

cell r may be written X_r , and Y_r has a similar meaning. It is convenient to regard 'cell N ' and 'cell O ' as synonymous, and likewise 'cell 1 ' and cell ' $N+1$ '. One can then say that for each r satisfying $1 \leq r \leq N$ cell r exchanges material by diffusion with cells $r-1$ and $r+1$. The cell-to-cell diffusion constant for X will be called μ , and that for Y will be called ν . This means that for unit concentration difference of X , this morphogen passes at the rate μ from the cell with the higher concentration to the (neighbouring) cell with the lower concentration. It is also necessary to make assumptions about the rates of chemical reaction. The most general assumption that can be made is that for concentrations X and Y chemical reactions are tending to increase X at the rate $f(X, Y)$ and Y at the rate $g(X, Y)$. When the changes in X and Y due to diffusion are also taken into account the behaviour of the system may be described by the $2N$ differential equations

$$\left. \begin{aligned} \frac{dX_r}{dt} &= f(X_r, Y_r) + \mu(X_{r+1} - 2X_r + X_{r-1}) \\ \frac{dY_r}{dt} &= g(X_r, Y_r) + \nu(Y_{r+1} - 2Y_r + Y_{r-1}) \end{aligned} \right\} \quad (r = 1, \dots, N). \quad (6.1)$$

If $f(h, k) : g(h, k) = 0$, then an isolated cell has an equilibrium with concentrations $X = h$, $Y = k$. The ring system also has an equilibrium, stable or unstable, with each X_r equal to h and each Y_r equal to k . Assuming that the system is not very far from this equilibrium it is convenient to put $X_r = h + x_r$, $Y_r = k + y_r$. One may also write $ax + by$ for $f(h + x, y + k)$ and $cx + dy$ for $g(h + x, y + k)$. Since $f(h, k) = g(h, k) = 0$ no constant terms are required, and since x and y are supposed small the terms in higher powers of x and y will have relatively little effect and one is justified in ignoring them. The four quantities a, b, c, d may be called the 'marginal reaction rates'. Collectively they may be described as the 'marginal reaction rate matrix'. When there are M morphogens this matrix consists of M^2 numbers. A marginal reaction rate has the dimensions of the reciprocal of a time, like a radioactive decay rate, which is in fact an example of a marginal (nuclear) reaction rate.

With these assumptions the equations can be rewritten as

$$\left. \begin{aligned} \frac{dx_r}{dt} &= ax_r + by_r + \mu(x_{r+1} - 2x_r + x_{r-1}), \\ \frac{dy_r}{dt} &= cx_r + dy_r + \nu(y_{r+1} - 2y_r + y_{r-1}). \end{aligned} \right\} \quad (6.2)$$

To solve the equations one introduces new co-ordinates ξ_0, \dots, ξ_{N-1} and $\eta_0, \dots, \eta_{N-1}$ by putting

$$\left. \begin{aligned} x_r &= \sum_{s=0}^{N-1} \exp\left[\frac{2\pi i r s}{N}\right] \xi_s, \\ y_r &= \sum_{s=0}^{N-1} \exp\left[\frac{2\pi i r s}{N}\right] \eta_s. \end{aligned} \right\} \quad (6.3)$$

These relations can also be written as

$$\left. \begin{aligned} \xi_r &= \frac{1}{N} \sum_{s=1}^N \exp\left[-\frac{2\pi i r s}{N}\right] x_s, \\ \eta_r &= \frac{1}{N} \sum_{s=1}^N \exp\left[-\frac{2\pi i r s}{N}\right] y_s. \end{aligned} \right\} \quad (6.4)$$

as may be shown by using the equations

$$\sum_{s=1}^N \exp\left[\frac{2\pi i r s}{N}\right] = 0 \quad \text{if } 0 < r < N, \\ = N \quad \text{if } r = 0 \text{ or } r = N, \quad (6.5)$$

(referred to in § 2). Making this substitution one obtains

$$\begin{aligned} \frac{d\xi_s}{dt} &= \frac{1}{N} \sum_{s=1}^N \exp\left[-\frac{2\pi i r s}{N}\right] \left[a x_r + b y_r + \mu \left(\exp\left[-\frac{2\pi i s}{N}\right] - 2 + \exp\left[\frac{2\pi i s}{N}\right] \right) \xi_s \right] \\ &= a \xi_s + b \eta_s + \mu \left(\exp\left[-\frac{2\pi i s}{N}\right] - 2 + \exp\left[\frac{2\pi i s}{N}\right] \right) \xi_s \\ &= \left(a - 4\mu \sin^2 \frac{\pi s}{N} \right) \xi_s + b \eta_s. \end{aligned} \quad (6.6)$$

Likewise
$$\frac{d\eta_s}{dt} = c \xi_s + \left(d - 4\nu \sin^2 \frac{\pi s}{N} \right) \eta_s. \quad (6.7)$$

The equations have now been converted into a quite manageable form, with the variables separated. There are now two equations concerned with ξ_1 and η_1 , two concerned with ξ_2 and η_2 , etc. The equations themselves are also of a well-known standard form, being linear with constant coefficients. Let p_s and p'_s be the roots of the equation

$$\left(p - a + 4\mu \sin^2 \frac{\pi s}{N} \right) \left(p - d + 4\nu \sin^2 \frac{\pi s}{N} \right) = bc \quad (6.8)$$

(with $\Re p_s \geq \Re p'_s$ for definiteness), then the solution of the equations is of the form

$$\begin{cases} \xi_s = A_s e^{p_s t} + B_s e^{p'_s t}, \\ \eta_s = C_s e^{p_s t} + D_s e^{p'_s t}, \end{cases} \quad (6.9)$$

where, however, the coefficients A_s, B_s, C_s, D_s are not independent but are restricted to satisfy

$$\begin{cases} A_s \left(p_s - a + 4\mu \sin^2 \frac{\pi s}{N} \right) = b C_s, \\ B_s \left(p'_s - a + 4\mu \sin^2 \frac{\pi s}{N} \right) = b D_s. \end{cases} \quad (6.10)$$

If it should happen that $p_s = p'_s$ the equations (6.9) have to be replaced by

$$\begin{cases} \xi_s = (A_s + B_s t) e^{p_s t}, \\ \eta_s = (C_s + D_s t) e^{p_s t}. \end{cases} \quad (6.9)'$$

and (6.10) remains true. Substituting back into (6.3) and replacing the variables x_r, y_r by X_r, Y_r (the actual concentrations) the solution can be written

$$\begin{cases} X_r = h + \sum_{s=1}^N (A_s e^{p_s t} + B_s e^{p'_s t}) \exp\left[\frac{2\pi i r s}{N}\right], \\ Y_r = k + \sum_{s=1}^N (C_s e^{p_s t} + D_s e^{p'_s t}) \exp\left[\frac{2\pi i r s}{N}\right]. \end{cases} \quad (6.11)$$

Here A_s, B_s, C_s, D_s are still related by (6.10), but otherwise are arbitrary complex numbers; p_s and p'_s are the roots of (6.8).

The expression (6.11) gives the general solution of the equations (6.1) when one assumes that departures from homogeneity are sufficiently small that the functions $f(X, Y)$ and $g(X, Y)$ can safely be taken as linear. The form (6.11) given is not very informative. It will be considerably simplified in § 8. Another implicit assumption concerns random disturbing influences. Strictly speaking one should consider such influences to be continuously at work. This would make the mathematical treatment considerably more difficult without substantially altering the conclusions. The assumption which is implicit in the analysis, here and in § 8, is that the state of the system at $t = 0$ is not one of homogeneity, since it has been displaced from such a state by the disturbances; but after $t = 0$ further disturbances are ignored. In § 9 the theory is reconsidered without this latter assumption.

7. CONTINUOUS RING OF TISSUE

As an alternative to a ring of separate cells one might prefer to consider a continuous ring of tissue. In this case one can describe the position of a point of the ring by the angle θ which a radius to the point makes with a fixed reference radius. Let the diffusibilities of the two substances be μ' and ν' . These are not quite the same as μ and ν of the last section, since μ and ν are in effect referred to a cell diameter as unit of length, whereas μ' and ν' are referred to a conventional unit, the same unit in which the radius ρ of the ring is measured. Then

$$\mu = \mu' \left(\frac{N}{2\pi\rho} \right)^2, \quad \nu = \nu' \left(\frac{N}{2\pi\rho} \right)^2.$$

The equations are

$$\begin{cases} \frac{\partial X}{\partial t} = a(X-h) + b(Y-k) + \frac{\mu'}{\rho^2} \frac{\partial^2 X}{\partial \theta^2}, \\ \frac{\partial Y}{\partial t} = c(X-h) + d(Y-k) + \frac{\nu'}{\rho^2} \frac{\partial^2 Y}{\partial \theta^2}, \end{cases} \quad (7.1)$$

which will be seen to be the limiting case of (6.2). The marginal reaction rates a, b, c, d are, as before, the values at the equilibrium position of $\partial f/\partial X, \partial f/\partial Y, \partial g/\partial X, \partial g/\partial Y$. The general solution of the equations is

$$\begin{cases} X = h + \sum_{s=-\infty}^{\infty} (A_s e^{p_s t} + B_s e^{p'_s t}) e^{is\theta}, \\ Y = k + \sum_{s=-\infty}^{\infty} (C_s e^{p_s t} + D_s e^{p'_s t}) e^{is\theta}, \end{cases} \quad (7.2)$$

where p_s, p'_s are now roots of

$$\left(p - a + \frac{\mu' s^2}{\rho^2} \right) \left(p - d + \frac{\nu' s^2}{\rho^2} \right) = bc \quad (7.3)$$

and

$$\begin{cases} A_s \left(p_s - a + \frac{\mu' s^2}{\rho^2} \right) = b C_s, \\ B_s \left(p'_s - a + \frac{\mu' s^2}{\rho^2} \right) = b D_s. \end{cases} \quad (7.4)$$

This solution may be justified by considering the limiting case of the solution (6.11). Alternatively, one may observe that the formula proposed is a solution, so that it only remains to prove that it is the most general one. This will follow if values of A_s, B_s, C_s, D_s can be found

to fit any given initial conditions. It is well known that any function of an angle (such as X) can be expanded as a 'Fourier series'

$$X(\theta) = \sum_{s=-\infty}^{\infty} G_s e^{is\theta} \quad (X(\theta) \text{ being values of } X \text{ at } t = 0),$$

provided, for instance, that its first derivative is continuous. If also

$$Y(\theta) = \sum_{s=-\infty}^{\infty} H_s e^{is\theta} \quad (Y(\theta) \text{ being values of } Y \text{ at } t = 0),$$

then the required initial conditions are satisfied provided $A_s + B_s = G_s$ and $C_s + D_s = H_s$. Values A_s, B_s, C_s, D_s to satisfy these conditions can be found unless $p_s = p'_s$. This is an exceptional case and its solution if required may be found as the limit of the normal case.

8. TYPES OF ASYMPTOTIC BEHAVIOUR IN THE RING AFTER A LAPSE OF TIME

As the reader was reminded in § 2, after a lapse of time the behaviour of an expression of the form of (6.11) is eventually dominated by the terms for which the corresponding p_s has the largest real part. There may, however, be several terms for which this real part has the same value, and these terms will together dominate the situation, the other terms being ignored by comparison. There will, in fact, normally be either two or four such 'leading' terms. For if p_{s_0} is one of them then $p_{N-s_0} = p_{s_0}$, since

$$\sin^2 \frac{\pi(N-s_0)}{N} = \sin^2 \frac{\pi s_0}{N},$$

so that p_{s_0} and p_{N-s_0} are roots of the same equation (6.8). If also p_{s_0} is complex then $\Re p_{s_0} = \Re p'_{s_0}$, and so in all

$$\Re p_{s_0} = \Re p'_{s_0} = \Re p_{N-s_0} = \Re p'_{N-s_0}.$$

One need not, however, normally anticipate that any further terms will have to be included. If p_{s_0} and p_{s_1} are to have the same real part, then, unless $s_1 = s_0$ or $s_0 + s_1 = N$ the quantities a, b, c, d, μ, ν will be restricted to satisfy some special condition, which they would be unlikely to satisfy by chance. It is possible to find circumstances in which as many as ten terms have to be included if such special conditions are satisfied, but these have no particular physical or biological importance. It is assumed below that none of these chance relations hold.

It has already been seen that it is necessary to distinguish the cases where the value of p_{s_0} for one of the dominant terms is real from those where it is complex. These may be called respectively the *stationary* and the *oscillatory* cases.

Stationary case. After a sufficient lapse of time $X_r - h$ and $Y_r - k$ approach asymptotically to the forms

$$\left. \begin{aligned} X_r - h &= 2\Re A_{s_0} \exp \left[\frac{2\pi i s_0 r}{N} + It \right], \\ Y_r - k &= 2\Re C_{s_0} \exp \left[\frac{2\pi i s_0 r}{N} + It \right]. \end{aligned} \right\} \quad (8.1)$$

Oscillatory case. After a sufficient lapse of time $X_r - h$ and $Y_r - k$ approach the forms

$$\left. \begin{aligned} X_r - h &= 2e^{It} \Re \left\{ A_{s_0} \exp \left[\frac{2\pi i s_0 r}{N} + i\omega t \right] + A_{N-s_0} \exp \left[-\frac{2\pi i s_0 r}{N} - i\omega t \right] \right\}, \\ Y_r - k &= 2e^{It} \Re \left\{ C_{s_0} \exp \left[\frac{2\pi i s_0 r}{N} + i\omega t \right] + C_{N-s_0} \exp \left[-\frac{2\pi i s_0 r}{N} - i\omega t \right] \right\}. \end{aligned} \right\} \quad (8.2)$$