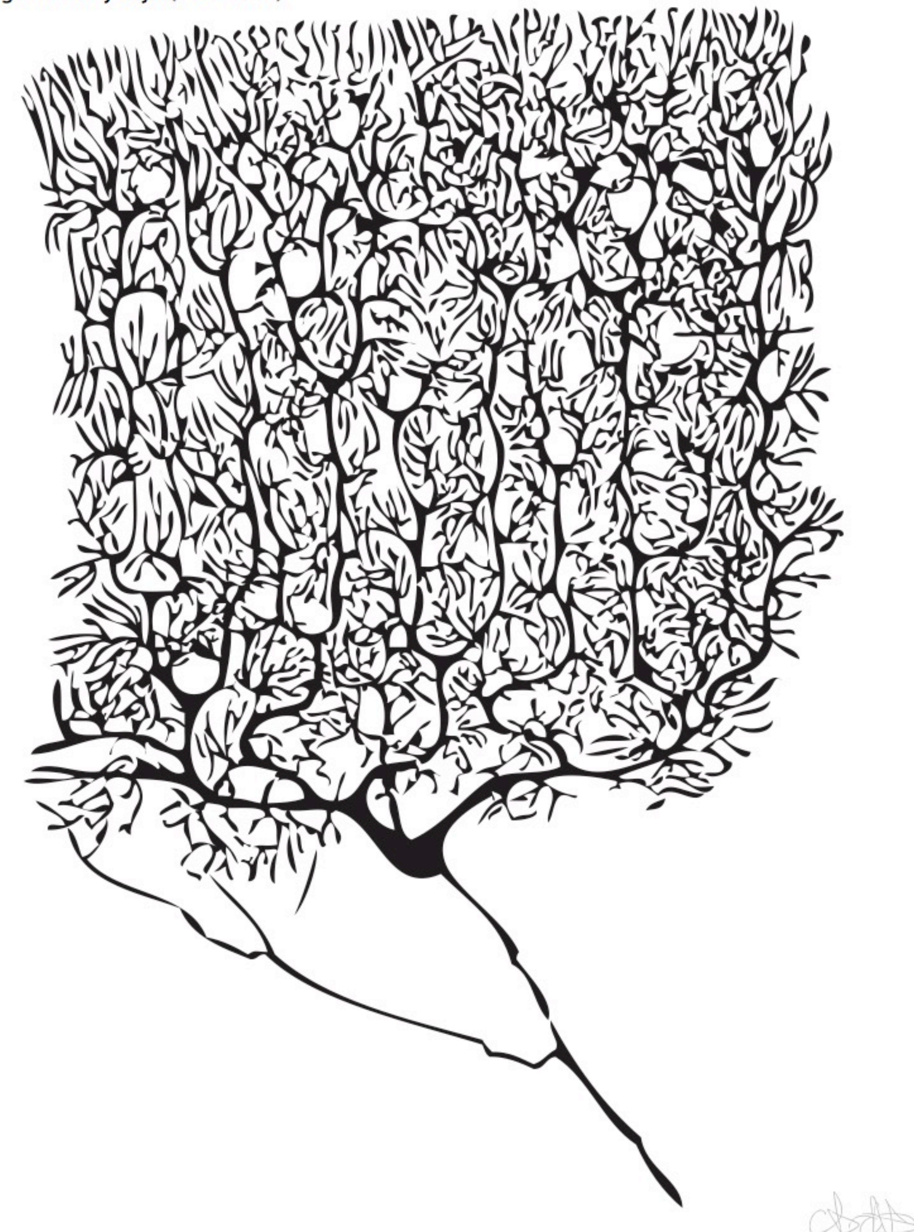
Cellular Electrodynamics



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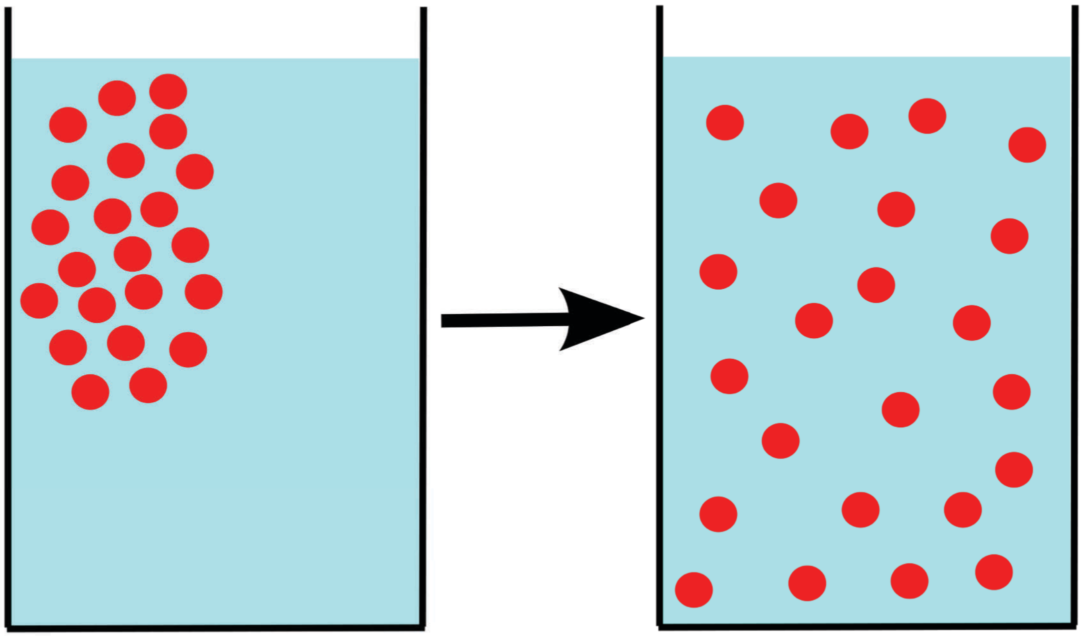
Website:
http://www.yorku.ca/cberge/4080W2020.html

York University
Winter 2020
BPHS 4080 Lecture 2

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

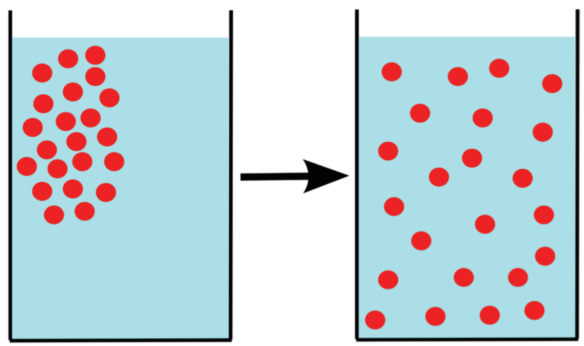
Diffusion

- According to wikipedia....



Diffusion

- According to wikipedia....



- According to the dictionary....

diffusion

[dih-**fyoo**-zhuh*uh* n]

Spell Syllables

Examples Word Origin

noun

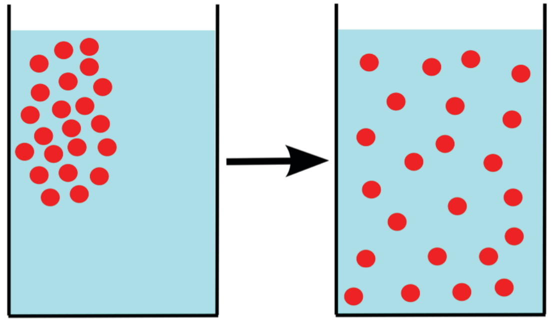
1. act of diffusing; state of being diffused.
2. prolixity of speech or writing; discursiveness.
3. *Physics.*
   a. Also called **migration**. an intermingling of molecules, ions, etc., resulting from random thermal agitation, as in the dispersion of a vapor in air.
   b. a reflection or refraction of light or other electromagnetic radiation from an irregular surface or an erratic dispersion through a surface; scattering.
4. *Movies.* a soft-focus effect resulting from placing a gelatin or silk plate in front of a studio light or a camera lens, or through the use of diffusion filters.
5. *Meteorology.* the spreading of atmospheric constituents or properties by turbulent motion as well as molecular motion of the air.
6. *Anthropology, Sociology.* Also called **cultural diffusion**. the transmission of elements or features of one culture to another.

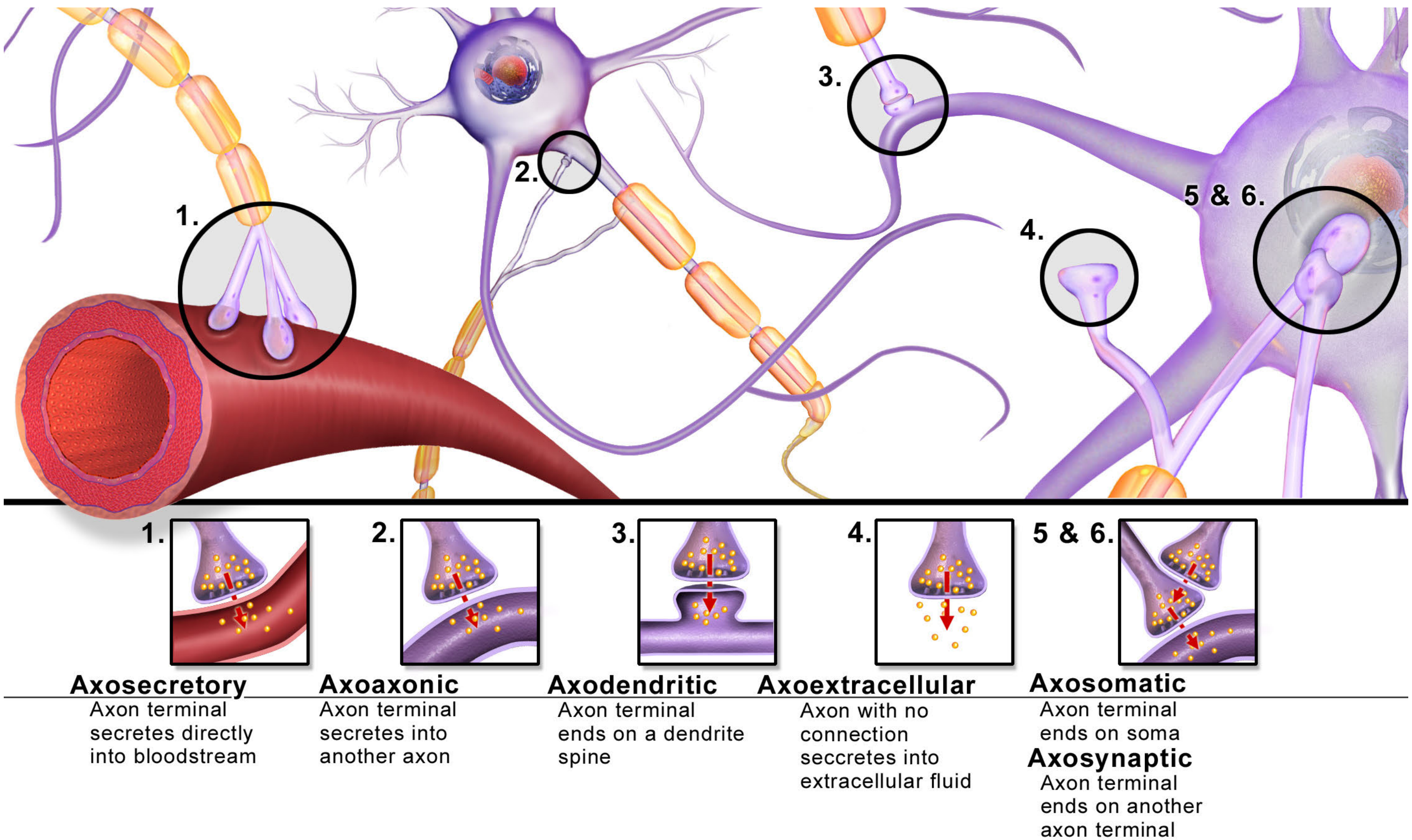
TECHNOLOGY FEATURE

A DEEP LOOK AT SYNAPTIC DYNAMICS

The processes behind neuronal communication have not yet been resolved in detail, but dyes, microscopy and protein analysis are beginning to fill in the gaps.

Synapses are crucial to the communication between neurons, but the events that happen there have been difficult to capture.

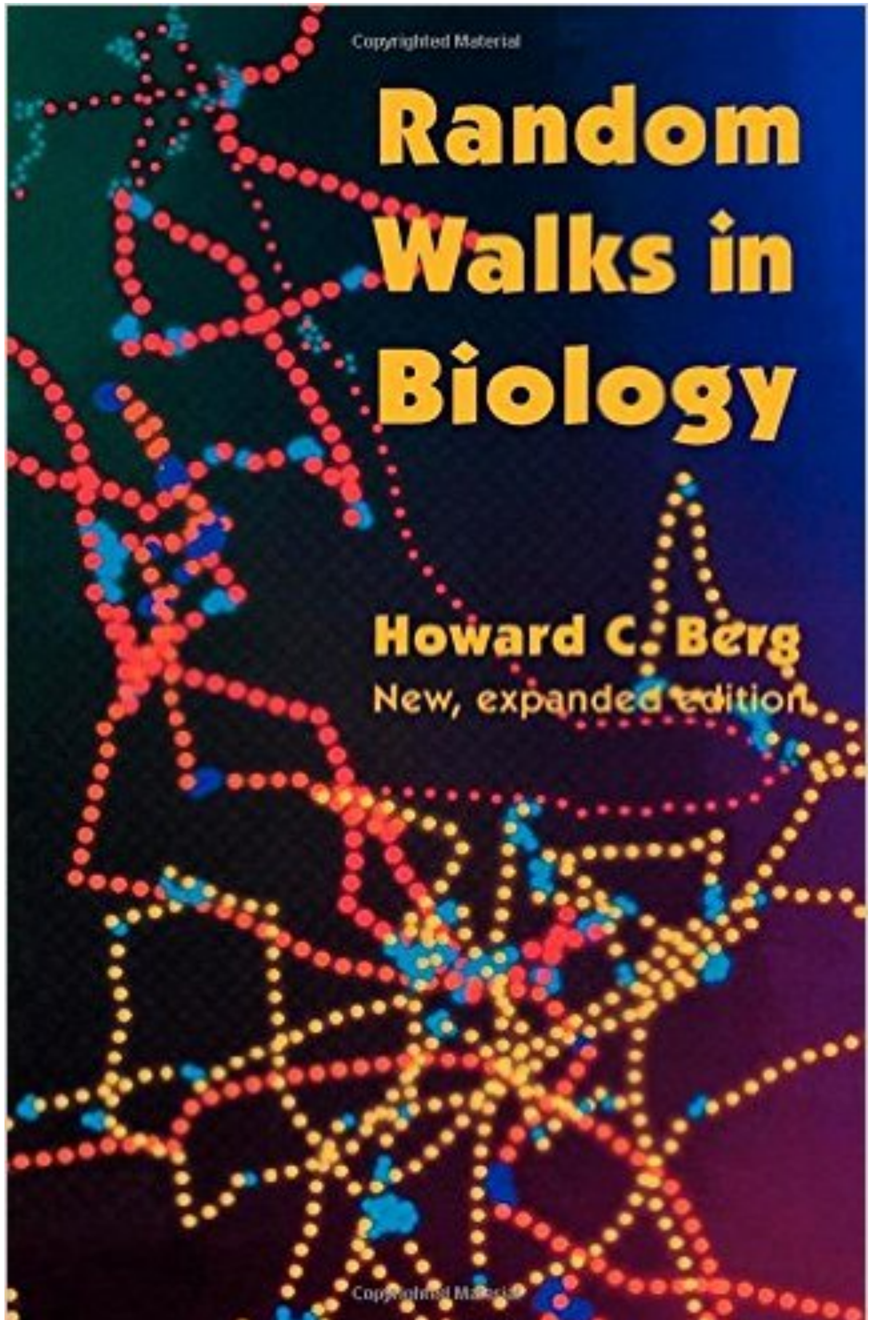



1.
2.
3.
4.
5 & 6.
Axosecretory
Axon terminal secretes directly into bloodstream
Axoaxonic
Axon terminal secretes into another axon
Axodendritic
Axon terminal ends on a dendrite spine
Axoextracellular
Axon with no connection seccretes into extracellular fluid
Axosomatic
Axon terminal ends on soma
Axosynaptic
Axon terminal ends on another axon terminal

Wikipedia

Random Walk with Drift (Marius Lehene)

Diffusion


Copyrighted Material
Random Walks in Biology
Howard C. Berg
New, expanded edition
Copyrighted Material

Diffusion

Chapter 1

Diffusion: Microscopic Theory

Diffusion is the random migration of molecules or small particles arising from motion due to thermal energy. A particle at absolute temperature T has, on the average, a kinetic energy associated with movement along each axis of $kT/2$, where k is Boltzmann's constant. Einstein showed in 1905 that this is true regardless of the size of the particle, even for particles large enough to be seen under a microscope, i.e., particles that exhibit Brownian movement. A particle of mass m and velocity v_x on the x axis has a kinetic energy $mv_x^2/2$. This quantity fluctuates, but on the average $\langle mv_x^2/2 \rangle = kT/2$, where $\langle \ \rangle$ denotes an average over time or over an ensemble of similar particles. From this relationship we compute the mean-square velocity,

$$\langle v_x^2 \rangle = kT/m, \tag{1.1}$$

and the root-mean-square velocity,

$$\langle v_x^2 \rangle^{1/2} = (kT/m)^{1/2}. \tag{1.2}$$

We can use Eq. 1.2 to estimate the instantaneous velocity of a small particle, for example, a molecule of the protein lysozyme. Lysozyme has a molecular weight 1.4×10^4 g. This is the mass of one mole, or 6.0×10^{23} molecules; the mass of one molecule is $m = 2.3 \times 10^{-20}$ g. The value of kT at 300°K (27°C) is 4.14×10^{-14} g cm^2/sec^2. Therefore, $\langle v_x^2 \rangle^{1/2} = 1.3 \times 10^3$ cm/sec. This is a sizeable speed. If there were no obstructions, the molecule would cross a typical classroom in about 1 second. Since the protein is not in a vacuum but is immersed in an aqueous medium, it does not go very far before it bumps into molecules of

Berg (1993)

Diffusion

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Some (remarkably deep) ideas right off the bat:

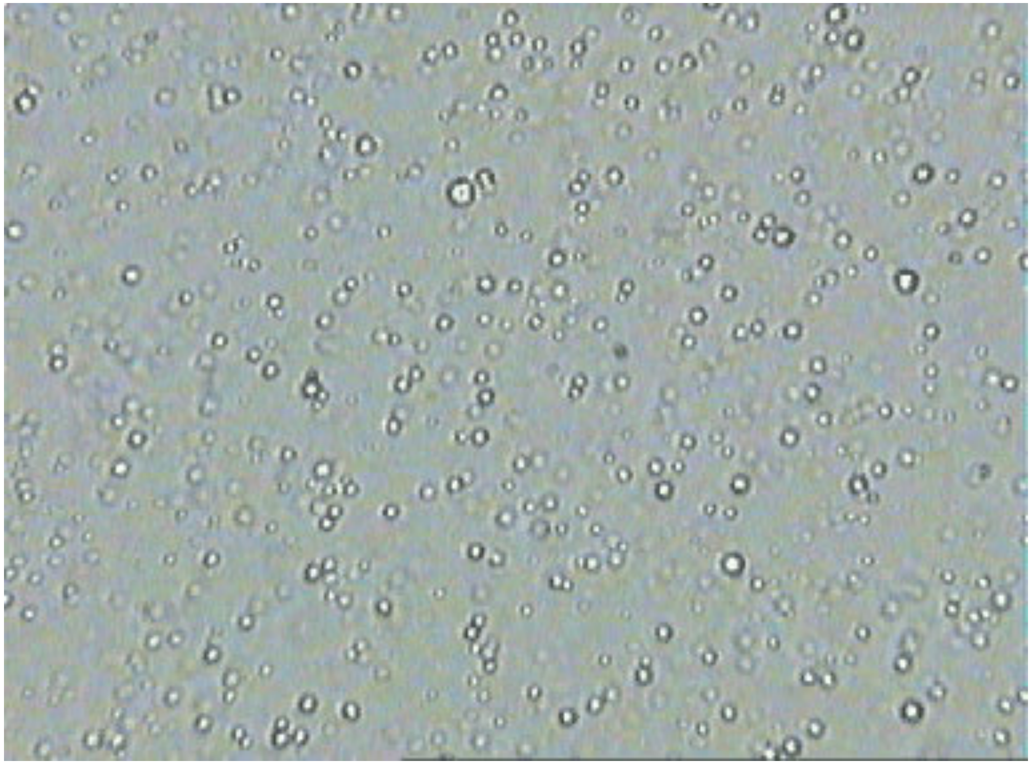
- Random walkers
- Temperature, Boltzmann's constant
- Einstein and 1905
- Mean-squared velocity, "ensemble"
- "Brownian movement"
- "Microscopic theory" (ch.2 is "Macroscopic theory")

→ A kernel of a deep idea is here, the distinction between "lots of little things" versus "big things"

[statistical mechanics being the thread tying things together]

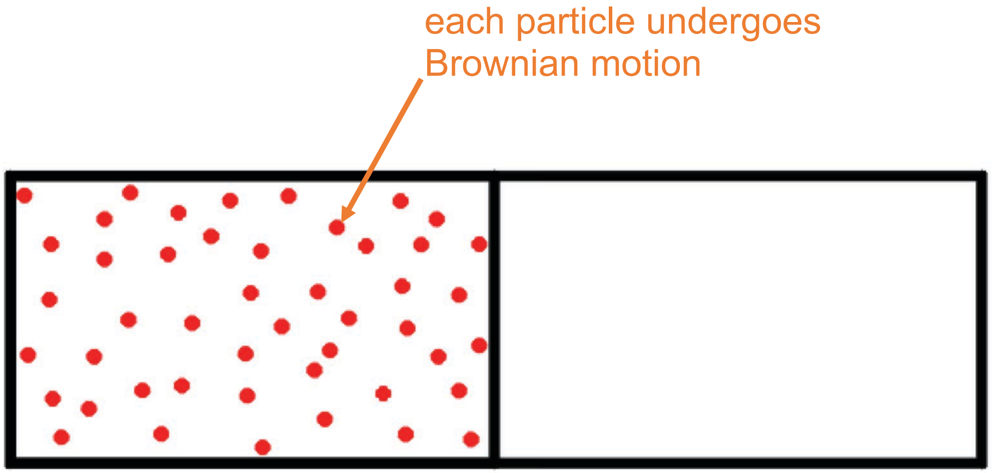
Berg (1993)

Brownian motion



http://www.microscopy-uk.org.uk/dww/home/hombrown.htm

Diffusion

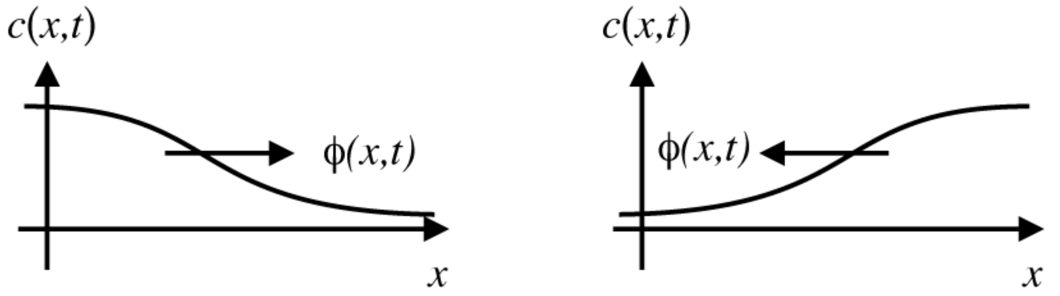


http://en.wikipedia.org/wiki/Image:Entropie.png

Diffusion (1-D)

- Thomas Graham (Scottish chemist, ~1828-1833)

[pioneered the concept of dialysis]

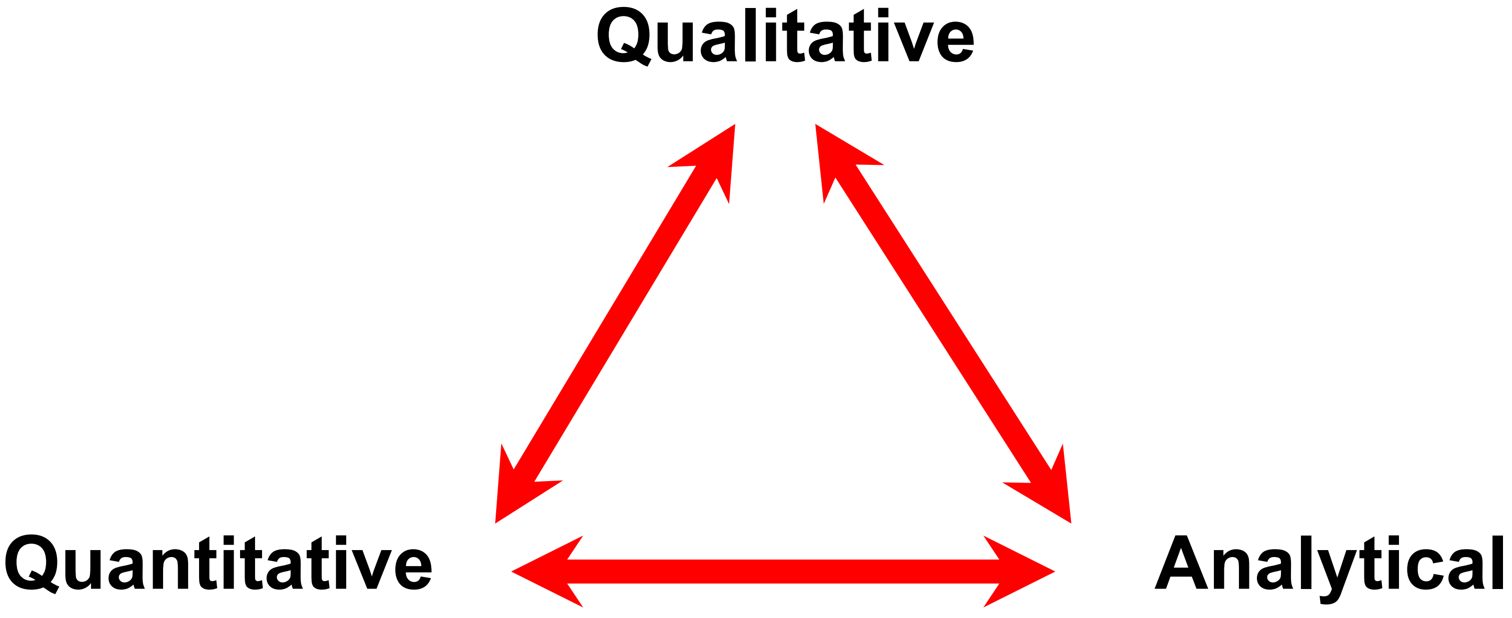


- Adolf Fick (German physiologist, ~1855)

[BTW: uncle to person who first successfully put a contact lens on a person in 1888!]

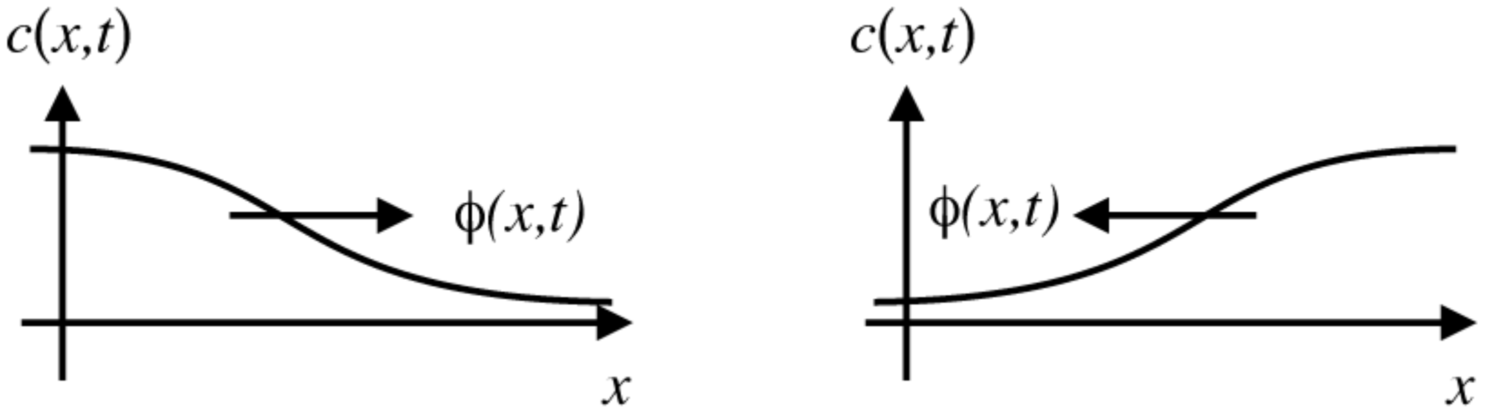
“ A few years ago, Graham published an extensive investigation on the diffusion of salts in water, in which he more especially compared the diffusibility of different salts. It appears to me a matter of regret, however, that in such an exceedingly valuable and extensive investigation, the development of a fundamental law, for the operation of diffusion in a single element of space, was neglected, and I have therefore endeavoured to supply this omission.”

- A. Fick (1855)


Qualitative
Quantitative
Analytical

Diffusion (1-D)

From Graham's observations (~1830):



Freeman

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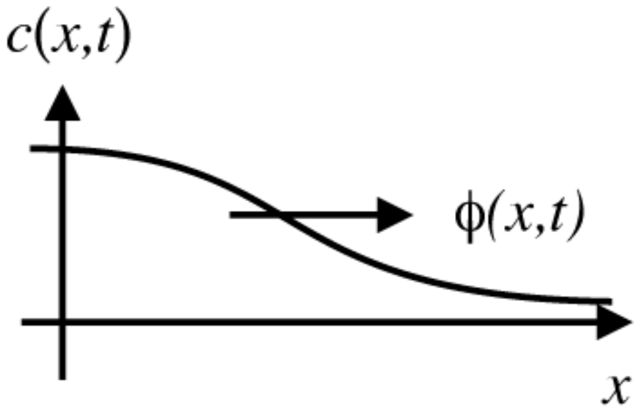
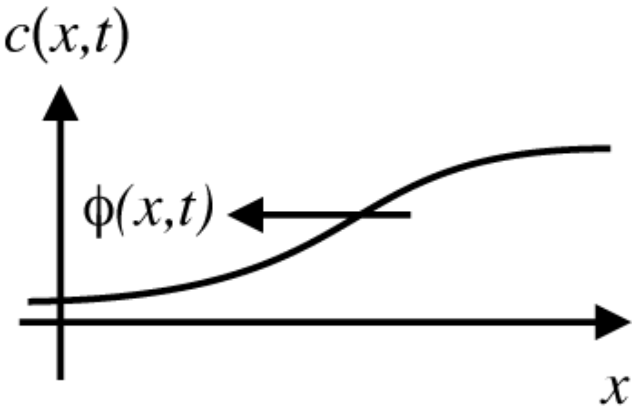




$c(x,t)$ — Concentration - of solute in solution [mol/m^3]

$\phi(x,t)$ — Flux - net # of moles crossing per unit time t through a unit area perpendicular to the x-axis [$mol/m^2 \cdot s$]

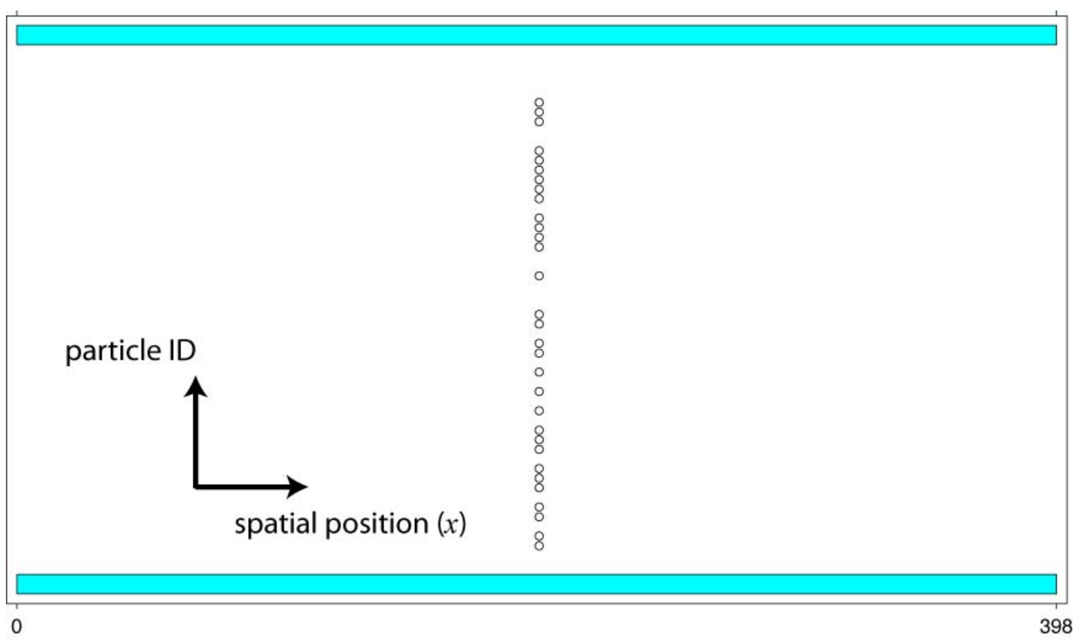
Note: flux is a vector!

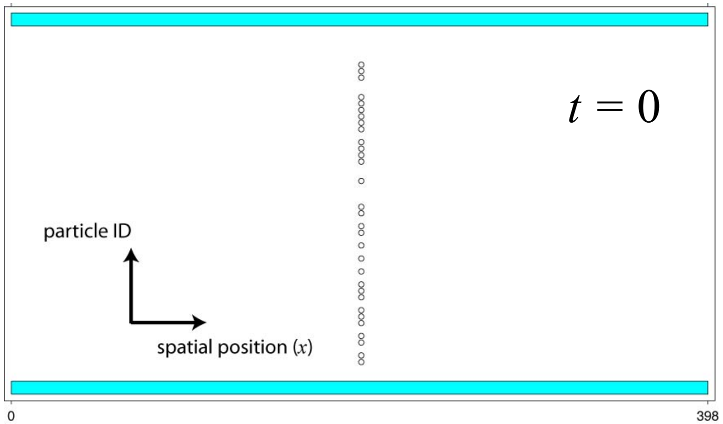
x, t — Position [m], Time [s]

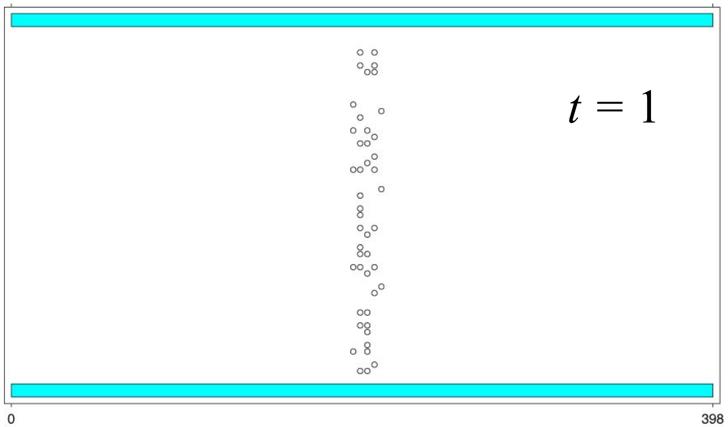
Short Excursion: Microscopic Basis for Diffusion

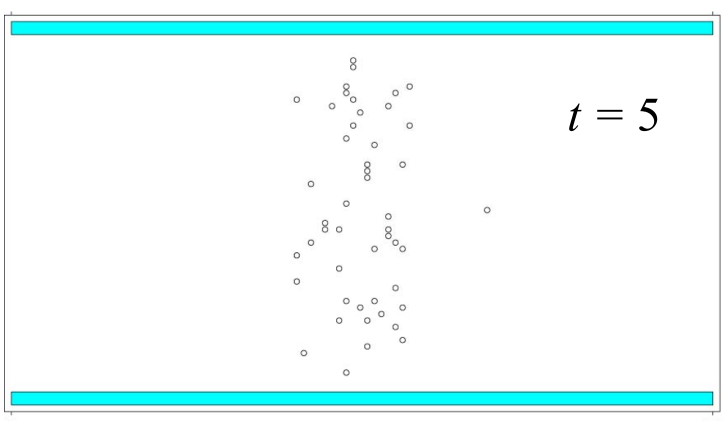
Brownian motion ⇒ 'Random Walker' (1-D)

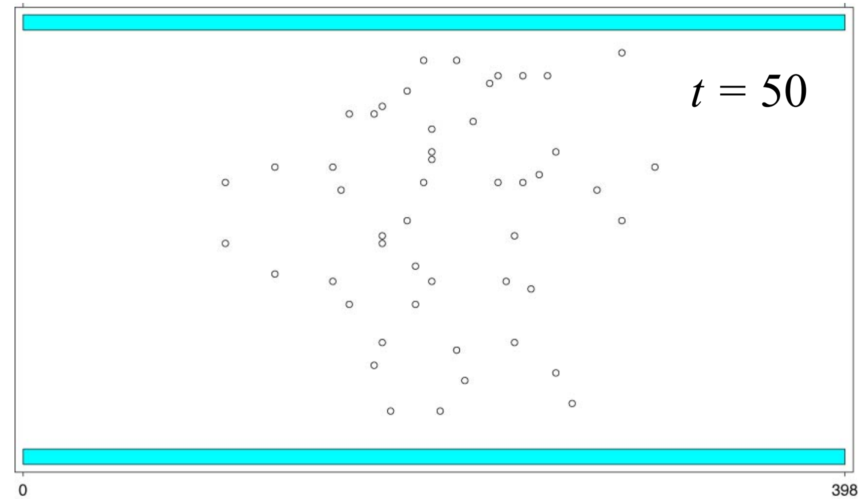
Ensemble of Random Walkers

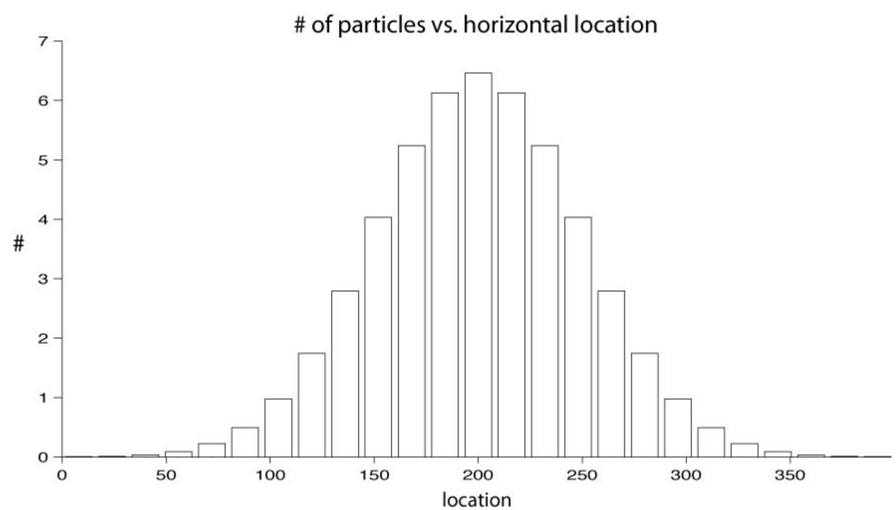



$t = 0$
particle ID
spatial position (x)
0
398


$t = 1$
0
398

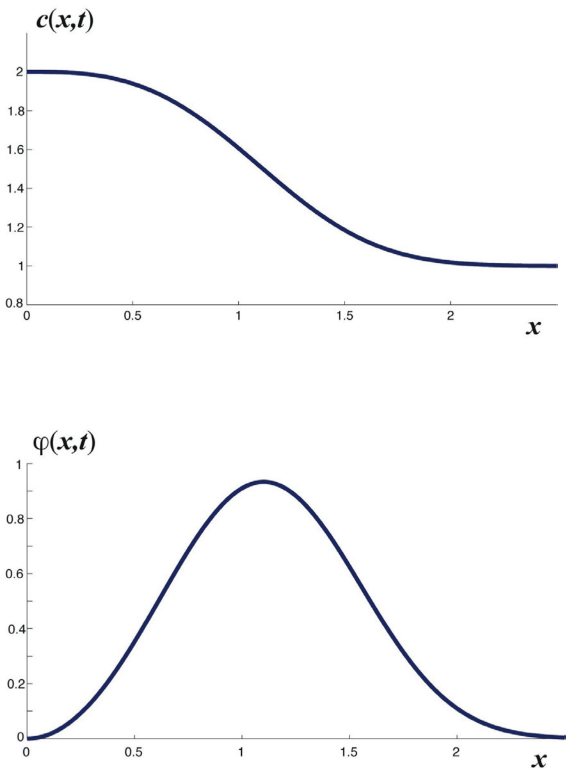

$t = 5$
0
398


$t = 50$
0
398

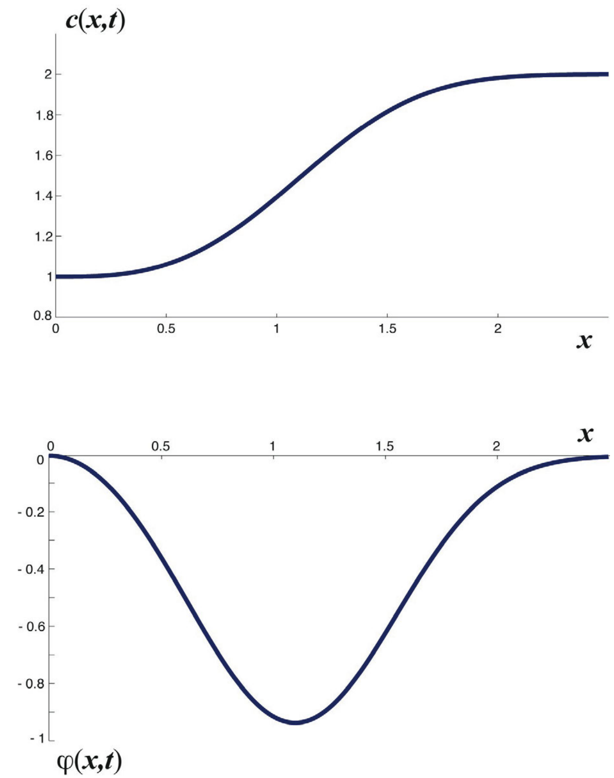

# of particles vs. horizontal location
#
location
0
1
2
3
4
5
6
7
0
50
100
150
200
250
300
350

<u>Fick's 1st Law</u> (1-D)

Profile 1



Profile 2



$$\phi(x,t) \propto -\frac{\partial c(x,t)}{\partial x}$$

Diffusion Constant (D)

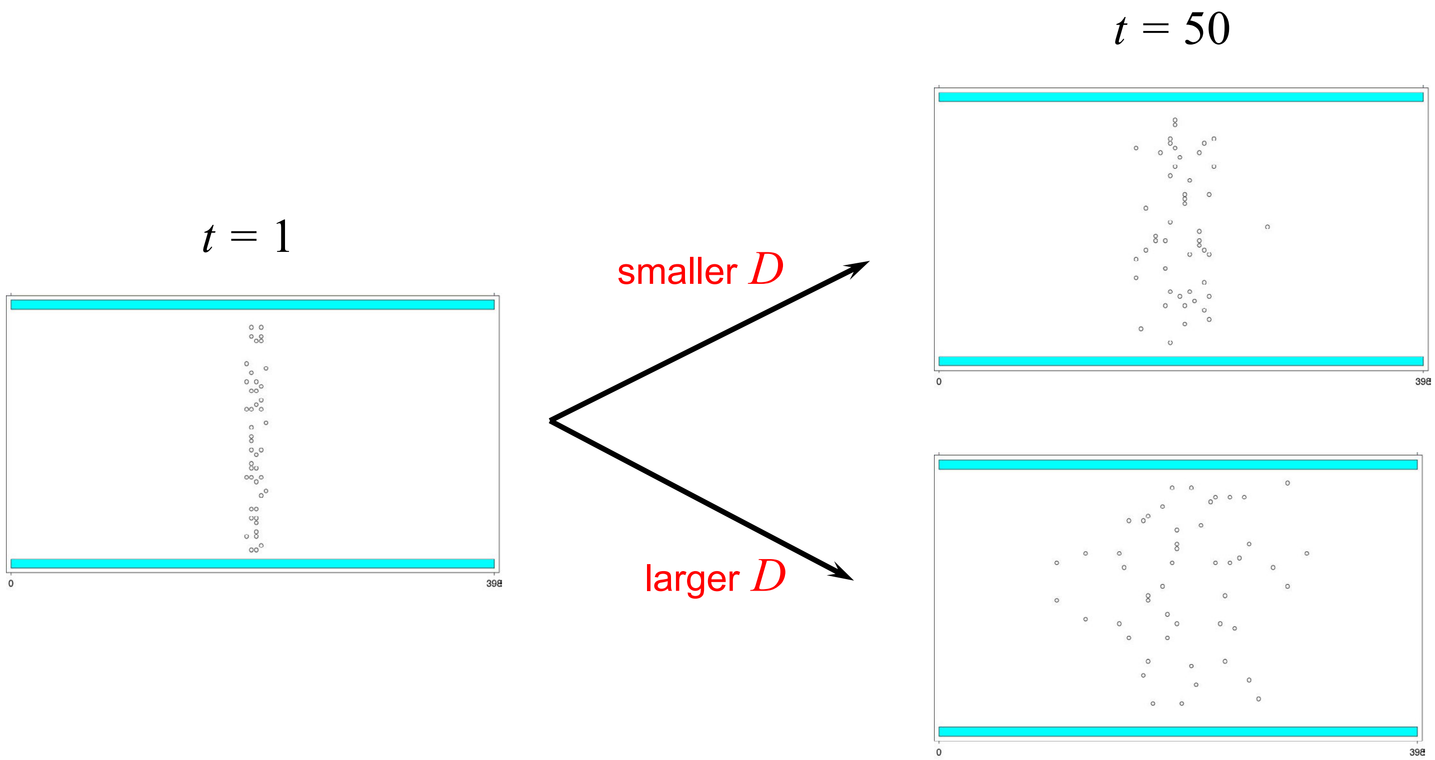
$$\phi(x,t) \propto -\frac{\partial c(x,t)}{\partial x}$$

constant of proportionality?

$$\boxed{\phi(x,t) = -D\frac{\partial c(x,t)}{\partial x}}$$

- diffusion constant is always positive (i.e., $D > 0$)
- determines time it takes solute to diffuse a given distance in a medium
- depends upon both solute and medium (solution)
- *Stokes-Einstein relation* predicts that D is inversely proportional to solute molecular radius

Diffusion Constant (D)



Generalizations

Higher Dimensions:

$$\phi(x,t) = -D\frac{\partial c(x,t)}{\partial x} \quad \longleftrightarrow \quad \vec{\phi} = -D\nabla c$$

$$\text{where} \quad \nabla c = \hat{x}\frac{\partial c}{\partial x} + \hat{y}\frac{\partial c}{\partial y} + \hat{z}\frac{\partial c}{\partial z} = \mathrm{grad}(c)$$

Analogous Flux Laws:

Heat Flow (Fourier): $$\phi_h = -\sigma_h\frac{\partial T}{\partial x}$$ *heat flow, thermal conductivity, and temperature*

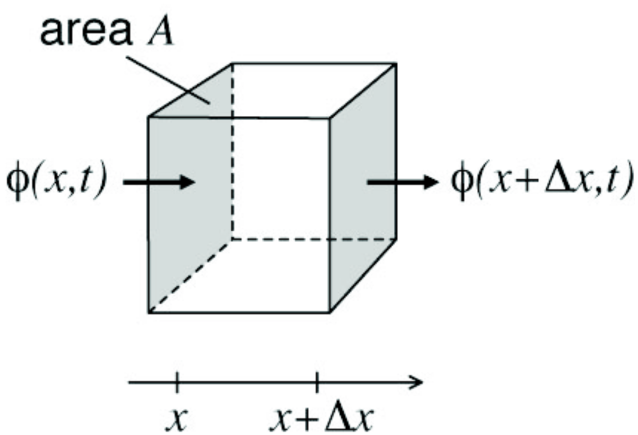
Electric Conduction (Ohm): $$J = -\sigma_e\frac{\partial \psi}{\partial x}$$ *current density, electrical conductivity, and electric potential*

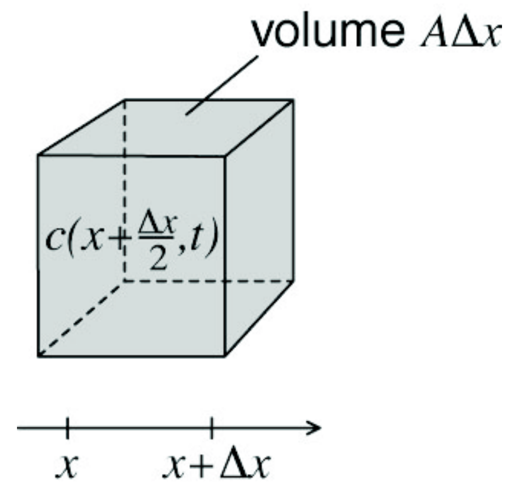
Convection (Darcy): $$\Phi_v = -\kappa\frac{\partial p}{\partial x}$$ *fluid flow, hydraulic permeability, and pressure*

Diffusion (Fick): $$\phi = -D\frac{\partial c}{\partial x}$$

Continuity equation

$\Rightarrow$ imagine a cube (with face area A and length Δx) and a time interval Δt

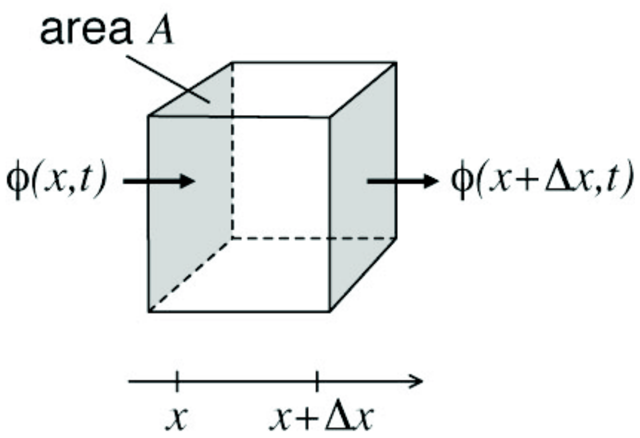


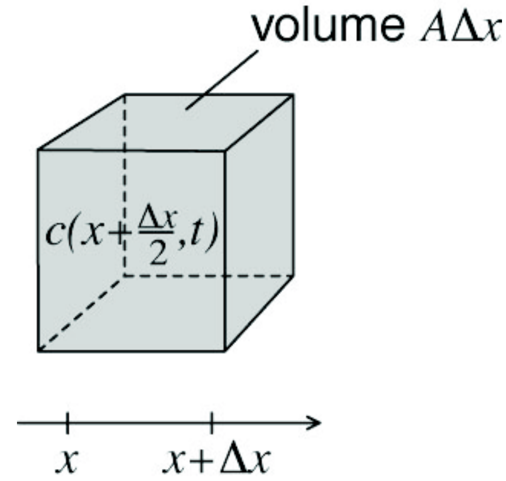


solute entering from *left* - solute exiting from *right* = change in amount of solute *inside* cube
(during time interval $[t,\ t+\Delta t]$) (during time interval $[t,\ t+\Delta t]$)

$$A\,\Delta t\,\phi(x,t) \qquad\qquad A\,\Delta x\,c(x,t)$$

Weiss





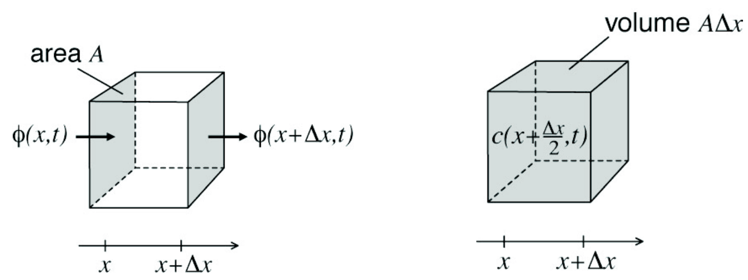
solute entering from left - solute exiting from right = change in amount of solute inside cube
(during time interval $[t, t+\Delta t]$) (during time interval $[t, t+\Delta t]$)

$$\underbrace{A\,\Delta t\,\phi(x,t+\Delta t/2)}_{\substack{\text{amount of solute entering}\\ \text{on left side of cube}}} - \underbrace{A\,\Delta t\,\phi(x+\Delta x,t+\Delta t/2)}_{\substack{\text{amount of solute leaving}\\ \text{on right side of cube}}} = \underbrace{A\,\Delta x\,c(x+\Delta x/2,t+\Delta t)}_{\substack{\text{amount of solute in cube at}\\ \text{the end of the interval}}} - \underbrace{A\,\Delta x\,c(x+\Delta x/2,t)}_{\substack{\text{amount of solute in cube at}\\ \text{the start of the interval}}}$$

$$-\frac{\phi(x+\Delta x,t+\Delta t/2)-\phi(x,t+\Delta t/2)}{\Delta x} = \frac{c(x+\Delta x/2,t+\Delta t)-c(x+\Delta x/2,t)}{\Delta t}$$

$$-\frac{\phi(x+\Delta x, t+\Delta t/2) - \phi(x, t+\Delta t/2)}{\Delta x} = \frac{c(x+\Delta x/2, t+\Delta t) - c(x+\Delta x/2, t)}{\Delta t}$$

$$\lim_{\Delta t, \Delta x \to 0} \quad \Longrightarrow \quad \boxed{\frac{\partial \phi}{\partial x} = -\frac{\partial c}{\partial t}}$$



$\Rightarrow$ conservation of mass within the context of our imaginary cube yielded the *continuity equation*

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

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

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

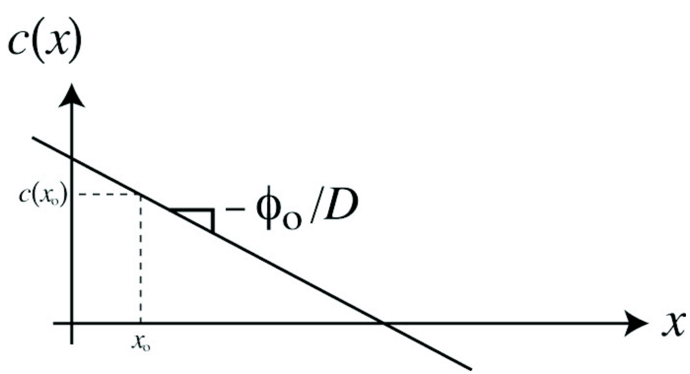
$D = 0 \Rightarrow$ non-diffusible solute is automatically at equilibrium

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

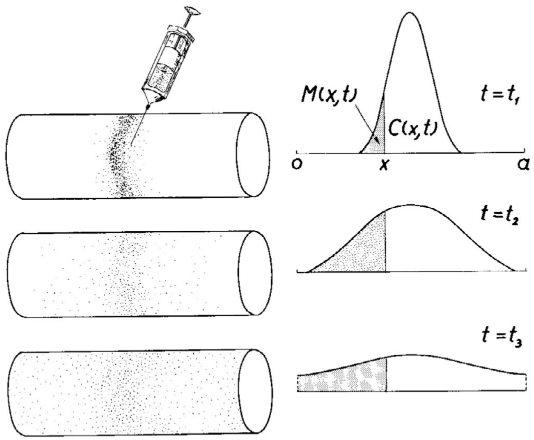
[Dirac delta function $\delta(x)$]

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:

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



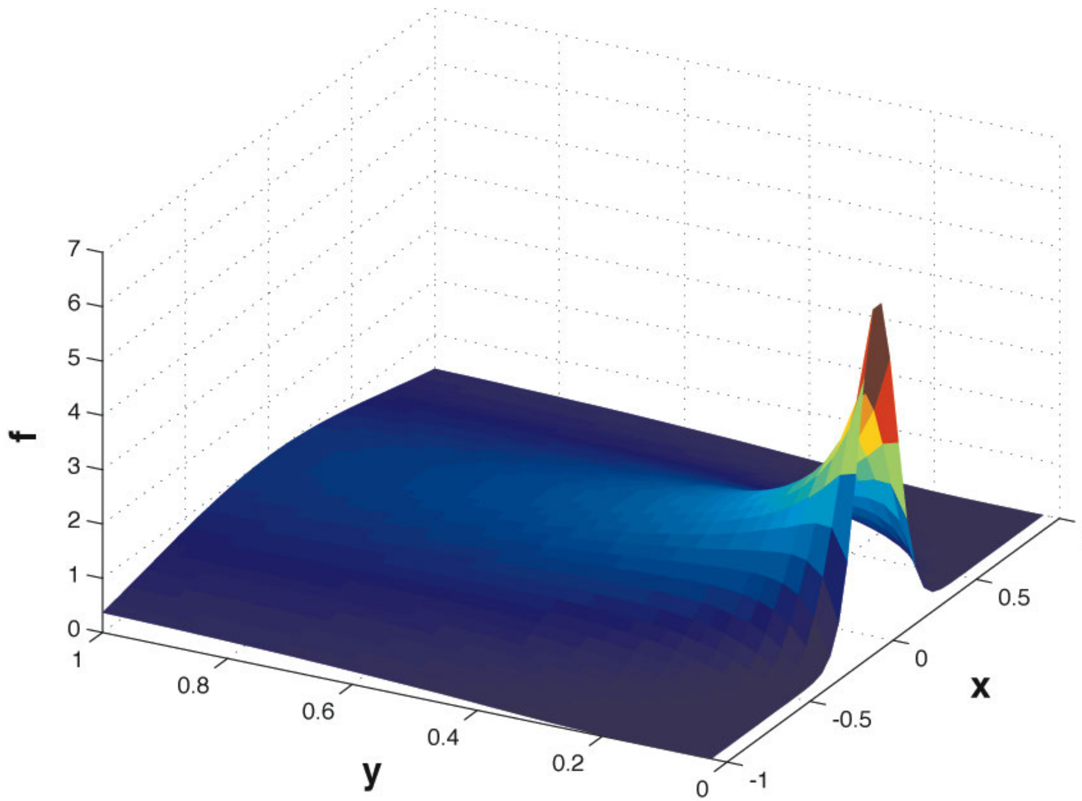
Batschelet Fig.12.5

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

Solution

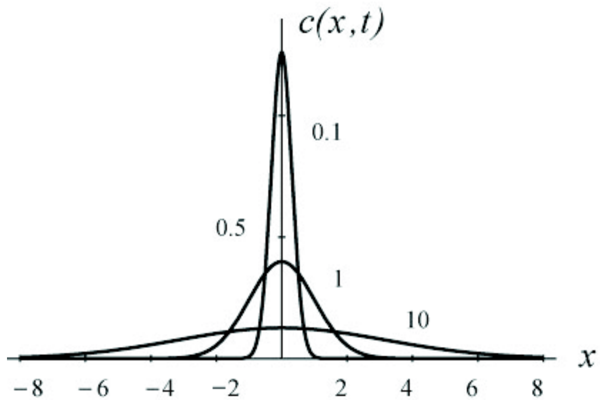
(for t > 0)

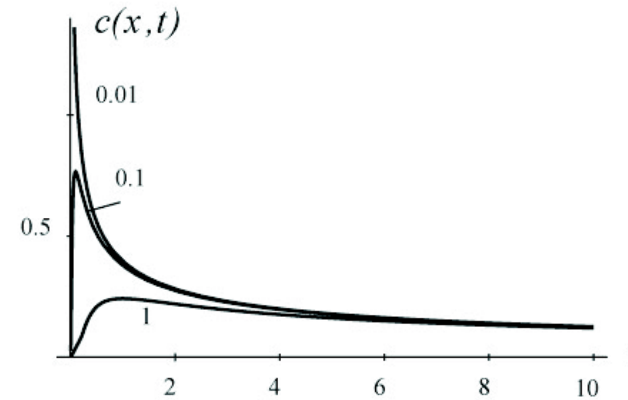
$$\boxed{c(x,t) = \frac{n_o}{\sqrt{4\pi D t}} e^{-x^2/4Dt}}$$

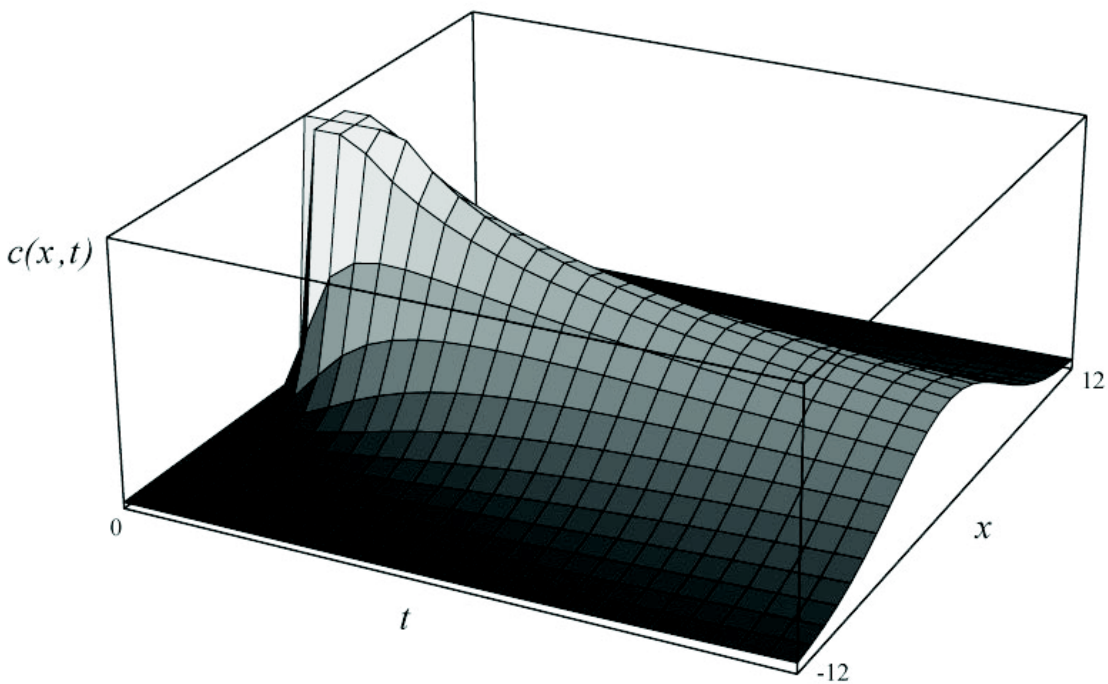


$$f(x, y) = \frac{1}{\sqrt{y}} e^{-x^2/y}$$

solution to
diffusion equation!







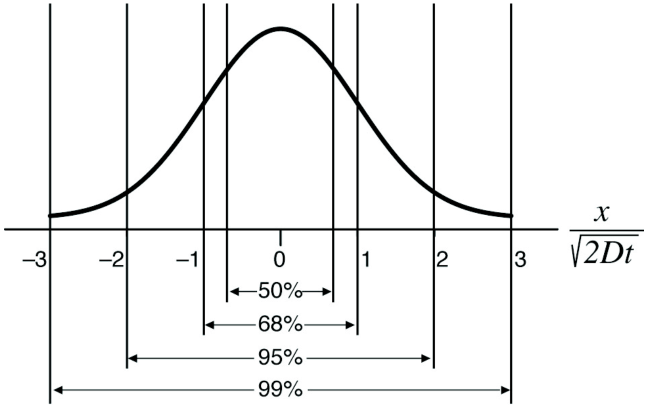
Weiss Fig.3.14 (modified)

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 $x_{1/2}$?

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

For small solutes (e.g. K^+ at body temperature) $D \approx 10^{-5} \ \frac{\mathrm{cm}^2}{\mathrm{s}}$

	$x_{1/2}$	$t_{1/2}$
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

Exercise

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 $D = 5 \times 10^{-6}\ \mathrm{cm^2/s}$.

→ 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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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.

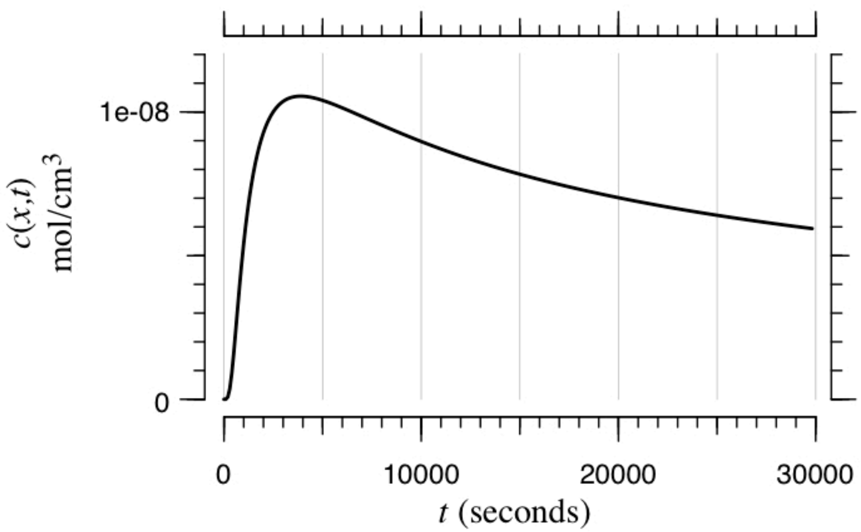
1.3 days

→ 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.

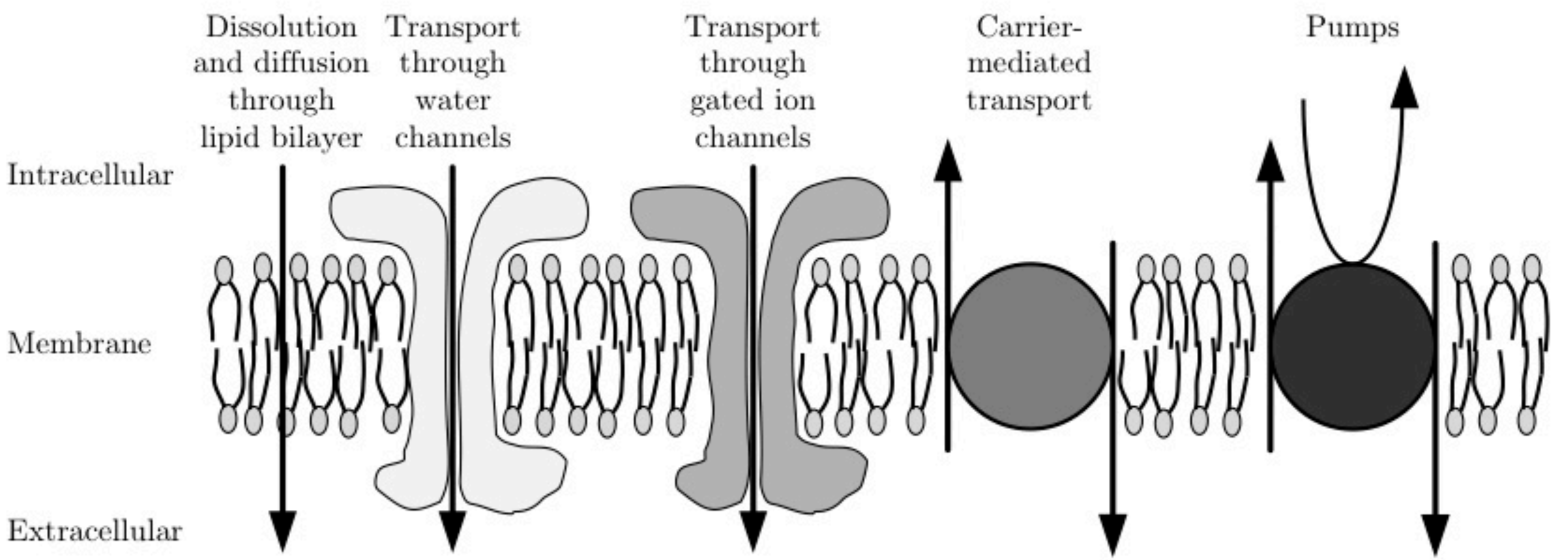
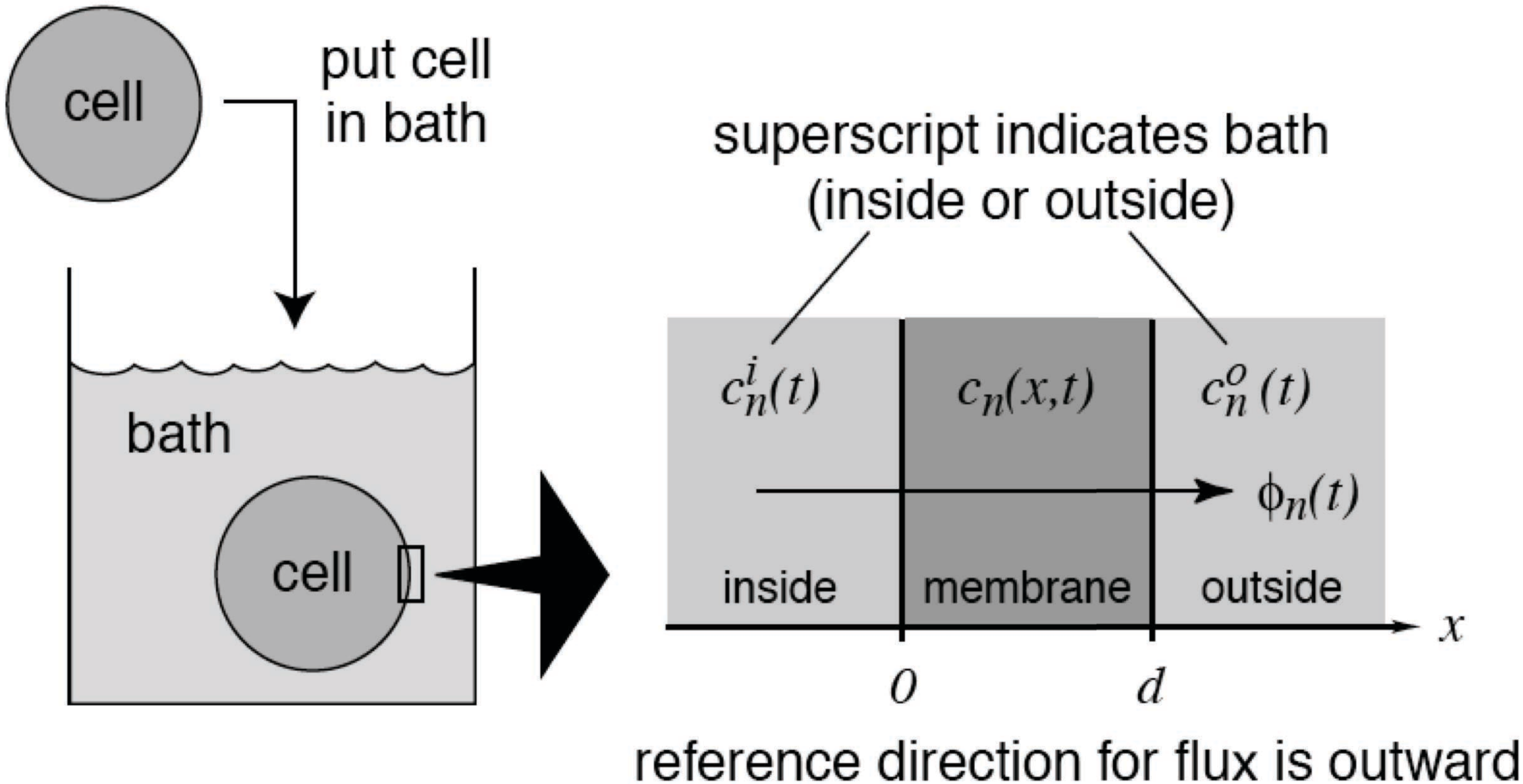

Dissolution and diffusion through lipid bilayer
Transport through water channels
Transport through gated ion channels
Carrier-mediated transport
Pumps
Intracellular
Membrane
Extracellular

Figure 2.19

Membrane Diffusion: Two-Compartment Geometry



Diffusion Through Cell Membranes: History 101

Diffusion through Cell Membranes

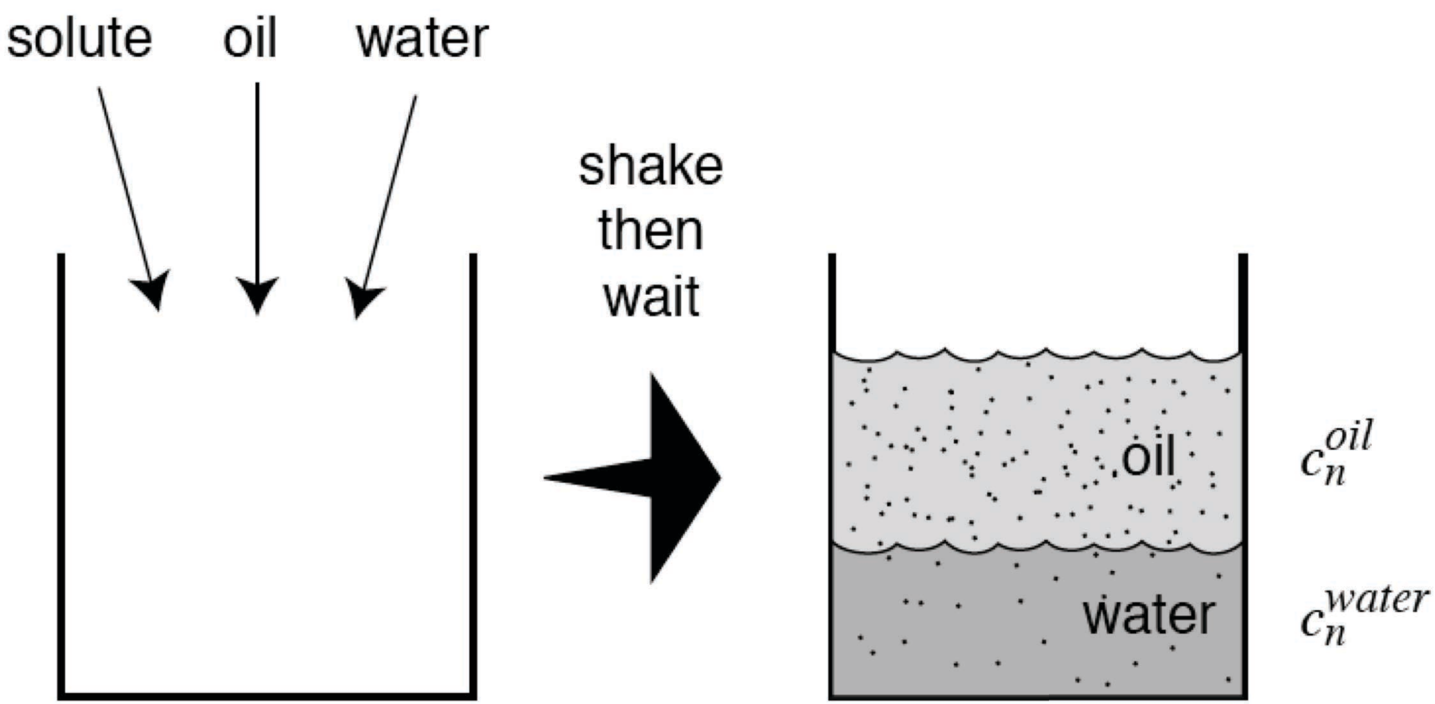
Charles Ernest Overton (late 1800s): first systematic studies
- qualitative:
  - put cell in bath with solute
  - wait, rinse, squeeze
  - analyze to see how much got in (+ = some; +++ = a lot)
- 100's of solutes, dozens of cell types
- surprising results: previously cell membranes had been thought to 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
  → membrane is lipid (specifically cholesterol and phospholipids)
- certain cells concentrate some solutes → active transport
- potency of anesthetics correlated with lipid solubility
  → 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

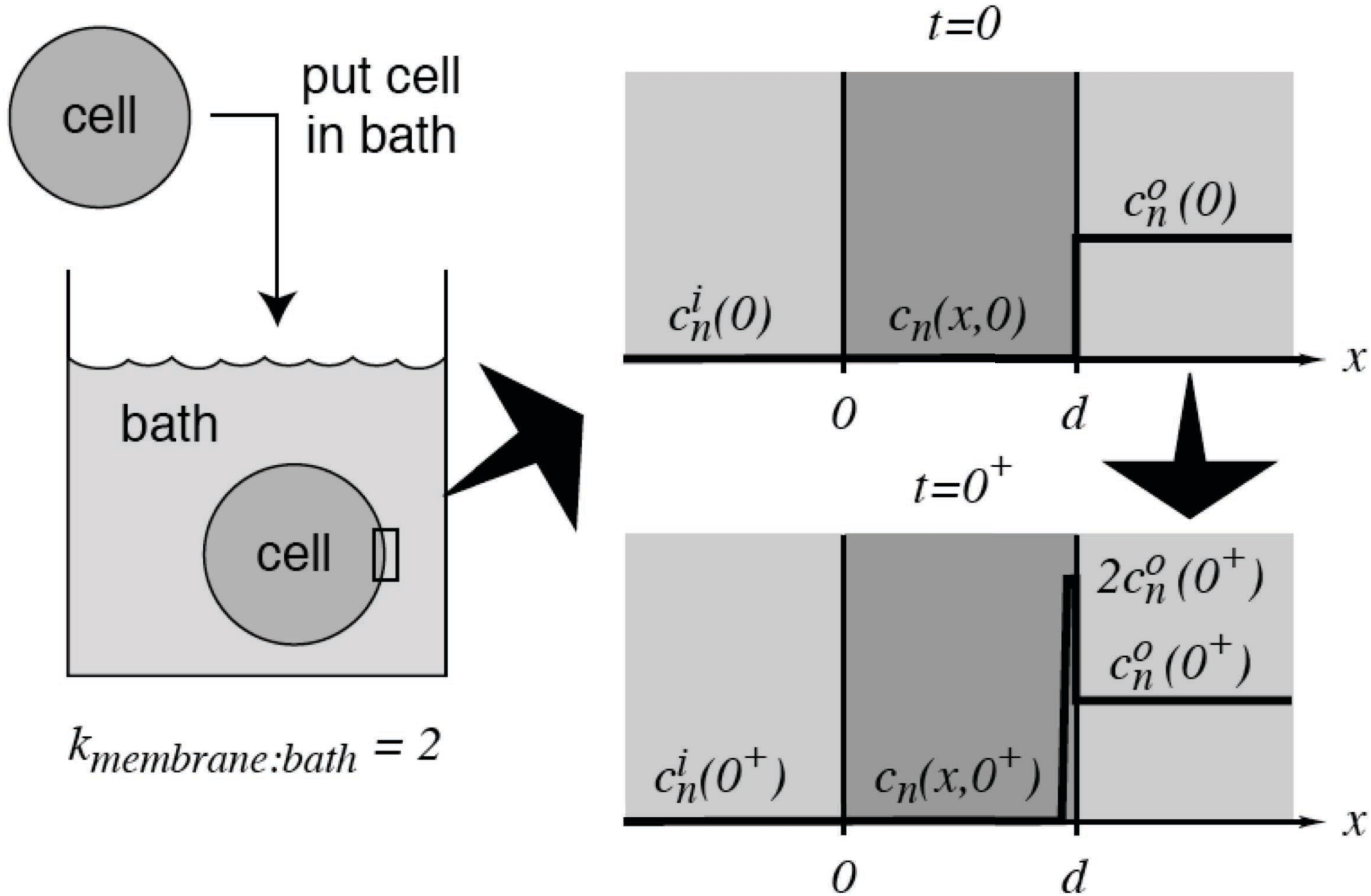
Step 1: Dissolve



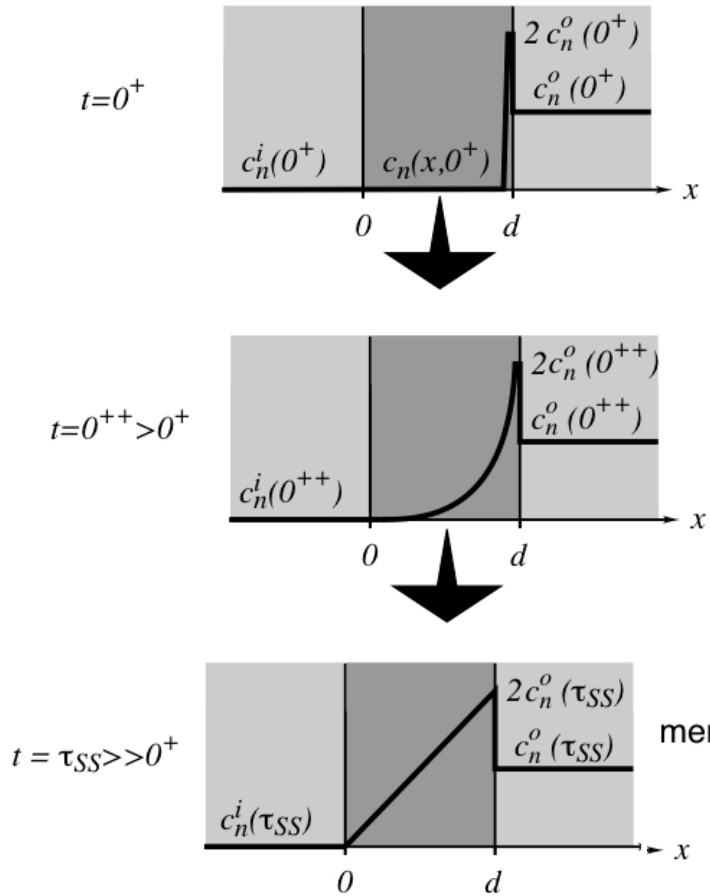
Equilibrium characterized by relative solubilities
of solute n in oil and water

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

Assume Dissolving is fast relative to diffusing



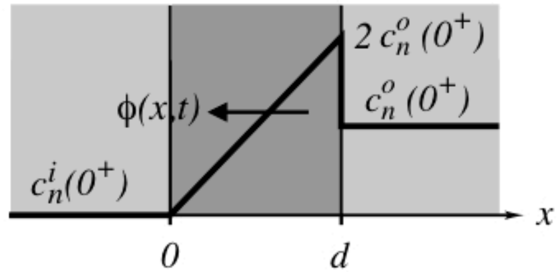
Step 2: Solute diffuses though membrane



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