Dissipative structures and the problem of biological pattern formation

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Usp. Fiz. Nauk **141**, 55–101 (September 1983)

Open systems that contain chemically reacting mixtures and are restrained from relaxation to thermodynamic equilibrium manifest a capability of characteristic collective effects. In particular, macroscopically ordered states (dissipative structures) can arise in them spontaneously. This study discusses the fundamental results of the theory of dissipative structures: potential multiplicity of states differing in type of spatial organization, the possibility of both spontaneous and induced transitions between these states, and a universal description of the dynamics of establishment of macroscopic order. The capability of self-organization of a broad set of physicochemical systems opens up the possibility of modeling processes of desymmetrization and complication of spatial organization during the embryonic development of multicellular organisms. The article reflects the most significant results in this field.

PACS numbers: 87.10. + e, 87.15.He

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1. INTRODUCTION

The advances of molecular biology and molecular genetics evident today would not have been possible without the substantial penetration of physical ideas and experimental methods into this field. This penetration has imparted a powerful stimulus to development in such problems on the molecular level of biological organization as the structure of the genetic apparatus of the cell, its reproduction, and principles of functioning, the principles of protein structure, the construction and molecular mechanisms of action of cell membranes, etc. (see the reviews on this topic in Uspekhi Fizicheskikh Nauk[1-3]). However, only in very recent time have physicists become seriously attracted to problems pertaining to the higher—supercellular—level of organization of life. On this level, individual cells now act as a whole. Therefore the entire set of molecular and submolecular intracellular processes must be taken into account in some way or another.

It is hard to anticipate that one can adequately treat the living cell—undoubtedly a macroscopic object—on the basis of the concepts of macroscopic physics that have been developed and well adapted to describing such objects as homogeneous liquids, gases, or crystals. With a macroscopic number of degrees of freedom, the behavior of the cell is very far from statistical. The extremely complex, irregular spatial organization of intracellular structures and the consequent space-time organization of physical, chemical, and biochemical processes has no analogs in nonliving nature. For this reason, the problem of describing the functioning of the cell in the language of the exact sciences usual in physics is hardly actually solvable at the contemporary stage. Does this mean that it is hopeless for the physicist to try to understand how the establishment of multicellular organization occurs during individual development (ontogenesis) of living beings? Can physics facilitate advance in this field, despite the deficiencies of understanding of the functioning of individual cells?

In the theory of multiparticle systems the situation is usual in which almost none of the physical quantities of interest can be calculated rigorously from fundamental principles. However, the partial lack of knowledge of the complex details does not impede our obtaining certain general results. An example of this is the dispersion relationships in the hydrodynamic theory of fluctuations.[4] The value of such results lies in the fact that they indicate which quantities of the theory accessible to experimental study prove to be insensitive to the multitude of dynamic characteristics not amenable to being taken into account. Analogously one can try to construct a theoretical picture of the formation of spatial organization on the multicellular level abstracted from the aforementioned complexity of the intracellular apparatus. Especial progress has been noted precisely along this pathway in recent time. In this review we present the considerable positive results that have been attained here already.

 0038-5670/83/090775-26$01.80

Why do the descendants copy in their appearance many of the features of the parents? The banal answer, "Because they receive from each of them half of their set of genes," will now satisfy hardly anyone. One can yet add a mass of important details, such as: the genes amount to regions of definite length arranged in the form of a linear chain in the giant molecule of DNA; information on the structure and functional properties of all proteins are coded in the form of sequences of monomeric links in DNA; one can describe the principles of extraction of this information in the process of protein synthesis, etc. However, these refinements do not eliminate the main question: how are the structural and functional properties of multicellular living systems produced during their individual development (embryogenesis)?

Histologists distinguish about two hundred cell types in the human body. Among the vertebrates—fishes, amphibians, reptiles, and mammals—there is a certain variation in the types of specialized cells. Yet the key to the differing organization of these living beings does not lie in the cells as such. We should seek it in the spatial arrangement of these fundamental building elements and in how this arrangement evolves in development.

Undoubtedly, the entire variety of types of specialized cells is programmed in the DNA of the single starting cell, the fertilized egg.[5] Thus, for each given cell all the possible discrete states (types of specialization) are coded in its own DNA. The problem lies only in how the correct choice—corresponding to the function of the given cell in the whole organism—of one of this multitude of states is made.

This choice (in biological terminology, *determination*) occurs in the process of development of the embryo. The cells at the early stages of embryogenesis can be specialized for any of the types present in the developed organism. At the same time, in the later stages of development of the embryo, as a rule, the types of specialization of the cells are irreversibly determined. What controls this determination?

As a preliminary, we should clarify a more fundamental question: is the process of determination of cells in the developing embryo associated with the creation of *new information*? In other words, is such a determination the result of remembering a random choice?[6,7]

Definitely, random events have their place in embryogenesis. For example, in cell divisions in the process of growth, the position of a newly formed cell or the displacement of a previously existing one are as a rule random.[8] At the same time, random events play no substantial role in determining the final "macroscopic" result of the process of individual development of the embryo. Otherwise the probability of birth of identical monozygotic twins would prove extremely small. The identical initial state (fertilized oocyte) and the identical conditions of development lead to completely identical results. This means that *the creation of new information does not occur in embryogenesis.*

a) Some experiments and generalizations

Experiments show that the factors controlling the determination of individual cells in the formation of multicellular structures do not lie under the direct control of the genes, but *are developed on the basis of the collective properties of multicellular ensembles.*[8] As a rule, an initially defined mass of cells as a whole is determined for the corresponding pattern formation, and only then do individual cells obtain the appropriate "instruction" for determination. We can explain and illustrate this conclusion with the example of experiments on rotating the rudiment of an extremity of amphibia.[8]

At a certain stage of development of a triton, one can distinguish a group of cells destined to produce an extremity. At the instant of performing the experiment, this pathway of development for the given group of cells as a whole is already determined. (If one transplants it onto another embryo at an arbitrary site, then the same extremity will still develop from the given mass of cells.) Without altering the position of this rudiment, one can change its orientation with respect to the rest of the embryo. Here it turns out that a rotation performed before a definite instant of the development of the rudiment leads to formation of an extremity oriented in a fixed way with respect to the external axes of symmetry of the embryo—corresponding to the position *after* the rotation. Thus the fate of the individual cells in the rudiment is altered, depending on its orientation.

However, if the rotation is performed after a certain instant, then the orientation of the developing extremity no longer adjusts to the new position of the rudiment. The further development of the extremity after the rotation occurs as though it had no connection with the rest of the body of the embryo. We note that the described changes in the character of development, which lead to total loss of the "sensing" of position in the external system of coordinates, take form gradually, as shown in Fig. 1. The presented data, which have been confirmed with many other rudiments, indicate that *the fate of the individual cells has not yet been determined up to the instant of determination of a certain mass of cells as a whole.*

The experiments of Spemann and Schotte[9] have been of fundamental significance for the further development

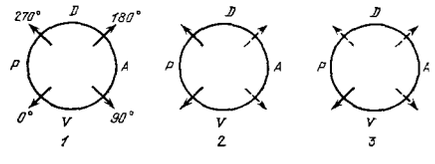

FIG. 1. Diagram of the results of experiments on rotating the rudiment of an extremity of a triton. Stepwise determination (1–3) of the direction of the extremity in the course of development; solid arrows—allowed directions of growth of the rudiment that are realized upon rotations; dashed arrows—directions forbidden at the given stage. *AP*—anterior-posterior axis of the embryo, *DV*—dorsal-ventral axis.

of understanding the mechanisms of embryogenesis. In these experiments a group of cells explanted from an arbitrary region of a frog embryo at an early stage of embryogenesis was transplanted into the region of the future mouth of an embryo of the same species. After transplantation, the characteristic structures of the mouth developed from the given group of cells. This is a typical *"positional" development*, which indicates, on the one hand, the undetermined character of the cells being transplanted, and on the other hand, the inductive effect of the underlying structures.

The results of an experiment in which the same region of a frog embryo was transplanted into the mouth region of the embryo of a different species, Triton, proved rather unexpected. In this case the typical mouth of a frog is formed from the transplant, and sharply differs from the mouth of a Triton. Thus the inductive action of the underlying layers of the mouth region is completely "abstract". This action dictates the development in the given position of a "mouth as a whole" without determining practically any detail of its structure.[8]

A very general rule is manifested in these experiments—the formation of a certain organ depends on the presence of a certain inductive action. The nature of this action proves to be similar for representatives of different species of organisms. However, the reactions to it are limited by the specific nature of the reacting tissue. This specificity is determined by the genetic constitution of the cells and their prior history of development.

b) Spatial ordering without movement of cells

A characteristic feature of supercellular organization is the concerted, coherent behavior of cells in cellular ensembles. Groups of identical cells form stable aggregates: tissues. The cells forming one tissue possess an identical regime of functioning, and this regime differs from that of the cells of other tissues. The aforementioned difference arises from the difference in the sets of proteins being synthesized by the cells, Here we touch upon one of the global problems of modern biology: the problem of differentiation of cells. In all its fullness, this problem is yet far from being solved. But we are interested in this study in a more special problem: *how is spatial order attained in ensembles of differentiated cells* (spatial differentiation)?

We know from experimental data that often the spatial differentiation of cells arises in initially homogeneous cellular ensembles, this process not being associated with the division of cells.[10] Thus a *spatially ordered assignment of specific states to an ensemble of identical cells with an identical initial state* takes place, so that the resultant ensemble of states forms a definite spatial structure.

As a rule, such transformations encompass cellular ensembles of from 10 to 100 cells.[10] The corresponding time intervals amount to hours.[10-12] The stated characteristic scales define the so-called *morphogenetic fields*—groups of cells manifesting concerted behavior in pattern forming processes. As an example, the whole embryo in the early stages of development constitutes a single morphogenetic field.[10] In the later stages in the embryo one can distinguish a number of morphogenetic fields. The modeling of the pattern-forming processes on the scale of individual morphogenetic fields is the fundamental topic of this study.

c) Positional information

In 1969 L. Wolpert formulated a set of statements generalizing the experimental data on the development of structures on the supercellular level.[10] Wolpert concluded that spatial differentiation is essentially a two-stage process. In the first stage a mechanism operates by which *positional information* (PI) is imparted to the cells of the morphogenetic field–information on the spatial position being occupied with respect to a certain reference point. The PI implies the existence of a certain physical property that varies in the system of coordinates of the morphogenetic field. The positional information of a cell unambiguously dictates the choice of its regime of functioning. The establishment of the PI precedes in time and is independent of the stage in which this choice is determined—the stage of *translation of the positional information*. Apparently the mechanisms responsible for the establishment of the PI are universal, i.e., they do not depend on the nature of the morphogenetic field.

Thus the geometry of the spatial organization that arises is completely determined in the first, faster stage of formation of the PI. Probably the mechanisms that act here do not involve directly the features and details of functioning of the differentiating cells. This circumstance is precisely why we can count on disentangling the mechanisms of establishment of the spatial order of cells by abstracting the treatment from the inaccessible details of the processes inside them.

d) The chemical basis of morphogenesis

Thirty years ago a paper of A. Turing[13] appeared with the title taken as the heading of this section. This happened before the birth of molecular biology, when practically nothing was known of the molecular mechanisms of the processes in the cell. What chemical basis could one have in mind? The "chemical" theory of Turing did not claim to describe the morphogenetic processes on the molecular level of chemical transformations. Nevertheless it yielded much of a fundamental understanding of the mechanisms of formation of spatial order in the ontogenesis of multicellular organisms.

The essence of Turing's study amounts to the following. Let reactions occur in the limited volume of a chemical reactor that can be described by macroscopic equations of chemical kinetics. Here the diffusion coefficients of the reagents are not so great that complete mixing in the reaction volume can occur in the characteristic times of occurrence of the reactions. In such a system one can always find a steady corresponding

to thermodynamic equilibrium—a homogeneous distribution of all the reagents throughout the volume. Turing studied the stability of this state, i.e., its physical realizability. It turned out that, under certain conditions, the homogeneous state can become unstable. In such a situation the system must manifest new collective features of behavior: in response to arbitrarily small perturbations it must leave its initial state and evolve into a new state. The fact that proved to be the most remarkable was that in the case of two chemically reacting and diffusing agents, a perturbation that destroys the stability of the homogeneous (symmetric) state possesses a lowered spatial symmetry, e.g., it can have the shape of a sine wave. If such a perturbation has arisen beyond the threshold of this instability, termed *Turing instability*, then it will develop without substantial change of shape, increasing only in amplitude. Under these conditions one can hope to find a new state in which the concentrations of the reagents are distributed in space in a certain ordered way. Finally, if this new state actually existed and were stable, then in real systems, which are always subject to fluctuation, the transition to it would occur spontaneously. Thus it is appropriate to speak of self-organization.

The experimental discovery of the chemical structures predicted by Turing served as a powerful impetus to development of the theory. The concept of "dissipative structures"[15,16] arose and became widespread. The phenomenology of the phenomenon—its macroscopic character that results from amplification of the fluctuational deviations—links it with a broad set of related phenomena of self-organization in nonequilibrium systems of differing physical nature. Generation of laser radiation, the macroscopic convective structures of Bénard in liquids, and chemical dissipative structures form a set of systems with similar behavior. Common to all of them is the interaction of a large number of subsystems, which leads to collective effects with characteristic spatial scales that substantially exceed the dimensions of the individual subsystems.

A new interdisciplinary field has taken shape and developed vigorously in the past decade—synergetics, in which effective methods are being developed for studying collective phenomena under nonequilibrium conditions. One can become better acquainted with it in a number of good reviews,[17-20] monographs,[21-24] and also in the collected volumes of the proceedings of the International Symposium "Synergetics".[25]

What relation do the dissipative structures in systems with chemical interactions and diffusion (*reaction-diffusion systems*) have with the specific spatial forms that take shape in the ontogenesis of multicellular organisms? Can these structures serve as models of the spatial order in the morphogenetic field?

A positive, albeit indirect, indication of this is the fact that chemical dissipative structures and morphogenetic structures manifest order with similar scales. For dissipative structures the characteristic dimensions are determined by such macroscopic parameters as the diffusion coefficients and times of kinetics:

$$l \sim \sqrt{D\tau}.$$

Crick[26] has called attention to the fact that, if one starts from the characteristic times of cellular dynamics (hours), taking as the diffusion coefficient the one for the molecules of organic compounds of medium molecular weight (10^2–10^3) in a medium with a viscosity close to that of the cell contents, then the estimate that one derives for the length scale proves to be 1 mm. This corresponds to cellular ensembles including something of the order of one hundred cells. We recall that precisely such ensembles constitute the morphogenetic fields. The stated range of molecular weights has not been taken at random for estimates. It includes such molecules as steroids, nucleotides, amino acids, low-molecular-weight peptides—the fundamental components of intracellular reactions. We also add that special channels have been found relatively recently in membranes at sites of cell contacts.[27] Molecules of the type listed above can diffuse through these channels.[27] Moreover, direct data exist on the diffusion of molecules of cyclic adenosine monophosphate (cAMP) between cells of embryonic tissue.[28] This substance plays a leading role in regulating the activity of genes and in many reactions of cellular metabolism.

Thus reaction-diffusion processes of the type of those that Turing discussed in very general form must have a relation to the actual events in morphogenetic fields. Turing himself proposed a considerably more concrete hypothesis[13]: chemical interactions and diffusion make possible the mechanism of spatial self-organization in multicellular ensembles. Or, in other words, *the positional information in the morphogenetic field arises spontaneously and is fixed by the concentration distribution of the reagents in a chemical dissipative structure.* The corresponding chemical agents have be been called *morphogens*.

We note that the idea of a concentration gradient of certain substances as the cause of spatial ordering of the processes in the morphogenetic field was widespread even before Turing's paper was published (see, e.g., Ref. 29). However, the content of Turing's hypothesis is considerably more constructive. By pointing out an overall mechanism of *onset* of a chemical gradient, it enables one to make concrete predictions of observed characteristics (such as spatial symmetry) of morphogenetic structures. These predictions can be directly compared with the data of experiments on real biological objects. Thus, on the one hand, the theory is subject to test, and on the other hand—it receives food for further development.

The spontaneous onset of dissipative structures, including reaction-diffusion systems, has already firmly become an object of study, and has even given rise to a certain independent branch of physics. At the same time, it has become a fixed tradition to "decorate" reviews on dissipative structures with references to biological applications. As a rule, such references in nonspecialized studies have no concrete content. At present this does not reflect the actual state of the matter. Already many concrete examples have been accumulated on actual objects that demonstrate the "biological significance" of dissipative structures.

Some examples of this type, in our view the most representative, have been included in this review.

2. SYMMETRY-BREAKING INSTABILITY. LINEAR ANALYSIS

It has become clear from Turing's work[13] that chemical interactions coupled with diffusional transport of the reacting molecules can serve as the cause of spontaneous excitation of collective modes with macroscopic scales of inhomogeneity. Just like the modes that arise in the equilibrium cooperative phenomena of the Goldstone modes, these modes involve formation of states (stationary spatial concentration distributions) that break the symmetry of the operator controlling the dynamics of the system. But this is no more than an external resemblance. Above all, the difference lies in the fact that a certain nonzero level of energy dissipation is required to excite and maintain the macroscopic inhomogeneities.[16] These states cannot be realized under conditions of thermodynamic equilibrium. Moreover, one cannot arrive at them by smooth extrapolation of the thermodynamic branch.[16] The latter must become dynamically unstable, and this gives rise to the macroscopic response to the microscopic events—the spontaneous fluctuations are amplified to macroscopic scales.

As we know,[30] the stationary states of a thermodynamic system departing from true equilibrium no further than the limits of validity of the Onsager relationships are stable. (In this regard, see also the earlier study of Ya. B. Zel'dovich,[87] which showed that in a closed system with chemical reactions, the equilibrium state is unique and stable.) This property is guaranteed by the theorem of minimum entropy production.[30] This implies that it is possible to substantiate the onset of macroscopically inhomogeneous states in an initially homogeneous system only outside the limits of the region of linear nonequilibrium thermodynamics, i.e., sufficiently remote from complete thermodynamic equilibrium. A mixture of chemically reacting substances can be kept from relaxing toward equilibrium only by continual influx of substrates and efflux of products from the reaction mixture. It is precisely under such conditions that the development and functioning of any biological system occurs.

Glansdorff and Prigogine[16] have adopted the aim of constructing a thermodynamic theory of stability outside the region of linear thermodynamics of irreversible processes. Upon adopting the postulate of local equilibrium,[1)] they concluded that the increment of specific entropy $\delta^2 S$ caused by the fluctuations can play the role of the Lyapunov function. This means that for stable stationary states the quantities $\delta^2 S$ and $\partial_t \delta^2 S$ must have opposite signs. With a given scheme of chemical transformations, the quantity $\partial_t \delta^2 S$ can be calculated by the laws of chemical kinetics from the deviations of the concentrations from the stationary state. Analysis of the signs of the quantities $\delta^2 S$ and $\partial_t \delta^2 S$ for concrete reaction mechanisms has shown that nonlinear effects associated with auto- and cross-catalytic stages can lead to instability of the thermodynamic branch.[16]

However, we should note that such a thermodynamic approach, while useful for a general understanding of the phenomenon, still is not more economical in calculations than direct analysis of the macroscopic equations of motion. Moreover, it is not at all constructive in treating states in the transcritical region of instability of the thermodynamic branch. It proves more informative here to study the dynamics of the harmonic modes, as enriched recently by new powerful methods. They will be discussed in Sec. 6. Here we shall undertake a more comprehensive elucidation of the mechanisms giving rise to symmetry-breaking instability (SBI) in reaction-diffusion systems.

The macroscopic equations of motion for a mixture of chemically interacting and diffusing components are derived by adding nonlinear local sources $f(C)$ (chemical reactions) to the diffusion equations:

$$\frac{\partial C_i}{\partial t} = f_i(C_1, \ldots, C_N; \alpha_1, \ldots, \alpha_M) + D_i \frac{\partial^2 C_i}{\partial x^2}, \quad i = 1, \ldots, N. \quad (1)$$

Here $C_1, \ldots, C_N$ are the concentrations of the N components of the mixture, and $\alpha_1, \ldots, \alpha_M$ are external parameters such as the rate constants of the chemical reactions, the reservoir (nonevolving) concentrations, etc. The form of the functions f_i ($\{C, \alpha\}$) is determined by the laws of chemical kinetics and will not be made more precise as yet. We note only that, in sufficiently complex chemical mixtures, one can expect practically any form of the function f_i (see Ref. 23). The reactions and diffusion are assumed to occur in a bounded one-dimensional volume. In the other sections we shall treat the cases of several spatial dimensions.

The conditions at the boundary must allow the existence of a thermodynamic branch, i.e., a stationary, spatially homogeneous solution of the system of equations (1). This requirement is satisfied either by the conditions of zero fluxes:

$$\left.\frac{\partial C_i}{\partial x}\right|_0 = \left.\frac{\partial C_i}{\partial x}\right|_L = 0, \quad i = 1, \ldots, N, \quad (2)$$

or (for a cyclic closed-region) by periodic boundary conditions:

$$C_i(0, t) = C_i(L, t), \quad \left.\frac{\partial C_i}{\partial x}\right|_0 = \left.\frac{\partial C_i}{\partial x}\right|_L, \quad (3)$$

or by values of the concentrations fixed at the boundaries:

$$C_i|_0 = C_i|_L = \overline{C}_i. \quad (4)$$

Here the values of the $\overline{C}_i$ correspond to the thermodynamic branch. The choice of any particular conditions is determined by the experimental situation and does not affect the discussions of this section.

We intend to elucidate under what conditions a transition becomes possible in systems described by the dynamic equations (1) from the homogeneous state $\overline{C}_i$ to a state of lower spatial symmetry. When $N \geq 3$, the problem proves to be too complex to treat by ana-

[1)] In local equilibrium the entropy is expressed locally in terms of the state parameters P, ρ, and T in the same way as is done for the entire volume in true equilibrium.

lytical methods. But even in a two-component system ($N=2$), the property that we need can be found, as was first shown by Turing.[13]

First let us convince ourselves that in a simpler ($N=1$) reaction-diffusion system an instability that leads to breaking of spatial homogeneity never arises under any conditions.

Let $\overline{C}(\alpha_1, \ldots, \alpha_M)$ be a homogeneous stationary solution of a kinetic equation of the type of (1) that depends on the set of external parameters $\{\alpha_j\}$ and which is obtained by smooth extrapolation from thermodynamic equilibrium with varying $\{\alpha_j\}$. The condition of stationarity $\partial C/\partial t = 0$ has the form

$$f(\overline{C}(\alpha_1, \ldots, \alpha_M)) = 0. \tag{5}$$

To elucidate the stability, let us examine the evolution of small inhomogeneous deviations $u(x, t) = C(x, t) - \overline{C}$. We can employ the linearized Eq. (1):

$$\frac{\partial u}{\partial t} = f'_C(\overline{C})u + D\frac{\partial^2 u}{\partial x^2}. \tag{6}$$

Upon using the ordinary procedure for separating the variables x and t and representing the solution of the equation that is derived for the coordinate-dependence in the form of a superposition of harmonic modes e^{ikx}, we arrive at the dispersion equation

$$\lambda(k) = \alpha - Dk^2, \text{ where } \alpha = f'_C(\overline{C}). \tag{7}$$

This relates the time decrement of the harmonic λ with its wave number k. An arbitrary solution of the linear equation (6) is represented in the form

$$u(x, t) = \sum_{l=0}^{\infty} a_l e^{ik_l x + \lambda(k_l)t}.$$

Within the limits of stability of the thermodyanmic branch we have $\alpha < 0$. As we can see from (7), we have the time index $\lambda(k_l) < 0$ in this case for all spatial mode $e^{ik_l x}$.

Instability upon varying the external parameters $\{\alpha_j\}$ can arise only as the result of vanishing of α. Here a homogeneous perturbation (zero-order harmonic $k_0 = 0$) brings the system out of equilibrium. Thus a homogeneous state corresponding to the thermodynamic branch can become unstable, but breaking of spatial symmetry does not occur here. The reason for this situation is the monotonic nature of the $\lambda(k)$ relationship A stronger statement also holds (see Refs. 31 and 32): in a one-component dynamic system of the form of (1) with bounday conditions (2) or (3), inhomogeneous stable states cannot exist, regardless of the form of the nonlinear source.

Already in the presence of two diffusing agents coupled by chemical reactions (a Turing system), the reason for the negative result that we have obtained—the monotonicity of $\lambda(k)$—is removed. We shall convince ourselves below that, in two-component reaction-diffusion systems, a transition accompanied by breaking of spatial homogeneity of the thermodynamic branch can occur. Such systems are the simplest ("basal"[19]) models for substantiating spatial self-organization.

a) Two-component systems. Mechanisms of Turing instability

When $N=2$, the linearized kinetic system for small deviations from a homogeneous stationary state $u = C_1(x, t) - \overline{C}_1$, $v = C_2(x, t) - \overline{C}_2$ has the form

$$\begin{aligned} \frac{\partial u}{\partial t} &= f_{uu}u + f_{uv}v + D_u\frac{\partial^2 u}{\partial x^2}, \\ \frac{\partial v}{\partial t} &= f_{vu}u + f_{vv}v + D_v\frac{\partial^2 v}{\partial x^2}. \end{aligned} \tag{8}$$

Again, upon substituting the solution in the form of a superposition of harmonic modes

$$(u, v) = \sum_{l=0}^{\infty} b_l \mathbf{q}_l e^{\lambda_l t + ik_l x},$$

we arrive at the characteristic equation that determines the dispersion law:

$$\text{Det}\,[-f_{ij} + \delta_{ij}\lambda - D_{ij}k^2] = 0, \quad i, j = 1, 2. \tag{9}$$

Now the equation relating λ and k is second-order in λ and fourth-order in k. Depending on the values of the set of parameters $\{f_{ij}; D_i\}$, we can face two typical situations, which are shown in Fig. 2.[23] While the case in Fig. 2a contains no new fundamental features as compared with $N=1$, that in Fig. 2b has such features. Here two new types of instability can arise. The first arises when the instability threshold $\text{Re}\lambda = 0$ is reached in the region of complex roots of the characteristic equation. As Fig. 2c implies, this can happen only when $k=0$. That is, the spatially homogeneous modes of the perturbation break the thermodynamic branch. However, the difference from the case $N=1$ consists of the fact that now $\text{Im}\lambda \neq 0$. Owing to this instability, the new regime proves to be ordered in time—synchronous oscillations (homogeneous throughout the volume) arise. This is not the case in which we are interested at present.

The second variety of critical situation occurs when a local maximum of the curve $\lambda(k)$ touches the axis $\text{Re}\lambda = 0$ in the region of real λ (Fig. 2d). This is the Turing instability. Here we have assumed that the spectrum of wave numbers in continuous. In a bounded system a discrete set of harmonic modes $e^{ik_l x} = \Psi_l$ is realized, with wave numbers k_l determined by the boundary conditions. In this case, Turing instability arises when the greatest of the numbers $\lambda(k_l)$ passes through zero.

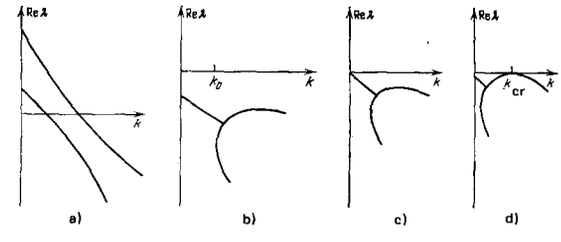

FIG. 2. Types of dependence of the time decrement $\text{Re}\lambda$ on the wave number k of harmonic modes of perturbation based on the characteristic equation (9). a) The case of two real branches of solutions of Eq. (9); b) two complex conjugate solutions of Eq. (9) transforming into a pair of real solutions when $k > k_0$; c) the dispersion relation $\lambda(k)$ at the threshold of excitation of homogeneous oscillations; d) the dispersion relation at the threshold of excitation of a dissipative structure.

Upon emerging into the transcritical region, a narrow range of modes e^{ikx} or a single critical mode (in case of limited dimensions) acquires a positive increment. Thus the system proves to be capable of singling out and amplifying definite harmonics from the unstructed noise (natural fluctuations). Upon growing, they can lead the system into a macroscopically ordered state. This new state is fully determined by the dynamic parameters, rather than by the random events inducing the transition. Here it is proper to use the term "self-organization". In the fourth section we shall take up the structures in the transcritical region, but for the present we shall try to define more precisely the features of a reaction-diffusion system that give rise to its capacity for self-organization. To do this, we shall idealize somewhat the critical situation by ignoring the properties of the linear reaction-diffusion system of general form that are noninformative near the instability threshold.

In the vicinity of the instability threshold, the modes with wave numbers outside a narriw interval including the critical mode k_{cr} should not affect the behavior of the system. These modes have a finite damping increment and hence at long times—of the order of the lifetime of the critical mode $\tau_{cr} \sim 1/\lambda_{cr} \to \infty$, they are not manifested. For this same reason, the existence of two branches of solutions of the dispersion equation (9) is not reflected in the behavior of the dynamic system.[33] Therefore we can use the smallness of λ and neglect λ^2 in comparison with λ.[33] Consequently $\lambda(k)$ will be equal to

$$\lambda = \frac{-\sigma + sk^2 - D_u D_v k^4}{-p + (D_u + D_v)k^2} = \alpha - \frac{\sigma - \alpha p}{-p + (D_u + D_v)k^2} - D_{\text{eff}} k^2. \qquad (10)$$

Here we have introduced the notation

$$\sigma = \operatorname{Det} f_{ij}, \quad p = \operatorname{Spur} f_{ij}, \quad s = D_u f_{vv} + D_v f_{uu},$$
$$\alpha = \frac{s - pD_{\text{eff}}}{D_u + D_v}, \quad D_{\text{eff}} = \frac{D_u D_v}{D_u + D_v}.$$

We can consider the simplified dispersion equation (10) to be the image in the k-representation of the linear equation of motion of the single-component system, in which the spatial couplings are established by two mechanisms: by diffusion—the term $-D_{\text{eff}}k^2$ in Eq. (10), and a nonlocal mechanism reflected in the term $-(\sigma - \alpha p)/[-p + (D_u + D_v)k^2]$. The first mechanism dominates at large wave numbers, i.e., with short-wavelength perturbations, while the second dominates at small k. We obtain the following equation in the variables x and t from the dispersion equation by inverse Fourier and Laplace transformation:

$$w_t = \alpha w - \gamma \int \exp\left(-\frac{|x - x'|}{R}\right) w(x', t) \frac{dx'}{R} + D_{\text{eff}} w_{xx},$$
$$R^2 = \frac{D_u + D_v}{|p|}; \quad \gamma = \alpha - \frac{\sigma}{p}. \qquad (11)$$

We note that the requirement of stability of a homogeneous distribution ($\bar{u} \equiv 0$, $\bar{v} \equiv 0$) with respect to the homogeneous perturbation modes $k = 0$ and to the requirement of nonmonotonicity of the $\lambda(k)$ curve yields the inequalities

$$p < 0, \quad \gamma = \alpha - \frac{\sigma}{p} > 0.$$

The equation of motion (11) describes an asymptotic dynamics (for large times) of an arbitrary two-component reaction-diffusion system near the instability threshold of the homogeneous state. Its advantage over the general equations of motion of the two component system consists of the fact that it no longer contains anything "superfluous", but includes in explicit form only the mechanisms necessary to enable SBI. *The main point here lies in the existence of two characteristic spatial scales: the scale of diffusional mixing* $\sim\sqrt{D_{\text{eff}}}$ *and a second scale* $\sim R$ *associated with nonlocal inhibiting effects*[33] (we call attention to the minus sign in front of the integral in Eq. (11)). Before we make more precise the quantitative relationships between the aforementioned characteristic dimensions, we shall try to find a more concrete and clear meaning of the corresponding mechanisms. To do this, we shall assume in addition that

$$f_{uu}, f_{uv} \gg f_{vv}, f_{vu}, \quad D_u \gg D_v.$$

Then the parameters of Eq. (11) can be directly related to the molecular parameters of the two agents a and h. Here a autocatalytically activates its own production, diffuses with the diffusion constant D_a, and is suppressed by the agent h. In turn, the dynamics of the latter is determined by its production, which is activated by a, by degradation, and also by diffusion with the constant D_h. The equations of motion describing these interrelationships have the form

$$T_a a_t = \varphi(a) - h + R_a^2 a_{xx}, \quad R_a^2 = D_a T_a,$$
$$T_h h_t = a - h + R_h^2 h_{xx}, \quad R_h^2 = D_h T_h. \qquad (12)$$

Here T_a and T_h are the characteristic time scales of the dynamics of a and h. If, moreover, the relationship holds that $T_a \gg T_h$, then in the rate-limiting stages of evolution the distribution $h(x, t)$ is quasistationary, while $a(x, t)$ varies in accordance with the kinetic equation

$$T_a a_t = \varphi(a) - \frac{1}{2R_h} \int \exp\left(-\frac{|x - x'|}{R_h}\right) a(x', t)\, dx' + R_a^2 a_{xx}. \qquad (13)$$

Upon linearization with respect to small deviations δa from a homogeneous stationary state, this equation becomes equivalent to that derived above upon reduction of an arbitrary two-component system near the threshold for self-organization (11). However, here the functions of realization of the two necessary modes of spatial interactions—local activating and nonlocal inhibiting—are divided among the two agents. Their molecular parameters determine both the instability point itself of the homogeneous state and the wave number of the harmonic mode of the unstable perturbation.

The $\lambda(k)$ relationship obtained from Eq. (13) has the form

$$T_a \lambda(k) = \alpha - \frac{1}{1 + R_h^2 k^2} - R_a^2 k^2, \quad \alpha = \varphi_a'(a_{st}).$$

From this we define more precisely the condition on the parameters necessary for existence of SBI. This condition arises from the requirement of existence of a maximum on the $\lambda(k)$ curve, and is expressed in the form[33]

$$R_h > R_a. \qquad (14)$$

Reaching the instability threshold $-\lambda(k_{cr}) = 0$ can be attained, e.g., by variation of the parameter α, whose critical value is

$$\alpha_{cr.}=2\frac{R_a}{R_h}-\left(\frac{R_a}{R_h}\right)^2.$$

The inequality (14) expresses the physical condition for appearance of spatial order in a reaction-diffusion system. Two kinetic effects are decisive: *local autocatalysis and long-range inhibition.*

Now let us turn to the experimental data.

b) Hydra. Mechanisms of self-organization

Typical features of the process of self-organization of biological forms are manifested even in the development of such a simple, and hence well studied, organism as hydra.[34] Its simplicity consists of a relatively small number of differentiated tissues organized in one spatial dimension. Figure 3 shows a crude diagram of the animal. This same diagram shows the scheme of transplantation experiments and experiments on regeneration, to which we shall refer.

Morphologically homogeneous zones (A and B) were dissected from a formed organism and placed in a nutrient medium. In about forty hours, these initially homogeneous fragments had regenerated a complete animal. An essential point here was that the process is not accompanied by growth of the regenerant. Consequently the obtained organs are proportionally diminished in dimensions. We shall refer to this feature of the regeneration process again in Sec. 7. But here it is important to pay attention to the reproducibility of the orientation of the "head-foot" axis: In the regenerant the direction from the head to the foot coincides with the original orientation of the animal.[34] This property indicates the presence of a certain asymmetry in the visually homogeneous tissue of the fragment, i.e., its *polarity*. The polarity owes its origin to an asymmetric distribution of some scalar property, rather than to a definite orientation of asymmetric cells.[35] According to the concept of a chemical gradient, this property is the concentration of a morphogen (see the Introduction). The gradient of the latter along the body fixes the direction of the polarity.

The type of specialization (belonging to some particular tissue) that the cells acquire in the process of regeneration is not determined by the absolute magnitude of the concentration of the morphogen at the onset of the regeneration process. This stems from the fact that the very small cells (×) can develop into a foot or into a head (Fig. 3a). The position of the organs is determined as the result of the process of establishment of the concentration gradient of the morphogen that occurs in the first stages of regeneration (~ an hour); in about five hours after dissecting out the fragment, although the future structures are not noticeable, the positional information coding for them has already been formed. This conclusion is based on the transplantation experiments shown schematically in Fig. 3b.

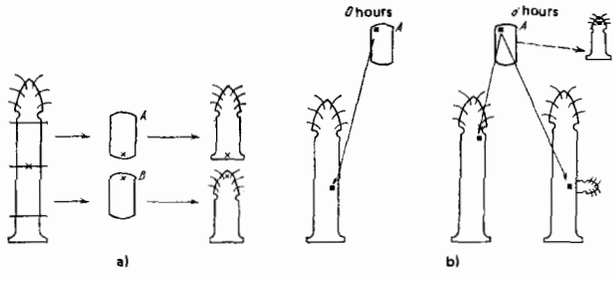

FIG. 3. Diagram of experiments on regeneration and transplantation in hydra. Regeneration of an animal from a morphologically homogeneous fragment. The cells marked with a cross × can develop into a foot (above) or into a head (below), depending on their position with respect to the rest of the excised fragment; b) transplantation of cells of the future head (black square) into the body of an adult animal. See text for more detailed explanation. The dashed line indicates the pathway of normal regeneration.

When cells of a fragment removed from it six hours after dissection are transplanted into the body of a grown, formed hydra, the adjacent tissues of the stem are stimulated to form a new head. This does not happen if cells of the future head of the fragment removed shortly after its dissection were transplanted.[36] The effect of "short-range activation"[37] is revealed in the stimulation by mature transplanted cells of the surrounding tissues to form a secondary head. These same experiments manifest the effect of "long-range inhibition"—a secondary head is not formed, even by fully mature cells of the transplant, if they are placed at an insufficient distance from the primary head of the acceptor organism.[36]

On the basis of these experiments, Gierer and Meinhardt[37] postulated the existence of two agents that lead to opposite effects in the process of formation of the morphogenetic structures of hydra. They are a locally acting "activator", which induces the morphogenesis of a head from cells adjacent to the transplantation site, and an "inhibitor", which suppresses the effect of the activator. The inhibitor is also produced at the transplantation site, but can diffuse to relatively great distances. The authors constructed a set of mathematical models—dynamic systems of the form (1) with $N=2$, a general feature of which was a nonlinear auto- and cross-catalytic effect of the activator, an inhibiting effect of the inhibitor, and a relationship between the diffusion coefficients $D_a < D_h$,[38-40] The models were studied by numerical methods,[38-40] and the results were compared with the experimental data on pattern-forming processes in a set of morphogenetic systems. Good agreement was obtained here (see Sec. 5 of this review on this topic).

It should be said that the demonstrated descriptive power of the "activator-inhibitor" model has stimulated attempts to discover experimentally the molecular agents themselves that fulfill the corresponding functions. The search has proved successful. In the same hydra, molecules have been found and characterized that that can activate the process of head formation, and also agents that suppress this process.[41] They proved to be: the activator is a peptide of molecular weight 1300; the inhibitor function is fulfilled by a basic agent of nonprotein nature and molecular weight less than 500. We note that the smaller molecular weight of the inhibitor corresponds well to the theoretical prediction of a larger diffusional mobility of this agent.

3. TWO-DIMENSIONAL DISSIPATIVE STRUCTURES. AN EXAMPLE FROM INSECT DEVELOPMENT

In this section we shall examine a single example of biological development in which chemical dissipative structures provide the key to understanding rather specific phenomena. We shall be dealing with the early stages of ontogenesis of the fruit fly drosophila (*Drosophila melanogaster*). The studies performed on this organism have furnished a mass of valuable experimental results in the field of biology of individual development.

Before taking up the concrete data, we shall give some information from enbryology on the general features of development of all insects. This minimal information will facilitate an understanding of the experimental data given here and also in Sec. 5.

The process of individual development of the embryo starts with the fertilization of the oocyte. After fertilization a series of synchronous divisions of the nuclei occurs inside the common cell envelope—the stage of *cleavage*, which lasts several hours. Then the daughter nuclei migrate through the cytoplasm to the periphery of the egg, where new cell walls soon appear between them. Thus a layer of cells is formed at the surface of the egg, called the *blastoderm*. At this stage there are still no visible signs of spatial organization of the cells. However, a more careful analysis shows that already at the blastoderm stage the embryo becomes stratified into discrete, nonoverlaping zones, or *compartments*. Groups of cells from the different zones of the blastoderm form the so-called *imaginal discs*—precursors of the future organs of the adult organism. The imaginal discs also undergo a series of compartmentations, after which they transform into the rudiments of the future tissues and organs. The compartments arise in a strictly defined sequence that indicates in which order the different spatial domains of the embryo obtain their appropriate program of development.[42,43]

The morphological features in the embryo are manifested in the next stage after the blastoderm—the stage of the *larva*. Figure 4 shows a diagram of the described

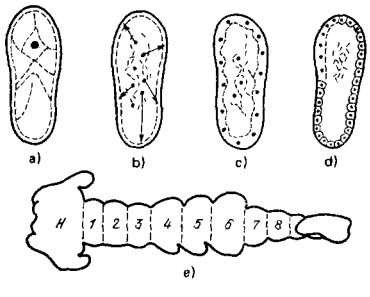

FIG. 4. Overall diagram of the early stages of development of insects. a) Fertilized egg cell; b) cleavage and migration of nuclei to the periphery of the egg; c) preblastoderm, nuclei not yet separated by membranes; d) blastoderm, appearance of cell walls between the nuclei; e) larva with 16 segments—precursors of the structures of the adult insect (*H*—head, segments, 8–16—abdomen).

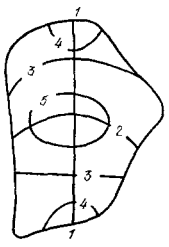

FIG. 5. Boundaries of the compartments of the imaginal disk of the wing of a fruit fly. The numbers correspond to the order of appearance of the boundaries.[45]

pathway of development of the embryo of insects. One can obtain more detailed information on the general stages of ontogenesis of insects from the pertinent textbooks (see, e.g., Ref. 34).

We have already noted that the imaginal dics, before transforming into the corresponding organs, undergo a series of transformations of spatial organization, or compartmentations. This process can be studied experimentally. The compartmentation of the imaginal disc of the wing of drosophila was studied in Ref. 44. Figure 5 shows schematically the pattern of compartments obtained on the basis of these data, where the numbers along the boundary lines correspond to the order of appearance of the boundaries. Kauffman and his associates[45] have proposed an interpretation of the pattern shown in Fig. 5 as the manifestation of chemical dissipative structures. Their argument is based on the evident similarity of shape of the boundary lines of the compartments with the nodal lines of the eigenfunctions of the diffusion operator ∇^2 in a planar region with an elliptical boundary. The approximation of an actual imaginal disc with a plane ellipse is a rather crude model. Nevertheless a calculation based on it proves to agree well with the experimental data.

Following the authors of Ref. 45, let us examine how the spatial self-organization of a reaction-diffusion system in a planar region with an elliptical boundary can occur. As above, here we allocate to the reaction-diffusion system the role of organizing the spatial differentiation of the cells of the given morphogenetic field. At the stage being discussed, the concentration distribution of the morphogen that fixes the positional information is being formed. The distribution of the cells observed experimentally[44] into the discrete compartments is the result of translation of this positional information. Translation presupposes the employment of a certain code. A very simple variant of a binary code proves sufficient in the compartmentation of the imaginal disc of the wing.[46] Namely, a cell at a given point in the morphogenetic field is specialized as type "I" if the local concentration of the morphogen exceeds a certain threshold value x_0, and as type "II" otherwise. In the adopted scheme the contour lines of the concentration x_0 must correspond to the boundaries of the compartment. Thus we can correlate the result of calculation—the concentration distribution in the chemical dissipative structure—with the distribution of the compartment boundaries found by experiment.

Let us turn again to the form derived above of the kinetic equation for a reaction-diffusion system near the threshold of dissipative Turing instability (11). We shall assume that the level of concentration of the morphogen in the initial homogeneous state of the reaction-diffusion system corresponds to the threshold value x_0. We shall be interested in the types of spatial ordering that take shape upon loss of stability of the given homogeneous state. The linear equation of motion near the instability threshold (which suffices for studying the geometry of the dissipative structures that arise and the order of their appearance) in the two-dimensional region Ω has the form

$$w_t = \alpha w - \gamma \int \exp\left(-\frac{|\mathbf{r}-\mathbf{r}'|}{R}\right) w(\mathbf{r}', t)\frac{d\mathbf{r}'}{R} + D_{\text{eff}}\nabla^2 w. \qquad (15)$$

This is a natural generalization of Eq. (11). The imaginal disc of the wing is separated from the surrounding tissues by a special membrane. We shall assume (following the authors of Ref. 45) it to be impenetrable to the morphogen. This implies that the conditions at the elliptical boundary C correspond to zero fluxes:

$$(\mathbf{n}\nabla w)|_{r\in C} = 0. \qquad (16)$$

The only evident parameter of development whose variation induces a transition from the initial homogeneous state x_0 ($w=0$ is Eq. (15)) to a state of lower spatial symmetry is the size of the region Ω. The latter increases in the course of ontogenesis owing to cell divisions. The variation in the size of the imaginal disc caused by growth of the embryo occurs considerably more slowly than the evolution of the concentration of the morphogen, owing to the relatively simple chemical transformations and diffusion. Therefore we shall assume the size to be a nonevolving parameter. When it is sufficiently small (smaller than the region of diffusional mixing), the only stable state for the system is the trivial state $w \equiv 0$. With growth of the embryo, when the size of the imaginal disc exceeds the size of the region of diffusional mixing, a second characteristic scale begins to be manifested—the scale of long-range "lateral" inhibition. Here the homogeneous state x_0 can become unstable. The spatial form of the new nonhomogeneous states is determined by the geometry of the unstable modes that destroy the symmetry of the initial state. Let us introduce as the coordinate system the natural coordinates of the ellipse $\mathbf{r} = (\xi, \eta)$ (see Fig. 6). Upon separating, as usual, the spatial and temporal variations, we find that the evolution of the spatial distribution $w(\xi, \eta, t)$ is represented in the form of a superposition of normal modes of the form

$$\begin{aligned} e^{\lambda_{nj}t}\Psi_{nj}(\mathbf{r}) &= \exp \lambda_{nj}t\, \mathrm{Ce}_n(\xi, s_{nj})\, \mathrm{ce}_n(\eta, s_{nj}), \\ e^{\lambda_{nj}t}\Psi_{nj}(\mathbf{r}) &= \exp \lambda_{nj}t\, \mathrm{Se}_n(\xi, s_{nj})\, \mathrm{se}_n(\eta, s_{nj}). \end{aligned} \qquad (17)$$

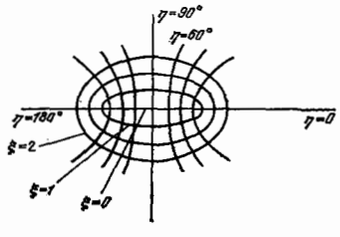

FIG. 6. Elliptic coordinates in a plane.

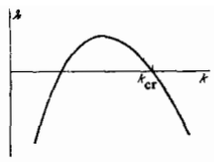

FIG. 7. The dispersion relation $\lambda(k^2)$ corresponding to Eq. (19) under the condition $\alpha > -\hat{L}^*(k^2_{\max})$.

Here $\mathrm{ce}_n(\eta, s_{nj})$ and $\mathrm{se}_n(\eta, s_{nj})$ are the periodic cosine and sine elliptical Mathieu functions of integral order, while $\mathrm{Ce}_n(\xi, s_{nj})$ and $\mathrm{Se}_n(\xi, s_{nj})$ are the corresponding modified functions.[47] In (17) we have $s_{nj} = h^2 k^2_{nj}$, where h is half the interfocal distance of the ellipse, and k_{nj} is an analog of the wave number. The sequence of values of k_{nj} is determined from the boundary condition

$$\frac{\partial \mathrm{Ce}_n(\xi, s_{nj})}{\partial \xi}\Big|_{\xi_0} = 0 \quad \text{or} \quad \frac{\partial \mathrm{Se}_n(\xi, s_{nj})}{\partial \xi}\Big|_{\xi_0} = 0 \qquad (18)$$

(here j is the number of zeros of the derivatives $\partial/\partial\xi$ in the interval $(0, \xi_0)$). The functions $\mathrm{Ce}_n\mathrm{ce}_n$ and $\mathrm{Se}_n\mathrm{se}_n$ have risen as eigenfunctions of the operator

$$\hat{L}w = \int \exp\left(-\frac{|\mathbf{r}-\mathbf{r}'|}{R}\right) w\, d\mathbf{r}' + D_{\text{eff}}\nabla^2 w,$$

which satisfies the given conditions (16) at the elliptical boundary. One obtains the following expression for the time decrement λ_{nj} of the mode $\{nj\}$ by substituting (17) into Eq. (16):

$$\begin{aligned} \lambda_{nj} &= \alpha + \hat{L}^*(k^2_{nj}), \\ \hat{L}^*(k^2) &= \int \exp\left(-\frac{|\rho|}{R}\right)\Psi(\rho)\, d\rho - D_{\text{eff}}k^2 \end{aligned} \qquad (19)$$

The character of the $\lambda(k^2)$ variation is that in Fig. 7. We shall assume that $\alpha > -\hat{L}^*(k^2_{\max})$. Then the maximum of the curve $\lambda(k)$ lies in the region of positive values of λ.

For each of the modes of the sequence (17), the boundary condition (18) fixes a definite value of the parameter s_{nj} that depends on the eccentricity of the ellipse. Consequently the corresponding wave numbers k_{nj} decline with growth as $1/h$. At sizes up to a certain critical size, the wave numbers k_{nj} lie on the declining section of the $\lambda(k)$ curve. Hence the decrement λ increases with increasing size h for all the normal modes of (17). The condition for excitation (passage of λ through zero) has the following common form for all modes:

$$\lambda = \alpha + \hat{L}^*(k^2_{\text{cr}}) = 0. \qquad (20)$$

However, the corresponding value of the size h for each mode is individual, owing to the relationship $s_{nj} = h^2_{nj}k^2_{\text{cr}}$. Figure 8 shows a possible growth trajectory (line with arrow) for which the eccentricity of the ellipse remains constant. Such a trajectory qualitatively agrees with experiment. In this case, as we see from Fig. 8, the order of excitation of the modes is[45]:

$$\mathrm{Ce}_{11}\mathrm{ce}_{11},\ \mathrm{Se}_{11}\mathrm{se}_{11},\ \mathrm{Ce}_{21}\mathrm{ce}_{21},\ \mathrm{Se}_{21}\mathrm{se}_{21},\ \mathrm{Ce}_{31}\mathrm{ce}_{31},\ \mathrm{Ce}_{01}\mathrm{ce}_{01}.$$

Figure 9 shows the nodal lines of these functions. As was proposed above, the nodal lines of the excited concentration structure are the lines of threshold value of the morphogen. The cells of the morphogenetic field

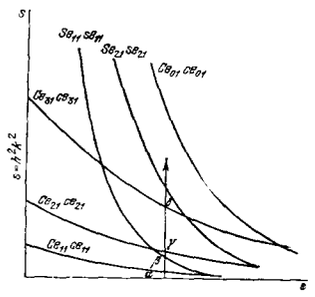

FIG. 8. Dependence of the parameter S_n on the eccentricity ε of the ellipse for certain eigenfunctions of the operator $\hat{L}$ in elliptic coordinates.[45] The arrow corresponds to the trajectory of growth with conservation of shape of the imaginal disk. The points α, β, γ, etc., define the critical size at which the corresponding inhomogeneous stationary solutions branch from the spatially homogeneous state.

choose one of the two possible directions of further specialization, depending on whether the local concentration of the morphogen is above or below the threshold level. If in addition the cells remember the entire sequence of determination events, then each of the terminal domains of identically specialized cells (compartments) can be determined by a unique combination of states from a small number of coupled pairs. In this case the final subdivision of the imaginal disc into compartments is obtained by superposition of Figs. 9a–f. The agreement of the pattern that arises (Fig. 9g) with that obtained experimentally (see Fig. 5) is evident.

Of course, the sketched scheme of the process of compartmentation is far from final completion. As an example, the problem remains unsolved of whether all stages of the process are covered by a single morphogen, or a new morphogen acts at each event of formation of a new compartmental boundary. The aim of subsequent experimentation is to clarify the situation However, what has been obtained is already considerable. Such a successful prediction of the geometry of the compartment boundaries and the sequence of their appearance lends great weight to the principal premise of the proposed explanation of the origin of the spatial organization in the given morphogenetic field. The leading role here belongs to the reaction-diffusion system, which undergoes spontaneous breaking of spatial symmetry owing to Turing instability.

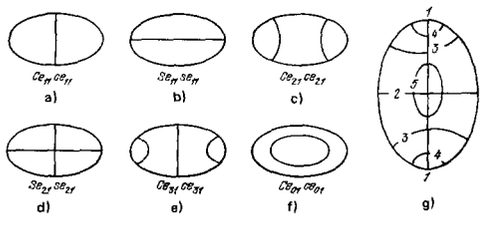

FIG. 9. Nodal lines of several of the first eigenfunctions of the operator $\hat{L}$ in the order in which the corresponding stationary distributions branch from the homogeneous state (see the preceding diagram). The modes $Se_{11}se_{11}$ and $Se_{21}se_{21}$ have been omitted in obtaining the superposition in Fig. 9g. (see Ref. 45).

We note that the comparison with experiment of such characteristics as the symmetry of spatial organization and the sequence of structures supplanting one another requires no assumptions on the concrete mechanisms of the chemical transformations. Only the overall symmetry of the region and the isotropic nature of the intercellular interactions arising from diffusional coupling (short-range for the activating agents and relatively long-range for the inhibitors) create the pattern that is obtained. Therefore, in essence, the comparison that has been performed is a test for the hypothesis if chemical dissipative structures as the source of the spatial order of the processes in multicellular ensembles.

4. STATES BEYOND THE INSTABILITY THRESHOLD OF THE THERMODYNAMIC BRANCH

Upon going into the transcritical region, the homogeneous state is no longer stable. We know from the linear approximation that the breakdown of this state gives rise to excitation of a quite definite degree of freedom. For reactions in a finite volume with a discrete set of normal modes (eigenfunctions of the diffusion operator), one of them, Ψ_{cr}, constitutes this singled-out degree of freedom. The linear approximation indicates that it relaxes very slowly (the decrement λ_{cr} approaches zero near the instability threshold) in the near precritical region and is amplified with a small increment in the near transcritical region. In the case of nondegenerate instability the characteristic numbers λ remain finite for all the remaining modes. This implies fast relaxation (in comparison with Ψ_{cr}). As we see, here the same situation takes shape as occurs near an equilibrium second-order phase transition, where the slowly relaxing parameter is the order parameter.[2)] Haken, who studied nonequilibium collective phenomena in the generation of laser radiation, first called attention to this analogy.[49]

Owing to the aforementioned slowness of the critical dynamics, one can construct closed equations of motion of the singled-out critical degree of freedom. Within the framework of this abbreviated description one can also study the nonlinear effects. The latter can only stabilize the new state by replacing the thermodynamic branch in the transcritical region. However, in addition the nonlinear contributions can substantially enrich the system with new types of collective effects. They include such effects as the appearance of multiple stable dissipative structures and transitions among them, secondary instabilities of stationary concentration distributions that are already inhomogeneous, and accompanying changes of spatial symmetry. To discover and study this variety of features of "nonlinear" behavior does not require any complication at all of the macroscopic dynamics of the system.

[2)]Upon continuing this analogy, one can find that large-scale correlations of fluctuations and also a number of fluctuation effects characteristic of equilibrium transitions are associated with slowness of critical relaxation. We shall not treat them in this review (see Ref. 48).

We shall start with the equation of motion of the "activator-inhibitor" model in the form (13) and try to simplify it by isolating the slow critical dynamics. In compact notation this equation appears as follows:

$$a_t = \hat{\Lambda}^{cr} a + \mu a + N(a). \tag{21}$$

Here the linear operator $\hat{\Lambda}^{cr}$ has the form

$$\hat{\Lambda}^{cr} a = \alpha^{cr} a + \int \exp\left(-\frac{|x-x'|}{R}\right) a(x') \frac{dx'}{R} + D a_{xx}. \tag{22}$$

The function $N(a)$ includes all the nonlinear contributions to the kinetics. The parameter μ gives the deviation from the instability threshold such that $\mu > 0$ corresponds to the transcritical situation, and $\mu < 0$ to the precritical. Below we shall assume a definite smallness of this quantity (and define it more precisely). For the sake of simplicity, we shall assume the parameter μ to be the only one varying in the system.

We shall restrict the treatment only to states that arise as the result of "soft" bifurcation of the thermodynamic branch. Then the amplitude of deviation from the initial state $\bar{a} = 0$ is small in connection with the smallness of the distance from the bifurcation point (we recall that the initial homogeneous state lying on the thermodynamic branch corresponds to the solution $a = 0$ of Eq. (21)). This enables us to take into account only the lowest powers of a in the expansion of the function $N(a)$ in a Taylor's series about $a = 0$. For stabilization of structures in the transcritical region, it proves sufficient to take into account terms no higher than a^3. Therefore we shall adopt for $N(a)$:

$$N(a) = -\beta a^3. \tag{23}$$

The quadratic term omitted in (23) leads, in the absence of degeneracy of the decrements in the linear problem, only to formal complications without changing anything in principle.

Further, we shall employ an expansion in the complete set of normal modes Ψ_l (eigenfunctions of the operator $\hat{\Lambda}^{cr}$) in the form

$$a(x, t) = \sum_{l=0}^{\infty} b_l(t) \Psi_l(x). \tag{24}$$

For boundary conditions of the zero-flux type, the set $\{\Psi_l\}$ amounts to

$$\Psi_l = \cos k_l x, \quad k_l = \frac{l\pi}{L}, \quad l = 1\ \ 2, \ldots, \Psi_0 = \frac{1}{2}.$$

The corresponding eigenvalues of the operator $\hat{\Lambda}^{cr}$ (the spectrum of its Fourier transform) are:

$$\Lambda_{l_{cr}} = 0, \quad \Lambda_{l \neq l_{cr}} < 0. \tag{25}$$

The subscript l_{cr} denotes the critical mode, which is neutrally stable at the threshold $\mu = 0$. Upon transforming to a basis of the normal modes, the kinetic equation (21) is transformed into an infinite system of ordinary differential equations in the amplitudes b_l (see Ref. 33). Thereupon we should make the self-consistent assumption[17]

$$|b_{l_{cr}}| \gg |b_l|.$$

It is justified by the closeness to the instability threshold, owing to which all the modes but the critical mode relax rapidly. Let us restrict the treatment to small deviations from the instability threshold, such that

$$\mu \ll |\Lambda_{l \neq l_{cr}}|. \tag{26}$$

Then at times $t \sim 1/\mu$ the number of evolving degrees of freedom is sharply abridged. The original infinite system of equations in the amplitudes b_l is shortened to the following:

$$\begin{aligned} \dot{b}_{cr} &= \mu b_{cr} - \frac{3}{4}\beta b_{cr}^3 + \frac{3}{16}\frac{\beta^2 b_{cr}^5}{\Lambda_{3l_{cr}}}; \\ b_{3l_{cr}} &\approx \frac{\beta}{4\Lambda_{3l_{cr}}} b_{cr}^3, \quad b_{l \neq l_{cr},\, 3l_{cr}} = 0(b_{cr}^3) \end{aligned} \tag{27}$$

(see Ref. 33). Hence it is clear that, when $\beta < 0$, the nontrivial solution $\bar{b}_{cr} = \pm\sqrt{4\mu/3\beta}$ exists until we reach the instability threshold of the trivial solution $\bar{b}_l \equiv 0$, which corresponds to the initial state. However, as we see from the equation of motion (27), the stationary solutions of $\bar{b}_{cr}$ are unstable. Thus, no stable nonhomogeneous states are obtained in the precritical bifurcation of the homogeneous state.

But if $\beta > 0$, then at the point $\mu = 0$ a pair of new nontrivial solutions $\bar{b}_{cr} = \pm\sqrt{4\mu/3\beta}$ branches off from the trivial solution $\bar{b}_l \equiv 0$ in a continuous fashion, now as the result of transcritical bifurcation. Both new branches in this case are stable.[33] The form of the spatial distribution $\bar{a}(x)$ that replaces the homogeneous state is determined by the expression

$$\bar{a}(x) = \pm \bar{b}_{cr}\left[\left(1 + \frac{\mu}{3\Lambda_{3l_{cr}}}\right)\Psi_{l_{cr}} - \frac{\beta}{4\Lambda_{3l_{cr}}}\bar{b}_{cr}^2 \Psi_{3l_{cr}}\right]. \tag{28}$$

Near the appearance threshold (small values of μ), the inhomogeneous states have the form of the sine waves $\Psi_{l_{cr}}$. With increasing μ this form smoothly distorts becoming more rectangular owing to the contribution of the odd harmonics $\Psi_{3l_{cr}}, \Psi_{5l_{cr}}$, etc. (see Ref. 33).

With increasing μ, the now already unstable thermodynamic branch undergoes a new bifurcation at $\mu_l = \Lambda_l$. The new branches of stationary solutions that arise here, at least near their point of appearance, are all unstable. However, this situation does not persist as we move into the transcritical region. It turns out that the new unstable branches undergo bifurcations at which other pairs of unstable solutions arise, but the initial branch itself consequently becomes stable (Fig. 10). This fact is found in analyzing the equations of motion for two unstable modes.[33]

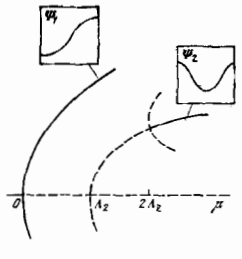

FIG. 10. Stationary diagram for the kinetic system (29)—dependence of the amplitudes of the harmonic stationary solutions on the bifurcation parameter μ. The solid lines correspond to stable stationary solutions of the (29), and the dashed lines to unstable solutions. The insets show the spatial variations of the stationary solutions of Eq. (21) corresponding to the stable branches.

Let l_1 be the first mode following the critical mode to acquire a positive increment. This happens at $\mu = \Lambda_{l_1}$. Let us assume that for all the rest of the modes $\Psi_{l \neq l_{cr}, l_1}$ the excitation threshold has not been reached yet, i.e., $\mu < |\Lambda_{l \neq l_{cr}, l_1}|$. In this case linear analysis predicts relaxation of the harmonics with $l \neq l_{cr}, l_1$, whereas both of the latter can be amplified. Now let us see what the nonlinear terms give under the assumption $|b_{l_{cr}}, b_{l_1}| \gg |b_l|$. The equations of motion for the two "large" amplitudes $b_{l_{cr}}$ and b_{l_1} are[33]

$$\begin{aligned} \dot{b}_{l_{cr}} &= \mu b_{l_{cr}} - \frac{3\beta}{4} b_{l_{cr}}^3 - \frac{3\beta}{2} b_{l_{cr}} b_{l_1}^2, \\ \dot{b}_{l_1} &= (\mu - \Lambda_{l_1}) b_{l_1} - \frac{3\beta}{4} b_{l_1}^3 - \frac{3\beta}{2} b_{l_1} b_{l_{cr}}^2. \end{aligned} \tag{29}$$

We can study them easily to obtain the stationary solutions and the nature of the stability of these solutions. The result of such analysis is given in the diagram of Fig. 10. As we see from the diagram, in the region $\mu > 2\Lambda_{l_1}$ we encounter the fact of non-single-valued nature of the stable solutions of the system (29), i.e., of the macroscopic states of the reaction-diffusion system. These states can be, e.g., a polar and a symmetric bipolar dsitribution, as in Fig. 10. They are not obtained from one another as a result of loss of stability, but both can be manifested under the same conditions. If the system, upon evolving from the homogeneous state, finds itself in one of them, then it can pass into the other only as the result of a "hard" excitation from outside. The source of such an excitation for morphogenetic systems can be experimental manipulation on the developing embryo. In the next section we shall try to impart concrete content to these as yet abstract possibilities.

Of no less interest is a replacement of a macroscopic regime that occurs spontaneously without external excitation. In order for this to happen, we must reach the instability threshold of a state that has arisen and become stabilized as a result of bifurcation of the thermodynamic branch. Sufficient (and perhaps also necessary) conditions for such a bifurcation are created when the primary bifurcation proves to be in a certain sense degenerate. More definitely, let us examine the case in which the critical mode $\Psi_{l_{cr}}$ amounts to a harmonic half-wave, i.e., $l_{cr} = 1$. We shall assume further that the two adjacent mdes with $l = 0$ and $l = 2$ have similar decrements Λ_0 and Λ_2, whereas all the rest are substantially larger:

$$|\Lambda_0, \Lambda_2| \ll |\Lambda_l|, \quad l \geqslant 3. \tag{30}$$

This situation is shown in Fig. 11. When $\mu > |\Lambda_0, \Lambda_2|$, the modes Ψ_0, Ψ_1, and Ψ_2 have positive increments in the linear approximation. These modes can be excited and must be taken into account, while the rest, which have a large damping decrement, are suppressed.[3)] The dynamics of the three excited degrees of freedom b_0, b_1, and b_2 is described by a system similar to (29) (see Ref. 33). All the information contained in this system on the character of the stationary states is reflected in the diagram of Fig. 12. A new element in

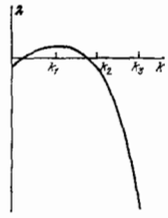

FIG. 11. Dependence of the time decrement λ on the wave number under the condition of fulfillment of the inequalities (30) (three quasidegenerate unstable modes).

comparison with Fig. 10 here is the bifurcation of the stable nonhomogeneous branch at the point A. At this point the system undergoes a spontaneous transition accompanied by a change in spatial organization, as we see from Fig. 12. We should note that closeness of decrements of specifically the modes Ψ_0, Ψ_1, and Ψ_2 is not necessary for the possibility of such a transition. One should obtain the same result (diagram of Fig. 12) if the condition with respect to close-lying decrements (30) were satisfied by the modes Ψ_0, Ψ_1, and Ψ_{2l}.[50]

All the stationary diagrams presented above are symmetric with respect to the initial thermodynamic branch: for every solution $\bar{a}(x)$ there is a reflected solution $-a(x)$ (for economy of space, Fig. 12 shows only half of all the stationary branches). This symmetry is not obligatory—it arose from the lack of a quadratic term in the adopted form of the nonlinear function $N(a)$. If there is no degeneracy in the linear problem (21) (the operator $\hat{\Lambda}^{cr}$ has a nondegenerate spectrum), then addition of the quadratic term only removes this symmetry. Otherwise the character of the bifurcation of the homogeneous state is not altered.

The pattern changes qualitatively in the presence of degeneracy in the linear problem. Figure 13 shows the character of the bifurcation of the homogeneous state $\bar{a} \equiv 0$ when the modes Ψ_l and Ψ_{2l} possess identical increments in the linear problem and a quadratic term a^2 is present in the expansion of the nonlinear function $N(a)$. A characteristic point here is that the excitation of the stable structure occurs in a drastic way—"with a jump in state".[51]

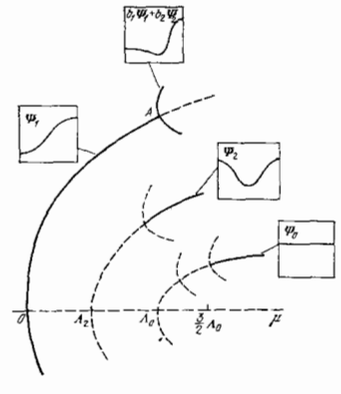

FIG. 12. Stationary diagram for three quasidegenerate unstable modes Ψ_0, Ψ_1, and Ψ_2.[33] The insets show the corresponding stable stationary profiles.

[3)] The interaction of modes is effected by the nonlinear contributions.

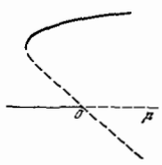

FIG. 13. Character of the bifurcation of the homogeneous state in the presence of a quadratic term in the function $N(a)$ and degeneracy in the linear problem in the modes Ψ_1 and Ψ_{21}.[51] The upper stable branch corresponds to mixed states.

Strongly degenerate bifurcation. At a low degree of degeneracy, when no more than three modes with wave numbers that are multiples of a common value have close increments, it presents no effort to study their interaction on the basis of a kinetic system such as (29). In the case of strong degeneracy, one cannot analyze the kinetic system for the amplitudes without the help of a computer. Exactly this situation arises for two-component reaction-diffusion systems with a sharp disproportion of characteristic diffusion lengths:

$$R_a \ll R_h.$$

In this case, as we can easily convince ourselves, the curve of the $\lambda(k)$ relationship proves to be very broad in the vicinity of its peak (see Eq. (10)). Consequently, even near the Turing bifurcation the interval of unstable modes can include, in addition to the fundamental mode, also harmonics with multiple wave numbers. The principal effect that this yields is that the dissipative structures cease to be harmonic or quasiharmonic. In the spatial distribution of the dynamic variables, extended regions ($\sim R_h$) of smooth variations are separated by narrow zones ($\sim R_a$) in which the "short-range" component undergoes considerable changes. This is the so-called contrast dissipative structures (Fig. 14). Owing to the stated disproportion of the spatial scales. one can study the contrast structures by qualitative methods in the spirit of the theory of nonlinear oscillations (see the series of studies by Kerner and Osipov[52]).

It turns out that the stationary problem has as solutions a *multitude* of contrast structures—including entire continua of structures with the same spatial period, and also completely nonperiodic structures.[52]

The material presented in this section shows that, rather than a single dissipative structure being stabilized beyond the instability threshold of the homogeneous state, in principle a whole spectrum of them can be stabilized. This multiplicity narrows the "interval" of initial perturbation that falls in the region of attraction of a certain macro state. The problem arises of the reproducibility of the process of structure formation.

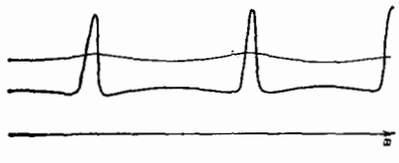

FIG. 14. Fragment of a contrast dissipative structure.[52] Bold line—spatial distribution for the "short-range" component, light line—for the "long-range" component.

In the region of high wave numbers k the relative density of modes is high, and also that of the possible macrostates. In order to realize one of them, one needs a better "aim" of the initial perturbation. Therefore it can be difficult to end precisely in a given state from the homogeneous state in the natural process of pattern formation. The way out of this difficulty is in the recursive method of building a structure. This is precisely how the regular arrangement of leaves on a growing stem is formed.[43]

5. MULTIPLE DISSIPATIVE STRUCTURES IN BIOLOGICAL EXPERIMENTATION

In the last section we saw that one can expect the appearance of several alternative stable macroscopically ordered states at a sufficient distance from the instability threshold of the thermodynamic branch (Fig. 10). As applied to morphogenetic fields, we should interpret this result as a non-single-valued determination of the positional information. Hence more then a single morphogenetic structure can prove to be realized in the same morphogenetic field. Is this actually what happens? The experiments cited below answer this question affirmatively.

Special experiments have been set up, beginning about in the twenties of this century, designed to seek the mechanisms that control the process of pattern formation. The results of a multitude of experiments have shown the influence on morphogenetic processes of such simple manipulations as constriction of the body of an embryo,[54] ultraviolet irradiation,[55] centrifugation,[56] etc. (for a review, see Ref. 57). The most convincing results, which we shall take up here, have been obtained in experiments on insect embryos.

In Ref. 54, eggs of the insect *Smittia* at the blastoderm stage were constricted transverse to the long axis at different sites. As a result only one segment proves to be lacking in the segmental structure of the larva (see the diagram of development of insects in Fig. 4), and differs depending on the site of constriction. Figure 16 shows a diagram of this experiment and the result obtained. The numbers at the top define the site of constriction (in percent of the length of the egg, measured from the pole in whose zone the abdomen will develop at the larva stage—the "abdominal"-pole). The inner series of numbers refers to the numbers of

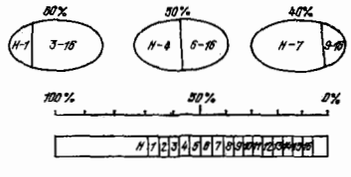

FIG. 15. Establishment of the positional information on the segment structure of larvae in experiments on constriction of the embryo at the blastoderm stage. Below—linear map of the blastoderm along the long axis of the egg.[39]

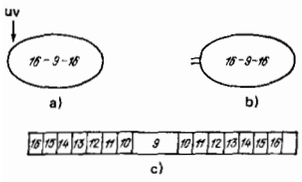

FIG. 16. Linear map of the blastoderm corresponding to symmetric (two-abdomen) larvae, after local ultraviolet irradiation (a) and puncture (b) in the region of the future head (for details, see text).

the segments existing in the structure of the larva. Evidently in this case the constriction impedes the development of the specific segment that normally develop from the region of the blastoderm lying at the constriction site. On the basis of such data, a linear map of the egg at the blastoderm stage was constructed, on which the zones were indicated that were responsible for the future segments of the larva[58] (Fig. 15).

While a local action at the blastoderm stage yields also a local effect (only one segment is affected) in the structure of the larva, experimental manipulations on the embryo at an earlier stage—cleavage turn out to lead to long-range effects. Figure 16 shows the result of local irradiation with ultraviolet light of a region of the egg belonging to the pole of the future head.[55] Two rather striking effects are found: first, an abdomen arises at the irradiated pole instead of the head of the normal embryo, i.e., the structure that normally develops at the opppsite end of the embryo, Second, in the middle region, instead of the normal fifth segment (see Fig. 4), segment No. 9 appears, which is usually formed in the abdominal region of the embryo. Here certain segments of the normal embryo (from *H* to No. 8) are not found at all. Interestingly, a fully similar structure in the abdominal region—segments from the 9th to the 16th—is obtained upon constriction of the egg in the middle at the cleavage stage.[54]

Another experimental fact also obtained in the cited studies is that the effect of formation of a symmetric "double-abdomen" larva disappears if the irradiation is applied to any region at a distance less than 75% of the length from the abdominal pole, rather than to the "head" end of the egg. In this case the irradiated embryo passes through the stage of a completely normal larva with all 16 segments in the proper order.

We should add that breakdown of normal development leading to formation of symmetric double-abdomen structures of the larva can be caused by highly nonspecific experimental actions. In addition to the mentioned ultraviolet irradiation, they are puncture of the egg in the zone of the future head at the cleavage stage[59] and centrifugation of the embryo at the same stage.[58] Certain genetic changes have been found that also induce spontaneous development of double-abdomen larvae.[60] Such a broad range of stimuli that transform the head zone indicates a certain instability of the positional information "normally" formed in this region. Moreover, we can conclude from the listed experimental data that the formation of the PI concerning spatial organization of the larva occurs at the cleavage stage. Precisely at this stage, local actions lead to global transformations of the spatial organization of the embryo.

We shall approach the interpretation of the presented experimental data from the standpoint of a model of a chemical gradient as the source of the positional information. Pursuing this idea, we assume that spatial control of the cellular differentiation is performed by a dynamic reaction-diffusion system. The PI is fixed by the spatial distribution of the concentration of a chemical reagent. This distribution is established as a stable stationary regime of the equations of motion of the reaction-diffusion system. We shall employ as the form of representation of the PI the linear division of the egg into zones responsible for the future segments of the larva (see Fig. 15).

Let us examine a reaction-diffusion system in which two components are coupled by the following interaction. One of them, a, autocatalytically activates its own synthesis and the synthesis of the second component, h, which in turn inhibits the synthesis of the first component. In addition, the agents diffuse in one-dimensional space, with the inhibitor h having a higher diffusional mobility than the activator a. A concrete example of a kinetic system with the cited properties, treated by Gierer and Meinhardt[37 39] for the interpretation of the discussed experiments has the form

$$\begin{aligned} a_t &= \frac{ca^2}{h} - \mu a + \rho_0 + D_a a_{xx}, \\ h_t &= ca^2 - \nu h + \rho_1 + D_h h_{xx}. \end{aligned} \tag{31}$$

As we saw in Sec. 2, this type of interaction presupposes the possibility of spontaneous origin of spatial order. To realize this possibility, we must have: a) kinetic parameters of the equations of motion c, μ, ν, etc., lying in the region of Turing instability of the homogeneous state (Here the set of modes of perturbation of the homogeneous state in the range of values of the wave number Δk acquires a positive increment.); b) dimensions of the spatial region L such that at least one mode satisfying the boundary conditions lies in the interval Δk. If we adopt as the boundary conditions zero fluxes across the boundaries, then requirement b) is satisfied when $k_l = l\pi L$ belongs to the interval Δk.

Evidently, as the size increases (growth occurs) of the homogeneous morphogenetic field, the first to satisfy condition b) is the mode with $l=1$, i.e., the harmonic half-wave. Let us assume that the "polar" dissipative structure formed here fluxes the positional information in establishing the normal organization of the egg as a sequence of zones having individual post-translational fates.

If we possess the stationary distribution of the morphogen from the calculation of the theoretical model (31)[4)] and the experimentally constructed mapping of the

[4)]An interaction of the "activation-inhibition" type of two components is necessary only for the appearance and maintenance of spatial order. As regards the translation of the PI, only one of the two agents may relate to it, say h. Then h is the morphogen.

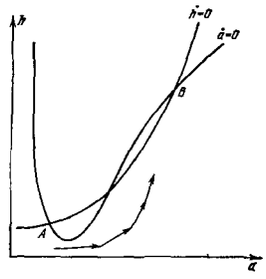

FIG. 17. Phase portrait of the "point" system of Meinhardt.[39] The arrows indicate an individual phase trajectory after removing h at the initial instant of time.

egg into the zones of the future sixteen segments, we can calibrate the scale of concentration h. Here each segment is matched with a certain interval Δh (Fig. 18). One can employ the calibration thus constructed also in interpreting the "non-normal" distributions of $h(x)$ by modeling the effects of experimental interactions. It remains only to elucidate how to model the perturbations introduced by these interactions.

Naturally, constriction of the egg in the experiments of Ref. 54 has as its main effect the interruption of diffusion of the agents a and h through the constricted region. This leads to the condition of zero diffusional fluxes $a_x = h_x = 0$ $(x = x_0)$. Puncture of the embryo[59] opens an efflux channel into the external medium for the reagents a and h. Consequently the concentration of a and h is lowered in the vicinity of the site where the puncture was made. This decrease is more significant for the inhibitor, since it has a higher diffusional mobility.

The perturbation produced by ultraviolet irradiation is the least obvious. It is not likely that the cellular biosynthetic apparatus is substantially affected here. In this case changes would be manifested in the structures of the larva, independently of the localization of the irradiated region), and this is not found experimentally. Most likely, the observed effect of ultraviolet irradiation arises from a direct action on the agents a and h. Meinhardt[39] considers that the agent h is modified so much upon irradiation that it drops out of the interactions described by the kinetic system (31). This hypothesis is corroborated by the fact that the effect of ultraviolet irradiation of the head zone is identical with the effect of direct removal from the reaction volume of the agents that occurs upon puncture in this same zone (see Fig. 16).

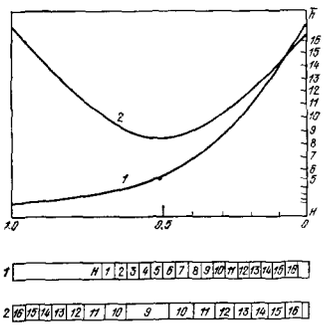

FIG. 18. Result of numerical calculation of the stationary problem (31). Curve 1—before perturbation, 2—after perturbation: $h(x, t_0) = 0$, $x > 0.75$. The positional information in these two cases is presented below.[39]

Thus we view that in the normal course of development the embryonic system acquires a polar organization. That is, the corresponding reaction-diffusion system (31) proves to be in a state of the "half-wave" type. The symmetric double-abdomen structures obtained upon experimental intervention indicate the existence of alternative bipolar states of the embryo. Such states can be formed as the result of transition to a new macrostate of the reaction-diffusion system. In the last section we have already concluded on the basis of a general analysis that multiple stable dissipative structures exist and transitions can occur among them. Now, upon turning to the concrete dynamics of the system (31), we shall try to model the type of perturbation that realizes the transition.

In analyzing the equations of motion (31), we have no grounds for assuming closeness to the self-organization threshold. Therefore we cannot employ the method of reduction of the last section. It remains to rely only on qualitative and numerical methods of study. Useful qualitative information is furnished by an analysis of the phase portrait of the "point" system (including only the local dynamics without diffusion terms). Figure 17 shows on the phase plane the zero-isoclines of the kinetic system:

$$\dot{a} = \frac{ca^2}{h} - \mu a + \rho_0,$$
$$\dot{h} = ca^2 - \nu h + \rho_1.$$

Let us assume that at the initial instant the system is in the lowest stable state (point A). The external intervention that removes the inhibitor h from the reactions causes the system to lie near the horizontal axis. According to the equations for small concentrations of the inhibitor, the rate of autocatalytic production of the activator is large. The fast growth of the concentration of a leads the system into the region of attraction of the upper stable point B. Further evolution is accompanied by growth of the concentrations of a and h, which stops with the accumulation of the inhibitor at the point B. A characteristic feature here is the fact that, in returning to a stable state, the system bypasses the nearest stable point and enters directly the zone of attraction of the more remote point.

This analysis suffices for a qualitative understanding of the experiments on ultraviolet irradiation of the head zone of the embryo. In this region, as we see from Fig. 18, the stationary profile of the concentration $h(x)$ has a gently shaping course. Therefore diffusion effects exert little influence, at least in the initial stages of evolution of the perturbation. For this same reason, the events in the head zone do not effect the state of the abdominal region. Owing to the increase in concentrations of h, the positional information for the "abdominal" segments takes shape in the "non-abdominal" half, and the embryo as a whole be-

comes symmetric, with two abdomens. The exact profile of the stationary distribution of $\bar{h}(x)$ obtained by numerical solution of the kinetic system (31)[39] is shown in Fig. 18. We see from the diagram that, in the central region of the new distribution, it proves to be elevated over the normal level. In line with the calibration of the h scale, segment No. 9 should develop here (instead of No. 5), as is observed experimentally.

The experimentally discovered difference in behavior upon irradiation of regions of the egg lying closer to the abdominal pole—in this case, as was noted, irradiation does not alter the structure of the larva in any way—is also explained on the basis of the dynamic model (31). These regions lie in a region of larger gradient of h in the "normal" distribution $\bar{h}(x)$ (see Fig. 18). When the inhibitor is removed from this zone, its diffusional influx from the abdominal half proves to be substantial. Consequently the concentration of h in the irradiation zone is restored more quickly than an effect of the local dynamics makes itself felt. Switching of the dynamic system to a new macrostate does not happen. The presented qualitative arguments are fully confirmed by numerical analysis of the equations of motion (31).[39]

6. UNIVERSAL EQUATIONS OF MOTION NEAR THE THRESHOLD OF SELF-ORGANIZATION

The two component reaction-diffusion systems of Turing amount to a "basal" model convenient for theoretical analysis. Up to now almost all the general problems of principle pertaining to self-organization in systems with chemical interactions and diffusion have been treated using this model. At the same time it is clear that two-component systems are a rather special case. Of course the variety of chemical mechanisms is not exhausted by such systems. On the contrary, we know that the real chemical interactions in cells are generally much more complex. Nevertheless the essential movements—the slow movements in the vicinity of the threshold for self-organization prove insensitive to this complexity. The details of the molecular mechanisms are not manifested in the critical dynamics. This implies that if we had found experimentally that a system lies near the threshold for self-organization, then, even if we do not know the chemistry of the processes occurring, we can predict its behavior.

Let us take up very briefly some features of the modern theory of critical phenomena. This small digression is warranted by the fact that the fundamental topic of this review—self-organization in nonequilibrium chemical and biological systems—manifests many features of similarity with phase transitions under conditions of thermodynamic equilibrium.

Apart from a small number of exactly solvable models in the theory of equilibrium second-order phase transitions, one cannot make a correct transition from the microscopic formulation of the model (assuming a complete knowledge of the Hamiltonian) to the macroscopic equation of state. At the same time, a set of experimental data definitely indicates that many specific details of the microscopic pattern cease to be essential if one is interested in the thermodynamic properties of the system in the vicinity of the critical point.[61] It suffices to recall the law of corresponding states for the critical point of the liquid-vapor transition or the universal relationships between the critical indices. Such a similarity of the critical behavior of systems highly different from the microscopic standpoint has stimulated interest in the general heuristic approaches in the theory.

In the current treatment of the phenomenon, the major accent is placed on the global characteristics of the object, such as its symmetry and space dimensionality, and many fine details of the interaction are ignored. The justification for proceeding in this way is given by the construction of Kadanov (see Ref. 61). Near the critical point, coherent behavior is manifested at distances exceeding all the microscopic scales in the system. When entire macroscopic regions behave like a unitary element, the fine details of the interaction between the particles of such regions do not affect the behavior of the latter. In such a situation the macroscopic properties are sensitive only to the global characteristics of the system.

Another distinguishing feature of critical dynamics is the slow relaxation of the large-scale fluctuations of the order parameter. This is precisely why all the features of critical behavior can be encompassed in one or several equations of motion amenable to theoretical study. Thus two essential features—the macroscopic scales of coherence and the slow dynamics of the singled-out degrees of freedom—enable a general analysis of the thermodynamic properties in the vicinity of the critical point for systems of highly differing microscopic nature.

As we shall show, we face a similar situation in treating physical, chemical, and biological systems far from thermodynamic equilibrium near the threshold for self-organizatoon. Here also the onset of macroscopic order (in time or space) proves to be associated with slow, large-scale motions of singled-out modes. Owing to this slowness, one can reduce the complex multicomponent kinetic system to the equation of motion of one or several essential degrees of freedom—an analog of the macroscopic description of critical phenomena in the language of the order parameter.

This section will be devoted to deriving the reduced equations of motion for transitions involving onset of spatial order in reaction-diffusion systems. Quite similar equations have been derived to describe non-equilibrium collective phenomena in systems of a different nature. This was done by Haken and Wunderlin[62] for generation of coherent radiation in a laser and by Newel and Whitehead[63] for the appearance of convective structures in a liquid in the case of Bénard instability. The cited studies analyzed the case of spatial dimensionality $d=1$. Nitzan and Ortoleva[64] studied spatial self-organization of reaction-diffusion systems in the more general case of spatial dimensionality $d>1$. A reduced description was obtained in Ref. 65 also for transitions with appearance of temporal organization in nonequilibrium chemical systems.

All the cited studies employed a conceptually common method based on expansion in a small parameter—the degree of closeness to the instability threshold. This method is applied often in analyzing bifurcations in nonlinear kinetic systems. Therefore it seems expedient to us to derive the reduced description in which we are interested with some degree of detail.

Turing bifurcation. Scales of parameters

The macroscopic equations of motion in multicomponent reaction-diffusion systems (see Eq. (1)) have the following form in vector notation:

$$\frac{\partial \mathbf{C}}{\partial t} = \mathbf{f}(\mathbf{C}) + \hat{D}\nabla^2\mathbf{C}. \tag{32}$$

The duffusion coefficients together with the kinetic parameters of the function f(C) (reservoir concentrations, rate constants) constitute the parameter space of the system $\{\Gamma_j\}$. We assume that in a certain region of this space the stable state is the homogeneous concentration distribution throughout the volume $\mathbf{C}_{eq}$, which is the asymptotically stable, stationary solution of the kinetic system (32). This presupposes that

$$\mathbf{f}(\mathbf{C}_{eq}) = 0. \tag{33}$$

Upon introducing in place of C the vector of deviations from the stationary state

$$\mathbf{c}(\mathbf{r}, t) = \mathbf{C}(\mathbf{r}, t) - \mathbf{C}_{eq} \tag{34}$$

and linearizing the original kinetic equation in the small deviations c, we obtain

$$\frac{\partial \mathbf{c}}{\partial t} = \hat{L}\mathbf{c} + \hat{D}\nabla^2\mathbf{c}. \tag{35}$$

Here we have

$$L_{ik} = \frac{\partial f_i}{\partial C_k}\Big|_{\mathbf{C}_{eq}}$$

One can construct an arbitrary solution of the linear problem (35) in the form of a superposition of vectors $\mathbf{q}^n(\mathbf{k})\exp(\lambda^n t + i\mathbf{k}\mathbf{r})$ with all possible k. Here $\mathbf{q}^n(\mathbf{k})$ and λ^n are the eigenvectors and eigenvalues of the matrix $\hat{L} - \hat{D}k^2$. The time decrement λ is connected to the wave number (k) by the dispersion relation that follows from the characteristic equation

$$\mathrm{Det}(\lambda\hat{I} - \hat{L} + \hat{D}k^2) = 0. \tag{36}$$

The spatially homogeneous stationary solution $\mathbf{C}_{eq}$ is an asymptotic state (as $t \to \infty$) of the system if the condition is satisfied that

$$\mathrm{Re}\,\lambda^n(k) < 0 \quad \text{for all} \quad n, k. \tag{37}$$

As the external parameters are varied in the region of parameter space where the condition (37) is satisfied, the state $\mathbf{C}_{eq}$ does not undergo qualitative changes, but varies smoothly. The system can acquire "new" qualities owing to passage through a point of structural instability at which[66]

$$\mathrm{Re}\,\lambda^0(k_{cr}) = 0. \tag{38}$$

If here the multiplicity of the eigenvalue λ^0 is odd, then the initial branch of states $\mathbf{C}_{eq}$ undergoes bifurcation—new branches of stationary states are created.[66] The situation corresponds to Turing bifurcation when the multiplicity is unity, $k_{cr} \neq 0$, and $\mathrm{Re}\lambda^n(k) < 0$ for all values of the wave number $k \neq k_{cr}$. In this case the eigenvalue λ^0 in the vicinity of the critical wave number k_{cr} is real, and moreover, $\lambda^0(k_{cr})$ is the maximum of the $\lambda^0(k)$ variation:

$$\frac{d\lambda^0}{dk}\Big|_{k_{cr}} = 0. \tag{39}$$

What we have said pertains also to the region of parameters close to the point of Turing bifurcation.

For simplicity, and without restricting the generality at all, we shall examine the onset of structural instability as only one parameter of the set $\{\Gamma_j\}$ varies. Here the values of all the rest correspond to the critical point.

We shall obtain the description of the dynamics near the critical point by employing an expansion in the small parameter $\gamma = \Gamma_1 - \Gamma_1^{cr}$. We should start with elucidating the scale factors for the space and time variations of the various quantities. We can do this on the basis of the characteristic equation (36). For definiteness, let only the matrix $\hat{L}$ depend on the parameter γ. We can consider this relationship to be analytic, which is equivalent to the assumption of smooth dependence of the homogeneous state $\mathbf{C}_{eq}$ itself on γ:

$$\hat{L}(\gamma) = \hat{L}^0 + \hat{L}^1\gamma + \hat{L}^2\gamma^2. \tag{40}$$

As we have already noted in Sec. 2, also $\Delta k = k - k_{cr}$ and λ^0 are small, as well as the parameter γ, near the threshold of dissipative instability. On the basis of this smallness, together with the condition (39), one can write the characteristic equation (36) approximately in the form

$$a\lambda^0(k, \gamma) + b(\Delta k)^2 + c\gamma = 0. \tag{41}$$

The orders of magnitude of Δk and λ^0 respectively determine the spatial and time scales of the critical dynamics. For a start, let all the terms in (41) have the same order of smallness, namely $O(\gamma)$. It is convenient to introduce the small number ε such that $\gamma = q\varepsilon^2$, $q = O(1)$.[64] Then we must have

$$\Delta k = O(\varepsilon), \quad \lambda^0 = O(\varepsilon^2). \tag{42}$$

This enables us to describe the critical dynamics in terms of the new "scaling" variables T and R[64]:

$$T = \varepsilon^2 t, \quad R = \varepsilon r. \tag{43}$$

The quantity $1/\varepsilon$ characterizes the scale of distances at which the perturbation deviates appreciably from the form of the pure harmonic $\exp(i\mathbf{k}_{cr}\cdot\mathbf{r})$, while $1/\varepsilon^2$ fixes the scale of the time of evolution of this deviation. Further, bearing in mind the smallness of the amplitude c near the instability threshold,[5)] we shall represent the solution $\mathbf{c}(\mathbf{r}, t)$ of Eq. (32) in the form of an expansion in the small parameter ε:

$$\mathbf{c}(\mathbf{r}, t) = \sum_{n=1}^{\infty} \varepsilon^n \mathbf{c}_n(\mathbf{r}, t). \tag{44}$$

[5)] The entire analysis of this section is suitable for the case of "soft" branching of the dissipative structures from the homogeneous state.

The existence of the two spatial scales $r \sim 1/k_{cr}$ and $R \sim (\Delta k)^{-1} \sim 1/\varepsilon$ suggests the form of the functions c_n[64]:

$$c_n(\mathbf{r}, t) \sim W_n(\mathbf{R}, t)\, c_n(\mathbf{r}, t)\, q_n. \tag{45}$$

Correspondingly we can replace the operations ∇ and $\partial/\partial t$ with

$$\nabla_r + \varepsilon \nabla_R \text{ and } \varepsilon^2 \frac{\partial}{\partial T}. \tag{46}$$

Now we should substitute (44)–(46) into Eq. (32) and examine the conditions of balance in the different orders of ε:

The intermediate stages of the calculation have been given in Ref. 64. The final results are the following:

1) *Dimensionality of the space* $d = 1$. The general form of the solution $c(x, t)$ to the accuracy of $O(\varepsilon)$ is

$$c_1(x, t) = q^0 (W(R, T)\, e^{ik_{cr}x} + \text{c.c.}), \tag{47}$$

Here q^0 is an eigenvector of the matrix $\hat{L}^0 - \hat{D}k^2$. In expression (47) the neutrally stable mode $e^{ik_{cr}x}$ (having a zero decrement) at the critical point $\gamma = 0$ is modulated by the amplitude W, which slowly varies in time and space. The dynamics of $W(R, T)$ is described by the equation[64]

$$\frac{\partial W}{\partial T} = a_1 W - a_2 |W|^2 W + a_3 \frac{\partial^2 W}{\partial R^2}. \tag{48}$$

Here the coefficients a_1, a_2, and a_3 are expressed in terms of the parameters of the original kinetic system (see Ref. 64). We note the fact that varying the scales of the quantities W, R, and T converts Eq. (48), which contains three parameters, into a universal form that does not depend on the values of the parameters[64]:

$$\frac{\partial W}{\partial T} = \pm W - |W|^2 W + \frac{\partial^2 W}{\partial R^2}. \tag{49}$$

Here the plus sign pertains to the transcritical region $\gamma > 0$, and minus to the precritical $\gamma < 0$.

The obtained universal form of the equation of motion contains no information on the number of dynamic variables (reaction components) in the original formulation (32) nor on the character of their interaction. This information is not needed to describe the slow large-scale critical dynamics. Such a universal form of the equation of motion can be compared with the law of corresponding states for the vicinity of the critical point of a van der Waals transition or with the laws of similarity in the theory of equilibrium second-order phase transitions.

In the equation for the stationary amplitude (obtained by putting $\partial W/\partial T = 0$ in (49)) we can easily recognize the phenomenological Ginzburg-Landau equation from the theory of superconductivity.[4] Evidently, in the transition from the homogeneous state to the dissipative structure, the amplitude W plays the same role as the condensate wave function in the Ginzburg-Landau equation in the transition to superconductivity. At the same time, we call attention to their differences. Equation (49) has been derived and holds for one-dimensional space. Its generalization to the case $d > 1$ does not reduce to replacing the operation $\partial^2/\partial R^2$ by a multidimensional Laplacian, as happens for the Ginzburg-Landau equation.

Let us study the stationary solutions of Eq. (49). First of all we find the real homogeneous solution $|\overline{W}| = 1$, which exists and is stable in the transcritical region. We conclude from Eq. (47) that it corresponds to the stationary distribution $c_1(x)$, which coincides in form with the critical mode. The stationary solution $\overline{W} = 0$, which corresponds to the original homogeneous branch, exists on both sides of the critical point, but is stable only in the precrtitical region. If we turn to the starting variables R, T, and W, it becomes evident that the distribution $c_1(x)$ continuously ("softly") branches from the homogeneous branch, with an amplitude increasing with increasing distance from the point of origin as $\sqrt{\gamma}$.

Interestingly, $|\overline{W}| = 1$ is not the sole stable solution in the transcritical region. A multitude (continuum) of other complex solutions also satisfies the stationary problem. Actually, if we represent $W(R)$ in the form $W = \rho e^{i\phi}$, we find directly from (49) the equations for $\rho(R, T)$ and $\phi(R, T)$:

$$\left.\begin{aligned} \rho_T &= \rho - \rho^3 + \rho_{RR} - \rho(\varphi_R)^2, \\ \rho\varphi_T &= 2\rho_R\varphi_R + \rho\varphi_{RR}. \end{aligned}\right\} \tag{50}$$

Any solution of the following form also is a stationary state:

$$\bar{\rho} = \text{const} \leqslant 1, \quad (\bar{\varphi}_R)^2 = 1 - \bar{\rho}^2. \tag{51}$$

The region where such solutions are realized as asymptotic states can be found, as always, by analyzing the evolution of small deviations from $\bar{\rho}$ and $\bar{\varphi}$ in the framework of the linear approximation. The corresponding analysis is performed without special difficulty and yields the following result. Among the multitude of solutions of (51), the asymptotically stable ones are those with $\bar{\rho}^2 > 2/3$.

We can easily understand what sort of additional states are these with a nonzero phase gradient. Upon substituting a complex $\overline{W}(R)$ into Eq. (47), we can convince ourselves that the corresponding distribution $c_1(x)$ amounts to a harmonic dissipative structure with a wave number differing from the critical value k_{cr}. Thus the multitude of solutions of (51) leads to a continuum of structures $c_1(x)$ that differ in spatial period. The corresponding wave numbers occupy a band Δk about k_{cr} that expands with increasing distance from the self-organization threshold[67] $\Delta k \sim \gamma^{1/2}$.

This continuum of possible structures, which involves the very origin of macroscopic ordering, though remarkable, is yet not unexpected. Here the situation is quite analogous to that in a superfluid liquid or in a superconductor, where, together with the appearance of a condensate wave function, an entire continuum of possible macroscopic states arises. We are considering nondissipative macroscopic motions—the flux of the superfluid component in liquid helium, and the superconductive electric current in a metal, which can be established below the λ-point. Just as in our case, these states differ in phase gradient of the complex order parameter. Always some one of the set of possible macroscopic states is realized. The choice of this state is fully determined by fixing the initial

value of the current or velocity.

In our case of concentration dissipative structures, the phase gradient of the harmonic distribution of concentrations also governs the macroscopic flux—the diffusional flux of matter. However, the essential difference is that this flux is now not homogeneous, but varies periodically with the distance. The stable existence of a diffusional flux, in contrast to the aforementioned macroscopic motions, is necessarily accompanied by dissipation of free energy. Hence it requires a constant influx of energy from outside. The fact that all of the indicated set of macroscopically distinguishable states can be realized for the same values of the external parameters indicates only that their appearance requires no special additional influxes of matter or energy. It suffices only to excite the system in an appropriate manner at the initial instant of time.

2) *Dimensionality of space* $d > 1$. When $d > 1$ there are fundamental differences in comparison with the one-dimensional case. They arise from the orientational degeneracy of the critical modes. Actually, the condition of criticality, defined as $\lambda^0(k_{cr})=0$ fixes only the modulus of the critical wave vector (see (36)), whereas its direction remains arbitrary. Now the general form of the solution of Eq. (34) will be, apart from terms of the order of $O(\varepsilon)$:

$$c_1(\mathbf{r}, t)=\sum_I W_I(R, T)\, e^{i\mathbf{k}^I\mathbf{r}}, \quad \mathbf{k}^{-I}=-\mathbf{k}^I; \quad W_{-I}=W_I^*. \tag{52}$$

Here the summation is performed over all possible orientations of the critical wave vector $\mathbf{k}^I$: $|\mathbf{k}^I|=k_{cr}$. Owing to the superposition of several one-dimensional harmonic distributions with wave vectors differing in direction, a cellular spatial organization must arise. It was shown in Ref. 64 that there are rigid selection rules for the possible directions I in the superposition (52). Namely: three dimensions I_1, I_2, and I_3 can be included, with the vectors $\mathbf{k}^{I_1}$, $\mathbf{k}^{I_2}$, and $\mathbf{k}^{I_3}$ forming an equilateral triangle. This means that the shape of the cell must be hexagonal.

The character of the branching of the cellular dissipative structures from the homogeneous state differs from that for one-dimensional distributions. It is found from the equation of motion for the slowly varying amplitudes $W_I(R, T)$. The idea of deriving these equations remains the same as in the one-dimensional case, but there are differences in the details. In particular, the "scaling" variables R and T are introduced in a different way (see Ref. 64). The final equations have the form

$$\frac{\partial W_I}{\partial T}=\omega_1 W_I+\omega_2\sum_J W_J W_{J(I)}, \quad \mathbf{k}_J+\mathbf{k}_{J(I)}=\mathbf{k}_I. \tag{53}$$

We note that here, as in the one-dimensional case, we can introduce new scales for the variables T and W_I:

$$\tilde{T}=\omega_1 T, \quad \tilde{W}_I=W_I\frac{\omega_2}{\omega_1}. \tag{54}$$

Consequently the system (53) acquires a universal form not depending on the parameters

$$\frac{\partial \tilde{W}_I}{\partial \tilde{T}}=\tilde{W}_I+\sum \tilde{W}_J\tilde{W}_{J(I)}. \tag{55}$$

It is not difficult to find the stationary values of the three nonzero amplitudes W_{I_1}, W_{I_2}, and W_{I_3}. The complete set of solutions is obtained from all possible permutations of the two combinations (1, 1, −1) and (−1, −1, 1).[64]

We call attention to the fact that the found nontrivial solutions exist on both sides of the instability threshold of the homogeneous solution ($W_I=0$). In this case the branch of nontrivial solutions intersects the initial branch $W_I=0$ at the critical point $\gamma_1=0$, but not at a right angle as for one-dimensional distributions. However, the states corresponding to the nontrivial solutions of the system are unstable on both sides of the critical point. This conclusion pertains only to the states that continuously branch from the homogeneous branch ($W_I=0$), rather than to cellular structures in general. A stable cellular spatial organization can arise, but in a first-order transition, i.e., with a discontinuity in state. The reduction procedure employed above is unsuitable for describing such transitions, since the deviation from the homogeneous branch can no longer be considered small.

Not only superpositions, but also pure one-dimensional periodic distributions can arise in the case of Turing instability in d-dimensional space. The orientation in space of such a one-dimensional dissipative structure is arbitrary, while the period is governed by the condition for Turing instability itself and by the characteristic equation (36). The one-dimensional structures compete with the cellular structures, since the condition for their excitation in the dynamic (rather than statistical) description is fulfilled for the same values of the parameters, when $\lambda^0(k_{cr})=0$. An interesting selection problem arises in this connection that has not yet been studied completely (see Ref. 68).

Apparently the problems that we have touched upon have greatest value in connection with the appearance of macroscopic order in hydrodynamics.[69] Up to now it has been possible in reaction-diffusion systems to observe only one-dimensional stationary dissipative structures (see Ref. 14). The situation is characteristic for pattern formation in biology in which the dimensions of the self-organizing volume are small in comparison with the characteristic spatial periods of the structures. In this case the boundary conditions remove the orientational degeneracy of the critical modes. For example, in the case of the elliptical boundary treated in Sec. 3, the type of spatial organization beyond the threshold for Turing instability is unequivocally determined. The lifting of degeneracy arises from the narrowing of the symmetry group of the problem upon imposition of the boundary conditions. In this connection the general group approach developed in Ref. 68 seems interesting. Here the universal reduced equations of motion in the neighborhood of the self-organization threshold are constructed on the basis of the irreducible representations of the symmetry group of the problem.

In essence, the abbreviated description obtained in

this section of the dynamics in the neighborhood of the self-organization threshold can be appraised as being the realization in a concrete case of the general idea of Bogolyubov. As we know, its content is: if one can single out in a system with many degrees of freedom a set of variables (secular variables) whose time scales of variation are large in comparison with the relaxation times of the other degrees of freedom, then this slow relaxation must fit a closed—"macroscopic" description. In the case of the hydrodynamic description, such slow parameters (as compared with the molecular variables) are the five macroscopic variables—the density, the components of the mean velocity, and the mean thermal energy. In our case near the threshold of an instability that breaks the symmetry of the homogeneous state, the secular parameter is the amplitude of the critical mode or the set of amplitudes in the case of degeneracy. These parameters prove to fit a closed description that depicts the "macroscopic" behavior for large time intervals. In going from the macroscopic parameters of state—concentrations—to the collective variables—amplitudes of modes, we sharply reduce the information needed to describe the dynamics of establishment of spatial organization. Thus, for example, Eq. (53) contains only two parameters characterizing the chemical interactions in the initial reaction-diffusion system, while this number does not depend on the degree of complexity of the latter. Of course, the reduced description of the critical dynamics does not enable one to predict either the actual point of spontaneous onset of spatial order or in general the potentiality for self-organization in concrete reaction-diffusion systems. In any chemical system of some degree of complexity this information can be obtained only by experiment. Upon possessing it, we can use the reduced equations of motion to draw conclusions regarding the geometry of the spatial order produced, and the manner in which this process occurs in time.

7. SIZE INVARIANCE OF MORPHOGENETIC STRUCTURES

A broad class of systems is known in embryology that manifests the capacity for regulation of structures in relation to the overall dimensions. In normal growth this regulation is expressed in maintaining unchanged proportions of the structures—the so-called size invariance. In experiments the capability of regulation reveals itself in the regeneration of structures after parts of them have been removed.[34,71] In Sec. 2 we have already cited such experiments in hydra (see Fig. 3a). Individual segments cut from the trunk of hydra and possessing no morphogenetic features in the initial state regenerate in time a complete animal with all the inherent elements of organization. This regeneration is not accompanied by growth. As a result one obtains dwarf organisms in which, however, "everything is in place". Over a broad range of sizes of the regenerating component, the relative dimensions of the parts of the developing organisms—the "head", the tentacles, the digestive zone, and the foot—remain constant. Thus the organism can not only regenerate its parts, but match their proportions.

As is assumed everywhere in this review, the spatial organization of the morphogenetic field is controlled by a reaction-diffusion system. However, it is easy to see that passive diffusion alone does not suffice as a basis for the property of size invariance of structures. In a reaction-diffusion system of the general type (1), the characteristic spatial scales of the dissipative structure are determined by the kinetic parameters of the chemical interactions and the diffusion coefficients. These are molecular parameters, which contain no information on the overall dimensions of the system.[6)]

In order that the condition of size invariance be satisfied in a reaction-diffusion system, the spatial coordinate and the size must enter into the equations of motion only in the form of the dimensionless combination $\xi = x/L$. If we make the corresponding substitution of the variable $x \to \xi$, then the kinetic equations (1) acquire the form

$$\frac{\partial C^j}{\partial t} = f^j(\{C\}) + \frac{D^j}{L^2}\frac{\partial^2 C^j}{\partial \xi^2}$$

As we see, a dependence on the size L is present in explicit form. The required dimensional invariance of the solutions will exist only in the case when $D^j \sim L^2$.

A coupling of the necessary form of the transport coefficient D^j with the overall size can arise as a consequence of a special mechanism of transport of the components of the reaction mixture that differs from passive diffusion.

As we know (see, e.g., Ref. 70), transport of chemical agents through a cell membrane can occur by one of three mechanisms: 1) Passive diffusion—this is made possible by the presence of special diffusion channels in the outer cell membrane.[27] 2) Facilitated diffusion, in which special molecules of carriers synthesized by the cell participate in transport. Just like passive diffusion, facilitated diffusion is directed to the size opposite to the concentration gradient of the reagents. 3) Active transport. Here the flux of the substance proves to be directed against its gradient owing to coupled reactions.

Let us take up the mechanism of facilitated diffusion. Let us assume the molecular scheme of transport of the reagent C^j through the cell membrane with participation of the carrier P^j proposed in Ref. 74:

$$C^j_{i-1} + P^j_i \underset{k}{\overset{k}{\rightleftarrows}} C^j_i + P^j_i \underset{k}{\overset{k}{\rightleftarrows}} C^j_{i+1} + P^j_i. \qquad (56)$$

Here the index i pertains to the number of the cell in the one-dimensional ensemble. If we assume that the sizes of the individual cells are small in comparison with the characteristic scales of the variations of the concentrations C^j and P^j and, as usual, transform the discrete index j to the continuous spatial coordinate $x = id_{cell}$, then we obtain the following kinetic equations for the concentration C^j:

$$\frac{\partial C^j}{\partial t} = 2d^2_{cell}k\frac{\partial}{\partial x}\left(P^j\frac{\partial C^j}{\partial x}\right) \qquad (57)$$

[6)] However, such systems nevertheless manifest a limited size invariance within a small range of variation of size.[72,75]

It has the form of a diffusion equation with the diffusion coefficient

$$D^j = 2d_{\text{kn}}^2 k P^j(x).$$

Upon adding a "reaction" term of general form to the kinetic equation (57), we obtain:

$$\frac{\partial C^j}{\partial t} = f^j(\{C\}) + \frac{\partial}{\partial x}\left(D^j(x)\frac{\partial C^j}{\partial x}\right). \quad (58)$$

It is precisely in the dependence of the diffusion coefficient on the local concentration $P^j(x)$ that the source of the coupling of D^j to the overall size L might lie. For this to happen it suffices that the molecules P^j should succeed in diffusing within the characteristic times of variation of the concentration C^j throughout the volume at whose boundaries the definite conditions on P^j have been set.

Othmer and Pate[73] have obtained the necessary form of the dependence $P^j \sim L^2$ by assuming that the dynamics of the distribution of P^j obeys a closed equation of motion

$$\frac{\partial P^j}{\partial t} = \varkappa + D_p \frac{\partial^2 P^j}{\partial x^2} \quad (59)$$

and that it occurs rapidly in comparison with the evolution of C^j. In the presence of a rapid outflux of P^j into the external reservoir the boundaries of the reaction volume can be regarded as absorbing, i.e., $P^j = 0$. Consequently the stationary profile of the concentration P^j is established:

$$P^j(\xi) = L^2 \frac{\varkappa}{2D_p}(\xi - \xi^2). \quad (60)$$

Here we have already introduced the dimensionless coordinate $\xi = x/L$. Thus the diffusion coefficient in the kinetic system proves to be proportional to the square of the lineal dimension, which yields the size invariance of all the solutions $C^j(x, t)$. As regards the possibility of spontaneous appearance of dissipative structures, this is not eliminated by the appearance in a reaction-diffusion system of a spatially dependent diffusion coefficient.[73]

Interestingly, for a long time after the publication of Turing's study, the mechanisms that he proposed for the appearance of morphogenetic structures was disputed by biologists on the grounds that it cannot explain the properties of size invariance (see, e.g., the very intelligent book by Waddington[76]). As we see from this section, in fact these objections can be easily answered.

8. SELF-ORGANIZATION OF SPATIAL FORM

Nowhere above have we been interested in the spatial displacements of cells. Our treatment was restricted only to the process of appearance of stratification of the cellular ensemble into types of specialization of cells (positional differentiation). As the concrete examples discussed in Secs. 3–5 show, in such cases there is no need to adduce cellular movements. However, clearly the processes of positional differentiation do not exhaust the entire variety of pattern-forming processes in the development of multicellular organisms. The bulk forms of the organs of the embryo cannot take shape without the participation of movement of both single cells and of entire groups of cells.

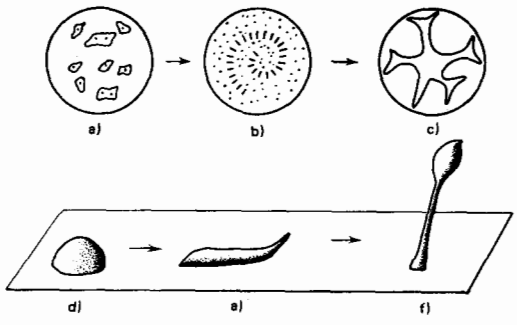

FIG. 19. Phases of the life cycle of the slime mold *Dictyostelium discoideum*. a) Single dividing amoebae; b) initial stage of aggregation (the characteristic spiral front of the cells moving toward the center of aggregation can be seen; this front coincides with the front of the cAMP wave propagating from the center[84]); c) later stage of aggregation (Figs. a–c are not to the same relative scales); d) hemispherical mound of early aggregate; e) migrating slug; f) fruiting body (sporangium with with spores at top).

The phenomenology of the morphogenetic movements is extremely varied. Despite the fact that the macroscopic pattern of these movements has been described in detail for many embryonic systems, the motive forces and mechanisms remain unelucidated in most cases.

In this section we shall present a treatment of the morphogeneis in a system where it takes on perhaps its simplest form. This system is a slime mold (*Dictyostelium discoideum* (*Dd*)). Owing to the presence of typical features of multicellular organisms with a relative simplicity of organization, this object has become in recent years one of the most popular objects of the biology of development. It presents a unique model for biophysics in which one can obtain answers, not only to the question "how and where do the cells move?" but also "precisely why in that way and to that place?".

Figure 19 shows schematically the total life cycle of *Dd*. Three characteristic quasistationary phases are distinguished.

I. *Solitary noninteracting amoebae*. This unicellular phase is accompanied by active cellular divisions and continues as long as the medium is rich in food. The collective form of existence of the amobae sets in upon exhaustion of the nutrients. Here individual (random) cells becomes centers of aggregation, collecting from the surrounding territory (~1 cm^2) about 10^5 cells per each center.[71]

II. *Quasistationary, now multicellular, form of existence—migrating slug*. The slug possesses a characteristic cartridge-like shape and certain features of behavior completely uncharacteristic of the isolated amoebae. For example, it can move as a whole in the direction of a light source. This phase of the life cycle of *Dd* can extend up to several days. It is supplanted by:

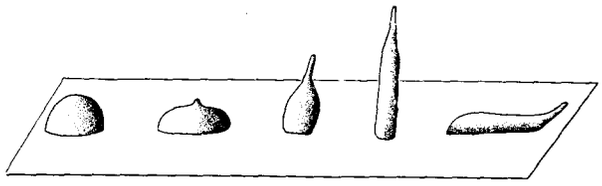

FIG. 20. Consecutive stages of transformation of the spatial shape of the aggregate from a hemispherical mound to a migrating slug.

III. A stationary state called the *fruiting body*. The formation of the fruiting body completes the life cycle of *Dd*. Here the previously started stratification of the cells into two types is completed—generative cells (spores) and vegetative cells (stalk). One can find more detailed information on the development of *Dd* in Ref. 71.

Two transitional pattern-forming processes lead to the two multicellular phases—the slug and the fruiting body. We shall be interested in the former. This process includes a hemispherical sound as the initial state and the cartridge shaped slug as the final state (Fig. 20).

For a qualitative understanding of the process, we must elucidate the origin of the motive forces for the individual cells and the reason for the directional concerted displacements in the cellular mass.

a) On movement

In this case the type of movement is the same as for many motile bacteria, namely—*chemotaxis*. Chemotaxis is the directional movement of cells induced by a concentration gradient of a certain substance (attractant) in the external medium. For *Dd* cells the attractant is the well known compound cAMP, which has already been mentioned in Sec. 1 in connection with intercellular communications. If the drop in concentration of cAMP on diametrically opposite sides of a cell exceeds a certain threshold value,[77] then the cell begins to "flow" in the direction of increasing concentration. One can describe this movement by introducing the "chemotactic" force[78,79]

$$F_{ch} = \mu_{\nabla} C. \tag{61}$$

Here C is the concentration of cAMP outside the cell. Thus, in order to substantiate the displacement of the *Dd* cells in the shape transformations of the aggregate, we must know how to trace the distribution of cAMP in it.

b) Distribution of attractant

In the aggregate of *Dd* the distribution of cAMP is established by the action of:

1) *local synthesis*; cAMP is produced in an enzymatic process induced in several spatially close cells[80];

2) *diffusion through the volume of the aggregate*; one usually uses the estimate $D \sim 10^{-5}$ cm^2/s for the diffusion coefficient[79];

3) *linear decay*; the decay, just like the synthesis of cAMP, arises from the activity of a certain enzyme. The characteristic time for this process amounts to $\tau \sim 10$ s.[81]

The given values of the parameters D and τ yield an estimate of the characteristic length scale

$$r_{ch} \sim \sqrt{D\tau} \approx 100\ \mu\text{m}.$$

With such a scale, the presence of the attractant produced in a localized source is appreciable.

The above verbal description corresponds to the following kinetic equation for the evolution of the concentration distribution $C(\mathbf{r}, t)$[82]:

$$\frac{\partial C}{\partial t} = -kC + D\nabla^2 C + Q\delta(\mathbf{r} - \mathbf{r}_A). \tag{62}$$

Here r_A is the position vector of the source cell (below termed for brevity an A-cell).

The boundary conditions for C stem naturally from the physical formulation of the problem. The flux of cAMP through the aggregate-air phase boundary must be zero, since cAMP is nonvolatile. Hence we have at this surface

$$\frac{\partial C}{\partial n}\Big|_{\Omega_1} = 0. \tag{63}$$

On the contrary, the absorption condition is satisfied at the surface of contact of the aggregate with the substratum:

$$C|_{\Omega_2} = 0. \tag{64}$$

This corresponds to outflux and dilution of cAMP in the substratum.

The characteristic time scale of the transformation of the form of the aggregate amounts to hours.[71] This greatly exceeds the characteristic time of evolution of the $C(\mathbf{r}, t)$ distribution, which, as we have stated, amounts to 10 s. Hence we can restrict the treatment to a quasistationary form of the distribution $C(\mathbf{r})$.

c) Movement of A-cells

Evidently, at any point within the aggregate, the concentration gradient ∇C has a non-negative component in the direction of the A-cell. Hence particles of the aggregate not too remote (within the radius r_{ch}) are attracted to the A-cell. If the latter is fixed, then we should expect a shape of the aggregate close to spherical. It is precisely the capability of the A-cells for chemotaxis and a certain asymmetry of the distribution $C(\mathbf{r})$ arising from the boundary conditions that cause the directional displacement of the A-cell, and the rest of the cells with it.[82]

In order to demonstrate the effect of the boundary, let us examine two simplified situations.[82] Let us pose the problem of diffusion in a half-space bounded by the plane Σ. In the plane Σ let us impose the following boundary conditions for the concentration C: a) absence of a flux $\partial C/\partial n|_{\Sigma} = 0$, and b) absorption $C|_{\Sigma} = 0$.

We can easily find the stationary solution of the problem (62) under the given boundary conditions by the

method of images. Let us place at the point r_A^*, which is mirror-symmetric with the original point, an image source. In the former case the intensity of the image must be the same as that of the original source—precisely in this case the condition is satisfied of zero flux across the plane Σ. In the latter case, in order to satisfy the condition $C|_\Sigma = 0$, we must assume an intensity of the image equal in magnitude and opposite in sign to that of the original source. Consequently the distributions of C in the two cases will be

$$C = \frac{Q}{\varkappa}\left[\frac{e^{-\varkappa|r-r_A|}}{|r-r_A|} + \frac{e^{-\varkappa|r-r_A^*|}}{|r-r_A^*|}\right],$$
$$C = \frac{Q}{\varkappa}\left[\frac{e^{-\varkappa|r-r_A|}}{|r-r_A|} - \frac{e^{-\varkappa|r-r_A^*|}}{|r-r_A^*|}\right], \quad \varkappa^2 = (D/k)^{-1}. \tag{65}$$

The first term, which is the same in both expressions, represents the "intrinsic field" of the source—this is precisely the distribution $C(r)$ for an isolated source. The second term is the "field" of the image, which allows for the effect of the boundary.

Evidently the intrinsic field cannot make the A-cell move, since it is symmetric. The image field breaks this symmetry. The existence of a gradient of the concentration C at the site of the original source is caused by the image source. The vector of the gradient lies along the normal *toward the plane under the condition of zero flux through it, and away from the plane under the condition of absorption.*[82] Correspondingly an A-cell is attracted to a surface impenetrable to the attractant and repelled from an absorbing surface. Upon recalling now the boundary conditions of the aggregate of *Dd*, we conclude that an A-cell must float to the top of the hemisphere, regardless of its initial position. Actually this surfacing reveals itself in the movements of the other cells of the aggregate, which are directed toward its top.[83] The described displacements of the A-cell create the necessary and sufficient prerequisites for the subsequent shape transformations of the aggregate.

d) Collective movements in the aggregate

The visible shape transformations of the cellular aggregate of *Dd* occur in two stages. First a nipple is formed at the top of the hemipshere (see Fig. 20). Its characteristic dimensions amount to 100 μm, while its time of formation is $T < 1$ hr. Elongation occurs in the next stage—extension in the vertical direction with unchanged volume of the aggregate. It is characteristic here than the extension and correspondingly the narrowing do not occur uniformly throughout the volume, but two extreme states coexist at each intermediate instant of time, as in Fig. 20.

The characteristic dimension of the nipple, which coincides with the characteristic scale of length for the concentration distribution of cAMP, indicates that chemotaxis is responsible for this phase of the spatial transformations of the aggregate. It is precisely in the region of characteristic dimension r_{ch} surrounding the source of cAMP that the gradient of the concentration C (chemotactic force) is still appreciable.

The stage of spatial transformations following nipple formation—elongation—now encompasses the entire aggregate, including the regions where chemotaxis cannot be the motive force (removed from the cAMP source by distances $r > 100$ μm).

The interpretation of this process faces no difficulties if we restrict the treatment to a "minimal" physical model that treats the cellular aggregate as a *continuous medium having a hydrostatic pressure and a surface tension.*[79,82]

The curvature of the surface in the region of the nipple determines the hydrostatic pressure:

$$p_t = p_0 + \frac{2\sigma}{R_t},$$

Here p_0 is the atmopsheric pressure, σ is in the surface-tension, and R_t is the radius of curvature. The pressure distribution in the remaining mass of the aggregate is determined by the condition of equilibrium. In a relatively narrow transition region (as compared with the maximum lineal dimension of the aggregate) in which the concentration gradient of cAMP differs from zero, the chemotactic force F_{ch} must equilibrate with the pressure gradient,

$$\mu\nabla C = \nabla p.$$

Hence we can find the pressure in that part of the aggregate where the concentration of the attractant is zero:

$$p_b = p_t - \mu C_t.$$

Here C_t is the concentration level C in the region of the nipple. This pressure unequivocally determines the curvature of the surface bounding this region:

$$p_b - p_0 = \sigma K.$$

Finally, having in mind the definite total volume of the aggregate, we can find its shape. Evidently the two conditions: fixed volume and constant radius of curvature $(1/K)$ correspond to a shape of the surface close to cylindrical (this is true when $K^{-3} \ll V$), which it actually is (see Fig. 20).

In the treatment that we have carried out the process of pattern formation is presented as the result of "interaction of mechanical and chemical" degrees of freedom. The outlining of the boundaries of the cellular mass in terms of the boundary conditions affects the form of distribution of cAMP. In turn the distribution of cAMP fixes the field of the chemostatic forces that alter the outlining of the boundaries of the aggregate. The component phases of this process—migration of the A-cell from the bulk to the surface of the aggregate, nipple formation, and elongation—amount to nothing other than successive stages of evolution of the system toward equilibrium.

In general, as it turns out, a simple model that treats the cellular mass as a "physical" continuum with only the specific feature that the mechanical movements are coupled via chemotaxis with a certain "chemical" system suffices for interpreting the process of self-organization of the spatial form.

9. CONCLUSION

The main idea that this review has aimed to convey can be expressed as follows. The complexity and uniqueness of biological structures is the result of a "complex" response to "simple" controlling factors.

The "complex" response means that both the genetic constitution of the cells of the given ensemble and the path of development that they follow in embryogenesis are essential. The spatial plan or map for the structure being formed is "simple". This plan is fixed by the inhomogeneous distribution of physical parameters (such as the concentrations of certain molecules) that affect the dynamics of the intracellular processes, i.e., the physiological state of the cells.

An important point is that the spatial plan of ordering of the cellular ensembles is, first, insensitive to the nature and individual features of the cells. The rules for its establishment are similar in quite different systems. Precisely in this regard it is "simple" and hence accessible to physiochemical treatment. Second, the spatial plan of a morphogenetic structure is not contained in any form and is not coded in the individual cells. It arises specifically as the product of the collective process of self-organization, which is expressed in the spontaneous appearance of dissipative structures.

In the past several years our knowledge concerning dissipative structures has been considerably deepended and broadened. Progress in the field of biological pattern formation is far from being appreciable to the same degree. The reason for the existing lag is in the lack of reliable information on the code that matches the "physiochemical" spatial map of the cellular ensemble with the morphogenetic structure.

On the basis of only such general physical characteristics as the geometry of the region and the boundary conditions, we can predict the form of the dissipative structure (map). Yet experimentally we are already presented with a structure in which a cellular reaction is imposed on the map. Without a knowledge of the corresponding code, neither does the observed morphogenetic structure tell us anything about the map, nor does the map determine the structure.

Among the variants of a code for reading the map, we should single out the so-called combinatorial code (this was discussed in Sec. 3 of this article). Cogent arguments have recently been obtained for it experimentally, in addition to convincing logical argumentation (see Ref. 85).

This review has not claimed to encompass totally the theory of dissipative structures and their application to biology. Certain aspects of the problem not touched on here are illuminated in a special publication on these problems.[86]

The author expresses his deep gratitude to M. V. Vol'kenshteĭn and M. A. Livshits for interest in the work and for fruitful discussions.

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Translated by M. V. King