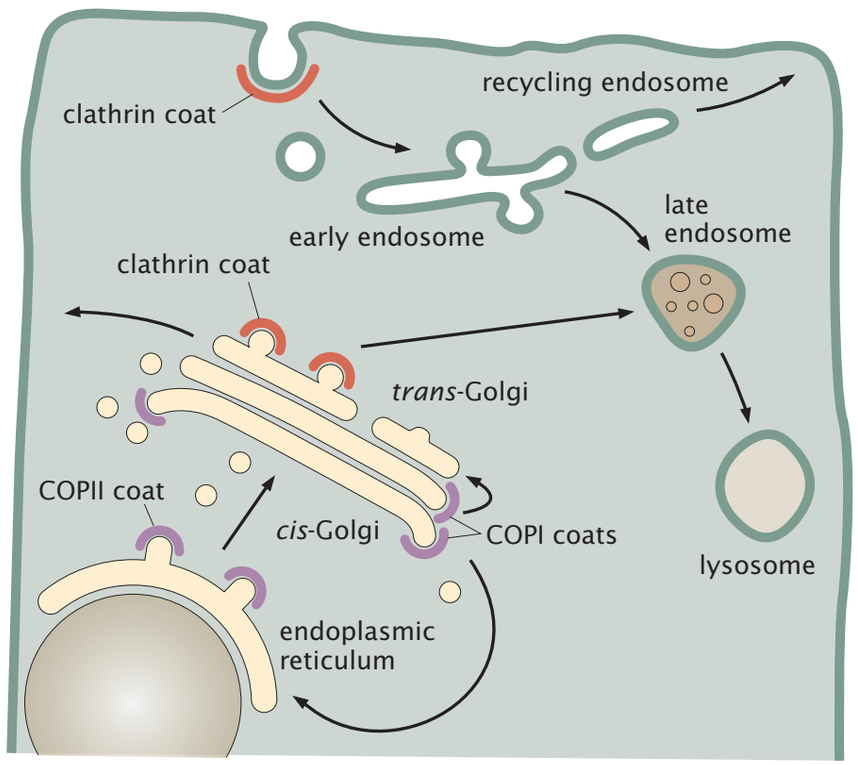
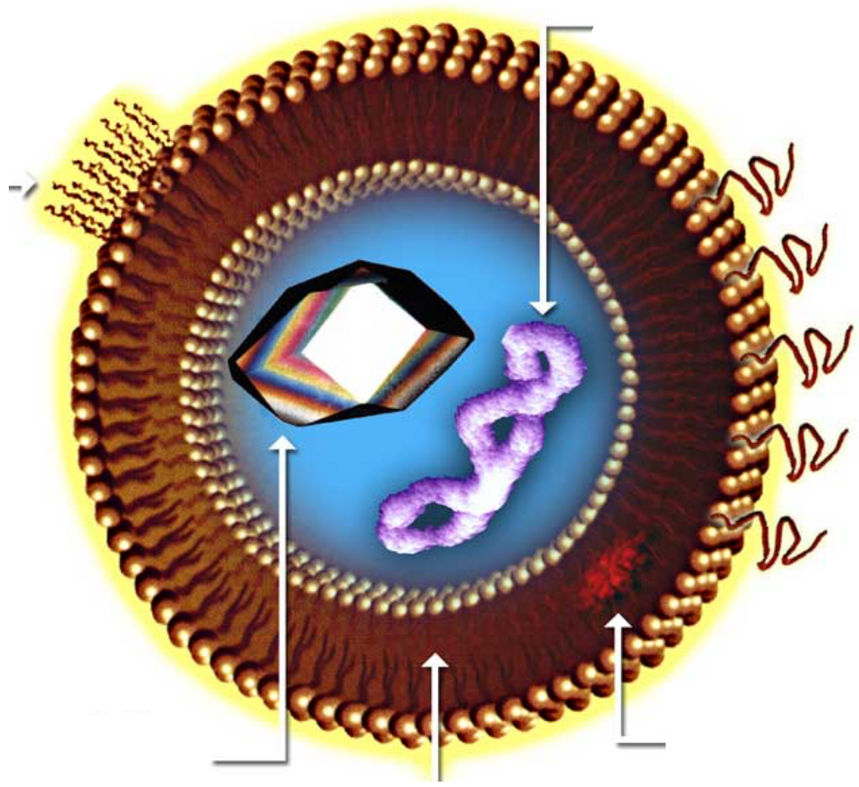
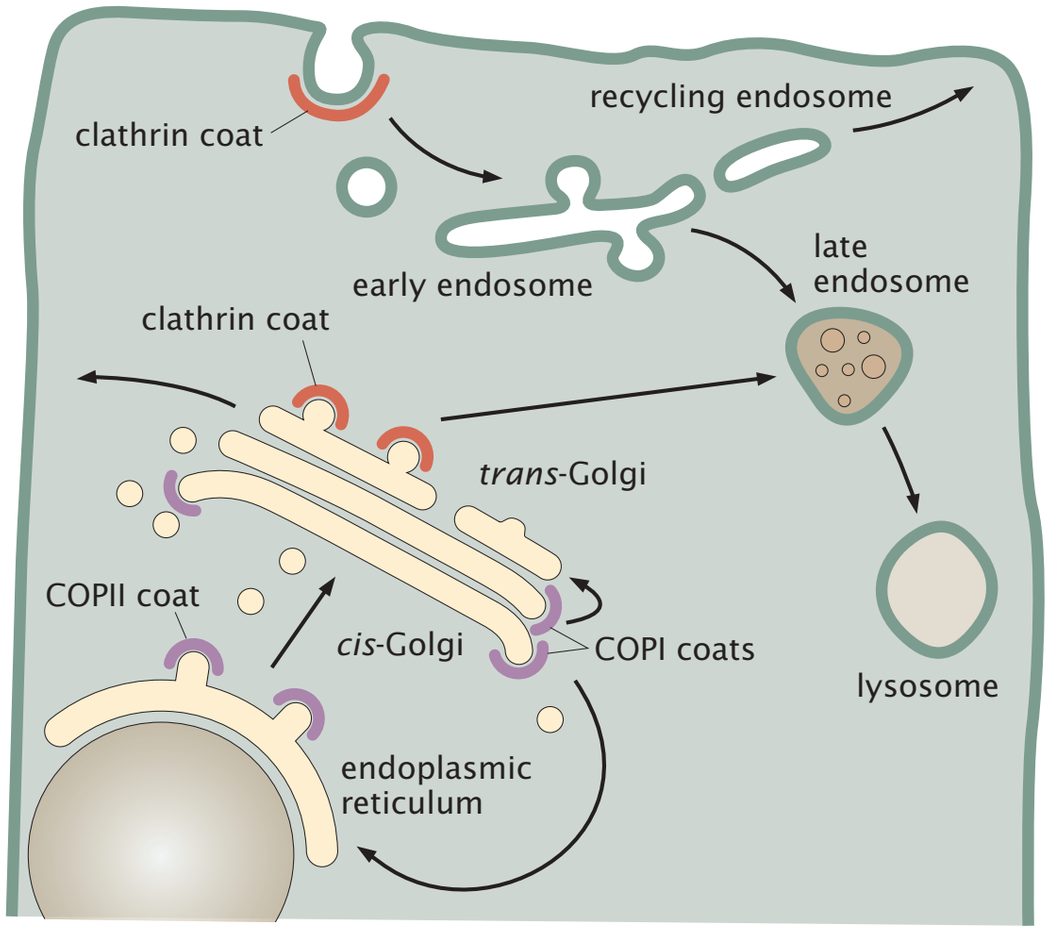
MAE 545: Lecture 16 (4/5)

Cellular transport via vesicles, viral entry into cells and drug delivery



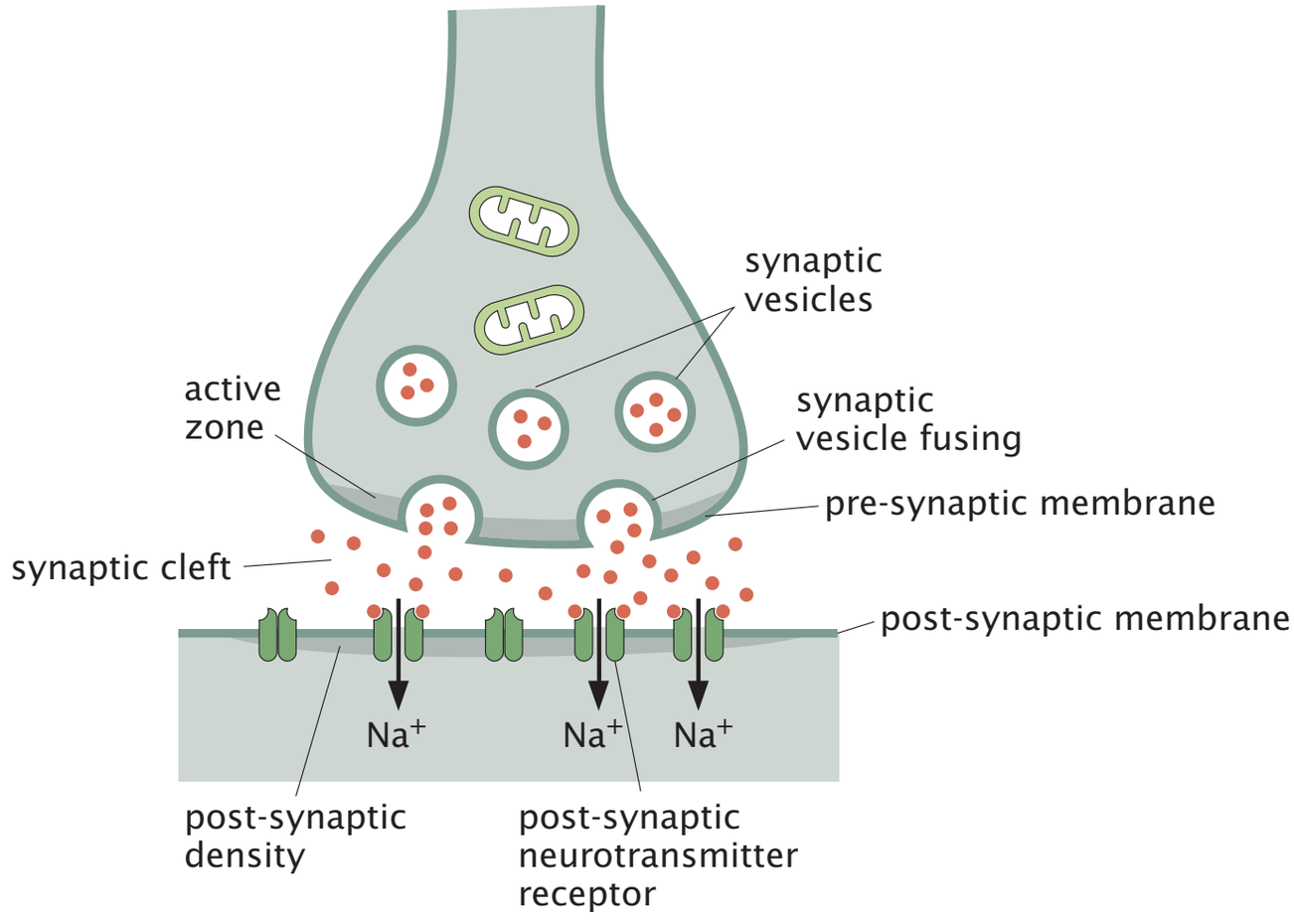


Small vesicles are used for cellular transport of molecules



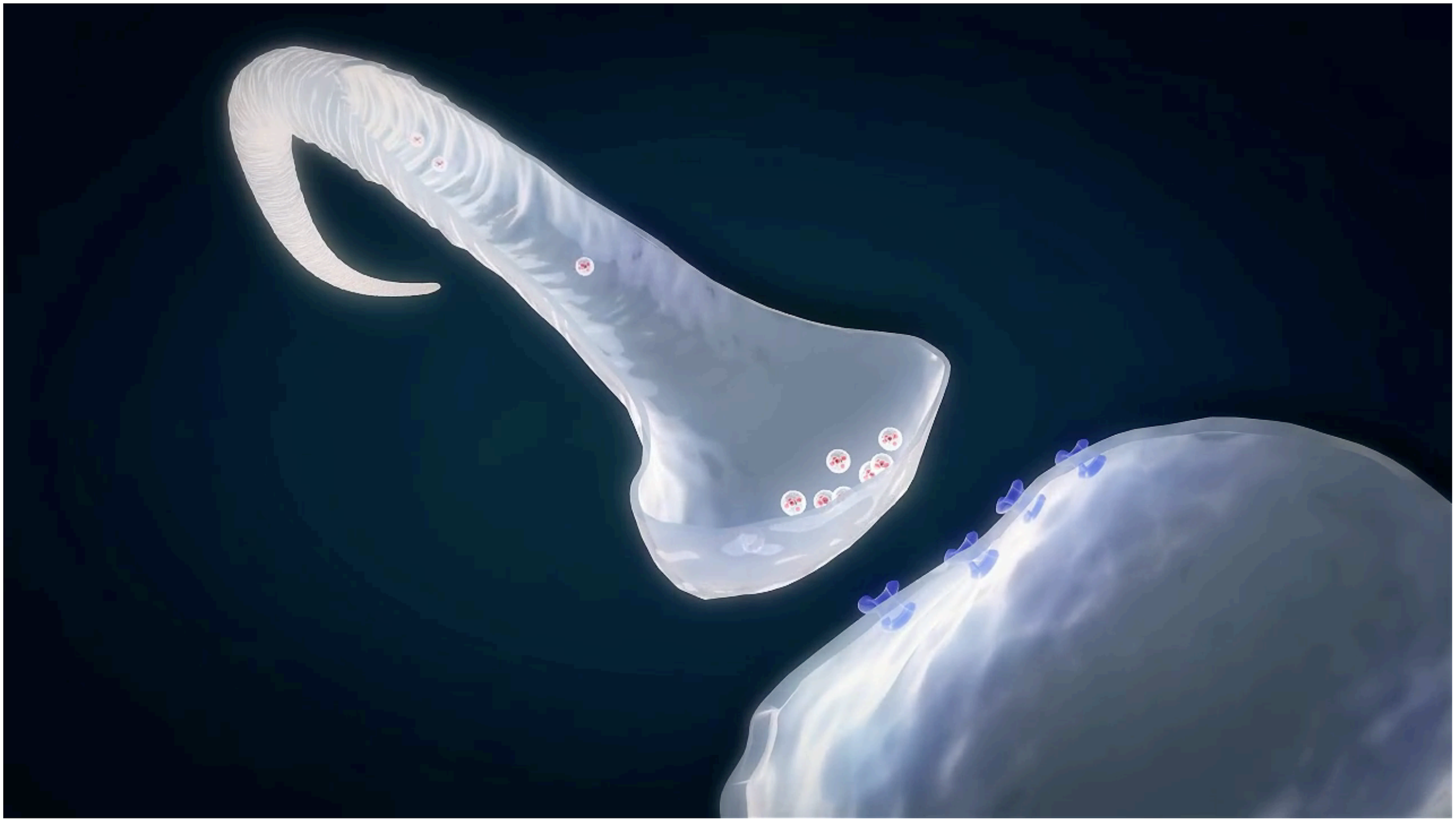
Vesicles are changing membrane topology!

transport of neurotransmitters in neuron cells



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

Transport of neurotransmitters in neuron cells



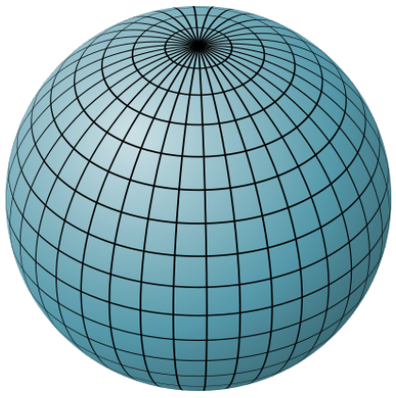
https://www.youtube.com/watch?v=FqTSYHtyHWE

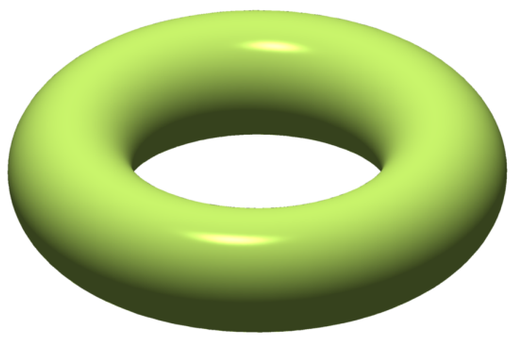
Gauss-Bonet theorem

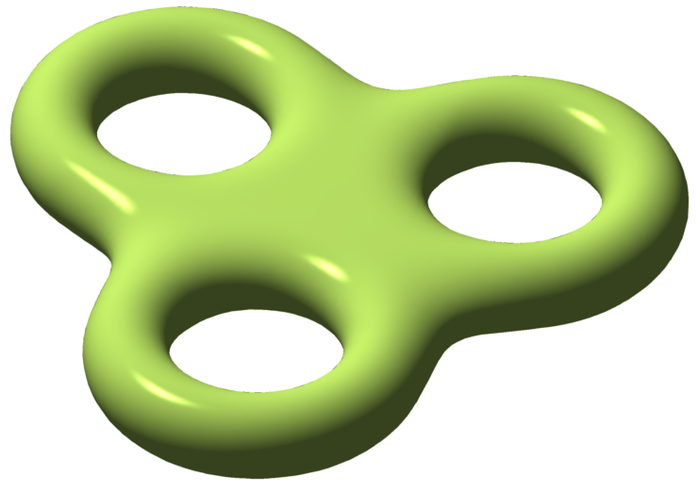
For closed surfaces the integral over Gaussian curvature only depends on the surface topology!

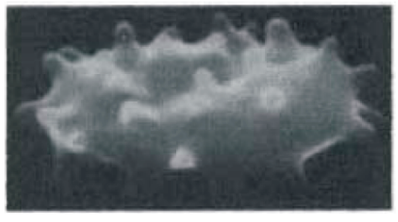
$$\int \frac{dA}{R_1 R_2} = 4\pi\,(1-g)$$

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









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

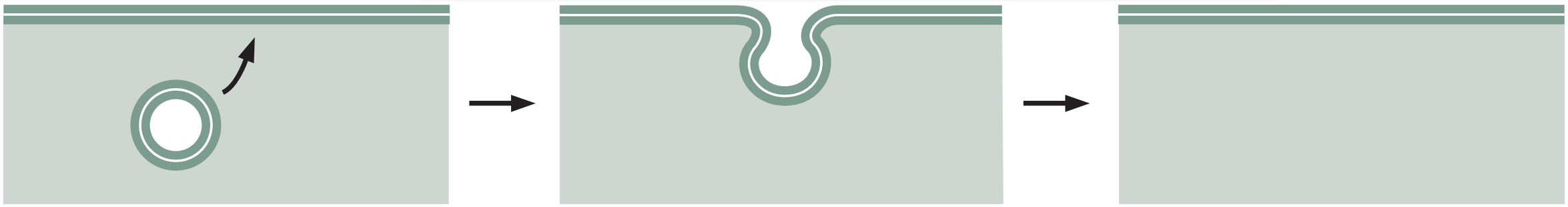
Vesicle fusion with membrane

Bending energy:

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

$\kappa \sim 20 k_B T$

$\kappa_G \sim -0.8\kappa$



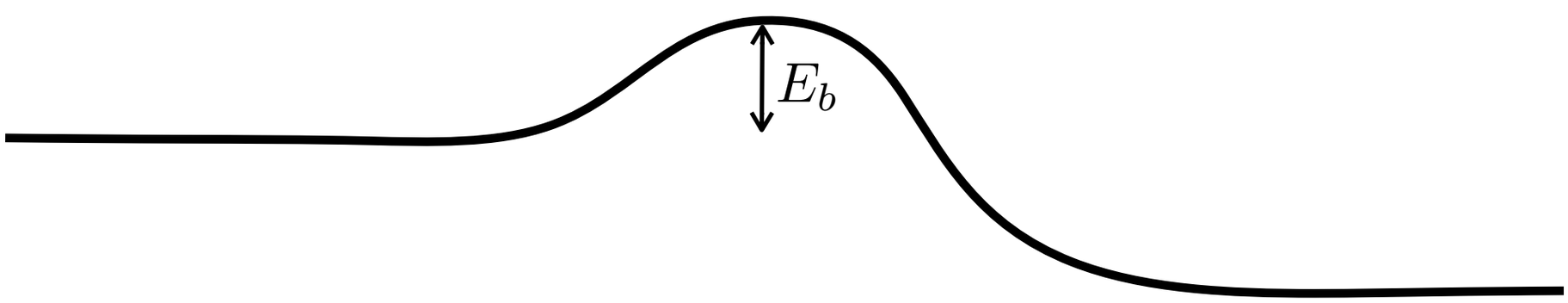
$E = 4\pi (2\kappa + \kappa_G)$

$E \sim +300 k_B T$

$E \approx 8\pi\kappa$

$E \sim +500 k_B T$

$E = 0$



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**

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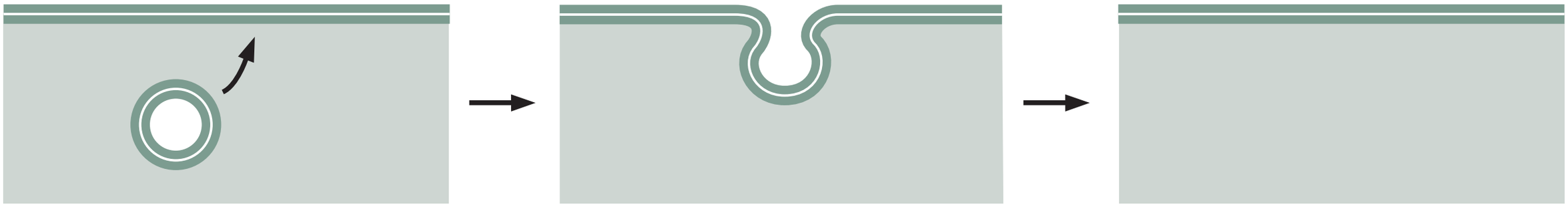
Vesicle fusion with membrane

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

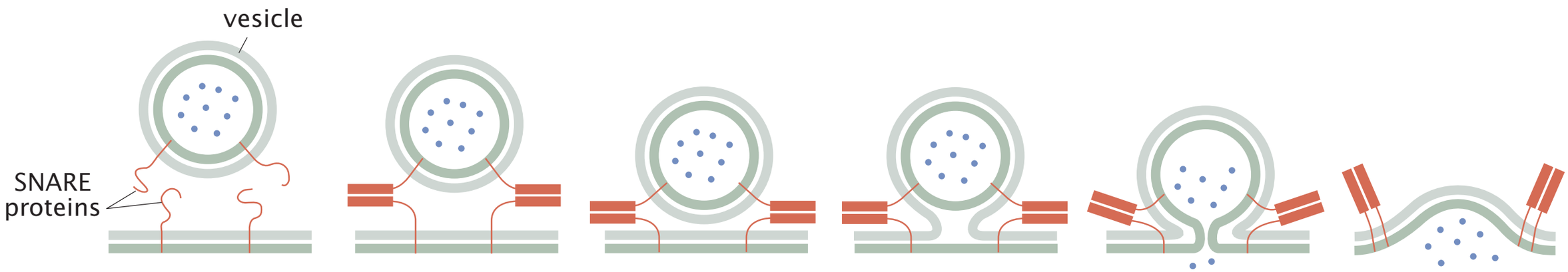


$$E = 4\pi\left(2\kappa + \kappa_G\right)$$
$$E \sim +300 k_B T$$

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

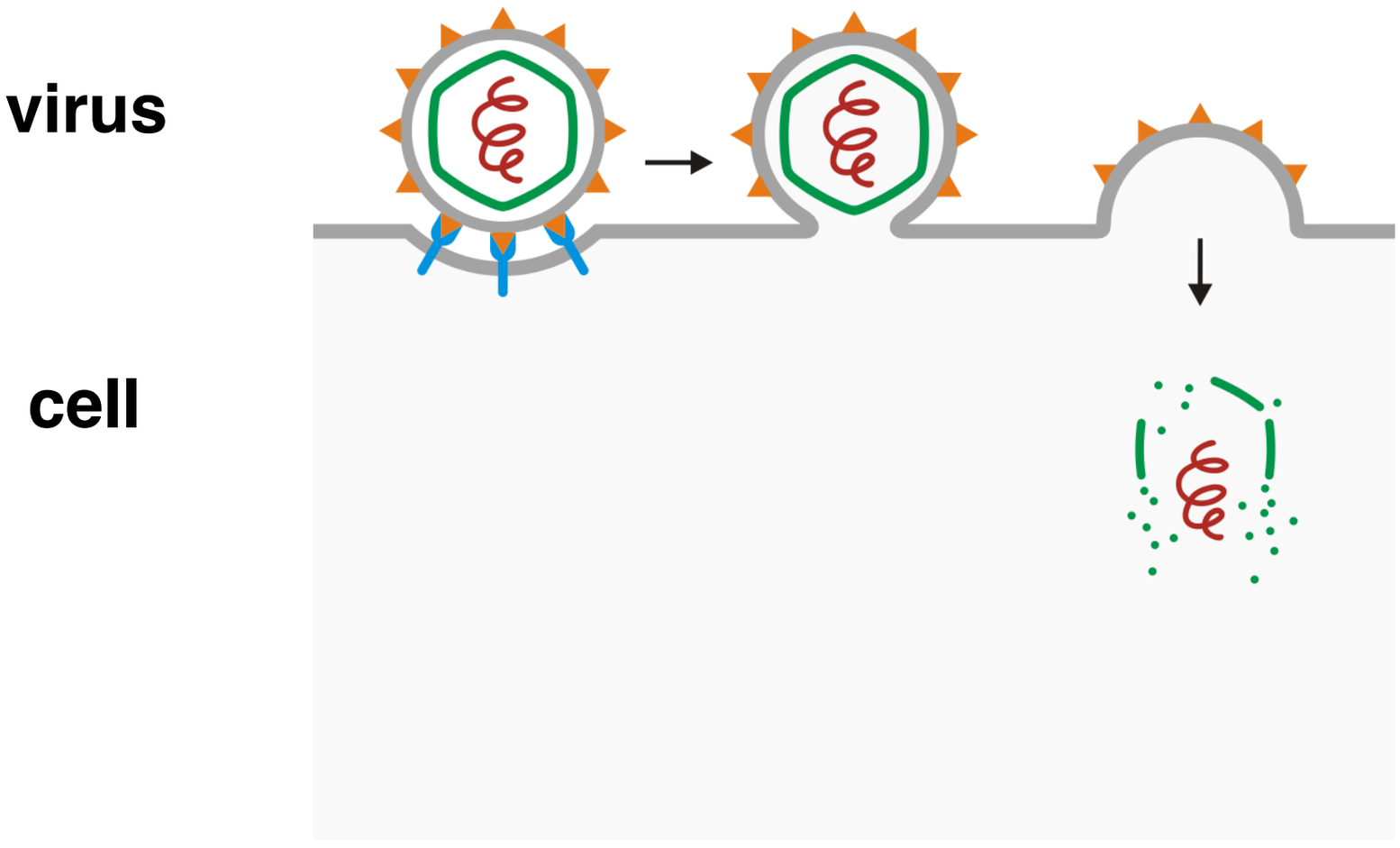
$$E = 0$$

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



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

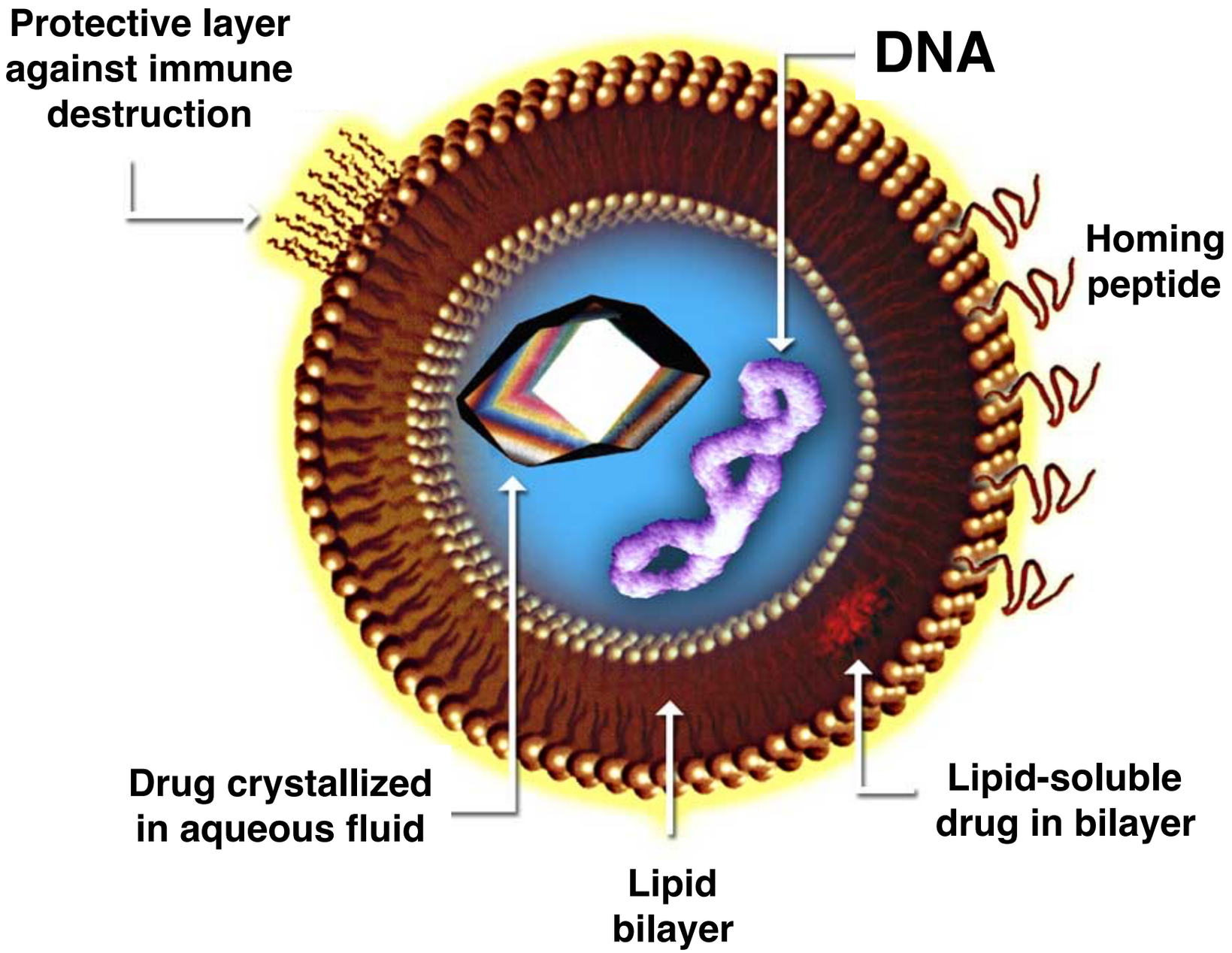
Viral entry to cell via receptor mediated membrane fusion



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

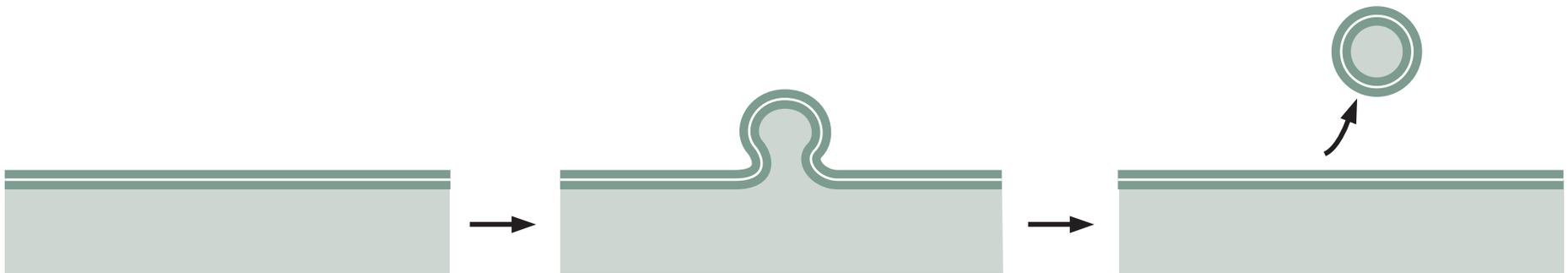


Targeted delivery to specific cells is achieved via binding of peptides to receptors expressed on the surface of target cells.

Wikipedia

Membrane budding

Creation of new vesicles costs energy!



$E = 0$

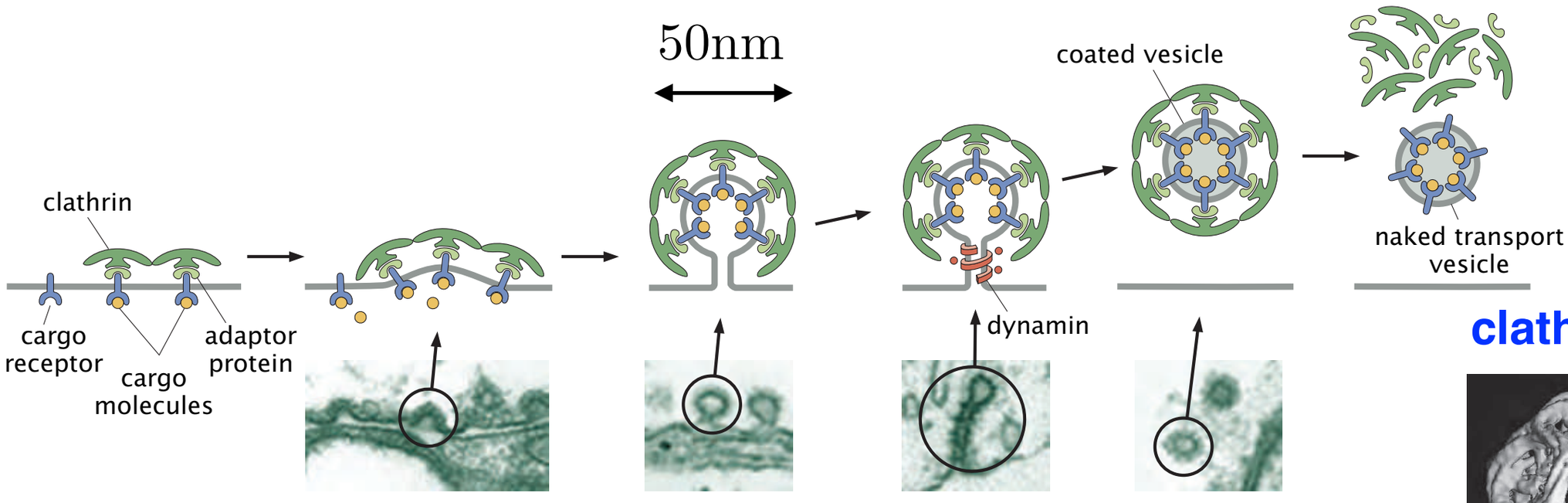
$E \approx 8\pi\kappa$

$E \sim +500 k_B T$

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

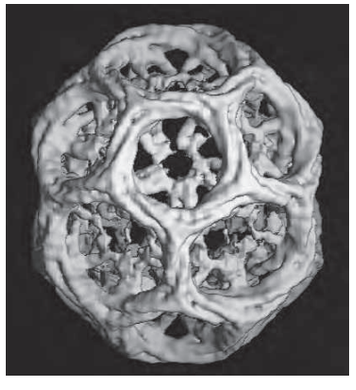
$E \sim +300 k_B T$

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

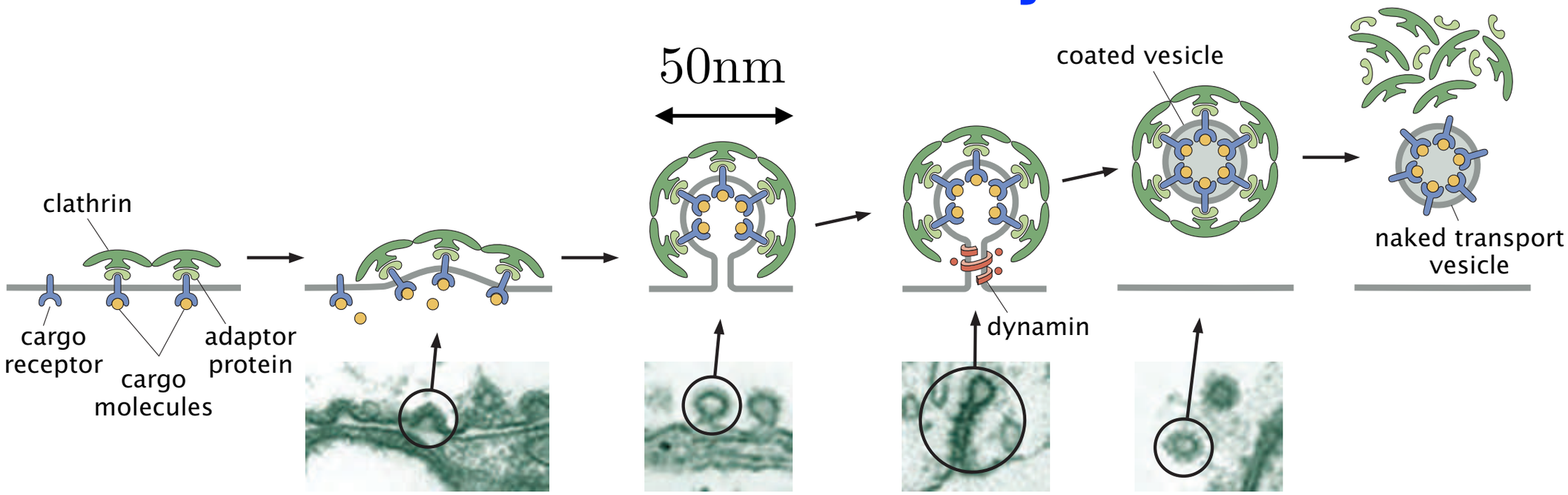


R. Phillips et al., Physical Biology of the Cell

clathrin cage

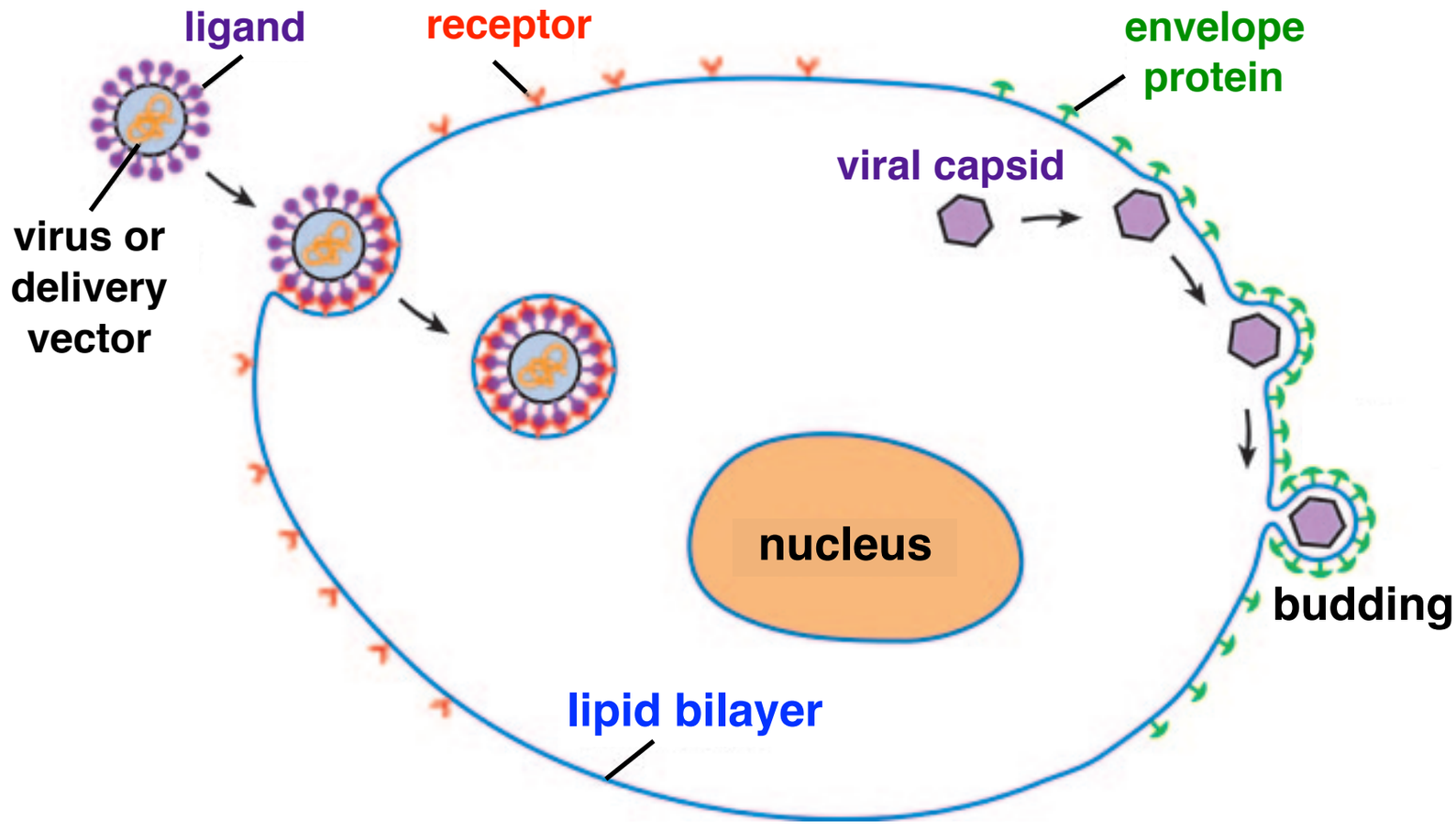


Clathrin-mediated endocytosis



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

Viral entry to cell via receptor mediated endocytosis

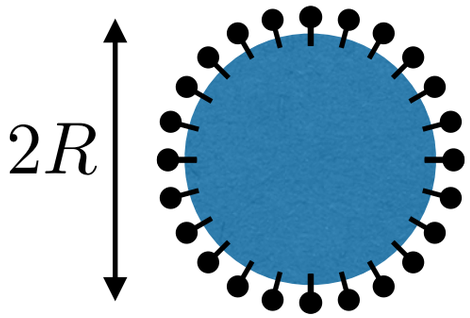


(similar process may help during budding of enveloped viruses)

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



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

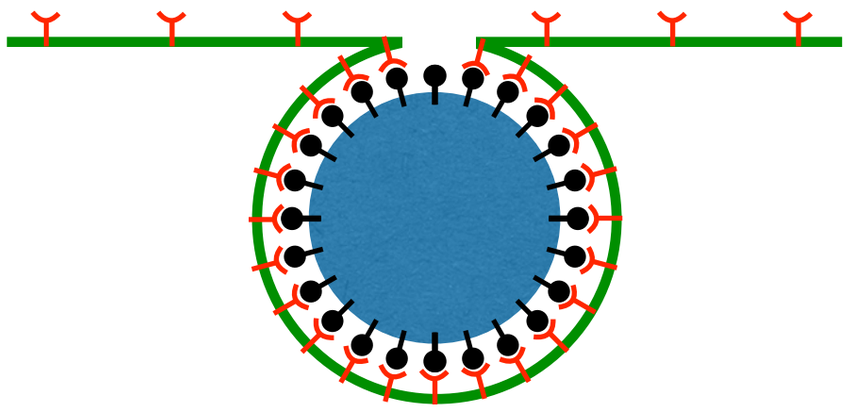
density of ligands

total number of ligands

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

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

density of receptors



bending energy

$E_{\mathrm{bend}} = 0$

$E_{\mathrm{bend}} = 8\pi\kappa$

binding energy of ligand-receptor pairs

$E_{\mathrm{bind}} = 0$

$E_{\mathrm{bind}} = -N_L U_b$

free energy due to mixing of receptors

$G_{\mathrm{mix}} = N k_B T \ln(n_0 A_0)$

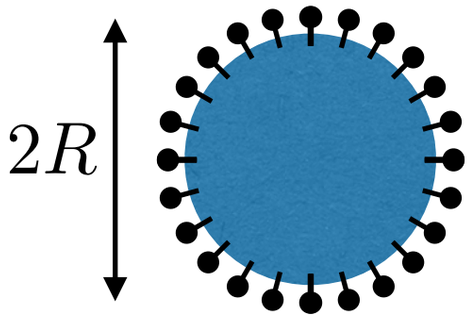
$G_{\mathrm{mix}} = (N - N_L) k_B T \ln(n_0 A_0) + N_L k_B T \ln(n_L A_0)$

total change of free energy

$$\Delta G = 8\pi\kappa - N_L U_b + N_L k_B T \ln(n_L/n_0)$$

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

Viral entry to cell via receptor mediated endocytosis



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

density of ligands

total number of ligands

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

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

density of receptors

receptor-ligand binding energy

$U_b \sim 15 k_B T$

bending rigidity

$\kappa \sim 20 k_B T$

total change of free energy

$$\Delta G = 8\pi\kappa - 4\pi R^2 n_L U_b + 4\pi R^2 k_B T n_L \ln(n_L/n_0)$$

Receptor mediated endocytosis is thermodynamically favorable when $\Delta G < 0$

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

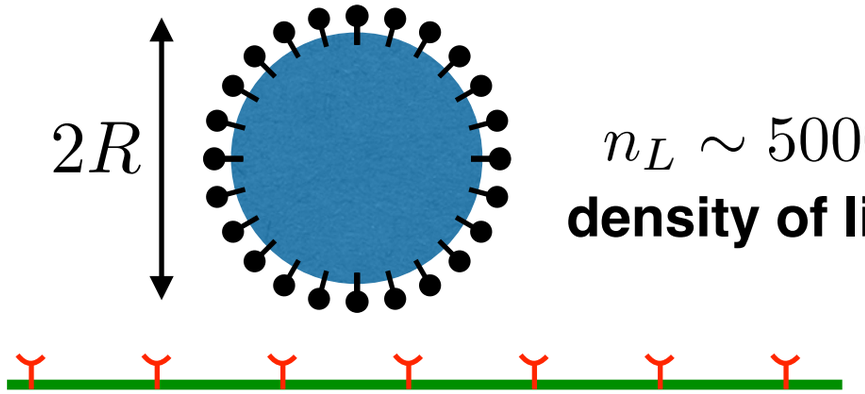
H. Gao *et al.*, PNAS **102**, 9469 (2005)

How fast is this process?

Viral entry to cell via receptor mediated endocytosis

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

Side view:

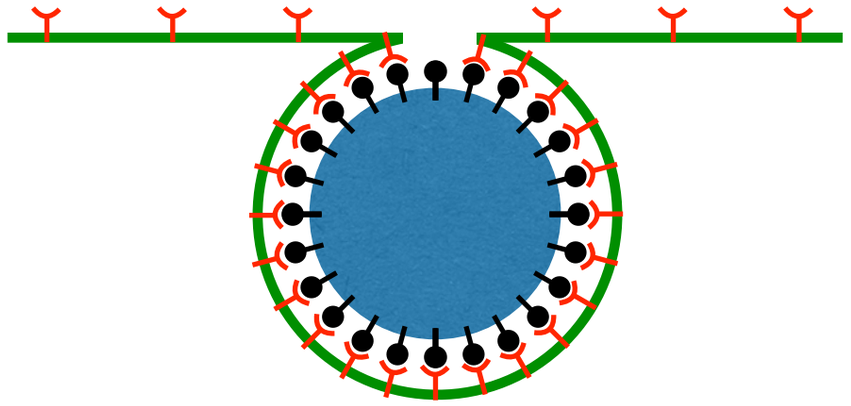


$n_L \sim 5000 \mu\mathrm{m}^{-2}$

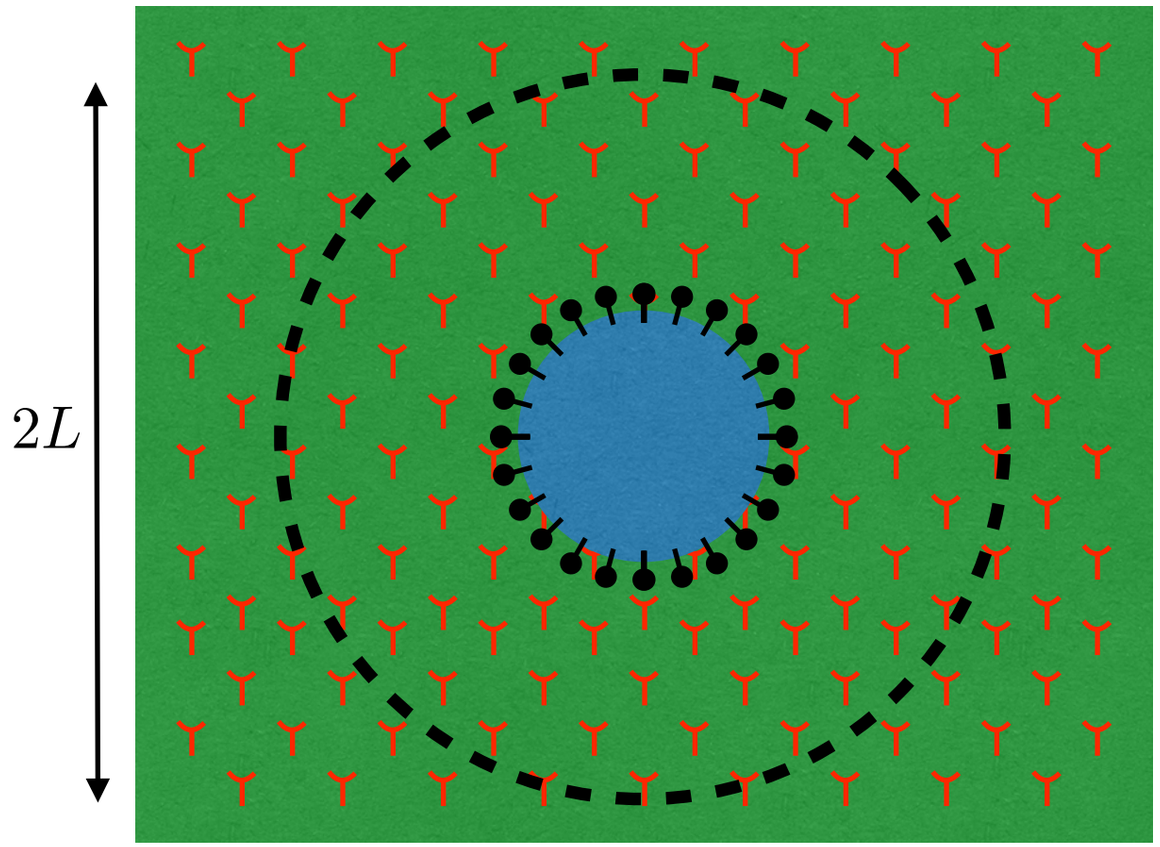
density of ligands

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

density of receptors



Top view:



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

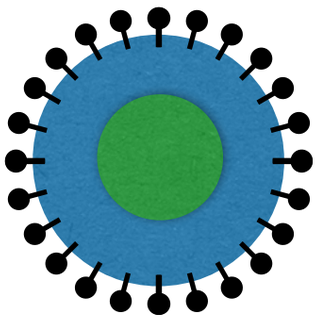
Need to recruit N_L receptors from circular region of radius L via diffusion

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

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

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

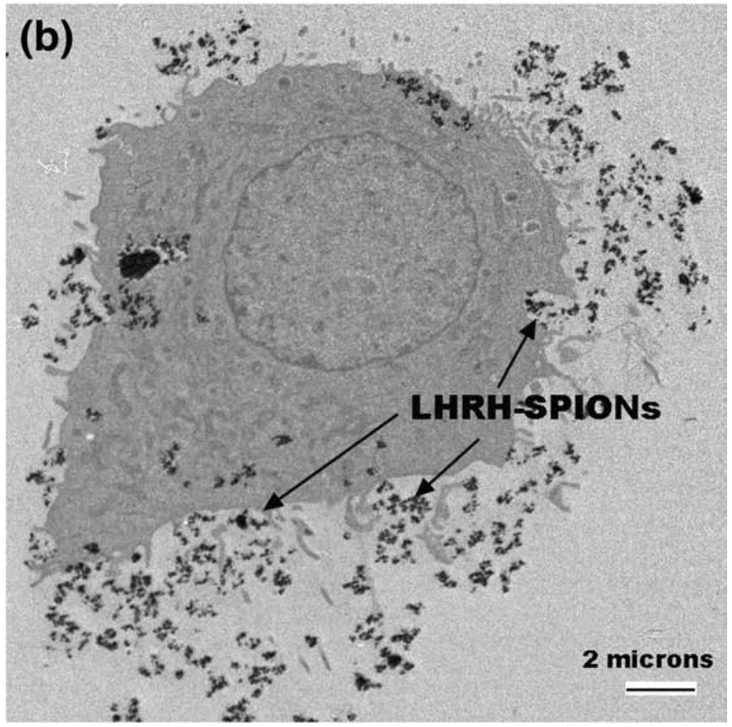
PEG coating

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)