

Molecular transport

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1 Introduction

In all the previous classes, we have considered the thermodynamic equilibrium and did not care how it was achieved, or how the system passes from one microstate to the other. In this document, we address the problem of dynamics by introducing two powerful and complementary methods, the diffusion equation and the Langevin equation. The former looks at the evolution of the concentration with time, hence focusing on the particles at the level of ensemble. The latter instead studies the dynamics of a single particle via a stochastic differential equation.

2 The diffusion equation

The diffusion equation is a partial differential equation which describes the time evolution of the space-dependent concentration profile $c(\mathbf{r}, t)$ under random motion of particles within a system. The physical idea is that, due to the random collisions with the molecules of the solvent, a particle in a solution eventually loses the memory of its velocity, i.e. if one looks at the system at sufficiently large time- and length-scales the motion of the particles will be completely random. A quantitative explanation of this concept will be provided in a subsequent section by means of the Langevin equation.

2.1 Derivation

In the present section, we take the randomness for granted and derive the diffusion equation in a simplified form. We consider a one-dimensional system where particles can sit in discretized positions $\dots, x - dx, x, x + dx, \dots$. The particles do not interact with each other, so that any number of particles can be found at a given point. We discretize also the time as $t, t + dt, \dots$. Within our simplified framework, we assume that in the time interval separating t and $t + dt$ a particle has probability q to jump on a neighboring site, so that it will stay at the same point with probability $1 - q$. Moreover, the particle jumps with equal probability to each neighbor. Therefore, starting from x at time t , the new location at time $t + dt$ will be

$$\begin{cases} x & \text{with probability } 1 - q, \\ x - dx & \text{with probability } \frac{q}{2}, \\ x + dx & \text{with probability } \frac{q}{2}. \end{cases} \quad (1)$$

Indicating with $N(x, t)$ the number of particles at position x at time t , due to mass conservation we thus expect the following updating rule:

$$N(x, t + dt) = (1 - q)N(x, t) + \frac{q}{2}N(x - dx, t) + \frac{q}{2}N(x + dx, t). \quad (2)$$

The first term on the right-hand side gives the contribution coming from the particles which were already at x and are staying there, while the second and third term are the contributions of particles jumping from $x - dx$ and $x + dx$, respectively. Considering small values of dt and dx , one can write¹

$$\begin{cases} N(x, t + dt) \simeq N(x, t) + \frac{\partial N}{\partial t} dt, \\ N(x - dx, t) \simeq N(x, t) - \frac{\partial N}{\partial x} dx + \frac{1}{2} \frac{\partial^2 N}{\partial x^2} dx^2, \\ N(x + dx, t) \simeq N(x, t) + \frac{\partial N}{\partial x} dx + \frac{1}{2} \frac{\partial^2 N}{\partial x^2} dx^2, \end{cases} \quad (3)$$

¹As will be apparent in a few lines, the first term for the development in t is sufficient, while for x we need to go up to the second term because the linear terms cancel each other out.

where it is intended that all derivatives are evaluated at x and t . The updating rule thus becomes

$$N(x, t) + \frac{\partial N}{\partial t} dt = (1 - q)N(x, t) + \frac{q}{2}N(x, t) - \frac{q}{2}\frac{\partial N}{\partial x}dx + \frac{q}{4}\frac{\partial^2 N}{\partial x^2}dx^2 + \frac{q}{2}N(x, t) + \frac{q}{2}\frac{\partial N}{\partial x}dx + \frac{q}{4}\frac{\partial^2 N}{\partial x^2}dx^2. \quad (4)$$

Some of the terms in the previous equation cancel each other out. After some simple manipulations, we are thus left with

$$\frac{\partial N}{\partial t} dt = \frac{q}{2}dx^2 \frac{\partial^2 N}{\partial x^2} \Rightarrow \frac{\partial N}{\partial t} = \frac{dx^2}{2dt} q \frac{\partial^2 N}{\partial x^2}. \quad (5)$$

The probability q of jumping mimicks the tendency of particles to move due to random collisions with the solvent. It is expected to depend on both the inertia of the particle (larger particles will be less likely to jump) and the viscosity of the solvent itself. Now, we consider the continuum limit of the previous equation, taken by considering $dt \rightarrow 0$ and $dx \rightarrow 0$, but such that dx^2/dt is kept constant. In this way, the prefactor is a constant that we define as $D \equiv dx^2 q / (2dt)$ and the equation becomes

$$\frac{\partial N}{\partial t} = D \frac{\partial^2 N}{\partial x^2}. \quad (6)$$

This is called the *diffusion equation* and D is the *diffusion coefficient*. Note that by dividing both sides by the size of the system (in this one-dimensional case it is the length, in three dimension it would be the volume), the diffusion equation also regulates the concentration $c(x, t)$:

$$\boxed{\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}}. \quad (7)$$

Alternatively, dividing by the total number of particles in the system, it also regulates the evolution of the probability distribution $p(x, t)$:

$$\frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2}. \quad (8)$$

We will usually consider the diffusion equation for the concentration, Eq.(7).

We note that the reasoning can be extended to more than one dimension, giving in general

$$\frac{\partial c}{\partial t} = D \nabla^2 c. \quad (9)$$

For instance, in three dimensions we have

$$\frac{\partial c}{\partial t} = D \nabla^2 c = D \frac{\partial^2 c}{\partial x^2} + D \frac{\partial^2 c}{\partial y^2} + D \frac{\partial^2 c}{\partial z^2}. \quad (10)$$

As a final note, we observe that the diffusion coefficient has dimensions of a square length divided by time.

2.2 Fick's laws

The derivation above implicitly considers some physical points that are worth stressing. To this aim, we devote this section to an alternative (yet very similar to the one given) derivation of the diffusion equation. Let us consider a certain point x . Our present aim is to quantify the amount of particles crossing x per unit time, which is called the *flux*² J . Following a similar approach as above, we consider a discretized system with consecutive points separated by a distance dx , and we focus on the points $x - dx/2$ and $x + dx/2$. In other words, in the discretization x corresponds to the midpoint between two lattice points. In a discretized time unit dt , the flux of particles is determined by the net exchange between $x - dx/2$ and $x + dx/2$. The total number of particles in $x - dx/2$ at time t is $c(x - dx/2, t)dx$, so that the number of particles passing from $x - dx/2$ to $x + dx/2$ is $c(x - dx/2, t)dx \cdot q/2$. Analogously, the number of particles going in the opposite direction is $c(x + dx/2, t)dx \cdot q/2$. Following the convention that a positive flux corresponds to particles going towards increasing values of x , the net amount of particles passing through x is thus

$$\frac{q}{2}c(x - \frac{dx}{2}, t)dx - \frac{q}{2}c(x + \frac{dx}{2}, t)dx . \quad (11)$$

The flux J is then obtained by dividing by the unit time dt :

$$\begin{aligned} J(x, t) &= \frac{1}{dt} \left[\frac{q}{2}c(x - \frac{dx}{2}, t)dx - \frac{q}{2}c(x + \frac{dx}{2}, t)dx \right] \simeq \\ &\frac{qdx}{2dt} \left[c(x, t) - \frac{\partial c}{\partial x} \frac{dx}{2} - c(x, t) - \frac{\partial c}{\partial x} \frac{dx}{2} \right] = \\ &- \frac{qdx^2}{2dt} \frac{\partial c}{\partial x}(x, t) . \end{aligned} \quad (12)$$

We recognize the diffusion coefficient in the prefactor, $D = qdx^2/(2dt)$. Hence, we find *Fick's first law*:

$$\boxed{J(x, t) = -D \frac{\partial c}{\partial x}(x, t)} . \quad (13)$$

Now, let us consider again a point x , which in this case we set as corresponding to a lattice point. In this way, the points $x - dx/2$ and $x + dx/2$ are midpoints apt for computing the flux. The total number of particles at x at time t is $c(x, t)dx$, while at time $t + dt$ is $c(x, t + dt)dx$.

²The flux is traditionally defined as the amount of particles crossing a section per unit time and per unit area, based on a three-dimensional system. Here, the section has 0 dimensions, hence we do not need to normalize by the area. To ease the visualization, we could think of a three-dimensional system with constant cross section A and where diffusion takes place along x . It is easy to see that the various equations in this section will be multiplied by A , so that the final normalization by the area will cancel A and lead to the same result that we find in the present derivation.

Mass conservation imposes that the change in the total number of particles at x is dictated by the fluxes at $x - dx/2$ and $x + dx/2$. Remembering that a positive flux corresponds to a net transfer of particles towards larger values of x , we see that the flux at $x - dx/2$ gives a positive contribution, while the one at $x + dx/2$ goes in the opposite direction. Summarizing, we thus obtain

$$c(x, t + dt)dx - c(x, t)dx = J(x - \frac{dx}{2}, t)dt - J(x + \frac{dx}{2}, t)dt \Rightarrow$$

$$dtdx \frac{\partial c}{\partial t}(x, t) \simeq J(x, t)dt - dt \frac{dx}{2} \frac{\partial J}{\partial x}(x, t) - J(x, t)dt - dt \frac{dx}{2} \frac{\partial J}{\partial x}(x, t) \Rightarrow \quad (14)$$

$$\boxed{\frac{\partial c}{\partial t}(x, t) \simeq -\frac{\partial J}{\partial x}(x, t)} .$$

This is called *Fick's second law* or *continuity equation*. Joining together both Fick's laws gives

$$\frac{\partial c}{\partial t}(x, t) \simeq -\frac{\partial J}{\partial x}(x, t) = D \frac{\partial^2 c}{\partial x^2}(x, t) , \quad (15)$$

which is the diffusion equation, Eq.(7).

2.3 Gaussian distribution of a point source

We are now interested in determining the time evolution of the concentration profile $c(x, t)$ of a system containing M molecules initially concentrated at the origin. This problem can be pictorially ascribed to what happens to a drop of oil once released on water, e.g. on a lake. The oil floats at the surface and starts spreading in all directions, with the central part of the growing spot being more concentrated (although less so as time goes on). Quantitatively, to solve the diffusion equation we need to set two boundary conditions (i.e. two spatial constraints, since the diffusion equation is of second order in space) and one initial condition (i.e. a time constraint, since the diffusion equation is of first order in time). We assume the environment to extend indefinitely, so that the only physically-reasonable boundary conditions are that the concentration is zero at infinite. As for the initial condition, we can formulate the localization of all the molecules at the origin by imposing $c(x, 0) = M \cdot \delta(x)$, where $\delta(x)$ is Dirac's delta. We consider the one-dimensional case.

Summarizing, we thus want to solve the following problem:

$$\begin{cases} \frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} , \\ c(\infty, t) = 0 , \\ c(-\infty, t) = 0 , \\ c(x, 0) = M\delta(x) . \end{cases} \quad (16)$$

2.3.1 Crash course on Fourier transforms

In order to solve the equation above, we need to resort to the Fourier transform $\hat{c}(k, t)$ of $c(x, t)$ with respect to space. We first dedicate a few words to the definition of a Fourier transform and a couple of properties that we need for our computation. The Fourier transform $\hat{f}(k)$ of a function $f(x)$ is defined as

$$\hat{f}(k) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{ikx} f(x) dx, \quad (17)$$

which can be defined only if the integral converges, i.e. f needs to go to zero at infinity and it has to do it fastly enough. If one knows $\hat{f}(k)$, the original function can be obtained by transforming back:

$$f(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-ikx} \hat{f}(k) dk. \quad (18)$$

A key property is related to the Fourier transform of the derivative:

$$\widehat{\frac{df}{dx}}(k) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{ikx} \frac{df}{dx} dx. \quad (19)$$

Since $e^{ikx} df/dx = d(e^{ikx} f)/dx - ik e^{ikx} f$, we have

$$\widehat{\frac{df}{dx}}(k) = \frac{1}{\sqrt{2\pi}} \cancel{e^{ikx} f(x)} \Big|_{x=-\infty}^{\infty} - \frac{ik}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{ikx} \frac{df}{dx} dx = -ik \hat{f}(k). \quad (20)$$

This procedure can be iterated, thus giving

$$\widehat{\frac{d^2 f}{dx^2}}(k) = (-ik)^2 \hat{f}(k) = -k^2 \hat{f}(k). \quad (21)$$

Another result that we need is the Fourier transform of the Dirac's delta:

$$\hat{\delta}(k) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{ikx} \delta(x) dx = \frac{1}{\sqrt{2\pi}}. \quad (22)$$

Finally, we will also need to compute the antitransform of a Gaussian function

$$\frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-ikx} e^{-\alpha k^2} dk. \quad (23)$$

To this aim, we rearrange the exponent in the following way:

$$\alpha k^2 + ikx = \alpha \left(k + \frac{ix}{2\alpha} \right)^2 + \frac{x^2}{4\alpha}. \quad (24)$$

Based on this, the antitransform can be written as

$$\frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-ikx} e^{-\alpha k^2} dk = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{4\alpha}} \int_{-\infty}^{\infty} e^{-\alpha \left(k + \frac{ix}{2\alpha} \right)^2} dx = \frac{1}{\sqrt{2\alpha}} e^{-\frac{x^2}{4\alpha}}, \quad (25)$$

where we used the known result $\int_{-\infty}^{\infty} e^{-\alpha(x+c)^2} dx = \sqrt{\pi/\alpha}$. Therefore, the Fourier (anti)transform of a Gaussian function is another Gaussian function.

2.3.2 Solving the diffusion equation

We now perform the Fourier transform with respect to space of both sides of the diffusion equation. Using Eq.(21), we obtain

$$\frac{\partial \hat{c}}{\partial t} = -k^2 D \hat{c} \Rightarrow \hat{c}(k, t) = \hat{c}(k, 0) e^{-k^2 D t} . \quad (26)$$

The initial condition is easily found by means of Eq.(22):

$$\hat{c}(k, 0) = M \hat{\delta}(k) = \frac{M}{\sqrt{2\pi}} . \quad (27)$$

Eq. (26) can thus be written as

$$\hat{c}(k, t) = \frac{M}{\sqrt{2\pi}} e^{-k^2 D t} . \quad (28)$$

Transforming back to the real space (i.e. the x coordinates) gives by means of Eq.(25)

$$c(x, t) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-ikx} \left(\frac{M}{\sqrt{2\pi}} e^{-k^2 D t} \right) dk = \frac{M}{\sqrt{2\pi}} \cdot \frac{1}{\sqrt{2Dt}} e^{-\frac{x^2}{4Dt}} = \frac{M}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}} , \quad (29)$$

i.e. collecting first and last side of the chain of equations

$$\boxed{c(x, t) = \frac{M}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}} , \quad (30)$$

The concentration profile at time t is thus a Gaussian function with zero mean (as expected from the symmetry of the problem) and variance equal to $2Dt$. This is in line with our expectations as described qualitatively above: as shown in Fig.1, the profile expands in time, yet showing a larger concentration at the center of the spot.

2.4 The mean-square displacement

As stated above, the variance of the concentration profile obtained starting from a point source grows linearly in time. Since the average is zero, this variance corresponds to $\langle x^2 \rangle$, i.e.

$$\boxed{\langle x^2 \rangle (t) = 2Dt} . \quad (31)$$

The quantity $\langle x^2 \rangle$ is called the *mean-square displacement* of the particles, and is a measure of the extension of the concentration distribution. The size of the “spot” containing the diffusing particles can be estimated as $\sqrt{\langle x^2 \rangle} = \sqrt{2Dt}$, i.e. it grows as the square root of time.

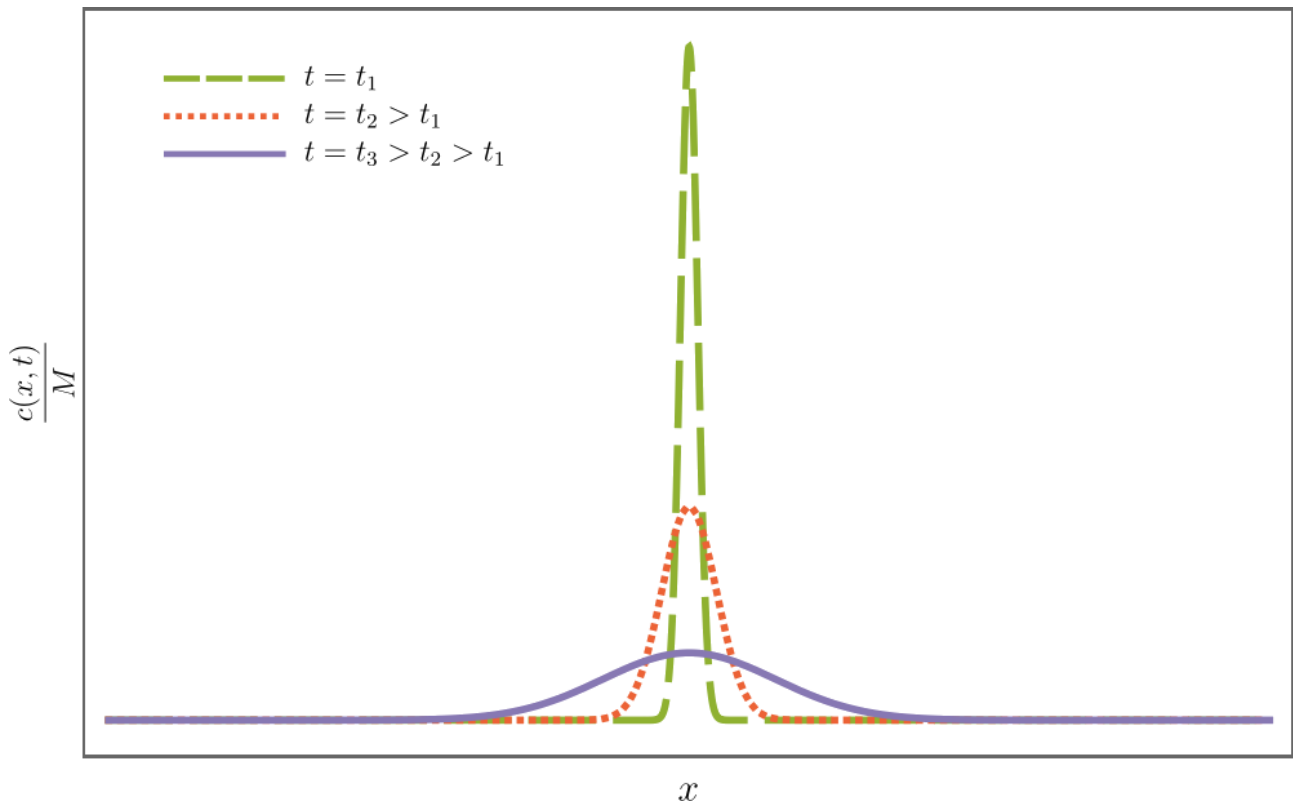


Figure 1: Plots of concentration profiles at three different times obtained starting from a point source.

We note that the problem of a point source can be readily generalized in more dimensions. Indeed, one only needs to substitute x and k by the vectors \mathbf{r} and \mathbf{k} . The definition of the Fourier transform in d dimensions becomes

$$\hat{f}(\mathbf{k}) = \frac{1}{(2\pi)^{\frac{d}{2}}} \int e^{i\mathbf{k}\cdot\mathbf{r}} f(\mathbf{r}) d\mathbf{r} \quad (32)$$

and similarly for the antitransform. All the calculations above can be repeated in the exact same way, and the final concentration is simply the multiplication of the contributions from the various dimensions, i.e. *the diffusion in each dimension is independent of the other dimensions*. The concentration profile thus reads

$$c(\mathbf{r}, t) = M \cdot \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}} \cdot \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{y^2}{4Dt}} \dots = \frac{M}{(4\pi Dt)^{\frac{d}{2}}} e^{-\frac{r^2}{4Dt}}. \quad (33)$$

The mean square displacement is thus obtained as

$$\langle r^2 \rangle = \langle x^2 \rangle + \langle y^2 \rangle + \dots = 2Dt \cdot d = 2dDt. \quad (34)$$

For instance, in two and three dimensions one finds $\langle r^2 \rangle = 4Dt$ and $\langle r^2 \rangle = 6Dt$, respectively.

As a final note, we observe that the typical time τ_L needed to travel a length L can be obtained by setting $L^2 \simeq \langle x^2 \rangle = 2D\tau_L$, so that

$$\boxed{\tau_L = \frac{L^2}{2D}}. \quad (35)$$

2.4.1 Fast derivation of the mean-square displacement

Eq. (31) can be derived rapidly without needing the explicit formula of $c(x, t)$ derived above. Indeed, we note that

$$\langle x^2 \rangle (t) = \frac{\int_{-\infty}^{\infty} x^2 c(x, t) dx}{M}, \quad (36)$$

where by construction the total number of particles is $M = \int_{-\infty}^{\infty} c(x, t) dx$. Deriving both sides with respect to time and making use of the diffusion equation, we find

$$\frac{d\langle x^2 \rangle}{dt} = \frac{1}{M} \int_{-\infty}^{\infty} x^2 \frac{\partial c}{\partial t} dx = \frac{D}{M} \int_{-\infty}^{\infty} x^2 \frac{\partial^2 c}{\partial x^2} dx. \quad (37)$$

Using the identity

$$x^2 \frac{\partial^2 c}{\partial x^2} = \frac{\partial}{\partial x} \left(x^2 \frac{\partial c}{\partial x} \right) - 2x \frac{\partial c}{\partial x} \quad (38)$$

and assuming that³ $x^2 \partial c / \partial x \rightarrow 0$ as $x \rightarrow \pm\infty$, one can thus write

$$\frac{d\langle x^2 \rangle}{dt} = -\frac{2D}{M} \int_{-\infty}^{\infty} x \frac{\partial c}{\partial x} dx. \quad (39)$$

Using the identity $x \partial c / \partial x = \partial(xc) / \partial x - c$ and considering that $xc \rightarrow 0$ as $x \rightarrow \pm\infty$, we find

$$\frac{d\langle x^2 \rangle}{dt} = \frac{2D}{M} \int_{-\infty}^{\infty} c(x, t) dx = 2D. \quad (40)$$

Since the initial condition imposes trivially that $\langle x^2 \rangle (0) = 0$, we thus find $\langle x^2 \rangle (t) = 2Dt$, which is the result reported in Eq.(31).

2.5 Diffusion vs advection

In many systems also advection is important, i.e. there is a net drift velocity v of the system. An example is provided by any microfluidic setup. If both diffusion and advection are present, they will each contribute to mass transport. The relative importance of each contribution can

³The usual behavior for c is to go to zero exponentially at large distances.

be assessed by estimating the time needed to move a particle along a distance L . The advective time is $\tau_{\text{adv}}(L) \sim L/v$, while from Eq.(35) the diffusion time is⁴ $\tau_{\text{diff}}(L) = L^2/(2D) \sim L^2/D$. The most important mechanism corresponds to the shortest transport time. In this regard, it is customary to quantify the relative weight of the two contributions by means of the *Peclet number*

$$Pe(L) = \frac{\tau_{\text{diff}}(L)}{\tau_{\text{adv}}(L)} \sim \frac{\frac{L^2}{D}}{\frac{L}{v}} = \frac{Lv}{D}. \quad (41)$$

If $Pe(L) \gg 1$, then advection is the leading mechanism, since diffusion is slower. In contrast, for $Pe(L) \ll 1$ diffusion is more important. We note that $Pe(L)$ increases with size, so that at small length scales diffusion will be leading, while it will be superseded by advection at large scales. The threshold length scale is set by D/v .

Problem. Imagine that you are running a microfluidic experiment where you want to suppress the effects due to diffusion of the particles under study at a length scale of $L = 1 \mu\text{m}$. The particles have a diffusion coefficient equal to $10^{-10} \text{ m}^2/\text{s}$. What is the minimum velocity of the fluid that you have to set? Since you want to look at what happens in windows of size L , what is the minimum time resolution at which you have to collect data?

2.6 Two applications

The diffusion equation has wide applications in biophysics. As an example, we mention the case of the experimental technique known as FRAP (Fluorescence Recovery After Photobleaching), which can be used to study e.g. the diffusion of lipids within a membrane. The idea is to tag the lipids by means of fluorescence, so that under normal conditions one sees at the microscope a uniform fluorescent sample. At a certain moment, by means of an intense and short laser pulse a small area of the sample is photobleached, i.e. the fluorophores are “burned”, as shown in the snapshot reported in the top panel of Fig.2 for $t = 0$. As time passes, the bleached lipids diffuse out of the central spot and are substituted there by unbleached ones. As a result (and since the rest of the sample acts as a reservoir), the fluorescence intensity increases with time until it eventually recovers completely (snapshots at $t = 15 \text{ s}$ and $t = 20 \text{ s}$ in the top panel of Fig.2). The intensity of the fluorescence signal is proportional to the concentration c_u of unbleached lipids. Indicating by c_b the concentration of bleached lipids, one has that at each point $c_u(\mathbf{r}) + c_b(\mathbf{r}) = c_0$, where c_0 is the overall lipid concentration. The intensity $I(\mathbf{r})$ of the signal will thus be equal to $I = a \cdot c_u = a(c_0 - c_b) = I_0 - ac_b$, where I_0 is the intensity corresponding to c_0 .

Quantitatively, the problem can be treated by means of a two-dimensional diffusion equation. Due to the symmetry of the problem, it is best to use cylindrical coordinates, so that the diffusion equation for c_b reads

$$\frac{\partial c_b}{\partial t} = D \cdot \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial c_b}{\partial r} \right) \quad (42)$$

⁴We are interested in length scales, so that we are dropping the numerical prefactors.

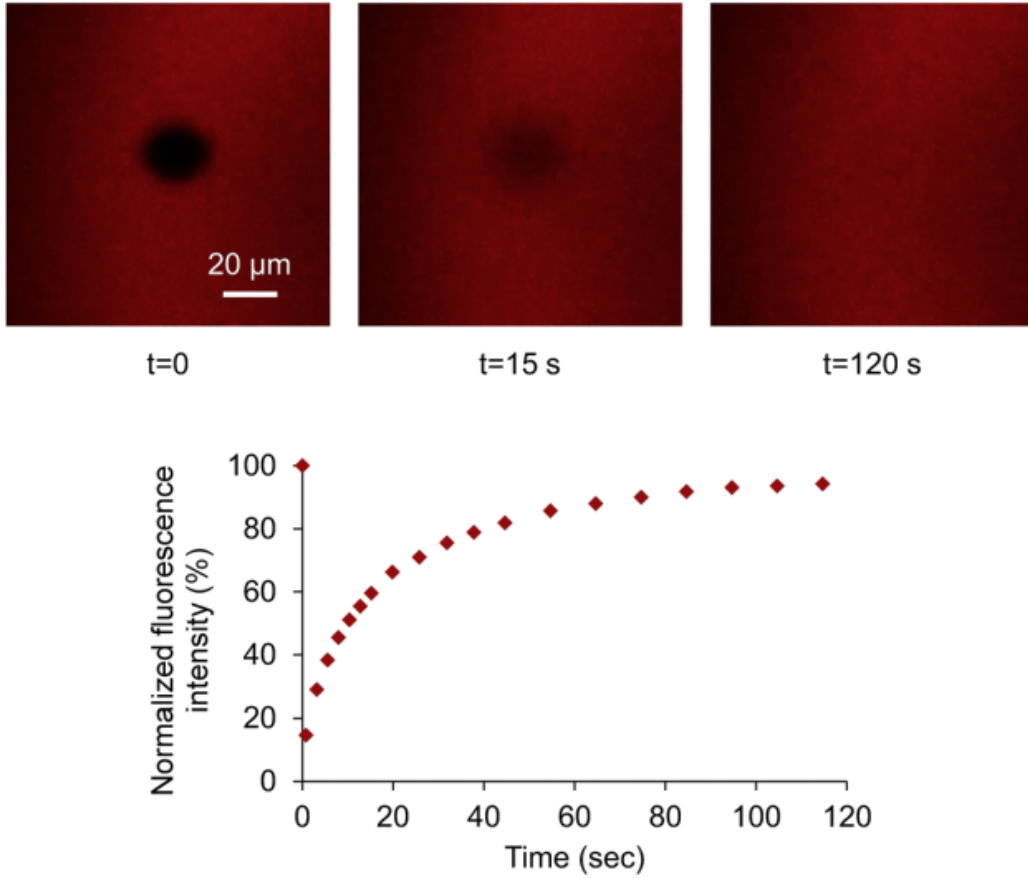


Figure 2: Top: representative time evolution of a FRAP sample, achieved thanks to the diffusion of bleached lipids outside of the central region and unbleached lipids towards the central region. Bottom: fluorescence intensity in the central spot as a function of time. Reprinted from F. Pincet et al., “FRAP to Characterize Molecular Diffusion and Interaction in Various Membrane Environments”, *PLoS ONE* **11**:e0158457.

The boundary conditions are that $c_b(\infty, t) = 0$, while the initial condition is

$$c_b(r, 0) = \begin{cases} c_i & \text{if } r \leq R \\ 0 & \text{if } r > R, \end{cases} \quad (43)$$

where R is the size of the bleached spot and c_i the concentration of bleached fluorophores (which depend on how efficient was the laser, i.e. on the intensity of the beam). This equation can be solved by means of the Bessel functions, but it is beyond our present scope. The only thing worth remarking is that one can then use the formula to fit the experimental data of intensity vs time (see bottom panel of Fig.2), thus extracting the value of D .

A second, more direct application is the technique called as Single-Particle Tracking. Quite

simply, in this case one follows fluorescently-labeled particles at the single-molecule level and, from the reconstructed random trajectory, obtain the diffusion coefficient by studying the mean-square displacement as a function of time. In a diffusive regime, as we know the dependence is linear, so that a fitting procedure leads to the determination of D . The same approach is used to extract D from molecular simulations, where one has access to the trajectory of each simulated particle and can thus easily obtain the mean-square displacement.

3 The Langevin equation

The diffusion equation focuses on the evolution of the distribution of particles, hence looking at the system as a whole. Here, we discuss a complementary approach, which focuses on the dynamics of a single particle by means of a *stochastic differential equation* (yet ordinary, in contrast with the partial derivative equation seen above). It can be shown formally that the two approaches are equivalent. Indeed, there is a whole set of stochastic systems which can be described equivalently by a stochastic differential equation (usually called “the Langevin equation” of the system) or by a diffusion-like equation (which is called the *Fokker-Planck equation* of the system). Although the two approaches are equivalent from a formal perspective, in practice one of them is usually most suited to solve a certain problem. Which of the two approaches is best depends on the particular problem under inspection. Therefore, the Langevin equation and the diffusion equation provide complementary tools in understanding the random motion of particles.

3.1 Derivation

As mentioned above, the Langevin equation focuses on a single particle. For simplicity, we consider here the one-dimensional case. We know from classical mechanics that a particle under the influence of an external potential $U(x)$ obeys the differential equation provided by Newton’s second law:

$$m \frac{d^2x}{dt^2} = - \frac{dU}{dx} . \quad (44)$$

The system conserves the total energy at any time, provided by the sum between U and the kinetic energy. In the case of a particle moving in a liquid such as water, the solvent particles act in two ways (connected to each other). On the one hand, there is a viscous drag opposing the movement of the particle and proportional to its speed, i.e. there is a force $-\gamma dx/dt$ acting on the particle, where γ is the *drag coefficient* and has the units of mass/time. On the other hand, the random collisions also provide an instantaneous force acting on the particle, whose random nature is captured by means of a stochastic variable. One can think of it as a “random kick” with variable intensity and direction. In Langevin’s approach, this force is introduced as a random variable $\zeta(t)$, where the t dependence is introduced to account for the fact that random kicks at different times are different from each other. Summarizing, the Langevin equation can be written as

$$\boxed{m \frac{d^2x}{dt^2} = - \frac{dU}{dx} - \gamma \frac{dx}{dt} + \zeta(t)} . \quad (45)$$

On the left-hand side, we have the inertial term. On the right-hand side, we find the potential term (as from Newton’s second law), the viscous drag term and the random term. As we will see, the last two terms are related to each other, which is expected since they are both originated from the collisions between the particle and the solvent. $\zeta(t)$ is a stochastic variable with zero mean, since collisions do not have any preferred direction. Moreover, it is assumed

that $\zeta(t)$ has a Gaussian distribution (i.e. it is white noise) with a certain variance σ^2 . Finally, it is also assumed that no correlation is present between two values of ζ taken at different times. Hence, we can summarize the assumed properties as

$$\boxed{\begin{cases} \langle \zeta(t) \rangle = 0 , \\ \langle \zeta(t)\zeta(t') \rangle = \sigma^2 \delta(t - t') , \end{cases}} \quad (46)$$

where $\delta(t)$ is Dirac's delta function.

3.2 Fluctuation-dissipation theorem

In order to determine the connection between the dissipation term $-\gamma dx/dt$ and the fluctuation term $\zeta(t)$ (particularly the value of σ), we consider the simple case of a particle moving in the absence of an external potential. Rather than looking at the position, we focus on the velocity $v = dx/dt$. The Langevin equation becomes

$$\frac{dv}{dt} = -\frac{\gamma}{m}v + \frac{1}{m}\zeta(t) . \quad (47)$$

If there was only the first term in the right-hand side, the solution would be trivially an exponential decay. Based on this, we define an auxiliary function $u(t)$ such that

$$v(t) = e^{-\frac{\gamma}{m}t} [v(0) + u(t)] . \quad (48)$$

Deriving both sides and making use of the Langevin equation, we see that (note that by construction $u(0) = 0$)

$$\frac{du}{dt} = \frac{1}{m}e^{\frac{\gamma}{m}t}\zeta(t) \Rightarrow u(t) = \frac{1}{m} \int_0^t e^{\frac{\gamma}{m}t'} \zeta(t') dt' . \quad (49)$$

Therefore, the equation for the velocity is

$$\boxed{v(t) = e^{-\frac{\gamma}{m}t}v(0) + \frac{1}{m}e^{-\frac{\gamma}{m}t} \int_0^t e^{\frac{\gamma}{m}t'} \zeta(t') dt' .} \quad (50)$$

Naturally, the random nature of ζ yields a random time evolution for the velocity. Nevertheless, we are interested in the average value of the square velocity. We take the square of both sides

of the previous formula, compute the average and make use of Eq.(46), obtaining

$$\begin{aligned}
\langle v^2(t) \rangle &= \\
e^{-\frac{2\gamma}{m}t} v(0)^2 + 2e^{-\frac{2\gamma}{m}t} v(0) \cdot \frac{1}{m} \int_0^t e^{\frac{\gamma}{m}t'} \langle \zeta(t') \rangle dt' + \frac{1}{m^2} e^{-2\frac{\gamma}{m}t} \int_0^t dt' \int_0^t dt'' e^{\frac{\gamma}{m}(t'+t'')} \langle \zeta(t') \zeta(t'') \rangle &= \\
e^{-\frac{2\gamma}{m}t} v(0)^2 + \frac{\sigma^2}{m^2} e^{-2\frac{\gamma}{m}t} \int_0^t dt' \int_0^t dt'' e^{\frac{\gamma}{m}(t'+t'')} \delta(t' - t'') &= \\
e^{-\frac{2\gamma}{m}t} v(0)^2 + \frac{\sigma^2}{m^2} e^{-2\frac{\gamma}{m}t} \int_0^t e^{\frac{2\gamma}{m}t'} dt' &= \\
e^{-\frac{2\gamma}{m}t} v(0)^2 + \frac{\sigma^2}{m^2} e^{-2\frac{\gamma}{m}t} \cdot \frac{m}{2\gamma} e^{\frac{2\gamma}{m}t'} \Big|_0^t &= \\
e^{-\frac{2\gamma}{m}t} v(0)^2 + \frac{\sigma^2}{2\gamma m} e^{-2\frac{\gamma}{m}t} \left(e^{\frac{2\gamma}{m}t} - 1 \right) &= \\
e^{-\frac{2\gamma}{m}t} v(0)^2 + \frac{\sigma^2}{2\gamma m} \left(1 - e^{-\frac{2\gamma}{m}t} \right) . &
\end{aligned} \tag{51}$$

Hence, we find the result

$$\boxed{\langle v^2(t) \rangle = e^{-\frac{2\gamma}{m}t} v(0)^2 + \frac{\sigma^2}{2\gamma m} \left(1 - e^{-\frac{2\gamma}{m}t} \right)} . \tag{52}$$

This result is pretty interesting, since it shows that the system loses memory of its initial state with a timescale set by $m/(2\gamma)$. Particularly, at large times, we end up with

$$\langle v^2(t) \rangle = \frac{\sigma^2}{2\gamma m} , \tag{53}$$

independently of the initial state. Now, at large times we expect the system to be equilibrated, so that the average value of the squared velocity should have its thermodynamic equilibrium value dictated by the equipartition theorem, i.e.

$$\frac{1}{2} m \langle v^2 \rangle = \frac{1}{2} k_B T \Rightarrow \langle v^2 \rangle = \frac{k_B T}{m} . \tag{54}$$

Comparing with the equation derived above we find

$$\frac{\sigma^2}{2\gamma m} = \frac{k_B T}{m} \Rightarrow \boxed{\sigma = \sqrt{2k_B T \gamma}} . \tag{55}$$

The boxed equation is the connection between the intensity of fluctuations (σ) and the strength of the viscous drag (γ). This case is an instance of a more general result called *fluctuation-dissipation theorem*. Finally, from Eq.(50), we can easily compute the average value of the velocity

$$\langle v(t) \rangle = e^{-\frac{\gamma}{m}t} v(0), \quad (56)$$

which is depicted in Fig.3a. Starting from $v(0)$, the average velocity decays exponentially to zero (note that this is the velocity *with sign*, not the average magnitude)

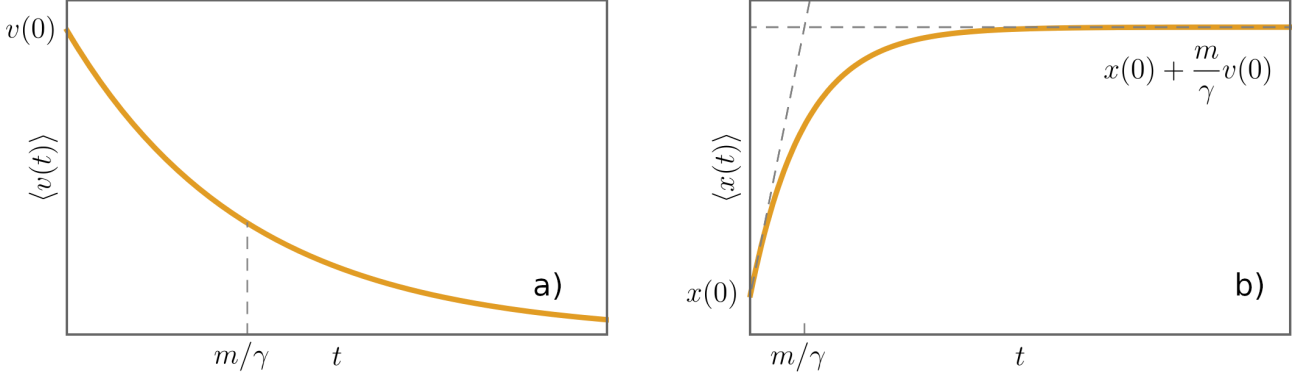


Figure 3: Time evolution of average velocity (a) and position (b) for a particle in the absence of an external potential.

Problem. Compute the average velocity obtained in a system under the presence of a constant force F . Hint: a constant force is obtained from a linear potential $U = -Fx$.

3.3 Position dynamics and Einstein relation

The evolution of the position with time can be obtained by integrating Eq.(50). We find

$$\begin{aligned} x(t) &= \\ x(0) + \int_0^t e^{-\frac{\gamma}{m}t'} v(0) dt' + \frac{1}{m} \int_0^t dt' e^{-\frac{\gamma}{m}t'} \int_0^{t'} dt'' e^{\frac{\gamma}{m}t''} \zeta(t'') &= \\ x(0) + \frac{m}{\gamma} v(0) \left(1 - e^{-\frac{\gamma}{m}t}\right) + \frac{1}{m} \int_0^t dt' e^{-\frac{\gamma}{m}t'} \int_0^{t'} dt'' e^{\frac{\gamma}{m}t''} \zeta(t'') . \end{aligned} \quad (57)$$

Therefore, the average position is

$$\langle x(t) \rangle = x(0) + \frac{m}{\gamma} v(0) \left(1 - e^{-\frac{\gamma}{m}t}\right) . \quad (58)$$

As shown in Fig.3b, at short times the position increases linearly as $\langle x(t) \rangle = x(0) + v(0)t$, i.e. as in the Newtonian case. This is called the *ballistic regime*. In contrast, for long times the average position reaches a plateau value dictated by the initial conditions. Interestingly, the long-time result $\langle x(\infty) \rangle = x(0) + (m/\gamma)v(0)$ coincides with what one would find with a sharp separation according to which the system is in the ballistic regime up to exactly $t^* = m/\gamma$ and after that it moves randomly.

Now we look at the evolution of the variance, $\langle [x(t) - \langle x(t) \rangle]^2 \rangle$. From our analysis based on the diffusion equation, We expect that at large times $\langle [x(t) - \langle x(t) \rangle]^2 \rangle \rightarrow 2Dt$. Before doing the actual computation, we rearrange Eq.(57) into a more treatable way. Particularly, we note that in the double integration the order of integration can be inverted as $\int_0^t dt' \int_0^{t'} dt'' (\dots) = \int_0^t dt'' \int_{t''}^t dt' (\dots)$. In this way we have

$$\begin{aligned}
x(t) &= x(0) + \frac{m}{\gamma}v(0) \left(1 - e^{-\frac{\gamma}{m}t}\right) + \frac{1}{m} \int_0^t dt' e^{-\frac{\gamma}{m}t'} \int_0^{t'} dt'' e^{\frac{\gamma}{m}t''} \zeta(t'') = \\
&x(0) + \frac{m}{\gamma}v(0) \left(1 - e^{-\frac{\gamma}{m}t}\right) + \frac{1}{m} \int_0^t dt'' e^{\frac{\gamma}{m}t''} \zeta(t'') \int_{t''}^t dt' e^{-\frac{\gamma}{m}t'} = \\
&x(0) + \frac{m}{\gamma}v(0) \left(1 - e^{-\frac{\gamma}{m}t}\right) - \frac{1}{\gamma} \int_0^t dt'' e^{\frac{\gamma}{m}t''} \zeta(t'') \left(e^{-\frac{\gamma}{m}t} - e^{-\frac{\gamma}{m}t''}\right) = \\
&x(0) + \frac{m}{\gamma}v(0) \left(1 - e^{-\frac{\gamma}{m}t}\right) + \frac{1}{\gamma} \int_0^t dt'' \zeta(t'') \left[1 - e^{-\frac{\gamma}{m}(t-t'')}\right] .
\end{aligned} \tag{59}$$

With the position written in this form, we now compute

$$\begin{aligned}
& \langle [x(t) - \langle x(t) \rangle]^2 \rangle = \\
& \frac{1}{\gamma^2} \int_0^t dt'' \int_0^t du'' \langle \zeta(t'') \zeta(u'') \rangle \left[1 - e^{-\frac{\gamma}{m}(t-t'')} \right] \left[1 - e^{-\frac{\gamma}{m}(t-u'')} \right] = \\
& \frac{1}{\gamma^2} \int_0^t dt'' \int_0^t du'' \sigma^2 \delta(t'' - u'') \left[1 - e^{-\frac{\gamma}{m}(t-t'')} \right] \left[1 - e^{-\frac{\gamma}{m}(t-u'')} \right] = \\
& \frac{2k_B T}{\gamma} \int_0^t dt'' \left[1 - e^{-\frac{\gamma}{m}(t-t'')} \right]^2 = \quad (\text{change variable } w \equiv t - t'') \quad (60) \\
& \frac{2k_B T}{\gamma} \int_0^t dw \left(1 - e^{-\frac{\gamma}{m}w} \right)^2 = \\
& \frac{2k_B T}{\gamma} \int_0^t dw \left(1 - 2e^{-\frac{\gamma}{m}w} + e^{-2\frac{\gamma}{m}w} \right) = \\
& \frac{2k_B T}{\gamma} t - \frac{4k_B T m}{\gamma^2} \left(1 - e^{-\frac{\gamma}{m}t} \right) + \frac{k_B T m}{\gamma^2} \left(1 - e^{-2\frac{\gamma}{m}t} \right) .
\end{aligned}$$

In the long-time limit, the previous expression reduces to $\langle [x(t) - \langle x(t) \rangle]^2 \rangle = (2k_B T/\gamma)t$, which is the expected linear behavior. Comparing this formula with Eq.(31), we thus obtain the *Einstein relation*

$$\boxed{D = \frac{k_B T}{\gamma}} . \quad (61)$$

Note that sometimes this relation is written as $D = \mu k_B T$, where $\mu \equiv 1/\gamma$ is the *mobility* of the particle. For a spherical particle of radius R , the drag coefficient can be estimated by means of Stokes' law as $\gamma = 6\pi\eta R$, where η is the viscosity of the solvent. Substituting this value in the previous formula gives the *Stokes-Einstein equation*

$$\boxed{D = \frac{k_B T}{6\pi\eta R}} . \quad (62)$$

Problem. Estimate the time needed by a particle of size R to travel a distance equal to its own size.

Problem. The viscosity of water at room temperature is of the order of⁵ 10^{-3} Pa·s. What is the order of magnitude of the diffusion coefficient of a particle of size $R \sim 1$ nm? What about a golf ball? How much time is needed for a golf ball to travel 1 cm just by diffusion in water? Do you think you will ever be able to detect the diffusive motion of a particle of macroscopic size?

⁵The Pascal (Pa) is the SI unit for pressure, and is defined as 1 Pa=1 N/m².

3.4 Brownian dynamics

We have seen that the timescale m/γ separates two dynamical regimes. For times much smaller than m/γ , one has the ballistic regime characterized by Newtonian dynamics. In contrast, for long times the system loses its memory, encoded in the inertia term of Eq.(45). In the latter case, the inertia term in Eq.(45) can be eliminated *a priori* and one is left with

$$0 = -\frac{dU}{dx} - \gamma \frac{dx}{dt} + \zeta(t) \Rightarrow \boxed{\frac{dx}{dt} = -\frac{1}{\gamma} \frac{dU}{dx} + \frac{\zeta(t)}{\gamma}} . \quad (63)$$

This limit is called the *overdamped limit* or the *Smoluchowski limit* of the Langevin equation and corresponds to the so-called *Brownian dynamics*.

Problem. Compute the time evolution of the mean square displacement in the Brownian dynamics. What is the relation between the result found and the full formula obtained above?

Problem. Consider a particle performing Brownian dynamics under the action of a harmonic potential $U = kx^2/2$. By dimensional analysis, compute the timescale needed for equilibration. Then, assuming $x(0) = 0$, compute the time evolution of the mean square displacement. What are the limiting behaviors obtained at short and long times? How does the long-time behavior compare to the result expected from thermodynamic arguments?

3.5 Relative diffusion

An interesting problem is that of the relative movement between two diffusing molecules. Let us denote their diffusion coefficients by D_1 and D_2 and let us assume that they both start from the same position $x = 0$. Assuming that they do not interact, what is their average squared distance as a function of time? The answer is pretty straightforward. Denoting as $x_1(t)$ and $x_2(t)$ the trajectories of the particles, we obtain

$$\Delta x^2(t) \equiv \langle [x_1(t) - x_2(t)]^2 \rangle = \langle x_1^2(t) \rangle + \langle x_2^2(t) \rangle - 2 \langle x_1(t)x_2(t) \rangle . \quad (64)$$

Remembering that $\langle x_i^2 \rangle(t) = 2D_i t$ and observing that the trajectories of the particles are uncorrelated, we find

$$\Delta x^2(t) = 2D_1 t + 2D_2 t - 2 \langle x_1(t) \rangle \langle x_2(t) \rangle = 2(D_1 + D_2)t \equiv 2D_{\text{rel}} t . \quad (65)$$

Therefore, the relative diffusion coefficient of non-interacting particles is just the sum of D_1 and D_2 !

3.6 Applications

Applications of the Langevin equations are mainly for theory and simulations. In particular, the Langevin approach is often used to provide thermostating for Molecular Dynamics simulations,

either to account implicitly for the presence of solvent (and thus avoid the high associated computational cost) or to introduce a simple way to keep the temperature of the solvent itself close to the desired value.

4 Subdiffusion

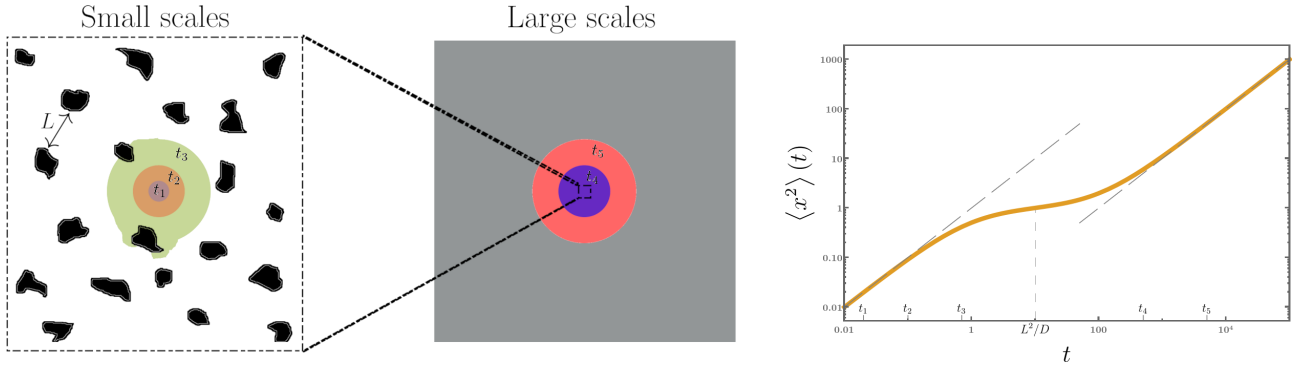


Figure 4: Example of a system with subdiffusive behavior. In this system, a set of obstacles are placed at a spacing of the order of L (left panel). For a particle diffusing starting from the center of the circles, the diffusion profile represented by the circles in left and center panels will show the evolution diffusive \rightarrow subdiffusive \rightarrow diffusive. Correspondingly, the mean-square displacement shows three regimes in time (right panel).

We end this document by considering diffusion in more complex situations. As one can expect, the presence of other molecules in the environment can influence the diffusive behavior of a particle and give rise to *non-diffusive* behavior. As an example, let us consider the system depicted in Fig.4 left. In this system there are a lot of obstacles randomly placed with average spacing equal to L . Now, let us consider a particle starting from the center of the figure. At short times (t_1, t_2), it will not notice the presence of obstacles, and the particle will diffuse according to its diffusion coefficient D , as denoted by the circular shape of the diffusion profiles depicted in the figure. Accordingly, in this time regime the mean-square displacement will grow linearly in time with slope $2D$, as shown in the right panel of Fig.4 for $t \leq t_2$. However, at a certain moment the particle will have a significantly probability of bouncing against the obstacles, which will then perturb the diffusion profile. For instance, at time t_3 the diffusion profile has a perturbed shape. Although being still driven by thermal fluctuations, the transport of the particle will now be slower than what expected from pure diffusion. Accordingly, the mean-square displacement will be sublinear in time, as shown in the right panel. In this regime, the transport of the particle is *subdiffusive*. Nevertheless, if one looks at long times (t_4, t_5), the length scales explored will be so large that the presence of obstacles will be seen as a continuum (central panel), so that the particle will again move diffusively. The mean square displacement will grow again linearly with time, although due to the obstacles the transport will be slower, i.e. the particle will move according to a certain *effective diffusion coefficient* $D_{\text{eff}} < D$ (see right panel). In a log-log plot, this means that the same slope is recovered (corresponding to a linear behavior), but the line will be shifted down (since the shift corresponds to the coefficient). The subdiffusive regime corresponds to the timescales closer to the natural scale set by the

spacing L and the diffusion coefficient D , i.e. L^2/D (right panel), since it is at these times that non-trivial bouncing effects are expected. If obstacles are distributed according to different spacings L_1, L_2, \dots , one expects that a diffusive behavior will be recovered once the time of observation is larger than any of the corresponding timescales. Therefore, in the theoretical case of a fractal structure of obstacles, the diffusive behavior will never be recovered!

Subdiffusion is extremely important in biophysics. Indeed, diffusion within the cellular environment takes place both under confinement (e.g. in organelles, in the nucleus, etc.) and under *crowding*: the large concentrations of molecules within the cytoplasm makes the road very trafficked, thus providing a lot of obstacles along the way.

Further reading

- J. Crank, “The Mathematics of Diffusion”, 2nd Ed., Clarendon Press (1975), Chapter 2
- N. G. Van Kampen, “Stochastic Processes in Physics and Chemistry”, 3rd Ed., Elsevier (2007), Chapter IX
- R. Delgado Buscalioni, notes on Diffusion (you can find them in the Moodle)