

THE CHEMICAL BASIS OF MORPHOGENESIS

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It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading.

1. A MODEL OF THE EMBRYO. MORPHOGENS

In this section a mathematical model of the growing embryo will be described. This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge.

The model takes two slightly different forms. In one of them the cell theory is recognized but the cells are idealized into geometrical points. In the other the matter of the organism is imagined as continuously distributed. The cells are not, however, completely ignored, for various physical and physico-chemical characteristics of the matter as a whole are assumed to have values appropriate to the cellular matter.

With either of the models one proceeds as with a physical theory and defines an entity called 'the state of the system'. One then describes how that state is to be determined from the state at a moment very shortly before. With either model the description of the state consists of two parts, the mechanical and the chemical. The mechanical part of the state describes the positions, masses, velocities and elastic properties of the cells, and the forces between them. In the continuous form of the theory essentially the same information is given in the form of the stress, velocity, density and elasticity of the matter. The chemical part of the state is given (in the cell form of theory) as the chemical composition of each separate cell; the diffusibility of each substance between each two adjacent cells must also

be given. In the continuous form of the theory the concentrations and diffusibilities of each substance have to be given at each point. In determining the changes of state one should take into account

- (i) The changes of position and velocity as given by Newton's laws of motion.
- (ii) The stresses as given by the elasticities and motions, also taking into account the osmotic pressures as given from the chemical data.
- (iii) The chemical reactions.
- (iv) The diffusion of the chemical substances. The region in which this diffusion is possible is given from the mechanical data.

This account of the problem omits many features, e.g. electrical properties and the internal structure of the cell. But even so it is a problem of formidable mathematical complexity. One cannot at present hope to make any progress with the understanding of such systems except in very simplified cases. The interdependence of the chemical and mechanical data adds enormously to the difficulty, and attention will therefore be confined, so far as is possible, to cases where these can be separated. The mathematics of elastic solids is a well-developed subject, and has often been applied to biological systems. In this paper it is proposed to give attention rather to cases where the mechanical aspect can be ignored and the chemical aspect is the most significant. These cases promise greater interest, for the characteristic action of the genes themselves is presumably chemical. The systems actually to be considered consist therefore of masses of tissues which are not growing, but within which certain substances are reacting chemically, and through which they are diffusing. These substances will be called morphogens, the word being intended to convey the idea of a form producer. It is not intended to have any very exact meaning, but is simply the kind of substance concerned in this theory. The evocators of Waddington provide a good example of morphogens (Waddington 1940). These evocators diffusing into a tissue somehow persuade it to develop along different lines from those which would have been followed in its absence. The genes themselves may also be considered to be morphogens. But they certainly form rather a special class. They are quite indiffusible. Moreover, it is only by courtesy that genes can be regarded as separate molecules. It would be more accurate (at any rate at mitosis) to regard them as radicals of the giant molecules known as chromosomes. But presumably these radicals act almost independently, so that it is unlikely that serious errors will arise through regarding the genes as molecules. Hormones may also be regarded as quite typical morphogens. Skin pigments may be regarded as morphogens if desired. But those whose action is to be considered here do not come squarely within any of these categories.

The function of genes is presumed to be purely catalytic. They catalyze the production of other morphogens, which in turn may only be catalysts. Eventually, presumably, the chain leads to some morphogens whose duties are not purely catalytic. For instance, a substance might break down into a number of smaller molecules, thereby increasing the osmotic pressure in a cell and promoting its growth. The genes might thus be said to influence the anatomical form of the organism by determining the rates of those reactions which they catalyze. If the rates are assumed to be those determined by the genes, and if a comparison of organisms is not in question, the genes themselves may be eliminated from the discussion. Likewise any other catalysts obtained secondarily through the agency of

the genes may equally be ignored, if there is no question of their concentrations varying. There may, however, be some other morphogens, of the nature of evocators, which cannot be altogether forgotten, but whose role may nevertheless be subsidiary, from the point of view of the formation of a particular organ. Suppose, for instance, that a 'leg-evocator' morphogen were being produced in a certain region of an embryo, or perhaps diffusing into it, and that an attempt was being made to explain the mechanism by which the leg was formed in the presence of the evocator. It would then be reasonable to take the distribution of the evocator in space and time as given in advance and to consider the chemical reactions set in train by it. That at any rate is the procedure adopted in the few examples considered here.

2. MATHEMATICAL BACKGROUND REQUIRED

The greater part of this present paper requires only a very moderate knowledge of mathematics. What is chiefly required is an understanding of the solution of linear differential equations with constant coefficients. (This is also what is chiefly required for an understanding of mechanical and electrical oscillations.) The solution of such an equation takes the form of a sum $\sum A e^{bt}$, where the quantities A , b may be complex, i.e. of the form $\alpha + i\beta$, where α and β are ordinary (real) numbers and $i = \sqrt{-1}$. It is of great importance that the physical significance of the various possible solutions of this kind should be appreciated, for instance, that

(a) Since the solutions will normally be real one can also write them in the form $\Re \sum A e^{bt}$ or $\sum \Re A e^{bt}$ (\Re means 'real part of').

(b) That if $A = A' e^{i\phi}$ and $b = \alpha + i\beta$, where A' , α , β , ϕ are real, then

$$\Re A e^{bt} = A' e^{\alpha t} \cos(\beta t + \phi).$$

Thus each such term represents a sinusoidal oscillation if $\alpha = 0$, a damped oscillation if $\alpha < 0$, and an oscillation of ever-increasing amplitude if $\alpha > 0$.

(c) If any one of the numbers b has a positive real part the system in question is unstable.

(d) After a sufficiently great lapse of time all the terms $A e^{bt}$ will be negligible in comparison with those for which b has the greatest real part, but unless this greatest real part is itself zero these dominant terms will eventually either tend to zero or to infinite values.

(e) That the indefinite growth mentioned in (b) and (d) will in any physical or biological situation eventually be arrested due to a breakdown of the assumptions under which the solution was valid. Thus, for example, the growth of a colony of bacteria will normally be taken to satisfy the equation $dy/dt = \alpha y$ ($\alpha > 0$), y being the number of organisms at time t , and this has the solution $y = A e^{\alpha t}$. When, however, the factor $e^{\alpha t}$ has reached some billions the food supply can no longer be regarded as unlimited and the equation $dy/dt = \alpha y$ will no longer apply.

The following relatively elementary result will be needed, but may not be known to all readers:

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

$$\text{but} \quad \quad \quad = N \quad \text{if } s = 0 \text{ or } s = N.$$

The first case can easily be proved when it is noticed that the left-hand side is a geometric progression. In the second case all the terms are equal to 1.