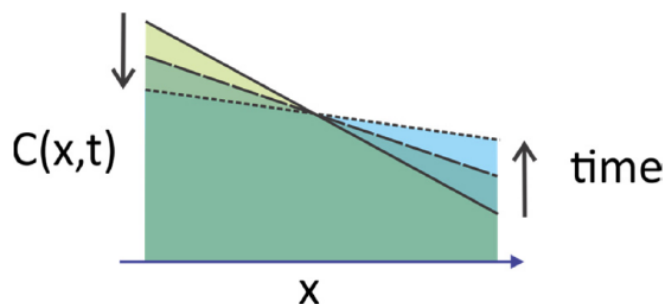


10.1: Continuum Diffusion

We are now going to start a new set of topics that involve the dynamics of molecular transport. A significant fraction of how molecules move spatially in biophysics is described macroscopically by “diffusion” and microscopically through its counterpart “Brownian motion”. Diffusion refers to the phenomenon by which concentration and temperature gradients spontaneously disappear with time, and the properties of the system become spatially uniform. As such, diffusion refers to the transport of mass and energy in a nonequilibrium system that leads toward equilibrium. Brownian motion is also a spontaneous process observed in equilibrium and non-equilibrium systems. It refers to the random motion of molecules in fluids that arises from thermal fluctuations of the environment that rapidly randomize the velocity of particles. Much of the molecular transport in biophysics over nanometer distances arises from diffusion.



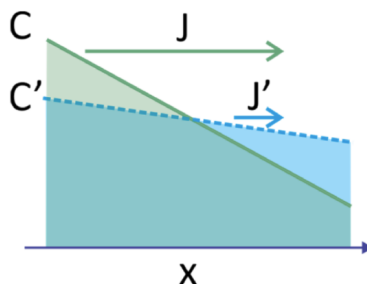
This can be contrasted with directed motion, which requires the input of energy and is crucial for transporting cargo to targets over micron-scale distances. Here we will start by describing diffusion in continuum systems, and in the next section show how this is related to the Brownian motion of discrete particles.

Fick's First Law

We will describe the time evolution of spatially varying concentration distributions $C(x, t)$ as they evolve toward equilibrium. These are formalized in two laws that were described by Adolf Fick (1855).¹ Fick's first law is the “common sense law” that is in line with everyone's physical intuition. Molecules on average will tend to diffuse from regions of higher concentration to regions of lower concentration. Therefore we say that the flux of molecules through a surface, J , is proportional to the concentration gradient across that surface.

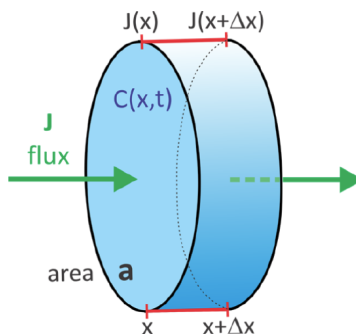
$$J = -D \frac{\partial C}{\partial x} \quad (10.1.1)$$

J is more accurately called a flux density, since it has units of concentration or number density per unit area and time. The proportionality constant between flux density J ($\text{mol m}^{-2} \text{s}^{-1}$) and concentration gradient (mol m^{-4}) which sets the timescale for the process is the diffusion constant D ($\text{m}^2 \text{s}^{-1}$). The negative sign assures that the flux points in the direction of decreasing concentration. This relationship follows naturally, when we look at the two concentration gradients in the figure. Both C and C' have a negative gradient that will lead to a flux in the positive direction. C will give a bigger flux than C' because there is more probability for flow to right. The gradient disappears and the concentration distribution becomes constant and time invariant at equilibrium. Note, in a general sense $\partial C / \partial x$ can be considered the leading term in an expansion of C in x .



Fick's Second Law

Fick's second law extends the first law by adding an additional constraint based on the conservation of mass. Consider diffusive transport along x in a pipe with cross-sectional area a , and the change in the total number of particles within a disk of thickness Δx over a time period Δt .



If we take this disk to be thin enough that the concentration is a constant at any moment in time, then the total number of particles in the slab at that time is obtained from the concentration times the volume:

$$N = aC(t)\Delta x$$

Within the time interval Δt the concentration can change and therefore the total number of particles within the disk changes by an amount

$$\Delta N = a\{C(t + \Delta t) - C(t)\}\Delta x$$

Now, the change in the number of particles is also dependent on the fluxes of molecules at the two surfaces of the disk. The number of molecules passing into one surface of the disk is $-aJ\Delta t$, and therefore the net change in the number of molecules during Δt is obtained from the difference of fluxes between the left and right surfaces of the disk:

$$\Delta N = -aJ(x + \Delta x) - J(x)\Delta t$$

Setting these two calculations of ΔN equal to each other, we see that the flux and concentration gradients for the disk are related as

$$\{C(t + \Delta t) - C(t)\}\Delta x = -\{J(x + \Delta x) - J(x)\}\Delta t$$

or rewriting this in differential form

$$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x} \quad (10.1.2)$$

This important relationship is known as a continuity expression. Substituting eq. (10.1.1) into this expression leads to **Fick's Second Law**

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (10.1.3)$$

This is the diffusion equation in one dimension, and in three dimensions:²

$$\frac{\partial C}{\partial t} = D \nabla^2 C \quad (10.1.4)$$

Equation (10.1.4) can be used to solve diffusive transport problems in a variety of problems, choosing the appropriate coordinate system and applying the specific boundary conditions for the problem of interest.

Diffusion from a Point Source

As our first example of how concentration distributions evolve diffusively, we consider the time-dependent concentration profile when the concentration is initially all localized to one point in space, $x = 0$. The initial condition is

$$C(x, t = 0) = C_0 \delta(x)$$

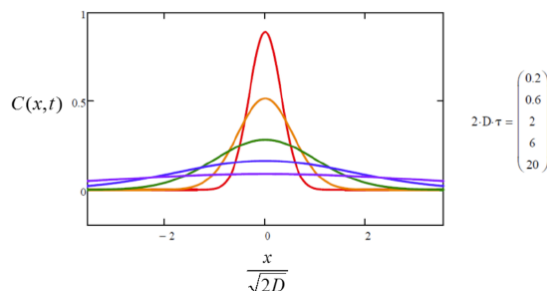
and the solution to eq. (10.1.3) is

$$C(x, t) = \frac{C_0}{\sqrt{4\pi Dt}} e^{-x^2/4Dt} \quad (10.1.5)$$

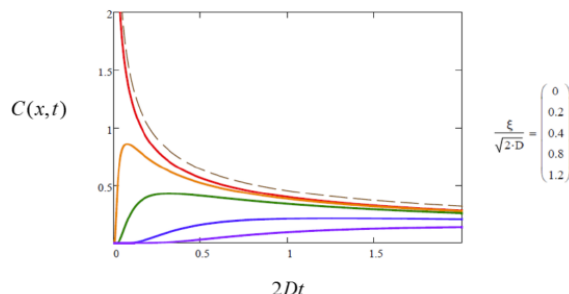
The concentration profile has a Gaussian form which is centered on the origin, $\langle x \rangle = 0$, with the mean square displacement broadening with time as:

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

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



Diffusive transport has no preferred direction. Concentration profiles spread evenly in the positive and negative direction, and the highest concentration observed will always be at the origin and have a value $C_{max} = C_0/\sqrt{4\pi Dt}$. Viewing time-dependent concentrations in space reveal that they reach a peak at $t_{max} = x^2/2D$, before decaying at $t^{-1/2}$ (dashed line below).



When we solve for 3D diffusion from a point source:

$$C(x, y, z, t = 0) = C_0 \delta(x) \delta(y) \delta(z)$$

If we have an isotropic medium in which D is identical for diffusion in the x , y , and z dimensions,

$$C(x, y, z, t) = \frac{C_0}{(4\pi Dt)^{3/2}} e^{-r^2/4Dt} \quad (10.1.6)$$

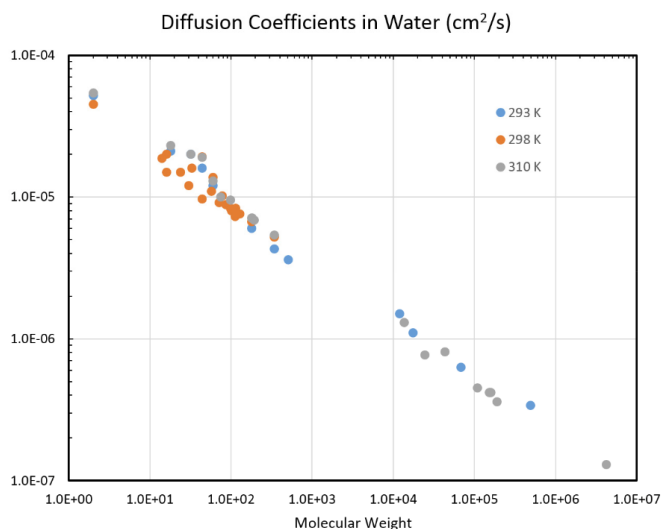
where $r^2 = x^2 + y^2 + z^2$. Calculating the mean square displacement from

$$\begin{aligned} \langle r^2 \rangle &= \frac{\int_0^\infty dr r^2 C(r, t)}{\int_0^\infty dr C(r, t)} \\ &= 6Dt \end{aligned}$$

or in d dimensions, $\langle r^2 \rangle = d(2Dt)$.

Diffusion Constants

Typical diffusion constants for biologically relevant molecules in water are shown in the graph below, varying from small molecules such as O_2 and glucose in the upper left to proteins and viruses in the lower right.



- For a typical globular protein, typically diffusion coefficients are:

in water $D \sim 10^{-10} \text{ m}^2/\text{s}$

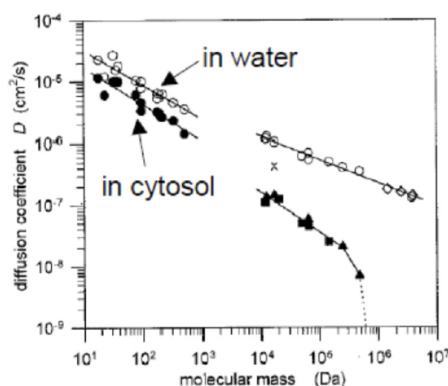
in cells $D \sim 10^{-12} \text{ m}^2/\text{s}$

in lipids $D \sim 10^{-14} \text{ m}^2/\text{s}$

$$\langle r^2 \rangle^{1/2} = 1 \mu\text{m}, \quad t \sim 0.4 \text{ sec in cells}$$

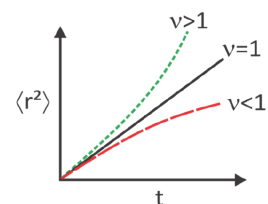
$$= 10 \mu\text{m}, \quad t \sim 40 \text{ sec in cells}$$

- Ions in water at room temperature usually have a diffusion coefficient of 0.6×10^{-5} to $2 \times 10^{-5} \text{ cm}^2/\text{s}$.
- Lipids:
 - Self-diffusion $10^{-12} \text{ m}^2/\text{s}$
 - Tracer molecules in lipid bilayers $1\text{-}10 \times 10^{-12} \text{ m}^2/\text{s}$



Anomalous Diffusion

The characteristic of simple diffusive behavior is the linear relationship between the mean square displacement and time. Deviation from this behavior is known as anomalous diffusion, and is characterized by a scaling relationship $\langle r^2 \rangle \sim t^\nu$. We refer to $\nu < 1$ as sub-diffusive behavior and $\nu > 1$ as super-diffusive. Diffusion in crowded environments can result in sub-diffusion.³



Thermodynamic Perspective on Diffusion

Thermodynamically, we can consider the driving force for diffusion as a gradient in the free energy or chemical potential of the system. From this perspective, in the absence of any other interactions, the driving force for reaching uniform spatial concentration is the **entropy of mixing**. For a mixture with mole fraction x_A , we showed

$$\begin{aligned}\Delta S_{mix} &= -Nk_B(x_A \ln x_A + x_B \ln x_B) & x_B &= 1 - x_A \\ &\approx -N_A k_B \ln x_A & \text{for } x_A &\ll 1\end{aligned}$$

We then use $\Delta F = -T\Delta S$ to calculate the chemical potential:

$$\begin{aligned}\mu_A &= \left(\frac{\partial F}{\partial N_A} \right)_{V,T} \\ \mu_a &\approx k_B T \ln x_A\end{aligned}$$

We see that a concentration gradient, means that the mole fraction and therefore chemical potential is different for two positions in the system. At equilibrium $\mu_A(r_1) = \mu_A(r_2)$, which occurs when $x_A(r_1) = x_A(r_2)$.

Thermodynamics does not tell you about rate, only the direction of spontaneous change(although occasionally diffusion is discussed in terms of a time-dependent “entropyproduction”). The diffusion constant is the proportionality constant between gradients in concentration or chemical potential and the time-dependent flux of particles. The flux density described in Fick’s first law can be related to μ_i , the chemical potential for species i :

$$J_i = \frac{-D_i C_i}{k_B T} \frac{\partial \mu_i}{\partial r_i}$$

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1. A. Fick, Ueber diffusion, Ann. Phys. 170, 59–86 (1855).
 2. This equation assumes that D is a constant, but if it is a function of space: $C = \nabla(D\nabla C)$. In three dimensions, Fick’s First Law and the continuity expression are: $J(r, t) = vC(r, t) - D\nabla C(r, t)$ and $dC(r, t)/dt = -\nabla \cdot J(r, t)$ where v is the velocity of the fluid. These expressions emphasize that flux density and velocity are vectors, whereas concentration field is a scalar.
 3. J. A. Dix and A. S. Verkman, Crowding effects on diffusion in solutions and cells, Annu. Rev. Biophys. 37, 247–263 (2008).

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