THE TIME NEEDED TO SET UP A GRADIENT: DETAILED CALCULATIONS

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INTRODUCTION

In embryological development there are many cells which acquire 'positional information' (see, for example, Wolpert, 1969) and it is plausible that this is obtained from the concentration of certain unknown chemicals (called here morphogens) which are diffusing down concentration gradients set up by sources and sinks at special places in the embryo. It is therefore important to be able to calculate how much time is needed to set up a steady concentration gradient. This problem has been discussed in a recent paper (Crick, 1970) which suggests that the times available are roughly what might be expected on theoretical grounds. Here we give the details of various calculations quoted in that paper.

The physics and mathematics of diffusion are fairly straight-forward. The classic references are two books: *The Conduction of Heat in Solids*, by Carslaw and Jaeger, 2nd edition, 1959 (here referred to as C. and J.) and *The Mathematics of Diffusion*, by J. Crank, 1956. Results which could not be obtained easily in an algebraical form were calculated by computer.

Although a tissue consists of discrete cells, we have often found it convenient to treat it as a continuous medium, in which the morphogen has a diffusion constant D cm^2/s. On the other hand, in calculations on the computer, this continuous medium has usually been approximated by a series of discrete points. Details of these computations will be given later. For reasons explained in the earlier paper (Crick, 1970) it is reasonable to calculate one-dimensional cases, at least in the first instance.

A SIMPLE LINEAR GRADIENT

Mathematically, the simplest model to consider is one having a source at the origin, holding the concentration there to the value C_0, and a sink at the point $x = L$, holding the concentration there to zero. If the diffusion constant, D, is everywhere the same, then after an infinite time the concentration will tend to the value

$$C = C_0 \frac{L-x}{L} \quad (0 \geqslant x \geqslant L). \tag{1}$$

(Note that this expression does not contain D. However, the flux per unit area does depend on D, and is given by (DC_0/L).)

The concentration will approach this final value asymptotically. To calculate the amount by which the concentration at any time differs from its final value we adapt the formula given in C. and J. p. 99, section 3·4, equation (1). The general value c for the concentration at the point x at time t is given by

$$c = C_0\frac{L-x}{L} - \frac{2C_0}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\left(\frac{n\pi x}{L}\right)\exp(-n^2\pi^2T)$$
$$+\frac{2}{L}\sum_{n=1}^{\infty}\sin\left(\frac{n\pi x}{L}\right)\exp(-n^2\pi^2T)\int_0^L f(x')\sin\left(\frac{n\pi x'}{L}\right)dx', \qquad (2)$$

where $c = f(x)$ at $t = 0$,

and thereafter $c = C_0$ at $x = 0$,

$c = 0$ at $x = L$.

We have expressed time in a convenient dimensionless form by putting

$$T = (Dt/L^2).$$

In the first instance let us assume that the initial concentration is everywhere zero (i.e. $f(x) = 0$). Then at any given time the ***maximum*** value of ΔC, the difference between the concentration and its final value, is at the midpoint $x = \frac{1}{2}L$, because of the symmetry of the problem. For this special case the value of ΔC is given by

$$\Delta C = -\frac{2C_0}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\frac{n\pi}{2}\exp(-n^2\pi^2T). \qquad (3)$$

If we only consider cases in which ΔC is small, we need take no more than the first two terms, so that

$$\Delta C = -\frac{2C_0}{\pi}[\exp(-\pi^2T) - \tfrac{1}{3}\exp(-9\pi^2T)\ldots] \qquad (4)$$

and usually the first term alone will suffice. In Fig. 1 we plot the value of $|\Delta C/C_0|$ against T (for the middle point). For example, if $|\Delta C/C_0|$ is taken as 1 %, then T has the value of 0·42.

We have also computed the whole course of the concentration curve for certain selected values of T, using equation (2).

Linear gradient with initial constant background

A smaller value of T (for a chosen value of $\Delta C/C_0$) can be obtained if we allow the tissue to have a *uniform* concentration of the morphogen at time zero. Let this be αC_0. To be of any advantage α must be less than unity. In this case equation (2) becomes

$$-\frac{\Delta C}{C_0} = \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\alpha(1-\cos n\pi)-1}{n}\sin\left(\frac{n\pi x}{L}\right)\exp(-n^2\pi^2T). \qquad (5)$$

It is only necessary to take the first two terms of this series, since for the particular times we are interested in, the third and higher terms are negligible (for $T = 0·1$, $n = 3$, $\exp(-n^2\pi^2T) = 2\times10^{-7}$). For the special case

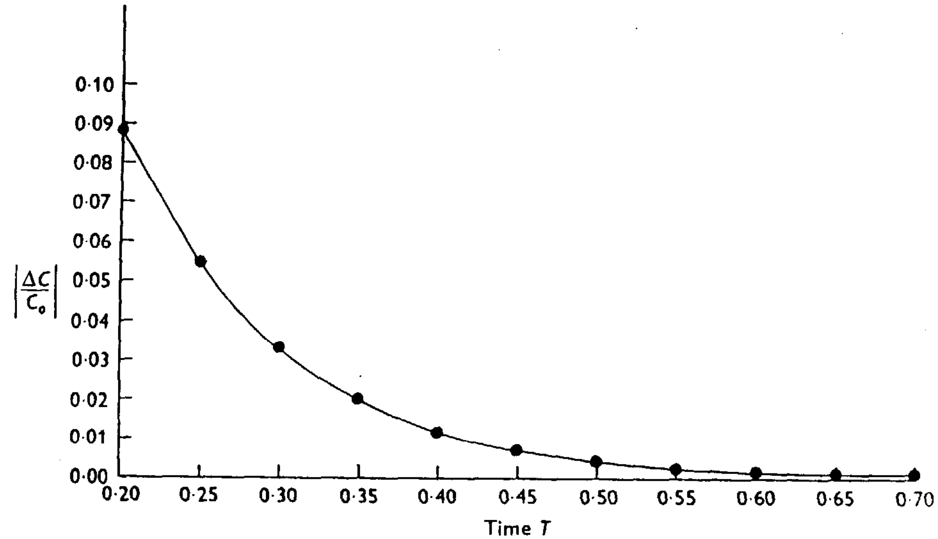

Fig. 1. $\Delta C/C_0$ for the mid-point of the gradient as it approaches its final value.

$\alpha = \frac{1}{2}$ the term having $n = 1$ is zero, and the maximum value of $|\Delta C|$ occurs at the points $x/L = \frac{1}{4}$ or $\frac{3}{4}$. It turns out that for values of α less than unity but not too close to $\alpha = \frac{1}{2}$ (that is, when α is between 0 and 0·4, or 0·6 and 1·0) we can neglect all but the first term. For $|\Delta C/C_0| = 0·01$ we easily derive the explicit equations:

at $\frac{x}{L} = \frac{1}{2}$, $\quad T = \frac{1}{\pi^2}\log_e\left|\frac{200}{\pi}(2\alpha-1)\right|$,

at $\frac{x}{L} = \frac{3}{4}$ or $= \frac{1}{4}$, $\quad T = \frac{1}{\pi^2}\log_e\left|\frac{100}{\pi}\sqrt{2}(2\alpha-1)\right|$

where T is, in this case, the time at which $|\Delta C/C_0|$ is 1 % *at the point under consideration*. By symmetry, T for $x/L = \frac{1}{4}$ with initial background αC_0 will be the same as T for $x/L = \frac{3}{4}$ with initial background $(1-\alpha)C_0$. The values thus obtained are set out in Table 1.

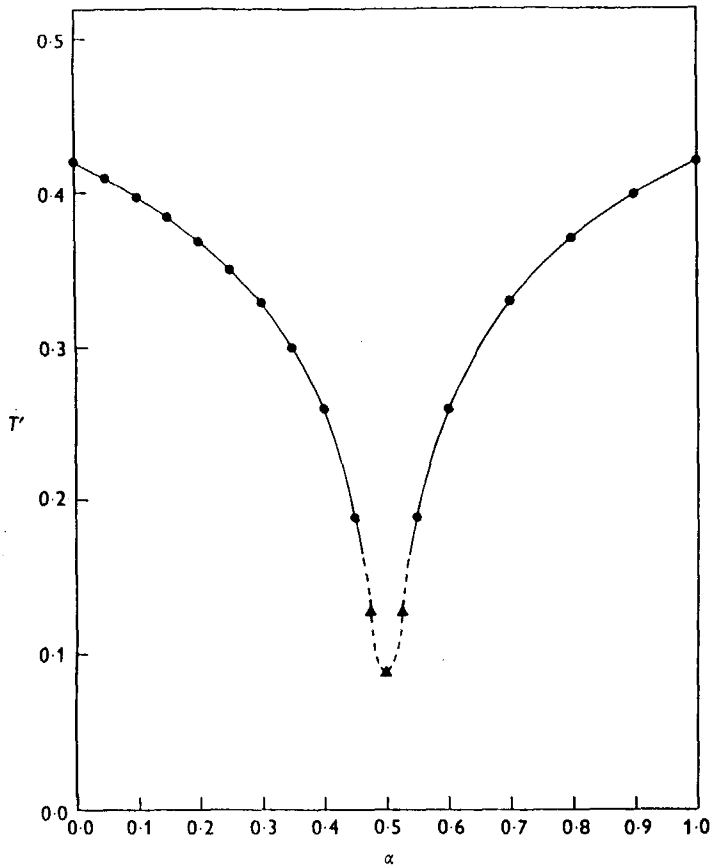

Fig. 2. Time taken for the concentration at all points to come within 1 % of their final values, for different initial backgrounds (αC_0).

Table 1

Values of T for $|\Delta C/C_0|$ equal to 0·01 *for the point specified*, for various values of the initial background αC_0, calculated using only a single (non-zero) term in the expansion. The value in brackets is inaccurate.

α	At $x/L = \frac{1}{2}$	At $x/L = \frac{1}{4}$ (for $0 < \alpha < 0·5$) or $x/L = \frac{3}{4}$ (for $0·5 < \alpha < 1·0$)	α
0·05	0·410	0·375	0·95
0·10	0·398	0·363	0·90
0·15	0·385	0·350	0·85
0·20	0·369	0·334	0·80
0·25	0·351	0·315	0·75
0·30	0·328	0·293	0·70
0·35	0·299	0·264	0·65
0·40	0·258	0·223	0·60
0·45	0·188	(0·15)	0·55
0·50	0·000	0·088	0·50

For values of α outside the limits 0·45 to 0·55 the last point to fall within the 1 % limit is always the mid-point. However, this is not true when $\alpha = \frac{1}{2}$, since ΔC at the mid-point is at all times zero (because of the symmetry), and the last point to fall within the 1 % limit is $x/L = \frac{1}{4}$ or $x/L = \frac{3}{4}$. For values of α in between 0·45 and 0·5 the last point will be somewhere between $x/L = \frac{1}{4}$ and $x/L = \frac{1}{2}$, and can be roughly estimated. For example, when $\alpha = 0·475$ the last point is approximately $x/L = 0·35$, when $T \approx 0·126$. We then adopt as a criterion the condition that *all* points on the gradient must be within 1 % of the final concentration difference between the ends of the gradient from their final values, and define T' as the time taken for this to occur. Fig. 2 shows the approximate value of T' for all values of α between 0 and 1. The values near $\alpha = \frac{1}{2}$, shown dotted in the curve, have been roughly estimated from computer calculations for $\alpha = 0·45$ and $\alpha = 0·475$.

It will be seen that although a rather small value of T' can be obtained if α is *exactly* $\frac{1}{2}$, the value of T' rapidly increases if α differs appreciably from this special value. However, if the level of α were within ± 10 % of this special value, T' would always be less than 0·19.

Other initial conditions

We have shown that if there is zero concentration initially, the time taken to set up an almost linear gradient is longer than for any other initial UNIFORM concentration less than C_0. By symmetry this time is the same as the time when the initial concentration is C_0 throughout.

We now prove that if the initial concentration has any arbitrary form, but is always less than C_0 (and always positive), it takes a shorter time to set up a nearly linear gradient than the simple case with zero initial background.

The time taken to set up the simple case is approximately $T = 0·4$.

When $T = 0·4$, $\exp(-\pi^2 T) = 0·0193$ and $\exp(-4\pi^2 T) = 1·7 \times 10^{-7}$. Looking at the concentration equation (2), the second term is

$$\frac{2C_0}{\pi} \sum_{n=1}^{\infty} \frac{1}{n} \sin\left(\frac{n\pi x}{L}\right) \exp(-n^2\pi^2 T).$$

When $n = 2$ and $T \approx 0·4$ this is always numerically less than $(1·7 \times 10^{-7})\, C_0/\pi$ and is clearly negligible.

When $n \geq 3$ and $T \approx 0·4$ the terms are very much smaller. Looking at the third term of the equation (2), since

$$0 < f(x) < C_0 \quad \text{by definition}$$

and

$$-1 \leq \sin\left(\frac{n\pi x}{L}\right) \leq +1 \quad \text{for all } x \text{ and } n,$$

$$-\int_0^L f(x)\,dx \leq \int_0^L f(x) \sin\left(\frac{n\pi x}{L}\right) dx \leq \int_0^L f(x)\,dx$$

and $$\int_0^L f(x)\,dx \quad \text{is clearly less than } C_0 L,$$

therefore $$-C_0 L \leqslant \int_0^L f(x) \sin\left(\frac{n\pi x}{L}\right) dx \leqslant C_0 L.$$

So $$\frac{2}{L}\sum_{n=1}^{\infty} \sin\left(\frac{n\pi x}{L}\right) \exp(-n^2\pi^2 T) \int_0^L f(x') \sin\left(\frac{n\pi x'}{L}\right) dx'$$

is also negligible for $n \geqslant 2$ when T is as great as 0·4.

So the concentration function ignoring $n \geqslant 2$ is

$$c = \frac{C_0(L-X)}{L} - 2\sin\left(\frac{\pi x}{L}\right)\exp(-\pi^2 T)\left[\frac{C_0}{\pi} - \frac{1}{L}\int_0^L f(x')\sin\left(\frac{\pi x'}{L}\right)dx'\right]$$

thus

$$\Delta C = 2\sin\left(\frac{\pi x}{L}\right)\exp(-\pi^2 T)\left[\frac{C_0}{\pi} - \frac{1}{L}\int_0^L f(x')\left(\sin\frac{\pi x'}{L}\right)dx'\right]. \qquad (6)$$

When $f(x) = 0$, initially we get

$$|\Delta C| = \frac{2C_0}{\pi}\sin\left(\frac{\pi x}{L}\right)\exp(-\pi^2 T),$$

as before, but $$0 \leqslant f(x') \leqslant C_0$$

and $$0 \leqslant \sin\left(\frac{\pi x}{L}\right) \leqslant 1 \quad \text{for all } x \text{ in the range} \quad 0 \leqslant x \leqslant L$$

therefore $$0 \leqslant \int_0^\infty f(x')\sin\left(\frac{\pi x'}{L}\right)dx' \leqslant C_0\int_0^L \sin\left(\frac{\pi x'}{L}\right)dx \leqslant \frac{2C_0 L}{\pi}.$$

Putting this in equation (6)

$$|\Delta C| \leqslant \frac{2C_0}{\pi}\sin\left(\frac{\pi x}{L}\right)\exp(-\pi^2 T)$$

and the equality is obviously the simple case $f(x) = 0$ initially. So no initial conditions, subject to the restrictions $0 \leqslant f(x) \leqslant C_0$ for $0 < x < L$, will produce longer times to set up a linear gradient than the case of initial uniform concentration of zero, provided that our criterion for setting up the gradient is such that $|\Delta C/C_0|$ is a small percentage.

SOME SPECIAL CASES

Step function

For times shorter than $T = 0{\cdot}4$ the terms in $n = 2$ will not be negligible. In particular, the term when $n = 2$ is

$$\sin\left(\frac{2\pi x}{L}\right)\exp(-4\pi^2 T)\left[\frac{2}{L}\int_0^L f(x')\sin\left(\frac{2\pi x'}{L}\right)dx' - \frac{C_0}{\pi}\right].$$

Clearly the largest possible value this can have at any time, within the conditions imposed on $f(x)$, will occur when

$$\frac{2}{L}\int_0^L f(x')\sin\left(\frac{2\pi x'}{L}\right)dx'$$

is as large, negatively as possible.

As the function $\sin(2\pi x'/L)$ is negative only for $x/L > \frac{1}{2}$, and $f(x)$ is always positive, the function which would give the largest possible value to this term is the step function:

$$f(x) = 0 \quad \text{for} \quad 0 \leqslant x/L < \tfrac{1}{2}$$
$$f(x) = C_0 \quad \text{for} \quad \tfrac{1}{2} \leqslant x/L \leqslant 1.$$

This integrates to give

$$-\frac{LC_0}{n\pi}(\cos n\pi - \cos \tfrac{1}{2}n\pi).$$

As far as $n = 2$ we get from equation (2)

$$\Delta C = -\frac{3C_0}{\pi}\sin\left(\frac{2\pi x}{L}\right)\exp(-4\pi^2 T)$$

(the term in $n = 1$ cancels to zero). When $x/L = \frac{1}{2}$ clearly $\Delta C = 0$ for all T. So we must examine the point $x/L = \frac{1}{4}$. When this is within 0·01 C_0 of its final value, we get

$$\frac{3C_0}{\pi}\sin\left(\frac{\pi}{2}\right)\exp(-4\pi^2 T) = \frac{C_0}{100},$$

$$T \approx \frac{1}{4\pi^2}\log_e\frac{300}{\pi}$$

$$\approx 0{\cdot}115.$$

Reverse gradient

If we start with $f(x) = (x/L)\, C_0$ (that is an exact reverse of the final gradient) and calculate concentration function as far as $n = 2$, from equation (2)

$$|\Delta C| = \frac{2C_0}{\pi} \sin\left(\frac{2\pi x}{L}\right) \exp(-4\pi^2 T).$$

Again the centre point is always $\frac{1}{2}C_0$, so we examine $x/L = \frac{1}{4}$:

$$\frac{C_0}{100} = \frac{2C_0 \exp(-4\pi^2 T)}{\pi},$$

$$T \approx \frac{1}{4\pi^2} \log_e \frac{200}{\pi}$$

$$\approx 0{\cdot}10_5.$$

As we have shown, when $T = 0{\cdot}1$, $\exp(-9\pi^2 T) = 2 \times 10^{-7}$ so the third and higher terms of equation (2) are negligible.

SUMMARY

Initial concentration function $f(x)$	Time to within $(C_0/100)\%$ of final value	Point considered	No. of terms
$f(x) = 0$ all x	0·42	$x/L = \frac{1}{2}$	3
$f(x) = \frac{1}{2}C_0$ all x	0·09	$x/L = \frac{1}{4}$	2
$f(x) = \frac{1}{20}C_0$ all x	0·41	$x/L = \frac{1}{2}$	1
Step function			
$f(x) = 0,\ 0 \leqslant x/L < \frac{1}{2}$	0·11₅	$x/L = \frac{1}{4}$	2
$f(x) = C_0,\ \frac{1}{2} \leqslant x/L \leqslant 1$			
Reverse step function			
$f(x) = C_0,\ 0 \leqslant x/L < \frac{1}{2}$	0·09	$x/L = \frac{1}{4}$	2
$f(x) = 0,\ \frac{1}{2} \leqslant x/L \leqslant 1$			
Reverse gradient			
$f(x) = C_0\, x/L$	0·10₅	$x/L = \frac{1}{4}$	2

Flux required to maintain the gradient

This can be expressed in a very simple manner. Once the gradient has been established the amount of the morphogen in the tissue, provided the sink holds the morphogen concentration at zero, is clearly $\frac{1}{2}C_0 LA$, where A is the area of the tissue perpendicular to the gradient. The flux needed to maintain it is $(ADC_0)/L$. We now calculate the time, t_f, needed for the source to produce the amount of morphogen in the tissue at any moment. Since

$$\frac{ADC_0}{L} = \frac{\frac{1}{2}C_0 LA}{t_f}$$

we obtain $t_f = \frac{1}{2}L^2/D$. Thus t_f is roughly equal to the time needed to set up the gradient from scratch to 1 % C_0 of its final value. In other words, if it takes three hours to set up a linear gradient to 1 %, the source will need to produce the amount of morphogen then in the tissue about every three hours. This assumes that D does not change after the gradient has been set up.

MORE COMPLICATED MODELS

The models so far discussed although convenient for calculation, have the disadvantage that the flux of the morphogen at the origin has to be very high at small values of the time. It is therefore necessary to consider other models in which the flux varies in a way which is biochemically more realistic.

The obvious type of model to try has a 'pump' at the origin producing the morphogen at a rate which varies with its concentration at that point. The destruction of the morphogen at the sink is specified in a similar way.

We have tried two such models. In the first model the sink destroyed the morphogen at a rate proportional to the concentration there, so that the flux at sink was equal to βC_L, where C_L is the concentration at the point $x = L$ and β is a constant. The source produced it according to the formula

$$\text{flux at source} = \beta(C' - c_0),$$

where c_0 is the concentration (not necessarily constant) at $x = 0$ and C' is a constant. It is easy to show that under these conditions the final gradient will run from $C' - (f_0/\beta)$ at $x = 0$ to the value f_0/β at $x = L$, where f_0 is the final steady flux. If we call the total difference C_R, then

$$C_R = C' - \frac{2f_0}{\beta}.$$

We have carried out the calculations for various values of m, where m is the maximum possible value of the ratio initial flux to final flux for the flux at the origin, and expressed the result as the values of T' for each of three values of $|\Delta C/C_R|$, namely 2, 1 and $\frac{1}{2}$ %. This is for the case of zero initial background. We have also calculated T' for the case with a uniform background equal to the mid-point value of the final gradient and another with 90 % of this value ($\alpha = 0{\cdot}50$ and $0{\cdot}45$). All these results are presented in Table 2. As can be seen, the times are considerably increased over those for our simple model. (In the simple model C_R and C_0 are the same.) However, we feel that Nature is quite likely to have evolved a more efficient pump, with sigmoid rather than linear characteristics. This might be expected to have the characteristics shown in Fig. 3. We have approximated to this by

Table 2. *Values of T' for the simple pump model*

	Final values of concn (× C')		No background			Background 0·5 C_0			Background 0·45 C_0		
m	Source	Sink	½%	1%	2%	½%	1%	2%	½%	1%	2%
10	0·90	0·10	0·79$_5$	0·68$_5$	0·57	0·16	0·13$_5$	0·11	0·43$_5$	0·32$_5$	0·21
25	0·96	0·04	0·58$_5$	0·51	0·42$_5$	0·13	0·10$_5$	0·08$_5$	0·31$_5$	0·23	0·15$_5$
50	0·98	0·02	0·53	0·45$_5$	0·38$_5$	0·11$_5$	0·09$_5$	0·07$_5$	0·27$_5$	0·20	0·13
100	0·99	0·01	0·50$_5$	0·44	0·36$_5$	0·11	0·09	0·07$_5$	0·26$_5$	0·19	0·12

Table 3. *Values of T' for the sigmoid pump model*

	Final values of concn (× C_0)		No background			Background 0·5 C_0			Background 0·45 C_0		
m	Source	Sink	½%	1%	2%	½%	1%	2%	½%	1%	2%
1·5	1·0	0·0	0·69$_5$	0·62	0·55	0·16	0·14$_5$	0·12$_5$	0·36$_5$	0·29	0·22$_5$
2·0	1·0	0·0	0·58$_5$	0·52	0·45	0·13$_5$	0·11$_5$	0·10	0·31$_5$	0·25	0·17$_5$
3·0	1·0	0·0	0·53$_5$	0·46	0·39	0·12	0·10	0·08$_5$	0·28$_5$	0·22	0·14$_5$
5·0	1·0	0·0	0·50$_5$	0·44	0·36$_5$	0·11	0·90	0·07$_5$	0·27$_5$	0·20	0·13

In both Tables 2 and 3 the value of T' is listed for four values of the pumping constant, three different initial backgrounds and three values of the maximum permitted percentage difference from the final value. (m is the maximum possible value of the ratio of initial flux to final flux at the source.)

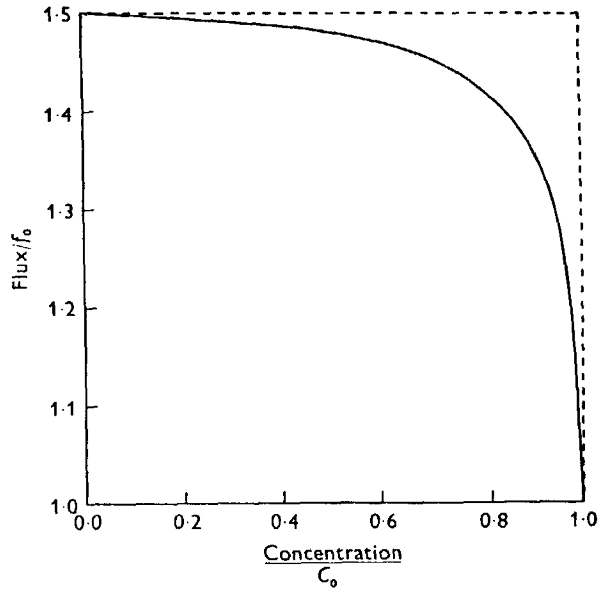

Fig. 3. The flux at the point $x = 0$ for sigmoid type of pump. (f_0 is the final flux required to maintain a linear gradient from C_0 to 0.) The dotted line shows the approximation used.

mposing a *maximum* value of the flux, both at the source and the sink, which operates from time zero onwards. When either the source or the sink reaches the final concentration (C_0 and 0 respectively), the concentration there is held constant from then on. This is (roughly) equivalent to the dotted line shown in Fig. 3. As in the simple model $C_R = C_0$. The results for T', where $|\Delta C/C_R|$ are ½, 1 or 2% are shown in Table 3 for $\alpha = 0$ (no background), $\alpha = 0{\cdot}50$ and $\alpha = 0{\cdot}45$.

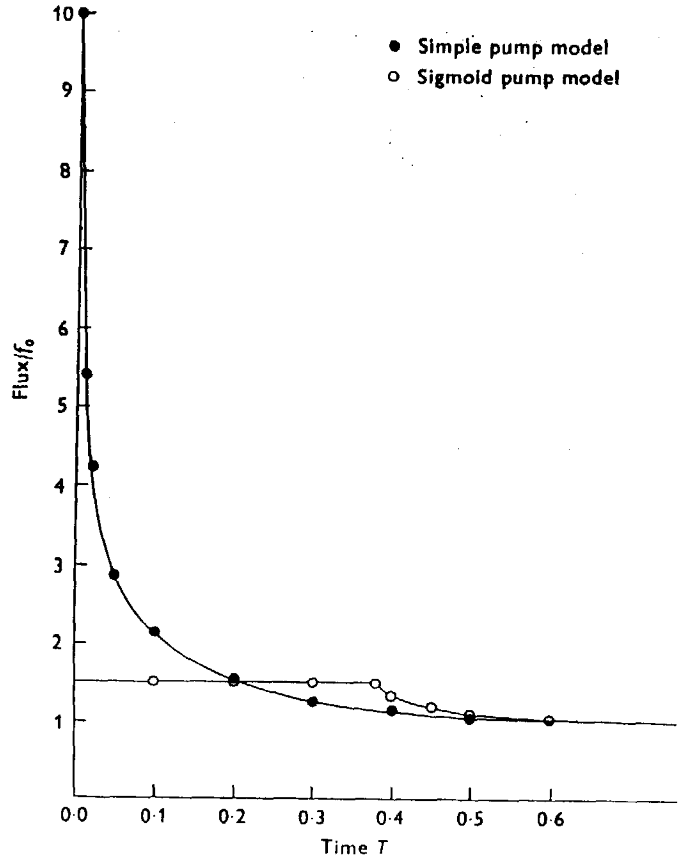

Fig. 4. The flux at the point $x = 0$ for both pump models.

Fig. 4 shows the variation of the flux at the origin with time for both the simple and sigmoid pump models. The cases shown are initial flux equal to 10 times the final flux for the simple pump ($m = 10$), and a maximum value of 1·5 for the sigmoid pump. These take comparable times to set up a linear gradient.

A comparison of Tables 2 and 3 shows that, as expected, the sigmoid pump is the more efficient, since it can reach a given value of T' for a lower value of the initial flux. However, the important point to notice is that for all the cases considered, the time T' is not increased grossly above the value for the 'mathematical' model described first.

Table 4. *Calculated concentrations for the simple model*

At the point $x/L = \frac{1}{2}$

	Algebraic method	Reiterative method
T = 0·05	0·11384 (C_0)	0·11446 (C_0)
0·1	0·26276	0·26288
0·15	0·35515	0·35511
0·2	0·41157	0·41148
0·25	0·44601	0·44591
0·3	0·46704	0·46696
0·35	0·47988	0·47981
0·4	0·48762	0·48766
0·45	0·49250	0·49246
0·5	0·49542	0·49540

With initial background 0·5 C_0 at the point $x/L = \frac{1}{4}$

	Algebraic method	Reiterative method
T = 0·05	0·70578 (C_0)	0·70560 (C_0)
0·1	0·74386	0·74376
0·15	0·74915	0·74912
0·2	0·74988	0·74988
0·25	0·74988	0·74988
0·3	0·75000	0·75000

The results presented in Tables 2 and 3 were calculated on a computer, for a model with twenty cells between $x = 0$ and $x = L$. The diffusion equation $(\partial c/\partial t) = D(\partial^2 c/\partial x^2)$ (where c is concentration; D, diffusion constant) was approximated as a finite difference equation:

$$c(x, t+\delta t) = c(x, t) + \frac{D\delta t}{(\delta x)^2}[c(x+\delta x, t) + c(x-\delta x, t) - 2c(x, t)] \qquad (7)$$

where $c(x, t)$ is the concentration at time t and the point x, δt is the time interval between each step, and δx the distance between each point. We took $D = 0{\cdot}01$, $\delta x = 0{\cdot}05L$ and $\delta t = 0{\cdot}01$ (the conversion to dimensionless time gave $T = (Dt/L^2) = 0{\cdot}01t$).

The concentrations $c(0, t)$ and $c(L, t)$ at the source and sink were changed according to the specifications for the flux of each model. In the simple

diffusion model, where it was possible to calculate the concentration easily algebraically, we compared the result with those obtained by the reiterative process using equation (7). These are shown in Table 4.

For the times we are interested in, the error is fairly small (although

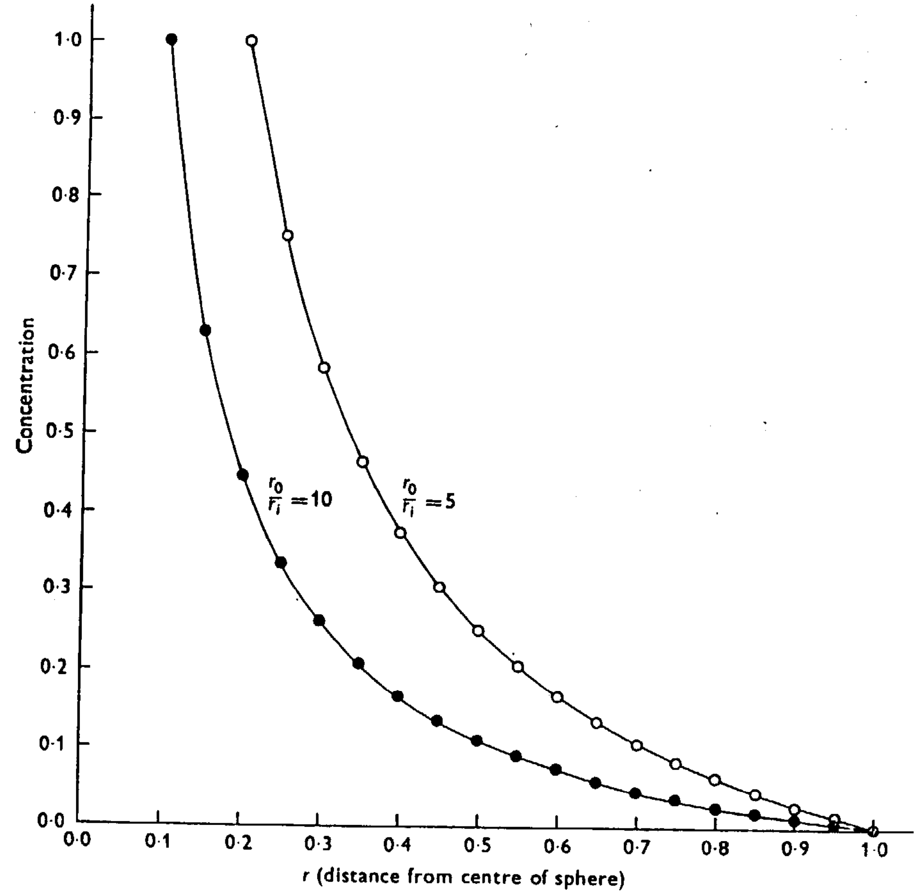

Fig. 5. The final gradients for the 3D cases.

slightly larger for cases with initial background of 0·5 C_0) where the concentrations reached the required values at small values of T.

So far our results have been for one-dimensional systems. However, our general conclusion is likely to apply equally well to systems having two or three dimensions. To illustrate this we have calculated the three-dimensional case of a hollow sphere. The inner radius (r_i) is held at concentration C_0 and the outer (r_o) at concentration zero. Computation was carried out for the ratio outer/inner radius ($= r_o/r_i$) either 5 : 1 or 10 : 1. The gradients obtained after infinite time (which naturally are not linear) are graphed in Fig. 5.

The calculations (not reproduced here) show that by the time $T = 0{\cdot}45$ the concentration is everywhere very close to the final values. In this case we define $T = Dt/(r_o - r_i)^2$. To compare our results with the linear one-dimensional case we have arbitrarily considered the point midway between the outer and inner radius, $\frac{1}{2}(r_o - r_i)$, and have plotted the approach to equilibrium with time in Fig. 6. The dotted line in each case shows the point at which the concentration has the same value as the *final* value at a point at a distance of one hundredth of the thickness away, i.e. at a distance

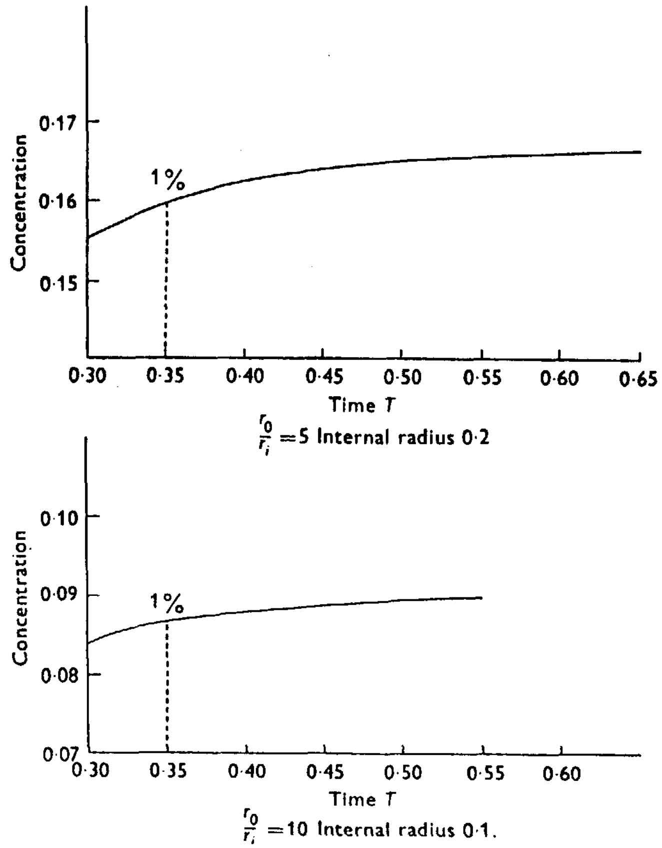

Fig. 6. The chosen point approaches its final value for both cases of the 3D spherical model.

of $(r_o - r_i)/100$ from the chosen point, since this gives some measure of the possible error of position which might be produced by an inaccurate gradient, and corresponds to the criterion adopted for the one-dimensional linear gradient. As can be seen, T, for this error is about $0{\cdot}35$ in both cases.

Although any comparison between the three-dimensional case and the one-dimensional case is necessarily inexact, these figures show that it takes a

similar sort of time to set up a gradient whatever the number of dimensions involved. This is, of course, exactly what one would expect from general arguments based on the random nature of diffusion.

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