

The real part of p_{s_0} has been represented by I , standing for 'instability', and in the oscillatory case its imaginary part is ω . By the use of the \mathcal{R} operation (real part of), two terms have in each case been combined in one.

The meaning of these formulae may be conveniently described in terms of waves. In the stationary case there are stationary waves on the ring having s_0 lobes or crests. The coefficients A_{s_0} and C_{s_0} are in a definite ratio given by (6.10), so that the pattern for one morphogen determines that for the other. With the lapse of time the waves become more pronounced provided there is genuine instability, i.e. if I is positive. The wave-length of the waves may be obtained by dividing the number of lobes into the circumference of the ring. In the oscillatory case the interpretation is similar, but the waves are now not stationary but travelling. As well as having a wave-length they have a velocity and a frequency. The frequency is $\omega/2\pi$, and the velocity is obtained by multiplying the wave-length by the frequency. There are two wave trains moving round the ring in opposite directions.

The wave-lengths of the patterns on the ring do not depend only on the chemical data a, b, c, d, μ', ν' but on the circumference of the ring, since they must be submultiples of the latter. There is a sense, however, in which there is a 'chemical wave-length' which does not depend on the dimensions of the ring. This may be described as the limit to which the wave-lengths tend when the rings are made successively larger. Alternatively (at any rate in the case of continuous tissue), it may be described as the wave-length when the radius is chosen to give the largest possible instability I . One may picture the situation by supposing that the chemical wave-length is true wave-length which is achieved whenever possible, but that on a ring it is necessary to 'make do' with an approximation which divides exactly into the circumference.

Although all the possibilities are covered by the stationary and oscillatory alternatives there are special cases of them which deserve to be treated separately. One of these occurs when $s_0 = 0$, and may be described as the 'case of extreme long wave-length', though this term may perhaps preferably be reserved to describe the chemical data when they are such that s_0 is zero whatever the dimensions of the ring. There is also the case of 'extreme short wave-length'. This means that $\sin^2(\pi s_0/N)$ is as large as possible, which is achieved by s_0 being either $\frac{1}{2}N$, or $\frac{1}{2}(N-1)$. If the remaining possibilities are regarded as forming the 'case of finite wave-length', there are six subcases altogether. It will be shown that each of these really can occur, although two of them require three or more morphogens for their realization.

(a) *Stationary case with extreme long wave-length.* This occurs for instance if $\mu = \nu = \frac{1}{4}$, $b = c = 1$, $a = d$. Then $p_s = a - \sin^2 \frac{\pi s}{N} + 1$. This is certainly real and is greatest when $s = 0$.

In this case the contents of all the cells are the same; there is no resultant flow from cell to cell due to diffusion, so that each is behaving as if it were isolated. Each is in unstable equilibrium, and slips out of it in synchronism with the others.

(b) *Oscillatory case with extreme long wave-length.* This occurs, for instance, if $\mu = \nu = \frac{1}{4}$, $b = -c = 1$, $a = d$. Then $p_s = a - \sin^2 \frac{\pi s}{N} \pm i$. This is complex and its real part is greatest when $s = 0$. As in case (a) each cell behaves as if it were isolated. The difference from case (a) is that the departure from the equilibrium is oscillatory.

(c) *Stationary waves of extreme short wave-length.* This occurs, for instance, if $\nu = 0$, $\mu = 1$, $d = I$, $a = I - 1$, $b = -c = 1$. p_s is

$$I - \frac{1}{2} - 2 \sin^2 \frac{\pi s}{N} + \sqrt{\left(2 \sin^2 \frac{\pi s}{N} + \frac{1}{2}\right)^2 - 1},$$

and is greatest when $\sin^2(\pi s/N)$ is greatest. If N is even the contents of each cell are similar to those of the next but one, but distinctly different from those of its immediate neighbours. If, however, the number of cells is odd this arrangement is impossible, and the magnitude of the difference between neighbouring cells varies round the ring, from zero at one point to a maximum at a point diametrically opposite.

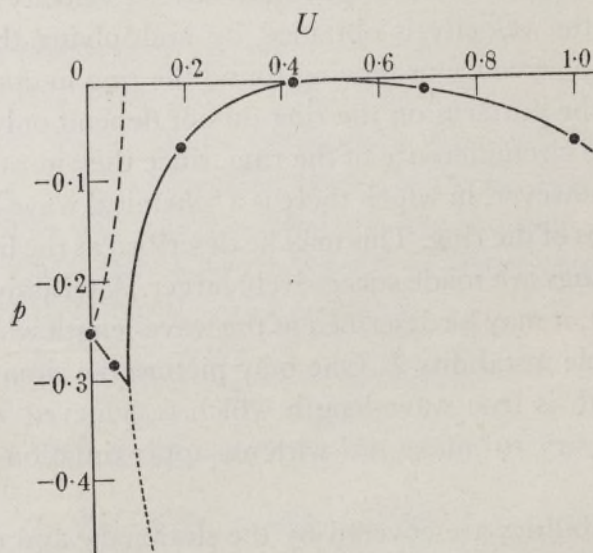


FIGURE 1. Values of $\mathcal{R}p$ (instability or growth rate), and $|\mathcal{I}p|$ (radian frequency of oscillation), related to wave-length $2\pi U^{-\frac{1}{2}}$ as in the relation (8.3) with $I=0$. This is a case of stationary waves with finite wave-length. Full line, $\mathcal{R}p$; broken line, $-|\mathcal{I}p|$ (zero for $U > 0.071$); dotted line, $\mathcal{R}p'$. The full circles on the curve for $\mathcal{R}p$ indicate the values of U, p actually achievable on the finite ring considered in §10, with $s=0$ on the extreme left, $s=5$ on the right.

(d) *Stationary waves of finite wave-length.* This is the case which is of greatest interest, and has most biological application. It occurs, for instance, if $a = I - 2$, $b = 2.5$, $c = -1.25$, $d = I + 1.5$, $\mu' = 1$, $\nu' = \frac{1}{2}$, and $\frac{\mu}{\mu'} = \frac{\nu}{\nu'} = \left(\frac{N}{2\pi\rho}\right)^2$. As before ρ is the radius of the ring, and N the number of cells in it. If one writes U for $\left(\frac{N}{\pi\rho}\right)^2 \sin^2 \frac{\pi s}{N}$, then equation (6.8) can, with these special values, be written

$$(p-I)^2 + \left(\frac{1}{2} + \frac{3}{2}U\right)(p-I) + \frac{1}{2}\left(U - \frac{1}{2}\right)^2 = 0. \quad (8.3)$$

This has a solution $p = I$ if $U = \frac{1}{2}$. On the other hand, it will be shown that if U has any other (positive) value then both roots for $p-I$ have negative real parts. Their product is positive being $\frac{1}{2}\left(U - \frac{1}{2}\right)^2$, so that if they are real they both have the same sign. Their sum in this case is $-\frac{1}{2} - \frac{3}{2}U$ which is negative. Their common sign is therefore negative. If, however, the roots are complex their real parts are both equal to $-\frac{1}{4} - \frac{3}{4}U$, which is negative.

If the radius ρ of the ring be chosen so that for some integer s_0 , $\frac{1}{2} = U = \left(\frac{N}{\pi\rho}\right)^2 \sin^2 \frac{\pi s_0}{N}$, there will be stationary waves with s_0 lobes and a wave-length which is also equal to the chemical wave-length, for p_{s_0} will be equal to I , whereas every other p_s will have a real part smaller than I . If, however, the radius is chosen so that $\left(\frac{N}{\pi\rho}\right)^2 \sin^2 \frac{\pi s}{N} = \frac{1}{2}$ cannot hold with an integral s , then (in this example) the actual number of lobes will be one of the two integers nearest to the (non-integral) solutions of this equation, and usually the nearest. Examples can, however, be constructed where this simple rule does not apply.

Figure 1 shows the relation (8.3) in graphical form. The curved portions of the graphs are hyperbolae.

The two remaining possibilities can only occur with three or more morphogens. With one morphogen the only possibility is (a).

(e) *Oscillatory case with a finite wave-length.* This means that there are genuine travelling waves. Since the example to be given involves three morphogens it is not possible to use the formulae of § 6. Instead, one must use the corresponding three morphogen formulae. That which corresponds to (6.8) or (7.3) is most conveniently written as

$$\begin{vmatrix} a_{11} - p - \mu_1 U & a_{12} & a_{13} \\ a_{21} & a_{22} - p - \mu_2 U & a_{23} \\ a_{31} & a_{32} & a_{33} - p - \mu_3 U \end{vmatrix} = 0, \quad (8.4)$$

where again U has been written for $\left(\frac{N}{\pi\rho}\right)^2 \sin^2 \frac{\pi s}{N}$. (This means essentially that $U = \left(\frac{2\pi}{\lambda}\right)^2$, where λ is the wave-length.) The four marginal reactivities are superseded by nine a_{11}, \dots, a_{33} , and the three diffusibilities are μ_1, μ_2, μ_3 . Special values leading to travelling waves are

$$\left. \begin{array}{lll} \mu_1 = \frac{2}{3}, & \mu_2 = \frac{1}{3}, & \mu_3 = 0 \\ a_{11} = -\frac{10}{3}, & a_{12} = 3, & a_{13} = -1, \\ a_{21} = -2, & a_{22} = \frac{7}{3}, & a_{23} = 0, \\ a_{31} = 3, & a_{32} = -4, & a_{33} = 0, \end{array} \right\} \quad (8.5)$$

and with them (8.4) reduces to

$$p^3 + p^2(U+1) + p(1 + \frac{2}{9}(U-1)^2) + U+1 = 0. \quad (8.6)$$

If $U = 1$ the roots are $\pm i$ and -2 . If U is near to I they are approximately $-1-U$ and $\pm i + \frac{(U-1)^2}{18}(\pm i - 1)$, and all have negative real parts. If the greatest real part is not the value zero, achieved with $U = 1$, then the value zero must be reached again at some intermediate value of U . Since P is then pure imaginary the even terms of (8.6) must vanish, i.e. $(p^2+1)(U+1) = 0$. But this can only happen if $p = \pm i$, and the vanishing of the odd terms then shows that $U = 1$. Hence zero is the largest real part for any root p of (8.6). The corresponding p is $\pm i$ and U is 1. This means that there are travelling waves with unit (chemical) radian frequency and unit (chemical) velocity. If I is added to a_{11} , a_{22} and a_{33} , the instability will become I in place of zero.

(f) Oscillatory case with extreme short wave-length. This means that there is metabolic oscillation with neighbouring cells nearly 180° out of phase. It can be achieved with three morphogens and the following chemical data:

$$\left. \begin{aligned} \mu &= 1, & \mu_2 &= \mu_3 = 0, \\ a_{11} &= -1, & a_{12} &= -1, & a_{13} &= 0, \\ a_{21} &= 1, & a_{22} &= 0, & a_{23} &= -1, \\ a_{31} &= 0, & a_{32} &= 1, & a_{33} &= 0. \end{aligned} \right\} \quad (8.7)$$

With these values (8.4) reduces to

$$p^3 + p^2(U+1) + 2p + U + 1 = 0. \quad (8.8)$$

This may be shown to have all the real parts of its roots negative if $U \geq 0$, for if $U = 0$ the roots are near to -0.6 , $-0.2 \pm 1.3i$, and if U be continuously increased the values of p will alter continuously. If they ever attain values with a positive real part they must pass through pure imaginary values (or zero). But if p is pure imaginary $p^3 + 2p$ and $(p^2 + 1)(U + 1)$ must both vanish, which is impossible if $U \geq 0$. As U approaches infinity, however, one of the roots approaches i . Thus $\Re p = 0$ can be approached as closely as desired by large values of U , but not attained.

9. FURTHER CONSIDERATION OF THE MATHEMATICS OF THE RING

In this section some of the finer points concerning the development of wave patterns are considered. These will be of interest mainly to those who wish to do further research on the subject, and can well be omitted on a first reading.

(1) *General formulae for the two morphogen case.* Taking the limiting case of a ring of large radius (or a filament), one may write $\left(\frac{N}{\pi\rho}\right)^2 \sin^2 \frac{\pi s}{N} = U = \left(\frac{2\pi}{\lambda}\right)^2$ in (6.11) or $\frac{s^2}{\rho^2} = U = \left(\frac{2\pi}{\lambda}\right)^2$ in (7.3) and obtain

$$(p - a + \mu'U)(p - d + v'U) = bc, \quad (9.1)$$

which has the solution

$$p = \frac{a+d}{2} - \frac{\mu'+v'}{2}U \pm \sqrt{\left\{\left(\frac{\mu'-v'}{2}U + \frac{d-a}{2}\right)^2 + bc\right\}}. \quad (9.2)$$

One may put $I(U)$ for the real part of this, representing the instability for waves of wave-length $\lambda = 2\pi U^{-\frac{1}{2}}$. The dominant waves correspond to the maximum of $I(U)$. This maximum may either be at $U = 0$ or $U = \infty$ or at a stationary point on the part of the curve which is hyperbolic (rather than straight). When this last case occurs the values of p (or I) and U at the maximum are

$$\left. \begin{aligned} p = I &= (d\mu' - av' - 2\sqrt{(\mu'v')}\sqrt{-bc})(\mu' - v')^{-1}, \\ U &= \left(a - d + \frac{\mu' + v'}{\sqrt{(\mu'v')}}\sqrt{-bc}\right)(\mu' - v')^{-1}. \end{aligned} \right\} \quad (9.3)$$

The conditions which lead to the four cases (a), (b), (c), (d) described in the last section are

(a) (Stationary waves of extreme long wave-length.) This occurs if either

$$(i) \ bc > 0, \quad (ii) \ bc < 0 \text{ and } \frac{d-a}{\sqrt{(-bc)}} > \frac{\mu'+v'}{\sqrt{(\mu'v')}}, \quad (iii) \ bc < 0 \text{ and } \frac{d-a}{\sqrt{(-bc)}} < -2.$$

The condition for instability in either case is that either $bc > ad$ or $a + d > 0$.

(b) (Oscillating case with extreme long wave-length, i.e. synchronized oscillations.) This occurs if

$$bc < 0 \quad \text{and} \quad -2 < \frac{d-a}{\sqrt{(-bc)}} < \frac{4\sqrt{(\mu'v')}}{\mu'+v'}.$$

There is instability if in addition $a+d > 0$.

(c) (Stationary waves of extreme short wave-length.) This occurs if $bc < 0$, $\mu' > v' = 0$. There is instability if, in addition, $a+d > 0$.

(d) (Stationary waves of finite wave-length.) This occurs if

$$bc < 0 \quad \text{and} \quad \frac{4\sqrt{(\mu'v')}}{\mu'+v'} < \frac{d-a}{\sqrt{(-bc)}} < \frac{\mu'+v'}{\sqrt{(\mu'v')}}, \quad (9.4a)$$

and there is instability if also

$$\frac{d}{\sqrt{(-bc)}} \sqrt{\frac{\mu'}{v'}} - \frac{a}{\sqrt{(-bc)}} \sqrt{\frac{v'}{\mu'}} > 2. \quad (9.4b)$$

It has been assumed that $v' \leq \mu' > 0$. The case where $\mu' \leq v' > 0$ can be obtained by interchanging the two morphogens. In the case $\mu' = v' = 0$ there is no co-operation between the cells whatever.

Some additional formulae will be given for the case of stationary waves of finite wave-length. The marginal reaction rates may be expressed parametrically in terms of the diffusibilities, the wave-length, the instability, and two other parameters α and χ . Of these α may be described as the ratio of $X-h$ to $Y-k$ in the waves. The expressions for the marginal reaction rates in terms of these parameters are

$$\left. \begin{aligned} a &= \mu'(v'-\mu')^{-1}(2v'U_0+\chi)+I, \\ b &= \mu'(v'-\mu')^{-1}((\mu'+v')U_0+\chi)\alpha, \\ c &= v'(\mu'-v')^{-1}((\mu'+v')U_0+\chi)\alpha^{-1}, \\ d &= v'(\mu'-v')^{-1}(2\mu'U_0+\chi)+I, \end{aligned} \right\} \quad (9.5)$$

and when these are substituted into (9.2) it becomes

$$p = I - \frac{1}{2}\chi - \frac{\mu'+v'}{2}U + \sqrt{\left(\left(\frac{\mu'+v'}{2}U + \frac{1}{2}\chi\right)^2 - \mu'v'(U-U_0)^2\right)}. \quad (9.6)$$

Here $2\pi U_0^{-\frac{1}{2}}$ is the chemical wave-length and $2\pi U^{-\frac{1}{2}}$ the wave-length of the Fourier component under consideration. χ must be positive for case (d) to apply.

If s be regarded as a continuous variable one can consider (9.2) or (9.6) as relating s to p , and dp/ds and d^2p/ds^2 have meaning. The value of d^2p/ds^2 at the maximum is of some interest, and will be used below in this section. Its value is

$$\frac{d^2p}{ds^2} = -\frac{\sqrt{(\mu'v')}}{\rho^2} \cdot \frac{8\sqrt{(\mu'v')}}{\mu'+v'} \cos^2 \frac{\pi s}{N} (1 + \chi U_0^{-1}(\mu'+v')^{-1})^{-1}. \quad (9.7)$$

(2) In §§ 6, 7, 8 it was supposed that the disturbances were not continuously operative, and that the marginal reaction rates did not change with the passage of time. These assumptions will now be dropped, though it will be necessary to make some other, less drastic,

approximations to replace them. The (statistical) amplitude of the 'noise' disturbances will be assumed constant in time. Instead of (6.6), (6.7), one then has

$$\left. \begin{aligned} \frac{d\xi}{dt} &= a'\xi + b\eta + R_1(t), \\ \frac{d\eta}{dt} &= c\xi + d'\eta + R_2(t), \end{aligned} \right\} \quad (9.8)$$

where ξ, η have been written for ξ_s, η_s since s may now be supposed fixed. For the same reason $a - 4\mu \sin^2 \frac{\pi s}{N}$ has been replaced by a' and $d - 4\nu \sin^2 \frac{\pi s}{N}$ by d' . The noise disturbances may be supposed to constitute white noise, i.e. if (t_1, t_2) and (t_3, t_4) are two non-overlapping intervals then $\int_{t_1}^{t_2} R_1(t) dt$ and $\int_{t_3}^{t_4} R_2(t) dt$ are statistically independent and each is normally distributed with variances $\beta_1(t_2 - t_1)$ and $\beta_1(t_4 - t_3)$ respectively, β_1 being a constant describing the amplitude of the noise. Likewise for $R_2(t)$, the constant β_1 being replaced by β_2 . If p and p' are the roots of $(p - a')(p - d') = bc$ and p is the greater (both being real), one can make the substitution

$$\left. \begin{aligned} \xi &= b(u + v), \\ \eta &= (p - a')u + (p' - a')v, \end{aligned} \right\} \quad (9.9)$$

which transforms (9.8) into

$$\frac{du}{dt} = pu + \frac{p' - a'}{(p' - p)b} R_1(t) - \frac{R_2(t)}{p' - p} + \xi \frac{d}{dt} \left(\frac{p' - a'}{(p' - p)b} \right) - \eta \frac{d}{dt} \left(\frac{1}{p' - p} \right), \quad (9.11)$$

with a similar equation for v , of which the leading terms are $dv/dt = p'v$. This indicates that v will be small, or at least small in comparison with u after a lapse of time. If it is assumed that $v = 0$ holds (9.11) may be written

$$\frac{du}{dt} = qu + L_1(t) R_1(t) + L_2(t) R_2(t), \quad (9.12)$$

where
$$L_1(t) = \frac{p' - a'}{(p' - p)b}, \quad L_2(t) = \frac{1}{p' - p}, \quad q = p + bL_1'(t). \quad (9.13)$$

The solution of this equation is

$$u = \int_{-\infty}^t (L_1(w) R_1(w) + L_2(w) R_2(w)) \exp \left[\int_w^t q(z) dz \right] dw. \quad (9.14)$$

One is, however, not so much interested in such a solution in terms of the statistical disturbances as in the consequent statistical distribution of values of u, ξ and η at various times after instability has set in. In view of the properties of 'white noise' assumed above, the values of u at time t will be distributed according to the normal error law, with the variance

$$\int_{-\infty}^t [\beta_1(L_1(w))^2 + \beta_2(L_2(w))^2] \exp \left[2 \int_w^t q(z) dz \right] dw. \quad (9.15)$$

There are two commonly occurring cases in which one can simplify this expression considerably without great loss of accuracy. If the system is in a distinctly stable state, then $q(t)$,

which is near to $p(t)$, will be distinctly negative, and $\exp \left[\int_w^t q(z) dz \right]$ will be small unless w is near to t . But then $L_1(w)$ and $L_2(w)$ may be replaced by $L_1(t)$ and $L_2(t)$ in the integral, and also $q(z)$ may be replaced by $q(t)$. With these approximations the variance is

$$(-2q(t))^{-1} [\beta_1(L_1(t))^2 + \beta_2(L_2(t))^2]. \quad (9.16)$$

A second case where there is a convenient approximation concerns times when the system is unstable, so that $q(t) > 0$. For the approximation concerned to apply $2 \int_w^t q(z) dz$ must have its maximum at the last moment $w (= t_0)$ when $q(t_0) = 0$, and it must be the maximum by a considerable margin (e.g. at least 5) over all other local maxima. These conditions would apply for instance if $q(z)$ were always increasing and had negative values at a sufficiently early time. One also requires $q'(t_0)$ (the rate of increase of q at time t_0) to be reasonably large; it must at least be so large that over a period of time of length $(q'(t_0))^{-\frac{1}{2}}$ near to t_0 the changes in $L_1(t)$ and $L_2(t)$ are small, and $q'(t)$ itself must not appreciably alter in this period. Under these circumstances the integrand is negligible when w is considerably different from t_0 , in comparison with its values at that time, and therefore one may replace $L_1(w)$ and $L_2(w)$ by $L_1(t_0)$ and $L_2(t_0)$, and $q'(w)$ by $q'(t_0)$. This gives the value

$$\sqrt{\pi} (q'(t_0))^{-\frac{1}{2}} [\beta_1(L_1(t_0))^2 + \beta_2(L_2(t_0))^2] \exp \left[2 \int_{t_0}^t q(z) dz \right], \quad (9.17)$$

for the variance of u .

The physical significance of this latter approximation is that the disturbances near the time when the instability is zero are the only ones which have any appreciable ultimate effect. Those which occur earlier are damped out by the subsequent period of stability. Those which occur later have a shorter period of instability within which to develop to greater amplitude. This principle is familiar in radio, and is fundamental to the theory of the superregenerative receiver.

Naturally one does not often wish to calculate the expression (9.17), but it is valuable as justifying a common-sense point of view of the matter. The factor $\exp \left[\int_{t_0}^t q(z) dz \right]$ is essentially the integrated instability and describes the extent to which one would expect disturbances of appropriate wave-length to grow between times t_0 and t . Taking the terms in β_1, β_2 into consideration separately, the factor $\sqrt{\pi} \beta_1 (q'(t_0))^{-\frac{1}{2}} (L_1(t_0))^2$ indicates that the disturbances on the first morphogen should be regarded as lasting for a time

$$\sqrt{\pi} (q_1(t_0))^{-\frac{1}{2}} (bL_1(t_0))^2.$$

The dimensionless quantities $bL_1(t_0), bL_2(t_0)$ will not usually be sufficiently large or small to justify their detailed calculation.

(3) The extent to which the component for which p_s is greatest may be expected to out-distance the others will now be considered in case (d). The greatest of the p_s will be called p_{s_0} . The two closest competitors to s_0 will be $s_0 - 1$ and $s_0 + 1$; it is required to determine how close the competition is. If the variation in the chemical data is sufficiently small it may be assumed that, although the exponents $p_{s_0-1}, p_{s_0}, p_{s_0+1}$ may themselves vary appreciably in time, the differences $p_{s_0} - p_{s_0-1}$ and $p_{s_0} - p_{s_0+1}$ are constant. It certainly can happen that

one of these differences is zero or nearly zero, and there is then 'neck and neck' competition. The weakest competition occurs when $p_{s_0-1} = p_{s_0+1}$. In this case

$$p_{s_0} - p_{s_0-1} = p_{s_0} - p_{s_0+1} = -\frac{1}{2}(p_{s_0+1} - 2p_{s_0} + p_{s_0-1}).$$

But if s_0 is reasonably large $p_{s_0+1} - 2p_{s_0} + p_{s_0-1}$ can be set equal to $(d^2p/ds^2)_{s=s_0}$. It may be concluded that the rate at which the most quickly growing component grows cannot exceed the rate for its closest competitor by more than about $\frac{1}{2}(d^2p/ds^2)_{s=s_0}$. The formula (9.7), by which d^2p/ds^2 can be estimated, may be regarded as the product of two factors. The dimensionless factor never exceeds 4. The factor $\sqrt{(\mu'\nu')/\rho^2}$ may be described in very rough terms as 'the reciprocal of the time for the morphogens to diffuse a length equal to a radius'. In equally rough terms one may say that a time of this order of magnitude is required for the most quickly growing component to get a lead, amounting to a factor whose logarithm is of the order of unity, over its closest competitors, in the favourable case where $p_{s_0-1} = p_{s_0+1}$.

(4) Very little has yet been said about the effect of considering non-linear reaction rate functions when far from homogeneity. Any treatment so systematic as that given for the linear case seems to be out of the question. It is possible, however, to reach some qualitative conclusions about the effects of non-linear terms. Suppose that z_1 is the amplitude of the Fourier component which is most unstable (on a basis of the linear terms), and which may be supposed to have wave-length λ . The non-linear terms will cause components with wave-lengths $\frac{1}{2}\lambda, \frac{1}{3}\lambda, \frac{1}{4}\lambda, \dots$ to appear as well as a space-independent component. If only quadratic terms are taken into account and if these are somewhat small, then the component of wave-length $\frac{1}{2}\lambda$ and the space-independent component will be the strongest. Suppose these have amplitudes z_2 and z_1 . The state of the system is thus being described by the numbers z_0, z_1, z_2 . In the absence of non-linear terms they would satisfy equations

$$\frac{dz_0}{dt} = p_0 z_0, \quad \frac{dz_1}{dt} = p_1 z_1, \quad \frac{dz_2}{dt} = p_2 z_2,$$

and if there is slight instability p_1 would be a small positive number, but p_0 and p_2 distinctly negative. The effect of the non-linear terms is to replace these equations by ones of the form

$$\frac{dz_0}{dt} = p_0 z_0 + Az_1^2 + Bz_2^2,$$

$$\frac{dz_1}{dt} = p_1 z_1 + Cz_2 z_1 + Dz_0 z_1,$$

$$\frac{dz_2}{dt} = p_2 z_2 + Ez_1^2 + Fz_0 z_2.$$

As a first approximation one may put $dz_0/dt = dz_2/dt = 0$ and ignore z_1^4 and higher powers; z_0 and z_1 are then found to be proportional to z_1^2 , and the equation for z_1 can be written $dz_1/dt = p_0 z_1 - kz_1^3$. The sign of k in this differential equation is of great importance. If it is positive, then the effect of the term kz_1^3 is to arrest the exponential growth of z_1 at the value $\sqrt{(p_1/k)}$. The 'instability' is then very confined in its effect, for the waves can only reach a finite amplitude, and this amplitude tends to zero as the instability (p_1) tends to zero. If, however, k is negative the growth becomes something even faster than exponential, and, if the equation $dz_1/dt = p_1 z_1 - kz_1^3$ held universally, it would result in the amplitude becoming

infinite in a finite time. This phenomenon may be called 'catastrophic instability'. In the case of two-dimensional systems catastrophic instability is almost universal, and the corresponding equation takes the form $dz_1/dt = p_1 z_1 + k z_1^2$. Naturally enough in the case of catastrophic instability the amplitude does not really reach infinity, but when it is sufficiently large some effect previously ignored becomes large enough to halt the growth.

(5) Case (a) as described in § 8 represents a most extremely featureless form of pattern development. This may be remedied quite simply by making less drastic simplifying assumptions, so that a less gross account of the pattern can be given by the theory. It was assumed in § 9 that only the most unstable Fourier components would contribute appreciably to the pattern, though it was seen above (heading (3) of this section) that (in case (d)) this will only apply if the period of time involved is adequate to permit the morphogens, supposed for this purpose to be chemically inactive, to diffuse over the whole ring or organ concerned. The same may be shown to apply for case (a). If this assumption is dropped a much more interesting form of pattern can be accounted for. To do this it is necessary to consider not merely the components with $U = 0$ but some others with small positive values of U . One may assume the form $At - BU$ for p . Linearity in U is assumed because only small values of U are concerned, and the term At is included to represent the steady increase in instability. By measuring time from the moment of zero instability the necessity for a constant term is avoided. The formula (9.17) may be applied to estimate the statistical distribution of the amplitudes of the components. Only the factor $\exp \left[2 \int_{t_0}^t q(z) dz \right]$ will depend very much on U , and taking $q(t) = p(t) = At - BU$, t_0 must be BU/A and the factor is

$$\exp [A(t - BU/A)^2].$$

The term in U^2 can be ignored if At^2 is fairly large, for then either $B^2 U^2 / A^2$ is small or the factor e^{-BUt} is. But At^2 certainly is large if the factor e^{At^2} , applying when $U = 0$, is large. With this approximation the variance takes the form $C e^{-\frac{1}{2} k^2 U}$, with only the two parameters C, k to distinguish the pattern populations. By choosing appropriate units of concentration and length these pattern populations may all be reduced to a standard one, e.g. with $C = k = 1$. Random members of this population may be produced by considering any one of the type (a) systems to which the approximations used above apply. They are also produced, but with only a very small amplitude scale, if a homogeneous one-morphogen system undergoes random disturbances without diffusion for a period, and then diffusion without disturbance. This process is very convenient for computation, and can also be applied to two dimensions. Figure 2 shows such a pattern, obtained in a few hours by a manual computation.

To be more definite a set of numbers $u_{r,s}$ was chosen, each being ± 1 , and taking the two values with equal probability. A function $f(x, y)$ is related to these numbers by the formula

$$f(x, y) = \sum u_{r,s} \exp \left[-\frac{1}{2} ((x - hr)^2 + (y - hs)^2) \right].$$

In the actual computation a somewhat crude approximation to the function

$$\exp \left[-\frac{1}{2} (x^2 + y^2) \right]$$

was used and h was about 0.7. In the figure the set of points where $f(x, y)$ is positive is shown black. The outlines of the black patches are somewhat less irregular than they should be due to an inadequacy in the computation procedure.

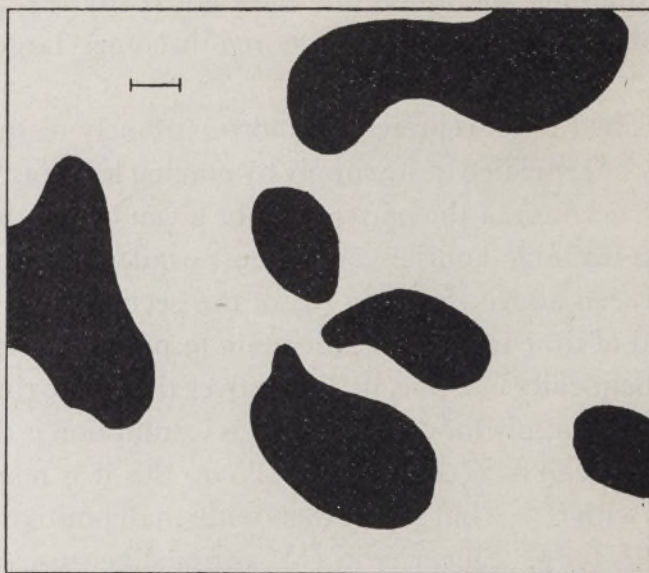


FIGURE 2. An example of a 'dappled' pattern as resulting from a type (a) morphogen system. A marker of unit length is shown. See text, §9, 11.

10. A NUMERICAL EXAMPLE

The numerous approximations and assumptions that have been made in the foregoing analysis may be rather confusing to many readers. In the present section it is proposed to consider in detail a single example of the case of most interest, (d). This will be made as specific as possible. It is unfortunately not possible to specify actual chemical reactions with the required properties, but it is thought that the reaction rates associated with the imagined reactions are not unreasonable.

The detail to be specified includes

- (i) The number and dimensions of the cells of the ring.
- (ii) The diffusibilities of the morphogens.
- (iii) The reactions concerned.
- (iv) The rates at which the reactions occur.
- (v) Information about random disturbances.
- (vi) Information about the distribution, in space and time, of those morphogens which are of the nature of evocators.

These will be taken in order.

(i) It will be assumed that there are twenty cells in the ring, and that they have a diameter of 0.1 mm each. These cells are certainly on the large rather than the small side, but by no means impossibly so. The number of cells in the ring has been chosen rather small in order that it should not be necessary to make the approximation of continuous tissue.

(ii) Two morphogens are considered. They will be called X and Y , and the same letters will be used for their concentrations. This will not lead to any real confusion. The diffusion constant for X will be assumed to be $5 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$ and that for Y to be $2.5 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$. With cells of diameter 0.01 cm this means that X flows between neighbouring cells at the