polysomes and to generate ribosomal subunits at low temperatures. In addition, we point out the remarkable discontinuity in subunit accumulation which occurs between 8° C and 10° C and have correlated this with the cessation of cell division. Preliminary experiments in which chick embryos were cooled also resulted in an accumulation of ribosomal subunits (J. Vournakis, private communication). It will be of interest to test the generality of this phenomenon in other organisms. Our conclusion from the present work is that some step in the condensation of ribosomal subunits on *E. coli* messenger RNA is prevented by the lowered temperature. The exact step at which the cold-induced block occurs is at present under investigation in an *in vitro* system.

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# Symmetry Breaking Instabilities in Biological Systems

by

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Some well known reactions can be used to illustrate that symmetry breaking chemical instabilities may be important in biological systems.

We have discussed the stability of purely dissipative systems involving chemical reactions but no hydrodynamic motion—for example, transport processes such as diffusion (refs. 1–4 and communication to international conference on theoretical physics and biology, Versailles, 1967; the earliest reference to these systems is ref. 5). We placed special emphasis on the possibility of symmetry breaking instabilities leading to a spontaneous "self-organization" of the system from the point of view of both space order and function. Such low entropy situations may arise in systems which cannot transform part of the energy or matter exchanged with the outside world into macroscopic internal order. States which have such properties have been called "dissipative structures". Their occurrence characteristically depends, on the one hand, on a minimum level of dissipation (that is, the system has to be sufficiently far from thermodynamic equilibrium) and, on the other hand, on specific non-linear types of kinetics leading to negative contributions to the thermodynamic stability condition (autocatalytic or cross catalytic effects).

As has already been mentioned[2,4], this type of requirement is compatible in principle with chemical reactions currently being investigated in biochemical processes. We wish to go further and argue in favour of the idea that many metabolic reactions work beyond the transition point corresponding to the appearance of a dissipative structure. This would be an important finding, for it implies that, to some extent at least, space differentiation is a consequence of chemical kinetics.

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## Space and Time Order in Chemical Systems

The problems of structural order and time order (oscillations in time around the steady state values) are closely related[2]. The latter phenomenon is, however, much better understood. Theoretical and experimental data have accumulated recently about short frequency oscillations in biochemical reactions (for example, ref. 6). A way of testing the idea we have presented would therefore be to investigate the time order implications of these results as far as symmetry breaking instabilities are concerned. These instabilities result from space dependent perturbations when diffusion is taken into account[1–4]. It is therefore interesting to investigate systems which involve time oscillations, from the point of view of their stability, and to look for instabilities with respect to diffusion.

Before we do that it might be useful to have in mind the general characteristics of chemical oscillations. (1) It is easy to show that oscillations around steady states can only occur if the system is far from equilibrium (outside the range of linear thermodynamics of irreversible processes[1,7]), and so systems where these oscillations are observed realize the basic condition for the possible occurrence of symmetry breaking instabilities. (2) Undamped oscillations may arise around stable steady states (the real part of the frequency corresponding to small perturbations then vanishes) or around unstable steady states. A simple example of the first is the well known Lotka–Volterra mechanism[8]. But in this case the characteristics of the oscillation depend on the perturbation. There is an infinite number of types of oscillation,

depending on the perturbation. On the contrary, if the oscillation proceeds around an unstable steady state there is only a very restricted number of limit cycles independent of the initial perturbations. (This distinction is based on the application of the Poincaré–Bendixson criterion; see, for example, ref. 9.)

This type of behaviour seems to be observed in biochemical oscillations. The oscillations are reproducible and do not seem to depend on the initial perturbation.

In agreement with this observation mathematical models based on the kinetic data available for some important biochemical reactions suggest that the oscillations belong to the second category and occur around unstable steady states[11,12]. Machine calculations on simple models[13] indicate that systems leading to oscillations of this type may also lead, for slightly different values of the kinetic parameters, to symmetry breaking as a result of instability in respect to diffusion.

## Oscillations around Unstable Steady States

We intend to illustrate the idea that as far as metabolic processes are concerned instabilities with respect to diffusion might be very common. We shall do this by investigating three characteristic examples, representing widely different catalytic properties, but typical of biochemical processes: (*a*) Chernavskaia and Chernavskii's model for the dark reaction of photosynthesis; (*b*) a substrate and product-inhibited enzyme reaction; (*c*) the product-activated enzyme reaction catalysed by phosphofructokinase in the glycolytic cycle. Each of these processes has already been studied in connexion with the problem of sustained chemical oscillations, and models giving satisfactory results from that point of view have been proposed. We do not wish to discuss possible improvements in such models, but to show that within the framework of the approximation leading to a good representation of their time-dependent behaviour, the same biochemical systems may become unstable with respect to diffusion. This indicates that the existence of dissipative structures is compatible with the experimental and theoretical data in the literature.

## Photosynthesis

Calvin's cycle has been reduced by Chernavskaia and Chernavskii[11] to the following simplified scheme

$$C_1 + X + C_5 \longrightarrow 2\,C_3 \qquad (1a)$$

$$2\,C_3 \longrightarrow C_6 \qquad (1b)$$

$$C_6 + C_3 \rightleftharpoons C_4 + C_5 \qquad (1c)$$

$$C_4 + C_3 \rightleftharpoons C_7 \qquad (1d)$$

$$C_7 + C_3 \rightleftharpoons 2\,C_5 \qquad (1e)$$

where $C_1$ represents the concentration of $CO_2$, which may be considered constant in time throughout the system. The other products, $X$, $C_3$, $C_4$, $C_5$, $C_6$, $C_7$, are respectively $NADPH_2$, triose-phosphate, tetrose-phosphate, ribulose-phosphate, hexose-phosphate and heptulose-phosphate. Furthermore, the scheme is based on the following assumptions: (1) $NADPH_2$ is furnished by the light phase at a rate proportional to the concentration of triose-phosphate in the system. (2) Triose-phosphate is furnished by the Krebs cycle and enters the system at constant rate. (3) The chemical transformations (1*c*, *d* and *e*) are completely reversible and much faster than the transformations (1*a* and *b*). Only the kinetic equations giving the time and space change of $C_3$ and $C_6$ need to be taken into account, and they can be written in the simplified form

$$\frac{\partial C_3}{\partial t} = \alpha_1 C_3^2 - \alpha_2 C_3 C_6 + \alpha_0 + D_3 \cdot \frac{\partial^2 C_3}{\partial \tau^2} \qquad (2)$$

$$\frac{\partial C_6}{\partial t} = \beta_1 C_3^2 - \beta_2 C_6^2 - \beta_3 C_3 C_6 + D_6 \cdot \frac{\partial^2 C_6}{\partial \tau^2} \qquad (3)$$

The only difference from the model of Chernavskaia and Chernavskii is that we have taken into account the diffusion of the products. Here $\alpha_1 C_3^2$ represents the difference between the formation of $C_3$ from ribulose, $CO_2$, $NADPH_2$ (reaction 1*a*) and the dimerization of triose into hexose (reaction 1*b*). On the other hand, $\alpha_1$ is given by $\alpha_1 = \alpha_1' C_1$ where $\alpha_1'$ is a constant coefficient dependent on the intensity of light. $C_1$ is the constant concentration of $CO_2$. $\alpha_2 C_3 C_6$ results from the transformation of $C_3$ following reactions (1*c*, *d* and *e*). $\alpha_0$ represents the triose coming from Krebs's cycle. $\beta_1 C_3^2$, $\beta_2 C_6^2$, $\beta_3 C_3 C_6$ represent respectively the formation of hexose from $C_3$, the conversion of $C_6$ into disaccharide, and the transformation of $C_6$ following reactions (1*c*, *d* and *e*).

It is easy to show that the stationary state solutions of equations (2) and (3) become unstable with respect to space dependent infinitesimal fluctuations when $\alpha_1$ is greater than the critical value

$$\alpha_{1c} = \frac{8}{7}\beta_1 \cdot \frac{D_3}{D_6} + 8\left(\frac{\beta_1 \alpha_0}{7} \cdot \frac{D_3}{D_6}\right)^{1/2} + \alpha_0 \qquad (4)$$

corresponding to a critical wavelength of inhomogeneity given by*

$$\lambda_c^2 = \frac{1}{4} \cdot \left(\frac{7 D_3 \cdot D_6}{\beta_1 \alpha_0}\right)^{1/2} \qquad (5)$$

Because the ratio $D_3/D_6$ is almost 1 and $\alpha_0$ may be made small, the critical value (4) is of the same order of magnitude as the value

$$\alpha_1 = \frac{8}{7}\beta_1 + \alpha_0$$

corresponding to the appearance of sustained oscillations. On the other hand, considering equation (5), it is clear that inhomogeneities can only be observed in a certain range. Indeed, if $D_3.D_6$ is much smaller or much greater than the chemical term $\beta_1.\alpha_0$, the critical wavelength tends to zero or to infinity. As a result no observable change would appear in the system.

We return to this point in more detail for our third example. But first we wish to consider an example in which the instability arises through a qualitatively different effect. In the strongly simplified model of photosynthesis just considered, the enzyme reactions play no explicit part. They have been absorbed in the definition of the kinetic constants. The instability therefore has its origin in the global autocatalytic nature of the photosynthetic cycle. It is not necessary, however, to take into account such a complicated global process in order to obtain chemical instabilities. Groups of elementary steps in which enzyme catalytic properties are explicitly taken into account can also lead to such phenomena. We believe that this is well illustrated by our next example which belongs to a rather common class of enzyme reaction.

## Inhibition by Substrate and Product

We wish to consider Sel'kov's model[10] for an enzyme reaction inhibited by the substrate and product

$$\xrightarrow{v_i} S_1 + E \underset{k-1}{\overset{k+1}{\rightleftharpoons}} S_1E \qquad (6a)$$

$$S_1E \xrightarrow{k+2} E + S_2 \xrightarrow{v_f} \qquad (6b)$$

$$S_1 + S_1E \underset{k-3}{\overset{k+3}{\rightleftharpoons}} S_1S_1E \qquad (6c)$$

* Equations (4) and (5) were obtained assuming the same relations among the $\alpha$ and $\beta$ parameters as Chernavskaia and Chernavskii, that is $\alpha_1 - \alpha_2 + \alpha_0 = 0$; $\beta_1 - \beta_2 - \beta_3 = 0$ and $\beta_2 = \frac{1}{7}\beta_1$; $\beta_3 = \frac{6}{7}\beta_1$.

$$S_2 + E \underset{k-4}{\overset{k+4}{\rightleftharpoons}} ES_2 \qquad (6d)$$

$$S_2 + S_1E \underset{k-5}{\overset{k+5}{\rightleftharpoons}} S_1ES_2 \qquad (6e)$$

$$S_2 + S_1S_1E \underset{k-6}{\overset{k+6}{\rightleftharpoons}} S_1S_1ES_2 \qquad (6f)$$

where $S_1$ represents the substrate, $S_2$ the product, $E$ the enzyme and $S_1E$ the active enzyme substrate complex. $ES_2$, $S_1S_1E$, $S_1ES_2$ and $S_1S_1ES_2$ are inactive enzyme complexes; $v_i$ is the rate at which $S_1$ enters the system and is given by $v_i = v_0 - k_{-i}S_1$; $v_f$ is the rate at which $S_2$ disappears

$$v_f = \frac{VS_2}{K_m + S_2}$$

following an enzymatically irreversible reaction. $V$ is the maximum rate when $S_2 \to \infty$ and $k_m$ is the Michaelis constant of this reaction. (The derivation of equations (7) and (8) assumes that $s_1 \approx s_2 \approx 1$ $e_0 \ll 1$; $k+4 = k+5 = k+6$; $k-4 = k-5 = k-6$; $k \pm 1, k \pm 2, k \pm 3, k \pm 4 \gg 1$.) The kinetic equations describing the system are then given by

$$\frac{\partial s_i}{\partial t} = v_i - \frac{k + 2e_0 \cdot \dfrac{s_1}{K_{s1}}}{\left(1 + \dfrac{s_2}{K_{s2}}\right)\left[1 + \dfrac{s_1}{K_{s1}} + \dfrac{K_{s1}}{K'_{s1}} \cdot \left(\dfrac{s_1}{K_{s1}}\right)^2\right]} + D_{s_1} \cdot \frac{\partial^2 s_1}{\partial \tau^2} \qquad (7)$$

$$\frac{\partial s_2}{\partial t} = -v_f + \frac{k + 2e_0 \cdot \dfrac{s_1}{K_{s1}}}{\left(1 + \dfrac{s_2}{K_{s2}}\right)\left[1 + \dfrac{s_1}{K_{s1}} + \dfrac{K_{s1}}{K'_{s1}} \cdot \left(\dfrac{s_1}{K_{s1}}\right)^2\right]} + D_{s_2} \cdot \frac{\partial^2 s_2}{\partial \tau^2} \qquad (8)$$

where

$$K_{s1} = \frac{k-1+k+2}{k+1}, \quad K'_{s1} = \frac{k-3}{k+3}, \quad K_{s2} = \frac{k-4}{k+4} \qquad (9)$$

and $e_0$ is the total quantity of enzyme.

Putting

$$\alpha = \frac{K_{s1}}{K'_{s1}} \qquad (10)$$

instability with respect to diffusion can be expressed in terms of this parameter. The critical value beyond which the system becomes unstable is given by

$$\alpha_c = \frac{D_{s2} \cdot K_{s2}}{D_{s1} \cdot K_{s1}} \cdot \frac{\xi^2(2\beta - \nu_0)^2}{\beta^2(\nu_0 - \beta)^2} \cdot \frac{1}{\left[1 + \sqrt{\dfrac{\nu_0 - \beta}{\beta}}\right] \cdot \left[1 + \sqrt{\dfrac{\beta}{\nu_0 - \beta}}\right]} \qquad (11)$$

and correspond to the critical wavelength

$$\lambda_c^2 = \frac{(\nu_0 - \beta) + \sqrt{\beta(\nu_0 - \beta)}}{\xi(2\beta - \nu_0)} \cdot \frac{D_{s1} K_{s1}}{k+2 \cdot e_0} \qquad (12)$$

with

$$\xi = \frac{k - iK_{s1}}{k+2 \cdot e_0}; \quad \nu_0 = \frac{v_0}{k+2 \cdot e_0}; \quad \beta = \frac{V}{k+2 \cdot e_0} \qquad (13)$$

It is immediately clear that equations (11) and (12) yield physically acceptable values when

$$\frac{\nu_0}{2} < \beta < \nu_0$$

In that case, for almost equal diffusion coefficients of $S_1$ and $S_2$, the instability is favoured when product inhibition is great.

## Reaction activated by Product

Catalytic processes of this type are rather exceptional in biology. But the phosphofructokinase reaction is well known, and can be described by the following model[12]. (A slightly different scheme where $\gamma$ is replaced by an explicit inhibition of the enzyme by ATP gives similar results. A detailed analysis will be published later.)

$$\xrightarrow{v_1} A_3 \qquad (14a)$$

$$A_3 + D_1 \underset{k-1}{\overset{k+1}{\rightleftharpoons}} D_3 \qquad (14b)$$

$$D_3 \xrightarrow{k+2} D_1 + A_2 \qquad (14c)$$

$$\gamma A_2 + D_2 \underset{k-3}{\overset{k+3}{\rightleftharpoons}} D_1 \qquad (14d)$$

$$A_2 \xrightarrow{k_2} \qquad (14e)$$

$A_3$ and $A_2$ are ATP and ADP; $D_1$, $D_3$, $D_2$ are respectively the active form of phosphofructokinase, the complex enzyme substrate, and the inactive form of the enzyme. Reactions (14*a*, *b*, *c* and *e*) are simply the rate of entry of substrate and exit of product—a Michaëlis–Menten process. This part of the mechanism, of course, is not responsible for the instability. It is reaction (14*d*) that destabilizes the time-independent steady states. In this case activation of the enzyme is catalysed by the product of the reaction. The coefficient $\gamma$ must not be considered as a stoichiometric coefficient, but rather as a parameter with a value adjusted so that the time behaviour of the system is in agreement with experience. This takes into account the fact that the enzyme activity is inhibited by the substrate[12]. Consequently we can expect to observe instabilities for small values of $v_1$. (This is in agreement with experience. Also the calculations are made assuming that $v_1 \ll 1$.) Indeed, when this is the case, and under quasistationary conditions the critical value of $v_1$ beyond which the instability appears is

$$v_1 = \sqrt[\gamma]{\frac{(k-1+k+2)k - 3\,k_2^\gamma}{(k+1 \cdot k+2 \cdot k+3\,D_0)} \cdot \frac{\left[D_2 D_3 \dfrac{(\gamma-1)}{(\sqrt{\gamma}-1)} - \dfrac{D_3}{D_2} \cdot (\sqrt{\gamma}-1)^2 \cdot k_2^2\right]}{[k_2 + (\sqrt{\gamma}-1) \cdot k_2]}} \qquad (15)$$

and

$$\lambda_c^2 = \frac{D_2}{(\sqrt{\gamma}-1) \cdot k_2} \qquad (16)$$

The results reported here lead to the conclusion that symmetry breaking chemical instabilities may indeed be important in biological systems. The space differentiation produced in this way is characterized by the maintenance of the gradients of the chemical potentials of the substances involved in the chemical reactions. Such gradients may in turn modify the physico-chemical state of chemical compounds, even if they do not participate directly in the reactions involved in the chemical instability.

The state of such systems can no longer be understood through a mere extrapolation of equilibrium or near

equilibrium conditions, for the instabilities introduce essentially new features.

It may be significant that the characteristic lengths we find are of the order $10^{-2}$–$10^{-4}$ cm (equations 5, 12 and 16). Such lengths are large with respect to molecular dimensions. This justifies *a posteriori* a macroscopic treatment of the type we have applied. On the molecular scale we may speak of local thermodynamic equilibrium.

The situation is somewhat similar to that when we compare fluids in laminar or turbulent motion. Again on the molecular scale, we do not expect any difference, for the range of correlation which appears beyond the critical Reynolds number is much larger than the characteristic range of molecular interactions.

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# Modifiable Synapses necessary for Learning

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Even the simplest types of synaptic modification might be the basis of memory; and both short term and long term memory may have similar mechanisms.

CHANGES in synapses in the brain may be the basis of at least some forms of memory. Several models have been put forward[1–8] to show that synapses which change in various different conditions can produce the input–output relations of learning behaviour in appropriate neuronal networks. And there has been some discussion[5,8–10] of the question of which of the many possible types of modifiable synapses could account for memory and which could not. This article shows that many of the simple types of modifiable synapses which were previously thought to be incapable of underlying memory are able to do so. The arguments that they would not be able to provide the basis of memory involved assumptions about the nature of temporal coding in the nervous system which cannot easily be justified. Thus a consideration of the logical capabilities of different types of modifiable synapses does not provide reasons for believing in the existence of some categories and not of others. But if one considers the number of anatomical structures required in a memorizing network it is possible to justify a preference for certain types of hypothetical synapses.

I shall also show here that even if the modifiable synapses tend to revert rapidly to their original states after modification, a nervous system which was suitably organized could nevertheless maintain a pattern of synaptic changes indefinitely once it had been set up. Such a process for maintaining memories could also lead the synapses to become eventually more permanently and irreversibly altered. Thus a model can be devised in which synaptic changes underlie both long and short term memory, and in which memories gradually acquire the increased stability in the face of disturbances of the brain which is characteristic of long established memories in both animals and man.

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## Logical Capabilities of Modifiable Synapses

Hebb[1] provided the first carefully defined model in which synaptic modification (requiring nearly simultaneous firing of the presynaptic axon terminal and of the postsynaptic cell) could account for learning behaviour. Shimbel[2] and Rosenblatt[3] have described in more quantitative detail various models in which postsynaptic thresholds and synaptic strengths vary when there are different combinations of postsynaptic and presynaptic firing. Eccles[4] pointed out, however, that although some forms of modifiable synapse had been found in the nervous system, models such as these were postulating different and more complicated forms. He suggested that synapses showing something like prolonged post-tetanic potentiation could be responsible for learning; but he did not show in detail any configurations which could achieve in this way even the simplest forms of learning. Burns[5,10] has queried Eccles's suggestion and proposed what amounts to a principle that alterations in the influence of a modifiable cell must depend on activity in more than just the cell which is modified. This principle seems to gain rigorous support from Brindley[8], who showed that a certain class of modifiable synapses (class A), which includes simple facilitating and fatiguing synapses, cannot give rise to the input–output relations corresponding to even the simplest type of classical conditioning in nets with single spike inputs. This conclusion of Brindley's only holds, however, for nervous systems with a particular sort of temporal coding. I shall not attempt here to define rigorously the classes into which different forms of temporal coding could be divided. But I shall show that if events recorded by the nervous system are coded as bursts of impulses rather than as single spikes, then it is possible to use synapses the modification of which results only from their own presynaptic firing to devise a model of any sort of learning or conditioning.