Consider again

\[ P(m, N) = \left( \frac{1}{2} \right)^N \frac{N!}{\left( \frac{N+m}{2} \right)! \left( \frac{N-m}{2} \right)!}. \]

Using \textbf{Stirling's approximation} for \( K! \) when \( K \) is large, we can show that when \( N \) and \( \lvert m \rvert \) are large, with \( m^2/N \) not too large, then

\[ P(m, N) \approx \sqrt{\frac{2}{\pi N}} e^{-m^2/2N}. \]

This is a good approximation even for quite small values of \( \lvert m \rvert \) and \( N \):–
<table>
<thead>
<tr>
<th>((m, N))</th>
<th>(P(m, N))</th>
<th>(\sqrt{\frac{2}{\pi N}} e^{-m^2/2N})</th>
<th>Relative Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\pm 2, 10))</td>
<td>0.2051</td>
<td>0.2066</td>
<td>0.73%</td>
</tr>
<tr>
<td>((\pm 5, 27))</td>
<td>0.09714</td>
<td>0.09668</td>
<td>0.5%</td>
</tr>
<tr>
<td>((\pm 200, 10000))</td>
<td>0.0010799</td>
<td>0.0010798</td>
<td>0.01%</td>
</tr>
</tbody>
</table>
We had

\[ P(m, N) = \left(\frac{1}{2}\right)^N \frac{N!}{\left(\frac{N+m}{2}\right)!\left(\frac{N-m}{2}\right)!} \approx \sqrt{\frac{2}{\pi N}} e^{-m^2/2N} \]

as \( N \to \infty \) and \( |m| \to \infty \) with \( m^2/N \) fixed and finite.

We now set \( x = m\delta \) and \( t = N\tau \), and let \( \delta \to 0 \) and \( \tau \to 0 \) while \( N \to \infty \) and \( |m| \to \infty \), in such a way that \( x \) and \( t \), as well as \( m^2/N \), stay fixed and finite at values of our choosing. Make sure you can see that this is possible!
Because

\[ m^2/N = \left( \frac{x}{\delta} \right)^2 \left( \frac{\tau}{t} \right) = \frac{x^2/t}{(\delta^2/\tau)}, \]

this requires that

\[ \frac{\delta^2}{2\tau} \quad (= D, \text{say}) \]

also remains fixed at some (positive) finite value.

Now consider \( \Delta x \) such that \( \delta \ll \Delta x \ll |x| \).

What is the probability \( P(x, t)\Delta x \) that the particle is in \( (x, x + \Delta x) \) at time \( t \)?
Ans: \[ P(x,t) \Delta x = \frac{\Delta x}{2\delta} P(m,N) \]

\[ \text{no. of possible locations in } (x, x + \Delta x) \]

\[ \text{probability of such a location} \]

\[
\begin{align*}
\text{Thus we arrive at } & \quad P(x,t) = \frac{P(m,N)}{2\delta} \approx \frac{1}{\sqrt{2\pi N\delta^2}} e^{-\frac{m^2}{2N}} \\
& \quad = \frac{e^{-\frac{x^2}{4Dt}}}{\sqrt{4\pi D}}
\end{align*}
\]

where \( x = m\delta, \ t = N \tau, \ D = \frac{\delta^2}{2\tau} \)

as before.
The formula

\[ P(x, t) = \frac{e^{-x^2/4Dt}}{\sqrt{4\pi Dt}} \]

is exact in the limit

\[ N \to \infty, \quad |m| \to \infty, \quad \delta \to 0, \quad \tau \to 0, \]

with

\[ m\delta = x, \quad N\tau = t, \quad \frac{\delta^2}{2\tau} = D, \quad \frac{m^2}{N} \]

all fixed and finite.

At any time we have a Gaussian (or normal) distribution of probability along the \( X \)-axis — the graph is a bell-shaped curve:-
\[ P(x,t) = \frac{1}{\sqrt{4\pi Dt}} \]
• The area under the curve is always 1 (conservation of probability):

\[ \int_{-\infty}^{\infty} \frac{e^{-x^2/4Dt}}{\sqrt{4\pi Dt}} \, dx = \frac{1}{\sqrt{\pi}} \int_{-\infty}^{\infty} e^{-y^2} \, dy = 1 \]

• As \( t \to 0_+ \), we have \( P(x, t) \to \delta(x) \) (infinite spike). This corresponds to a “bolus injection” of a finite quantity of diffusate at \( x = 0 \) at \( t = 0 \).

• Note that the distribution spreads over a distance \( L \) in a time determined by \( L \approx \sqrt{2Dt} \), or \( t \approx L^2 / 2D \). To go twice as far takes four times as long! To go ten times as far takes a hundred times as long, and so on. This is the characteristic behaviour of the random walk that we saw before. (See p. 1.13)
• The constant $D$ is called the **diffusion coefficient**. The bigger is $D$, the faster is the diffusion (spreading). Particles with $D$ twice the size, spread in half the time.

• For a big molecule like lysozyme in water, $D \approx 10^{-6} cm^2/sec$. To get across a swimming pool of width $L \approx 10m \approx 1000cm$ would take about $5 \times 10^{11} sec$, or 15,000 years. (Contrast with p. 1.3)

• But to get across the width of a bacterium, $\approx 10^{-4} cm$, takes only $5 \times 10^{-3} sec$.

This is why diffusion is such an important transport mechanism on microscopic biological scales.
• **Aside:** While $P(x, t)$ is a nice smooth function (infinitely differentiable), the path $x(t)$ in the limit is typically continuous but nowhere differentiable.
Such a path is said to describe (a realisation of) **Brownian motion**.
(Look again at the figure on p. 1.15)

• Suppose now that there is a very large number $\mathcal{N}$ of particles, all performing 1-D random walks (independently), parallel to the $X$-axis:
$t / \tau = (x / \delta)^2$
At time $t$, the number of particles here is $N \cdot P(x, t) \delta$.

- About $\frac{1}{2} \delta \cdot g \cdot L$, and
- About $\frac{1}{2} \delta \cdot g \cdot R$, across plane at $x$, in next time-interval of length $\tau$. 

At time $t$, the number of particles here is $N \cdot P(x, t + \frac{\delta}{2}, t) \delta$.

- About $\frac{1}{2} \delta \cdot g \cdot R$, and
- About $\frac{1}{2} \delta \cdot g \cdot L$, across plane at $x$, in next time-interval of length $\tau$. 

Area of cross-section = $A$.
The net number crossing L to R across a plane of cross-sectional area $A$ at $x$, in the time interval $[t, t + \tau]$ is

$$\approx \frac{1}{2} NP(x - \frac{\delta}{2}, t) \delta - \frac{1}{2} NP(x + \frac{\delta}{2}, t) \delta$$

The net flux L to R per unit area per unit time, at position $x$ at time $t$, is therefore

$$J_1(x, t) \approx -\frac{1}{2} \mathcal{N} \left[ P(x + \frac{\delta}{2}, t) - P(x - \frac{\delta}{2}, t) \right] \delta / A \tau$$

$$= -\frac{\delta^2}{2 \tau} \left[ \frac{NP(x + \frac{\delta}{2}, t) - NP(x - \frac{\delta}{2}, t)}{A \delta} \right]$$

$$= -D \left[ \frac{NP(x + \frac{\delta}{2}, t) - NP(x - \frac{\delta}{2}, t)}{A \delta} \right]$$
Now the number of particles per unit volume at $x, t$ is the concentration of diffusate

$$c(x, t) \approx \frac{NP(x, t) \delta}{A \delta}.$$  

Then we have

$$J_1(x, t) \approx -D \left[ \frac{c(x + \frac{\delta}{2}, t) - c(x - \frac{\delta}{2}, t)}{\delta} \right].$$

As $\delta \to 0$, we get

$$J_1(x, t) = -D \frac{\partial c(x, t)}{\partial x}$$

— Fick’s first equation.
•Aside: partial differentiation:–

Given a function of several (independent) variables

\[ F(x, y, \theta, t, \ldots), \]

then \( \frac{\partial F}{\partial x} \) means: differentiate with respect to \( x \), treating \( y, \theta, t, \ldots \) like constants.

Similarly \( \frac{\partial F}{\partial \theta} \) means: differentiate with respect to \( \theta \), treating \( x, y, t, \ldots \) like constants. And so on.
EX: \[ F(x, y, \theta) = 3x^2y \cos(\theta) + e^{6y} \]

\[ \Rightarrow \frac{\partial F}{\partial x} = 6xy \cos(\theta), \quad \frac{\partial F}{\partial y} = 3x^2 \cos(\theta) + 6e^{6y}, \]

\[ \frac{\partial F}{\partial \theta} = -3x^2y \sin(\theta). \]

Then (order of differentiation doesn’t matter!)

\[ \frac{\partial^2 F}{\partial \theta \partial x} = -6xy \sin(\theta) = \frac{\partial^2 F}{\partial x \partial \theta} \]

and

\[ \frac{\partial^3 F}{\partial \theta \partial x \partial y} = -6x \sin(\theta), \quad \text{etc.} \]
• Going back to flux of particles, consider the changing concentration in the box of volume $AS$:

\[ \begin{align*}
\text{Area of cross-section} &= A \\
J(x,t) &\rightarrow J(x+\delta, t)
\end{align*} \]

# particles in box at time $t$
\[\approx c(x,t)AS\]

# particles in box at time $t+\tau$
\[\approx c(x,t+\tau)AS\]

Net flux of particles into box
\[\approx J(x,t)A\tau - J(x+\delta, t)A\tau\]

Therefore (conservation of particles)
\[\left[ c(x,t+\tau) - c(x,t) \right] AS \approx \left[ J(x,t) - J(x+\delta, t) \right] A\tau\]

or
\[\frac{c(x,t+\tau) - c(x,t)}{\tau} \approx -\frac{J(x+\delta, t) - J(x, t)}{\delta}\]
As $\tau \to 0, \delta \to 0$, we get

$$\frac{\partial c(x, t)}{\partial t} = - \frac{\partial J_1(x, t)}{\partial x}$$

— Fick’s second equation.

Substituting in from Fick’s first equation, we get

$$\frac{\partial c(x,t)}{\partial t} = - \frac{\partial}{\partial x} \left[ -D \frac{\partial c(x,t)}{\partial x} \right]$$

$$\Rightarrow \frac{\partial c(x, t)}{\partial t} = D \frac{\partial^2 c(x, t)}{\partial x^2}$$

— 1-dimensional diffusion equation.
• This is a partial differential equation (PDE) with

  1 dependent variable \( c \)

  2 independent variables \( x, t \).

The PDE expresses conservation of number of particles during their random walks.

• It is important to see that this PDE must hold whenever we have a very large number of ‘random walkers,’ no matter how we distribute their starting positions on the \( X \)-axis.
In the special case that we start them all at \( x = 0 \) at \( t = 0 \), we know that

\[
c(x, t) \left( \approx \frac{\mathcal{N} P(x, t)}{A} \right) \approx \mathcal{N} \frac{1}{A \sqrt{4\pi D t}} e^{-x^2/4Dt}.
\]

It follows that the function

\[
P(x, t) = \frac{1}{\sqrt{4\pi D t}} e^{-x^2/4Dt}
\]

must satisfy the 1-D diffusion equation:
Check:
\[
\frac{\partial P(x,t)}{\partial t} = \frac{1}{\sqrt{4\pi D}} \frac{3}{2} \left\{ t^{-\frac{1}{2}} e^{-x^2/4Dt} \right\}
\]
\[
= \frac{1}{\sqrt{4\pi D}} \left\{ \frac{-1}{2} t^{\frac{3}{2}} e^{-x^2/4Dt} \right\}
+ t^{\frac{1}{2}} \left( \frac{x^2}{4Dt^2} \right) e^{-x^2/4Dt} \right\}
\]
\[
= \frac{1}{\sqrt{4\pi D}} e^{-x^2/4Dt} \left\{ -\frac{1}{2} t^{\frac{3}{2}} + \frac{x^2}{4D} t^{\frac{-3}{2}} \right\}
\]

\[
\frac{\partial P(x,t)}{\partial x} = \frac{1}{\sqrt{4\pi D}} \left\{ t^{-\frac{1}{2}} \left( -\frac{2x}{4Dt} \right) e^{-x^2/4Dt} \right\}
\]
\[
= \frac{1}{\sqrt{4\pi D}} \left\{ -\frac{x}{2D} t^{-\frac{3}{2}} e^{-x^2/4Dt} \right\}
\]

\[
\frac{\partial^2 P(x,t)}{\partial x^2} = \frac{1}{\sqrt{4\pi D}} \left\{ -\frac{1}{2D} t^{-\frac{3}{2}} e^{-x^2/4Dt}
- \frac{x}{2D} t^{-\frac{3}{2}} \left( \frac{-2x}{4Dt} \right) e^{-x^2/4Dt} \right\}
\]

\[
D \frac{\partial^2 P(x,t)}{\partial x^2} = \frac{1}{\sqrt{4\pi D}} \left\{ -\frac{1}{2} t^{-\frac{3}{2}} + t^{-\frac{3}{2}} \frac{x^2}{4D} \right\} e^{-x^2/4Dt}
\]
\[
= \frac{\partial P(x,t)}{\partial t}
\]
Many other simple functions satisfy the 1-D diffusion equation, for example

(1) \( c(x, t) = e^{-\alpha^2Dt} \sin(\alpha x), \quad \alpha = \text{const.} \)

(2) \( c(x, t) = Ax + B, \quad A, B = \text{consts.} \)

(3) \( c(x, t) = A \text{erf} \left( \frac{x-a}{\sqrt{4Dt}} \right), \quad A, a = \text{const.}, \)

where

\[
\text{erf}(z) = \frac{2}{\sqrt{\pi}} \int_0^z e^{-y^2} \, dy
\]

— the error function. See the graphs of \( y = \text{erf}(2z), y = \text{erf}(z), \) and \( y = \text{erf}(z/2) \) in the next figure:
A typical mathematical problem in diffusion is to find $c(x, t)$ in some region of interest, for times $t > 0$, given some information about the initial state, at $t = 0$, and about what is happening at the boundaries of the region. This is called an initial and boundary value problem for the diffusion equation (IVP & BVP).

A great many problems of this type have been solved, by various methods. [See for example, H.S. Carslaw and J.C. Jaeger, *Conduction of Heat in Solids* (Oxford UP, 1959), and J. Crank, *The Mathematics of Diffusion* (Oxford UP, 1975).]