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

experiments simulations $v = 0.950$

\[ \Delta a_0 = -0.858 \]

\[ \Delta a_0 = -0.358 \]

\[ \Delta a_0 = 0.072 \]

anionic amphipaths, high salt, high pH, cholesterol enrichment

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)
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.
Protein aggregation and diseases

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

(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**

\(\alpha\)-synuclein aggregates in dopamine producing nerve cells

Loss of dopamine neurotransmitters results in movement disorders

- Normal neuron
- Neuron affected by Parkinson’s
- Transmitter
- Movement Disorders

**Alzheimer’s disease**

- Healthy neurons
- Diseased neurons
- Amyloid plaques (toxic)
- Tau tangles (disintegration of microtubules)
DNA stores genetic information encoded with sequence of bases.

DNA structure

- Chromosome
- Nucleosome
- Histone
- Gene
- Nucleotide

Nucleotide base pairs:
- Guanine
- Cytosine
- Adenine
- Thymine

Cell
- Nucleus
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

protein
Chaperons assist with protein folding and prevent protein aggregation

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

ribosome translation of mRNA to proteins

isolated proteins in chaperonin chambers fold into their compact native state

B. Alberts et al., Molecular Biology of the Cell
Chaperons assist with disassembly of protein aggregates

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

Small vesicles are used for cellular transport of molecules

transport of neurotransmitters in neuron cells

Vesicles are changing membrane topology!

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:

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

\[
E = 4\pi (2\kappa + \kappa_G)
\]

\[
E \sim +300k_B T
\]

\[
E \approx 8\pi\kappa
\]

\[
E \sim +500k_B T
\]

\[
E = 0
\]

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:

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

\( E_b \) \hspace{1cm} \text{height of energy barrier}

\( t_0 \) \hspace{1cm} \text{time between successive attempts for crossing the barrier}
Vesicle fusion with membrane

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

\[
E = 4\pi (2\kappa + \kappa_G) \\
E \approx +300k_B T
\]

\[
E \approx 8\pi \kappa \\
E \approx +500k_B T
\]

\[E = 0\]

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, …
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.