Biophysics I (BPHS 4080)

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Website: http://www.yorku.ca/cberge/4080W2018.html

York University
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Lecture 3

Reference/Acknowledgement:
- TF Weiss (Cellular Biophysics)
- D Freeman

Diffusion equation

1. Fick's First Law:

$$\phi = -D\frac{\partial c}{\partial x}$$

+

2. Continuity Equation:

$$\frac{\partial \phi}{\partial x} = -\frac{\partial c}{\partial t}$$

$$\boxed{\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}}$$

(Fick's Second Law)

Diffusion processes

i.e., solutions to $\phi = -D\frac{\partial c}{\partial x}$ $\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$

1. Equilibrium: Zero flux and concentration is independent of time

$D \neq 0 \Rightarrow$ concentration is independent of space and time

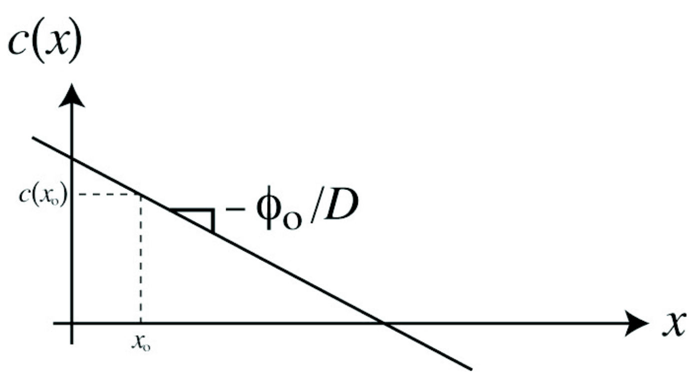
$D = 0 \Rightarrow$ non-diffusible solute is automatically at equilibrium

2. Steady-state: Flux can be non-zero, but flux and concentration are independent of time

$$\frac{\partial \phi}{\partial x} = 0 \quad \Rightarrow \quad \int \phi_o \, dx = \int -D \, dc \quad \Rightarrow \quad c(x) = c(x_o) - \frac{\phi_o}{D}(x - x_o)$$

[integrate Fick's 1st Law]

[x_o is a reference location where the concentration is known]



Freeman

Diffusion processes

3. Impulse Response: Point-source of particles (n_o mol/cm^2) at t = 0 and x = 0

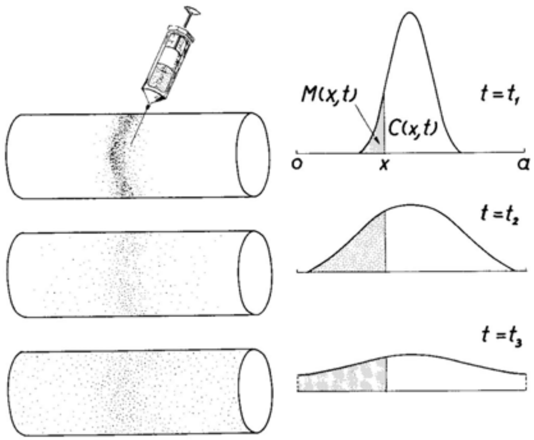
[Dirac delta function $\delta(x)$]

given the inital/boundary conditions:

$$c(x,t) = n_o \delta(x) \quad \text{at} \quad t = 0 \quad \text{where} \quad \int_{-\infty}^{\infty} \delta(x)\, dx = 1$$

need to solve:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$



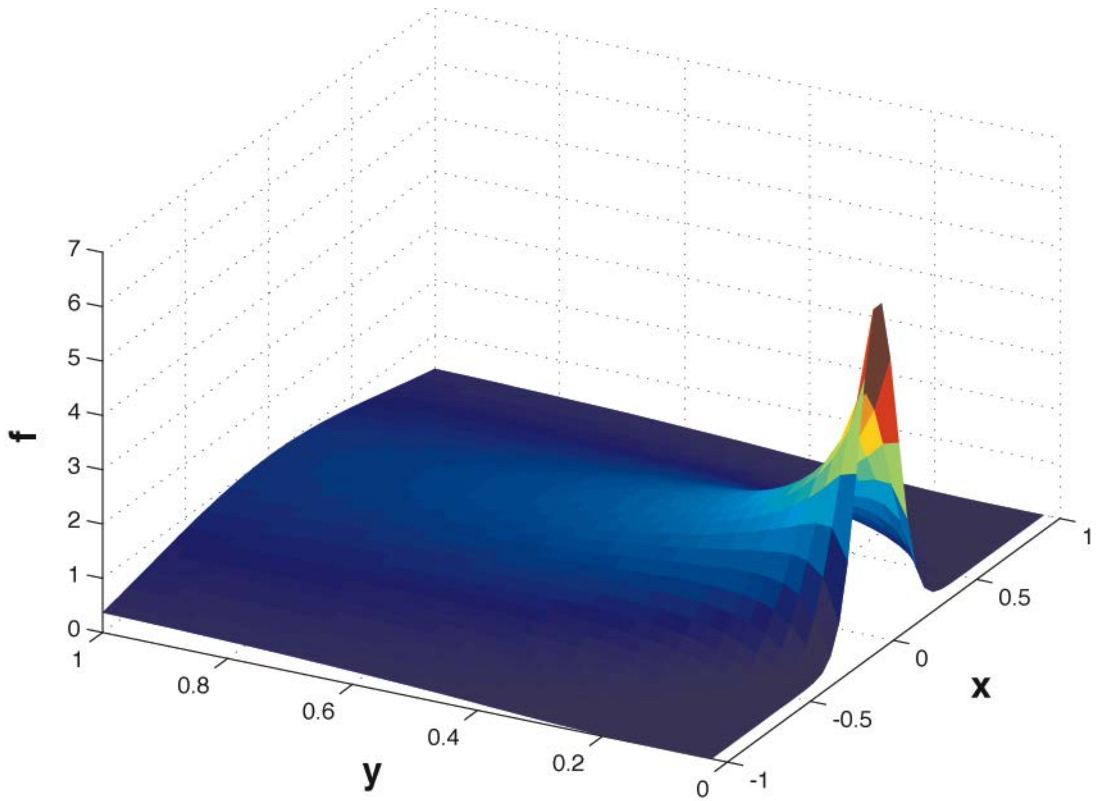
Batschelet Fig.12.5

[Aside: solution can be found by a # of different methods, one being by separation of variables and using a Fourier transform]

Solution

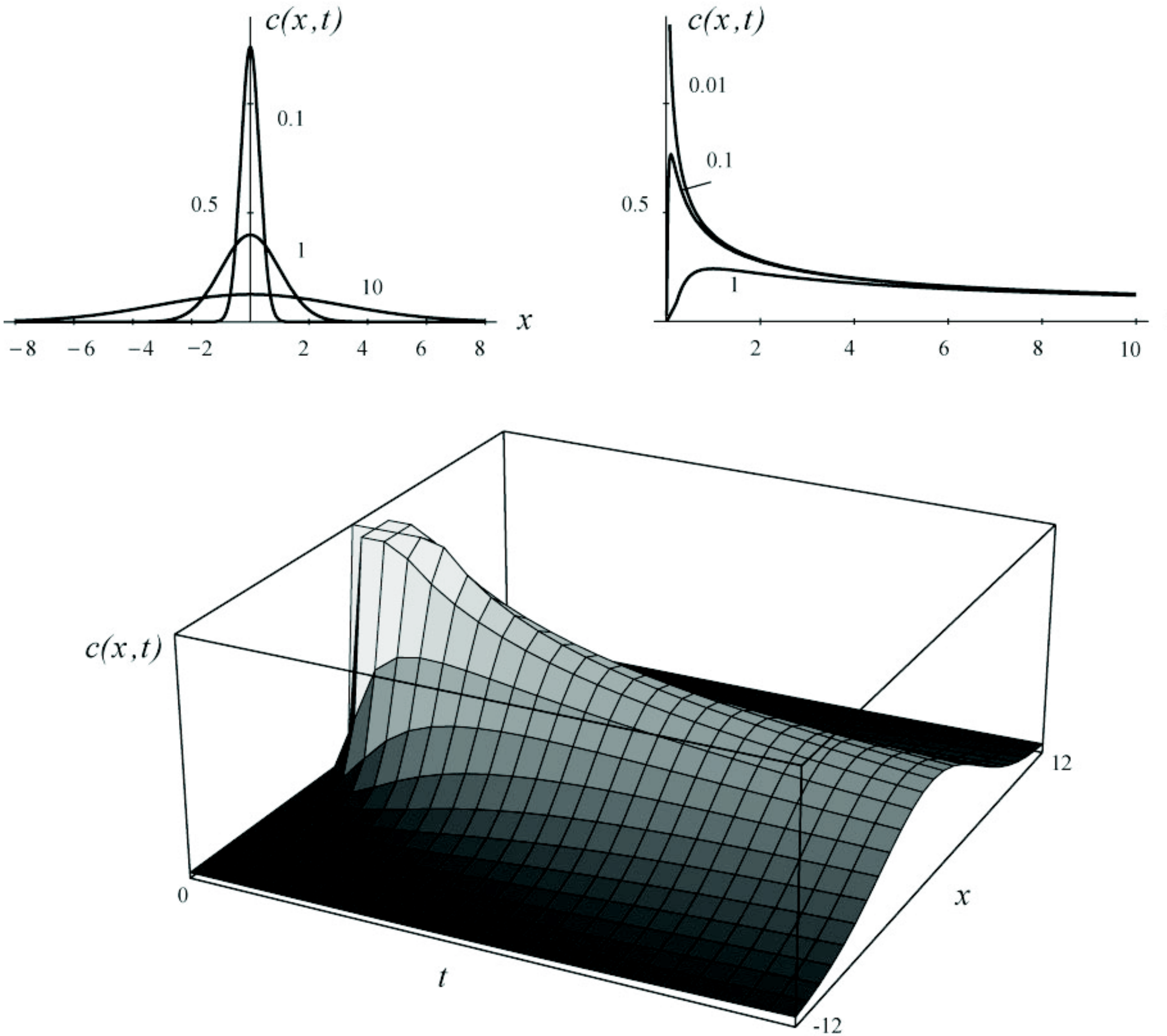
(for t > 0)

$$c(x,t) = \frac{n_o}{\sqrt{4\pi D t}} e^{-x^2/4Dt}$$



$$f(x,y) = \frac{1}{\sqrt{y}} e^{-x^2/y}$$

solution to
diffusion equation!



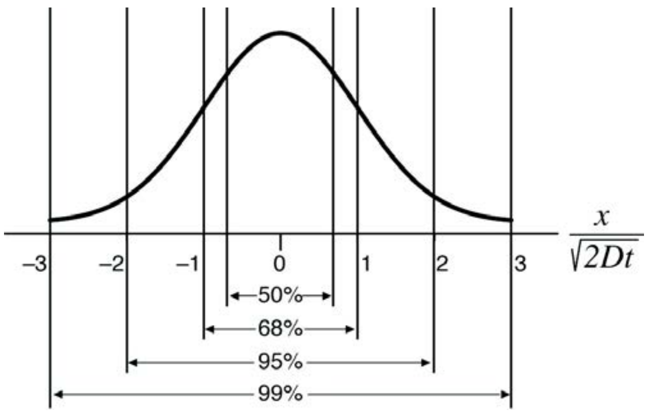
Weiss Fig.3.14 (modified)

Importance of Scale

$$c(x,t) = \frac{n_o}{\sqrt{4\pi D t}} e^{-x^2/4Dt}$$

Gaussian function with zero mean and standard deviation:

$$\sigma = \sqrt{2Dt}$$



Question: How long does it take ($t_{1/2}$) for ~1/2 the solute to move at least the distance $x_{1/2}$?

$$\frac{x_{1/2}}{\sqrt{2Dt_{1/2}}} \approx \frac{2}{3} \quad \Longrightarrow \quad t_{1/2} \approx \frac{x_{1/2}^2}{D}$$

For small solutes
(e.g. K^+ at body temperature)

$$D \approx 10^{-5} \ \frac{\text{cm}^2}{\text{s}}$$

	$x_{1/2}$	$t_{1/2}$
membrane sized	10 nm	$\frac{1}{10}$ μsec
cell sized	10 μm	$\frac{1}{10}$ sec
dime sized	10 mm	10^5 sec ≈ 1 day

Freeman

<u>Exercise</u>

At a junction between two neurons, called a synapse, there is a 20 nm cleft that separates the cell membranes. A chemical transmitter substance is released by one cell (the pre-synaptic cell), diffuses across the cleft, and arrives at the membrane of the other (post-synaptic) cell. Assume that the diffusion coefficient of the chemical transmitter substance is $D = 5 \times 10^{-6}$ cm^2/s.

→ Make a *rough estimate of the delay caused by diffusion of the transmitter substance across the cleft. What are the limitations of this estimate? Explain.*

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→ Make a *rough estimate of the delay caused by diffusion of the transmitter substance across the cleft. What are the limitations of this estimate? Explain.*

Answer

Consider the time it takes for ½ to cross the cleft, then we have approximately 1 us (1×10^{-6} s). However, this calculation:

- Ignores the cleft geometry (e.g., not infinite baths)
- There is nothing special about ½ the solute here (perhaps only a few molecules are needed, or perhaps a lot are)

Exercise

To wiggle your big toe, neural messages travel along a single neuron that stretches from the base of your spine to your toe. Assume that the membrane of this neuron can be represented as a uniform cylindrical shell that encloses the intracellular environment, which is represented as a simple saline solution. The diameter of the shell is 10 μm and the length is 1 m. Assume that 10^{-15} moles of dye are injected into the neuron at time t = 0 and at a point located in the center of the neuron, which we will refer to as the point z = 0. Assume that the dye diffuses across the radial dimension so quickly that the concentration of dye c(z,t) depends only on the longitudinal direction z and time t. Assume that the diffusivity of the dye in the intracellular saline is $D = 10^{-7}$ cm^2/s and that the membrane is impermeant to the dye.

→ Determine the amount of time t_1 required for 5% the injected dye to diffuse to points outside the region −1 mm< z < 1 mm.

→ Determine the amount of time t_2 required for half the injected dye to diffuse to points outside the region −1 mm< z < 1 mm. Determine the ratio of t_2 to t_1. Briefly explain the physical significance of this result.

→ Determine the amount of time t_3 required for 5% the injected dye to diffuse to points outside the region −10 mm< z < 10 mm. Determine the ratio of t_3 to t_1. Briefly explain the physical significance of this result.

Answers

→ Determine the amount of time t_1 required for 5% the injected dye to diffuse to points outside the region −1 mm< z < 1 mm.

3.5 hours

→ Determine the amount of time t_2 required for half the injected dye to diffuse to points outside the region −1 mm< z < 1 mm. Determine the ratio of t_2 to t_1. Briefly explain the physical significance of this result.

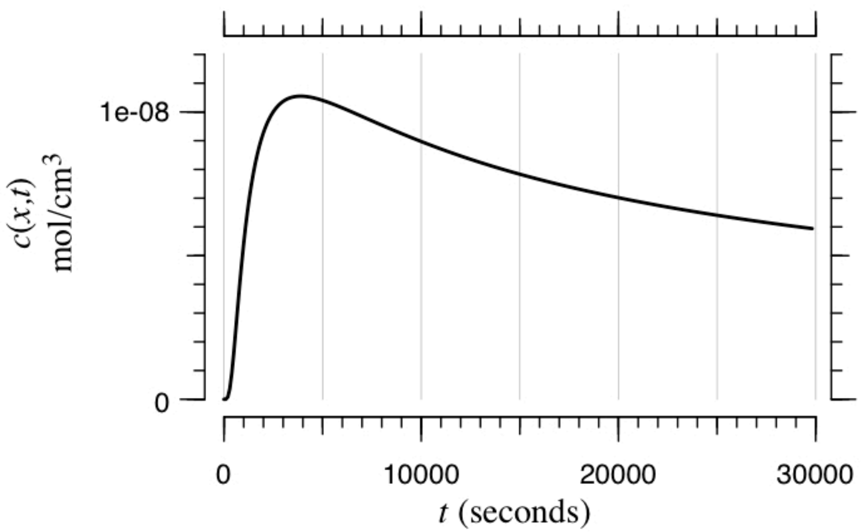
1.3 days

→ Determine the amount of time t_3 required for 5% the injected dye to diffuse to points outside the region −10 mm< z < 10 mm. Determine the ratio of t_3 to t_1. Briefly explain the physical significance of this result.

14.5 days

Exercise

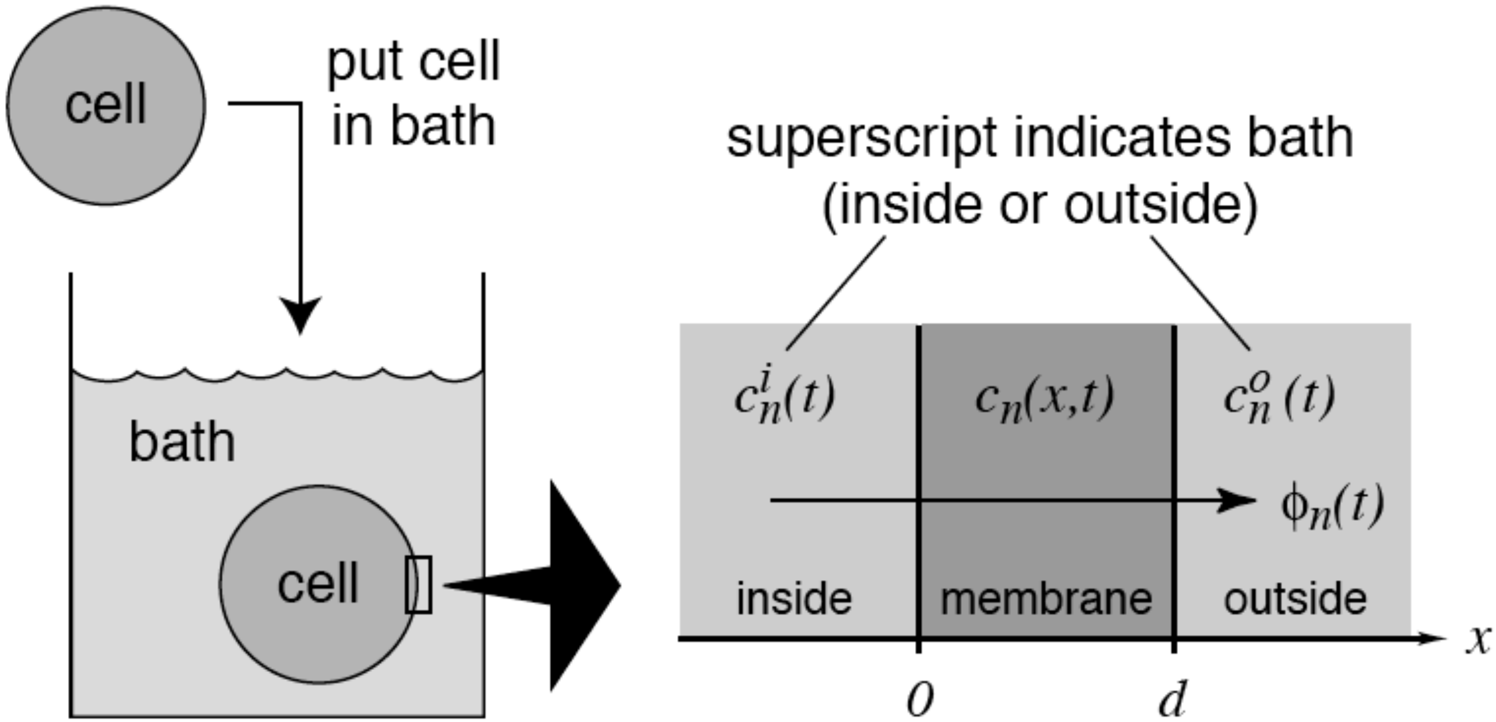
To wiggle your big toe, neural messages travel along a single neuron that stretches from the base of your spine to your toe. Assume that the membrane of this neuron can be represented as a uniform cylindrical shell that encloses the intracellular environment, which is represented as a simple saline solution. The diameter of the shell is 10 µm and the length is 1 m. Assume that 10^{-15} moles of dye are injected into the neuron at time t = 0 and at a point located in the center of the neuron, which we will refer to as the point z = 0. Assume that the dye diffuses across the radial dimension so quickly that the concentration of dye c(z,t) depends only on the longitudinal direction z and time t. Assume that the diffusivity of the dye in the intracellular saline is $D = 10^{-7}$ cm^2/s and that the membrane is impermeant to the dye.



The following plot shows the concentration of dye as a function of time for a particular point at z0 > 0.

→ Determine z0.

Membrane Diffusion: Two-Compartment Geometry



reference direction for flux is outward

Diffusion Through Cell Membranes: History 101

Diffusion through Cell Membranes

Charles Ernest Overton (late 1800s): first systematic studies

- qualitative:
  - put cell in bath with solute
  - wait, rinse, squeeze
  - analyze to see how much got in (+ = some; +++ = a lot)
- 100's of solutes, dozens of cell types
- surprising results: previously cell membranes had been thought to be impermeant to essentially everything but water

Overton's Rules:

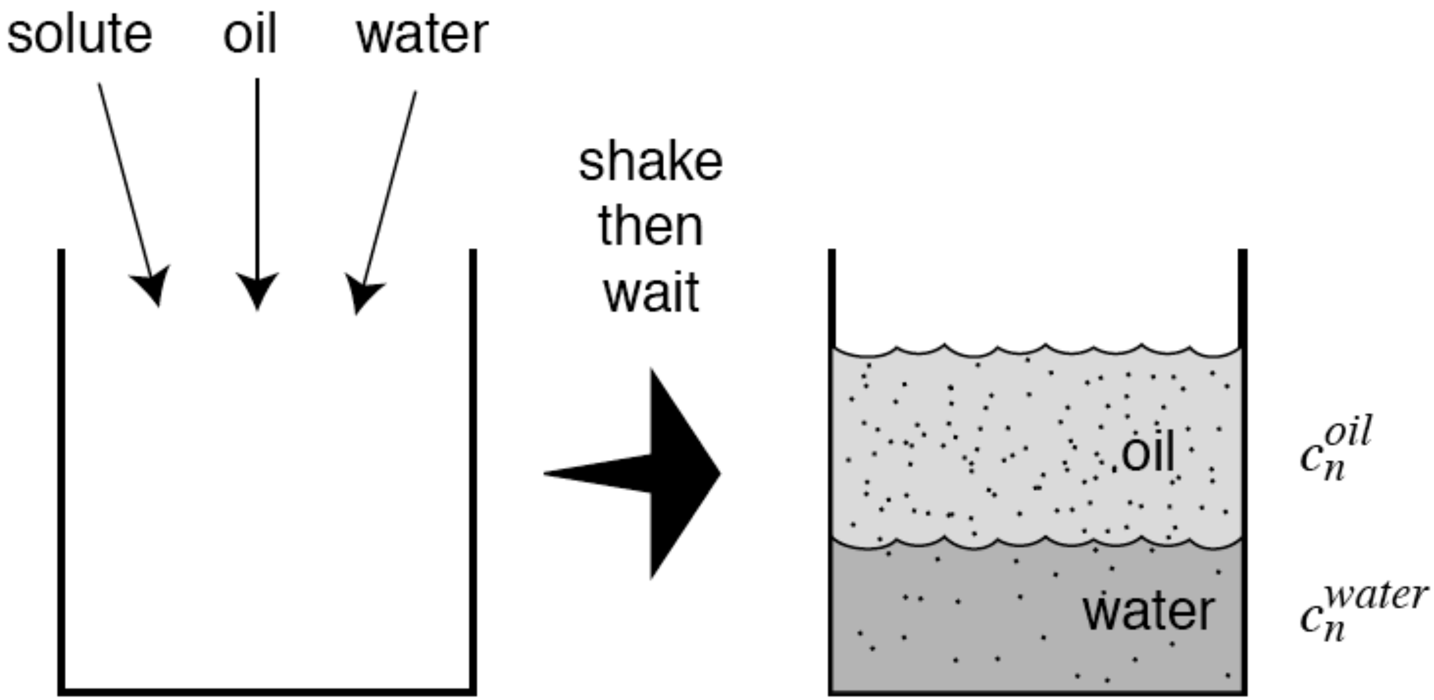
- cell membranes are semi-permeable
- relative permeabilities of plant and animals cells are similar
- permeabilities correlate with solubility of solute in organic solvents $\rightarrow$ membrane is lipid (specifically cholesterol and phospholipids)
- certain cells concentrate some solutes $\rightarrow$ active transport
- potency of anesthetics correlated with lipid solubility $\rightarrow$ Meyer-Overton theory of narcosis
- muscles don't contract in sodium-free media

Diffusion through Cell Membranes

Paul Runar Collander (1920-1950): first quantitative studies

- large cells (cylindrical algae cells, 1 mm diameter, 1 cm long)
- bathe cell in solute for time t_1, squeeze out cytoplasm, analyze
- repeat with new cell and new time t_2
- plot intracellular quantity versus time
- fit with exponential function of time (two-compartment theory)
- infer permeability from time constant

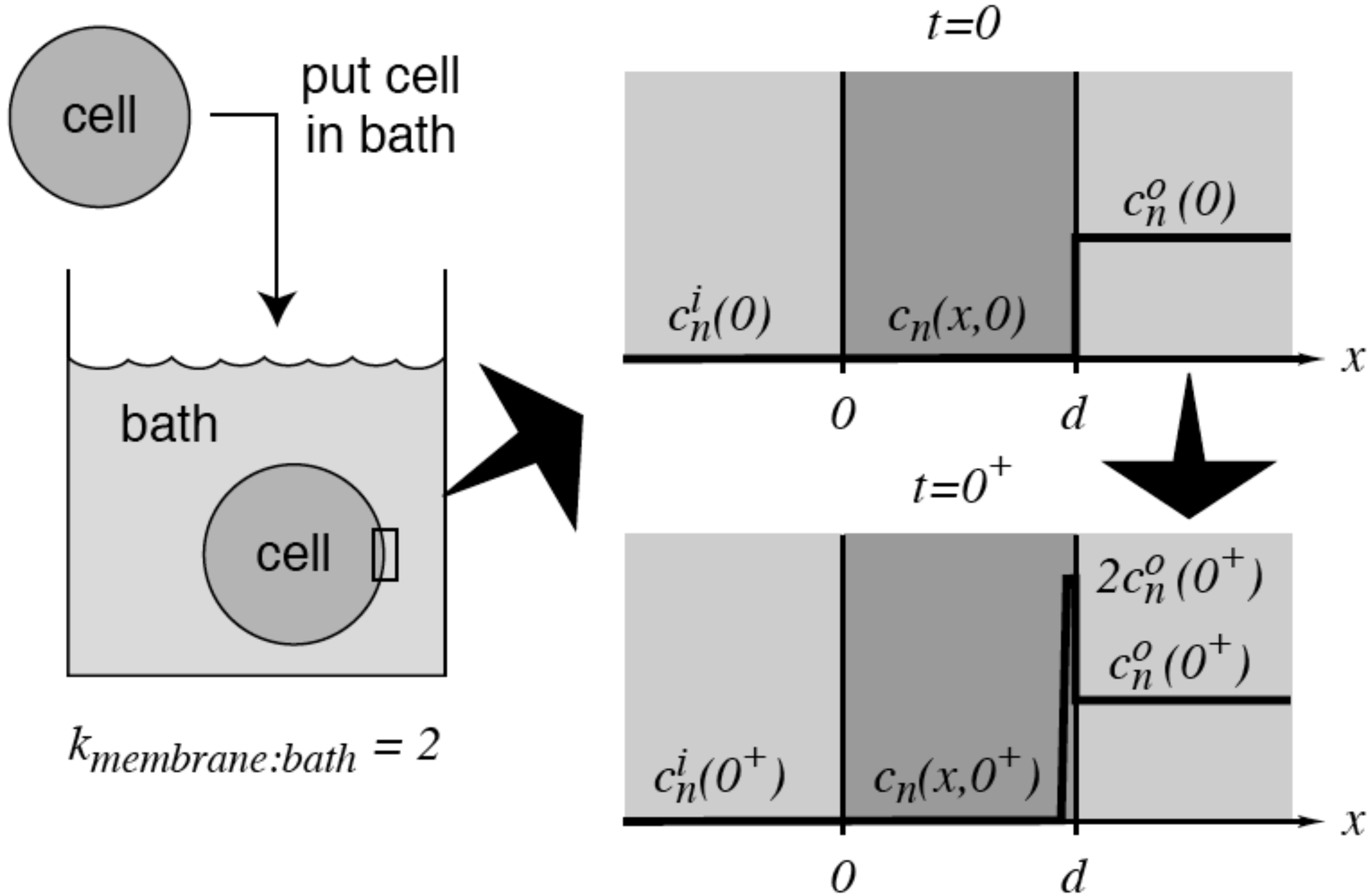
Step 1: Dissolve



Equilibrium characterized by relative solubilities of solute n in oil and water

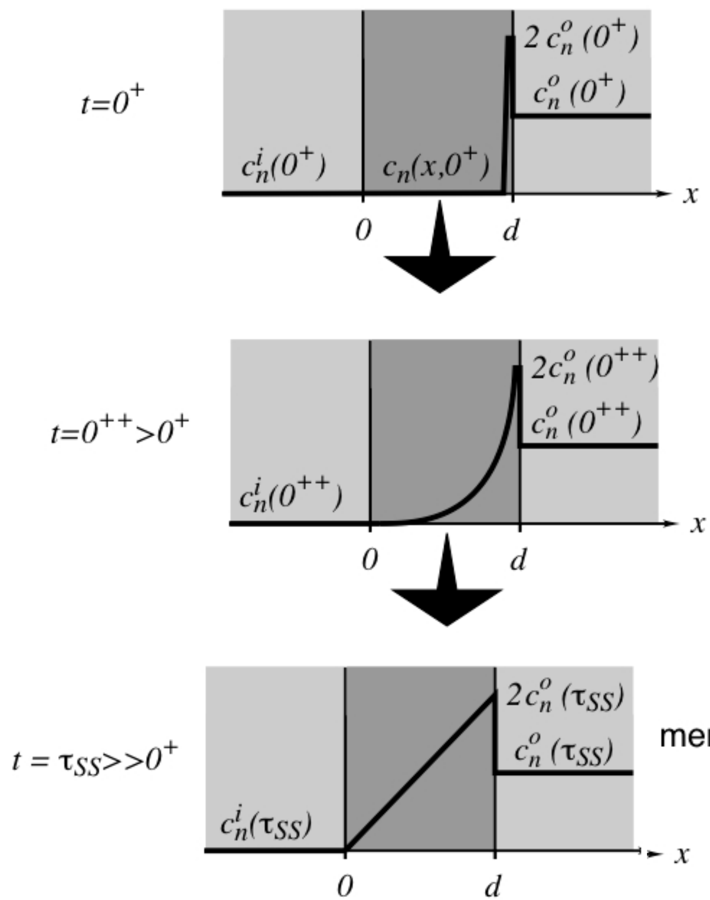
$$\text{partition coefficient } k_{oil:water} = \frac{c_n^{oil}}{c_n^{water}}$$

Assume Dissolving is fast relative to diffusing



Freeman

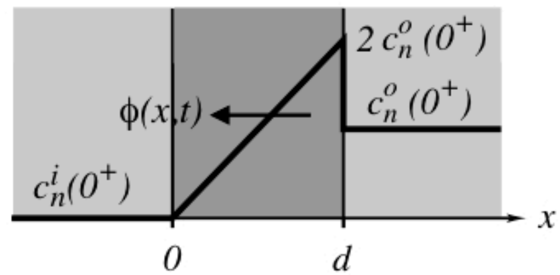
Step 2: Solute diffuses though membrane



steady state
membrane time constant

$$\tau_{SS} = \frac{d^2}{\pi^2 D}$$

Step 3: Solute enters the cell



$$c_n(x,t) = c_n(0,t) + \frac{x}{d}(c_n(d,t) - c_n(0,t))$$

$$= k_n c_n^i(t) + \frac{k_n x}{d}(c_n^o(t) - c_n^i(t))$$

$$k_n = k_{membrane:bath}$$

$$= k_{membrane:cytoplasm}$$

Fick's law: $\phi_n(t) = -D_n \dfrac{\partial c_n(x,t)}{\partial x}$

$$= -D_n \frac{c_n(d,t) - c_n(0,t)}{d}$$

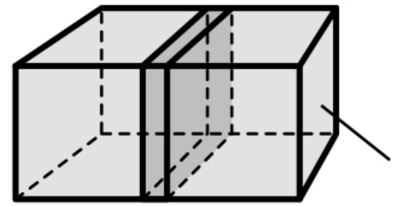
$$= \frac{D_n k_n}{d}(c_n^i(t) - c_n^o(t))$$

$$\boxed{\phi_n(t) = P_n\,(c_n^i(t) - c_n^o(t)) \;\; ; \;\; P_n = \frac{D_n k_n}{d}}$$

Fick's law for membranes

P_n = permeability of membrane to solute n

Step 4: Concentration in cell changes: two-compartment diffusion



Assume

- $\mathcal{V}_i$ and $\mathcal{V}_o$ constant
- well-stirred baths: $c_n^i(t)$, $c_n^o(t)$
- solute is conserved and membrane is thin: $c_n^i(t)\mathcal{V}_i + c_n^o(t)\mathcal{V}_o = N_n$
- membrane always in steady state: $\phi_n(t) = P_n(c_n^i(t) - c_n^o(t))$

By continuity,

$$A\phi_n(t) = -\frac{d}{dt}(c_n^i(t)\mathcal{V}_i) = \frac{d}{dt}(c_n^o(t)\mathcal{V}_o)$$

$$\frac{d}{dt}c_n^i(t) = -\frac{AP_n}{\mathcal{V}_i}(c_n^i(t) - c_n^o(t)) = -\frac{AP_n}{\mathcal{V}_i}\left(c_n^i(t) - \frac{1}{\mathcal{V}_o}N_n + c_n^i(t)\frac{\mathcal{V}_i}{\mathcal{V}_o}\right)$$

$$\frac{d}{dt}c_n^i(t) + AP_n(\frac{1}{\mathcal{V}_i} + \frac{1}{\mathcal{V}_o})c_n^i(t) = \frac{AP_nN_n}{\mathcal{V}_i\mathcal{V}_o}$$

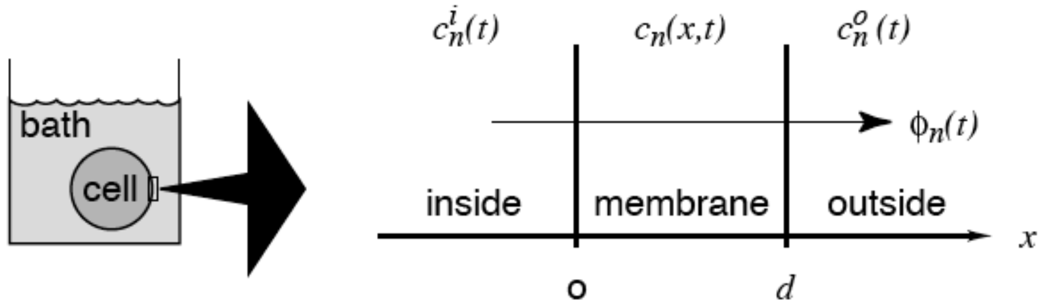
First-order linear differential equation with constant coefficients, therefore

$$c_n^i(t) = c_n^i(\infty) + [c_n^i(0) - c_n^i(\infty)]e^{-t/\tau_{EQ}}$$

$$c_n^i(\infty) = \frac{N_n}{\mathcal{V}_i + \mathcal{V}_o} \qquad \tau_{EQ} = \frac{1}{AP_n(\frac{1}{\mathcal{V}_i} + \frac{1}{\mathcal{V}_o})}$$

Membrane Diffusion: Summary

Membrane diffusion



Dissolve and diffuse model

- solute outside cell dissolves into cell membrane
- solute diffuses through membrane
- solute dissolves into cytoplasm

Membrane time constant $t_{SS} = \dfrac{d^2}{\pi^2 D_n}$

Fick's law for membranes: $\phi_n(t) = P_n\,(c_n^i(t) - c_n^o(t))\;;\quad P_n = \dfrac{D_n k_n}{d}$

Two-compartment diffusion

Cell time constant $t_{EQ} = \dfrac{1}{AP_n\left(\dfrac{1}{V_o} + \dfrac{1}{V_i}\right)}$

Dynamics of Membrane Diffusion

- Numerical solution to eqns.

- Arbitrary initial condition (top)

- Fast dynamics (middle)

- Steady-state set up (middle)

- Eventually, the two compartments change (bottom)

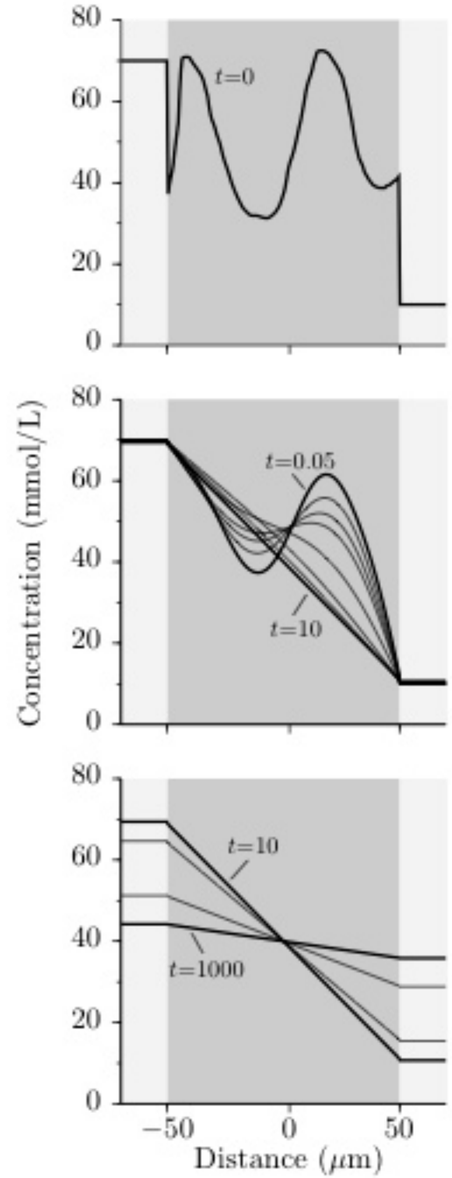
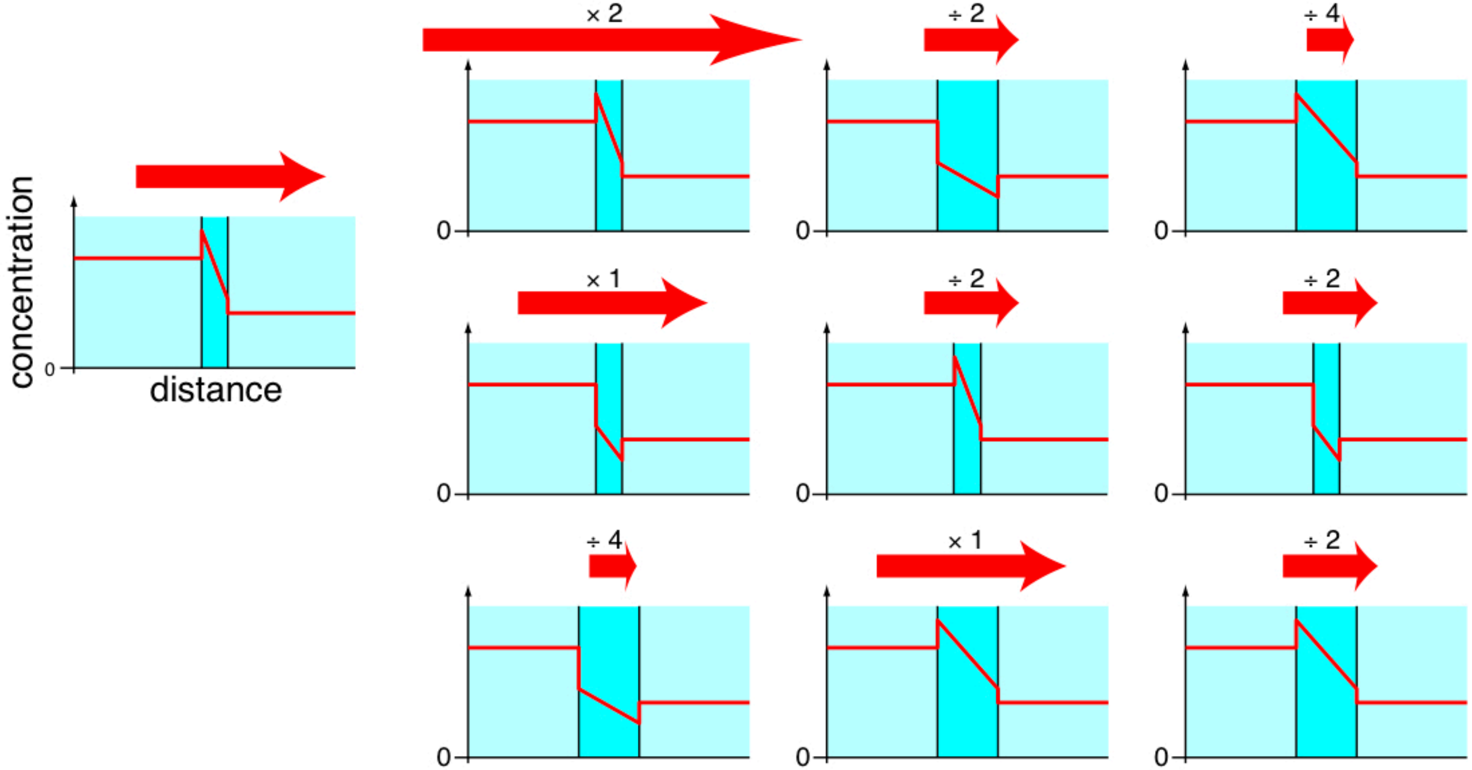


Figure 3.30

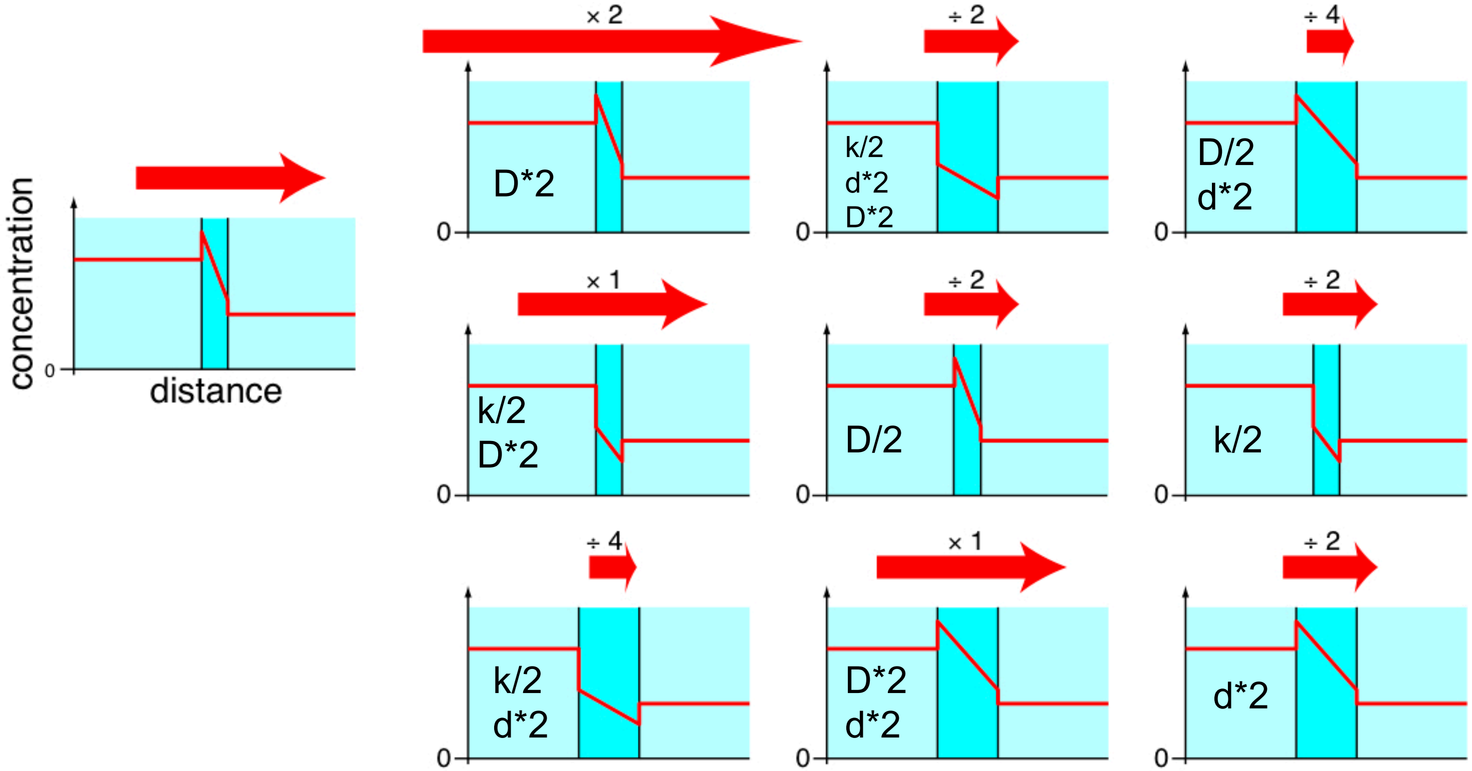
Effect of changing parameters on flux: What is being changed?



$$\phi_n(t) = P_n\,(c_n^{\,i}(t) - c_n^{o}(t)) \;\; ; \;\; P_n = \frac{D_n k_n}{d}$$

Fick's law for membranes

P_n = permeability of membrane to solute n



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Fick's law for membranes

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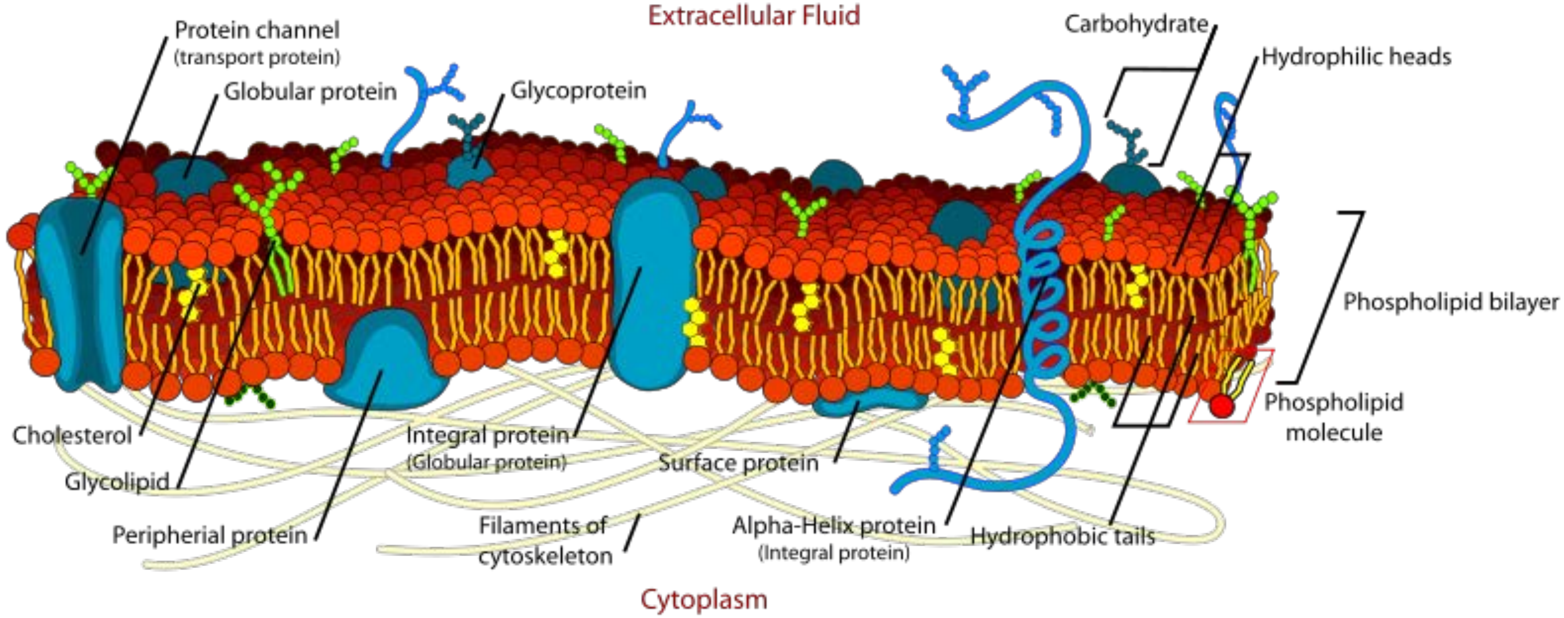
Question(s)

→ What are cell membranes made of?

→ How does one go about determining such?



→ It is only relatively recently we had a picture such as this!!

Wikipedia