

# BE/APh 161: Physical Biology of the Cell

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## 9 Molecular diffusion and random walks

In this lecture, we will study **diffusion**, both from a continuum perspective, and from the perspective of individual particles undergoing random walks. In doing so, we will explore some useful concepts about conservation laws in continuum mechanics and statistical treatment of random walks.

### 9.1 Conservation of mass in a continua

We think about diffusion in a **continuum**, that is ignoring the particulate nature of matter and considering properties that vary continuously in space, like densities and concentrations. In this context, we think of diffusion as the tendency for a species to redistribute in space, going from regions of high concentration to regions of low concentration.

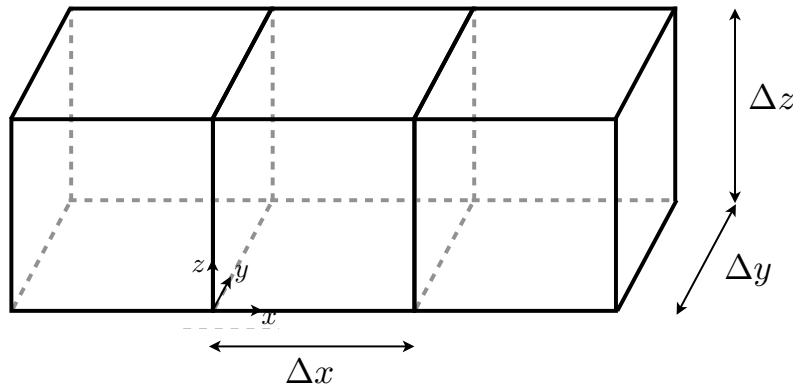


Figure 18: Three adjacent control volumes. We are considering the center control volume; note where the origin of the coordinate axis system is.

To build the theoretical framework, we can think about dividing space up into little boxes called **control volumes**, also called **volume elements**. Consider three control volumes sketched in Fig. 18. We will consider the center control volume. Material can move in and out of this control volume. For now, we will only consider movement in the  $x$ -direction, and we will consider the mass of a species of interest, e.g. a specific protein, which we will denote with a subscript  $i$ . Let  $m_i(x, t)$  be the mass of this species at position  $x$  at time  $t$ . This may seem odd to define a mass at a *point* in space. Herein lies one of the key assumptions behind defining continua, and I ask you to suspect disbelief as accept that we can define such a thing. We can then do some accounting of mass in our control volume. This may be written using a seemingly trivial word equation.

$$\text{accumulation} = \text{input} - \text{output} + \text{generation} - \text{consumption}. \quad (9.1)$$

We can write the respective terms in the accounting equation for some time interval  $\Delta t$ .

$$\text{accumulation} = m_i(x, t + \Delta t) - m_i(x, t), \quad (9.2)$$

$$\text{input} = j_{i,x}(x - \Delta x, t) \Delta y \Delta z \Delta t, \quad (9.3)$$

$$\text{output} = j_{i,x}(x, t) \Delta y \Delta z \Delta t, \quad (9.4)$$

$$\text{generation} - \text{consumption} = \text{terms from chemical rate laws}. \quad (9.5)$$

We will neglect chemical reactions for now, but are easy to put in later. We have defined by  $j_{i,x}$  the  $x$ -directional **flux** of mass of species  $i$ . A flux is the rate of flow per surface area. The flux  $j_{i,x}$  is then the mass that flows through the surface of the control volume per area per time. So, if we write down our mass accounting, we get

$$m_i(x, t + \Delta t) - m_i(x, t) = j_{i,x}(x - \Delta x, t) \Delta y \Delta z \Delta t - j_{i,x}(x, t) \Delta y \Delta z \Delta t. \quad (9.6)$$

Dividing both sides by  $\Delta x \Delta y \Delta z \Delta t$  gives

$$\frac{m_i(x, t + \Delta t) - m_i(x, t)}{\Delta x \Delta y \Delta z \Delta t} = \frac{j_{i,x}(x - \Delta x, t) - j_{i,x}(x, t)}{\Delta x}. \quad (9.7)$$

We note that  $m_i / \Delta x \Delta y \Delta z$  is the density, or mass concentration, of the species of interest, which we will define as  $\rho_i$ . This gives

$$\frac{\rho_i(x, t + \Delta t) - \rho_i(x, t)}{\Delta t} = \frac{j_{i,x}(x - \Delta x, t) - j_{i,x}(x, t)}{\Delta x}. \quad (9.8)$$

Now, if we take the limit of  $\Delta x$  and  $\Delta t$  both going to zero and use the finite difference formulas, we get

$$\frac{\partial \rho_i}{\partial t} = -\frac{\partial j_{i,x}}{\partial x}, \quad (9.9)$$

or including chemical reactions,

$$\frac{\partial \rho_i}{\partial t} = -\frac{\partial j_{i,x}}{\partial x} + \text{rxns}. \quad (9.10)$$

This result generalizes to three dimensions as

$$\frac{\partial \rho_i}{\partial t} = -\nabla \cdot \mathbf{j}_i + \text{rxns}, \quad (9.11)$$

where  $\nabla$  is the gradient operator, and  $\mathbf{j}_i$  is the vector-valued flux. This is, in fact, a general form of a conservation law.

$$\text{rate of change} = \text{negative divergence of a flux} + \text{net generation}. \quad (9.12)$$

This is an important equation to keep in mind and is generally true for any conserved quantity that can be described in a continuum.

### 9.1.1 General conservation laws in continua

We can more elegantly write the conservation law we have just described. Consider an arbitrarily shaped control volume, shown in Fig. 19. We define by  $\mathbf{n}$  the unit normal vector pointing out of the surface. The rate of change of a conserved quantity  $\xi$  in the volume element is given by the net flux of that quantity into the volume element,  $\mathbf{j}_\xi$ , integrated over the entire surface. Written out, this is

$$\frac{\partial}{\partial t} \int dV \xi = - \int dS \mathbf{j}_\xi \cdot \mathbf{n}. \quad (9.13)$$

The **Gauss divergence theorem** says that

$$\int dS \mathbf{j} \cdot \mathbf{n} = \int dV \nabla \cdot \mathbf{j}. \quad (9.14)$$

Applying the Gauss divergence theorem, taking the time differential into the integral in (9.13), and rearranging gives

$$\int dV \left( \frac{\partial \xi}{\partial t} + -\nabla \cdot \mathbf{j}_\xi \right) = 0. \quad (9.15)$$

This must be true for any arbitrary control volume, so the integrand must be zero. This gives

$$\frac{\partial \xi}{\partial t} = -\nabla \cdot \mathbf{j}_\xi. \quad (9.16)$$

For conservation of mass of a given species,  $\xi = \rho_i$ , as we have already derived.

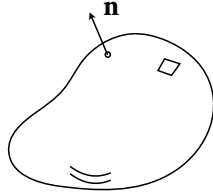


Figure 19: A volume element with a unit normal pointing out of its surface.

### 9.1.2 Advective flux

We may have an **advective flux**, which comes from flowing of material. Imagine that species  $i$  is translating with velocity  $\mathbf{v}_i$ . Then, the advective flux is  $\mathbf{j}_i = \rho_i \mathbf{v}_i$ . This is the rate that mass of species  $i$  flows through the surface of the control volume per unit time. Then, the conservation law reads

$$\frac{\partial \rho_i}{\partial t} = -\nabla \cdot \mathbf{j}_i = -\nabla \cdot (\rho_i \mathbf{v}_i). \quad (9.17)$$

If we sum over all species,

$$\sum_i \left( \frac{\partial \rho_i}{\partial t} = -\nabla \cdot (\rho_i \mathbf{v}_i) \right) = \frac{\partial \rho}{\partial t} = -\nabla \cdot (\rho \mathbf{v}), \quad (9.18)$$

where  $\mathbf{v}$  is the bulk velocity and  $\rho$  is the density of the material. Applying the chain rule, this is

$$\frac{\partial \rho}{\partial t} = -\rho \nabla \cdot \mathbf{v} - \mathbf{v} \cdot \nabla \rho. \quad (9.19)$$

If the material is **incompressible**, or if it has constant density, then  $\partial \rho / \partial t = 0$  and  $\nabla \rho = 0$ , then

$$\nabla \cdot \mathbf{v} = 0. \quad (9.20)$$

This is known as the **continuity equation**, true for an incompressible material, such as water or cytoplasm.

## 9.2 Fick's laws and diffusive flux

To treat diffusion, we need to write an expression for the diffusive flux of species  $i$ ,  $\mathbf{j}_i$ .<sup>12</sup> We can think about this phenomenologically. We know from experience that if you put a high concentration

<sup>12</sup>We do seem to be overloading the symbol  $\mathbf{j}_i$ . It will always be clear what kind of flux we are talking about by context.

of, say, food coloring in the middle of a glass of water, diffusion brings the food coloring for areas of high concentration to areas of low concentration. Therefore, the flux of diffusing species goes in the opposite direction of the concentration gradient, i.e., from high to low. So, to first order, the diffusive flux should be proportional to the gradient of concentration. We call the constant of proportionality  $D_i$ , referred to as a **diffusion coefficient**, or **diffusivity**. The result is

$$\mathbf{j}_i = -D_i \nabla \rho_i. \quad (9.21)$$

Instead of writing the mass flux, we could instead write the particle flux. Redefining  $\mathbf{j}_i/M \rightarrow \mathbf{j}_i$ , where  $M$  is the molecular mass, we can write the expression for the particle flux as

$$\mathbf{j}_i = -D_i \nabla c_i. \quad (9.22)$$

This is known as **Fick's first law**.

Substituting Fick's first law into the general statement of conservation gives

$$\frac{\partial c_i}{\partial t} = D_i \nabla^2 c_i, \quad (9.23)$$

a result known as **Fick's second law**.

### 9.3 Statistical treatment of diffusion

Having derived<sup>13</sup> a partial differential equation describing diffusive dynamics, we will now treat diffusion statistically, taking a particulate view. A diffusing particle moves around space due to repeated bombardments by solvent molecules, which are themselves sailing around driven by thermal energy.

To model how the diffusing particle moves, we will again restrict ourselves to one dimension and later generalize to three. We can think of a diffusing particle as making a small hop, either left (negative  $x$ -direction) or right (positive  $x$ -direction) due to collisions with solvent molecules. Let  $\ell$  be the distance of the hop and let  $\tau$  be the amount of time it takes to make a hop. In some amount of time  $t$ , the diffusing particle will take  $n = t/\tau$  total hops. We take each hop to be independent of all others, and the diffusing particle has a 50/50 chance of taking a left or right hop. So, the number  $r$  of rightward hops out of a total of  $n$  the particle takes is Binomially distributed with probability  $1/2$ , or

$$r | n \sim \text{Binom}(n, 1/2). \quad (9.24)$$

We know the mean and variance of a Binomial distribution, so we can readily write down

$$\text{mean } r = \langle r \rangle = n/2, \quad (9.25)$$

$$\text{variance of } r = \langle r^2 \rangle - \langle r \rangle^2 = n/4. \quad (9.26)$$

From these,

$$\langle r^2 \rangle = \frac{n}{4} + \frac{n^2}{4} = \frac{n}{4}(n+1). \quad (9.27)$$

While it is useful to know these moments of  $r$  in terms of  $n$ , we would really like to know the moments of the total displacement from the origin,  $x$ , in terms of  $t$ . We know how these variables are related.

$$x = \ell r - \ell(n-r) = \ell(2r-n), \quad (9.28)$$

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<sup>13</sup>We did not really derive, but reasoned, I would say.

$$t = n\tau. \quad (9.29)$$

Thus, we have

$$\langle x \rangle = \ell(2\langle r \rangle - n) = \ell\left(2\frac{n}{2} - n\right) = 0. \quad (9.30)$$

This means that, on average, the diffusing particle ends up at the origin. Importantly, this is *on average*. The particle does make excursions away, which is why it is important to compute the second moment.

$$\begin{aligned} \langle x^2 \rangle &= \langle \ell^2(2r - n)^2 \rangle = \ell^2 \langle 4r^2 + n^2 - 4nr \rangle = \ell^2 (4\langle r^2 \rangle + n^2 - 4n\langle r \rangle) \\ &= \ell^2 (n(n+1) + n^2 - 2n^2) = \ell^2 n = \ell^2 \frac{t}{\tau} \end{aligned} \quad (9.31)$$

So, the mean  $x$  is zero and the variance is  $\langle x^2 \rangle - \langle x \rangle^2 = \langle x^2 \rangle = \ell^2 t / \tau$ .

For large  $n$ , the **de Moivre-Laplace theorem** states that the Binomial distribution is well-approximated by a Gaussian distributed with the same mean and variance as the Binomial. Thus, we have

$$r | n \sim \text{Norm}(n/2, \sqrt{n}/2), \quad (9.32)$$

or, more conveniently,

$$x | t \sim \text{Norm}(0, \ell\sqrt{t/\tau}). \quad (9.33)$$

We can write out the probability density function for the displacement  $x$  as

$$P(x; t) = \frac{1}{\sqrt{2\pi\ell^2 t/\tau}} \exp\left[-\frac{x^2}{2\ell^2 t/\tau}\right]. \quad (9.34)$$

This is convenient because the de Moivre-Laplace theorem allows us to write probability of displacements, which we started modeling as a discrete random walk, as a continuous probability distribution. This enables differentiation and integration of the distribution.

This can be generalized to three dimensions by using a trivariate Gaussian distribution. The covariance matrix is diagonal because the steps along the orthogonal directions are uncorrelated.

$$P(\mathbf{x}; t) = \left(\frac{1}{2\pi\ell^2 t/\tau}\right)^{3/2} \exp\left[-\frac{\mathbf{x} \cdot \mathbf{x}}{2\ell^2 t/\tau}\right]. \quad (9.35)$$

## 9.4 Connection to the diffusion equation

We have previously derived a partial differential equation describing diffusive dynamics,

$$\frac{\partial c}{\partial t} = D\nabla^2 c. \quad (9.36)$$

How does this connect to the statistical treatment?

It stands to reason that  $c(\mathbf{x}, t)$  is proportional to  $P(\mathbf{x}; t)$ , or

$$c(\mathbf{x}, t) = n_0 P(\mathbf{x}; t), \quad (9.37)$$

where  $n_0$  is the total number of particles present. If we imagine particles concentrated in a small area of a large volume  $V$ ,

$$n_0 = \int dV c(\mathbf{x}, t) \approx \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dy \int_{-\infty}^{\infty} dz c(\mathbf{x}, t)$$

$$= \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dy \int_{-\infty}^{\infty} dz n_0 P(\mathbf{x}; t) = n_0. \quad (9.38)$$

If we plug  $c(\mathbf{x}, t) = n_0 P(\mathbf{x}; t)$  into the PDE for diffusive dynamics, we get

$$\frac{\partial P(\mathbf{x}; t)}{\partial t} = D \nabla^2 P(\mathbf{x}; t). \quad (9.39)$$

We can compute the derivatives from our expression for  $P(\mathbf{x}; t)$ , (9.35).

$$\frac{\partial P}{\partial t} = \frac{1}{2} \left( \frac{x^2}{\ell^2 t^2 / \tau} - \frac{1}{t} \right) P(\mathbf{x}; t), \quad (9.40)$$

$$\nabla^2 P = \frac{\tau}{\ell^2} \left( \frac{x^2}{\ell^2 t^2 / \tau} - \frac{1}{t} \right) P(\mathbf{x}; t). \quad (9.41)$$

Therefore, for (9.39) to hold, we must have

$$D = \frac{\ell^2}{2\tau}. \quad (9.42)$$

Therefore,

$$P(\mathbf{x}; t) = \left( \frac{1}{4\pi Dt} \right)^{3/2} \exp \left[ -\frac{\mathbf{x} \cdot \mathbf{x}}{4Dt} \right]. \quad (9.43)$$

Or, in one dimension,

$$P(x; t) = \frac{1}{\sqrt{4\pi Dt}} \exp \left[ -\frac{x^2}{4Dt} \right]. \quad (9.44)$$

Note that we have now found the Green's function to the diffusion equation (also known as the heat equation) using statistical arguments!

Now that we have the probability density function, we can again consider the moments. The mean displacement is again zero, and the variance is

$$\langle \mathbf{x} \cdot \mathbf{x} \rangle = \langle x^2 \rangle + \langle y^2 \rangle + \langle z^2 \rangle = 6Dt. \quad (9.45)$$

In one dimension this is  $2Dt$ , and in two dimensions it is  $4Dt$ . Importantly, the mean square displacement varies linearly with time.

## 9.5 Stokes-Einstein-Sutherland relation

We have already discussed that diffusion is driven by thermal energy. How, then, can we connect the parameter describing diffusion, the diffusion coefficient, to the thermal energy  $k_B T$ ? You will work this out in your homework, deriving the **Einstein-Smoluchowski equation**,

$$D = \frac{k_B T}{f}, \quad (9.46)$$

where  $f$  is the frictional drag on the diffusing particle, also known as the inverse motility. The frictional drag depends on the shape of the particle. There is a good discussion on this in Howard Berg's book *Random Walks in Biology*. For a sphere, George Stokes worked out that  $f = 6\pi\eta a$ , where  $a$  is the radius of the sphere. Then, we get the **Stokes-Einstein-Sutherland relation**,

$$D = \frac{k_B T}{6\pi\eta a}. \quad (9.47)$$