

Biological order, structure and instabilities¹

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I. INTRODUCTION

The problem of the origin of life belongs clearly to physics as well as to biology and it is not surprising that this question is well appropriate in discussing the relation between these two disciplines.

It is customary to decompose the general problem of the origin of life into two parts. On the one side, independently of what a living system may be, it is clear that its functioning can only be conceived in a medium already prepared to accept life. A long *chemical evolution* is therefore a necessary prerequisite of life and at the same time determines, to a large extent, the chemical composition of actual living systems. A second and equally important aspect is to determine the type of events which lead from inanimate to living objects. Necessarily, this part of the problem is dealt with by studying the actual biological structures and functions and then trying suitable extrapolations to the past.

In this review we mainly deal with this second point. Here, discussions are often centred around a certain number of general themes. This is still so in most recent publications (Lwoff, 1962; Monod, 1970; Jacob, 1970; see also the books edited by Whyte, Wilson & Wilson 1969; Grene 1969; Koestler & Smythies, 1969) and indicates that the questions thus raised correspond to quite fundamental problems. In this introduction we shall try to state and briefly comment on some of these topics. We will then indicate how one can formulate these questions in more precise terms which permit the construction of models and the deduction of specific predictions based on thermodynamics of irreversible processes.

I. I. *What is the status of living objects in respect to the second law of thermodynamics?*

It is generally accepted that the present biological order reflects the effect of structures acquired during a long evolution (Lwoff, 1962): it is the capacity to capture and transmit past experience that characterizes the living systems. The remarkable fact is that this idea of biological evolution, which emerged in the nineteenth century, appears to be really conflicting with the idea of evolution formulated in thermodynamics:

(a) In biology or in sociology, the idea of evolution is associated with an irreversible increase of organization giving rise to the creation of more and more complex structures.

(b) In thermodynamics and statistical mechanics, the second law is formulated as the Carnot–Clausius principle. In its modern version, the content of this law is as follows. There exists a function, the entropy S , which depends on the macroscopic state of the system. For systems exchanging energy and matter with the surroundings, the entropy variation dS during a time dt may be decomposed as

$$dS = d_e S + d_i S, \quad (1)$$

where $d_e S$ is the *entropy flow* from the surroundings and $d_i S$ the *entropy production* from irreversible processes inside the system. The second law then implies that for all physical processes

$$d_i S \geq 0, \quad (2)$$

the equality applying only at equilibrium. In the limit of an isolated system (energy E is constant) $d_e S = 0$ and (2) becomes

$$(dS)_E \geq 0. \quad (3)$$

Entropy therefore increases irreversibly for an isolated system.

Evolution is always directed to a continuous disorganization, i.e. the destruction of structures introduced by initial conditions. The work of Boltzmann has added a new important element: irreversibility in thermodynamics expresses a statistical law of evolution to the ‘most probable’ state corresponding to the state of maximum disorder.

Ever since its formulation it was realized that the second law of thermodynamics has wide implications. The extension of the thermodynamic concept of evolution to the world as a whole leads to the idea that ‘structure’ originated in some distant, ‘golden age’ (Whyte *et al.* 1969).

Since then this order is annihilated in a progressive chaos corresponding to the 'most probable' state.

The biological evolution points precisely to the opposite direction. Is it possible to reconcile these two apparently opposite aspects of evolution?² It is true that biologists insist nowadays on the fact that the second law applies to a system as a whole—living system + environment (Lwoff, 1962; Monod, 1970; Jacob, 1970) and that this is perfectly compatible with an entropy lowering in the organism, and that Darwin himself attributes to natural selection the irreversible evolution to more organized structures in living systems. In other terms, it is because natural selection favours exceptional situations corresponding to a sort of 'statistical fluctuation' that exceptions, i.e. organized structures, finally become the rule in biology (Jacob, 1970). However, these general arguments cannot suffice for solving the problem. One would like to be more precise and attribute the effects to definite physical laws. And at this point the conflict reappears because one is really confronted with different types of behaviour. For instance, if we let two liquids mix, diffusion takes place with a progressive forgetting by the system of its initial conditions. This is a typical example of situations described by an increase of entropy. On the contrary, in biological systems heterogeneity is the rule: inequalities between concentrations are maintained by chemical reactions and active transport. *Coherent behaviour* is really the characteristic feature of biological systems (Weiss, 1968).

What is the attitude to take? Do there exist two different, irreducible types of physical laws? The difference in behaviour is so drastic that this question has been asked repeatedly (Elsasser, 1958).

While a general answer is perhaps too difficult at present, the physicist may help by pointing out that there exist in physical chemistry a wealth of systems with two types of behaviour: systems behaving 'chaotically' (thermodynamically) in some cases and in a coherent way in others. At least in these cases there exists then only one type of physical law but different physical situations. Generally speaking, the destruction of structures is the situation which prevails in the neighbourhood of thermodynamic equilibrium. On the contrary, as we shall see in the subsequent paragraphs, creation of structures *may* occur, with *specific non-linear kinetic laws* beyond the domain of stability of the states showing the usual thermodynamic behaviour.

² We here follow closely some recent papers by I. Prigogine (1967*b*, 1969) and the monograph by Glansdorff & Prigogine (1971).

Closely related to the first theme is the problem of randomness and order.

I. 2. *Randomness and order*

The most detailed analysis of order made in physics refers to equilibrium situations. It is well known that at thermodynamic equilibrium entropy reaches a maximum for an isolated system, free energy reaches a minimum for a system of given temperature and volume, and so on. The appearance of ordered structures is favoured by lowering the temperature. Indeed equilibrium structures correspond to a competition between energy and entropy. At sufficiently low temperature energy becomes the dominant factor (the entropy contribution to free energy being then small) and the system reaches a configuration favouring a minimum of potential energy.

We may call this the *Boltzmann order principle* because it is expressed through the competition between energy E and temperature in the Boltzmann factor $\exp(-E/kT)$. This competition on the molecular level is then amplified on the macroscopic level when phenomena such as phase transitions, ferromagnetism or partial miscibility are involved.

One of the most interesting problems of statistical physics and thermodynamics is to extend the concept of order *to non-equilibrium situations* for systems in which the appearance of ordered structures in thermodynamic equilibrium would be very unlikely. Even very simple examples show how subtle one has to be. Consider a horizontal fluid layer heated from below (Bénard problem). A temperature gradient is created which opposes the effects due to the gravitational force. For small values of this gradient (i.e. for states close to equilibrium) what happens is simply a transfer of heat by conduction in a fluid at rest. But for a critical value of the gradient there appears an internal convective motion, which is established spontaneously (Bénard instability). Moreover the convective motion is organized in the form of very regular patterns, e.g. hexagonal cells. This is a typical phenomenon of structuration which requires a high degree of co-operativity from the molecular point of view. Indeed, below instability the energy of the system is distributed in the random thermal motion of the molecules. Beyond the Bénard point it appears at least partly as the energy of macroscopic regular motion. At thermodynamic equilibrium the probability that a macroscopic number of molecules (of the order of 10^{20}) spontaneously organizes to a regular flow pattern would be vanishingly small. It is only because the external constraint (temperature

gradient) drives the system sufficiently far from equilibrium that the system may give rise to ordered, highly co-operative structures.

In all these phenomena a new ordering principle not reducible to the Boltzmann order principle appears. In the Bénard instability there exists also a competition (Glansdorff & Prigogine, 1971) but of completely different dynamical type, as it involves dissipative processes (in this case viscous dissipation and dissipation of heat) and convection through fluctuations. There exists therefore a second ordering principle which we may call briefly '*order through fluctuations*'.

We shall show in the subsequent paragraphs that such phenomena may also arise in far from equilibrium chemical processes relevant to biology.

1.3. *Chance or law*

The preceding discussion brings up the question of the role of chance versus the role of deterministic laws in the formation of order; that is, situations corresponding to a low entropy. This is an especially crucial point in biology which has been raised repeatedly: What is the type of description one may apply to the evolution of biological systems? Is life the realization of the 'most improbable' or has it originated with probability 'one' following a 'deterministic' course?

One generally associates classical physics with a deterministic causal description. However, in problems involving a large number of degrees of freedom such a description may not be sufficient. The main reason is that the existence of many degrees of freedom implies automatically the existence of fluctuations, i.e. of spontaneous deviations from some average, macroscopic behaviour. In most cases the appearance of a fluctuation of a given type may be treated as a random event obeying definite probabilistic laws. On the other hand, once the fluctuation arises, the system responds in some way according to some macroscopic laws.

Let us see on a simple example how these two elements may co-operate rather than be in opposition. Consider again the Bénard problem. Suppose that there appears a small fluctuation, δE_{kin} in the kinetic energy, tending to establish a macroscopic convection pattern. If δE_{kin} vanishes for $t \rightarrow \infty$ the state of fluid at rest will be stable; if δE_{kin} increases with time a new state will be reached corresponding to a fluid in convective motion. As we saw before, this indeed happens beyond the Bénard instability. In more technical terms, there exists a dimensionless quantity known as the Rayleigh number, whose value determines the stability

properties of the system. Beyond the threshold corresponding to a critical value of this number fluctuations are amplified and the system becomes unstable.

The main point to realize is therefore the following: a new structure or organization (such as the cellular convection pattern appearing beyond the Bénard instability) is always the result of an instability. It originates in a fluctuation, i.e. in a fundamentally stochastic element. A fluctuation is usually followed by a response that brings the system back to the original state and which is a perfectly deterministic process. It is only at the point of formation of a new structure that *fluctuations are amplified*, reach a macroscopic level and finally stabilize to a new regime representative of the structure arising beyond instability. Once this effect is allowed by the boundary conditions imposed on the system, it will happen with probability one, provided the fluctuation is created initially by some mechanism.

In this example a physical phenomenon involves elements of both chance and determinism which co-operate rather than conflict. In fact fluid dynamics contains a wealth of similar examples: laminar-turbulent transition, formation of finite amplitude surface waves, and so on. This general feature is a direct consequence of the non-linearity of the equations of hydrodynamics which implies the existence of many possible solutions. What decides then the occurrence of a given type of regime is the stability of the corresponding solution under the conditions imposed on the system.

One of the aims of this review will be to relate the stability theory of non-linear systems to thermodynamics of irreversible processes. This means that one has to incorporate in some way in the thermodynamic description the response of the system to fluctuations, i.e. to build a *generalized thermodynamics* which will also include a macroscopic theory of fluctuations.

One of the main results of this approach will be to show (cf. §§III-V) that most of the properties of hydrodynamic instabilities are shared by systems obeying non-linear chemical kinetic laws with the additional important feature that the variety of non-linear situations is by orders of magnitude greater in chemical kinetics. The evolution of such systems could then involve a succession of instabilities arising from certain types of fluctuations (stochastic element) followed by a deterministic evolution to a new type of regime. Order through fluctuations implies always both a microscopic and a macroscopic element and therefore both chance and

law. The implications of this result to the evolution of biological systems will also be discussed in some detail.

The study of the architecture of ordered systems brings up the fourth general theme we wish to mention in this introduction.

1.4. *Hierarchical structure organization*

It is generally admitted that biological systems consist of a superposition of co-ordinated structures and functions of increasing complexity. This hierarchy in structure seems also to be a characteristic feature of other systems such as systems interacting with gravitational forces (Whyte *et al.* 1969; Haggerty, 1970). In biology the situation is complicated by the fact that systems governing fundamental processes appear to be so strongly connected that one is tempted to think of them as a whole rather than consisting of more elementary, loosely connected parts.

Many workers in biology have felt that the only appropriate language to discuss this type of situation is *the systems theory* description, in particular the ideas based on *automata theory*. For a very lucid exposition of this point of view we refer to R. Rosen (in Whyte *et al.* 1969). A seemingly opposed attitude is adopted by molecular biologists claiming that a knowledge of the lowest relevant level of biological activity (in particular the information encoded in DNA) determines the properties at higher levels.

In this review we will approach the problem of hierarchical structures by trying to relate the existence of different levels of organization to a succession of instabilities. Indeed, the behaviour of living objects is largely determined by a number of key chemical reactions and transport processes. Now, in chemistry non-linearity is a general rule and may appear in a practically infinite number of varieties by orders of magnitude more complex than in hydrodynamics. It is therefore likely to have instabilities and multiple transitions to more and more ordered states. A state of given complexity would then contain the 'memory' of the past instabilities, each one of which would have contributed in the appearance of a new feature essential for the stability and maintenance of the final state. This would be the information which has to be transmitted. We shall come back to this problem.

After this introduction we shall now discuss briefly, in the next section, the general ideas of thermodynamics of irreversible processes and their applications to the study of stability of non-linear systems. In sections III and IV we shall develop a few representative examples of chemical systems

giving rise to ordered structures. In section V we shall try to situate the living systems in respect to the laws of thermodynamics and compare some features of biological structures and functions to the behaviour of the examples of sections III and IV. Section VI will be devoted to general comments on the implications of the results and on possible future developments.

II. THERMODYNAMICS OF IRREVERSIBLE PROCESSES

II. 1. *The linear region*

The starting-point is to decompose the entropy variation dS according to equation (1) and to perform a macroscopic analysis of the two parts $d_e S$ and $d_i S$. In classical thermodynamics one deals essentially with equilibrium situations where the entropy production vanishes. In non-equilibrium thermodynamics one studies macroscopic states on the basis of their entropy production.

The explicit form of the entropy production may be derived from the balance equation of mass, momentum and energy once the assumption of *local equilibrium* is made (Glansdorff & Prigogine, 1971). Analytically, this assumption implies first that a local formulation of non-equilibrium thermodynamics is possible. And, secondly, that in this formulation the local entropy will be expressed in terms of the same relations involving the same state variables as in equilibrium. It has been shown that the validity of the local equilibrium assumption implies that collisional effects are sufficient to eliminate large deviations of the momenta distribution functions from local Maxwellian distribution (Glansdorff & Prigogine, 1971). This condition is certainly satisfied in dense media or under conditions of biological interest.

One may now proceed in the calculation of the entropy production per unit time and volume, σ , defined by

$$P = \frac{d_i S}{dt} = \int dV \sigma \quad (\sigma \geq 0). \quad (4)$$

The final result is

$$\sigma = \sum_i J_i X_i. \quad (5)$$

We obtain a bilinear form summed over all irreversible processes i , of suitably defined flows (or rates) J_i associated with these irreversible processes, and of generalized forces X_i giving rise to these flows. In the

case of chemical reactions which will be of special interest in this review, we have

$$J_i = v_i, \\ X_i = \frac{\mathcal{A}_i}{T} = - \frac{\sum_{\rho} v_{\rho i} \mu_{\rho}}{T}. \quad (6)$$

v_i is the reaction rate, \mathcal{A}_i the corresponding affinity, T the temperature, μ_{ρ} the chemical potential of constituent ρ and $v_{\rho i}$ the stoichiometric coefficient of ρ in the i th reaction.

The first development of non-equilibrium thermodynamics based on equation (5) was in the *linear range* defined by the relations (see Prigogine, 1947, 1967*a*; de Groot & Mazur, 1962)

$$J_i = \sum_j L_{ij} X_j, \quad (7)$$

where the *phenomenological coefficients* L_{ij} are in general functions of the thermodynamic state variables.

The assumption of linear relations between flows and forces is especially restrictive in the following two cases:

(a) *Inertial effects*. Whenever a system is not at mechanical equilibrium, the coupling between dissipative and convective processes leads to effects of a new type which cannot be treated by the methods of linear theory. An example is the Bénard instability described in the previous section.

(b) *Chemical effects*. To obtain a linear relation between reaction rate and affinity we need the condition (cf. equation (6) and assume an ideal system)

$$|\mathcal{A}/RT| \ll 1, \quad (8)$$

where R is the gas constant. Inequality (8) is generally not satisfied except in the immediate neighbourhood of equilibrium. In the general case, it is necessary to adopt non-linear phenomenological laws. We notice that the local equilibrium assumption may still be valid beyond the domain of linear relations, equation (7) (Glansdorff & Prigogine, 1971).

Within the linear region, two quite general theorems may be proven which have both wide implications. In the first place, Onsager has shown that it is always possible to choose the flows and forces such that the matrix $[L_{ij}]$ be symmetrical (Onsager, 1931*a, b*):

$$L_{ij} = L_{ji}. \quad (9)$$

These celebrated Onsager *reciprocity relations* were later generalized by Casimir (1945) to a wider class of irreversible phenomena.

A second theorem proves the existence of a general *variational principle* for irreversible processes in the linear domain. The problem is formulated as follows. Consider a non-isolated system, e.g. a closed system which can exchange energy with the outside world, or an open system which can exchange both energy and matter ($d_e S \neq 0$). In this case, and provided the boundary conditions imposed on the system remain time-independent, the system may tend to a permanent regime other than equilibrium. This will be a *steady non-equilibrium state*. Let us choose the flows $\{J_i\}$ such that at this state one has

$$J_i^{(0)} = \sum_j L_{ij} X_j^{(0)} = 0 \quad (i = 1, \dots, \gamma), \quad (10)$$

and at the same time the coefficients L_{ij} become constants. Consider finally the entropy production σ per unit volume and time as a function of the generalized forces $\{X_i\}$ ($i = 1, \dots, \gamma$). It has then been proven by I. Prigogine (1947; see also Glansdorff & Prigogine, 1971) that σ is a minimum at the steady state with respect to variations of the generalized forces compatible with the boundary conditions. This *minimum entropy production theorem* proves that σ is a non-equilibrium state function playing the same role as the thermodynamic potentials in equilibrium theory. In particular the minimum property guarantees the stability of the steady state. Alternatively, the theorem provides an *evolution criterion*, as it implies that a physical system will necessarily evolve to the steady non-equilibrium state starting from an arbitrary state close to it. The whole evolution is thus cast in a compact thermodynamic principle. Analytically this may be expressed in the form

$$\int dV d\sigma/dt \leq 0. \quad (11)$$

In spite of the interest of such general properties it is necessary to recognize that in the linear range the possibility of formation of new, ordered structures has to be ruled out. By its very stability, the linear domain is an extrapolation of the equilibrium regime and implies a monotonic approach to a single steady state, once equilibrium itself is stable. In order to relate the concept of *evolution* to the concept of *structure* it will now be necessary to generalize thermodynamics to the non-linear region.

II. 2. *Non-linear thermodynamics*

We have already stressed earlier in this section that in order to deal with inertial or chemical effects it will be necessary to extend thermodynamics to include non-linear phenomena. An interesting point is that it is still possible to analyse this domain by the methods of macroscopic physics. The reason for this is that the local equilibrium assumption remains valid for all phenomena of fluid dynamics described by the Stokes–Navier equations and in all chemical reactions involving activation energies of the order of several RT 's (Glansdorff & Prigogine, 1971).

We shall now briefly describe an extension of thermodynamics to non-linear phenomena which has been worked out during the last years by Glansdorff & Prigogine (1971). The main idea of the approach is to extend in some sense the minimum entropy production theorem.

It is straightforward to verify that inequality (11) does not extend trivially beyond the linear region. Instead, one may proceed as follows. Recalling the general expression (5) for σ we decompose $d\sigma$ as follows:

$$\left. \begin{aligned} d\sigma &= d_J\sigma + d_X\sigma, \\ d_J\sigma &= \sum_i X_i dJ_i, \\ d_X\sigma &= \sum_i J_i dX_i. \end{aligned} \right\} \quad (12)$$

Consider first purely dissipative systems without convective motion. One then proves that, provided these systems are subject to time-independent boundary conditions and the equilibrium state remains stable, the following inequality is always satisfied

$$\int dV d_X\sigma \leq 0. \quad (13)$$

The equality applies in the steady state only. Inequality (13) will be referred to as *the evolution criterion*. We see that in the non-linear domain one has to split the entropy production variation in order to obtain a general inequality. For systems undergoing mechanical motion inequality (13) extends in a more complicated form which will not be discussed here (Glansdorff & Prigogine, 1971).

The mathematical analysis of the differential form $d_X\sigma$ shows that, in general, $d_X\sigma$ is not a total differential of some state function. In the domain of local equilibrium assumption the effects which are responsible for this property are due to chemical reactions. It is only in the limit of linear phenomena and of validity of the Onsager relations that $d_X\sigma$ becomes the differential of a state function, the half of entropy production.

In this case the evolution criterion reduces to the theorem of minimum entropy production. In a few exceptional cases it is also possible to transform $d_X \sigma$ to a total differential by introducing suitable integrating factors.

The property of $d_X \sigma$ not to be a total differential implies that no true variational principle exists far from equilibrium and therefore that the stability of steady states is not always ensured. One is thus led to the search for independent stability criteria. We shall outline the derivation of a stability criterion in the limit when only chemical reactions are considered. This is not a very serious restriction: we have just seen that it is mainly because of chemical reactions that $d_X \sigma$ becomes a non-total differential.

We first give the explicit form of inequality (13) for chemical reactions. Referring to equations (6) and (12) and assuming that the system is maintained at constant temperature we obtain

$$\left. \begin{aligned} \sum_i v_i d\mathcal{A}_i &\leq 0 \\ \sum_i v_i^0 d\mathcal{A}_i &= 0 \end{aligned} \right\} \text{at the steady state.} \quad (14)$$

In (14) it is understood that i is such that the affinities \mathcal{A}_i are all independent. This may always be achieved by forming suitable linear combinations of velocities and affinities of the individual reactions. With this choice of v_i, \mathcal{A}_i the equality in (14) implies that

$$v_i^0 = 0 \quad \text{at the steady state.} \quad (15)$$

Imagine now that the steady state of the system is perturbed as a result of a random fluctuation or of an external disturbance. Let $\delta v_i, \delta \mathcal{A}_i$ be the fluctuations in v_i, \mathcal{A}_i :

$$\begin{aligned} v_i &= v_i^0 + \delta v_i = \delta v_i, \\ \mathcal{A}_i &= \mathcal{A}_i^0 + \delta \mathcal{A}_i. \end{aligned} \quad (16)$$

The variation of entropy production due to the fluctuations of the affinities will be (cf. equations (12) and (16))

$$T \delta_X \sigma = \sum_i v_i \delta \mathcal{A}_i = \sum_i \delta v_i \delta \mathcal{A}_i. \quad (17)$$

Suppose now $\delta_X \sigma < 0$. Then according to inequality (14) its variation will also be negative and $\delta_X \sigma$ will never go to zero. In other words, the

fluctuation will never be damped. We obtain therefore the stability criterion (Prigogine, 1969; Glansdorff & Prigogine, 1971)

$$T \delta_X \sigma = \sum_i \delta v_i \delta \mathcal{A}_i \geq 0 \quad (18)$$

for all fluctuations compatible with the equations of evolution.

This criterion may also be formulated in terms of the entropy excess due to fluctuations. Let s_0 be the specific steady-state entropy, s the specific entropy of a state reached by a random fluctuation. We expand s around s_0 and take the limit of small fluctuations:

$$s = s_0 + \delta s + \frac{1}{2} \delta^2 s + \dots \quad (19)$$

From equilibrium stability theory one has (Glansdorff & Prigogine, 1971)

$$\delta^2 s \leq 0. \quad (20a)$$

On the other hand, one can show straightforwardly (Glansdorff & Prigogine, 1971) that

$$\frac{\partial}{\partial t} \frac{1}{2} \delta^2 s = \delta_X \sigma = \frac{1}{T} \sum_i \delta v_i \delta \mathcal{A}_i. \quad (20b)$$

$\delta_X \sigma$ is the excess entropy production due to fluctuations. Inequalities (20a) and (18) constitute an equivalent stability criterion, much in the spirit of Lyapounov stability theory (Minorski, 1962). $\delta^2 s$ is seen to play the role of a thermodynamic Lyapounov function.

Inequality (18) contains a complicated interplay between the different reactions. The stability of the system will be threatened as soon as there are processes contributing a negative amount to the excess entropy production. A more detailed study shows that this is indeed true for autocatalytic and for some type of cross-catalytic reactions. We again find in more precise terms what was already conjectured in §I, i.e. that nonlinearities are necessary for the occurrence of instabilities. Of equal importance of course, is the fact that the system operates at a finite distance from thermodynamic equilibrium.

It is instructive to look at the stability criterion from still another standpoint—that of fluctuation theory. Consider first an isolated system in equilibrium. It has been shown by Einstein that the probability of fluctuations around equilibrium is given by

$$P \propto \exp [\Delta S/k] \quad (21a)$$

(see Glansdorff & Prigogine, 1971) where ΔS is the entropy change around equilibrium ($\Delta S < 0$ for a fluctuation) and k is Boltzmann's

constant. For small fluctuations ΔS may be expanded to second-order quantities.³ Since for an isolated system at equilibrium S is a maximum, equation (21 a) can be reduced to

$$P \propto \exp [(\delta^2 S)_{\text{eq}}/2k]. \quad (21 b)$$

Recently it has been shown (Glansdorff & Prigogine, 1971; Lax, 1960; Nicolis & Babloyantz, 1969; Nicolis, 1971) that Einstein's fluctuation theory may be extended to non-equilibrium states, at least for wide classes of model systems. Equation (21 b) is now replaced by

$$P \propto \exp [(\delta^2 S)_0/2k] \quad (22)$$

where $(\delta^2 S)_0$ is calculated around a steady non-equilibrium state. Comparing with equation (20) we see that one can now understand the mechanism of an instability in terms of fluctuation theory. Starting with $(\delta^2 S)_0 < 0$ around some reference state, the system will always remain close and finally decay to this state which will correspond to the most probable configuration, as long as $(\partial/\partial t)(\delta^2 S)_0$ is positive. On the other hand, for $(\partial/\partial t)(\delta^2 S)_0$ negative, P will first decrease. The system will then evolve to a new regime corresponding to the most probable state.

III. CHEMICAL INSTABILITIES IN HOMOGENEOUS MEDIA

When a reference state of a system becomes unstable, the system tends to a new regime which may correspond to a completely different type of behaviour. In order to investigate the various possibilities, we first formulate the problem of instabilities in a somewhat more general form. Consider a non-linear system of chemical reactions describing, e.g. the conversion of a set of initial products $\{A\}$ to the final products $\{F\}$ and let $\{X, Y, \dots\}$ represent the values of concentrations of the intermediates. In a 'black box' notation:

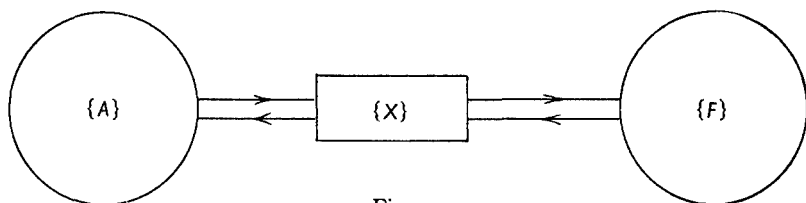


Fig. 1

³ In fluctuation theory S is considered to be a function of a set of *macroscopic* observable quantities $\{a_1, \dots, a_n\}$, with $n \ll N$; N being the number of degrees of freedom of the system.

It is understood that the system $\{X, Y, \dots\}$ is open to $\{A\}$, $\{F\}$ and subject to time-independent conditions. It is convenient to measure the deviation from equilibrium by the value of some parameter R which depends on the overall affinity, i.e. on the ratios of $\{A\}$, $\{F\}$ and on the equilibrium constant. The first point to notice in the system just described

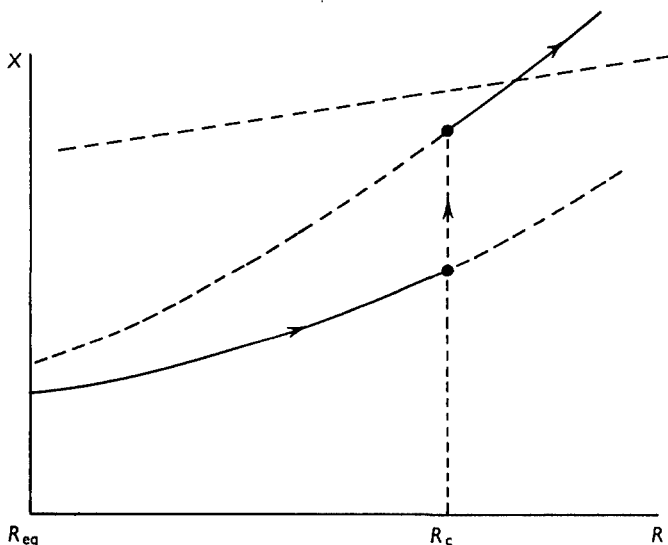


Fig. 2. Steady-state concentration of a chemical intermediate as a function of the parameter R measuring the deviation from equilibrium. Broken lines correspond to unstable solutions of the kinetic equations.

is that, owing to the non-linearity of the equations of evolution of the intermediates, there is a possibility, *a priori*, for more than one steady state. At equilibrium ($R = R_{eq}$) the correct solution is known independently as the one minimizing the free energy (at constant temperature and volume). Imagine now that R deviates more and more from R_{eq} . For $|R - R_{eq}|$ 'small' the equilibrium solution first changes smoothly and we obtain a branch referred to as the *thermodynamic branch*. All states on this branch are stable by the minimum entropy production theorem. Again, amongst all possible regimes, this theorem determines, independently of the details of the kinetics, the correct steady-state solution. As $|R - R_{eq}|$ now gets larger, the stability of the states of the thermodynamic branch is no longer automatically ensured. If at some point R_c , the excess entropy production (20b) may become negative, the system may leave abruptly the thermodynamic branch and go to a new state which now becomes stable.

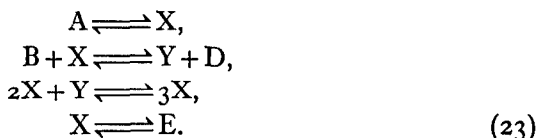
The transition value R_c is a *thermodynamic threshold* for the appearance of instabilities. Its explicit value depends on the deviation from equilibrium, i.e. on the level of dissipation. In addition, it depends strongly on the detailed kinetics of the chemical reactions. This is to be contrasted with the behaviour prevailing in fluid dynamics. The Stokes–Navier equations satisfy a set of similitude theorems, which define a restricted number of dimensionless parameters influencing the stability properties. In chemical kinetics the variety of non-linear situations is practically infinite and the stability properties are strongly dependant on the kinetics.

What are the properties of the new states arising beyond the instability of the thermodynamic branch? Is it possible to associate with these instabilities the appearance of ordered structures of a new type? Such non-equilibrium structures would differ from equilibrium ones (such as crystals) in that their maintenance would necessitate the continuous exchange of energy and matter with the outside world. For this reason, they can be called *dissipative structures*.

The detailed study of non-equilibrium instabilities has shown that such structures are indeed possible. Generally speaking, one can show that on the new branch, one may have one of the following possibilities: (a) time organization, (b) space organization, (c) multiple steady states.

We will briefly discuss these possibilities on a simple example, assuming that the initial and final product concentrations are maintained space and time-independent. The more realistic case of inhomogeneous media is studied in the following section.

We consider the following reaction scheme



The autocatalytic step involving a trimolecular reaction is a convenient way to introduce non-linearity which, as we saw earlier, is a necessary prerequisite for the occurrence of instabilities. The system is open to A, B, D, E, which are maintained space and time-independent. Let us for simplicity set all kinetic constants equal to unity. The deviation of the state of the system (23) from equilibrium is then given by the concentration ratios A/E and B/D . Equilibrium itself corresponds to

$$\left(\frac{A}{E}\right)_{\text{eq}} = \left(\frac{B}{D}\right)_{\text{eq}} = 1. \tag{24a}$$

The study of the system is greatly simplified in the limiting case

$$D \rightarrow 0, \quad E \rightarrow 0. \quad (24b)$$

Physically, this implies that products D and E are removed as soon as they are produced. The affinity of the corresponding reactions tends then to infinity, i.e. the system operates at 'infinite distance' from equilibrium. Once this is admitted, a further simplification will be adopted which consists in neglecting back reactions in the remaining two steps involved in (23). The scheme thus becomes completely irreversible. Still, it is possible to define the continuation of the thermodynamic branch, which is simply given by the homogeneous steady-state solution

$$X_0 = A, \quad Y_0 = B/A. \quad (25)$$

Let us assume for simplicity that the system evolves in a single space-dimension, r . The chemical kinetic equations representing (23) read (we take the limit of an ideal mixture):

$$\left. \begin{aligned} \frac{\partial X}{\partial t} &= A - (B + 1)X + X^2 Y + D_X \frac{\partial^2 X}{\partial r^2}, \\ \frac{\partial Y}{\partial t} &= BX - X^2 Y + D_Y \frac{\partial^2 Y}{\partial r^2}. \end{aligned} \right\} \quad (26)$$

D_X , D_Y are the diffusion coefficients of X and Y. One of the most important questions in the far from equilibrium behaviour of the system of equations (26) concerns the stability of the thermodynamic solution (25). To answer this question, we have to test the behaviour around (25) of *all kinds of fluctuations that may be present*. This can be carried out either by explicitly solving equations (26) or by the thermodynamic methods outlined in the previous section, i.e. by determining the conditions for which the excess entropy production vanishes. We briefly describe below the results corresponding to two largely different types of fluctuations.

(a) Suppose first that the initial fluctuation is practically independent of space (Glansdorff & Prigogine, 1971). In this case it is sufficient to study equation (26) after suppressing the diffusion terms. One then finds that for

$$B > B_c, \quad B_c = A^2 + 1 \quad (27)$$

state (25) is unstable. Beyond instability, the system evolves to an undamped periodic regime which is represented in Fig. 3. One shows that this regime is attained independently of the initial conditions. Its

characteristics, for instance, the period or amplitude of the oscillation, are therefore intrinsic properties of the system and do not depend on the initial conditions: we have what is known in non-linear mathematics as a limit cycle behaviour (Minorski, 1962).

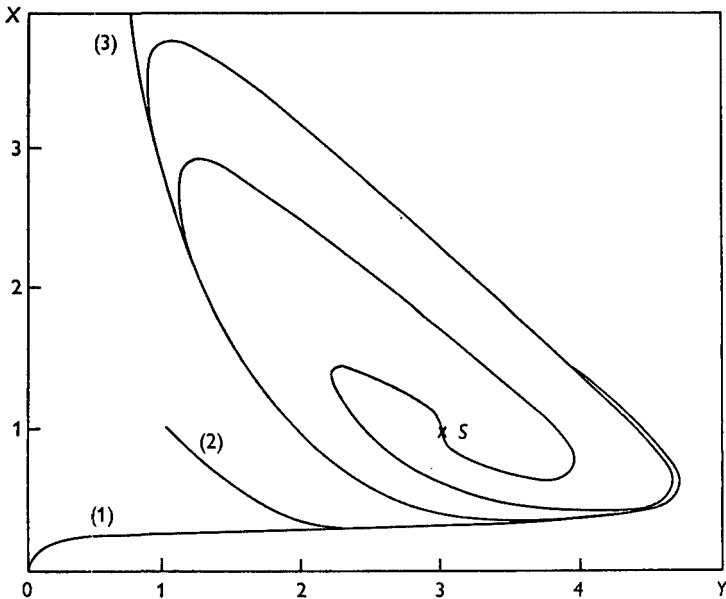


Fig. 3. Approach to a limit cycle in the model (23) for $A = 1$, $B = 3$ and for different initial conditions.

Beyond instability fluctuations behave therefore in a completely different way as around equilibrium or below instability. In the latter cases, fluctuations either decay exponentially or at most they spire around the steady state by performing damped oscillations. Far from equilibrium and beyond instability, the fluctuations are amplified. The system leaves the steady state and goes to a uniquely determined orbit (in our example) or to a discrete set of orbits (in general). This kind of 'ergodic' behaviour is characteristic of a chemical clock. It may be shown that the orbit representing the clock is always asymptotically stable. In conclusion, a chemical clock is characterized by a markedly *coherent behaviour*. The somewhat more familiar periodic behaviour observed in conservative systems (small or finite amplitude oscillations of the pendulum, Volterra-Lotka oscillators, etc.; see Minorski, 1962) is, on the contrary, typically incoherent: a continuum of amplitudes and periods is

available and the corresponding orbits are not asymptotically stable (Minorski, 1962; Lefever & Nicolis, 1971). Conservative systems may not exhibit the coherent behaviour characteristic of a chemical clock.

(b) Suppose now that the initial fluctuation is non-uniform in space. Again one shows that the steady state (25) becomes unstable for values of B beyond some critical value B_c . This time B_c depends on A as well as

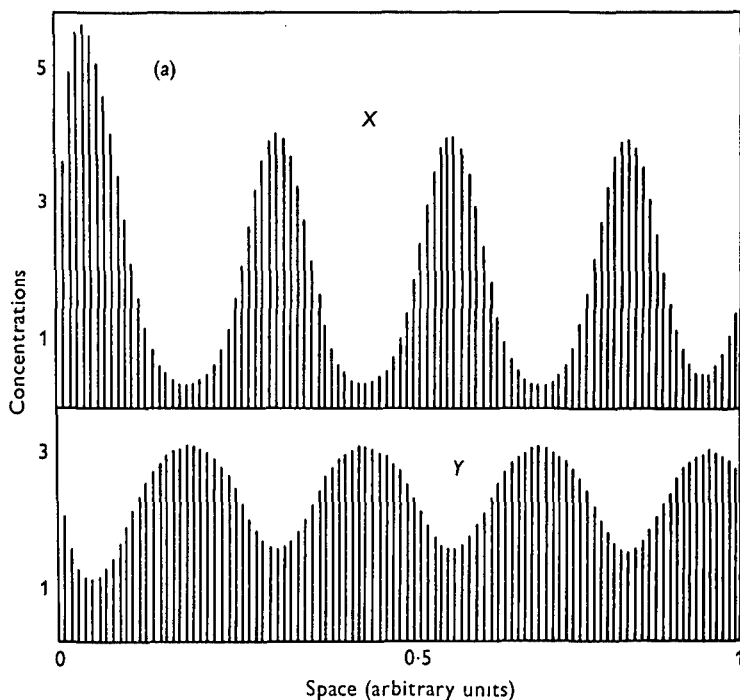


Fig. 4. Space-dependent steady-state distribution for system (23) arising beyond a symmetry-breaking instability. The concentrations of X and Y in the boundaries are maintained equal to the homogeneous steady-state values $X = 2$, $Y = 2.62$. The numerical values chosen for the different parameters are: $A = 2.00$, $B = 5.24$, $D_X = 1.6 \times 10^{-3}$, $D_Y = 8 \times 10^{-3}$.

on the diffusion coefficients D_X , D_Y . For B slightly beyond B_c , fluctuations with wavelength around a critical value λ_c depending on A , D_X , D_Y are amplified and the system leaves state (25). It finally stabilizes to a new steady state which now is space-dependent (Lefever, 1968*a, b*). Figure 4 represents the spatial distribution of X and Y in this state. The wavelength of the spatial periodicity is roughly determined by λ_c , which is the wavelength of the fastest-growing fluctuation beyond the transition.

We obtain a spatial structure arising beyond an instability which changes the symmetry properties of the system, as the latter becomes spontaneously inhomogeneous (*symmetry breaking* instability). Its properties are markedly different from the classical behaviour of equilibrium structures. In particular, its formation requires a thermodynamic threshold corresponding to a minimum level of dissipation: the dissipative structure is a giant fluctuation stabilized by the flow of energy and matter from the outside world. It is easily verified that the configuration represented in Fig. 4 has a lower entropy compared to the uniform steady-state entropy. This entropy decrease is translated by the emergence of space order. We have here an example of 'order through fluctuations'.

Further comments on the significance of dissipative structures are given in the next section. We close this paragraph by observing that the system described by scheme (23) leads to a single uniform steady state. It is possible to construct non-linear chemical models which, under the influence of non-equilibrium constraints, may acquire multiple steady states and exhibit transitions between these states. A detailed study of a number of models may be found in the book by Glansdorff & Prigogine (1971).

IV. LOCALIZED DISSIPATIVE STRUCTURES IN INHOMOGENEOUS MEDIA

IV. 1. *Stability analysis*

We shall now discuss the implications of instabilities in the more general case where the condition of a uniform initial and final product distribution is relaxed. This certainly corresponds to a more realistic situation. Most of the systems realized in laboratory experiments or operating under physiological conditions are subject to a flow of energy or matter arising from the maintenance of non-uniform constraints. In addition, we will see in this section that the non-uniformity of initial and final product distribution introduces essentially new features and is responsible for the appearance of new types of solution of the kinetic equations.

We again illustrate the different types of behaviour on the simple example introduced in the previous section, equation (23). The kinetic equations giving the time evolution of X and Y are still given by (26). This time, however, the concentration of products A and B, which appear as parameters, depends on r . We observe that product B is coupled to X through the term BX , whereas product A appears additively. To avoid

the complication arising from this B - X coupling we assume that B is still maintained uniform and only let A be distributed non-uniformly. According to scheme (23) the evolution of A will be given by the equation

$$\frac{\partial A(r, t)}{\partial t} = -A(r, t) + D_A \frac{\partial^2 A(r, t)}{\partial r^2}. \quad (28)$$

The simplicity of equations (26) and (28) lies thus in the fact that A obeys a *closed* equation which may be solved to completely determine $A(r, t)$. System (26) is then to be solved for X and Y only, A being a given function of r .

The solution of equations (26) and (28) will be subject to the following boundary conditions:

$$\left. \begin{aligned} A(0) &= A(l) = \bar{A} \\ X(0) &= X(l) = \bar{X} \\ Y(0) &= Y(l) = \bar{Y} \end{aligned} \right\} \quad (0 \leq r \leq l). \quad (29)$$

We first study the steady-state solution of equations (26) and (28) reducing to state (25) in the limit $D_A \rightarrow \infty$, corresponding to a uniform distribution of A . This generalized 'thermodynamic solution' corresponds now to a non-uniform configuration and cannot be determined exactly. Rather, it has been necessary to perform numerical calculations combined with the use of the local potential variation technique (Herschkowitz-Kaufman & Platten, 1971). The result is shown in Figs. 5 and 6. We notice that the form of X and Y is still very closely approximated by equation (25) (with A now depending on r) and is only slightly modified by diffusion.

The next step is to study the stability of the profiles shown in Fig. 6.⁴ Again the problem cannot be solved exactly because of the space-dependence of the coefficients of equation (26). It is still possible, however, to apply the same variational technique as before (Herschkowitz-Kaufman & Platten, 1971). The result is the *non-equilibrium phase diagram* shown in Fig. 7. For simplicity the parameters A , D_A and D_X have been held constant. We see that one may define on Fig. 7 three domains:

(a) A stable domain, I. Fluctuations around steady states belonging to this domain regress in time.

(b) An unstable domain, II, where steady states undergo instabilities. The increase of fluctuations is monotonic in this domain.

⁴ Equation (28) determines a single steady-state profile for $A(r)$ (Fig. 5) which is always stable.

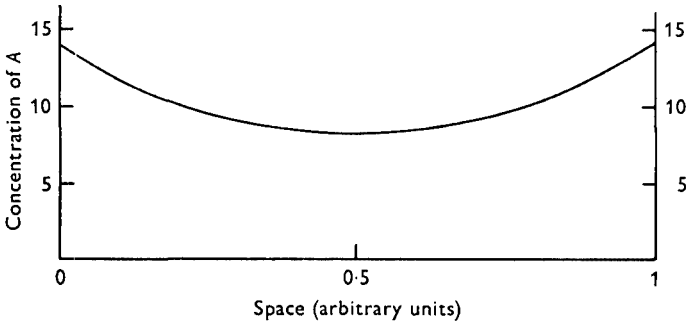


Fig. 5. Steady-state profile of A for $\bar{A} = 14.0$ and $D_A = 197 \times 10^{-3}$.

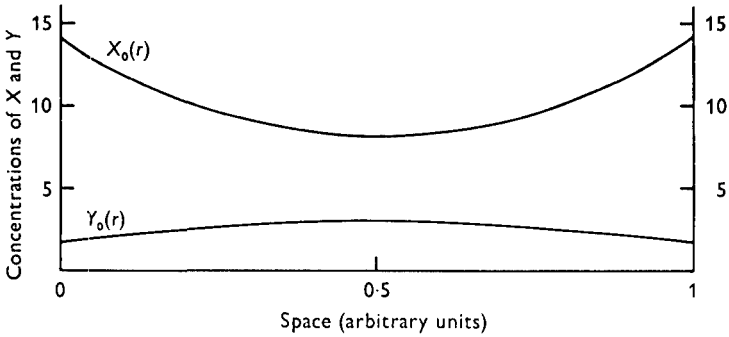


Fig. 6. Steady-state solution of equations (26) reducing to the 'thermodynamic' solution (25) in the limit of uniform distribution of A . The following numerical values have been chosen: $D_X = 1.05 \times 10^{-3}$, $D_Y = 5.25 \times 10^{-3}$, $B = 26.0$, $\bar{X} = 14.0$, $\bar{Y} = 1.86$.

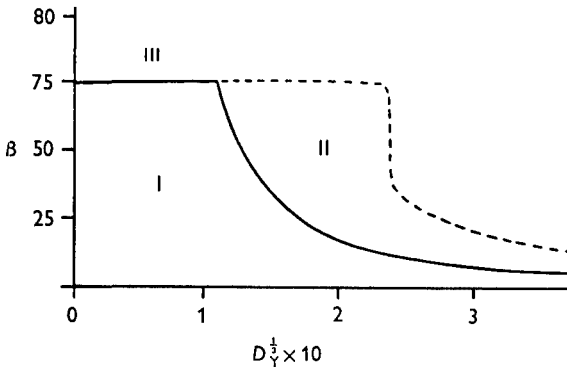


Fig. 7. Stability diagram in the B - D_Y plane for $\bar{A} = 14.0$, $D_A = 197 \times 10^{-3}$, $D_X = 1.05 \times 10^{-3}$.

(c) A second unstable domain, III, where fluctuations are amplified and undergo at the same time oscillations.

We shall now describe in some detail the behaviour of the system beyond instability for steady states belonging to domains II and III.

IV. 2. *Localized steady-state dissipative structures* (Herschkowitz-Kaufman & Nicolis, 1971)

We set

$$\left. \begin{aligned} A &= A_0(r) + \alpha(r, t), \\ X &= X_0(r) + x(r, t), \\ Y &= Y_0(r) + y(r, t), \end{aligned} \right\} \quad (30)$$

where A_0, X_0, Y_0 are the steady-state solutions represented in Figs. 5 and 6. We have chosen

$$\left. \begin{aligned} D_A &= 197 \times 10^{-3}, & \bar{A} &= 14.0, \\ D_X &= 1.05 \times 10^{-3}, & D_Y &= 5.25 \times 10^{-3}, \\ \bar{X} &= \bar{A} = 14.0, & \bar{Y} &= B/\bar{A} = 1.86. \end{aligned} \right\} \quad (31)$$

We imagine that as a result of a fluctuation the steady state is perturbed and we follow by the Runge-Kutta method the time evolution of the perturbation as defined in equation (30). The numerical analysis carried out on the CDC 6400 computer of the University of Brussels shows that for $B \lesssim 22.0$ the perturbations die out and the original state is restored. On the contrary, for, e.g. $B = 26.0$, the perturbations are amplified and the original state (X_0, Y_0) which now belongs to the domain II of Fig. 7 is unstable.⁵

The numerical analysis shows that the system finally attains a new steady state. The latter is represented in Fig. 8. For convenience the space $0 \leq r \leq l = 1$ has been divided into 78 equal intervals defined by points 1-79. As in § III, we again observe that the system has reached an ordered state corresponding to a spatial organization of components X and Y, which organization is maintained by the flow of matter through the boundaries. In this respect this state is a *dissipative structure* of the type similar to the state shown in Fig. 4.

The new and very important feature appearing, however, in Fig. 8 and which was absent in earlier investigations is that the dissipative structure

⁵ Equations (26) have been integrated numerically by setting A at its steady state (cf. Fig. 5). This is justified by the fact that A_0 is always a stable configuration and by the choice $D_A \gg D_X, D_Y$ which implies that the concentration profile A relaxes very rapidly to A_0 .

is *localized* in space. It seems as if, depending on the values of parameters such as B, D_x and D_y , the system determines its own 'natural' boundaries (points 20 and 59 in Fig. 8), which are distinct from the boundaries corresponding to points 0 and $l = 1$. It is within this characteristic domain that the system develops a sharp, short wavelength structure. This interesting localization effect which is clearly due to the non-uniform distribution of A in the system, becomes less pronounced as B increases

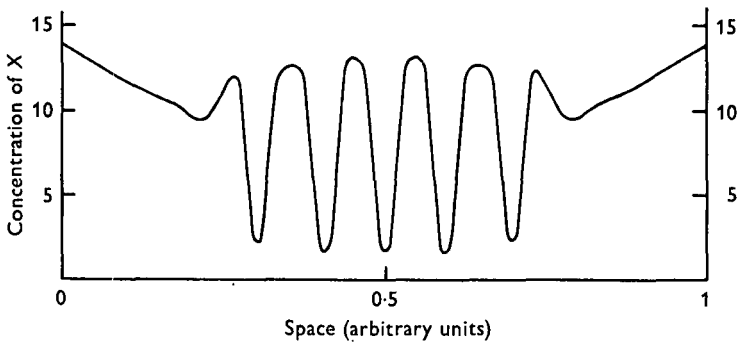


Fig. 8. Localized steady-state dissipative structure arising beyond the point of instability of the profile shown in Fig. 6. The numerical values of the various parameters are the same as Fig. 6.

and D_y increases with respect to D_x . For instance, it disappears for $B \gtrsim 50$. The dependence on B may easily be understood on the basis of the stability analysis of the homogeneous steady-state solution (Lefever, 1968*a, b*), which shows that the system becomes unstable for B sufficiently large compared to A . If now B exceeds the critical homogeneous value corresponding to the largest A in the system (i.e. the value \bar{A} of A at the boundaries) the instability and the subsequently occurring dissipative structure will extend throughout the system. Similarly the dependence on D_y is due to the fact that for D_y close to D_x the system can no longer sustain a steady-state dissipative structure. For decreasing D_y the dissipative structure region therefore shrinks until it disappears for $D_y \rightarrow D_x$.

A very interesting question is the stability and uniqueness of the dissipative structures represented in Fig. 8. In the homogeneous case $D_A \rightarrow \infty$ it has been shown (Lefever, 1968*a, b*) that for a discrete system of two boxes permeable to substances X and Y there were two symmetric steady states beyond instability, both extremely stable for perturbations smaller than their average separation. In the case of 78 intervals con-

sidered in Fig. 8 and more generally in the limit of a continuous system the situation is more complex. Preliminary investigations have shown (Herschkowitz-Kaufman & Nicolis, 1971*b*) that the system admits several forms of dissipative structures, each one depending on the type of initial fluctuation and being stable for certain classes of perturbations only.⁶

We therefore begin to understand, in quantitative terms, the role of the statistical element in the description of a system such as the one studied in this section. In addition to the 'causal laws' given by equations (26) we have to know, e.g. the position in which the system is more likely to be disturbed by a random fluctuation. The probability of this event will determine the subsequent evolution by choosing one among the many possible solutions *a priori* available for the system. This choice, which appears as a simplified type of 'information', represents the *historical element* which has to be added to the system to determine, together with the causal laws, its future evolution. Recalling the discussion of points 2-4 in the Introduction we are led to a first parallelism between dissipative structure formation and certain features occurring in early stages of biogenesis and the subsequent evolution to higher forms. The analogy would even become closer if the model we discuss has further critical points of unstable transitions. One would then obtain a hierarchy of dissipative structures each one enriched further by the information content of the previous ones through the 'memory' of the initial fluctuations which created them successively. We come back to this point in section VI.

IV. 3. *Concentration waves* (Herschkowitz-Kaufman & Nicolis, 1971)

We now place ourselves in the unstable domain III of Fig. 7 and more specifically in the domain of B large and D_Y close to D_X . To be specific, we keep the same values of \bar{A} , \bar{X} , \bar{Y} , D_A , D_X as before and set

$$B = 77.0, \quad D_Y = 0.66 \times 10^{-3}. \quad (32)$$

The problem is, again, to study the evolution in time of the perturbations $x(r, t)$ and $y(r, t)$ around the steady-state profiles of X and Y . For the numerical values given in (32) the latter are of a form similar to that given in Fig. 5 and are not reproduced here. The space $0 \leq r \leq l = 1$ is now divided into 39 intervals by points 1-40. The numerical calculations

⁶ This non-uniqueness property is a direct consequence of the non-linearity of the system.

have again been performed on the CDC 6400 computer of the University of Brussels.

The result is, first, that the steady state is unstable and the system now attains asymptotically, a dissipative structure which is both space and time-dependent. This regime is rapidly stabilized to a time periodic state. Figs. 9–12 show the space-dependence of X corresponding to

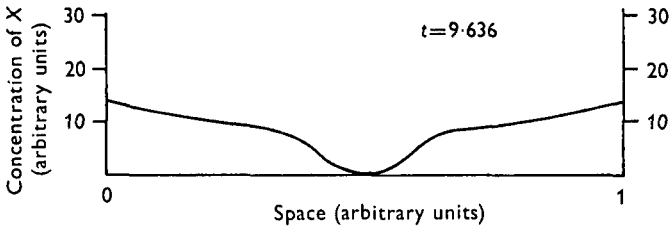


Fig. 9. Spatial distribution of X at a certain stage of its periodic evolution. A well is formed and propagates outwards. The following numerical values of the parameters have been chosen: $D_X = 1.05 \times 10^{-3}$, $D_Y = 0.66 \times 10^{-3}$, $B = 77.0$, $\bar{X} = 14.0$, $\bar{Y} = 1.86$.

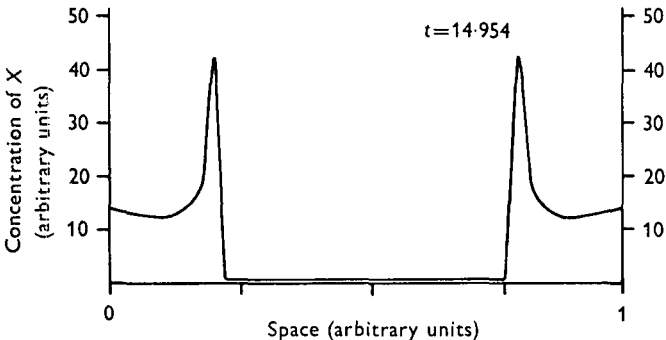


Fig. 10. Spatial distribution of X during the part of the period corresponding to a slow build-up of X at points 9 and 31.

certain characteristic stages of temporal evolution. Imagine that at $t = t_0$ we start with a profile of roughly the same type as in Fig. 6. A well is then formed around the point in the middle and propagates outwards (Fig. 9). After a time interval $\Delta t \simeq 1.47$ propagation stops at two points (points 9 and 31 for the numerical values given in equation (32)). At these points X starts building up slowly during an interval $\Delta t \simeq 4.10$ (cf. Fig. 10). As soon as X reaches a maximum value a new propagation stage starts, this time directed towards the middle point. This part of the motion is

extremely rapid; it only lasts $\Delta t \simeq 0.33$ (cf. Fig. 11). Finally (cf. Fig. 12) the two propagating fronts 'collide' and X decreases slowly to the initial profile. The duration of this part is $\Delta t \simeq 2.50$. After this the whole phenomenon repeats and the system passes through exactly the same stages.

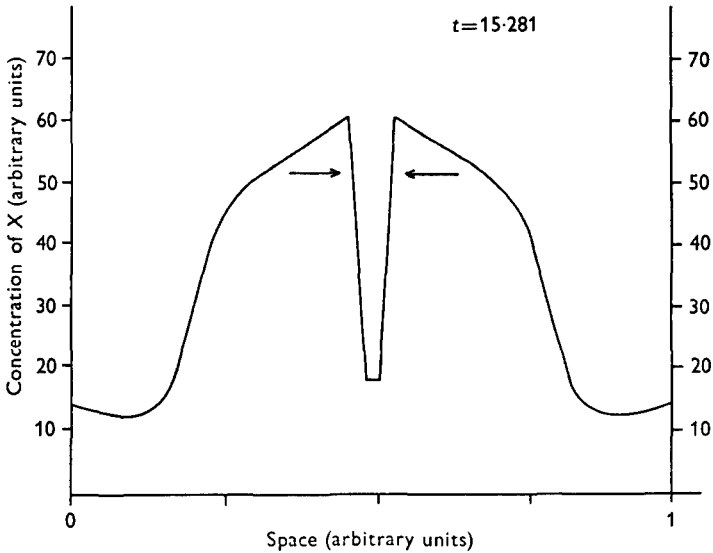


Fig. 11. Spatial distribution of X during the rapid propagation of the two wavefronts toward the middle point.

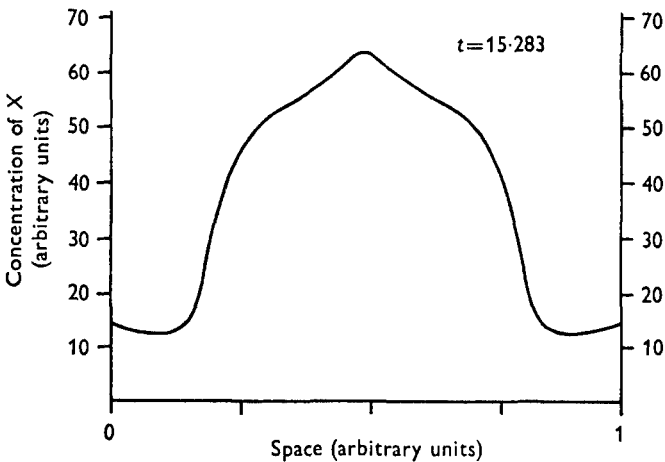


Fig. 12. Spatial distribution of X during the slow overall decrease of concentration to the initial profile.

The results reported in Figs. 9–12 imply that the system exhibits a *wave-like solution*. This is also confirmed by the observation that in the region between the two build-up points (cf. Fig. 10) the system performs locally discontinuous or relaxation oscillations (Lavenda, Nicolis & Herschkowitz-Kaufman, 1971). Fig. 13 represents the form of these oscillations for the middle point 20. Oscillations also extend a little

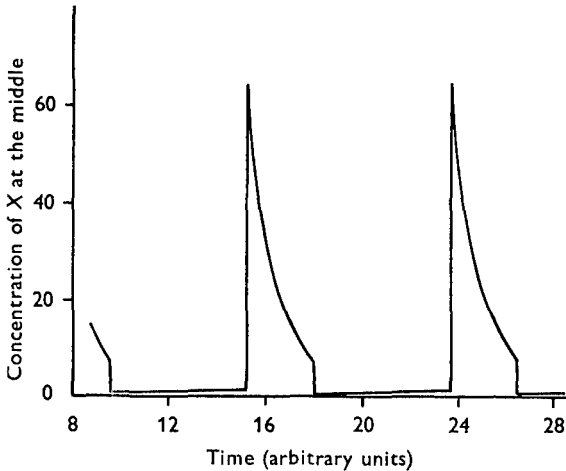


Fig. 13. Time variation of the concentration of X at the middle point (point 20).

farther than the build-up points but in the form of small amplitude, smooth periodic motions. The main point is, however, that these local oscillations do *not* organize to form a standing wave. Rather, during a part of the overall motion, there are two stages corresponding to the *propagation of wavefronts*, either outwards (cf. Fig. 9) or inwards (cf. Fig. 11). The velocity of propagation of these fronts, in addition to its dependence on the parameters, depends also on the local concentration of X . For instance at the build-up point 9 (cf. Fig. 10), where propagation first starts, the maximum value of concentration, i.e. the concentration at the wavefront, is $X_9 \simeq 43.0$ and the propagation velocity is $c_9 \simeq 0.66$. At point 11, $X_{11} \simeq 58.0$ and $c_{11} \simeq 0.90$, while at point 16, $X_{16} \simeq 62.5$ and $c_{16} \simeq 0.94$. We see that the propagation velocity increases with concentration and rapidly reaches a saturation value. This property is the result of the *non-linear character of the wave* due to the non-linearity of the chemical kinetic equations (26).

For the same values of the parameters the velocity of spread of X due to a simple diffusion would be

$$C_{\text{diff}} \simeq \frac{D_X}{\Delta r} = \frac{1.05 \times 10^{-3}}{\frac{1}{39}},$$

or

$$C_{\text{diff}} \simeq 0.04.$$

We see that the wave-like propagation of X is faster by at least one order of magnitude compared to diffusion. In addition, diffusion would always direct X to a low concentration region. For the propagation along the wavefront the situation may be the opposite; an example is seen in Fig. 9.

In addition to the propagation the wave also is found to go through stages with a slow evolution of concentration which apparently is dominated by diffusion. Still, however, during these steps the system performs, locally, relaxation oscillations.

Let us also compile a few other characteristic properties of these concentration waves:

(i) During the fast build-up of X in the region about the middle (cf. Figs. 11, 13) the overall concentration $X + Y$ remains practically constant, i.e. the system obeys a conservation condition. The meaning of this condition has been analysed by Lavenda *et al.* (1971).

(ii) For given values of the parameters the position of the two points r_1, r_2 of build-up of the maxima of X (cf. fig. 10) are automatically determined. The system has again, as in the previous subsection, a *natural boundary* separating a region of dissipative structure ($r_1 \leq r \leq r_2$) and a region where the continuation of the thermodynamic close to equilibrium behaviour prevails (r close to the boundaries 0 and 1). For \bar{A}, D_X given, the position of the points r_1 and r_2 depends strongly on the ratio D_Y/D_X . For $D_Y/D_X = 1$, r_1, r_2 coincide with the points which are at a state of marginal stability with respect to limit cycle formation according to the criterion of stability of the homogeneous steady-state solution (cf. equation (27)). For $D_Y/D_X \neq 1$ the points move outwards and the wave becomes more and more delocalized as D_Y becomes very small.

(iii) The period of oscillation at the various points of the dissipative structure becomes longer as $D_Y/D_X \rightarrow 1$.

Also between different points there seems to be a synchronization leading to a single overall period of oscillation. On the other hand there is a fairly pronounced phase difference from point to point. For instance, in the case of the numerical values given in equation (32), for points 9 and 20 the delay between the two maxima formation is approximately of

$\Delta t \simeq 0.33$ or 13° . For the same choice of numerical values the overall period of the wave is equal to 8.4. The dependence of the phase difference on the local value of concentration is non-linear. Let us emphasize that the existence of a phase difference seems to be due to diffusion rather than to any difference between periods of oscillations of the individual points. In fact, as we observed before, individual periods synchronize to a single, overall period characteristic of the wave.

The result that a set of chemical kinetic equations such as equations (26) which form a parabolic system, may give rise to wave-like solutions is due to some very interesting analytic properties of these equations. A detailed analytic study, however, meets with several difficulties and is presently under investigation by Narasimha, Nicolis & Herschkowitz-Kaufman (1971). We only notice here that preliminary studies indicate that during the propagation phases (cf. Figs. 9, 11) the system of equation (26) behaves as a hyperbolic system. On the other hand, during the build-up phase (cf. Fig. 10) and the slow-motion phase represented in Fig. 12 the motion is practically determined from the local limit cycle behaviour and from diffusion, whose effect is to modify the amplitude of oscillations and give rise to phase differences between various points.

We conclude this discussion of localized dissipative structures by stressing once more the striking differences in the functions performed by the system in these states and in the states on the thermodynamic branch. First, it is reasonable to expect that localization is a plausible mechanism for stabilizing a dissipative structure with respect to abrupt changes of the chemical environment. On the other hand, a characteristic property of localized structures is to produce great amounts of a particular substance during a short period of time (cf. Fig. 13) and in a limited region of space (cf. Figs. 8, 11). This is a very efficient way to perform regulatory functions involving thresholds and being sharply localized in space and time. Finally, concentration waves are a plausible mechanism for *propagation and transmission of information* in the form of chemical signals, whereas the steady-state localized structures could be useful, as we saw before, for the *storage* of information. The biological significance of such functions will be discussed in §§ V and VI.

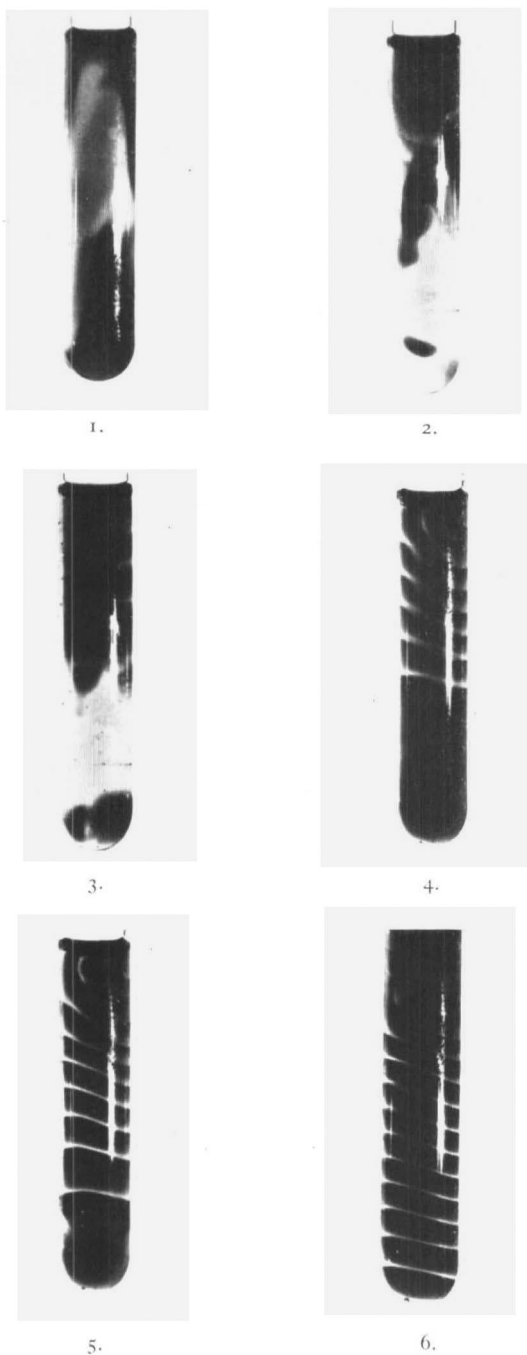


Fig. 14. Different stages of formation of the dissipative structure shown in Fig. 15. First-stage: temporal oscillation. Second stage: appearance of a small inhomogeneity. Last four stages: appearance and propagation of spatial patterns in the form of horizontal bands. Temporal oscillations are still present.

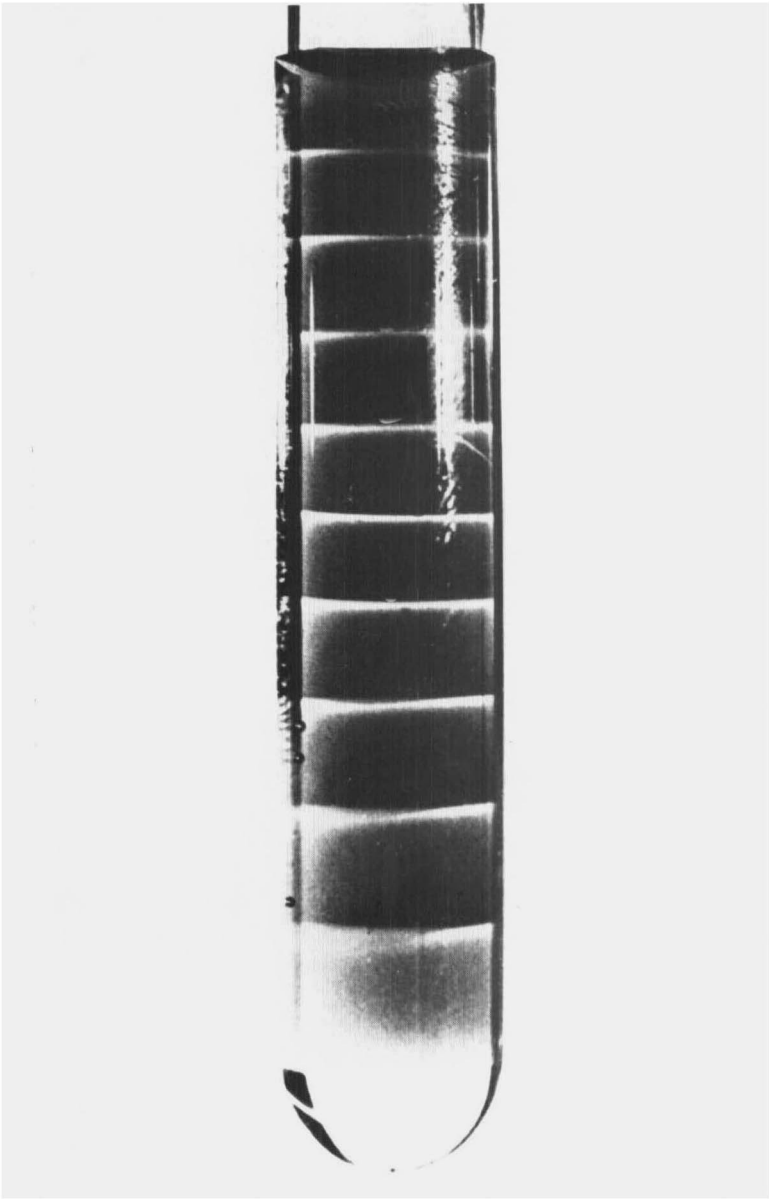


Fig. 15. Spatial dissipative structure for the Zhabotinski reaction: the Ce^{3+} and Ce^{4+} ions are assembled in alternative horizontal bands (dark lines represent an excess concentration of Ce^{3+}).

types of instabilities (leading, for example, to a spatially ordered state). We may thus expect that most of the models discussed above will also provide examples of symmetry-breaking instabilities. This has been verified explicitly (Prigogine *et al.* 1969) for Sel'kov's models (Sel'kov, 1968*a, b*).

A number of examples of instabilities leading to multiple steady-state transitions is also available. For more details see Glansdorff & Prigogine (1971, chapter XVI).

Let us now turn to the experimental aspects of dissipative structures. There are at present two sources of experimental evidence for dissipative structure formation coming, respectively, from organic and biochemical reactions.

The best-known organic example is a reaction in which cerium ions catalyse the oxydation of analogs of malonic acid by bromate (Zhabotinski, 1964). When this reaction occurs in a continuously stirred medium, sustained oscillations in the concentration of intermediates are observed for certain ranges of values of initial product concentration and temperature. The stability and perfect reproducibility of the results suggest beyond doubt that they correspond to limit cycle type oscillations, i.e. that they really occur beyond a dissipative instability. For slightly different values of concentrations an evolution to a spatially organized state is observed (Busse, 1969; Herschkowitz-Kaufman, 1970). Figs. 14 and 15 show respectively the intermediate stages of evolution and the stabilization of the system to the final steady state. Dark lines correspond to an excess of Ce^{3+} and light ones to an excess of Ce^{4+} .⁷ Of special interest is the fact that the spatially ordered structure (Fig. 15) is attained only after the thermodynamic branch becomes unstable with respect to oscillations (first two stages shown in Fig. 14), which in turn become unstable with respect to diffusion (last stages shown in Fig. 14).

The experiments described by Herschkowitz-Kaufman (1970) and Zhabotinski (1964) have been carried out in closed system. As a result the structure is maintained for a limited time (of the order of hours).⁸ However, the sharpness of the structure, the reproducibility of the results and the rapid emergence or disappearance of the patterns shown in Fig. 15 in comparison with their lifetime suggest that the effect is really a dissipative structure arising beyond a symmetry-breaking instability. We have

⁷ In the experiment of Herschkowitz-Kaufman (1970) a redox indicator was used (ferroine). As a result only the Ce^{3+} and Ce^{4+} concentrations were observed locally corresponding, respectively to red and blue colours.

⁸ Recently Vavilin, Zhabotinski & Zaikin (1968) reported an experiment carried out in an open system.

concrete, experimental evidence of a coherent behaviour which is perfectly compatible with the laws of thermodynamics and chemical kinetics. The properties of the system in this state are so different compared to the properties in the original, homogeneous mixture that one really may think of the configuration shown in Fig. 15 as a *new state of matter*.

While the usual phase separation or partial miscibility is a macroscopic manifestation of Boltzmann's order principle, the partial phase separation in the Zhabotinski reaction corresponds to a macroscopic amplification of fluctuations. It illustrates in a most striking way the 'order from fluctuations' principle.

Finally, when the same reaction occurs in a thin layer of unstirred solution, a propagation of wavefronts initiated from different centres is observed (Zaikin & Zhabotinski, 1970). At every point in space the system undergoes relaxation oscillations involving a short oxydation phase and a longer reduction phase. For long times the waves coming from different centres 'collide' and mutually annihilate. When a wave from a high-frequency centre reaches a low frequency one the overall phenomenon eventually synchronizes at the highest frequency. Qualitatively, these observations are very similar to the picture given in Figs. 9-13 and to the synchronization of the various oscillation centres at a single overall period shown in the model of §IV.

It is curious to observe that the same system may give rise to several types of dissipative structures by only slight changes of the boundary conditions. Together with the results of §§III and IV, this implies that systems showing a limit cycle behaviour are also likely to occur, at different experimental conditions, in spatially ordered states. This is an important point since, as we shall now see, the experimental evidence of instabilities in biochemical reactions is practically limited to the observation of sustained oscillations. We shall discuss separately evidence related to the three types of dissipative structures developed in the previous sections.

V. 2. *Oscillations in the enzymatic reactions*

Experimentally, sustained oscillations have been observed and established beyond doubt for glycolysis. Most of the experiments have been carried out by Hess (1962) and Betz & Chance (1965). Theoretical studies attribute these oscillations to the enzyme phosphofructokinase, which is an allosteric enzyme and may be activated by the products ADP and FDP and inhibited by the substrate ATP. Sel'kov (1968*a, b*) and Higgins (1964) have worked out models to represent the observed oscillations. In

particular, Sel'kov was able to show that the experimental data can be interpreted in terms of a mechanism involving an unstable transition point and a limit cycle thereafter. In his model the allosteric character of phosphofructokinase is taken into account through a phenomenological factor, γ , describing the stoichiometry of its activation by ADP ($\gamma > 1$). Recently, Goldbeter & Lefever (1971) have constructed a model taking into account explicitly the allosteric effects and which is free from phenomenological factors. Again the agreement between the predictions and the experimental data is very satisfactory.

Oscillations have also been reported to occur in the synthesis of enzymes in the cellular level. Theoretical studies attribute these effects to the induction and repression mechanisms of the Jacob–Monod type (Monod & Jacob, 1961; Griffith, 1968). We do not expand this point here, as the experimental evidence is much weaker than for enzymic reactions.

V. 3. *Symmetry-breaking instabilities and concentration waves*

The intimate relation between limit cycle and spatial structure formation which was repeatedly stressed in this section suggests that the systems under V. 2 could also give rise to spatially ordered states. This point was further developed by Prigogine *et al.* (1969). In particular it was shown that for values of the parameters in the physiological range, Sel'kov's model for glycolysis predicts a symmetry-breaking transition. An experimental verification of this prediction is, however, lacking.

The emergence of spatial order and the transmission of information in a previously homogeneous system is also a central problem in embryogenesis and, more generally, in all problems involving cell differentiation. The localized dissipative structures of the type studied in §IV may provide the basis for a quantitative study of such information transfer processes. Moreover the existence of chemical waves substantiates the concept of 'organizing waves' recently postulated in the literature (Wolpert, 1968; Cohen, 1969). The main feature of these waves is that the concentration of a characteristic morphogen is periodic and the phase of the oscillation is controlled via a wavelike propagation mechanism. In §IV we have shown that all these features may arise in certain classes of non-linear chemical reactions operating beyond instability.⁹

⁹ An analysis of morphogenetic processes in terms of the stability properties of the evolution equations has also been made by Thom (1971). Furthermore, Keller & Segel (1970) have been able to analyse the first stages of slime mold aggregation in terms of the stability properties of the equations of evolution of the chemical substances mediating the aggregation.

The question of space order formation in the *cellular and macromolecular level* is one of the deepest problems in biology which remains practically open. Intuitively it is difficult to avoid the feeling that spatial dissipative structures have not contributed, in an essential way, to the first biogenetic steps and therefore implicitly, to the formation of the macromolecular and cellular structures themselves. In particular, the possibility of creating, in a limited region of space, concentrations of certain key substances by order of magnitudes larger than in the homogeneous, prebiotic mixture, may be very significant in the process of evolution. Once these substances are assembled together the probability for certain important reactions is enhanced and the system begins to evolve to biologically relevant configurations.¹⁰

The whole point requires further study. Additional comments are also made in the subsequent section.

V. 4. *Multiple steady states*

The problem of multiple steady states is of primary importance in all phenomena involving the 'all-or-nothing' type of transition. For instance, for suitable critical values of parameters a system may depart abruptly from a steady state and go to a new one which has, roughly speaking, the same symmetry as the former but differs in the level of concentration of certain characteristic substances.

There exist at least two types of all-or-nothing effects in biology: the process of differentiation in higher organisms and the functioning of excitable membranes.

(i) *The problem of differentiation.* Monod & Jacob (1961) have proposed a number of models describing differentiation. One of these models has been analysed by Cherniavskii, Grigorov & Polyakova (1967) and by Babloyantz & Nicolis (1971). They find indeed that there exist critical regions where the system can switch to a regime such that a given type of substance is produced preferentially. A different type of model, also suggested by Monod & Jacob, is completely independent of the metabolic activity of the enzymes, and describes a system which is switched on from one 'inactive' state to a second 'active' one by contact with a specific inducer.

(ii) *Excitable membranes.* Roughly speaking, a biological excitable membrane, such as the membrane of a nervous cell, may exist in two permanent states: one polarized (associated with the maintenance of

¹⁰ We are indebted to Professor M. Eigen for this remark.

different ionic charges in the two sides) and one depolarized state resulting from the former upon passage of a pulse or upon a change in permeability. Blumenthal, Changeux & Lefever (1970) have shown recently that this depolarization may be quantitatively interpreted as a transition arising beyond the point of instability of the polarized state which lies beyond the thermodynamic branch. This instability is due to the difference in the ionic concentrations, which play here the role of the constraint keeping the system in a far from equilibrium state. On the other hand, experimental observations establish that the transition is indeed in the form of an all-or-nothing effect both for biological and artificial membranes.

VI. CONCLUDING REMARKS AND FURTHER DEVELOPMENTS

A characteristic feature of chemical instabilities is that their occurrence depends on a minimum level of dissipation and on specific non-linear types of kinetics. The dissipative structure attained subsequently is a really *new state of matter* induced by a flow of free energy under non-equilibrium conditions. In this new state we have a new physical chemistry on a *supermolecular level* while the laws referring to the molecular level remain unchanged and given by the quantum mechanical or classical equations of motion.

As we have seen in the previous section, it is quite plausible to expect that, in the prebiological stage, the occurrence of dissipative structures may have enabled the system to reach and maintain the far from equilibrium conditions necessary for the occurrence of certain key reactions permitting further evolution. In addition, we have shown that predictions based on the concept of dissipative structure permit to interpret a number of biological functions on the cellular level observed on actual living systems (e.g. glycolytic oscillations, membrane excitation, and so on).

On a more general level, we may say that the ideas developed in this review provide an answer to some of the philosophical questions raised in the introduction. The emergence of order, the role of probabilistic and causal events, the dependence of structure on the previous history, the hierarchization of structures, are all seen to be consequences of far from equilibrium thermodynamics applied to certain types of non-linear systems. No reference to concepts other than the laws of chemical kinetics and fluctuation theory had to be made.

Looking now on future developments, we feel that the theory of dissipative structures has to be developed along at least three major directions.

In the first place the problem of fluctuations in chemical composition and in the chemical mechanism itself requires further study. Of particular interest is the behaviour of fluctuations in the neighbourhood of unstable transitions. To a great extent, it will determine the mechanism by which the system leaves the unstable state and evolves to a dissipative structure. Some preliminary results in this direction have been obtained recently by the authors (Nicolis & Prigogine, 1971).

The problem of stability and fluctuations is closely related to the problem of evolution in biology. Broadly speaking, to discuss evolution one has to develop a more synthetic view of the ideas outlined in the foregoing sections, covering large classes of systems and including the possibility of a succession of instabilities. More specifically, we may divide the general question into two parts, corresponding to the most primitive and to the most advanced stages in prebiotic evolution:

(a) The formation of relatively high polymers having a certain biological function that the constituting monomers are unable to perform. An obvious example is the problem of polymerization leading to macromolecules which have the ability to serve as templates for their own reproduction and for the synthesis of other macromolecules.

(b) Assuming that a population of macromolecular species including the necessary apparatus for synthesis on templates is present, what is the direction of the subsequent evolution?

Both aspects have received attention recently. Concerning point (a) we have considered the simplest possible problem of formation of a low homopolymer. The specific question is to determine the type of processes leading to an enhancement of the polymer population which would not be possible in a usual linear polymerization process. Preliminary investigations by Goldbeter, Babloyantz & Nicolis (1971) show that the conditions for this increased efficiency are essentially twofold. First, it is necessary to subject the system to a *non-equilibrium* flow of monomers. Secondly, *autocatalytic* processes such as the increase of reaction rate for polymerization due to already synthesized polymers are also very important. Under these two conditions, it is possible to construct several chemically plausible schemes having multiple steady states and the ability to jump from a 'thermodynamic' branch of low polymer concentration to a new state where the polymer population may increase by orders of magnitude.

Further study is necessary to extend the model to high homopolymers and to include several types of monomers.

Point (b) has been investigated quite recently by Eigen (1971). He assumes that the macromolecular species undergo a kinetics of competing populations. He is then able to show that the system may evolve, by a mechanism of successive instabilities, to a final state characterized by some type of genetic code.

Finally, large-scale processes such as growth and development in higher organisms are another type of example where the concept of instabilities seems to be of importance. Of particular interest is the possibility of transfer of information over macroscopic distances in the form of chemical signals (cf. §IV).

The realization of the programme outlined in this section requires clearly a close collaboration between physicists, organic chemists, biochemists and molecular biologists.

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VII. REFERENCES

- BABLOYANTZ, A. & NICOLIS, G. (1971). Chemical instabilities and multiple steady-state transitions in Jacob-Monod-type models. *J. theor. Biol.* (in the Press).
- BETZ, A. & CHANCE, B. (1965). Phase relationship of glycolytic intermediates in yeast cells with oscillatory metabolic control. *Archs Biochem. Biophys.* **109**, 585-91.
- BLUMENTHAL, R., CHANGEUX, J. P. & LEFEVER, R. (1970). Membrane excitability and dissipative instabilities. *J. Membrane Biol.* **2**, 351-74.
- BUSSE, H. (1969). A spatial periodic homogeneous chemical reaction. *J. phys. Chem., Ithaca.* **73**, 750.
- CASIMIR, H. B. G. (1945). On Onsager's principle of microscopic reversibility. *Rev. mod. Phys.* **17**, 343.
- CHERNIAVSKII, D., GRIGOROV, L. & POLYAKOVA, M. (1967). In *Oscillatory Processes in Biological and Chemical Systems*. Moscow: Nauka.
- COHEN, M. (1969). In *Some Mathematical Questions in Biology*. 136th Meeting AAAS, Boston.
- DE GROOT, S. R. & MAZUR, P. (1962). *Non-equilibrium Thermodynamics*. Amsterdam: North Holland Publ. Co.

- EIGEN, M. (1971). Self organization of matter and the evolution of biological macromolecules. *Naturwissenschaften* (in the Press).
- ELSASSER, W. M. (1958). *The Physical Foundation of Biology*. Oxford: Pergamon Press.
- GLANSDORFF, P. & PRIGOGINE, I. (1971). *Thermodynamic Theory of Structure, Stability and Fluctuations*. New York: Wiley-Interscience.
- GOLDBETER, A. & LEFEVER, R. (1971). Dissipative structures for an allosteric model. Application to glycolytic oscillations. *Biophys. J.* (in the Press).
- GOLDBETER, A., BABLOYANTZ, A. & NICOLIS, G. (1971). (In preparation.)
- GRENE, M. ed. (1969). *The Anatomy of Knowledge*. London: Routledge and Kegan Paul.
- GRIFFITH, J. S. (1968). Mathematics of cellular control processes I and II. *J. theor. Biol.* **20**, 202-16.
- HAGGERTY, M. J. (1970). Non-Markoffian kinetic theory and hierarchical cosmologies. *Physica, 's Grav.* **50**, 391-6.
- HERSCHKOWITZ-KAUFMAN, M. (1970). Structures dissipatives dans une réaction chimique homogène. *C. r. hebd. Séanc. Acad. Sci., Paris*, **270C**, 1049-52.
- HERSCHKOWITZ-KAUFMAN, M. & NICOLIS, G. (1971a). Localized spatial structures and non-linear chemical waves in dissipative systems. *J. chem. Phys.* (in the Press).
- HERSCHKOWITZ-KAUFMAN, M. & NICOLIS, G. (1971b). (In preparation.)
- HERSCHKOWITZ-KAUFMAN, M. & PLATTEN, J. K. (1971). Chemical instabilities and localized structures in non-homogeneous media. *Bull. Acad. r. Belg. (Cl. Sci.)* **57**, 26-40.
- HESS, B. (1962). In *Funktionelle und morphologische Organisation der Zelle*. Berlin: Springer-Verlag.
- HIGGINS, J. (1964). A chemical mechanism for oscillation of glycolytic intermediates in yeast cells. *Proc. natn. Acad. Sci. U.S.A.* **51**, 989-94.
- JACOB, F. (1970). *La logique du vivant*. Paris: Gallimard.
- KELLER, E. F. & SEGEL, L. A. (1970). Initiation of slime mold aggregation viewed as an instability. *J. theor. Biol.* **26**, 399-415.
- KOESTLER, A. & SMYTHIES, J. R. ed. (1969). *Beyond Reductionism*. London: Hutchinson.
- LAVENDA, B., NICOLIS, G. & HERCHKOWITZ-KAUFMAN, M. (1971). Chemical instabilities and relaxation oscillations. *J. theor. Biol.* (in the Press).
- LAX, M. (1960). Fluctuations from the non-equilibrium steady state. *Rev. mod. Phys.* **32**, 25-64.
- LEFEVER, R. (1968a). Dissipative structures in chemical systems. *J. chem. Phys.* **49**, 4977-78.
- LEFEVER, R. (1968b). Stabilité des structures dissipatives. *Bull. Acad. r. Belg. (Cl. Sci.)* **54**, 712-19.
- LEFEVER, R. & NICOLIS, G. (1971). Chemical instabilities and sustained oscillations. *J. theor. Biol.* **30**, 267-84.
- LWOFF, A. (1962). *Biological Order*. Cambridge, Mass.: M.I.T. Press.
- MINORSKI, N. (1962). *Non-linear Oscillations*. Princeton: Van Nostrand.

- MONOD, J. (1970). *Le Hasard et la nécessité*. Paris: Seuil.
- MONOD, J. & JACOB, F. (1961). Teleonomic mechanisms in cellular metabolism, growth and differentiation. *Cold Spring Harb. Symp. on quant. Biol.* **26**, 389-401.
- MORALES, M. & MCKAY, D. (1967). Biochemical oscillations in controlled systems. *Biophys. J.* **7**, 621-5.
- NARASIMHA, R., NICOLIS, G. & HERSCHKOWITZ-KAUFMAN, M. (1971). (In preparation.)
- NICOLIS, G. & BABLOYANTZ, A. (1969). Fluctuations in open systems. *J. chem. Phys.* **51**, 2632-7.
- NICOLIS, G. (1971). Stability and dissipative structures in open systems far from equilibrium. *Adv. chem. Phys.* **19**, 209-324.
- NICOLIS, G. & PRIGOGINE, I. (1971). Fluctuations in non-equilibrium systems. *Proc. natn. Acad. Sci. U.S.A.* (in the Press).
- ONSAGER, L. (1931). Reciprocal relations in irreversible processes, I and II. *Phys. Rev.* **37**, 405-26: **38**, 2265-79.
- PRIGOGINE, I. (1947). *Etude thermodynamique des processus irréversibles*. Liège: Desoer.
- PRIGOGINE, I. (1967*a*). *Introduction to Thermodynamics of Irreversible Processes*, 3rd ed. New York: Wiley-Interscience.
- PRIGOGINE, I. (1967*b*). Temps, structure et entropie. *Bull. Acad. r. Belg. (Cl. Sci.)* **53**, 273-87.
- PRIGOGINE, I. (1969). Structure, dissipation and life. In *Theoretical Physics and Biology*, ed. M. Marois. Amsterdam: North Holland Publ. Co.
- PRIGOGINE, I., LEFEVER, R., GOLDBETER, A. & HERSCHKOWITZ-KAUFMAN, M. (1969). Symmetry-breaking instabilities in biological systems. *Nature, Lond.* **223**, 913-16.
- SEL'KOV, E. E. (1968*a*). Self-oscillations in glycolysis. *Eur. J. Biochem.* **4**, 79-86.
- SEL'KOV, E. E. (1968*b*). Self-oscillations in glycolysis. Simple single frequency model. *Mol. Biol.* **2**, 252-66.
- SPANGLER, R. A. & SNELL, F. M. (1961). Sustained oscillations in a catalytic chemical system. *Nature, Lond.* **191**, 457-8.
- SPANGLER, R. A. & SNELL, F. M. (1967). Transfer function analysis of an oscillatory model chemical system. *J. theor. Biol.* **16**, 381-405.
- THOM, R. (1971). *Stabilité structurelle et la morphogénèse*. New York: Benjamin Publ. (in the Press).
- TURING, A. M. (1952). The chemical basis of morphogenesis. *Phil. Trans. Roy. Soc. Lond. B* **237**, 37-72.
- VAVILIN, V. A., ZHABOTINSKI, A. M. & ZAIKIN, A. N. (1968). Effect of ultraviolet radiation on the oscillating oxidation reaction of malonic acid derivatives. *Russ. J. phys. Chem.* **42**, 1640-51.
- WALTER, C. (1969). The absolute stability of certain types of controlled biological systems. *J. theor. Biol.* **25**, 39-52.
- WEISS, P. (1968). *Dynamics of development: Experiments and Inferences*. New York: Academic Press.

- WHYTE, L. L., WILSON, A. G. & WILSON, D. (ed.) (1969). *Hierarchical Structures*. New York: American Elsevier Publ. Co.
- WOLPERT, L. (1968). In *Towards a Theoretical Biology*, ed. C. Waddington. Edinburgh University Press.
- ZAIKIN, A. N. & ZHABOTINSKI, A. M. (1970). Concentration wave propagation in two-dimensional liquid-phase self-oscillating systems. *Nature, Lond.* **225**, 535-7.
- ZHABOTINSKI, A. M. (1964). Periodic course of oxidation of malonic acid in solution. *Biophysics* **9**, 306-11.