Topic 8: Diffusion

(Chapter 13 in book)

Overview:

How does thermal energy cause things to move?

How do molecules spread out in time?

Why do things flow when there are concentration gradients?

How well can cells detect diffusing molecules in their environment?

Thermal motion - diffusion

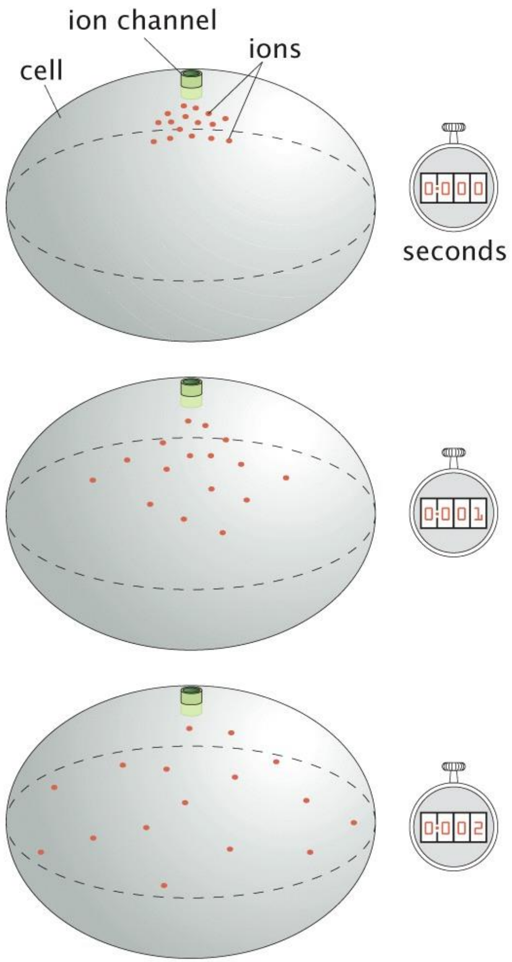


Figure 13.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

When a molecule is put into a bath at a particular temperature, it gets random kicks from the thermal energy in the bath

These random kicks cause it to perform a random walk

This random walk is called ‘Brownian motion’ after the scientist who observed cells undergoing random motion under a microscope

for small molecules, these random kicks are not small and can lead them to move rapidly and distribute uniformly

this random motion generated by thermal noise is the process of diffusion

Diffusion can be slow and fast

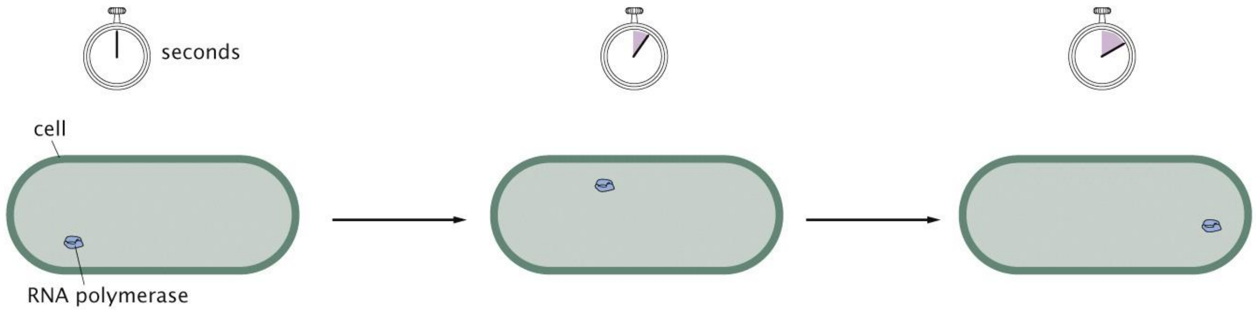


Figure 13.2a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

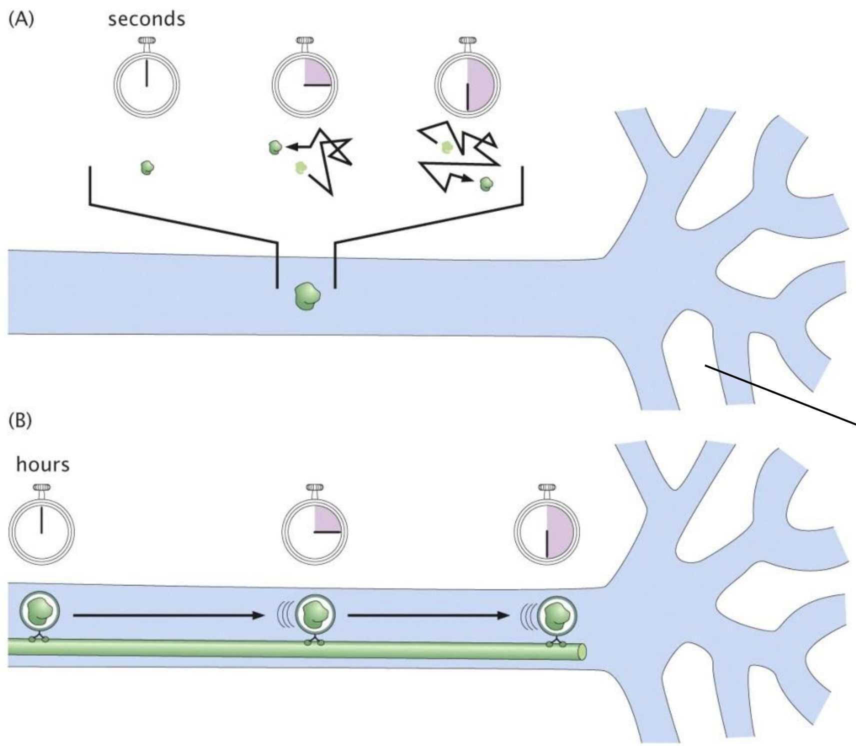


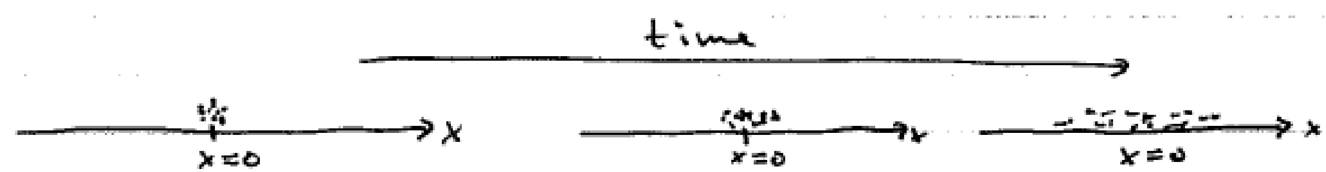
Figure 13.5 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

In E. coli, whose size ~ microns, diffusion moves thing across the cell in less than a second. So things tend to be well mixed.

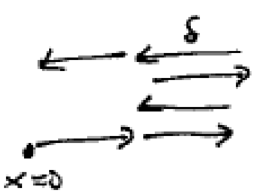
In nerve cells, whose size > milimeters → meters, diffusion is too slow, on the order of days, so molecular motors are used to shuttle cargo down the cell (from ‘Random Walks in Biology’ by H. Berg

- Consider N particles, each moving with an average speed $v_x = \sqrt{kT/m}$

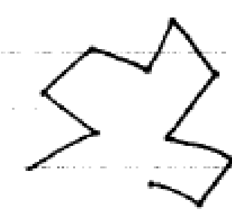
- How do they spread in time?



- If we look @ one molecule's walk:



or in 2D



① On average it collides every Δt seconds, and during this time has moved $\delta = \pm v_x \Delta t$.
② The $\pm$ simply expresses that it moves with equal probability to the left and right.
③ Particles are independent – motion doesn't depend on the others

$\underline{\langle x \rangle}$:

- let $x_i(n) \equiv$ position of ith particle after n steps.

$$x_i(n) = x_i(n-1) \pm \delta \qquad \text{(50\% moves left/right)}$$

so

$$\langle x(n) \rangle = \frac{1}{N} \sum_{i=1}^{N} x_i(n)$$

$$= \frac{1}{N} \sum_{i=1}^{N} \left(x_i(n-1) \pm \delta \right) = \frac{1}{N} \sum_{i=1}^{N} x_i(n-1) + \cancelto{0}{\frac{1}{N} \sum_{i=1}^{N} \pm \delta}$$

$$= \langle x(n-1) \rangle$$

so

if $\langle x(0) \rangle = 0$ then $\langle x(n) \rangle = 0$ for all time

$\Rightarrow$ on average there is no net drift of the particles from $x=0$ – they remain centred.

$\underline{\langle x^2 \rangle}$:

$$\langle x^2(n) \rangle = \frac{1}{N} \sum_{i=1}^{N} \left(x(n-1) \pm \delta \right)\left(x(n-1) \pm \delta \right)$$

$$= \frac{1}{N} \sum_{i=1}^{N} \left(x(n-1)^2 \pm 2\delta \overset{\nearrow 0}{\cancel{x}(n-1)} + \delta^2 \right)$$

so

$$\langle x^2(n) \rangle = \langle x(n-1)^2 \rangle + \delta^2$$

Start with: $\langle x(0)^2 \rangle = 0 \Rightarrow \langle x(1)^2 \rangle = \delta^2$

$$\Rightarrow \langle x(2)^2 \rangle = \langle x(1)^2 \rangle + \delta^2 = 2\delta^2 \quad \text{etc....}$$

so $\langle x(n)^2 \rangle = n\delta^2$

but, & total time, $t = n\Delta t$ so $n = t/\Delta t$

or

$$\langle x^2(t) \rangle = \left(\frac{\delta^2}{\Delta t} \right) t$$

rewrite: $\boxed{\langle x^2(t) \rangle = 2Dt}$

Diffusion relation:

rewrite: $\boxed{\langle x^2(t)\rangle = 2Dt}$

where

$$D = \frac{1}{2}\frac{\delta^2}{\Delta t} = \frac{1}{2} v_x^2 \Delta t$$

$\equiv$ Diffusion coefficient $[m^2/t]$

3D: $\boxed{\langle \vec{r}^{\,2}(t)\rangle = 6Dt}$

2D: $\boxed{\langle \vec{r}^{\,2}(t)\rangle = 4Dt}$

So the particles spread in time & this is characterized by the diffusion coeff D.

Diffusion: some #'s

Or,

$$\sqrt{\langle x^2 \rangle} = \sqrt{2Dt}$$

So diffusing particles, spread out as $\sqrt{t}$ instead of as t as a ballistic particle would

Table 13.1: Table of diffusion coefficients for different molecules. (Data for GFP from M. B. Elowitz et al., *J. Bacteriol.* 181:197, 1999 and yeast data from W. F. Marshall et al., *Curr. Biol.* 7:930, 1997.)

Molecule	Diffusion coefficient
Potassium ion in water	$\approx 2000\ \mu m^2/s$
GFP in *E.coli* cytoplasm	$\approx 7\ \mu m^2/s$
DNA in yeast nucleus	$5 \times 10^{-4}\ \mu m^2/s$

For a small ion in water in a bacteria, time for a diffusing particle to traverse the cell is:

$$t = \frac{<x^2>}{2D} = \frac{(1\ \mu m)^2}{2\ 2000\ \mu m^2/s} \sim \text{milliseconds}$$

so things mix fast in bacteria

For a neuron with a length around 1 cm, $t = \frac{<x^2>}{2D} = \frac{(1\ cm)^2}{2\ 2000\ \mu m^2/s}$ ~ 14 hours!!!

so diffusion is not a good way to move material around in a neuron

Random Walks: Binomial distribution

At a given time, what is the distribution of x?

- Consider a particle can move to the right with probability p, the prob of moving left is $q = 1-p$.

- Particle makes n moves, k are to the right. say it's, $r\,r\,l\,r\,l \ldots l\,r$, k r's.

$$\text{Prob} = p^k q^{n-k}$$

- Prob of k moves to the right → there are $\frac{n!}{k!(n-k)!}$ sequences that have k moves to the right.

so

$$P(k) = \frac{n!}{k!(n-k)!} p^k q^{n-k} \equiv \text{binomial dist'n}$$

Now: $x(n) = k\delta - (n-k)\delta = (2k-n)\delta$

so $\langle x(n) \rangle = (2\langle k \rangle - n)\delta$

where $\langle k \rangle = np$ for binomial

if $p = 1/2 \Rightarrow \langle x(n) \rangle = 0$

and

$$\langle x^2(n)\rangle = \langle [(2k-n)\delta]^2\rangle = (4\langle k^2\rangle - 4\langle k\rangle n + n^2)\delta^2$$

$$\& \quad \langle k^2\rangle = (np)^2 + npq$$

again for $p = 1/2$, $\langle x^2(n)\rangle = n\delta^2$

Now for diffusing particles, n & np are large! In one second, a particle will take about $\underline{\underline{10^{12}}}$ steps.

- When n & np are large, the binomial distribution becomes a gaussian, so

$$P(k)\,dk = \frac{1}{(2\pi\sigma^2)^{1/2}} e^{-(k-\mu)^2/2\sigma^2} dk$$

where $\mu = np = \langle k\rangle$ & $\sigma = npq = \langle k^2\rangle - \langle k\rangle^2$

Converting this to spatial (assignment):

$$\boxed{P(x)\,dx = \frac{1}{(4\pi Dt)^{1/2}} e^{-x^2/4Dt}\,dx}$$

So the distribution of positions for a diffusing particle, follows a Gaussian distribution

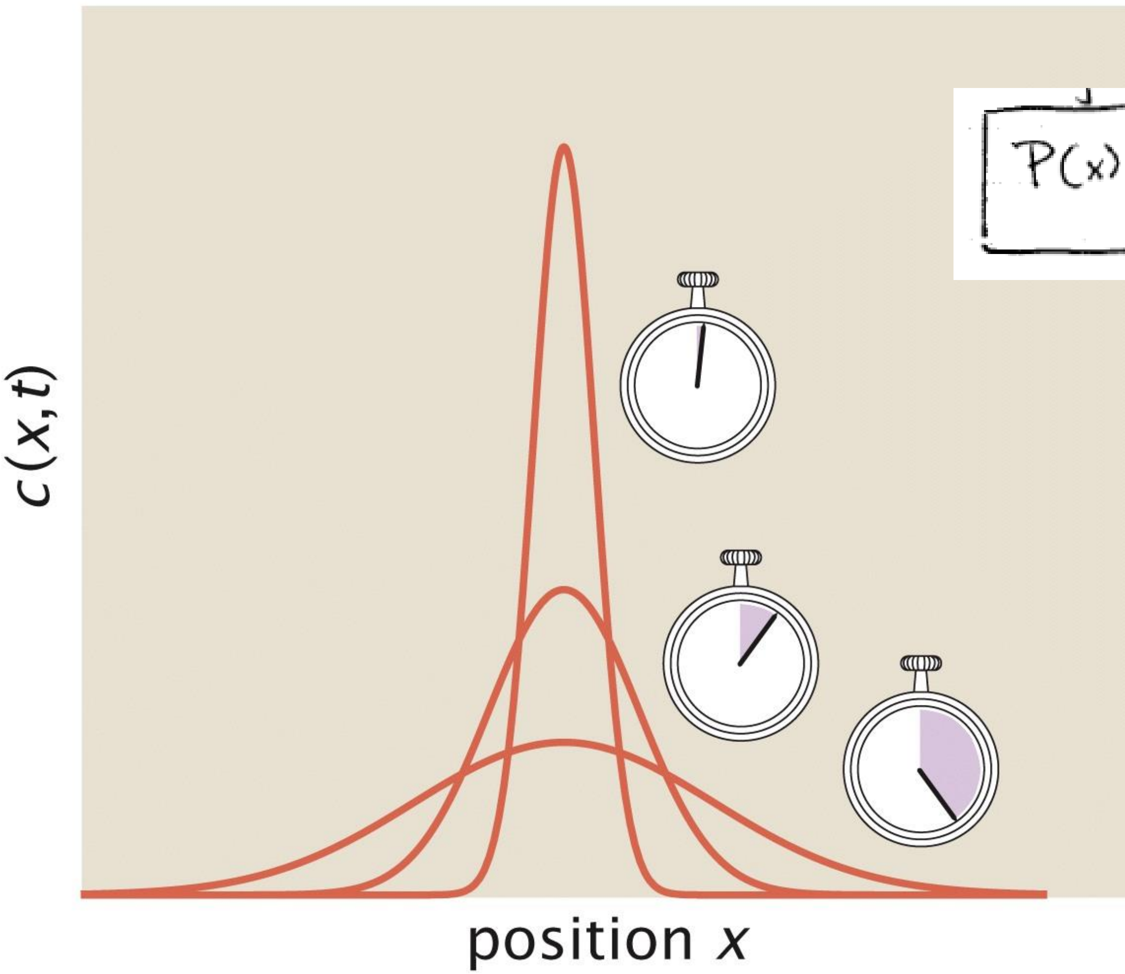


Figure 13.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

$$P(x)\,dx = \frac{1}{(4\pi D t)^{1/2}} e^{-x^2/4Dt}\,dx$$

spreads in time

Macroscopic diffusive transport: Fick's Equations

Previously, we were looking at the statistical behaviour of single diffusing particles.

Q: Can we derive an equation that will describe the dynamics of a concentration of particles diffusing in solution?

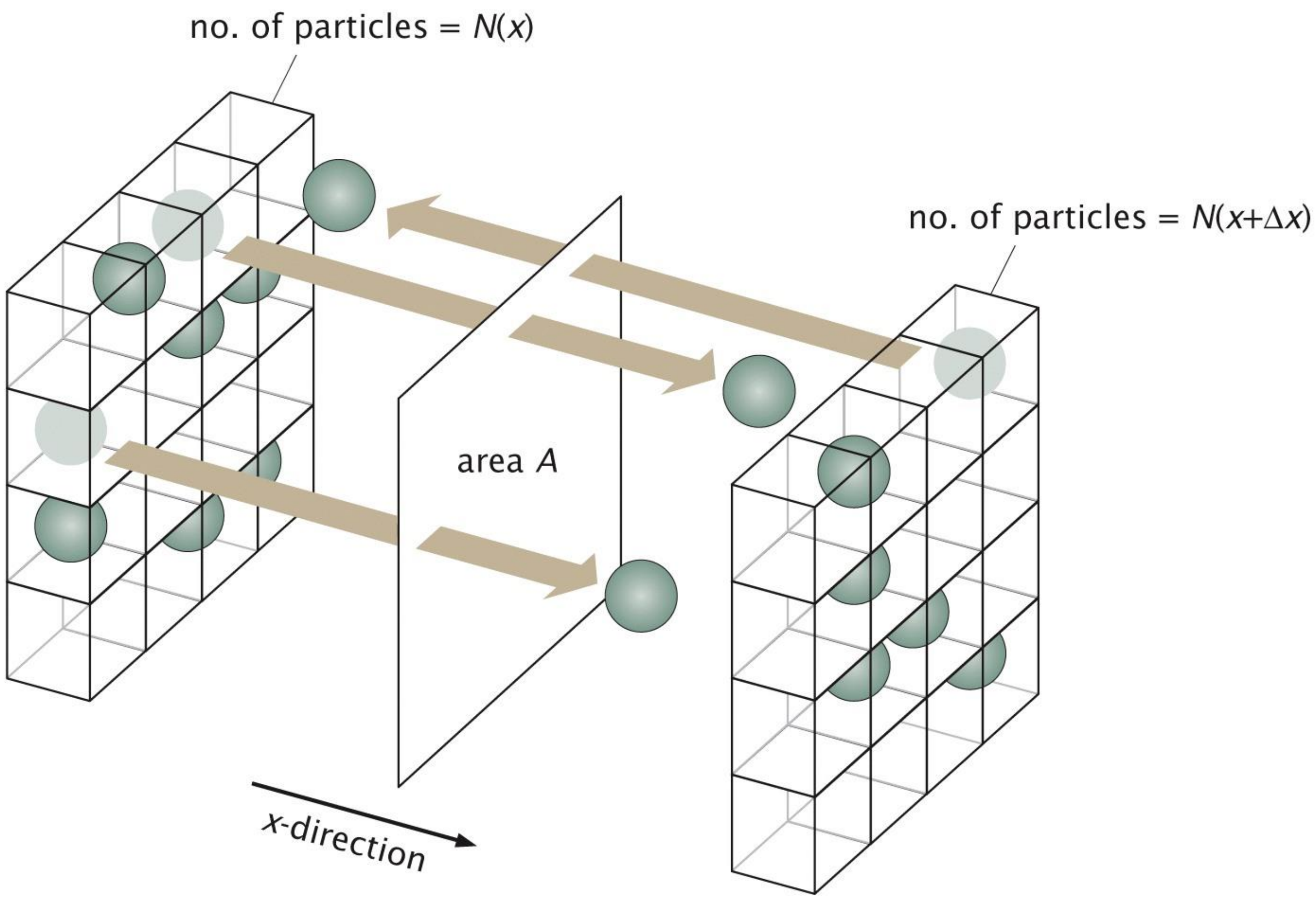


Figure 13.11 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Continuity Equation:

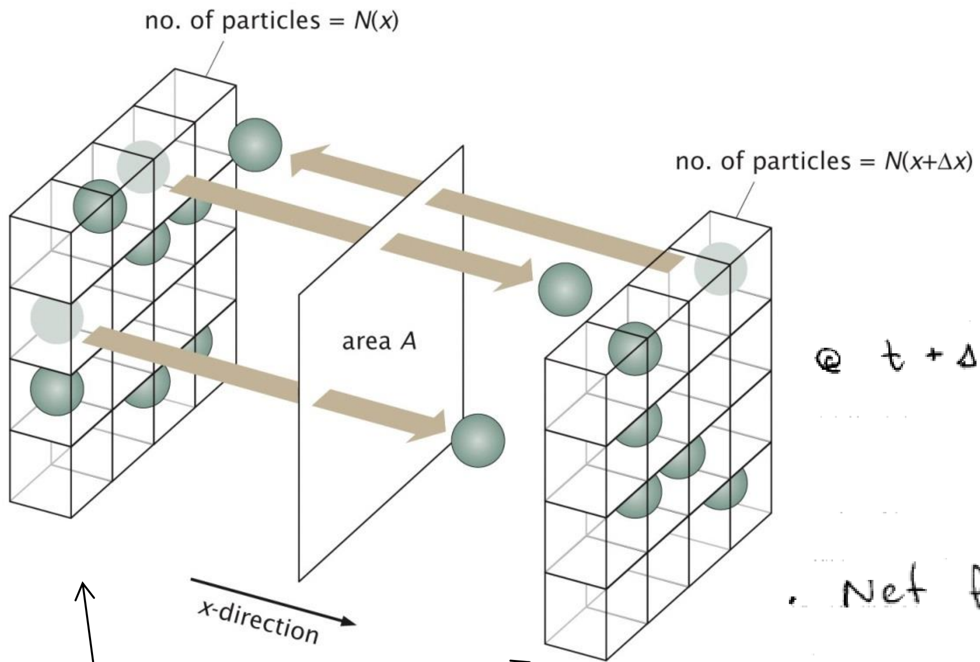


Figure 13.11 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

50/50 chance of moving left or right

Q: what is the flux of particles through the area A? flux = #/s/area

@ $t+\Delta t$: $\frac{1}{2}N(x)$ move right across A

$\frac{1}{2}N(x-\delta)$ move left across A

Net flow: $\frac{1}{2}N(x) - \frac{1}{2}N(x+\delta)$

Define flux: $j = -\frac{1}{2}\frac{[N(x+\delta) - N(x)]}{A\,\Delta t} \equiv$ #/second/area

$\times(\delta^2/\delta^2)$:

$$j = -\left(\frac{\delta^2}{2\Delta t}\right)^{D} \frac{1}{\delta}\left[\overbrace{\frac{N(x+\delta)}{A\delta}}^{C(x+\delta)} - \overbrace{\frac{N(x)}{A\delta}}^{C(x)}\right]$$ concentration

$$= -D\left[\frac{C(x+\delta) - C(x)}{\delta}\right]$$

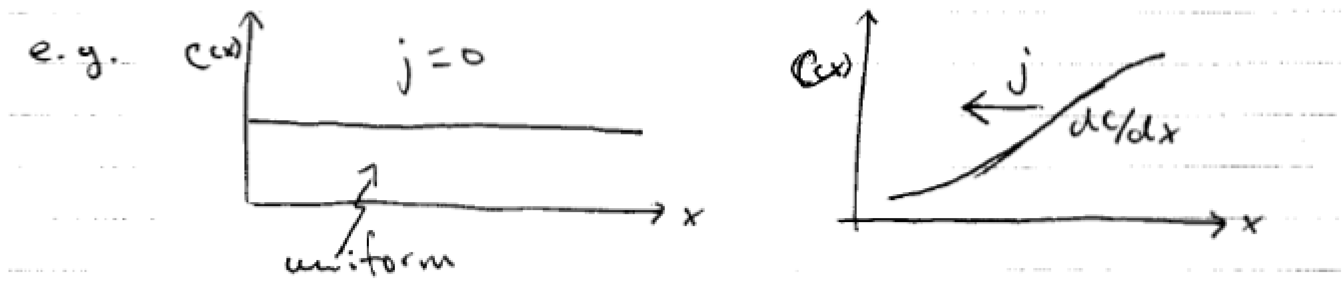
$$\boxed{j = -D\frac{dC(x)}{dx}}$$

Continuity equation: continued

So,

$$\boxed{j = -D\,\frac{dc(x)}{dx}}$$

thus if there is a concentration gradient, there will be a flux of particles



Particles diffuse from regions of high concentration to low. There is NO external force. It is an entropic force, that arises because there is more entropy when the system is well mixed, i.e a uniform concentration.

Diffusion equation:

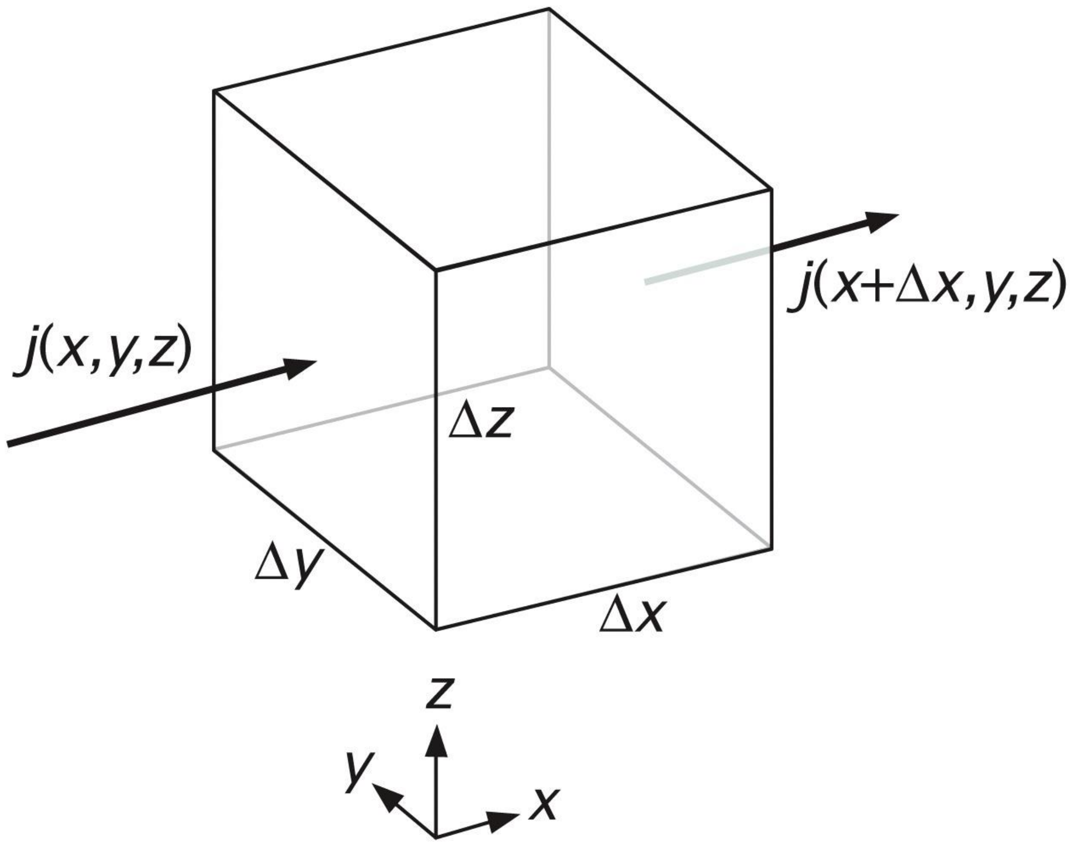


Figure 13.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

How does the concentration change at a given location and in time given that there are fluxes in the system?

Diffusion equation derivation:

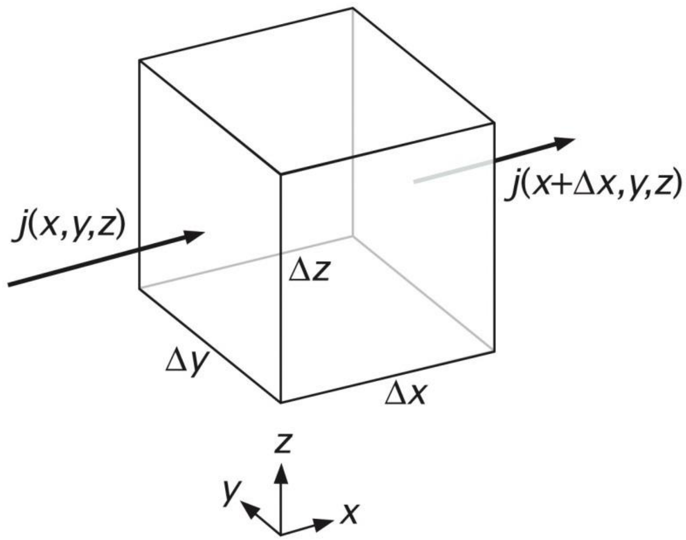


Figure 13.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

There are $j(x)A\,\Delta t$ entering from left and $j(x+\Delta x)A\,\Delta t$ leaving from the right

So the concentration change per unit time,

$$\frac{c(t+\Delta t)-c(t)}{\Delta t} = -\frac{1}{\Delta t}\left[j(x+\Delta x)-j(x)\right]\frac{A\,\Delta t}{A\,\Delta x}$$

Or as dt and dx → 0, these become derivatives, so

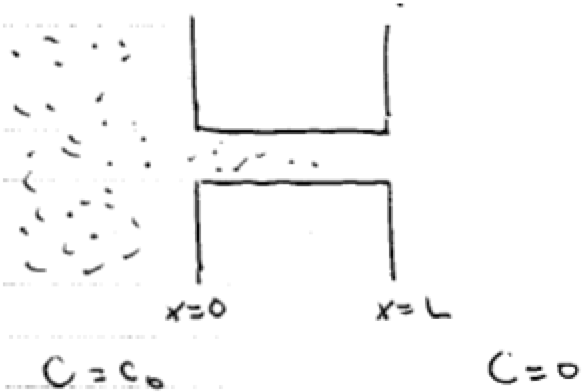
$$\frac{c(t+\Delta t)-c(t)}{\Delta t} = \frac{dc}{dt} = -\left[\frac{j(x+\delta)-j(x)}{\delta}\right] = -\frac{dj}{dx}$$

using Fick's Law:

$$\boxed{\frac{dc}{dt} = -D\frac{d^2c}{dx^2}} \equiv \text{Diffusion equation.}$$

This is a partial differential equation which in practice is hard to solve. We will just take known solutions

Applications of diffusion equation: diffusion through pore



- Salt diffusing through pore. One side @ concentration C_0 & the other @ $C=0$.

What is $C(x)$?

- However @ intermediate times, the system comes to quasi-equilibrium where $C(x)$ doesn't change with time so $dc/dt = 0$.

So $\Rightarrow$ $\frac{d^2c}{dx^2} = 0$

- What function has zero curvature and begins @ $C(0) = C_0$ & ends @ $C(L) = 0$?

- Ans: A line from C_0 to 0 @ $x=L$

so $C(x) = C_0\left(1 - \frac{x}{L}\right)$

flux: $j = -D\frac{dc}{dx}$

$j = \frac{DC_0}{L}$

Applications: Cell detecting diffusing nutrients

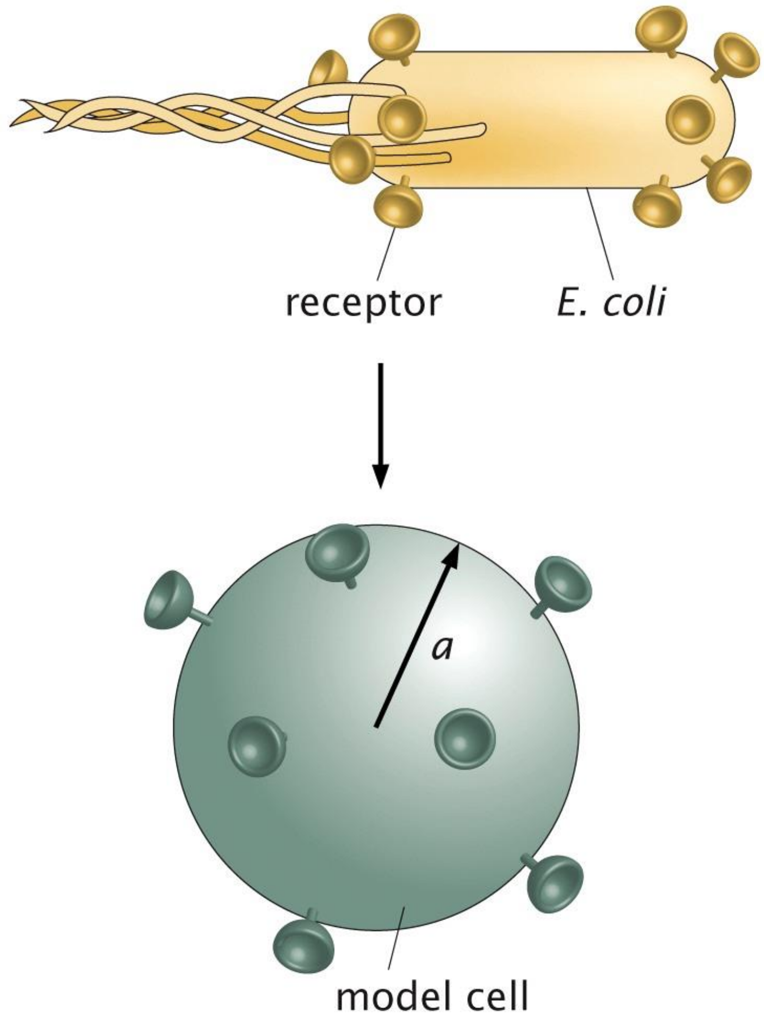
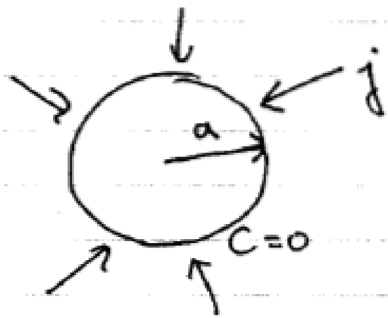


Figure 13.21 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Consider a perfectly absorbing spherical cell,



$C = C_0$
$@\ r = \infty$

Solution: $C(r) = C_0\left(1 - \frac{a}{r}\right)$

$$j(r) = -DC_0 \frac{a}{r^2}$$

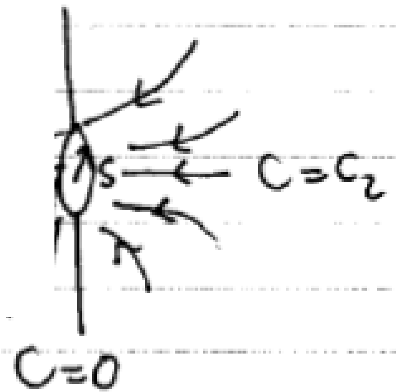
so

net inward current: $I = 4\pi a^2\, j(a)$

$$I = 4\pi D a C_0$$

Note: the diffusive current into the cell only goes as the radius of the cell and NOT the area

Applications: Disc like receptor



Hard math:

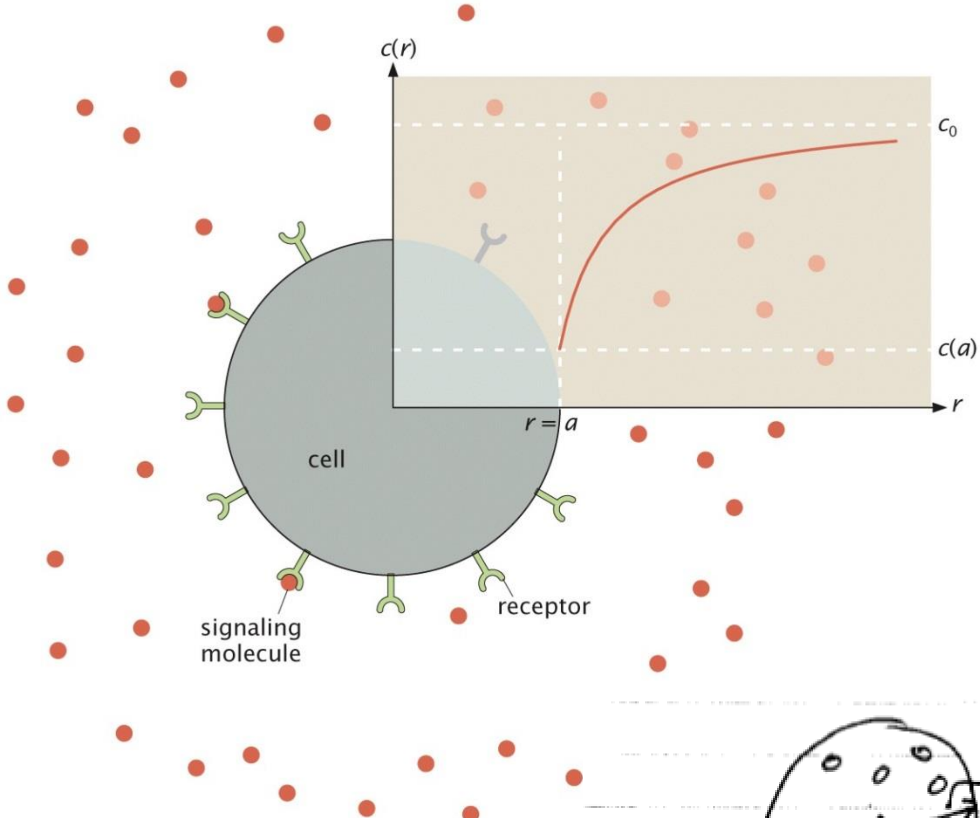
$$I = 4 D s C_0$$

again, current goes just as the radius.

So we have the current for a i) perfectly absorbing sphere and ii) a perfectly absorbing disc-like receptor

Q: What about the current for N disc-like receptors on a cell's surface?

Applications: Receptors on a cell



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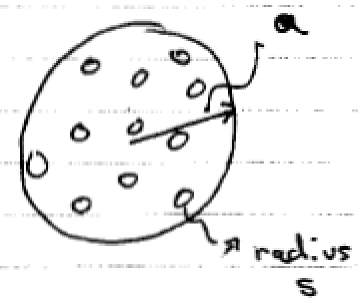


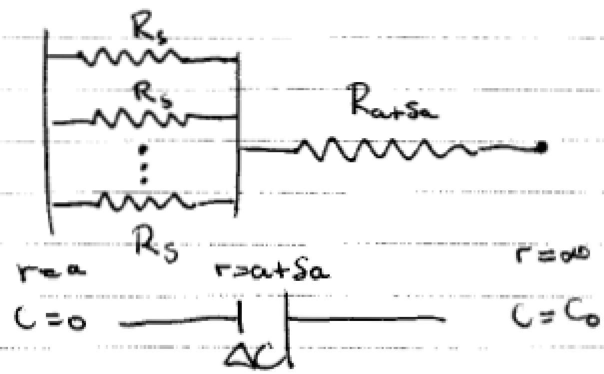
$C = C_0$
@ $r = \infty$

- For small N: $I = N(4Ds\,C_0)$
- For large N (cell is completely covered): $I = 4\pi D a C_0$

Applications: Receptors on a cell – equivalent circuit

- What happens in between? for intermediate N?

Coupled resistors : $I = \Delta C / R$, $R \equiv$ resistance



$$R_a = \frac{1}{4\pi D a}$$

$$R_s = \frac{1}{4 D s}$$

- Total resistance: $R = R_{a+\delta a} + \dfrac{R_s}{N} = \dfrac{1}{4\pi D(a+\delta a)} + \dfrac{1}{4NDs}$

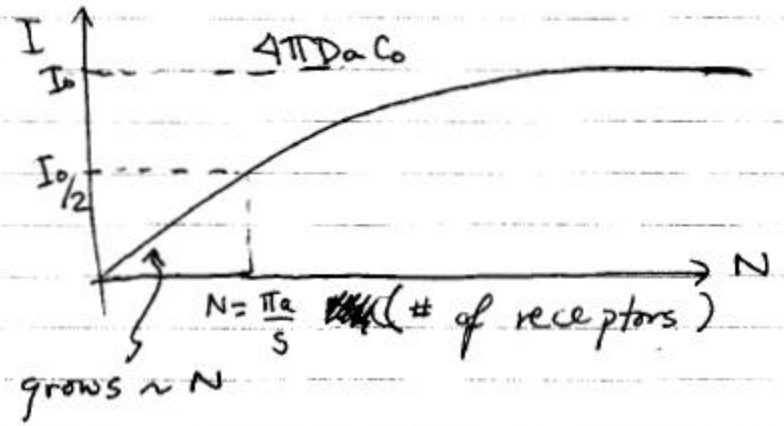
- Since $\delta a \ll a$:

$$R \cong \frac{1}{4\pi D a} + \frac{1}{4NDs} = \frac{1}{4\pi D a}\left(1 + \frac{\pi a}{Ns}\right)$$

so

$$I = \frac{\Delta C}{R} = \frac{4\pi D a C_0}{\left(1 + \frac{\pi a}{Ns}\right)}$$

Cell Signalling: some #'s



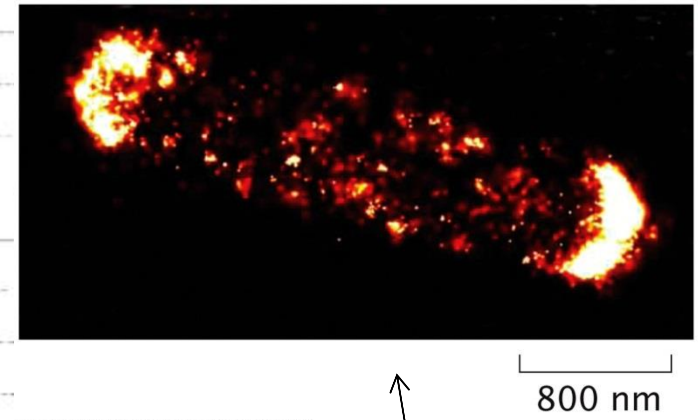


Figure 13.23b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

chemotaxis receptors on surface of E. coli

- has correct limits: for small N: $I \sim 4NDsC_0$

  for large N: $I \sim 4\pi D a C_0$

#'s: Cell: $a = 5\,\mu m$; $s = 10\,\text{Å}$

N such that $I = \frac{I_0}{2} \rightarrow N = \frac{\pi a}{s}$

so

$$N = (3.14)\frac{(5 \times 10^{-6})}{(10 \times 10^{-10})} = 15\,700 \text{ receptors}$$

- amount of surface covered? $\frac{N\pi s^2}{4\pi a^2} \sim 1 \times 10^{-4}$

  $\therefore$ there's lots of room on the surface.

Summary:

- Diffusing particles are carrying out a random walk
- the RMS distance goes as $\sqrt{t}$
- the distribution of positions of diffusing particles is a Gaussian
- derived the diffusion equation
  - particles flow from high to low concentrations
- Looked at some solutions to diffusion equation:
  - steady-state concentration in a chanel
  - absorption by spherical cell
  - absorption by disc-like receptor
- Found that cells can detect chemical signals almost as well as having the whole cell covered with only a small % of receptors