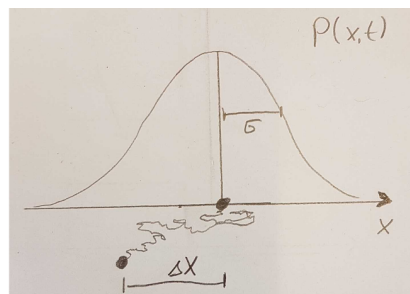


Transport by diffusion

What are typical values of diffusion coefficients?

- GFP in eukaryotic cells: $\sim 25\mu\text{m}^2/\text{s}$
- GFP in prokaryotic cells: $\sim 10\mu\text{m}^2/\text{s}$
- mRNA (actin in mouse): $\sim 0.2\mu\text{m}^2/\text{s}$
- H_2O molecule in H_2O : $\sim 2000\mu\text{m}^2/\text{s}$
- H^+ molecule in H_2O : $\sim 7000\mu\text{m}^2/\text{s}$

How long does it take for a protein to diffuse distance Δx ?



After time t , a particle has typically moved a distance of the standard deviation $\Delta x \sim \sigma$.

$$\Delta x = \sqrt{2Dt} \quad \Rightarrow \quad t = \frac{\Delta x^2}{2D}$$

For a typical $D = 10\mu\text{m}^2/\text{s}$, we thus expect:

- across a bacterium: $\Delta x = 1\mu\text{m}$: $t = 0.05\text{s}$
- across a eukaryotic cell: $\Delta x = 10\mu\text{m}$: $t = 5\text{s}$
- one millimeter: $\Delta x = 1000\mu\text{m}$: $t = 50000\text{s} = 830\text{m} = 14\text{h}$
- along a peripheral axon: $\Delta x = 1\text{m}$: $t = 5 \times 10^10\text{s} = 1600\text{y}$

Hence diffusion is fast on short distances, but completely inadequate on long distances.

Interpretation as concentrations

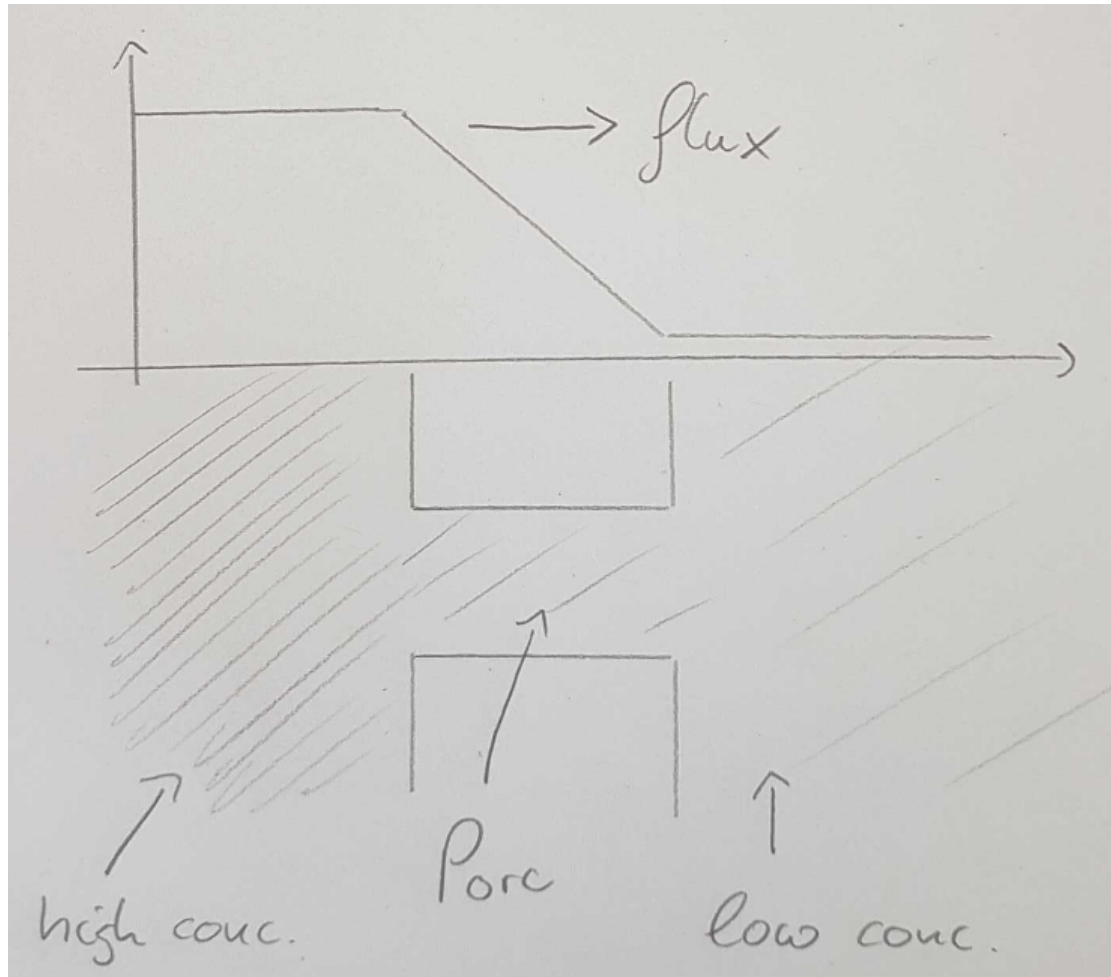
So far: $P(x, t)$ described the probability of finding a randomly moving particle at position x after time t .

Alternative: $P(x, t)$ can be interpreted as a concentration, describing the density of many molecules that move by diffusion.

Diffusive flux

Above, we asked how long it takes for a single protein to move a distance Δx in an arbitrary direction. When there are many molecules and concentration differences, such undirected motion can result in macroscopic fluxes.

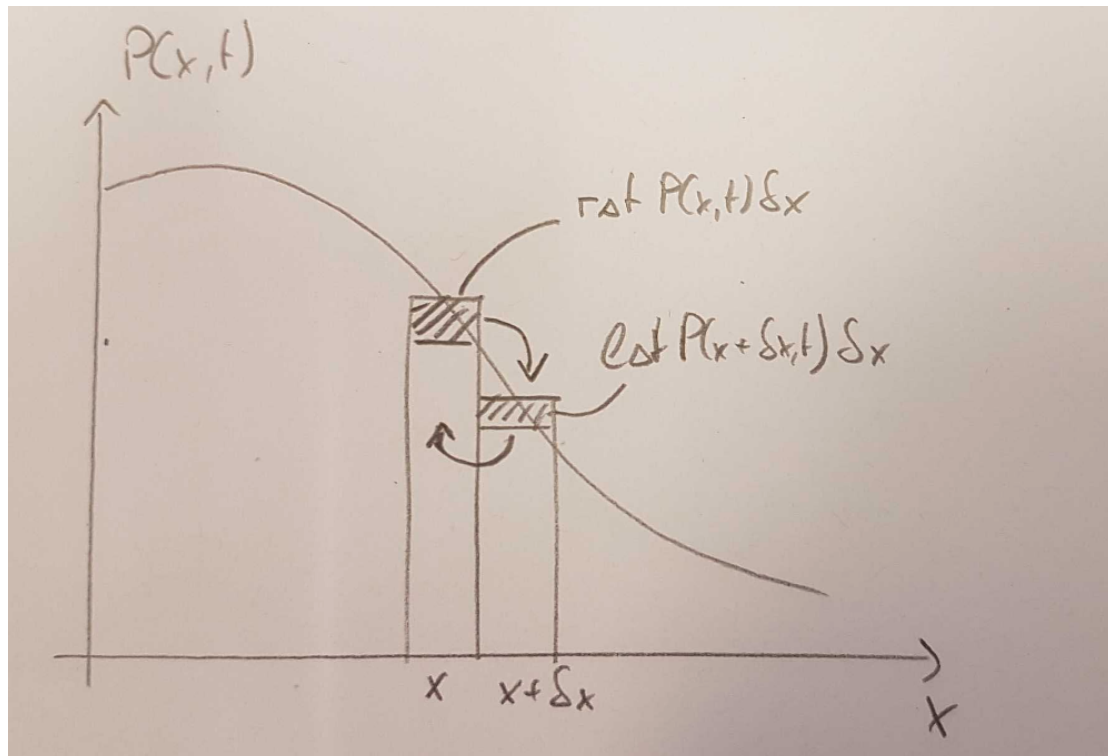
Consider the following situation that might arise across a membrane pore:



It is intuitive that in this situation, diffusion will equilibrate the concentrations on the two ends of the pore, resulting in a net-flux from left to right.

Fick's law and flux

According to the above intuition, we expect a net flux from regions with high to low concentrations. Let's look at how much moves from x to $x + \delta x$ in a discretized version:



Here, we assume $v = 0$ (no directed transport) such that

$$r = l = \frac{D}{\delta x^2}$$

Now the net amount that moves from x to $x + \delta x$ is

$$r \Delta t P(x, t) \delta x - l \Delta t P(x + \delta x, t) \delta x = \frac{D \Delta t}{\delta x} [P(x, t) - P(x + \delta x, t)]$$

Since we have

$$\frac{P(x, t) - P(x + \delta x, t)}{\delta x} \rightarrow \frac{\partial P(x, t)}{\partial x}$$

The expression above reduces to

$$j(x, t) \Delta t = -D \Delta t \frac{\partial P(x, t)}{\partial x}$$

This defines the diffusive flux

$$j(x, t) = -D \frac{\partial P(x, t)}{\partial x}$$

This result, known as **Fick's law**, is intuitive: The net flux of particles is proportional to D and the slope of $P(x, t)$.

Flux through a pore

Above we derived that the diffusive flux is proportional to D and the slope of the concentration profile. To calculate the flux through a pore, we therefore need to determine how $P(x, t)$ varies across the pore.

If the pore is narrow and the volumes left and right are large, we expect this process to take a long time with an approximately constant concentration profile across the pore. A constant profile corresponds to a zero time-derivative:

$$\frac{\partial P(x, t)}{\partial t} = 0 = D \frac{\partial^2 P(x, t)}{\partial x^2}$$

where we set $v = 0$ since there is no directed transport, just diffusion. We will drop the index t since we are looking for a steady state solution.

The fact that the second derivative $\frac{\partial^2 P(x)}{\partial x^2}$ is zero means that the first derivative is constant.

$$\frac{\partial P(x)}{\partial x} = \text{const} = \alpha$$

A constant first derivative implies that the solution is a straight line:

$$P(x) = \alpha x + \beta$$

where α and β are parameters that need to be determined from the boundary condition.

In this case, the boundary conditions are simply the requirement that $P(x)$ matches the concentration of the reservoir at either end of the pore.

$$P(x) = c_l + (x - x_l) \frac{c_r - c_l}{x_r - x_l} = c_l + (x - x_l) \frac{\Delta C}{L}$$

where ΔC is the concentration difference and L is the length of the pore.

So far, we have pretended our problem is one-dimensional and only considered the coordinate that runs through the pore. In reality, the pore is of course three-dimensional and has a cross-sectional area. The quantity we have calculated is therefore a flux density, rather than the total flux and needs to be multiplied by the area A .

The total flux is hence

$$J = -D \frac{A \Delta C}{L}$$

Let's do a quick check of the dimensions and units:

- D has units $\mu m^2/s$
- A is an area with units μm^2
- ΔC is a concentration with units $\text{stuff}/\mu m^3$
- L is a length μm

Together, the flux therefore has units stuff/s , as it should.

Diffusive flux through the nuclear pore

- $D = 10 \mu m^2/s$
- Diameter $d = 30 nm = 0.03 \mu m$. The cross-section
 $A = \pi (0.015)^2 \mu m^2 = 7 \times 10^{-4} \mu m^2$
- $\Delta C = 10^{-6} M$
- $L = 0.03 \mu m$

With these numbers, we expect that the diffusive flux is

$$J = 2.3 \times 10^{-7} M \mu m^3/s$$

We can turn this into a more intuitive quantity:

$$1M = 6 \times 10^{23} \text{ molecules per liter} = 6 \times 10^8 \text{ molecules per } \mu m^3$$

Hence the flux through the pore is approximately

$$J \approx 140 \text{ molecules}/s$$

Dig deeper:

- Have a look at the paper by [Ribbeck et al](https://doi.org/10.1093/emboj/20.6.1320) doi:10.1093/emboj/20.6.1320 who measured transport through the nuclear pore.
- How would the expression for the flux look for finite $v > 0$ (and hence $r \neq l$)?

In []: