• Drug delivery through the skin.

There is great interest world-wide in developing methods of drug delivery that don't involve injections. The nicotine patch is an example. Unfortunately, the skin is designed to keep things out, not to let them in! In the following analysis, D is an 'effective' diffusion coefficient that is much smaller – up to 4 orders of magnitude smaller – than for the same drug diffusing in water. This is to take account of the structure of the *stratum corneum*:–

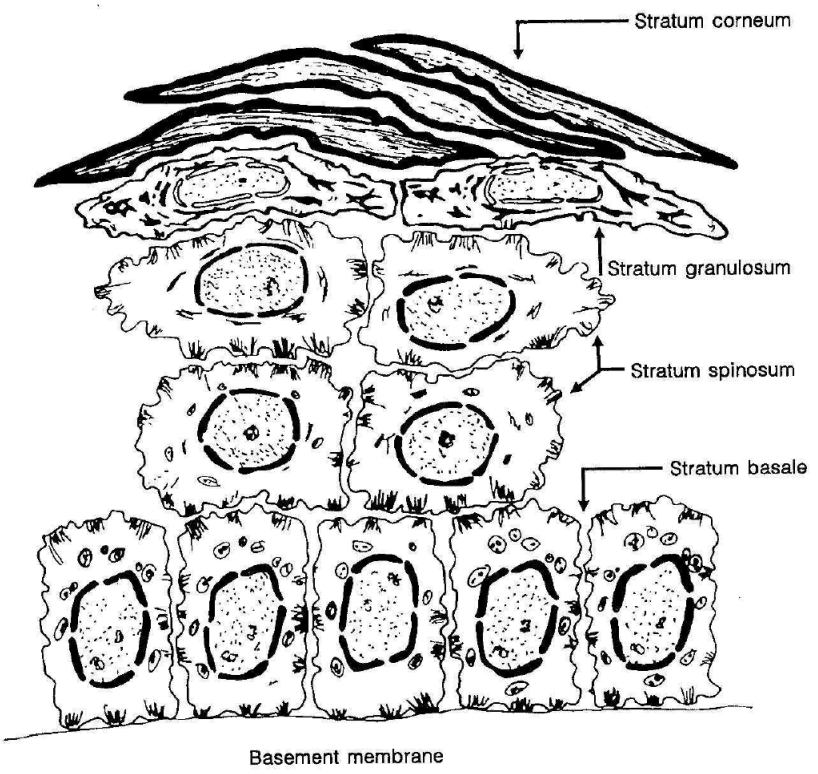


Figure 1: A representation of the epidermis displaying the cells of the different layers.

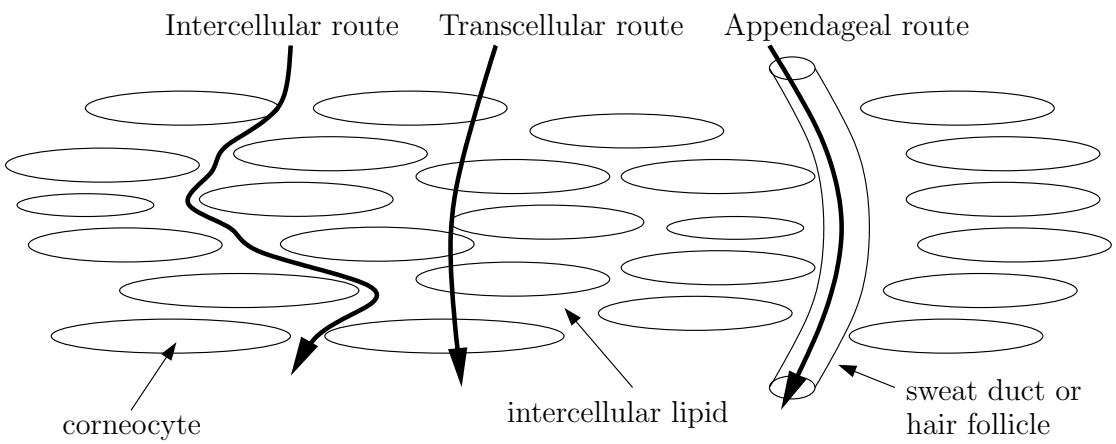


Figure 3: Representation of the intercellular, transcellular and appendageal pathways for passive solute permeation through the stratum corneum.

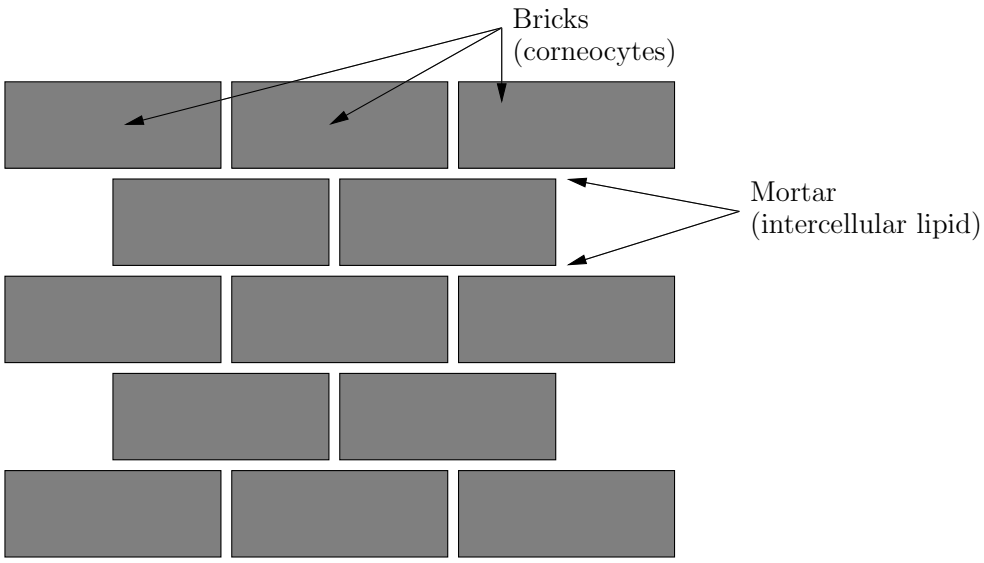
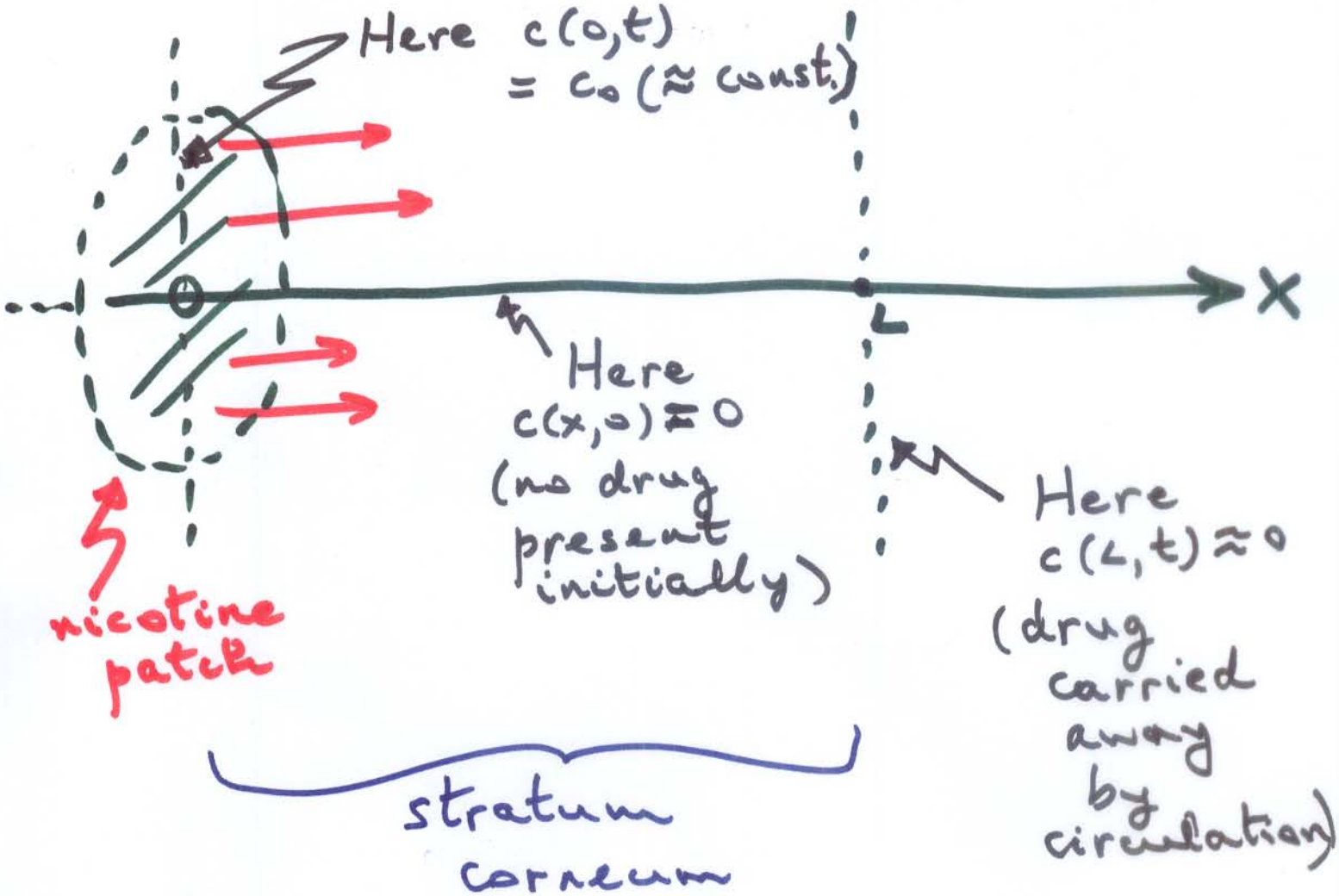


Figure 2: A simple depiction of the structure of the stratum corneum with bricks representing corneocytes and mortar representing the intercellular lipids. Also reflected in the figure is the fact that the corneocytes comprise the bulk of the stratum corneum and that the intercellular lipid is the only continuous domain.

EX: Drug delivery through the skin



•The mathematical problem:–

Find $c(x,t)$ for $0 \leq x \leq L$ and $t \geq 0$ such that

$$\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2} \quad \text{for} \quad 0 < x < L \quad \text{and} \quad t > 0 \qquad \text{(PDE)} \tag{3.1}$$

$$c(x,0) = 0 \quad \text{for} \quad 0 < x < L \qquad \text{(Initial Condition)} \tag{3.2}$$

$$c(0,t) = c_0 \quad \text{for} \quad t > 0 \qquad \text{(Boundary Condition A)} \tag{3.3a}$$

$$c(L,t) = 0 \quad \text{for} \quad t > 0 \qquad \text{(Boundary Condition B)} \tag{3.3b}$$

- Here is one form of the solution:–

$$c(x,t) = c_0(1 - x/L)$$

$$-\tfrac{2c_0}{\pi}\left\{\sin(\pi x/L)e^{-\pi^2 Dt/L^2} + \tfrac{1}{2}\sin(2\pi x/L)e^{-4\pi^2 Dt/L^2}\right.$$

$$\left. +\tfrac{1}{3}\sin(3\pi x/L)e^{-9\pi^2 Dt/L^2} + \ldots\right\} \qquad (3.4)$$

Note the pattern.

- This solution, obtained using Fourier series, is quite surpising if you haven't seen it before. In the first place, $c(x,t)$ is a concentration and must be nonnegative everywhere, but the $\sin$ functions are not!

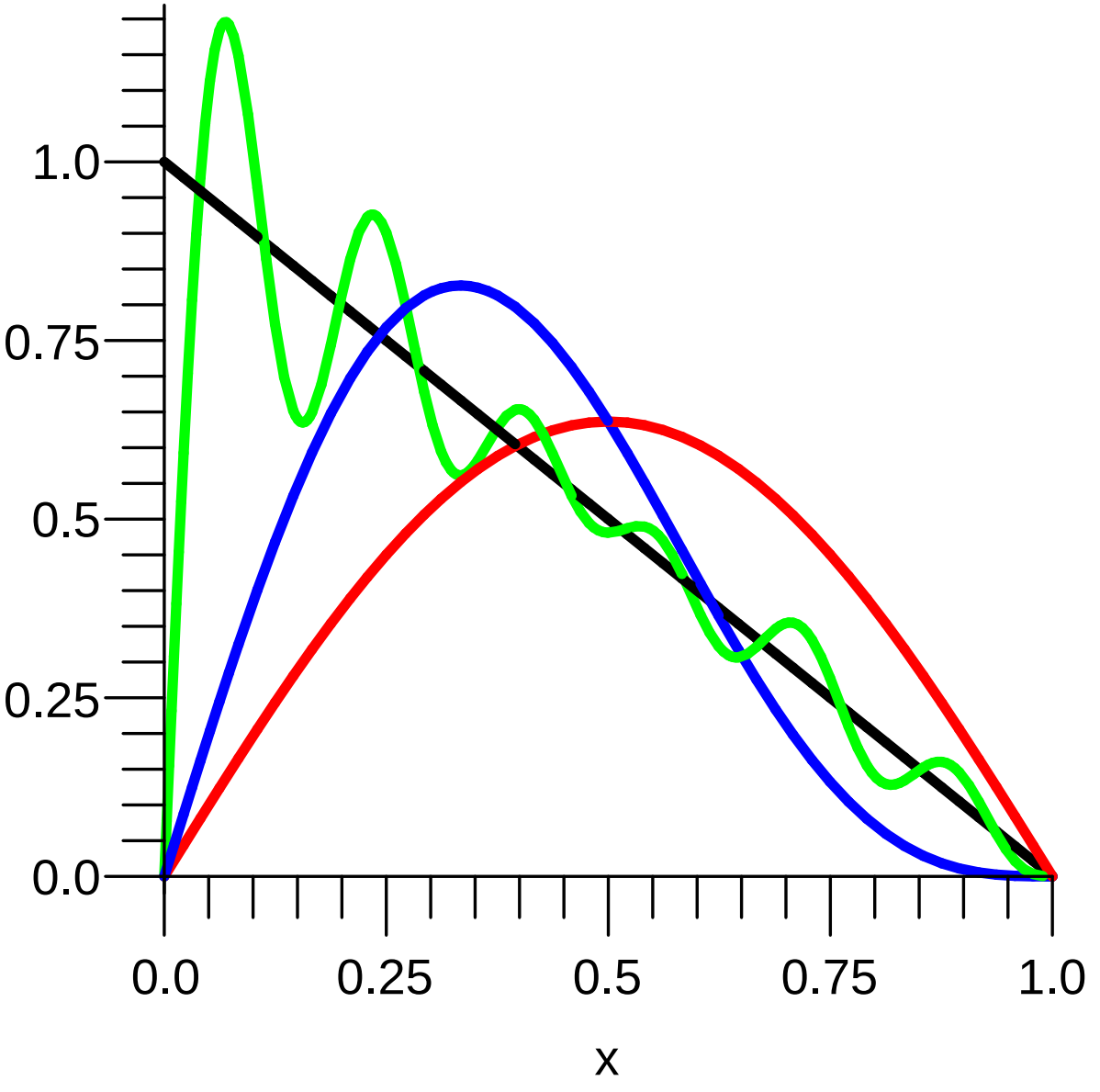
•Roughly speaking, the meaning of the solution (3.4) is: The more terms that we take in the series, the better the approximation to the exact solution of the problem.

•To check that (3.4) does provide a solution, note firstly that each term on the RHS satisfies the 1-D diffusion PDE (3.1) (see p. 2.20), and hence so does the whole RHS. Secondly, note that the two BCs (3.3a,b) are also satisfied. It remains to check that the IC (3.2) is satisfied.
Setting $t = 0$ in both sides of formula (3.4), we see that this requires

$$1 - x/L = \frac{2}{\pi}\left\{\sin(\pi x/L) + \frac{1}{2}\sin(2\pi x/L) + \frac{1}{3}\sin(3\pi x/L)\ldots\right\},$$

which is just as surprising as (3.4).

- Is it so? See the figures showing the approximations to the LHS given by the first one, first two and first twelve terms from the RHS.


1.0
0.75
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0.0
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0.5
0.75
1.0
x

•In a similar way, (3.4) defines successive approximations to $c(x,t)$ at each time t.

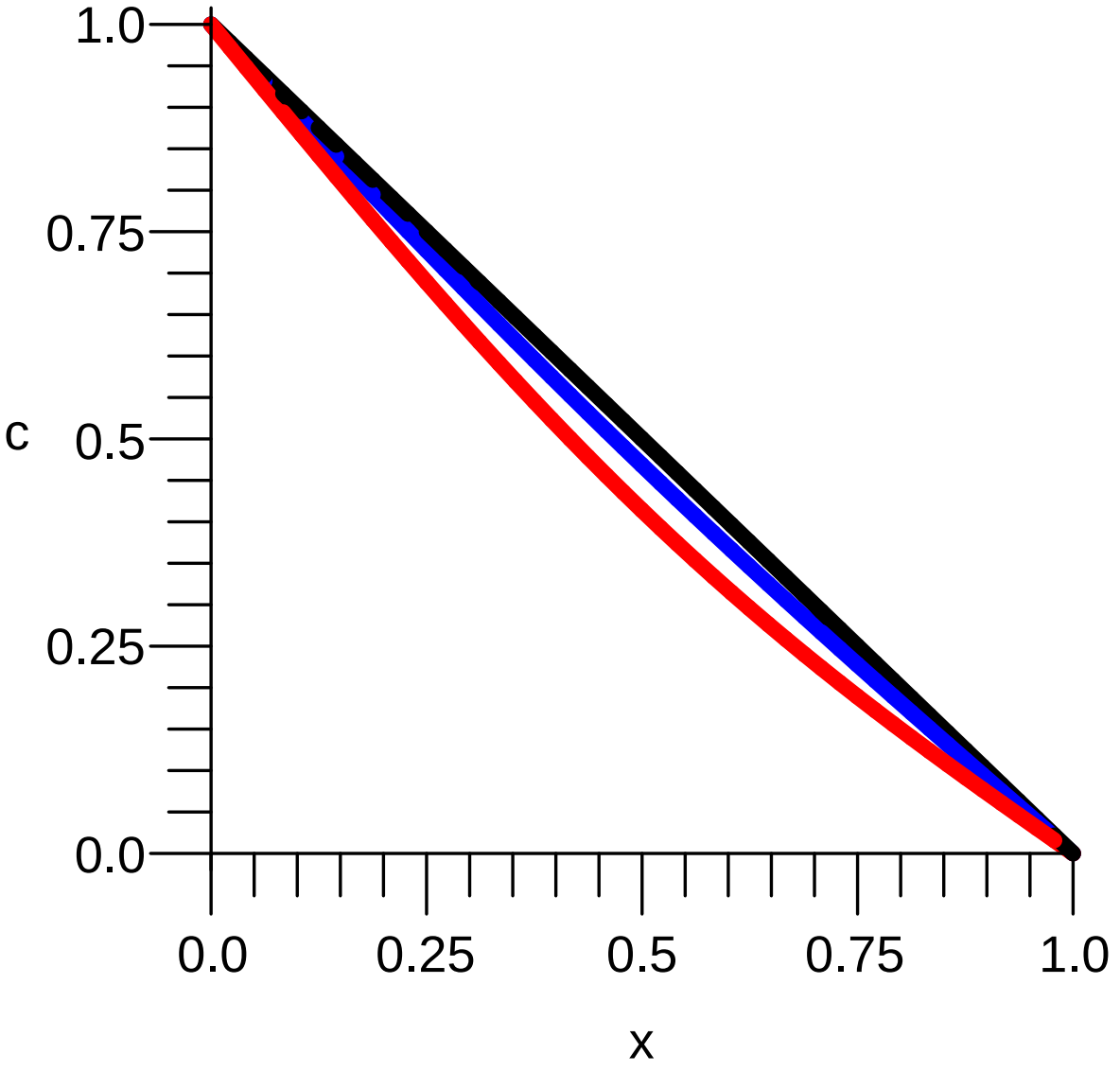
• Now note that the bigger is t, the more rapidly the successive terms in the RHS of (3.4) decrease in value. This form of solution to our problem is particularly useful at 'large' times $t \gg L^2/\pi^2 D$, when taking just a few terms provides a good approximation to $c(x,t)$.

•Note also that as $t \to \infty$, the solution $c(x,t) \to c_0(1 - x/L)$, which is a time-independent solution of the PDE. (See again p. 2.20) It describes the steady-state situation that the system approaches as $t \to \infty$.

•See the next figure , which shows the graphs of the steady-state concentration $c(x, \infty)$ and the approximation

$$c(x,t) \approx c_0(1 - x/L) - \frac{2c_0}{\pi} \sin(\pi x/L) e^{-\pi^2 Dt/L^2}$$

at $t = 2L^2/\pi^2 D$ and $t = 3L^2/\pi^2 D$.


1.0
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c
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0.25
0.5
0.75
1.0
x

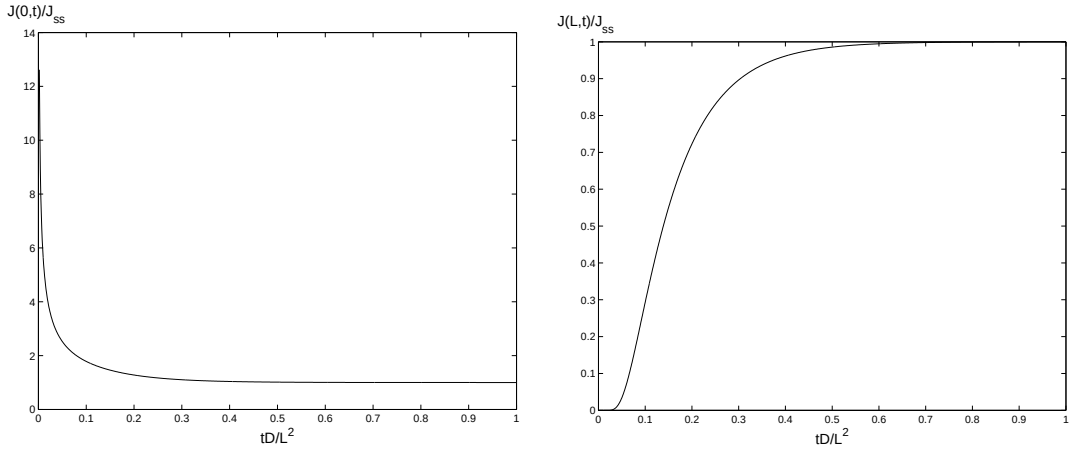
•We are interested in the flux of drug into the circulation inside the skin. Thus we want $J_1(L,t)$. From (3.4) and Fick's first equation we have

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

$$= \frac{Dc_0}{L}\left\{1 + 2\cos(\pi x/L)e^{-\pi^2 Dt/L^2} + 2\cos(2\pi x/L)e^{-4\pi^2 Dt/L^2} + \ldots\right\} \quad (3.5)$$

•Note the steady-state value of the flux is Dc_0/L, independent of x.

•For large times, a good approximation to $J_1(x,t)$ is given by the first couple of terms in (3.5).



(a) $J(0,t)$ Vs tD/L^2 (b) $J(L,t)$ Vs tD/L^2

Figure 5: Flux at the boundaries *versus* t for one-dimensional diffusion. (a) $x = 0$ and (b) $x = L$.

- From (3.5) we have

$$J_1(L,t) = \frac{Dc_0}{L}\left\{1 - 2e^{-\pi^2 Dt/L^2} + 2e^{-4\pi^2 Dt/L^2} - \dots\right\}$$

Of greatest interest is $Q(t)$, the amount of drug that has passed into the circulation up to time t, through cross-sectional area A at $x = L$:–

$$Q(t) = \int_0^t A\, J_1(L,\tau)\, d\tau$$

$$= \frac{ADc_0}{L}\left[\tau - 2\left(\frac{-L^2}{\pi^2 D}\right)e^{-\pi^2 D\tau/L^2} + 2\left(\frac{-L^2}{4\pi^2 D}\right)e^{-4\pi^2 D\tau/L^2} - \dots\right]_{\tau=0}^{\tau=t}$$

$$= \frac{ADc_0}{L}\left\{t + \frac{2L^2}{\pi^2 D}\left(e^{-\pi^2 Dt/L^2} - \tfrac{1}{4}e^{-4D\pi^2 t/L^2} + \dots\right)\right.$$

$$\left. - \frac{2L^2}{\pi^2 D}\left(1 - \tfrac{1}{4} + \tfrac{1}{9} - \dots\right)\right\}$$

- So

$$Q(t) = \frac{ADc_0}{L}\left\{t - \frac{L^2}{6D} + \frac{2L^2}{\pi^2 D}\left(e^{-\pi^2 Dt/L^2} - \frac{1}{4}e^{-4D\pi^2 t/L^2} + \dots\right)\right\}.$$

- As time $t \to \infty$, we see that $\quad Q(t) \approx \frac{ADc_0}{L}\left(t - \frac{L^2}{6D}\right)$.

- The intercept of this linear function on the t-axis is called the **time lag** of the system, $\quad t_{lag} = \frac{L^2}{6D}$. It gives a measure of how long it takes the nicotine patch to reach its full effectiveness.

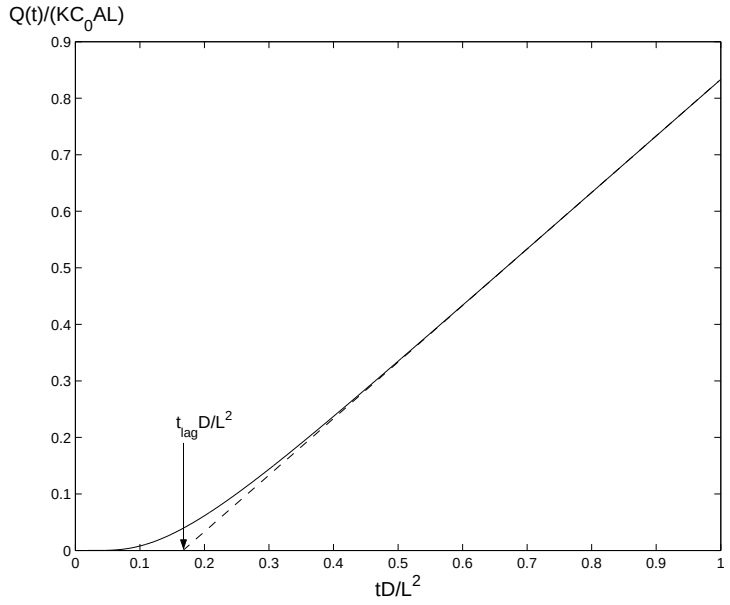


Figure 6: $Q(t)/(ALKC_0)$ *versus* tD/L^2 for one-dimensional diffusion, showing $t_{lag}D/L^2 = 1/6$.

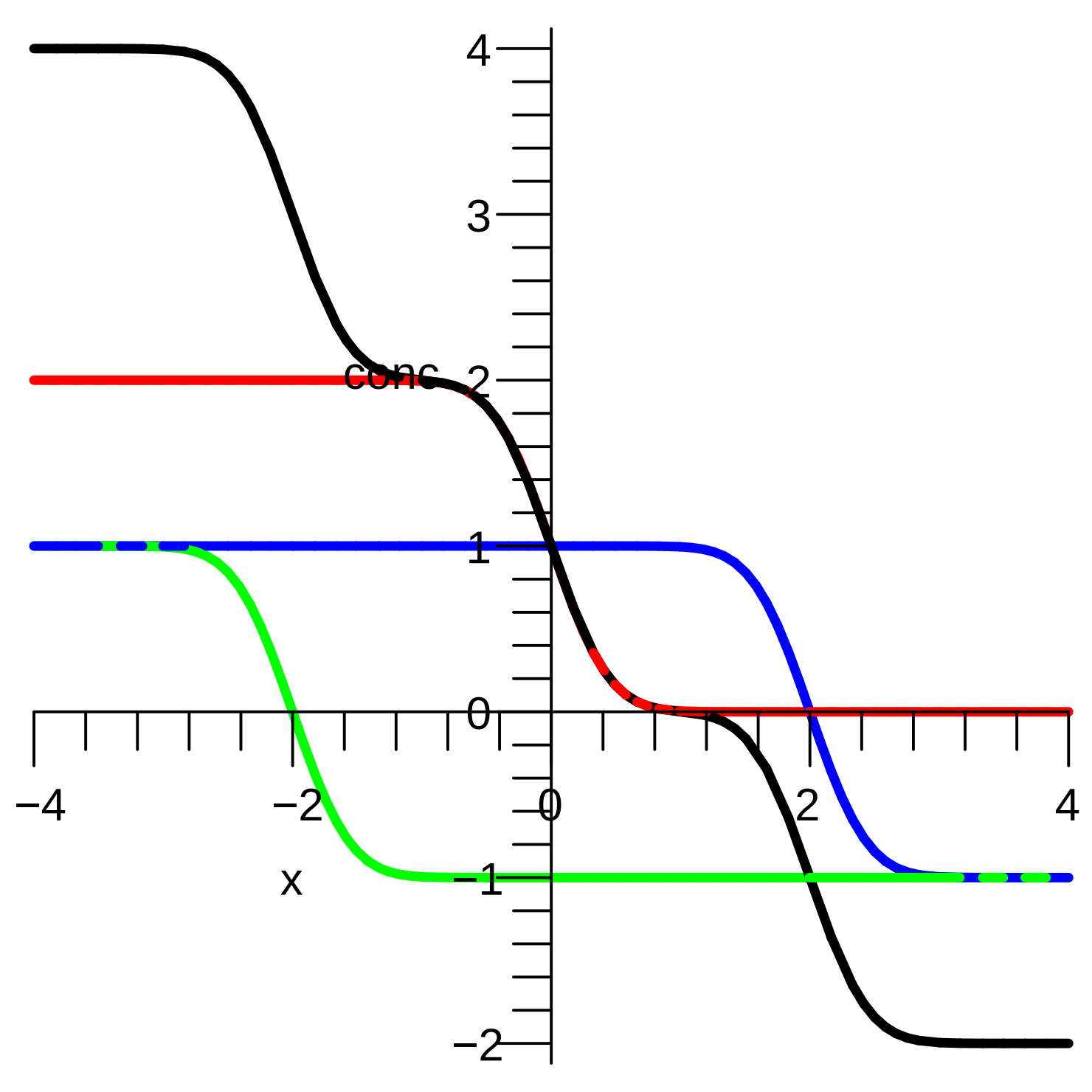
- Remarkably, there is another form for the solution of our problem:–

$$c(x,t) = c_0 \Big(1 - \mathrm{erf}(x/\sqrt{4Dt})$$

$$-\{\mathrm{erf}([x-2L]/\sqrt{4Dt}) + \mathrm{erf}([x+2L]/\sqrt{4Dt})\}$$

$$-\{\mathrm{erf}([x-4L]/\sqrt{4Dt}) + \mathrm{erf}([x+4L]/\sqrt{4Dt})\} - \ldots \Big) \qquad (3.6)$$

which looks completely different from, but is equivalent to (3.4). Note firstly that it is a solution of the PDE, because each term on the RHS is a solution. (See again p. 2.20). It is particularly useful for 'small' times $t \ll L^2/4D$, when the terms in the series successively make much smaller contributions.


conc
4
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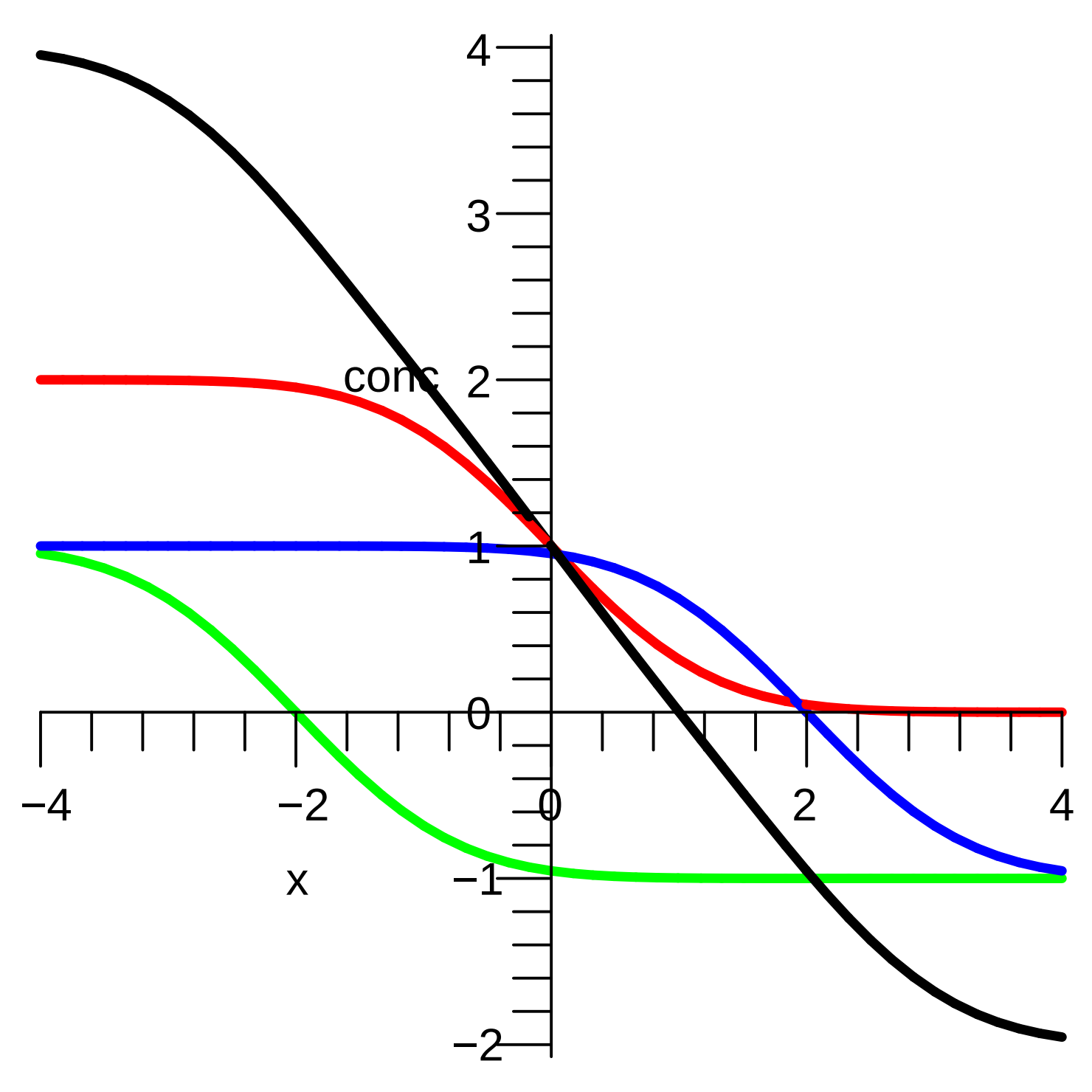
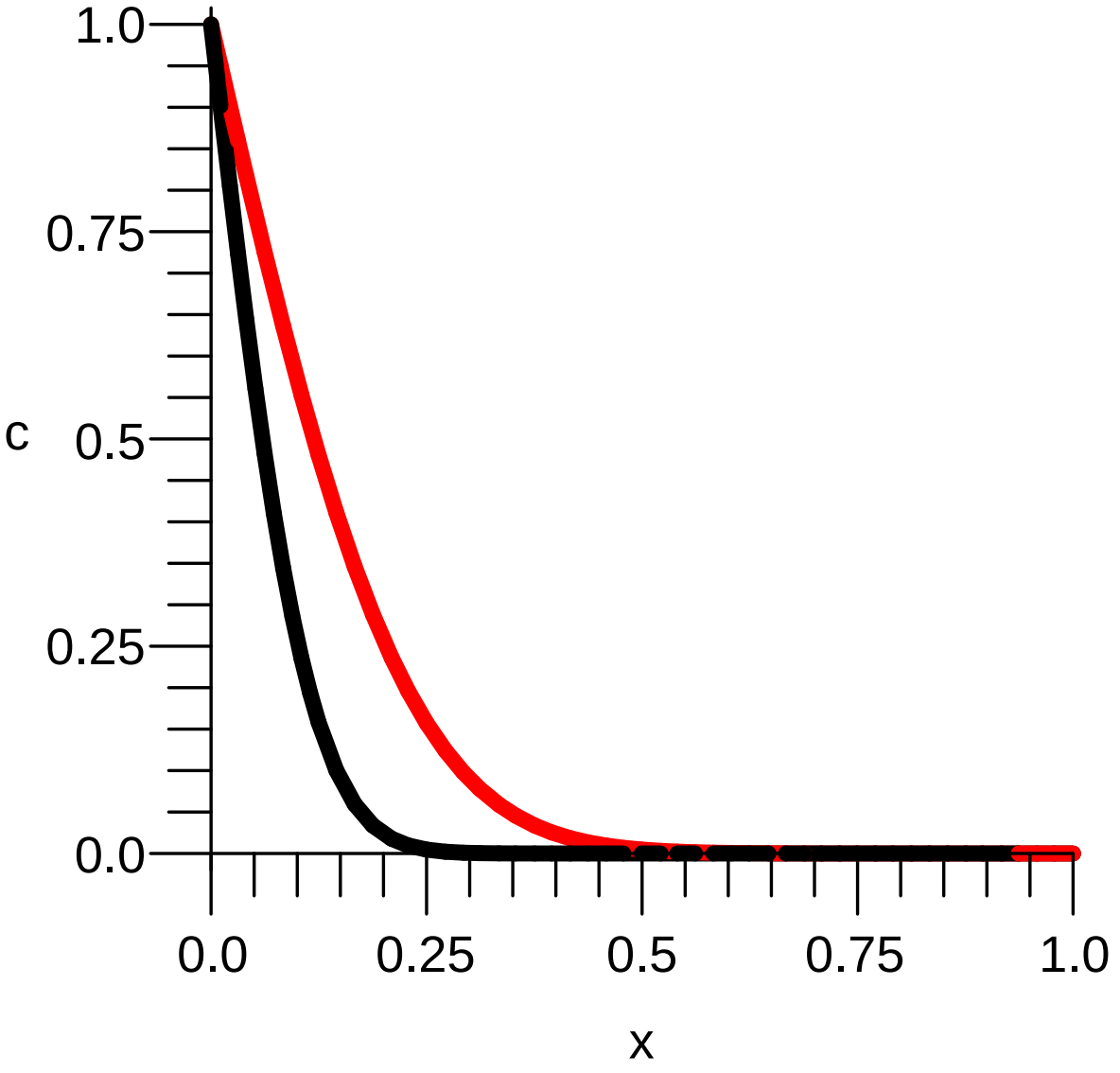
x


4
3
conc
2
1
0
−4
−2
0
2
4
x
−1
−2

- The next figure shows the approximation

$$c(x,t) = c_0 \left(1 - \mathrm{erf}(x/\sqrt{4Dt})\right)$$

at times $t = L^2/256D$ and $t = L^2/64D$, just after the patch is applied.


1.0
0.75
0.5
0.25
0.0
c
0.0
0.25
0.5
0.75
1.0
x

•Using (3.4) or (3.6) with enough terms, we can use the computer to show the form of $c(x,t)$ at any time:–

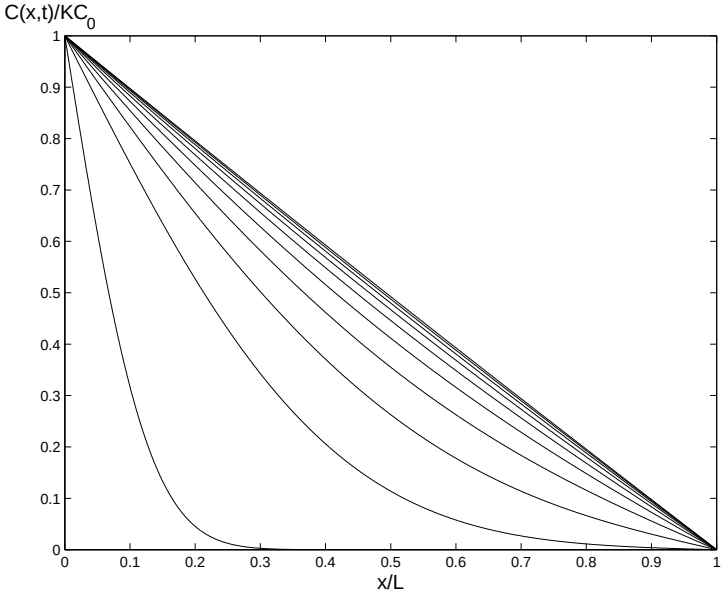


Figure 4: Concentration profiles for one-dimensional diffusion for a number of times. The curves moving towards the linear, steady-state profile correspond to times starting with $0.0005L^2/D$ and increments of $0.05L^2/D$.

- Let's move on to **diffusion in three dimensions.**

We now have a concentration of substance (diffusate) $c(x, y, z, t)$ with diffusion coefficient D, and there is now a flux component J_1 in the x-direction, J_2 in the y-direction and J_3 in the z-direction, with

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

$$J_2(x, y, z, t) = -D\frac{\partial c(x,y,z,t)}{\partial y}$$

$$J_3(x, y, z, t) = -D\frac{\partial c(x,y,z,t)}{\partial z}$$

replacing Fick's first equation in 1-D.

- We can combine these in a nice way using vector notation:

$$\vec{J}(\vec{r},t) = -D\vec{\nabla}(\vec{r},t) \qquad \text{(Fick's first equation in 3-D)}$$

$$\vec{J} = (J_1, J_2, J_3)\,, \quad \vec{\nabla} = (\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z})\,, \quad \vec{r} = (x, y, z).$$

$\vec{J}$ the flux vector

$\vec{\nabla}$ the gradient vector operator ('del')

$\vec{r}$ the position (or coordinate) vector

- Fick's second equation becomes

$$\frac{\partial c(x,y,z,t)}{\partial t} = -\{\frac{\partial J_1(x,y,z,t)}{\partial x} + \frac{\partial J_2(x,y,z,t)}{\partial y} + \frac{\partial J_3(x,y,z,t)}{\partial z}\}.$$

Combining Fick's equations we now get

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

— **the 3-D diffusion equation.**

This is often written as $\frac{\partial c(\vec{r},t)}{\partial t} = D\nabla^2 c(\vec{r},t)$

where ∇^2 is the **Laplacian operator.**