

Today's class:

## Diffusive transport in the cell

*This lecture largely follows the section 3.4.2 and  
Chapter 13 in the book ‘Physical Biology of the Cell’ by Philips et al.*

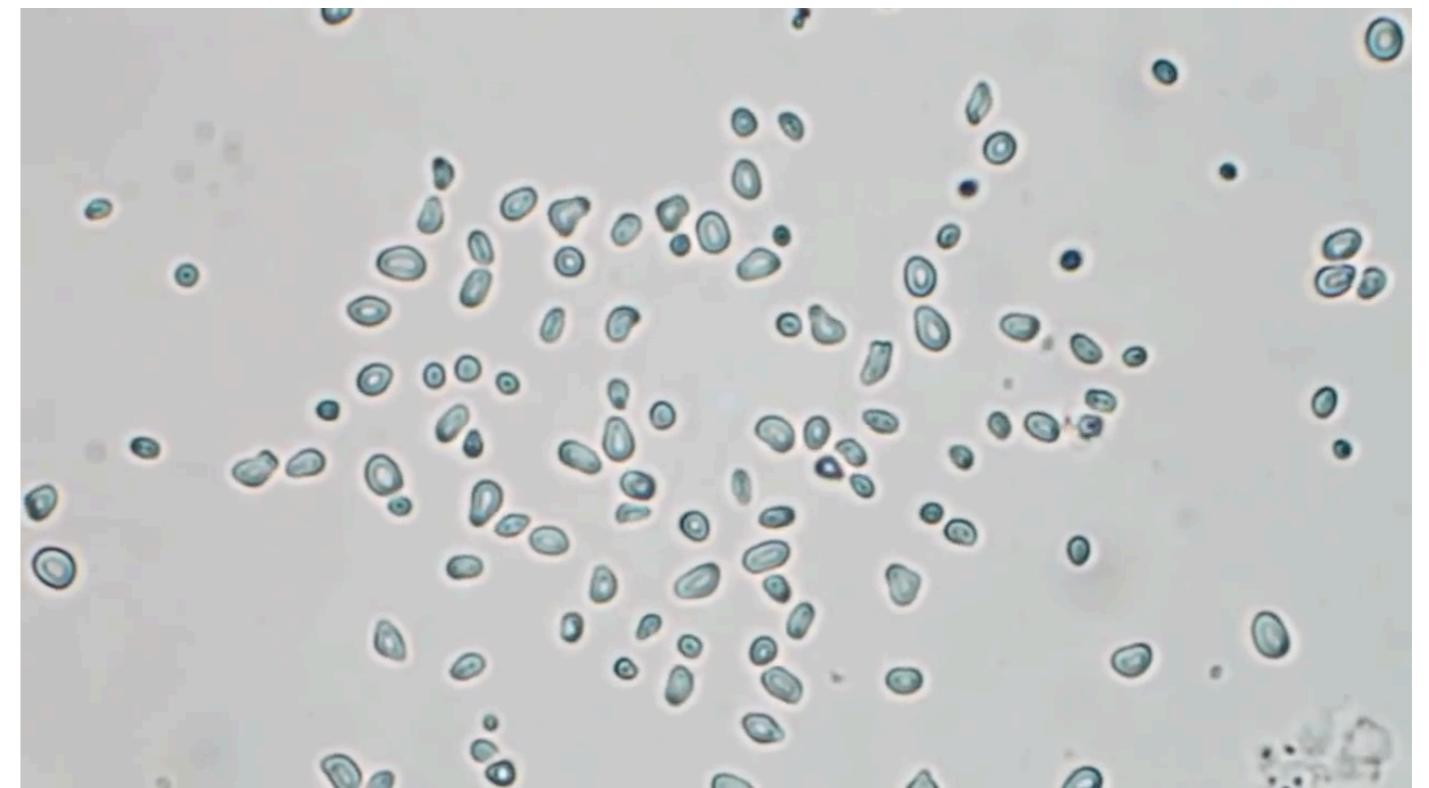
# What is diffusion?

Diffusion is the random motion of microscopic particles in solution

Brownian motion

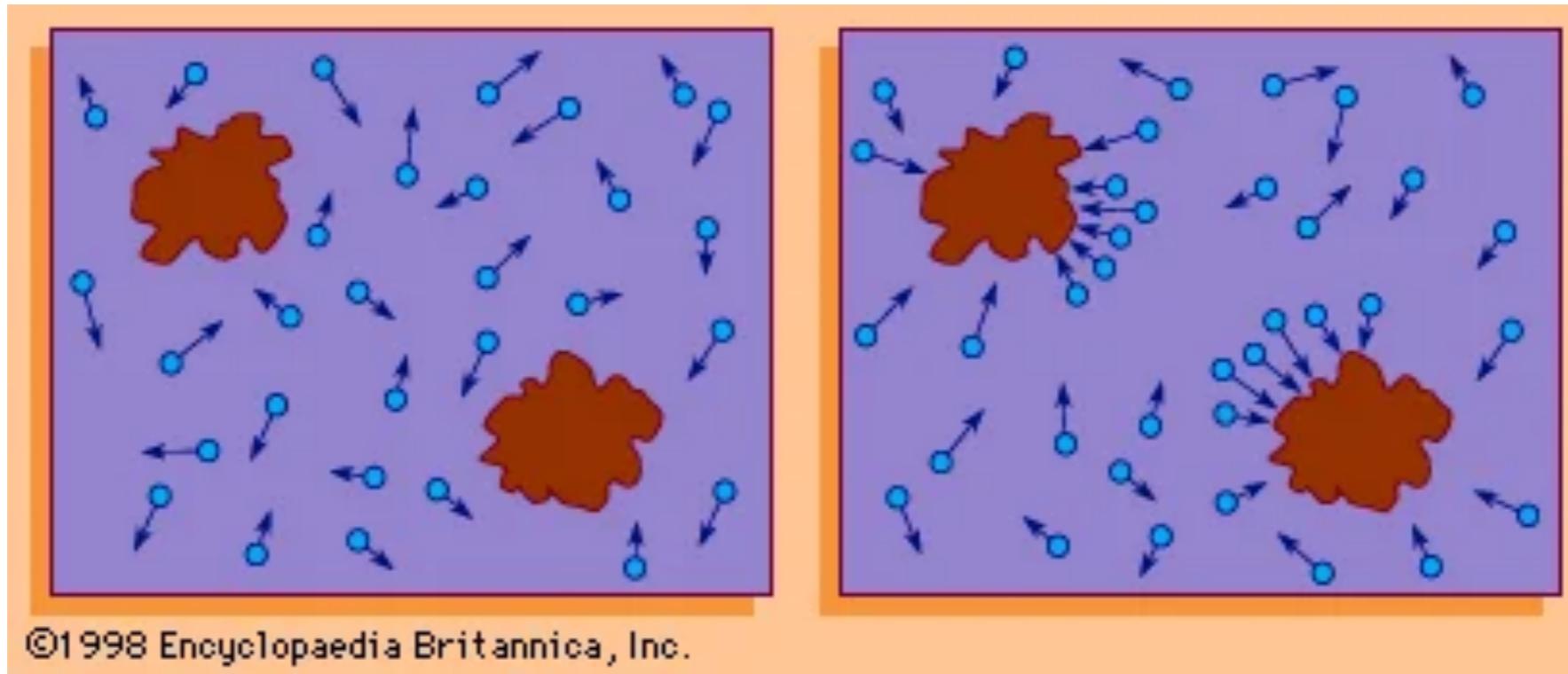


Robert Brown



Diffusion is a macroscopic manifestation of Brownian motion at the microscopic level that equilibrates concentration of a molecule

## Brownian motion originates from random kicks from solvent molecules



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random discrepancy between the molecular pressures of the solvent  
on different surfaces of the particle cause Brownian motion

## Brownian motion is driven by thermal energy

Thermal energy = energy available because of temperature

Thermal energy is measured in units of  $k_B \times T$

$k_B$  = Boltzmann constant

$T$  = absolute temperature expressed in K

Estimate thermal energy for  $T = 298\text{ K}$

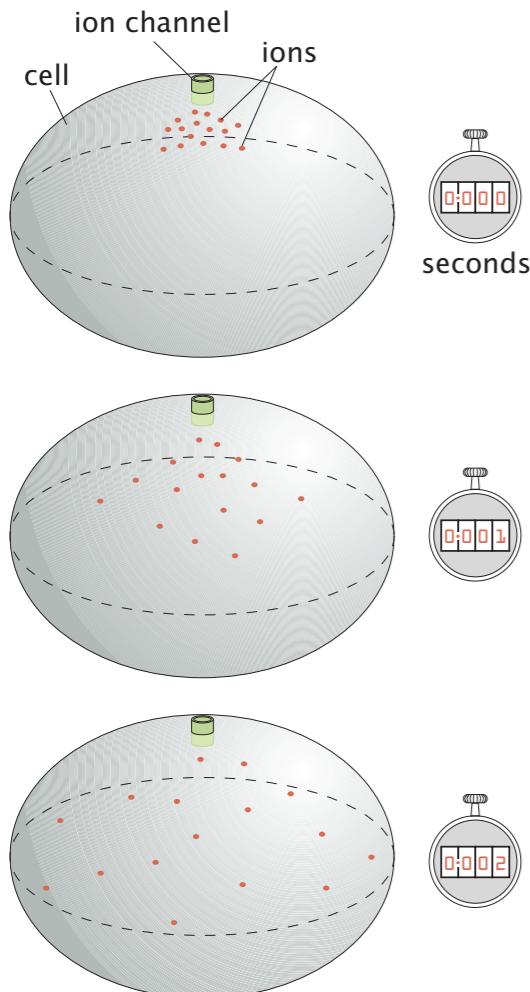
$$k_B T = (1.38 \times 10^{-23} \text{ JK}^{-1}) \times 298 \text{ K}$$

$$= 4.1 \text{ pN nm}$$

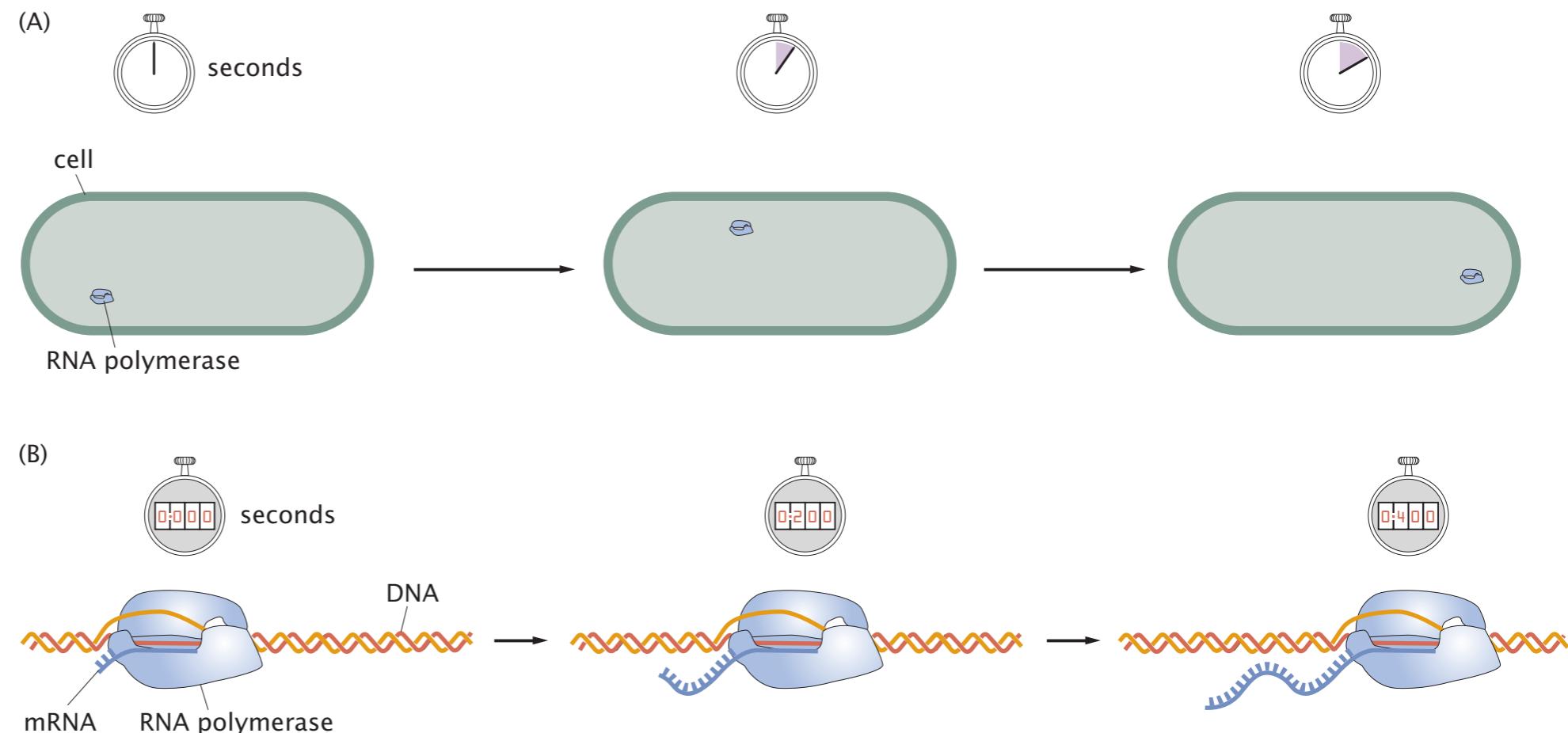
This is an important scale of energy for the cell as many molecular motor proteins exert a few pN forces across a few nm lengths

So, the deterministic force they generate competes with thermal forces  
This means thermal forces are often important for biological processes

# Diffusive motion is an inevitability but the cell gets around it when needed



## Contrast of diffusive and active transport



Diffusion of ions after  
opening of an ion  
channel

## Passive transport

Passive transport is the movement of molecules through the process of diffusion. In contrast, the active transport of molecules in cells is driven by chemical energy—usually the hydrolysis of ATP or other nucleoside triphosphates.

# Biological Distances Measured in Diffusion Times

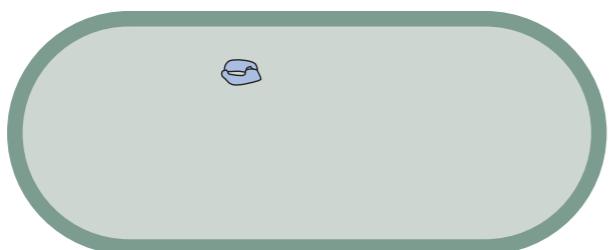
Diffusion time = time required for a diffusing molecule/particle to travel a certain distance

Formally, diffusion time  $t_{\text{diffusion}} \approx x^2/D$

$x$  = distance traveled

$D$  = diffusion constant of the particle

Time scale to move proteins in the cell



$$t_{E.\text{coli}} \approx \frac{L_{E.\text{coli}}^2}{D}$$

*E. coli* cell dimension  $\approx 1 \mu\text{m}$

Typical  $D$  of proteins in water  $\approx 100 \mu\text{m}^2 \text{ s}^{-1}$

$$t_{E.\text{coli}} \approx \frac{1 \mu\text{m}^2}{100 \mu\text{m}^2 \text{s}^{-1}} = 0.01 \text{ s}$$

# Diffusion Times can be a measure for concentration

$$t_{diffusion} \approx \frac{x^2}{D}$$

Let's consider a solution of concentration  $c$

$$c = \frac{n}{V}$$

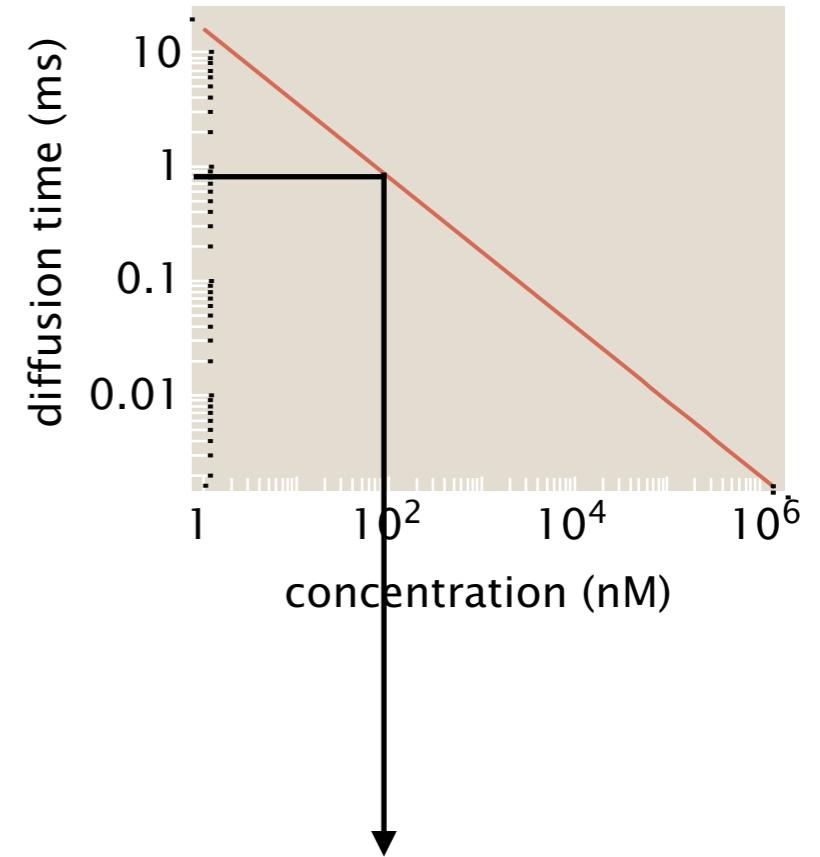
$$V \propto c^{-1}$$

If  $x$  is the mean spacing between molecules then  $x^3 \propto V$

$$x \propto c^{-1/3}$$

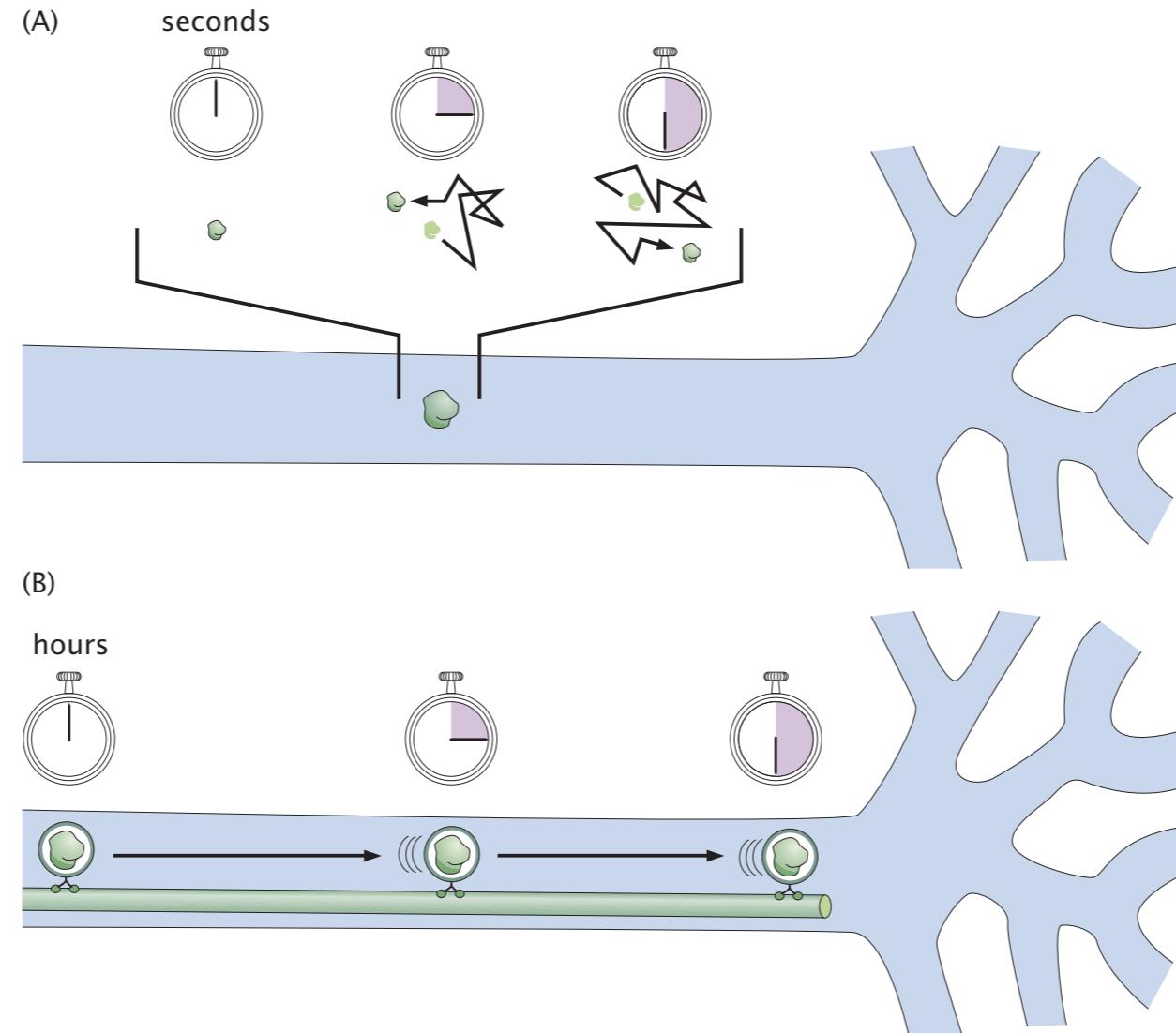
⇒ lower concentrations indicate larger intermolecular spacings

⇒ longer time needed for any molecule to meet another via diffusion



Characteristic timescale for reactants to find each other at 100 nM conc is about 1 ms

# Diffusion is not effective over large cellular distances



$$t_{diffusion} \approx \frac{x^2}{D}$$

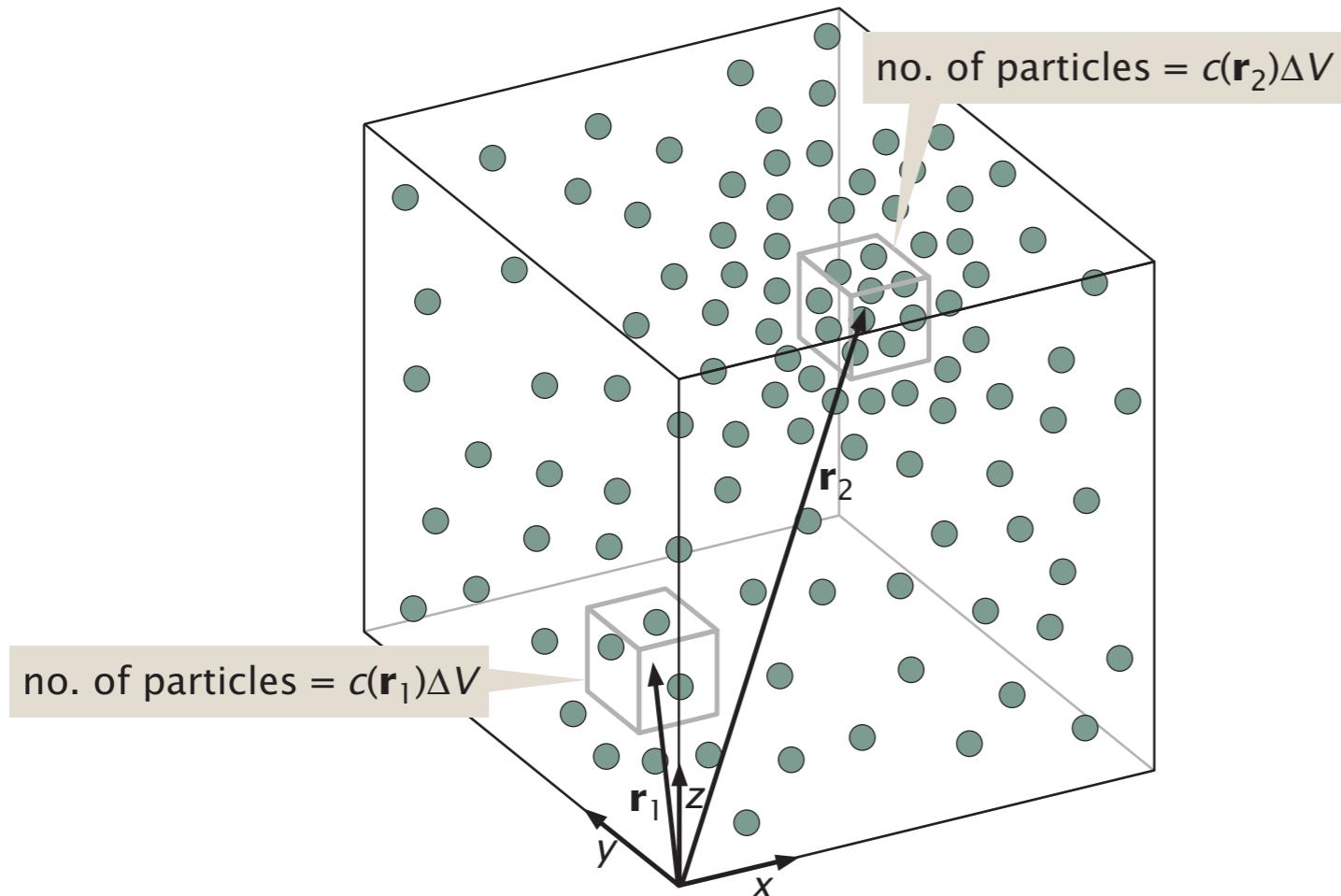
Nerve cell dimension  $\approx 10$  cm

Using  $D$  of proteins in water  $\approx 100 \mu\text{m}^2 \text{s}^{-1}$

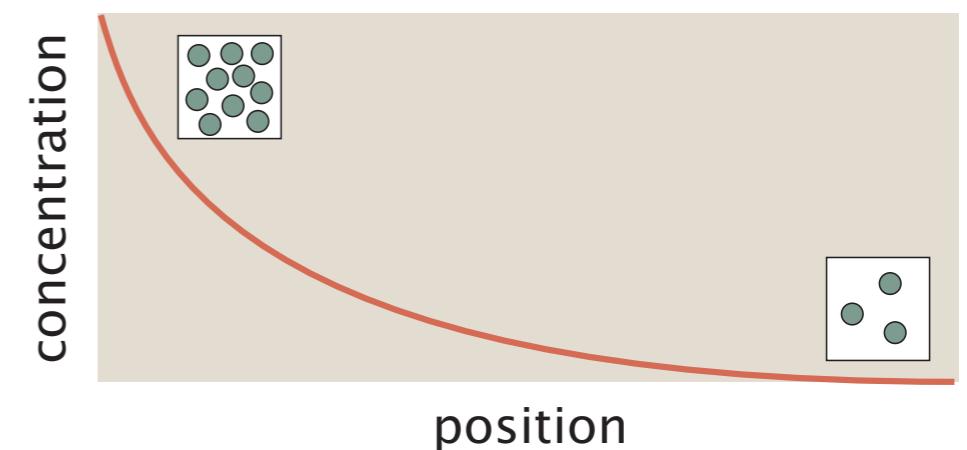
$$t_{Nerve} \approx \frac{10 \text{ cm}^2}{100 \mu\text{m}^2 \text{s}^{-1}} = 10^8 \text{ s}$$

Passive transport across so large distances is ineffective! So cell uses motor proteins to do active transport to reduce transport timescales. Like kinesin motor moves on microtubules at a speed of  $\sim 1 \mu\text{m/s}$ . Similarly, we have developed heart which actively pumps blood to tissues.

# The concept of concentration field

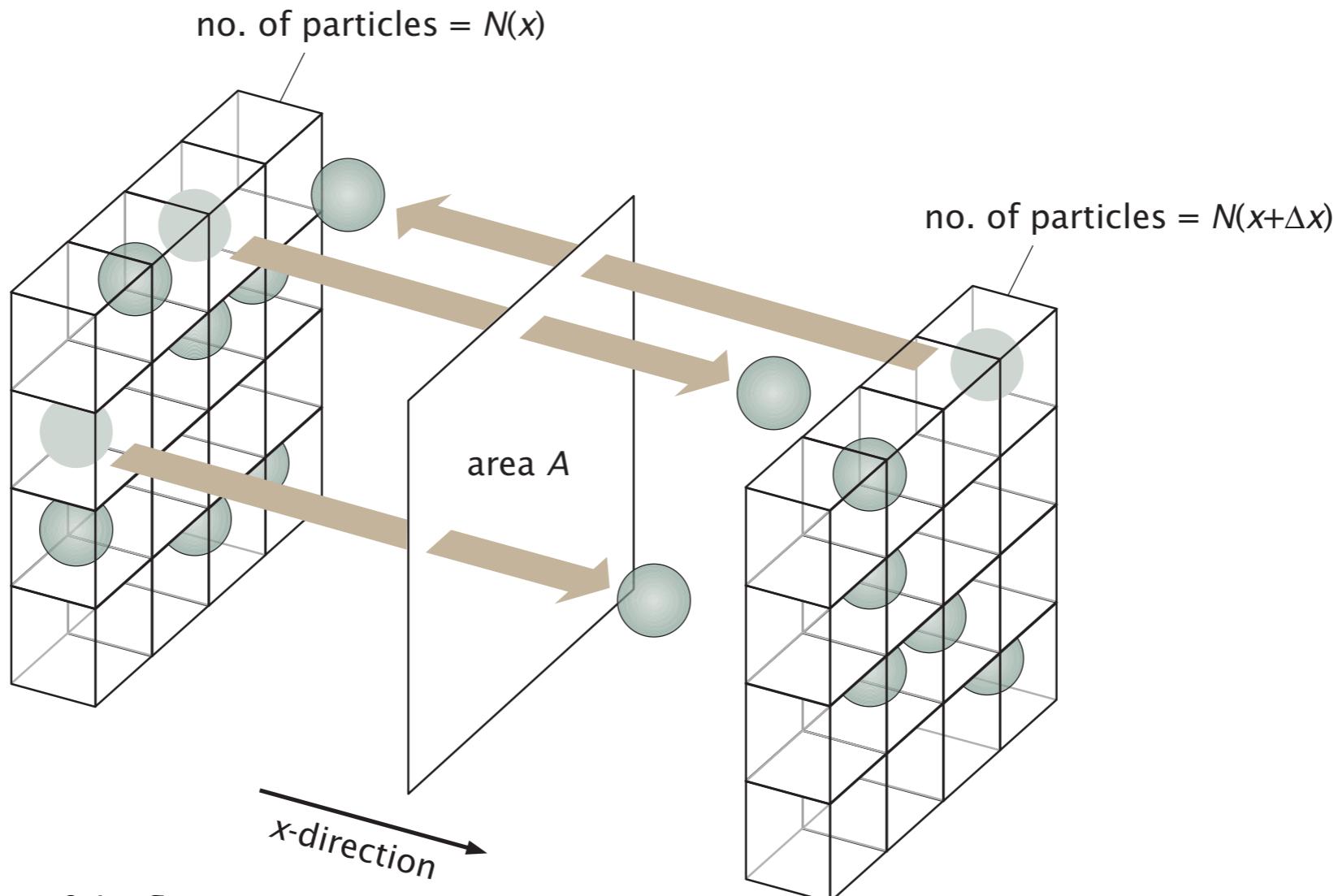


But concentration can vary over long distances and set up gradients



The system is divided up into small boxes of volume  $\Delta V$ . The overall concentration field is changing sufficiently slowly that in each small box the “concentration” is constant.

# The concept of molecular flux



**Figure 13.11:** Schematic of the flux concept. In one dimension, space is discretized into a series of planes separated by a distance  $\Delta x$ . Particles can hop left or right, and the flux across the plane between two adjacent planes is computed by counting the net number of particles crossing unit area per unit time.

## Molecular flux, $J(x)$

The flux of molecules in a direction  $x$  is the rate at which molecules cross a unit area of an imaginary plane perpendicular to the  $x$  axis.

Similar components along  $y$ - and  $z$ -axes can be defined to get the flux vector

# Fick's laws of mass transport

## Fick's laws

Fick's laws are differential equations that describe the net movements of molecules in solutions. They can be solved to give the distribution of molecules after a specific time from a given starting distribution.

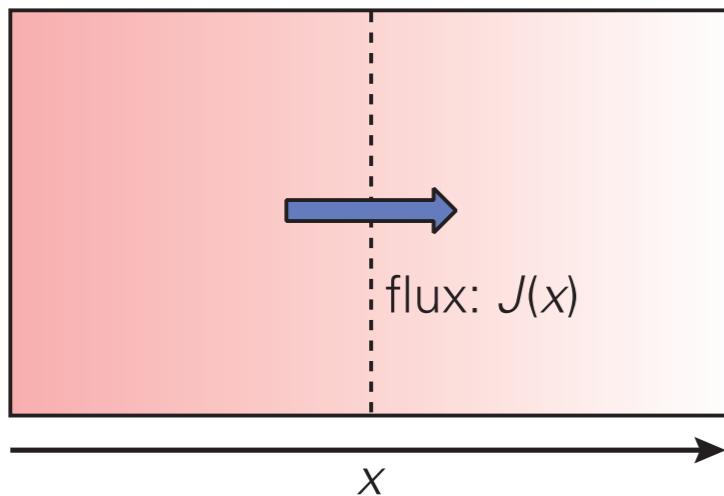
## Fick's first law

Flux is proportional to the concentration gradient

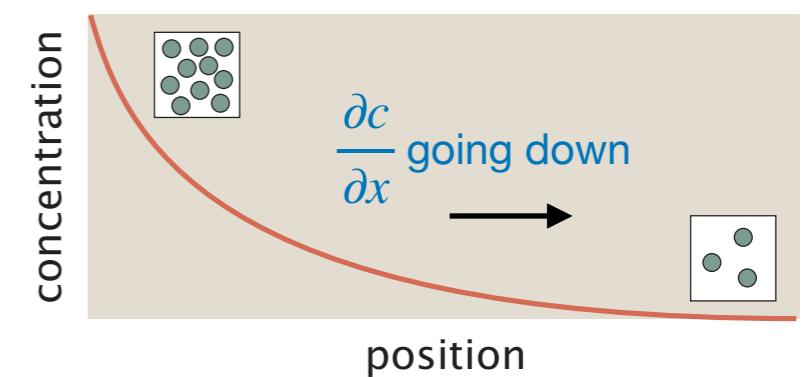
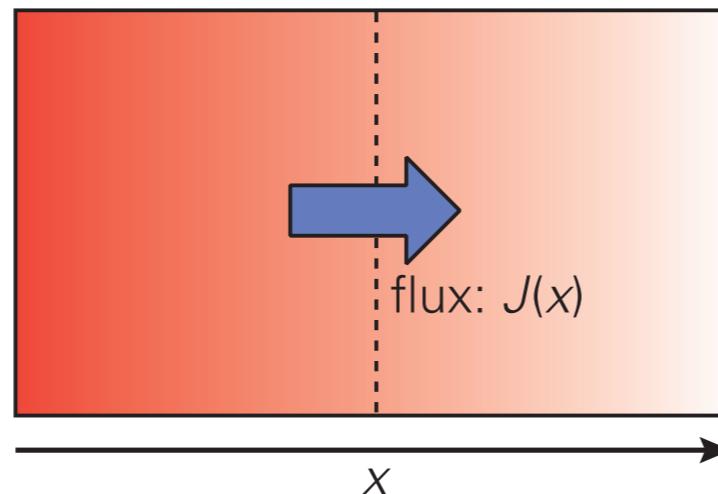
Along any direction, say x-axis, molecular flux

$$j(x) \propto - \left[ \frac{\partial c}{\partial x} \right]_{y,z}$$

Shallow conc gradient, low flux



Steep conc gradient, high flux



-ve sign makes sure that the molecules always move down the concentration gradient

## Fick's first law provides the definition of diffusion constant

$$j(x) \propto - \left[ \frac{\partial c}{\partial x} \right]_{y,z} \implies j(x) = -D \left[ \frac{\partial c}{\partial x} \right]_{y,z}$$

Here  $D$  is the diffusion constant

How can we estimate the dimension of  $D$ ?

$$\text{Dimension of } j = \frac{\text{no . of molecules}}{\text{area} \times \text{time}} = [L^{-2}T^{-1}]$$

$$\text{Dimension of } \frac{\partial c}{\partial x} = \frac{\text{no . of molecules}}{\text{volume} \times \text{length}} = [L^{-3}L^{-1}] = [L^{-4}]$$

$$\text{Dimension of } D = \frac{[L^{-2}T^{-1}]}{[L^{-4}]} = [L^2T^{-1}]$$

### Diffusion constant

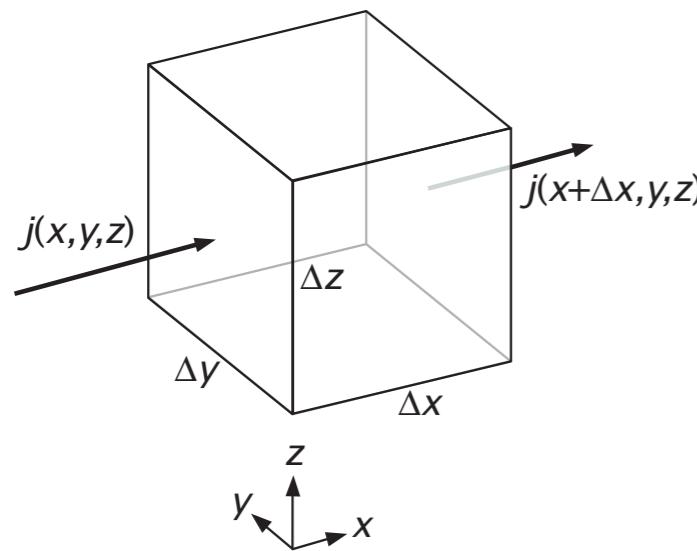
The diffusion constant,  $D$ , is a parameter that describes the average rate of motion of a molecule in solution. The units of the diffusion constant are  $\text{cm}^2 \cdot \text{sec}^{-1}$ .

**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	$\approx 2000 \mu\text{m}^2/\text{s}$
GFP in <i>E.coli</i> cytoplasm	$\approx 7 \mu\text{m}^2/\text{s}$
DNA in yeast nucleus	$5 \times 10^{-4} \mu\text{m}^2/\text{s}$

Value of  $D$  depends on properties of the solute particle, solute-solvent interaction and temperature

# Fick's first Law and Conservation of Mass



**Figure 13.12:** Mass transport out of a small volume element. The fluxes across the faces of the box change the number of particles in that volume.

Rate at which no. of particles in the box change

$$\frac{\partial N_{\text{box}}}{\partial t} = \frac{\partial c}{\partial t} \Delta x \Delta y \Delta z.$$

Mass conservation in the box can be written as

$$\frac{\partial c}{\partial t} \Delta x \Delta y \Delta z = j(x, y, z) \Delta y \Delta z - j(x + \Delta x, y, z) \Delta y \Delta z.$$

First order Taylor expansion of  $j(x + \Delta x) = j(x) + \frac{\partial j}{\partial x} \Delta x$

Using that result

$$\frac{\partial c}{\partial t} \Delta x \Delta y \Delta z \approx j(x, y, z) \Delta y \Delta z - \left[ j(x, y, z) + \frac{\partial j}{\partial x} \Delta x \right] \Delta y \Delta z.$$

$$\frac{\partial c}{\partial t} = - \frac{\partial j}{\partial x}.$$

We can rewrite this using Fick's first law

## Fick's second Law

Rearranged Fick's first law

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

$$\Rightarrow \frac{1}{D} \frac{\partial J(x,t)}{\partial x} = -\frac{\partial^2 c(x,t)}{\partial x^2}$$

Putting above in the previous result

$$\frac{\partial c}{\partial t} = -\frac{\partial j}{\partial x}.$$

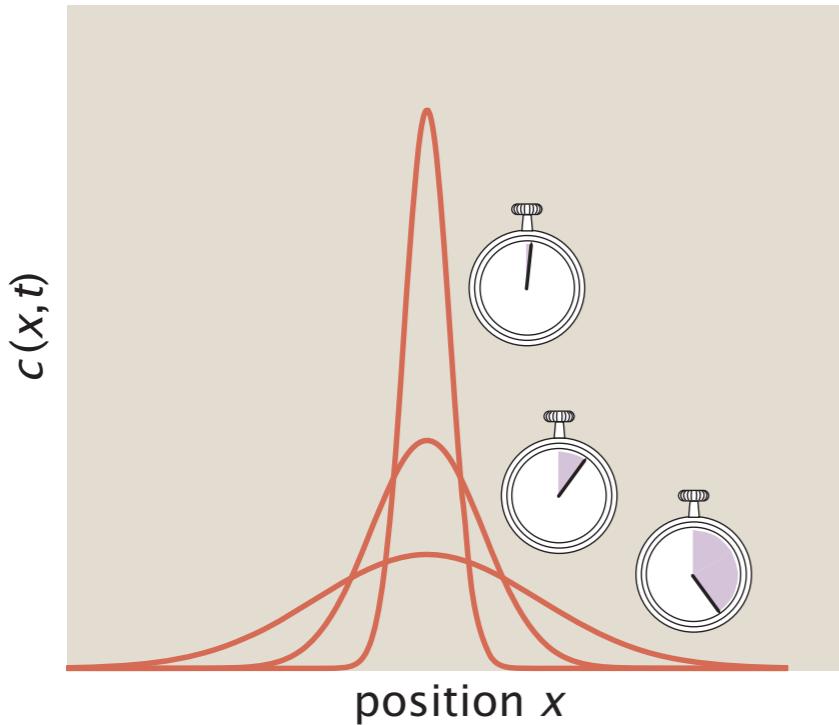
$$\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2}$$

classic law of diffusion in one dimension  
or the diffusion equation

Here we made a key assumption that  $D$  is a constant

This is true for most purposes, except in heterogeneous media where  $D$  might be space/conc depd

# Properties of the Diffusion Equation



**Figure 13.15:** Time evolution of the concentration field. The plot shows the solution for the diffusion equation at different times for an *initial* concentration profile that is a spike at  $x = 0$ .

Solution to the diffusion equation

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

Gaussian function

Broadening of the concentration profile is given by the second moment

$$\langle x^2 \rangle = \frac{\int_{-\infty}^{+\infty} x^2 \frac{N}{\sqrt{4\pi Dt}} e^{-x^2/4Dt} dx}{N} = \frac{1}{\sqrt{4\pi Dt}} \int_{-\infty}^{+\infty} x^2 e^{-x^2/4Dt} dx,$$

Here we use the Gaussian integral  $\int_{-\infty}^{\infty} e^{-\alpha x^2} dx = \sqrt{\frac{\pi}{\alpha}}$ ,

$$\int_{-\infty}^{+\infty} x^2 e^{-\alpha x^2} dx = -\frac{\partial}{\partial \alpha} \int_{-\infty}^{+\infty} e^{-\alpha x^2} dx = -\frac{\partial}{\partial \alpha} \sqrt{\frac{\pi}{\alpha}} = \frac{\sqrt{\pi}}{2\alpha^{3/2}}.$$

Therefore,  $\langle x^2 \rangle = \frac{1}{\sqrt{4\pi Dt}} \int_{-\infty}^{+\infty} x^2 e^{-x^2/4Dt} dx = \frac{1}{\sqrt{4\pi Dt}} \frac{\sqrt{\pi}}{2} (4Dt)^{3/2} = 2Dt.$

# Diffusion constant can be measured from the diffusion equation

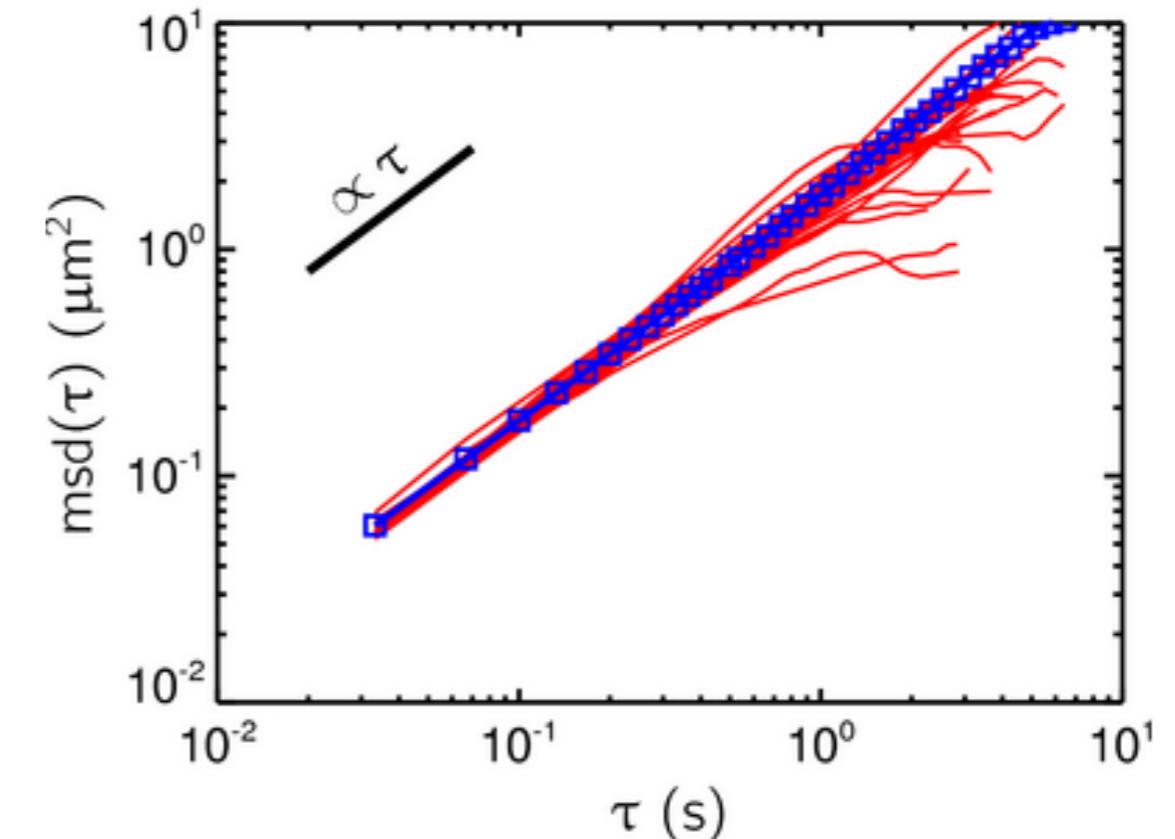
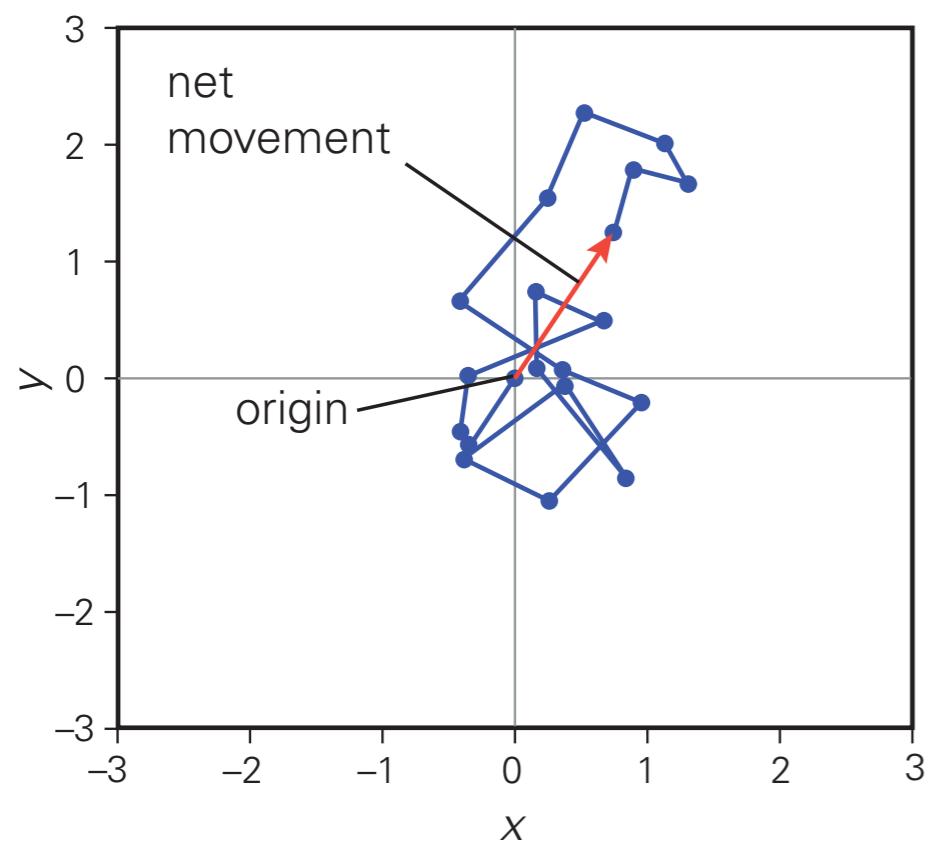
Recall that in one dimensional diffusion,

$$\langle x^2 \rangle = 2Dt$$

Mean-square displacement

Net displacement w.r.t origin is small

But mean-square displacement w.r.t origin grows with time



Mean-squared displacement  $msd(\tau)$  vs.  $\tau$  of 1.1  $\mu m$ -diameter sphere in water at 23°C. The blue points are from a time and ensemble average calculation, and each red line is computed from a time-average over a single trajectory. The black line indicates the linear scaling  $msd(\tau) \propto \tau$ .

Slope of the MSD (blue line) can be used to find  $D$

Slope for 2D diffusive motion =  $4D$

Slope for 3D diffusive motion =  $6D$