Diffusive processes and Brownian motion

A liquid or gas consists of particles—atoms or molecules—that are free to move. We shall consider a subset of particles, such as a dissolved solute or a suspension, characterized by a *number density*

$$\frac{\Delta N}{\Delta V} = n(x, y, z, t) \qquad (1)$$

that in general depends on position and time.

The flux of particles across a plane perpendicular to the x-axis[1] is the number density times the mean velocity in that direction,

$$j_x \overset{df}{=} n \langle v_x \rangle . \qquad (2)$$

If the particles are moving randomly, then it is clear that the number that cross the plane (moving in the negative x-direction) must be proportional to the density immediately to the right of the plane (say, at position $x + \delta x/2$); conversely, those moving to the right must be proportional to the density just to the left of the plane (say, at $x - \delta x/2$) so the flux will be

$$j_x \, \delta x = D\left[n(x - \delta x/2) - n(x + \delta x/2)\right]$$
$$\approx -D \frac{\partial n}{\partial x} \delta x .$$

That is, the equation

$$j_x = -D \frac{\partial n}{\partial x} \qquad (3)$$

defines the *diffusion constant, D.*

Since there is nothing special about the x-direction[2] we can express the flux of particles resulting from diffusion as[3]

$$\vec{j} = -D \, \nabla n . \qquad (3')$$

However, if the particles are neither created nor destroyed they must obey a *conservation law*[4]

$$\frac{\partial n}{\partial t} + \nabla \cdot \vec{j} = 0 ; \qquad (4)$$

hence by substituting the flux resulting from diffusion into the conservation equation we obtain the *diffusion equation*

$$\frac{\partial n}{\partial t} = D \, \nabla^2 n . \qquad (5)$$

Many physical phenomena are described by equations of this form, including heat conduction in a solid, transport of radiation through a dense atmosphere, and movement of neutrons through fissionable material (or shielding, for that matter). Since the underlying physical behavior (that the diffusion equation models) is the same in these examples, it is not surprising they can be described by the same equation.

1. Random walk model of diffusion

To get a feeling for the physical meaning of diffusion we shall now examine several different ways to describe this phenomenon. A diffusing particle is subjected to a variety of collisions that we can consider random, in the sense that each such event

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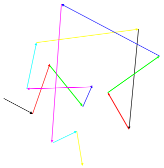
1. That is, the number of particles per unit area per unit time that cross the surface.
2. Here is another example of the use of symmetry to generalize a result.
3. Eq. 3′ is known as Fick’s Law.
4. The conservation law can be verified using Gauss’s Theorem.

is virtually unrelated to its predecessor. It makes no difference whether the particle is a molecule of perfume diffusing in air, a solute molecule in a solution, a colloid in a suspension, a neutron in a nuclear reactor, or a photon beating its way outward from the center of a star.



One mathematical model used to describe such a process is the *random walk*[5]. In one dimension it looks something like this: a clock ticks at intervals δt; at each tick, the particle moves one step to the left (with probability α), one step to the right (with probability β), or remains where it is (with probability[6] $1-\alpha-\beta$). Thus, using the rules for combining probabilities we find that the probability for the particle to be at x (literally, in the interval $[x, x+\delta x]$) at time $t + \delta t$ is

$$\begin{aligned} p(x, t+\delta t) &= \\ &\alpha\, p(x+\delta x, t) + \beta\, p(x-\delta x, t) \\ &+ p(x, t)\left(1-\alpha-\beta\right). \end{aligned} \tag{6}$$

For now we shall consider the case where leftward and rightward movements are equally likely, *i.e.* $\alpha = \beta$: in that case, expanding both sides in Taylor's series we find

$$\frac{\partial p}{\partial t} = \alpha \frac{(\delta x)^2}{\delta t} \frac{\partial^2 p}{\partial x^2} + O(\delta t) + O(\delta x^4)$$

thus, if we define a diffusion constant

$$D = \alpha \frac{(\delta x)^2}{\delta t}$$

and extend the same idea to 3 dimensions, we derive the diffusion equation

$$\frac{\partial p}{\partial t} = D \nabla^2 p . \qquad \text{(Einstein)} \tag{7}$$

Of course this is the equation for the probability of a single particle being in the volume element $dx\, dy\, dz$ around the point $\vec{x}$. We may well ask how the probability $p(\vec{x}, t)$ is related to the number density $n(\vec{x}, t)$. In some sense it is obvious that if the behavior of a single particle is described by $p(\vec{x}, t)$, then a system of N independently moving particles is carrying out a measurement of $p(\vec{x}, t)$, and that we can estimate this probability in terms of the number density *via*

$$p(\vec{x}, t) \approx \frac{n(\vec{x}, t)}{N} . \tag{8}$$

The mean and variance of the position

In order for $p(\vec{x}, t)$ to represent a probability density, it must satisfy several restrictions. First, it must be positive, since it is no more possible to define a negative probability than a negative concentration. Second, the probability of the particle being *somewhere* is unity, *i.e.*

$$\iiint d^3x\, p(\vec{x}, t) = 1 . \tag{9}$$

Equation 9 is sometimes called a *normalization condition*.

The mean, or expected, value of—say—the x-coordinate of a particle is defined to be

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[5] Sometimes called a "drunkard's walk".

[6] Since it can only perform three mutually exclusive actions, the probabilities must sum to unity.

$$\langle x\rangle \overset{df}{=} \iiint d^3x\, p(\vec{x}, t)\, x\, ; \qquad (10)$$

from the diffusion equation we can deduce that

$$\frac{d}{dt}\langle x\rangle = D\int_{-\infty}^{\infty} dx\, x\, \frac{\partial^2 q(x, t)}{\partial x^2} = 0$$

where we have defined

$$q(x, t) = \iint dy\, dz\;\; p(x, y, z, , t)\, .$$

Since

$$\frac{d}{dt}\langle x\rangle = 0$$

we see that

$$\langle x\rangle = \text{constant.}$$

However, even though the *average* position of a diffusing particle does not change, the *variance* of its position is a function of time. The variance is defined by

$$\mathrm{Var}(x) \overset{df}{=} \left\langle (x - \langle x\rangle)^2 \right\rangle \qquad (11)$$

$$\equiv \langle x^2\rangle - \langle x\rangle^2\, .$$

Once again working directly with Eq. 7 (the diffusion equation) we see that

$$\frac{d}{dt}\mathrm{Var}(x) = D\int_{-\infty}^{\infty} dx\, \frac{\partial^2 q(x, t)}{\partial x^2}\, (x - \langle x\rangle)^2$$

$$\equiv 2D\, , \qquad (12)$$

or

$$\mathrm{Var}(x) = 2D\, t\, . \qquad (13)$$

That is, the expected mean-square deviation of a particle from its initial position increases linearly with time. Put another way, the distance a diffusing particle travels in time t is proportional to $\sqrt{t}$.

2. Stochastic differential equation

We can take another approach to the random walk by analyzing the motion of an object subject to a time-dependent random force $f(t)$. Newton's Second Law yields the differential equation

$$m\ddot{x} + \gamma\dot{x} = f(t) \qquad \text{(Langevin)} \qquad (14)$$

where we have included viscous drag[7]. Changing variables to $v = \dot{x}$ we may write the solution to the equation

$$\dot{v} + \frac{\gamma}{m}v \overset{df}{=} \dot{v} + \frac{1}{\tau}v = \frac{f(t)}{m}$$

as

$$v(t) = v_0\, e^{-t/\tau} + \frac{1}{m}e^{-t/\tau}\int_0^t du\, e^{u/\tau} f(u)\quad .$$

Now what do we mean by a "random force"? If we could observe a system described by the above equation many times, each time the force would be a different function of time. Suppose we were to average over K experiments:

$$\langle\, f(t)\,\rangle \overset{df}{=} \frac{1}{K}\sum_{k=1}^{K} f_k(t)\, .$$

If the force has no propensity to move an object in one direction rather than the other, it must be true that $\langle\, f(t)\,\rangle = 0$. Thus the average velocity is just

$$\langle v(t)\rangle = v_0\, e^{-t/\tau}, \qquad (15)$$

which for times short compared with τ is whatever velocity the object had before the force began to act; but for long times viscous drag decreases it asymptotically to zero.

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[7] Stokes' Law, for example, gives the drag on a sphere of radius r as $(6\pi\eta r)v$.

Next consider the mean-square velocity: we see that an object subject to a random force will eventually acquire mean-squared velocity

$$\langle v^2 \rangle = v_0^2 \, e^{-2t/\tau} + \tag{16}$$

$$\int_0^t du \, e^{(u-t)/\tau} \int_0^t dw \, e^{(w-t)/\tau} \frac{\langle f(u) f(w) \rangle}{m^2}$$

Now what else can we say about the "autocorrelation function"

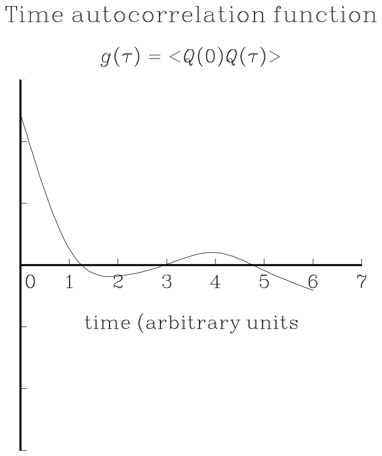
$$g(u,w) \overset{df}{=} \langle f(u) \, f(w) \rangle \, ?$$

By definition it is symmetric:

$$g(u, w) = g(w, u) \, ;$$

moreover, if the random force is to characterize thermal equilibrium at a definite temperature, T, there can be no absolute dependence on time, that is,

$$g(u+\tau, w+\tau) \equiv g(u, w) \, .$$



For this to be true,

$$g(u, w) = g(u - w) \, .$$

Finally, since the forces must fluctuate in sign (in order for them to average to zero) it must be the case that $g(s)$ is largest for $s=0$ and falls rapidly as $|s|$ increases. The behavior of a typical correlation function is shown below.

If the random force fluctuates on a time scale short compared with the relaxation time τ, we may approximate it by "white noise" (in which all frequencies are equally represented in the power spectrum[8]), giving the autocorrelation function

$$\langle f(u) \, f(w) \rangle \approx \sigma^2 \, \delta(u - w) \, . \tag{17}$$

For times long compared with τ we find

$$\langle v^2 \rangle \to \frac{\sigma^2}{2m\gamma} \, . \tag{18}$$

If we note that in a thermal bath at temperature T the average kinetic energy (in one direction) of a particle of mass m is[9]

$$\frac{1}{2} m \langle v^2 \rangle = \frac{1}{2} kT$$

we may evaluate σ^2 as

$$\sigma^2 = 2\gamma \, kT \, .$$

What does this have to do with diffusion? Since we know the velocity in terms of the driving force, we may integrate with respect to time to find the position:

$$x(t) = x_0 + \int_0^t du \, v(u) \quad ; \tag{19}$$

for long times the mean position is

$$\langle x \rangle \to x_0 + v_0 \, \tau \, ,$$

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[8] Equation 17 will be derived in an Appendix.

[9] This is the equipartition hypothesis of statistical mechanics. Alternatively we may regard it as a definition of temperature.

that is, the mean position is constant (as was predicted by the diffusion equation).

What about the variance of the position? A simple calculation based on the preceding assumptions (regarding the statistical properties of $f(t)$) yields the asymptotic formula

$$\left\langle \left(x(t) - \langle x \rangle \right)^2 \right\rangle \to \frac{2kT}{\gamma} t \tag{20}$$

from which we may conclude that the diffusion constant is

$$D = \frac{kT}{\gamma} . \tag{21}$$

Equation 21 was first given by Einstein.

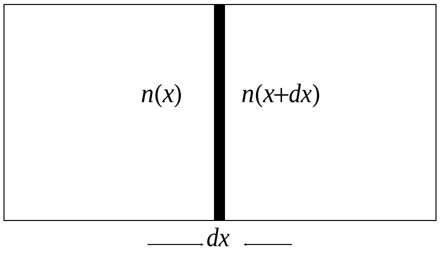
3. Thermal "force" and osmotic pressure

Einstein's starting point for the derivation of Eq. 21 was somewhat different from that given here. He used the fact that the osmotic pressure of a solute in a dilute solution[10]

$$P = nkT \tag{22}$$

is identical in form to the perfect gas law.

How are osmotic pressures measured? To do this we need a *semi-permeable* membrane—that is, one through which molecules of the solvent can pass freely, but that blocks molecules of the solute. Many biological phenomena arise from membranes permeable to some molecules but not to others, so this is a subject worth study.



If we imagine such a membrane separating a solution containing the solute from a region of pure solvent, the solute particles exert extra pressure on the side where they are present, and the resulting force can be measured.

Einstein then visualized the net force acting on a thin slab, of thickness dx and area A, in a solution of nonuniform density. In the situation illustrated below. The thermodynamic force acting on the slab is

$$f_x = A\, p(x) - A\, p(x+dx)$$

$$= A\, kT \left[n(x) - n(x+dx) \right]$$

The x-component of the thermodynamic force acting on the volume Adx is then

$$f_x = -kT \frac{\partial n}{\partial x} A dx ,$$

or more generally,

$$n \vec{f} = -kT \nabla n , \tag{23}$$

where we have replaced the volume Adx by the specific volume, $1/n$.

In the presence of viscous drag γ, the (mean) drift velocity will be

$$\langle \vec{v} \rangle = \frac{\vec{f}}{\gamma}$$

corresponding to particle flux

$$\vec{j} = n \langle \vec{v} \rangle = \frac{n \vec{f}}{\gamma} = -\frac{kT}{\gamma} \nabla n . \tag{24}$$

Comparing with Eq. 3′ we find Einstein's result, Eq. 21.

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[10] This was discovered empirically by van't Hoff in 1887.

4. Brownian motion and diffusion

Historically, the importance of Einstein's derivation of the diffusion constant in terms of viscous drag and the Boltzmann constant k was that it offered a way to estimate Avogadro's number *via*

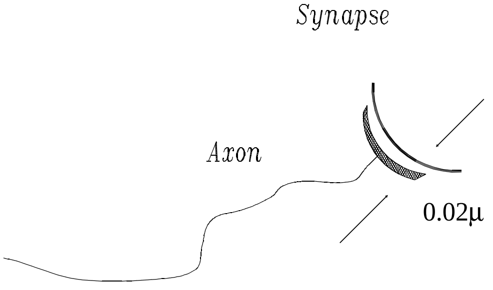
$$N_A \overset{df}{=} \frac{R}{k} .$$

Einstein proposed observing the Brownian motion of microscopic spheres—large enough that the idea of viscosity applies to their drag, but small enough that they would be subject to observable fluctuations in position (resulting from the statistical fluctuations in numbers of molecules hitting from one side or another, in a given time). For such a sphere the drag coefficient is given by Stokes' Law:

$$\gamma = 6\pi \eta r$$

where η is the coefficient of viscosity and r the radius of the sphere. Since these are measureable quantities; and since the diffusion coefficient can be measured by observing the behavior of a large number of such particles with respect to time, Boltzmann's constant k can be measured. The French experimental physicist J.B. Perrin received the Nobel Prize of 1926 for his measurements of N_A (applying the ideas of Einstein).

5. Diffusion across a synapse



A synapse is a junction between an axon and a nerve cell, muscle or organ. Although the transmission of information across the junction can take place as an electrical signal, more usually when the impulse travelling down an axon reaches a synaptic plate a *neurotransmitter* (that is, a specialized chemical) is emitted that must diffuse across the junction, which is typically 2×10^{-6} cm, or 200 Å across. It would be interesting to know how long the chemical signal takes to cross the junction.

We may imagine the process as one-dimensional diffusion. Dimensional analysis or alternatively, the random walk picture, tells us that the mean-square distance scales with time as

$$\langle x^2 \rangle = 2D t$$

where D is the diffusion constant. Putting in a distance 200 Å and a diffusion constant characteristic of organic molecules,

$$D \sim 2\times10^{-6} \text{ cm}^2/\text{sec} ,$$

we find

$$t \sim 10^{-6} \text{ sec.}$$

That is, the synaptic time delay is negligible compared with the delay resulting from the speed of a neural pulse, ~27 m/sec.

6. How a cell eats

As Purcell has shown[11], because the Reynolds number for a cell-sized object is so low, a cell

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[11] E.M. Purcell, *Am. J. Phys.* **45** (1977) 3-11.

cannot pursue food because the food simply is pushed out of the way. Therefore a cell in the a nutrient medium receives its food by diffusion. Bacterial chemotaxis, as Berg[12], and Berg and Purcell[13] have shown takes place primarily to enable a cell to move to a place where the feeding (by diffusion!) is richer.

Now what applies to a 1μ bacterium also applies to a 10μ cell in the human body. Consider, *e.g.* a spherical cell receiving its food by diffusion. Assume that any food molecule touching the cell membrane is immediately removed from the medium, either by adhesion or ingestion. Then the concentration of such molecules at the cell's surface is zero. Conversely, assuming nutrient is being supplied a long way away from the cell, in equilibrium (that is, $\partial c/\partial t = 0$) the concentration at large distances is some constant, c_∞ .

A current

$$\vec{j} = -D\nabla c$$

flows toward the cell, giving the net rate of ingestion as

$$J \overset{df}{=} \frac{dN}{dt} = -\iint_{r=a} \vec{j} \cdot d\vec{S} \;.$$

Because the concentration is time-independent, the diffusion equation reduces to the Laplace equation. By symmetry, for a spherical cell the concentration can depend only on the radial distance r. The boundary conditions are

$$\begin{aligned} c(r{=}a) &= 0 \\ \lim_{r\to\infty} c(r) &= c_\infty \;. \end{aligned}$$

Defining $c(r) = \phi(r) + c_\infty$ we seek a solution of the Laplace equation that has a certain value at $r = a$ and vanishes at ∞ . We do not need the solution inside the cell radius. From elementary electrostatics we see the solution is

$$\phi(r) = -\, c_\infty \frac{a}{r} \,,$$

or

$$c(r) = c_\infty \left(1 - \frac{a}{r}\right).$$

The flux is then in the inward radial direction, giving the cell's rate of ingestion as

$$J = 4\pi a^2 D c_\infty \frac{a}{a^2} \equiv 4\pi D\, c_\infty\, a \;.$$

The important point to notice is that the rate of ingestion is proportional to the linear dimension of the cell, rather than to its area. Although this is a result we could have obtained (absent the 4π) dimensionally, it is worth noting that it arises from the probabilistic nature of diffusion. Once a molecule has wandered within ingestion range of the cell's surface, it remains in that vicinity for some time. So the cell gets numerous chances to snag it.

For a disk-shaped cell of radius a one can solve the corresponding electrostatic problem of an ellipsoidal cell in ellipsoidal coordinates and let two axes of the ellipsoid become equal and set the third to zero. This is done in Smythe[14]. The result is, for a two-sided disk,

$$J = 8D\, c_\infty\, a$$

and for a one-sided absorbing disk, just half that. Berg and Purcell give the result for a spherical non-absorbing cell of radius a whose surface is covered with N absorbing disks of (much smaller) radius s:

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[12] H.C. Berg, *Nature* **254** (1975) 389-392.

[13] H.C. Berg and E.M. Purcell, *Biophysical Journal* **20** (1977) 193-219.

[14] William R. Smythe, *Static and dynamic electricity, 3rd ed.* (McGraw-Hill Publishing Co., Inc., New York, 1968).

$$J = 4\pi D c_{\infty} a \times \frac{Ns}{Ns + \pi a}.$$

The point is that because only the linear dimension is involved, the absorbing sites can occupy a small fraction of a cell's surface *area* and yet result in a cell whose ingestion efficiency is close to maximal.

This somewhat surprising result explains how cells efficiently absorb a broad spectrum of different molecules without having their surfaces excessively cluttered with specialized receptors.