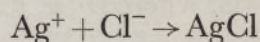


The relative degrees of difficulty of the various sections are believed to be as follows. Those who are unable to follow the points made in this section should only attempt §§ 3, 4, 11, 12, 14 and part of § 13. Those who can just understand this section should profit also from §§ 7, 8, 9. The remainder, §§ 5, 10, 13, will probably only be understood by those definitely trained as mathematicians.

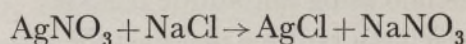
3. CHEMICAL REACTIONS

It has been explained in a preceding section that the system to be considered consists of a number of chemical substances (morphogens) diffusing through a mass of tissue of given geometrical form and reacting together within it. What laws are to control the development of this situation? They are quite simple. The diffusion follows the ordinary laws of diffusion, i.e. each morphogen moves from regions of greater to regions of less concentration, at a rate proportional to the gradient of the concentration, and also proportional to the 'diffusibility' of the substance. This is very like the conduction of heat, diffusibility taking the place of conductivity. If it were not for the walls of the cells the diffusibilities would be inversely proportional to the square roots of the molecular weights. The pores of the cell walls put a further handicap on the movement of the larger molecules in addition to that imposed by their inertia, and most of them are not able to pass through the walls at all.

The reaction rates will be assumed to obey the 'law of mass action'. This states that the rate at which a reaction takes place is proportional to the concentrations of the reacting substances. Thus, for instance, the rate at which silver chloride will be formed and precipitated from a solution of silver nitrate and sodium chloride by the reaction



will be proportional to the product of the concentrations of the silver ion Ag^+ and the chloride ion Cl^- . It should be noticed that the equation



is not used because it does not correspond to an actual reaction but to the final outcome of a number of reactions. The law of mass action must only be applied to the *actual* reactions. Very often certain substances appear in the individual reactions of a group, but not in the final outcome. For instance, a reaction $A \rightarrow B$ may really take the form of two steps $A + G \rightarrow C$ and $C \rightarrow B + G$. In such a case the substance G is described as a catalyst, and as catalyzing the reaction $A \rightarrow B$. (Catalysis according to this plan has been considered in detail by Michaelis & Menten (1913).) The effect of the genes is presumably achieved almost entirely by catalysis. They are certainly not permanently used up in the reactions.

Sometimes one can regard the effect of a catalyst as merely altering a reaction rate. Consider, for example, the case mentioned above, but suppose also that A can become detached from G , i.e. that the reaction $C \rightarrow A + G$ is taken into account. Also suppose that the reactions $A + G \rightleftharpoons C$ both proceed much faster than $C \rightarrow B + G$. Then the concentrations of A , G , C will be related by the condition that there is equilibrium between the reactions $A + G \rightleftharpoons C$ and $C \rightarrow A + G$, so that (denoting concentrations by square brackets) $[A][G] = k[C]$ for some constant k . The reaction $C \rightarrow B + G$ will of course proceed at a rate proportional to $[C]$, i.e. to $[A][G]$. If the amount of C is always small compared with the amount of G one can say that the presence of the catalyst and its amount merely alter the mass action constant

for the reaction $A \rightarrow B$, for the whole proceeds at a rate proportional to $[A]$. This situation does not, however, hold invariably. It may well happen that nearly all of G takes the combined form C so long as any of A is left. In this case the reaction proceeds at a rate independent of the concentration of A until A is entirely consumed. In either of these cases the rate of the complete group of reactions depends only on the concentrations of the reagents, although usually not according to the law of mass action applied crudely to the chemical equation for the whole group. The same applies in any case where all reactions of the group with one exception proceed at speeds much greater than that of the exceptional one. In these cases the rate of the reaction is a function of the concentrations of the reagents. More generally again, no such approximation is applicable. One simply has to take all the actual reactions into account.

According to the cell model then, the number and positions of the cells are given in advance, and so are the rates at which the various morphogens diffuse between the cells. Suppose that there are N cells and M morphogens. The state of the whole system is then given by MN numbers, the quantities of the M morphogens in each of N cells. These numbers change with time, partly because of the reactions, partly because of the diffusion. To determine the part of the rate of change of one of these numbers due to diffusion, at any one moment, one only needs to know the amounts of the same morphogen in the cell and its neighbours, and the diffusion coefficient for that morphogen. To find the rate of change due to chemical reaction one only needs to know the concentrations of all morphogens at that moment in the one cell concerned.

This description of the system in terms of the concentrations in the various cells is, of course, only an approximation. It would be justified if, for instance, the contents were perfectly stirred. Alternatively, it may often be justified on the understanding that the 'concentration in the cell' is the concentration at a certain representative point, although the idea of 'concentration at a point' clearly itself raises difficulties. The author believes that the approximation is a good one, whatever argument is used to justify it, and it is certainly a convenient one.

It would be possible to extend much of the theory to the case of organisms immersed in a fluid, considering the diffusion within the fluid as well as from cell to cell. Such problems are not, however, considered here.

4. THE BREAKDOWN OF SYMMETRY AND HOMOGENEITY

There appears superficially to be a difficulty confronting this theory of morphogenesis, or, indeed, almost any other theory of it. An embryo in its spherical blastula stage has spherical symmetry, or if there are any deviations from perfect symmetry, they cannot be regarded as of any particular importance, for the deviations vary greatly from embryo to embryo within a species, though the organisms developed from them are barely distinguishable. One may take it therefore that there is perfect spherical symmetry. But a system which has spherical symmetry, and whose state is changing because of chemical reactions and diffusion, will remain spherically symmetrical for ever. (The same would hold true if the state were changing according to the laws of electricity and magnetism, or of quantum mechanics.) It certainly cannot result in an organism such as a horse, which is not spherically symmetrical.

There is a fallacy in this argument. It was assumed that the deviations from spherical symmetry in the blastula could be ignored because it makes no particular difference what form of asymmetry there is. It is, however, important that there are *some* deviations, for the system may reach a state of instability in which these irregularities, or certain components of them, tend to grow. If this happens a new and stable equilibrium is usually reached, with the symmetry entirely gone. The variety of such new equilibria will normally not be so great as the variety of irregularities giving rise to them. In the case, for instance, of the gastrulating sphere, discussed at the end of this paper, the direction of the axis of the gastrula can vary, but nothing else.

The situation is very similar to that which arises in connexion with electrical oscillators. It is usually easy to understand how an oscillator keeps going when once it has started, but on a first acquaintance it is not obvious how the oscillation begins. The explanation is that there are random disturbances always present in the circuit. Any disturbance whose frequency is the natural frequency of the oscillator will tend to set it going. The ultimate fate of the system will be a state of oscillation at its appropriate frequency, and with an amplitude (and a wave form) which are also determined by the circuit. The phase of the oscillation alone is determined by the disturbance.

If chemical reactions and diffusion are the only forms of physical change which are taken into account the argument above can take a slightly different form. For if the system originally has no sort of geometrical symmetry but is a perfectly homogeneous and possibly irregularly shaped mass of tissue, it will continue indefinitely to be homogeneous. In practice, however, the presence of irregularities, including statistical fluctuations in the numbers of molecules undergoing the various reactions, will, if the system has an appropriate kind of instability, result in this homogeneity disappearing.

This breakdown of symmetry or homogeneity may be illustrated by the case of a pair of cells originally having the same, or very nearly the same, contents. The system is homogeneous: it is also symmetrical with respect to the operation of interchanging the cells. The contents of either cell will be supposed describable by giving the concentrations X and Y of two morphogens. The chemical reactions will be supposed such that, on balance, the first morphogen (X) is produced at the rate $5X - 6Y + 1$ and the second (Y) at the rate $6X - 7Y + 1$. When, however, the strict application of these formulae would involve the concentration of a morphogen in a cell becoming negative, it is understood that it is instead destroyed only at the rate at which it is reaching that cell by diffusion. The first morphogen will be supposed to diffuse at the rate 0.5 for unit difference of concentration between the cells, the second, for the same difference, at the rate 4.5. Now if both morphogens have unit concentration in both cells there is equilibrium. There is no resultant passage of either morphogen across the cell walls, since there is no concentration difference, and there is no resultant production (or destruction) of either morphogen in either cell since $5X - 6Y + 1$ and $6X - 7Y + 1$ both have the value zero for $X = 1$, $Y = 1$. But suppose the values are $X_1 = 1.06$, $Y_1 = 1.02$ for the first cell and $X_2 = 0.94$, $Y_2 = 0.98$ for the second. Then the two morphogens will be being produced by chemical action at the rates 0.18, 0.22 respectively in the first cell and destroyed at the same rates in the second. At the same time there is a flow due to diffusion from the first cell to the second at the rate 0.06 for the first morphogen and 0.18 for the second. In sum the effect is a flow from the second cell to the first at the

rates 0.12, 0.04 for the two morphogens respectively. This flow tends to accentuate the already existing differences between the two cells. More generally, if

$$X_1 = 1 + 3\xi, \quad X_2 = 1 - 3\xi, \quad Y_1 = 1 + \xi, \quad Y_2 = 1 - \xi,$$

at some moment the four concentrations continue afterwards to be expressible in this form, and ξ increases at the rate 2ξ . Thus there is an exponential drift away from the equilibrium condition. It will be appreciated that a drift away from the equilibrium occurs with almost any small displacement from the equilibrium condition, though not normally according to an exact exponential curve. A particular choice was made in the above argument in order to exhibit the drift with only very simple mathematics.

Before it can be said to follow that a two-cell system can be unstable, with inhomogeneity succeeding homogeneity, it is necessary to show that the reaction rate functions postulated really can occur. To specify actual substances, concentrations and temperatures giving rise to these functions would settle the matter finally, but would be difficult and somewhat out of the spirit of the present inquiry. Instead, it is proposed merely to mention imaginary reactions which give rise to the required functions by the law of mass action, if suitable reaction constants are assumed. It will be sufficient to describe

(i) A set of reactions producing the first morphogen at the constant rate 1, and a similar set forming the second morphogen at the same rate.

(ii) A set destroying the second morphogen (Y) at the rate $7Y$.

(iii) A set converting the first morphogen (X) into the second (Y) at the rate $6X$.

(iv) A set producing the first morphogen (X) at the rate $11X$.

(v) A set destroying the first morphogen (X) at the rate $6Y$, so long as any of it is present.

The conditions of (i) can be fulfilled by reactions of the type $A \rightarrow X$, $B \rightarrow Y$, where A and B are substances continually present in large and invariable concentrations. The conditions of (ii) are satisfied by a reaction of the form $Y \rightarrow D$, D being an inert substance and (iii) by the reaction $X \rightarrow Y$ or $X \rightarrow Y + E$. The remaining two sets are rather more difficult. To satisfy the conditions of (iv) one may suppose that X is a catalyst for its own formation from A . The actual reactions could be the formation of an unstable compound U by the reaction $A + X \rightarrow U$, and the subsequent almost instantaneous breakdown $U \rightarrow 2X$. To destroy X at a rate proportional to Y as required in (v) one may suppose that a catalyst C is present in small but constant concentration and immediately combines with X , $X + C \rightarrow V$. The modified catalyst reacting with Y , at a rate proportional to Y , restores the catalyst but not the morphogen X , by the reactions $V + Y \rightarrow W$, $W \rightarrow C + H$, of which the latter is assumed instantaneous.

It should be emphasized that the reactions here described are by no means those which are most likely to give rise to instability in nature. The choice of the reactions to be discussed was dictated entirely by the fact that it was desirable that the argument be easy to follow. More plausible reaction systems are described in § 10.

Unstable equilibrium is not, of course, a condition which occurs very naturally. It usually requires some rather artificial interference, such as placing a marble on the top of a dome. Since systems tend to leave unstable equilibria they cannot often be in them. Such equilibria can, however, occur naturally through a stable equilibrium changing into an unstable one. For example, if a rod is hanging from a point a little above its centre of gravity

it will be in stable equilibrium. If, however, a mouse climbs up the rod the equilibrium eventually becomes unstable and the rod starts to swing. A chemical analogue of this mouse-and-pendulum system would be that described above with the same diffusibilities but with the two morphogens produced at the rates

$$(3+I)X-6Y+I-1 \quad \text{and} \quad 6X-(9+I)Y-I+1.$$

This system is stable if $I < 0$ but unstable if $I > 0$. If I is allowed to increase, corresponding to the mouse running up the pendulum, it will eventually become positive and the equilibrium will collapse. The system which was originally discussed was the case $I = 2$, and might be supposed to correspond to the mouse somehow reaching the top of the pendulum without disaster, perhaps by falling vertically on to it.

5. LEFT-HANDED AND RIGHT-HANDED ORGANISMS

The object of this section is to discuss a certain difficulty which might be thought to show that the morphogen theory of morphogenesis cannot be right. The difficulty is mainly concerned with organisms which have not got bilateral symmetry. The argument, although carried through here without the use of mathematical formulae, may be found difficult by non-mathematicians, and these are therefore recommended to ignore it unless they are already troubled by such a difficulty.

An organism is said to have 'bilateral symmetry' if it is identical with its own reflexion in some plane. This plane of course always has to pass through some part of the organism, in particular through its centre of gravity. For the purpose of this argument it is more general to consider what may be called 'left-right symmetry'. An organism has left-right symmetry if its description in any right-handed set of rectangular Cartesian co-ordinates is identical with its description in some set of left-handed axes. An example of a body with left-right symmetry, but not bilateral symmetry, is a cylinder with the letter P printed on one end, and with the mirror image of a P on the other end, but with the two upright strokes of the two letters not parallel. The distinction may possibly be without a difference so far as the biological world is concerned, but mathematically it should not be ignored.

If the organisms of a species are sufficiently alike, and the absence of left-right symmetry sufficiently pronounced, it is possible to describe each individual as either right-handed or left-handed without there being difficulty in classifying any particular specimen. In man, for instance, one could take the X -axis in the forward direction, the Y -axis at right angles to it in the direction towards the side on which the heart is felt, and the Z -axis upwards. The specimen is classed as left-handed or right-handed according as the axes so chosen are left-handed or right-handed. A new classification has of course to be defined for each species.

The fact that there exist organisms which do not have left-right symmetry does not in itself cause any difficulty. It has already been explained how various kinds of symmetry can be lost in the development of the embryo, due to the particular disturbances (or 'noise') influencing the particular specimen not having that kind of symmetry, taken in conjunction with appropriate kinds of instability. The difficulty lies in the fact that there are species in which the proportions of left-handed and right-handed types are very unequal. It will be as well to describe first an argument which appears to show that this should not happen.