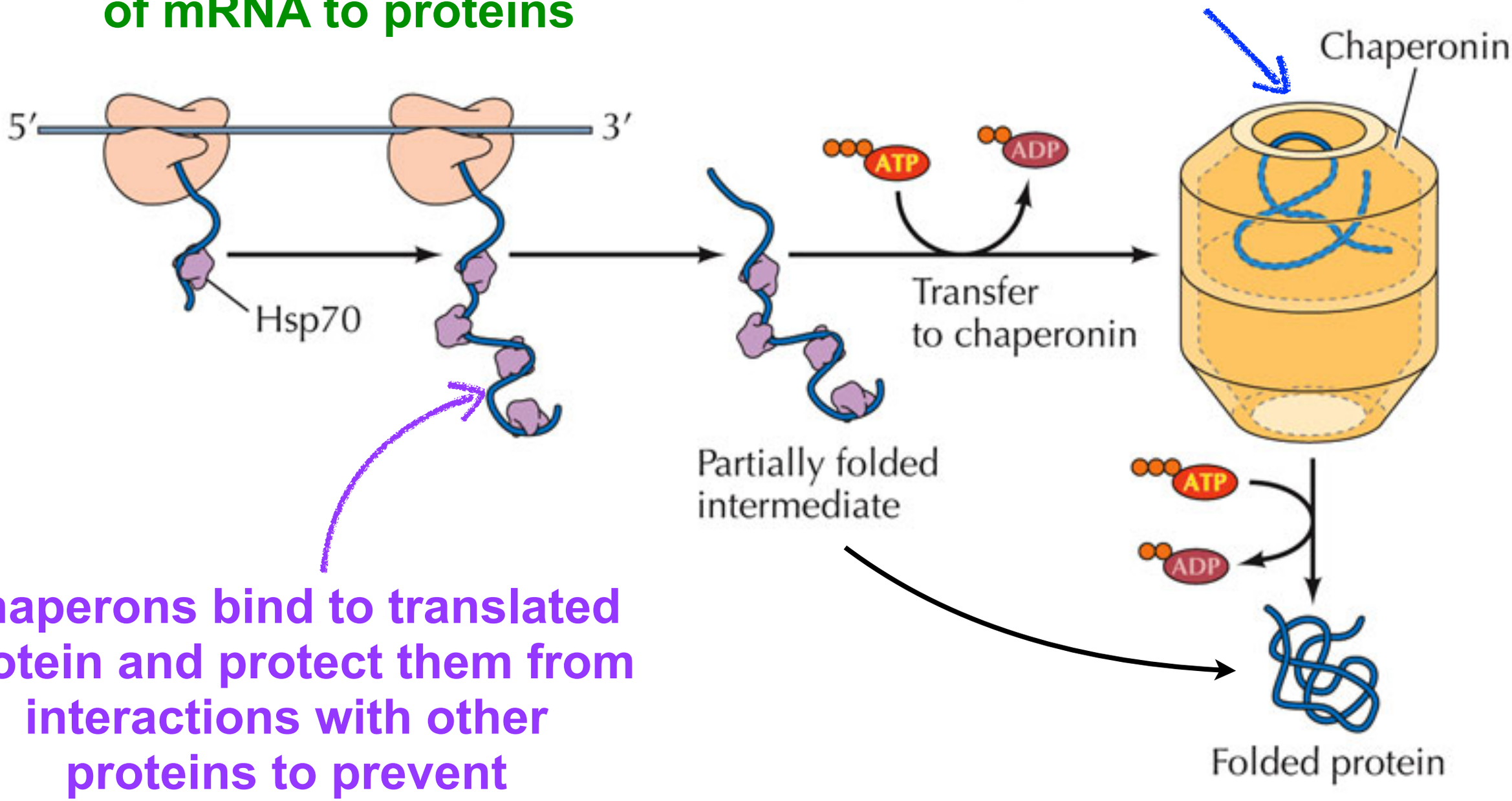
Translation of mRNA



Chaperons assist with protein folding and prevent protein aggregation

ribosome translation of mRNA to proteins

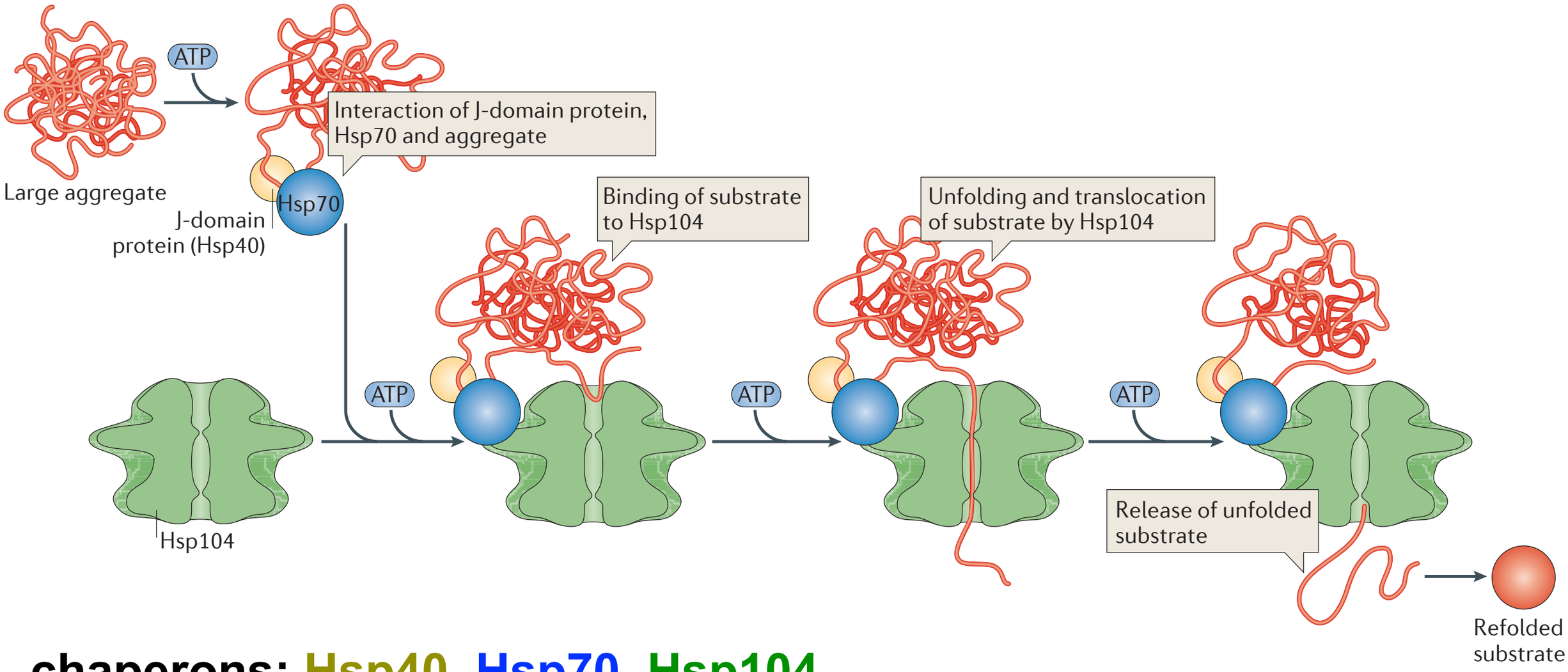
isolated proteins in chaperonin chambers fold into their compact native state



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

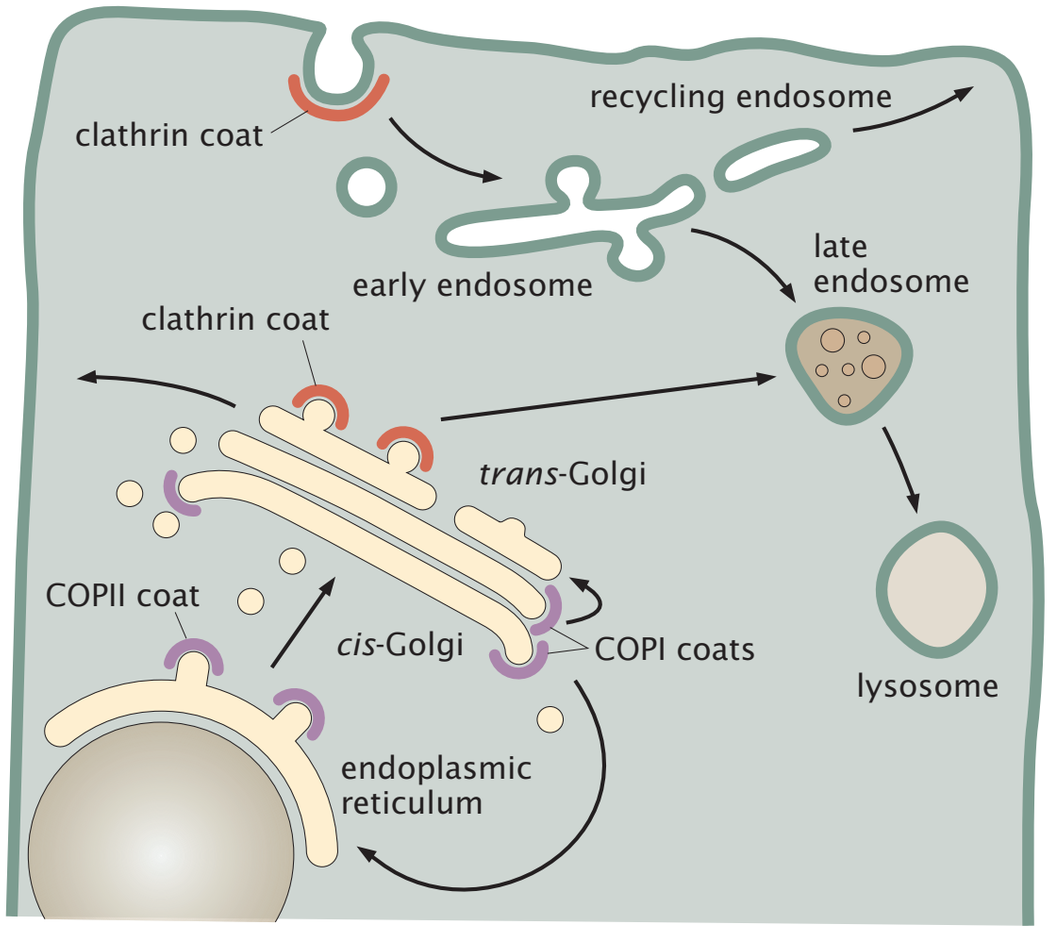


chaperons: Hsp40, Hsp70, Hsp104

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

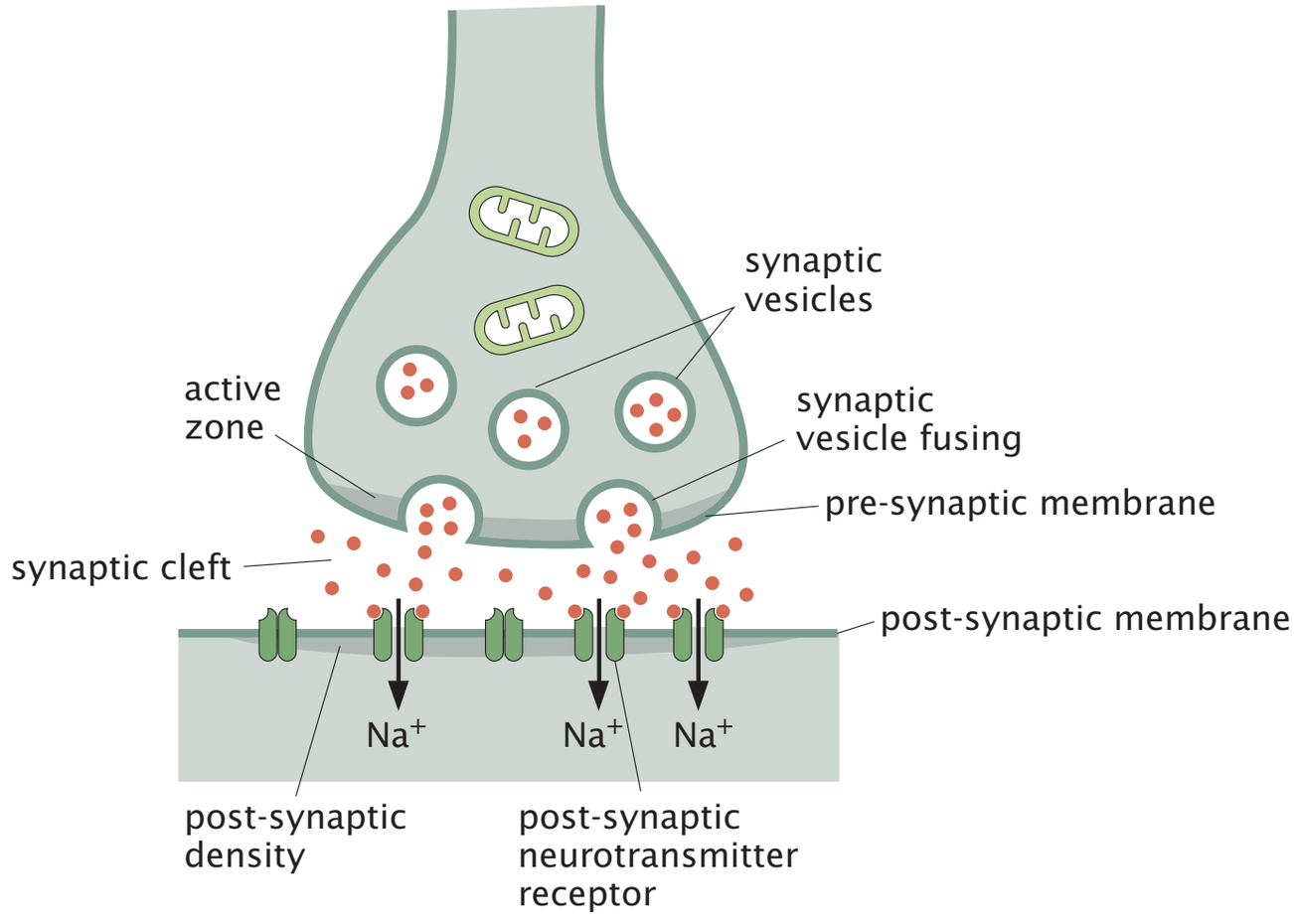
S. M. Doyle *et al.*, Nat. Rev. Mol. Cell Biol. **14**, 617 (2013)

Small vesicles are used for cellular transport of molecules



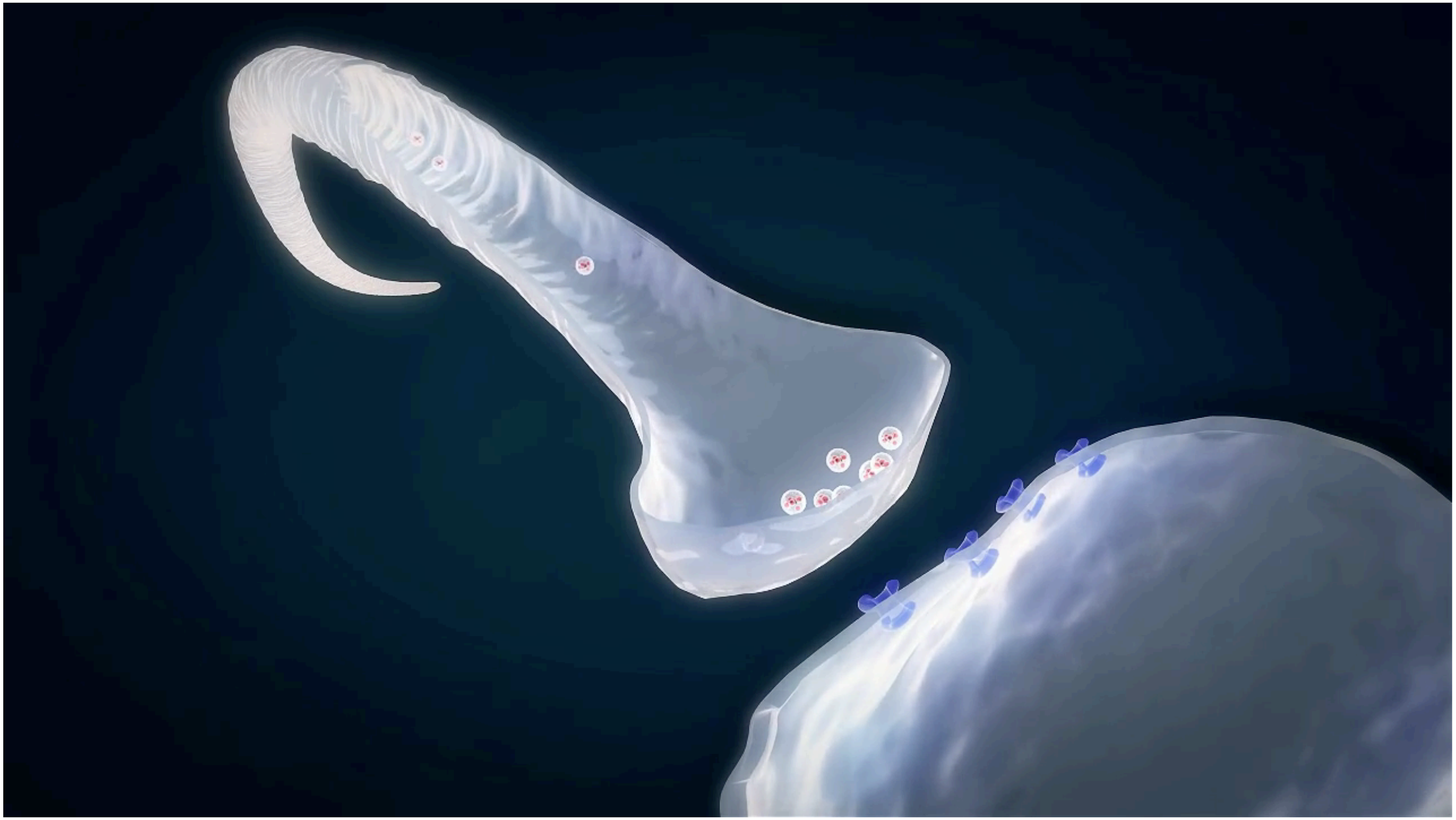
Vesicles are changing membrane topology!

transport of neurotransmitters in neuron cells



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

Transport of neurotransmitters in neuron cells



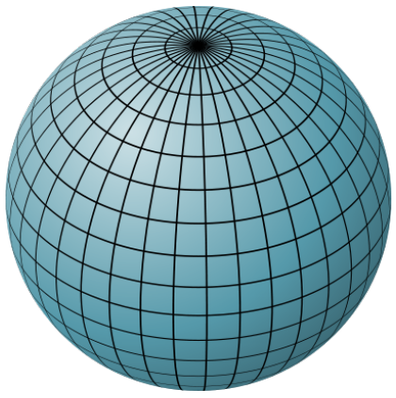
https://www.youtube.com/watch?v=FqTSYHtyHWE

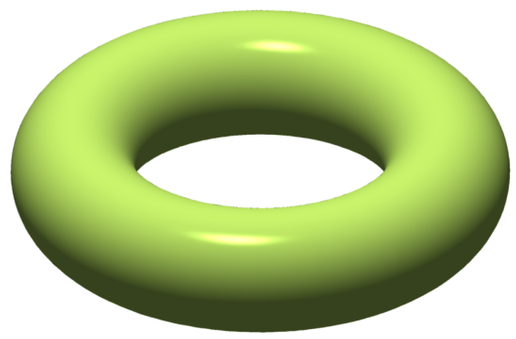
Gauss-Bonet theorem

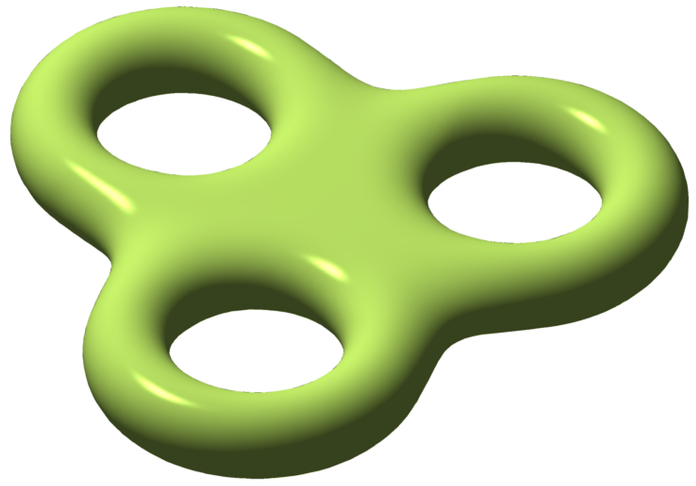
For closed surfaces the integral over Gaussian curvature only depends on the surface topology!

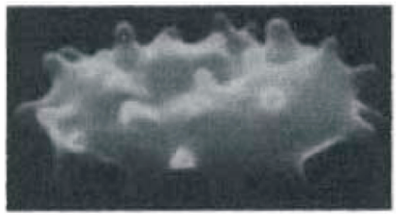
$$\int \frac{dA}{R_1 R_2} = 4\pi\,(1-g)$$

$g = 0$ $g = 1$ $g = 2$ $g = 3$





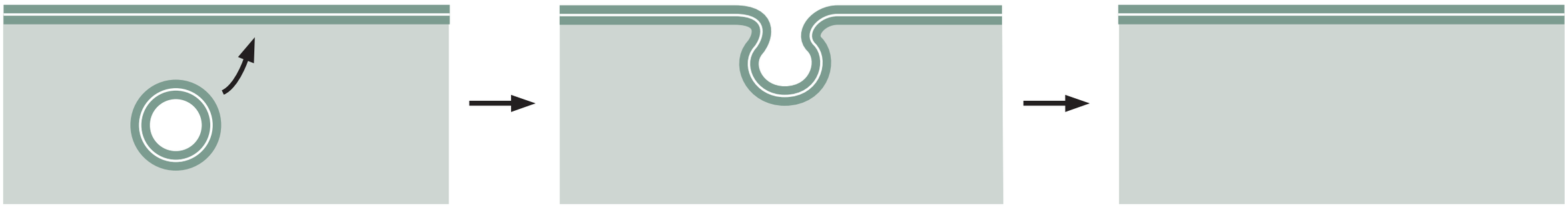




Creation of new vesicles or fusion of vesicles modifies the genus *g!*

Vesicle fusion with membrane

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



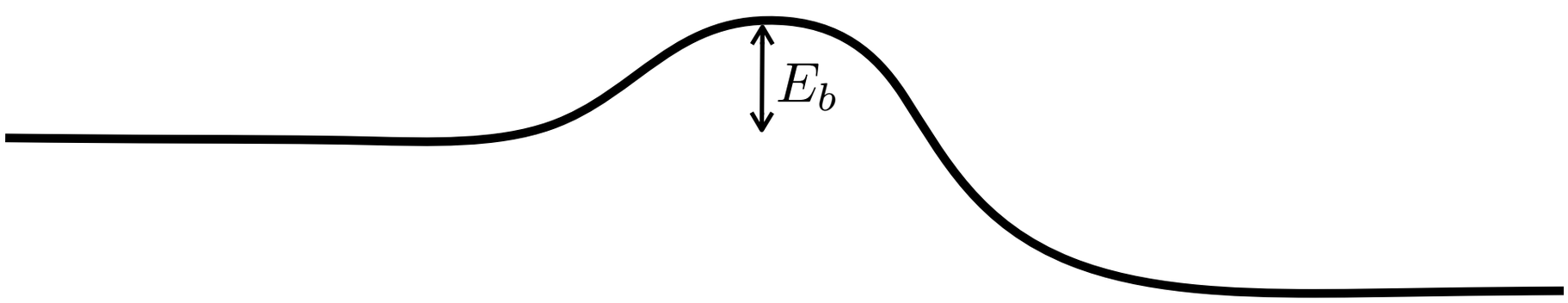
$E = 4\pi (2\kappa + \kappa_G)$

$E \sim +300 k_B T$

$E \approx 8\pi\kappa$

$E \sim +500 k_B T$

$E = 0$



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:

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

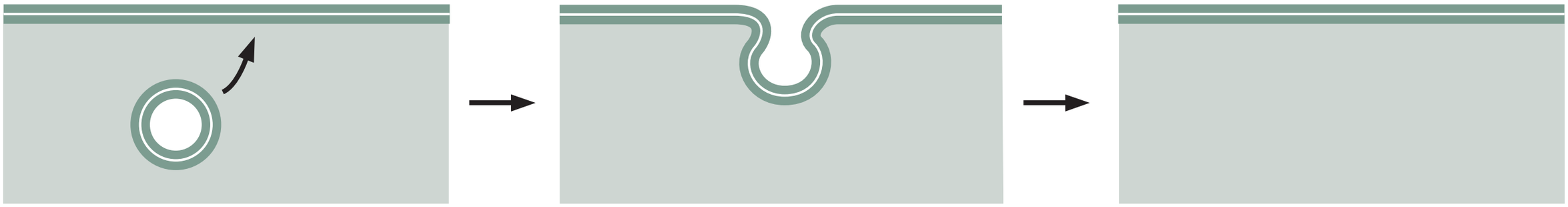
E_b **height of energy barrier**

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!

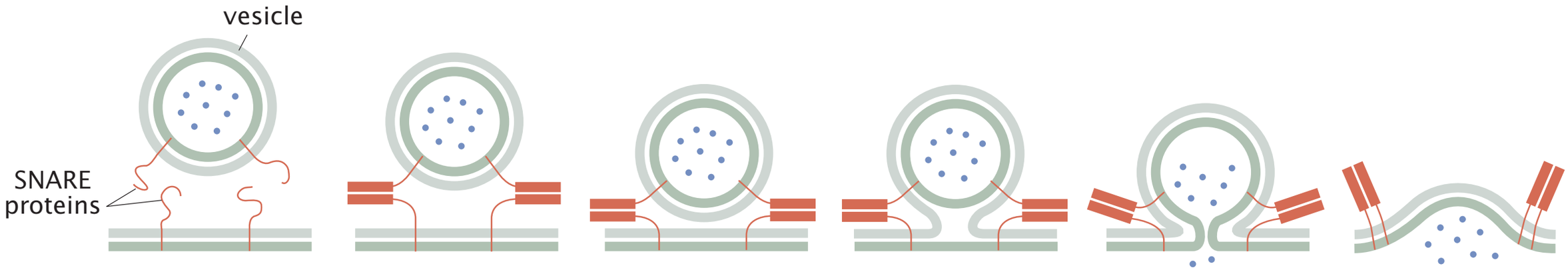


$$E = 4\pi\left(2\kappa + \kappa_G\right)$$
$$E \sim +300 k_B T$$

$$E \approx 8\pi\kappa$$
$$E \sim +500 k_B T$$

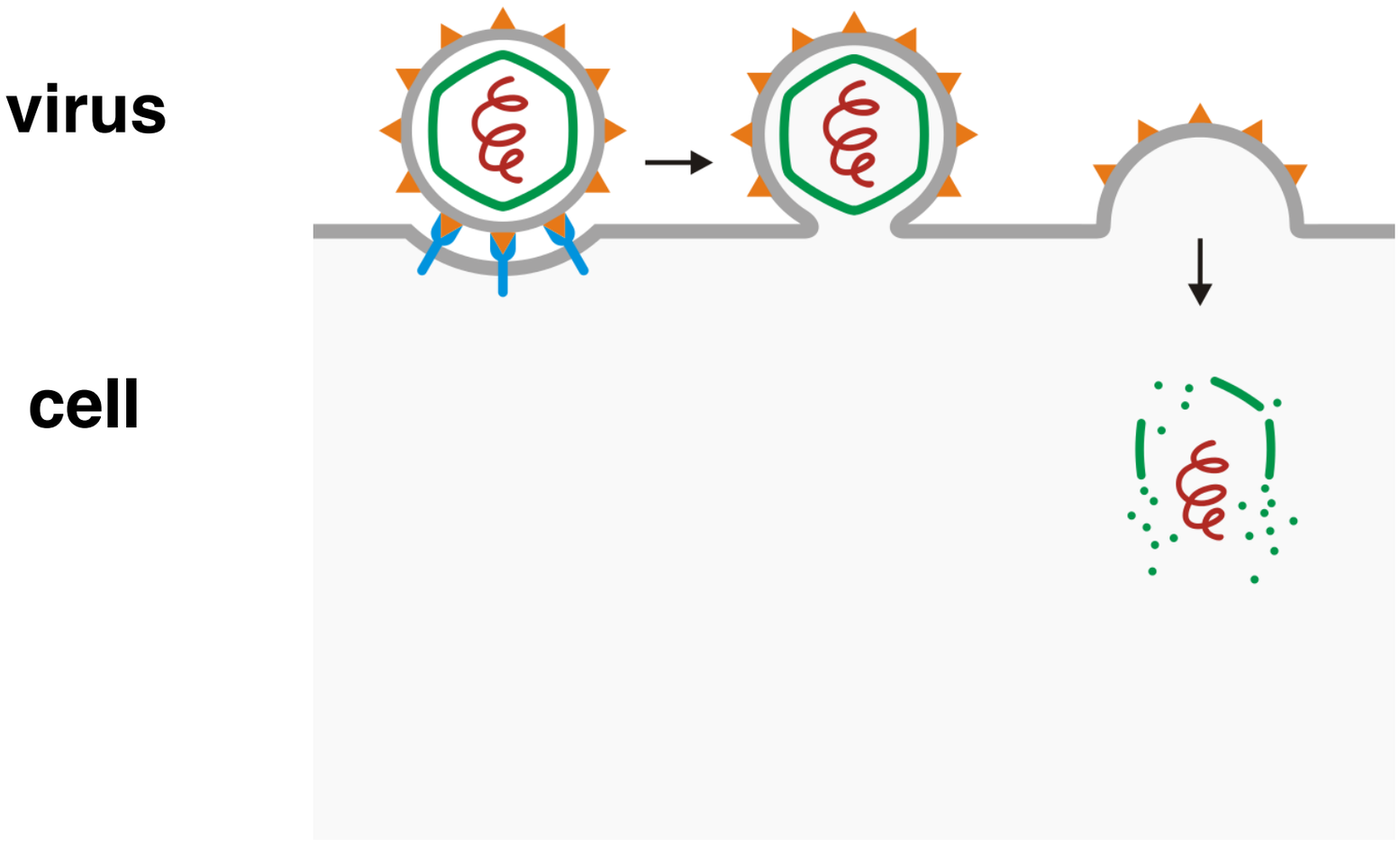
$$E = 0$$

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



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

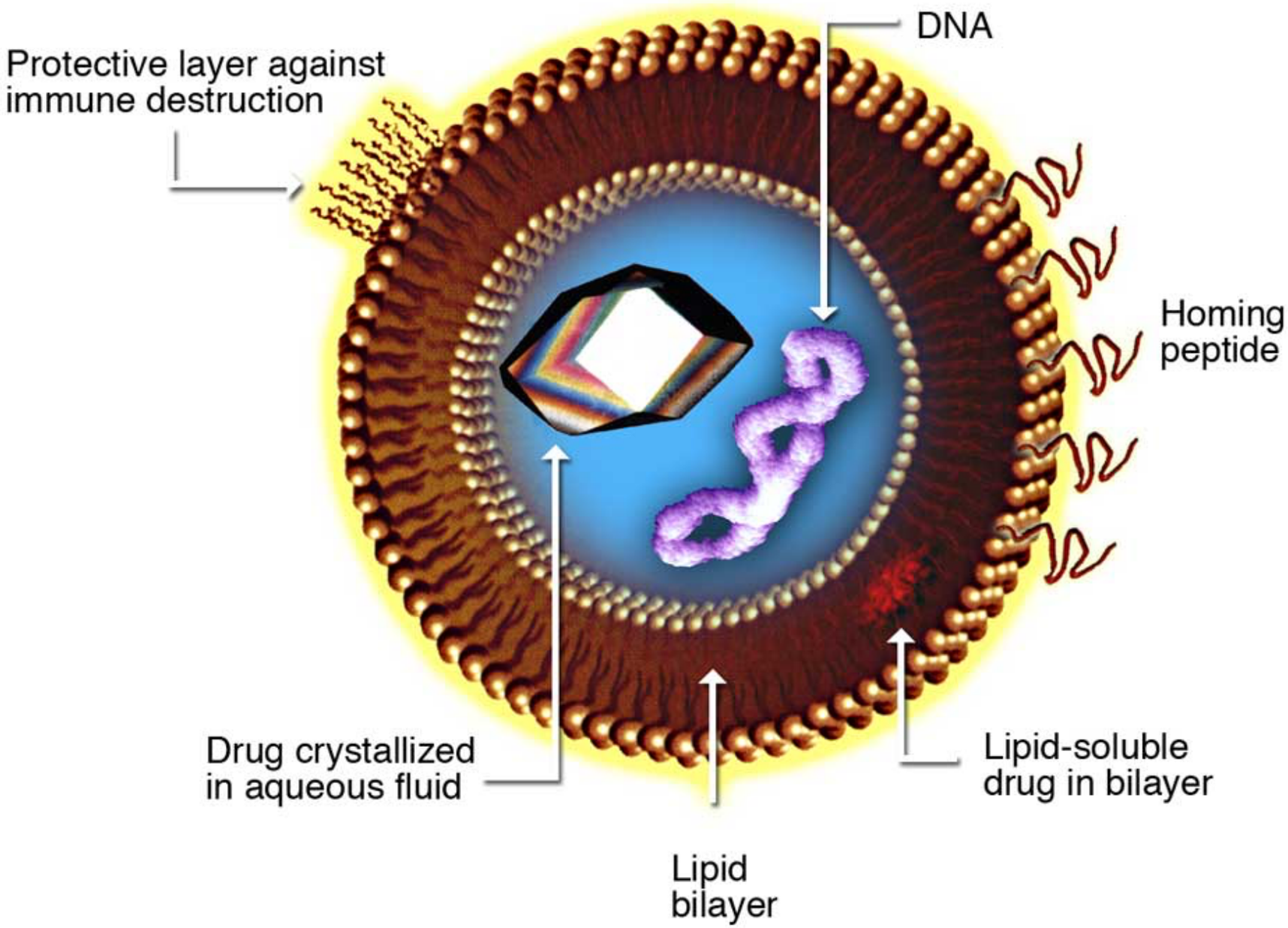
Viral entry to cell via receptor mediated membrane fusion



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