Physical Principles in Biology
Biology 3550
Fall 2016

Lecture 33

More on Lipids and Membranes

Bilayer Permeability and the Origins of Life

Wednesday, 16 November

©David P. Goldenberg
University of Utah
goldenberg@biology.utah.edu

Phospholipids and Bilayers

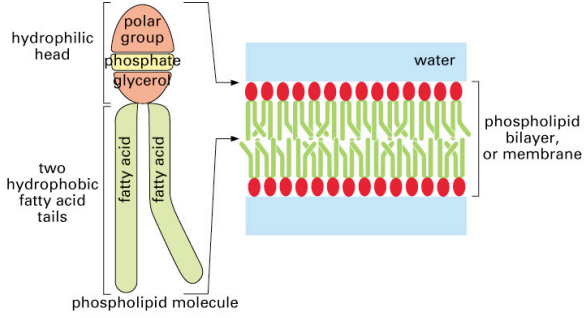
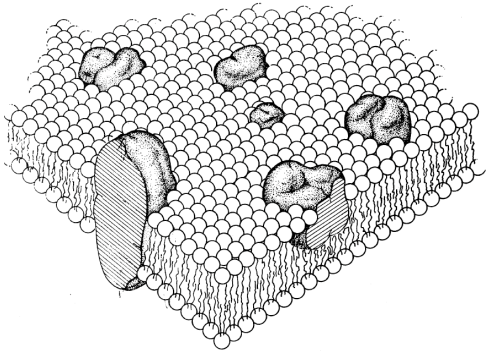


Figure 2–22. Molecular Biology of the Cell, 4th Edition.

- Large two dimensional sheets.
- Non-polar tails sequestered away from water.
- Polar head groups exposed to water on each side.

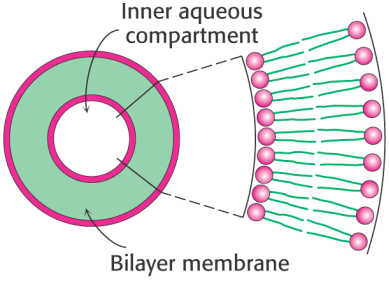
General Structure of Biological Membranes



- Proteins embedded in bilayer control passage of other molecules.
- Many other functions of membrane proteins!

Singer, S. & Nicolson, G. (1972). The fluid mosaic model of the structure of cell membranes. *Science*, 175, 720–731. http://dx.doi.org/10.1126/science.175.4023.720

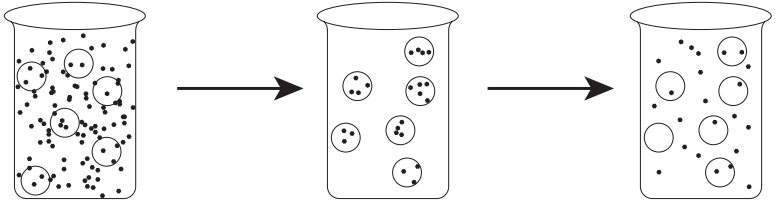
Phospholipids Form Vesicles



From Berg, Tymoczko & Stryer, Biochemistry, 6th Ed.

- Bilayers close on themselves to eliminate edges.
- 50 nm–1 μM in diameter.
- Function in vivo to store and transport specific molecules (*e.g.,* neurotransmitters)
- Formed experimentally by vigorously mixing bilayers in water.

Using Vesicles to Measure Permeability of Bilayers



- Form vesicles in presence of molecules of interest.
- Separate vesicles from external molecules.
- Allow molecules to diffuse across bilayers.
- Separate vesicles from external molecules and measure concentrations.
- What determines rate of escape?
  Fick's first law!

Diffusion Across Vesicle Bilayer

- Fick's first law: $J = -D\dfrac{dC}{dx}$
- Concentration gradient: $\dfrac{dC}{dx} \approx \dfrac{C_{\text{in}} - C_{\text{out}}}{\text{Bilayer thickness}}$
- A new parameter commonly used in this and other contexts: permeability coefficient, P (not to be confused with pressure!).

  Represents combination of diffusion coefficient and membrane thickness:

  $$P = \frac{D}{\Delta x}$$

  Units:

  $$\mathrm{m}^2/\mathrm{s} \div \mathrm{m} = \mathrm{m}/\mathrm{s}$$

Fick's First Law Expressed Using the Permeation Coefficient

$$J = -D\frac{dC}{dx} \approx -D\frac{\Delta C}{\Delta x} = -P\Delta C$$

- In practice: Measure flux and calculate P

$$P = -\frac{J}{\Delta C}$$

- What do we need to know?
  - Concentration of molecules inside vesicle and out.
  - Rate of molecules diffusing (moles/time).
  - Surface area of vesicles (J has units of $\mathrm{mol} \cdot \mathrm{m}^{-2}\mathrm{s}^{-1}$).
  - Don't need to know membrane thickness!
- P reflects both molecule and bilayer (or other kind of membrane)

Clicker Question #1

What kind of ions or molecules would you expect to have the **largest** permeability coefficients for phospholipid bilayers?

1. Sugars
2. Amino acids
3. Water
4. Nucleotides
5. Small ions like Na^+, K^+ or Cl^-

All answers count for now!

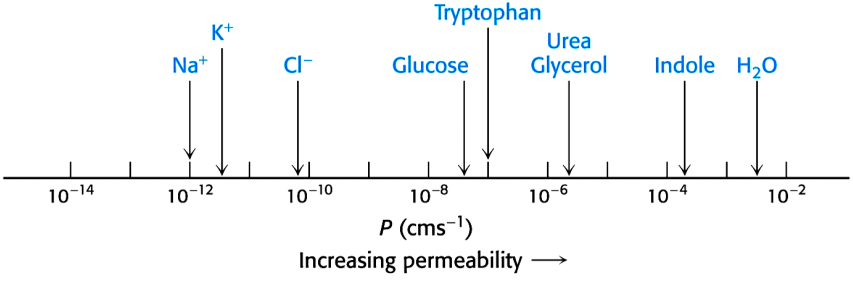
Clicker Question #2

What kind of ions or molecules would you expect to have the **smallest** permeability coefficients for phospholipid bilayers?

1. Sugars
2. Amino acids
3. Water
4. Nucleotides
5. Small ions like Na^+, K^+ or Cl^-

All answers count for now!

Measured Permeability Coefficients



- Range of permeabilities is extremely wide: 9 orders of magnitude.
- Charged ions have very low permeability.
- Polar small molecules have low to medium permeabilities.
- Permeability of water is actually quite high!

From Berg, Tymoczko and Stryer, Biochemistry.

Comparing Permeability Across Bilayers with Diffusion Coefficients in Water

- $P = D/\Delta x$
- Can calculate an "effective diffusion coefficient" by assuming a value for Δx.

  $D = P\Delta x$

  Assume $\Delta x = 40\,\text{nm}$
- For ions:

  $D = P\Delta x = 10^{-11}\,\text{cm/s} \times 40\,\text{nm}$

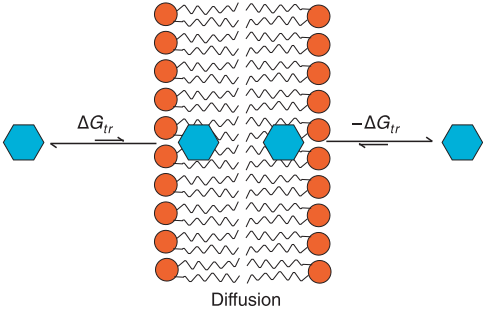
  $= 10^{-13}\,\text{m/s} \times 4{\times}10^{-8}\,\text{nm}$

  $= 4{\times}10^{-21}\,\text{m}^2/\text{s}$
- For small polar molecules:

  $D = P\Delta x = 10^{-7}\,\text{cm/s} \times 40\,\text{nm}$

  $= 4{\times}10^{-17}\,\text{m}^2/\text{s}$
- Compare to $D = 10^{-10}\,\text{m}^2/\text{s}$ for small molecules in water.

Quantitative Model for Permeability



- Molecule equilibrates between aqueous and lipid phases.
- Molecule diffuses across lipid phase.
- Diffusion is rate limiting.

$$P = K_{\text{tr}} D / \Delta x$$

K_{tr} is equilibrium constant between phases.

- Model works quite well to predict permeability coefficients from measured ΔG_{tr} and diffusion coefficients.
- Permeability correlates strongly with solubility in non-polar liquids.

An Alternative Model

- Bilayers randomly form holes that quickly reseal.
- What would this model predict?

Some Questions about the Origins of Life on Earth

What are some of the fundamental things that organisms have to do?

- Collect nutrients from environment.
- Convert nutrients into useful forms of energy.
- Build complicated macromolecules, including enzymes and genetic material.
- Create compartments bounded by membranes.
- Reproduce themselves.

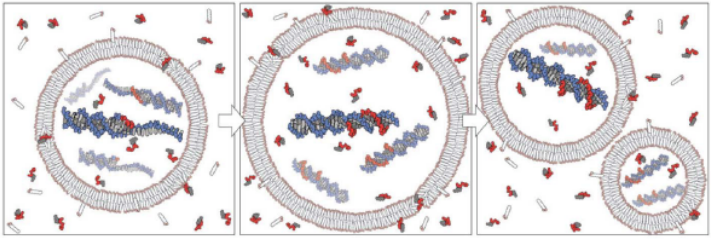
Which came first, proteins or nucleic acids?

- Genetic information is encoded by nucleic acids.
- Proteins are needed to synthesize nucleic acids.
- Now know that some RNA molecules have catalytic activities, suggesting that something like RNA may have come before proteins and DNA.

When Did Membranes Enter the Picture?

- Compartmentalization would favor local reactions and prevent competing reactions from stealing reagents.
- Without pores, bilayers prevent escape of molecules, but also their entry!
- Some fatty acids can form bilayers that small polar and charged molecules can cross, but that larger molecules can’t.

A Model for Primitive Proto-cells



- Primitive reactions lead to formation of polymers, possibly RNA-like.
- Polymers become trapped in semi-permeable vesicles.
- Precursors to polymers diffuse into vesicles and add to the polymers, effectively trapping them.
- Polymers grow, forcing vesicles to grow, and eventually divide.

Mansy, S. S., Schrum, J. P., Krishnaurthy, M., Tobé, S., Treco, D. A. & Szostak, J. W. (2008). *Nature*, 454, 122–125. http://dx.doi.org/10.1038/nature07018