ON SPONTANEOUS ASYMMETRIC SYNTHESIS

by

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I am informed by my colleague Professor W. MOORE that there is still widely believed to be a problem of explaining the original "asymmetric synthesis" giving rise to the general optical activity of the chemical substances of living matter. I have long supposed that this was no problem on the basis of a supposition that the initial production of life is a rare event. We may take as the defining property of a living entity the ability to reproduce its own kind. Omitting such simple entities as flames, which are included by such a definition, and confining attention to chemical molecules, the complexity of any having this essential property of life is likely to be great enough to make it highly improbable that it has a centre of symmetry. It is likely, in fact, to contain α-amino acids which are necessarily asymmetric. Then, if the production of living molecules is an infrequent process, compared with the rate of multiplication of living molecules, the whole earth is likely to be extensively populated with the progeny of the first before another appears. In fact they may have so modified the environment by then that no other has a chance of generation. There are, of course, variants of this hypothesis: *e.g.* that a second living molecule is produced before the progeny of the first has colonised the whole earth, and competes successfully with it for nutrient material, "starving", or even "poisoning" the other out of existence. This leads to the same result, and depends essentially on the same initial hypothesis, that spontaneous germination of life is a rare event.

On the other hand, Dr. J. C. FISHER of the G.E.C. Laboratories in Schenectady, in a conversation during the summer of 1951, argued that this initial hypothesis was neither theoretically well-founded nor necessary to explain the facts of observation, such as the optical asymmetry of living matter. I gather from Professor MOORE that there are a number of people to whom a simple mathematical demonstration of the correctness of FISHER's latter contention will appear profitable.

A simple and sufficient life model for the present purpose is a chemical substance which is a catalyst for its own production and an anti-catalyst for the production of its optical antimer. We shall suppose both to be present, in concentrations n_1 and n_2 respectively, and their rate of increase to be given by equations

$$\frac{\mathrm{d}n_1}{\mathrm{d}t} = (k_1 - k_2\, n_2)\, n_1 \qquad (1)$$

$$\frac{\mathrm{d}n_2}{\mathrm{d}t} = (k_1 - k_2\, n_1)\, n_2 \qquad (2)$$

where k_1 and k_2 are positive.

Subtracting we have

$$\mathrm{d}(n_1 - n_2)/\mathrm{d}t = k_1(n_1 - n_2) \tag{3}$$

and hence

$$(n_1 - n_2) = (n_{01} - n_{02})\, \mathrm{e}^{k_1 t} \tag{4}$$

where n_{01}, n_{02} are initial values: *i.e.* the excess of one over the other increases exponentially; whereas the total, $(n_1 + n_2)$, governed by the differential equation

$$\mathrm{d}(n_1 + n_2)/\mathrm{d}t = k_1(n_1 + n_2) - 2\, k_2\, n_1\, n_2 \qquad 5)$$

has a slower relative rate of increase.

Eliminating dt from (1) and (2) we have

$$\frac{\mathrm{d}n_1}{\mathrm{d}n_2} = \frac{(k_1 - k_2\, n_2)n_1}{(k_1 - k_2\, n_1)n_2} \tag{6}$$

and hence

$$n_1/n_2 = (n_{01}/n_{02}) \text{ exp. } [k_2\, (n_1 - n_2 - n_{01} + n_{02})/k_1] \tag{7}$$

Combining (4) and (7)

$$n_1/n_2 = (n_{01}/n_{02}) \text{ exp. } [k_2\, (n_{01} - n_{02})(\mathrm{e}^{k_1 t} - 1)] \tag{8}$$

i.e. this ratio increases at a more than exponential rate if $n_{01} - n_{02}$ is positive, and decreases correspondingly if this initial difference is negative.

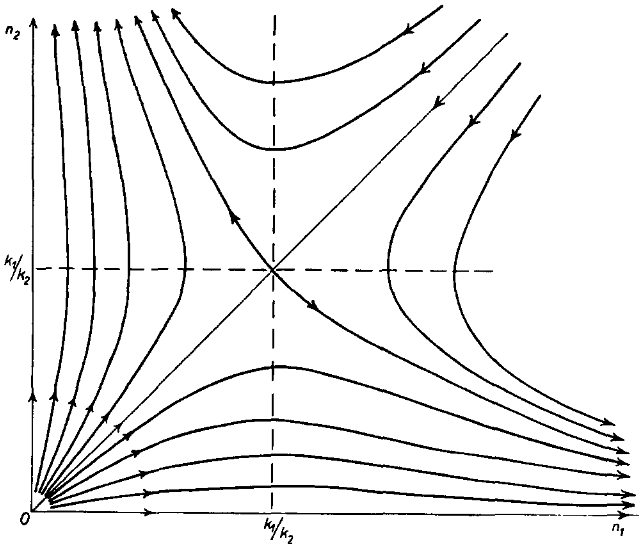

Fig. 1

Fig. 1 shows a sketch of the general form of the solutions of equations (1), (2), constructed by the simple technique of sketching curves which everywhere have the correct slope. In this diagram, time is proportional to the logarithm of the distance from the line $n_2 = n_1$. Every starting point not on this line leads to one of the asymptotes $n_2 = 0$ or $n_1 = 0$. The curves shown include those in which $(n_1 + n_2)$ first diminishes with time, but curves starting with small values can never enter this region.

The interaction between the antimers expressed by the second term on the right of equations (1) and (2) may be interpreted either as a lethal interaction whenever they meet, or as a tendency of the presence of either to diminish the reproduction rate of the other. The latter interpretation is only permissible so long as n_1 and n_2 are less than k_1/k_2.

Thus equality of n_1 and n_2 represents a condition of unstable equilibrium. This result depends on the presence of the term representing specific mutual antagonism, If we set up equations representing unspecific antagonism, an equally deleterious effect upon net reproduction rate due to crowding with members of either species, thus:

$$\frac{\mathrm{d}n_1}{\mathrm{d}t} = [k_1 - k_2(n_1 + n_2)]\, n_1 \tag{9}$$

$$\frac{\mathrm{d}n_2}{\mathrm{d}t} = [k_1 - k_2(n_1 + n_2)]\, n_2 \tag{10}$$

we obtain by subtraction and addition

$$\mathrm{d}(n_1 - n_2)/\mathrm{d}t = k_1(n_1 - n_2) - k_2(n_1 - n_2)(n_1 + n_2) \tag{11}$$

and
$$\mathrm{d}(n_1 + n_2)/\mathrm{d}t = k_1(n_1 + n_2) - k_2(n_1 + n_2)^2 \tag{12}$$

Eliminating dt from these equations gives us

$$\frac{\mathrm{d}(n_1 - n_2)}{\mathrm{d}(n_1 + n_2)} = \frac{n_1 - n_2}{n_1 + n_2} \tag{13}$$

and by quadrature of (12) and (13) and some rearranging we obtain

$$(n_1 + n_2) = \text{const.}\ (n_1 - n_2) = \frac{k_1/k_2}{1 \pm \mathrm{e}^{-k_1 t}} \tag{14}$$

The minus sign in the right hand expression of (14) refers to branches of the solution corresponding to negative values of $(n_1 + n_2)$, or to large values falling to the asymptote k_1/k_2. The positive sign gives the branch in which we are interested, with an S shaped curve leading from low values to the same asymptote. An integration constant corresponding to a shift of the time zero has been omitted.

With these equations, any initial disproportion is preserved, but not amplified. As soon, however, as we add terms $- k_3 n_1 n_2$, representing specific antagonism, to the right hand sides of equations (9) and (10) we obtain in place of (13)

$$\frac{\mathrm{d}\ln(n_1 + n_2)}{\mathrm{d}\ln(n_1 - n_2)} = 1 - \frac{2k_3 n_1 n_2}{(n_1 + n_2)[k_1 - k_2(n_1 + n_2)]} \tag{15}$$

which is less than 1 in the case $(n_1 + n_2) < k_1/k_2$ in which we are interested. *I.e.*, the difference increases faster than the sum: so that equality of n_1 and n_2 is once again unstable.

The source of an initial disproportion might be an asymmetry in the environment, *e.g.* circular polarisation of light. This however is unnecessary. The finiteness of the numbers involved is sufficient. If we suppose an initial spontaneous generation rate k_0, this is swamped by reproduction after a certain time, when

$$n_1 \sim n_2 \sim k_0/k_1 \tag{16}$$

These values may be taken as our n_{01} and n_{02}. They will probably differ by a number of the order of magnitude of their square roots. Uniform reproduction would therefore produce a disproportion of the order of magnitude $1/\sqrt{n_0}$. There will also be statistical fluctuations in the numbers reproduced. These are of the order of magnitude of the square root of the number generated, while any existing difference $(n_1 - n_2)$ increases in the mean more than proportionally to the number generated. The latter will therefore usually dominate the later fluctuations. There is always a chance that the sign of the difference may reverse, but the chance becomes very small once the difference becomes large. Two analogies may be useful here. The "shot effect" can always be relied upon to initiate oscillation in an unstable electronic circuit within a short time, and the early shocks are of chief importance, though the phase of the oscillation is unpredictable. And a marble rolling downhill, starting on the crown of the road, will assuredly find its way to one gutter or the other. Though there is always a chance that after straying to the right a lucky sequence of collisions with pebbles in the road surface will throw it back to the left, it is more likely to continue towards the side where it happens to be at the moment. The distance travelled before reaching a gutter might be infinite, but its statistical variation is not actually very large.

Let us therefore assume the presence of an initial disproportion, and disregard later fluctuations, to calculate the time required for the disproportion to grow to a large value. Inspection of Fig. 1 shows that the whole process, starting from small values of $(n_1 + n_2)$, divides roughly into three parts: one in which $(n_1 + n_2)$ increases up to the order of magnitude of $\sqrt{2k_1/k_2}$, (the unstable equilibrium value, when the numbers are exactly equal): a second stage in which $|n_1 - n_2|$ increases while $(n_1 + n_2)$ undergoes little change until the disproportion is large: and a third stage in which the total quantity increases, being composed of essentially one component only. In the first stage the mutual poisoning effect is negligible: we therefore have

$$(n_1 + n_2) \sim (n_{01} + n_{02})e^{k_1 t} \tag{17}$$

The time taken for the first stage is

$$t_1 \sim \frac{1}{k_1} \ln \frac{k_1/k_2}{n_{01} + n_{02}} \tag{18}$$

The time for the second is

$$t_2 \sim \frac{1}{k_1} \ln \frac{n_{01} + n_{02}}{n_{01} - n_{02}} \tag{19}$$

Assuming, therefore, that k_1/k_2 is considerably larger than the initial numbers, and $n_{01} - n_{02}$ is not zero, these two times are of roughly similar order of magnitude and cannot be as large as corresponds to 100 "generations" for any acceptable values of the numbers involved.

According to equations (9), (10) with the additional terms $- k_3 n_1 n_2$, the time for the second stage would be much longer than that for the first, if k_3 is smaller than k_2. If k_3 is larger than k_2, it is only in the third stage that the behaviour significantly alters.

The conditions we have assumed up to now correspond to a well-mixed system —a laboratory flask for example. In a larger imperfectly mixed system, such as an ocean, we may conceive of the unbalance being in opposite directions in various places, leading to separate colonies of the two kinds. Let us suppose such colonies to have formed, and built up to concentrations large enough for significant mutual poisoning where they mix. There will then be boundary surfaces between the colonies, where the concentrations are equal: either species diffusing to the wrong side of the boundary will have a diminished chance of survival, so that homogeneity will be preserved in the interior of each colony. But wherever the boundary is curved the species diffusing inwards raises the concentration more than the species diffusing outwards: so that the boundary tends to move towards the side from which it is concave. This is the law of motion of soap-bubble films in a froth, coarsening by the diffusion of air through them (though with only two species we cannot have complex cell-structures as we can in soap-bubbles, or the grains of a polycrystalline metal which obey a similar law). Any enclave or salient of the one species, surrounded by the other, will progressively shrink. In the outcome, a single species should survive. An exception occurs when two seas are connected by a strait. A different species could survive in each sea, with the boundary running stably from cape to cape.

Taken as a description of a possible stage in the evolution of life, our picture is of course highly idealised. If the hypothesis of frequent origination is a true one, it is likely that more than just two original forms would be produced. But the principles we have considered should generally apply, and the restriction to just two kinds, differing only in symmetry, provides us with relatively simple equations exhibiting a property generally to be expected in mutually antagonistic self-reproducing systems.

The main conclusion established is that spontaneous asymmetric synthesis is a natural property of life, which may be present in simpler autocatalytic systems. A laboratory demonstration may not be impossible.

SUMMARY

The kinetic equations of growth of symmetrically mutually antagonistic self-reproducing systems are considered and shown to lead to instability. It follows that spontaneous asymmetric synthesis is a natural property of life: a laboratory demonstration is not necessarily impossible.

RÉSUMÉ

Les équations cinétiques de la croissance de systèmes auto-reproductibles mutuellement antagonistes symétriquement, permettent de conclure à l'instabilité. Il en résulte que la synthèse asymétrique spontanée est une propriété naturelle de la vie: une démonstration expérimentale n'est pas nécessairement impossible.

ZUSAMMENFASSUNG

Es werden die kinetischen Wachstumsgleichungen von symmetrisch wechselseitig antagonistischen, sich selbstvermehrenden Systemen betrachtet und gezeigt, dass sie zu Instabilität führen. Es folgt, dass die spontane asymmetrische Synthese eine natürliche Eigenschaft des Lebens ist: eine Laboratoriumsdemonstration ist nicht notwendigerweise unmöglich.

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