Physics and biology

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This review examines the relationship between physics and biology. The views of Bohr, Wigner, Elsasser, and Schrödinger are discussed, and the inadequacy is discussed of "physical vitalism," which holds that the currently-existing physics (thermodynamics and quantum mechanics) contradicts biology. Non-equilibrium thermodynamics is treated, both linear and non-linear. The necessity is emphasized of working with the value of information in studying biological processes. Eigen's theory of selection and evolution of biological macromolecules is analyzed, and it is shown that the parameter of selective value does not correspond to the value of information. The physical meaning of the genetic code is discussed, as well as physical approaches to certain problems of molecular biology, in particular, enzymatic catalysis. Physics, considered as the overall science of the structure and properties of matter and fields, suffices for understanding biological phenomena, and its current conceptions do not face any limits of applicability in biology.

1. The extreme complexity of the spatially heterogeneous structure and the time behavior of living organisms, starting with the individual cell, poses very difficult problems for natural science. We are still far from a real scientific understanding of life, and hence also far from reproducing it artificially. However, reliable foundations have been established in the latter half of the 20th Century for solving these problems—primarily through the rise and development of molecular biology. The creation of molecular genetics and the establishment of the mechanism of synthesis of proteins and of the genetic code mark the discovery of the secrets of heredity and variability, which are very important manifestations of life. These grandiose advances now permit us to approach the much more complex problems of development and differentiation of cells, morphogenesis and cancerogenesis, and behavior of an organism as a whole system. Striking biological facts and regularities have been established here, but their explanation is a matter for the future. The higher nervous activity (memory, thought, and consciousness) has been studied even less.

Only two lines of scientific thought are possible in biology—tertium non datur. Either we must acknowledge that we cannot explain life from the general principles of exact natural science, physics and chemistry, or such an explanation is possible and we must find it. Both the affirmative and negative views require scientific proofs. If such proofs have been or will be found, then the problem is no longer philosophical in nature, but becomes a concrete topic of natural science. Thus, it boils down to the problem of the relationship between biology and physics, i.e., the problem of whether we can explain biological phenomena on the basis of the general laws that characterize the structure and properties of matter (substances and fields).

People often speak of the impossibility of "reducing" something more complex to something simpler, or biology to physics. The so-called reductionism is considered to be some inadmissible heresy. However, as we see it, any discussions on reducibility or irreducibility are simply meaningless. The problem is not that of subordinating biology to physics, but of elucidating the unity of living and non-living nature or the lack of such a unity. The qualitative difference between a frog and a quartz crystal is quite obvious,—but the question is asked in this way: can one explain or not the structure and properties of these material objects by unified scientific laws, i.e., by using physics? We must also note that notions of irreducibility have always hindered the development of science. Irreducibility in biology is equivalent to vitalism. Actually, physics, as the science of matter and fields, is in no way simpler than biology. The concept of reductionism here is false, and with much better grounds we should speak of the integration of science. Moreover, it is pertinent to recall the similar discussions on the relationship between chemistry and physics that seemed topical twenty years ago. Now it is quite clear that there are no phenomena in chemical transformations but physical ones, and chemistry is "reduced" to quantum mechanics, statistical mechanics, and physical kinetics. This does not alter to any extent the independence and significance of the great science of chemistry. Conversely, chemistry has acquired a deeper and more general foundation. Here also what is manifested is not reductionism, but integratism of modern natural science.

How then is the posed problem to be solved? Evidently, the ideas of the vitalist biologists remote from physics, who have included some very great embryologists, zoologists, etc. (H. A. E. Driesch, L. S. Berg, A. G. Gurvich, etc.) are now of no interest. Purely biological argumentation here is insufficient; one cannot judge on the content of the most general biological laws without going outside their boundaries. However, the most prominent representatives of physical thought have solved the problem of the relationship between physics and biology in a different way.

2. In a series of articles and reports, Bohr[1] started with the principle of complementarity in treating this problem. At first he thought that knowledge of a living organism as an atomic-molecular system fundamentally supplements a knowledge of it as a whole organism. In this sense, life is not explainable, and it must be treated as a primary postulate like the quantum of action in quantum mechanics. Bohr's views changed later (perhaps influenced by the growth of molecular biology), and he no longer spoke of a fundamental, but of a practical complementarity determined by the extreme complexity of the organism.[2] Bohr clearly pointed out the change in his views in a letter to the present author that was published in the book[3].

On the contrary, Schrödinger started in his remarkable book[4] with the possibility of physical interpreta-

tion of life. He formulated general principles of thermodynamics of life processes, and he posed a number of questions whose answers later gave rise to molecular biology. Schrödinger's book has played an important stimulating role in the actual development of science.

A monograph by Elsasser[5] shows the incompatibility of life with the established principles of physics. Elsasser considers the increase in the bulk of information in a developing organism to be unexplainable, and he calls this a "biotonic" law. Elsasser's arguments have been criticized in detail by Raven[6] and also in the book[7]. First, the estimate itself of the amount of information in a cell or in an organism is quite arbitrary, and what is essential is not the amount of information, but the informational program of development (see[8]). Second, the amount of information is supplementary to entropy. Hence, assertion of "biotonicity" essentially implies assertion that a living organism violates the second law of thermodynamics. By ignoring the properties of an organism as an open system, Elsasser transforms it into a perpetual motion machine of the second kind.

Wigner thought that the self-reproduction of biological molecules and organisms contradicts quantum mechanics.[9] Biological objects are so complex that it is impossible in principle to treat their behavior on the basis of quantum mechanics. The probability of existence of self-reproducing states is practically equal to zero. We can represent the Hamiltonian controlling the behavior of a complex system as a disordered symmetrical matrix. The state of the organism is described by a vector $\mathbf{v}$ in the space of states, and we shall denote the analogous vector for the food materials by $\mathbf{w}$. The overall vector for the organism plus its food is

$$\Phi = \mathbf{v} \times \mathbf{w}.$$

After reproduction,

$$\Psi = \mathbf{v} \times \mathbf{v} \times \mathbf{r},$$

where $\mathbf{r}$ characterizes the waste products of the food and the coordinates of the two organisms. We have an N-dimensional space of the organism and an R-dimensional space for $\mathbf{r}$. If the "collision" matrix S that gives rise to the final state as the result of interaction of the organism and the food is disordered and random, then

$$v_\lambda v_\lambda r_\mu = \sum_{\lambda', \lambda', \mu'} S_{\lambda\lambda\mu,\ \lambda'\lambda'\mu'} v_{\lambda'} v_{\lambda'} w_{\lambda'\mu'}.$$

This relationship corresponds to N^2R equations. The number of unknowns is: N values of v, R values of r, and NR values of w, i.e., $N + R + NR$. This is much less than the number of equations, so that it would be a miracle if these unknowns were to satisfy the written relationship.

This calculation is quite rigorous if we consider the matrix to be disordered. Following Elsasser, Wigner considers even the reduplication of the double helix of DNA to follow the "biotonic" law.

Actually, as Eigen[10] has rigorously shown, the matrix S is not disordered. Wigner does not take account of the instructional properties of informational macromolecules. Hence, all this discussion has no relation to reality, and Wigner's conclusion that we must modify the laws and concepts of quantum mechanics as applied to biology proves to be false. Nevertheless, application of quantum mechanics to macroscopic systems (and an organism is fundamentally macroscopic; see[4]) requires special treatment.

The ideas of biotonicity, which we can define as "physical vitalism", are refuted. However, the very fact that they arose reflects real difficulties in the construction of a physical theory of fundamental biological phenomena.

The customary formulation of a physical law is causal in nature. It answers the question: "because of what?". It determines the cause of a phenomenon, dynamic or statistical.

Conversely, a biological law is formulated finalistically as a rule. It answers the question: "for what?". Thus, the phylogenetic development of the giraffe gave rise to its very long neck in order that giraffes could feed on the leaves of high trees. In natural selection, the organisms survive that are most adapted to the conditions of the environment—this is the goal of natural selection.

The contradiction between biology and physics appears to be a contradiction between the finalistic and causal descriptions of phenomena. However, this is an apparent controversy.

Any physical law expressed by some variational principle becomes finalistic in nature. We recall the principles of Maupertuis and Fermat, Le Chatelier's law, and Lenz's rule. We can formulate the second law of thermodynamics for isolated systems by starting with statistical causal laws; conversely, we can consider the goal of an evolving system to be to attain maximum entropy, and write the law in the form

$$(\delta S)_e = 0, \quad (\delta^2 S)_e < 0.$$

One can transcribe established physical laws from causal to finalistic terms, and vice versa. Evidently, the predominant finalism in biology is determined by the extreme complexity of the phenomena and the enormous difficulties of finding a causal explanation for them. In physics, such an explanation is reduced in the final analysis to an atomic-molecular explanation. It is unusually hard to trace the path from the atomic structure of the matter comprising an organism to the evolution of species. As we have seen, many people think that there is no such path at all.

3. Two great theories of evolution were constructed in the 19th Century. The first of these, the second law of thermodynamics, gives the law of evolution of matter in an isolated system toward its most probable state characterized by maximum disorder and maximum entropy. The second theory, Darwin's theory of biological evolution, on the other hand, gives the law of evolution of living systems from the least perfected microorganisms to the highly ordered structure of the organism Homo sapiens with his thinking brain. There is a real contradiction between these theories: biological evolution and phylogenesis (and also ontogenesis) does not agree in any way with equilibrium thermodynamics. The following alternative interpretations of this contradiction can be made:

1. The laws of physics are not applicable to living nature. Organisms do not obey the second law, and an impassable chasm exists between biology and physics.

2. One can avoid the chasm by creating a completely new physics encompassing both living and non-living

nature. Similar situations have been found in science—finding the limits of applicability of classical physics led to the foundation of quantum mechanics and the theory of relativity.

3. There is really no chasm. One can start with the already established principles of thermodynamics and expand it in such a way that ontogenesis and phylogenesis acquire a natural physical interpretation.

The first interpretation is the vitalistic one. The second corresponds to the conceptions of Elsasser and Wigner. We have seen that they are wrong. However, we can reject both the first and second interpretations as a whole only if we rigorously prove the third.

A living organism is a non-equilibrium, open system. The Soviet biologist Bauer who perished prematurely is hardly the first to note the importance of the thermodynamic non-equilibrium nature of an organism.[11] According to Bauer, the fundamental law of biology is: "... Living systems are never in equilibrium, and they exert a constant effort against equilibrium at the expense of their free energy ...". Further on, he says: "The non-equilibrium state of living matter, and hence its constantly conserved capacity for work arises from ... the molecular structure of the living matter, and the source of the work performed by living systems is in the final analysis the free energy that is intrinsic to this molecular structure and to this state of the molecules." Bauer foresaw the subsequent development of science, but his studies (which are now only of historical interest) remained without being understood by his contemporaries, and moreover, by some recent commentators (see, e.g.[12]).

Later, Bertalanffy clearly formulated ideas of the non-equilibrium nature of a living organism as an open system.[13] A non-equilibrium steady state can be realized in such a system, which Bertalanffy called a "flowing equilibrium" (Fliessgleichgewicht).

Schrödinger's book cited above[4] gives a qualitative treatment of the thermodynamic properties of an organism as an open system. The ordered nature of an organism increases or remains constant, not in spite of the second law, but because of the laws of thermodynamics. The order is maintained by the outflow of entropy into the environment. The organism grows and develops, since it "feeds on negative entropy". If we isolate an organism along with the materials needed for its existence, then the second law will hold in the complete isolated system, and the entropy will increase.

In this sense, the "aperiodic crystal"—the organism—resembles an ordinary growing crystal. Crystallization of a liquid is accompanied by loss of entropy, which is superposed on an increase in entropy of the coolant. One cannot crystallize a liquid held in an adiabatic container.

These elementary arguments imply that there is no "biotonicity" in the increase in the amount of information in an organism. Information is equivalent to negentropy, and information also increases in the crystallization of a liquid.

Thus, the contradiction between the high degree of order of an organism and the second law is eliminated. However, this still does not explain biological evolution, phylogenesis, and ontogenesis.

4. The ideas that have been presented are qualitative in nature. A rigorous quantitative formulation requires construction of a thermodynamics of open systems, a thermodynamics of non-equilibrium processes. Since time enters into the description of such processes in explicit form, one is no longer speaking of thermodynamics, but of physical kinetics. A fundamental contribution to the development of this field was made by Onsager,[14] who treated coupled processes that occur near equilibrium. In this case, the relationship between the generalized fluxes and the generalized forces is linear:

$$J_i = \sum_j L_{ij} X_j.$$

The principle of microscopic reversibility implies that the phenomenological coefficients L_{ij} form a symmetric matrix, i.e.,

$$L_{ij} = L_{ji}.$$

Correspondingly, the entropy production per unit time per unit volume

$$\sigma = \sum_i J_i X_i \geqslant 0 \tag{1}$$

is expressed by the quadratic formula

$$\sigma = \sum_{i,j} L_{ij} X_i X_j.$$

Prigogine has developed a consistent formalism for this linear region.[15] Let us restrict ourselves to the biologically very important case of chemical reactions. We introduce the generalized force quantity: the affinity divided by the absolute temperature. The affinity (see[16]) is expressed by the formula

$$\mathcal{A}_i = -\sum_k \nu_{ik} \mu_k,$$

where i is the index number of the chemical reaction, the ν_{ik} are the stoichiometric coefficients, and the μ_k are the chemical potentials. Hence,

$$\mathcal{A}_i = -RT\left[\ln K_i - \ln\left(\prod_k a_k^{\nu_{ik}}\right)\right],$$

where the K_i are the equilibrium constants and the a_k are the activities, and the affinity vanishes in a state of equilibrium. The generalized force $\mathcal{A}_i$ corresponds to the generalized flux, which is the rate of the chemical reaction. Let us introduce the reaction coordinate ξ_i such that

$$d\xi_i = dn_k/\nu_{ik}.$$

Then the differential of the free energy is

$$dG = \sum_i \mathcal{A}_i \, d\xi_i$$

and the rate of reaction is

$$v_i = \dot{\xi}_i = \sum_k L_{ik}\mathcal{A}_k/T = (1/T)\sum_k L_{ik} \sum_l (\partial \mathcal{A}_k/\partial \xi_l)_{T,p}\, \delta\xi_l;$$

v_i also vanishes at equilibrium. The entropy production is

$$\sigma = (1/T^2)\sum_{i,k} L_{ik}\mathcal{A}_i\mathcal{A}_k \geqslant 0. \tag{2}$$

The condition of linearity, i.e., closeness to equilibrium, implies that

$$\mathcal{A}_i \ll RT.$$

Eq. (2) gives the criterion for stability of equilibrium. Hence, the entropy fluctuation near equilibrium is

$$\delta_i S = (1/T)\sum_k \mathcal{A}_k \, \delta\xi_k \leqslant 0,$$

or

$$\sum_k (\partial \mathcal{A}_k/\partial \xi_k)_c (\delta\xi_k)^2 \leqslant 0,$$

since $\partial A_k/\partial \xi_k < 0$.

We note that a variable like ξ that characterizes the deviation of a system from equilibrium was first introduced by Mandel'shtam and Leontovich[17] in a study on absorption of sound in liquids.

A simple example of an autocatalytic reaction X + Y $\rightleftarrows$ 2X is described by the formulas[10]

$$v = \vec{k}[X][Y] - \overleftarrow{k}[X]^2 \quad (3)$$

and

$$\mathcal{A} = RT[\ln K - \ln([X]/[Y])].$$

We have the following expression for the fluctuation $\delta[X]$ at constant $[Y]$:

$$\delta v = \vec{k}[Y]\,\delta[X] - 2\overleftarrow{k}[X]\,\delta[X]$$

and, since $v[Y] \approx \overleftarrow{k}[X]$ near equilibrium,

$$\delta v = -\overleftarrow{k}[X]\,\delta[X].$$

We also have

$$\delta\mathcal{A} = -(RT/[X])\,\delta[X]. \quad (4)$$

Equation (1) implies that

$$d\sigma = d_J\sigma + d_X\sigma = \sum_i X_i\,dJ_i + \sum_i J_i\,dX_i.$$

In our case,

$$v_i = v_i^{(e)} + \delta v_i = \delta v_i,$$
$$A_i = A_i^{(e)} + \delta A_i = \delta A_i$$

and

$$T\delta_X\sigma = \sum_i v_i\,\delta\mathcal{A}_i = \sum_i \delta v_i\,\delta\mathcal{A}_i.$$

Hence,

$$\delta_X\sigma = R\overleftarrow{k}(\delta[X])^2 \geqslant 0.$$

This is the condition for stable equilibrium.

The significance of linear non-equilibrium thermodynamics for biology consists in the following:

1) The thermodynamics describes and explains the coupling (via the non-diagonal coefficients L_{ik}) of the chemical and other kinetic processes that can be realized in open systems.

2) The thermodynamics gives a description of non-equilibrium steady states and shows that in these states the entropy production is a minimum (the theorem of Glansdorff and Prigogine[18]), i.e.,

$$d_X\sigma = \sum_k J_k\,dX_k \leqslant 0,$$

where the equality sign refers to the steady state.

Coupling of kinetic processes is characteristic of biological systems. In particular, it determines the very important transport properties of biological membranes and their artificial models. It turns out that one can actually apply linear thermodynamics here (see[19]).

Discussion of steady states is necessary for further development of nonlinear non-equilibrium thermodynamics.

Linear thermodynamics is in no position to explain the processes of growth and differentiation of cells, and the appearance of new structures. Autocatalysis near equilibrium does not give rise to growth of a system, since under these conditions the catalyst accelerates equally both the forward and backward reactions. The attempts found in the literature to describe ontogenesis within the framework of linear thermodynamics are utterly false (see, e.g.[20]). The periodic processes characteristic of living systems also cannot be realized near equilibrium. In fact, if we diagonalize the matrix L_{ik} and the tensor $(\partial A_k/\partial \epsilon_l)_{T,p}$ (see[14]), we can write the transformed kinetic equations

$$v_i' = \dot{\xi}_i' = \lambda_i\,\delta\xi_i'$$

with the solutions

$$\delta\xi_i' = \delta\xi_i'^{(0)}\,e^{-t/\tau_i},$$

where $\tau_i = -\lambda_i^{-1} > 0$. That is, the deviation from equilibrium decays exponentially without oscillations.

The article by Prigogine and Nicolis that appears in this same issue of Uspekhi [Quart. Rev. Biophys. 4 (2/3), 107 (1971)] gives a sketch of nonlinear non-equilibrium thermodynamics. Nonlinearity and instability can be treated by the methods of thermodynamics if the local entropy is expressed in terms of the same variables as in an equilibrium system. The distribution function of the coordinates and velocities does not deviate greatly from equilibrium. Appearance of a new structure (a dissipative structure) in an open system is always the result of instability. The fluctuations are amplified in a region far from equilibrium (see also[21]). The fluctuation near a stable steady (but not equilibrium) state is characterized by the condition of "excess entropy production":

$$\delta_X\sigma = \sum_k \delta J_k\,\delta X_k \geqslant 0.$$

For a chemical system,

$$T\delta_X\sigma = \sum_k \delta v_k\,\delta A_k \geqslant 0.$$

A steady state proves to be unstable if $\delta_X\sigma < 0$. Let us return to the reaction X + Y $\rightleftarrows$ 2X. Far from equilibrium, in contrast to Eq. (3),

$$v = \vec{k}[X][Y]$$

and at constant $[Y]$, $\delta v = \vec{k}[Y]\delta[X]$. As before, the value of δA is given by Eq. (4). We have

$$\delta_X\sigma = -\vec{k}R([Y]/[X])(\delta[X])^2 < 0,$$

That is, at constant $[Y]$ such a system is unstable, and it cannot attain a steady state.

Prigogine and his associates have shown that, owing to chemical instabilities, autocatalytic homogeneous systems far from equilibrium can form structural inhomogeneities in space and time, and can give rise to oscillating structures. Such structures are non-equilibrium; they are dissipative structures. They have been obtained in vitro in a series of studies by Zhabotinskiĭ (see[22]), some of which have been cited by Prigogine and Nicolis. There are weighty reasons for thinking that the "biological structuring" in ontogenesis is precisely of this nature.

I must emphasize that instability in chemical reactions, in particular, in chain processes (explosive reactions),[23] had been studied in detail earlier by the school of N. N. Semenov (see[24]). Prigogine's contribution consists in constructing a phenomenological generalized thermodynamics and in creating a formalism applicable both to equilibrium and to dissipative systems.

5. Thus, very general physical concepts prove in principle to be applicable to treating evolution of both species and organisms—ontogenesis and phylogenesis.

Thus the contradiction between thermodynamic and biological evolution is eliminated.

The next step must consist in creating a theory of biological evolution that is no longer phenomenological, but atomic-molecular, and that takes account of the actual structure and properties of biologically functional molecules. The fundamental phenomenon that demands physical interpretation is natural selection. The problem arises of interpreting it in exact molecular terms, i.e., in the final analysis, in the language of quantum mechanics. As we have seen, this type of problem seemed insolvable to Wigner.

By what concepts and ideas should we be guided here? There have been attempts to interpret evolution on the basis of ideas of information theory, which operates only with the concept of the amount of information. The eminent Soviet biologist I. I. Shmal'gauzen has "translated" the evolutionary theory into the language of this theory. theory.[25] Such a "translation" greatly clarifies the picture, and makes it distinct and full of physical content. It rids evolutionary theory of its reversions to qualitative speculation and teleology. However, these important studies do not solve the stated problem. The reason for this is clear. The amount of information is complementary to entropy. Hence, when using this concept, information theory cannot give more than thermodynamics in its classical form without treating the kinetics of formation of dissipative structures. In order to interpret biological phenomena, one must study the creation of information, and of instructive, programming action of molecular and supermolecular information. That is, one must study the value of information, rather than just its amount as expressed in bits (or in cal/degree). First of all, the value of the informational, instructive program is essential in natural selection.

The incredible complexity of biologically evolving systems (populations of living organisms) makes it as yet unreal to construct a physical theory of evolution as a whole. One evidently must treat the simplest models, and first of all molecular prebiological evolution. Modern natural science starts with the theory of abiogenic origin of life that was first developed by A. I. Oparin.[26] According to this theory, informational macromolecules like the nucleic acids and proteins can arise from relatively simple organic compounds that were formed on the Earth under the conditions of its original reducing atmosphere. It has been shown experimentally (see[27]) that amino acids, nucleotides, etc., can arise from very small and simple molecules under the action of an electric discharge or short-wavelength irradiation.

In an extensive paper,[10] as well as in the condensation of it published in this issue of Uspekhi, the Nobel laureate M. Eigen presents his theory of prebiological evolution of macromolecules. This work is important, both in solving the above-discussed relationship between physics and biology, and also in the further development of science.

Eigen considers an open system that exchanges monomers with its environment. Polymerization and decomposition of polymers that have been formed occur within the system. Polymerization occurs by self-instructed reproduction for any sequence of units, including false copies. These processes are described by kinetic equations that are generally nonlinear and that take account of inexact copying of macromolecules, or mutation. Such a system shows threshold properties and segregation: if the parameters that characterize the rate of reproduction exceed those for the rate of decomposition of the macromolecules, then the macromolecules will grow. In the opposite situation they will "die out". However, imposition of external restrictions (constant reaction forces or constant reaction fluxes) give rise to selection within the system. A complex but physically meaningful parameter, the selective value, arises in the equations, and a criterion for selection is found. Approximate solution of the equations shows that all macromolecules "die out" in time but the species having the maximum selective value.

In the biological literature, Darwin's theory is often treated as a tautology: survival of the fittest is survival of the survivors. Eigen's theory shows that this is not so. The criterion of selection, which is directly related to the imposed external conditions, gives a physical meaining for the term "fittest."

However, the presented deterministic treatment of selection is insufficient. It takes no account of the randomness of appearance of mutants, of the fact that autocatalytic amplification leads to macroscopic expression of indeterminate microscopic events. It also takes no account of the statistical fluctuations to which the growth process is subjected.

Therefore we must study concretely the relationship between chance and necessity in macromolecular natural selection. Eigen solves this problem by using the mathematical apparatus of Markov chains. The results of analysis show that the conclusions from the deterministic theory suffer certain changes. Only in rare cases do small selectional advantages give to macromolecules c chances to "survive" and take the dominating position. The process of selection is stochastic and indeterminate. However, even here a physically meaningful criterion of selection remains.

Eigen's theory fully agrees with the thermodynamic theory of steady states of Prigogine and Glansdorff, and rests on it. The introduction of the "selective value" implies the construction of an information theory that includes creation of information. Information is a molecular property, and it is estimated from the ability of macromolecules to reproduce themselves.

Further on, Eigen turns to concrete biopolymers. Starting with the experimental results obtained in molecular biophysics, Eigen analyzes the ability of nucleic acids and proteins to undergo stable selection. In contrast to the proteins, the nucleic acids have the property of self-instructed assembly from monomers owing to the complementarity between "mother" and "daughter" chains. However, this complementarity is not absolute, and a calculation taking account of the experimental data shows that the nucleic acids alone cannot bring about a selection of macromolecules having a high enough information content. On the other hand, proteins without nucleic acids have no inner complementarity, and they contain "too much" information. This implies too small a probability of self-amplifying mutation, and inability of the system to free itself of a network of "parasitic" chains.

Eigen shows that a real hypercycle built of nucleic acids and the protein enzymes synthesized with their participation, the latter in turn governing the reproduction of the nucleic acids and the protein synthesis, will

make possible selection of macromolecules having a bulk of information sufficient and necessary for the creation of a living system. This reveals the physical meaning of the genetic code.

Eigen was able to compare the theory with experiment by analyzing the results of Spiegelman.[28] Let us present briefly the content of these important studies.

The so-called Qβ-phage that infects bacterial cells synthesizes its own RNA replicase. This is an enzyme that catalyzes the replication of the RNA of the phage, i.e., its multiplication.

Qβ-replicase is fully specific: it recognizes only Qβ-RNA, but not any other RNA. Spiegelman performed experiments on "evolution in a test tube." He put replicase and activated monomers (nucleoside triphosphates) in a test tube, into which he introduced a small amount of Qβ-RNA as a primer or template. Template replicational synthesis of RNA occurred. He transferred a small fraction of the synthesized RNA to the next test tube containing replicase and monomers, etc. Here he gradually shortened the incubation time of the reaction mixture. Eighty transfers in all were performed. Finally he got RNA molecules that had lost up to 85% of their original links, but which interacted with replicase as before. Thus he carried out a selection of those RNA molecules that are synthesized most rapidly.

6. Eigen's study tried to construct a physical theory of natural selection on a molecular level. His general conclusion of the decisive selective and evolutionary advantages of nucleoprotein hypercycles is quite convincing. However, the reasons for these advantages do not reduce to those pointed out by Eigen.

I. M. Lifshitz has called attention to the fact that Eigen's theory neglects one important fact. Selective value, as expressed by the kinetic parameter $W_i^{(0)}$, is not correlated unambiguously with the primary structure of the chain. Mutations can arise in chains, and template synthesis can occur with errors without changing the parameter $W_i^{(0)}$. Template reduplication is based on recognizing individual units and their nearest neighbors. Thus, for example, a double mutational substitution

$$\ldots CA\underline{B}BD\ldots CA\underline{C}BD\ldots \rightarrow \ldots CA\underline{C}BD\ldots CA\underline{B}BD\ldots$$

cannot affect the value of $W_i^{(0)}$, that is, ultimately it cannot affect the rate of synthesis of the chain as a whole.

Of course, a double mutation has low probability. A single replacement of a link of the chain alters $W_i^{(0)}$, but when the number N of links is large, this change is very small. The relative change in the rate of template synthesis upon replacing one link is of the order of magnitude of N^{-1}. Let us assume that a replacement has caused $W_i^{(0)}$ to increase by a correspondingly small amount. Selection takes time. If a second mutation appears within the time of preferential survival of the "master copies" that restores $W_i^{(0)}$ to its former value, then a new "master copy" will not arise. Hence, the selective value $W_i^{(0)}$ does not express the value of information.

No matter how small the probabilities of mutations and replication errors might be, chains will arise in the system after a sufficient time that are degenerate in their $W_m^{(0)}$ value, but which differ in their primary structures. If the chains are long enough, then the number of degenerate macromolecules becomes very large. Ultimately, the most probable state of the system will correspond to the maximum variety of primary structures of chains having identical values of $W_m^{(0)}$. The selection equilibrium proves to be unstable. Following the selection stage treated rigorously by Eigen, a stage of relaxation to a degenerate state will set in. Thus, the system will not evolve, but degenerate. Selection in the first stage is not equivalent to evolution.

Eigen shows that genuine self-instructed reproduction, just like the complementary reproduction of polynucleotide chains, cannot give rise to selection of sufficiently long informational macromolecules, owing to the limited specificity of recognition. However, the trouble doesn't consist in this alone. In view of the above, these types of reproduction must unavoidably lead to a degenerate system, even with much more precise reproduction.

The information contained in a chain does not acquire value in simple or complementary reproduction, since here it is not the primary structure of the chain as a whole that is recognized, but individual successive units. The information in the chain acquires value in two cases: first, in translation of the primary structure of a polynucleotide into that of a polypeptide; second, in the presence of an enzyme that accelerates template reproduction (replicase or polymerase) and that recognizes a rather extended region of the polynucleotide chain. In the former case, all of the translated information possesses value, but in the latter case, only the information contained in the region of the chain recognized by the replicase does so.

The described experiments of Spiegelman (see[28]) in which selection of Qβ-RNA molecules was realized belong to the latter case. RNA replicase recognizes a considerable region of the RNA chain. It is precisely this region that has informational and selective value. Hence, this region undergoes selection in the multiple passages of the system performed under conditions of gradually shortened incubation time. The regions of the RNA chain that lack selective value are lost in this process.

Translation creates the selective value of DNA, owing to the biological functionality of the synthesized proteins. Translation consists in recoding the information. The value of the information contained in a protein chain is determined by the fact that the biological function of a protein is fixed by its primary structure with a high degree of specificity. In other words, the functional spatial structure of a protein is determined by the informational sequence of its amino acid residues. The selection of proteins is based on their spatial structures. But this entails selection of the primary structures of proteins, and hence, that of the primary structures of tRNA and DNA.

Both methods by which the information contained in DNA acquires value are realized in the hypercycle discussed by Eigen.

Eigen correctly emphasizes the decisive selective and evolutionary advantages of nucleoprotein hypercycles. True selection and evolution are possible precisely in such systems. But can we call them prebiological? Isn't such a hypercycle the simplest model of the actual biosynthetic system of a cell? The next step in building a model of the cell might consist in having the subsidiary proteins of the hypercycle that don't catalyze RNA synthesis give rise to membranes and compart-

mentalization, thus changing the boundary conditions of the system. In the replicon model,[29] the membranes directly govern the reduplication of DNA.

Prebiological selection of nucleic acids might arise in the presence of randomly-formed polypeptides having replicase activity. Enzymatic catalysis of reduplication sharply increases the rate of the latter, and thus increases the selective value $W_i^{(0)}$. However, the cycle is not yet closed. That is, until the creation of a replicase is instructed by nucleic acids, such a selection is unstable, and not promising for evolution.

As Eigen writes, the existence of a hypercycle is determined by the existence of a code and a mechanism of translation. The problem of how the code originated and evolved to the current situation remains open, in spite of a number of reasonable speculations (see[10,30]). At present, other problems are of real importance, namely, the relationship between the primary structure and the functional spatial structure of a protein and the corresponding non-random nature of the code.

It was shown in[31] that the contemporary code has a certain reliability: unit mutations that replace polar amino acids with nonpolar and vice versa are twice as improbable as mutations that preserve the class of residue. I can make this statement more exact and develop it.

In a crude approximation, the spatial shape of a protein globule is determined by the relationship between the hydrophobic and hydrophilic amino-acid residues in the protein chain.[32,33] According to C. Tanford, the degree of hydrophobicity can be characterized by the change in free energy ΔF when an amino acid is transferred from ehtanol to water.[34] The 20 amino acids are arranged in a series starting with tryptophan ($\Delta F = 3000$ cal/mole) and ending with glutamine ($\Delta F = -100$). For glycine, which has no side chain, $\Delta F = 0$. Let us calculate the mean difference ΔF for an arbitrary replacement of any amino acid residue by another. It amounts to 1280. Let us denote the RNA codon by xyz. The value of ΔF upon replacement of an amino-acid residue owing to a single mutational replacement of a nucleotide is 1000 when x is replaced, 1280 for y, and 340 for z. As averaged over the three nucleotides, $\overline{\Delta F} = 870$, which is considerably less than 1280. The mean value of $\overline{\Delta F}$ of the hydrophobicities of the original and substituent residue for 70 mutants of human hemoglobin amounts to 834, for six cytochromes it is 900, and for mutants of tryptophan synthetase A it is 1030. Analysis of 423 substitutions from comparing six homologous proteins of different types (cytochrome c, hemoglobins, insulins A and B, and ferredoxin) gives $\overline{\Delta F} = 772$.

Brandts[33] has shown that, in order to understand the structure of a globule, it is rational to classify the amino-acid residues into three groups: hydrophobic (H), which lie within the globule (alanine, valine, isoleucine, leucine, methionine, proline, tyrosine, threonine, tryptophan, and phenylalanine), polar or charged (P), which lie at the surface of the globule (arginine, aspartic acid, histidine, glutamic acid, and lysine), and neutral (N), which lie either inside or on the surface of the globule (asparagine, glycine, glutamine, serine, and cysteine).[33] In random substitutions, the fraction of the most damaging substitutions P → H and H → P is 26.3%. The fraction of the substitutions P → P and H → H that affect the structure of the globule least is 29.0%. These numbers are related as 1.0 : 1.1. The substitutions determined by unit mutations in codons are characterized by the fractions 12.2% and 41.8%—the ratio is reduced to 1.0 : 3.4.

Thus the code ensures a nonrandom nature of mutations and a high level of stability of the types of residues. Thus the spatial structure of the globule also has a certain mutational stability. These facts imply that the aqueous environment has an important role in the creation of the code: the properties of the amino acids that are determined by this environment are important. Hence, the aqueous medium must be taken into account directly in treating molecular selection and evolution.

The ideas and methods of calculation that Eigen has developed promise much. We can suppose that one can also analyze more complex selective and evolutionary systems on their basis, and approach the devising of a theory of differentiation of cells, morphogenesis, antibody synthesis, etc.

7. The above material shows that we reach the molecular level of organization of systems in studying the fundamental theoretical problems of biology. The true interpretation of biological phenomena is atomic-molecular. Eigen's theory belongs to the field of molecular biology and molecular biophysics.

The establishment of molecular biology implies the building of a firm bridge between physics and biology. The posing and solution of the problem of the genetic code and the discovery of the molecular nature of heredity and variability (mutations) ultimately reduce to a quantum-mechanical treatment of these phenomena.

The field of physics involved with studying the structure and properties of proteins, nucleic acids, and other biologically functional molecules is called molecular biophysics.

Evidently the study of isolated biological molecules poses no epistemological problems. A molecule of a protein or nucleic acid as such does not live, and in this sense, it does not differ from a molecule of any other substance. However, this does not imply that biologically functional molecules (macromolecules) lack specific properties. It is precisely these properties that are responsible for biological behavior, and they determine the vital activity of organisms and biological evolution.

The macromolecules of proteins and nucleic acids are informational molecules. The primary structure of these chain molecules, i.e., the sequence links of different types (20 types in proteins and 4 in DNA) is equivalent to a certain text that has a quite definite physical meaning. The message written on DNA programs the synthesis of proteins, i.e., the heredity of the organism. The protein texts are responsible for all the varied functions of the proteins, and primarily for enzymatic catalysis. To use Eigen's expression, we can say that the function of DNA is legislative, and that of proteins is executive. Both functions are chemical in nature—the cell and the organism are very complex chemical machines.

The specificity of biopolymers does not reduce to the existence of the primary structure. Their chain structure itself determines special physical properties. Both synthetic and biological macromolecules are chains that have some degree of flexibility. Flexibility implies the ability of a chain to assume different conformations by rotations about the single chemical bonds. Synthetic homopolymer molecules coil up in solution into random

fluctuating coils. The modern theory of the equilibrium physical properties of these coils (statistical mechanics of chain molecules) is based on the rotational-isomer model.[34] Each link of the chain can occur in several different, discrete conformational states. The conformational statistics of macromolecules treated as cooperative systems permits one to calculate the dimensions, dipole moments, and polarizabilities of macromolecular coils, and to construct a theory of polymer solutions and a theory of rubber elasticity.[35]

A further deepening of the theory has begun in the studies of I. M. Lifshitz,[36] who has taken account of the existence of "memory" in a macromolecular chain, i.e., the fixed sequence of chemical bonds. Thus even a homopolymer chain is not in equilibrium. This leads to features of fluctuational behavior that are responsible for the specific properties of disordered coils and organized polymer globules.

As Lifshitz's theory shows, a compact homopolymer globule should consist of a relatively rigid core and a strongly fluctuating shell. The free-energy values adopted by such a system are discrete. The globule, which is a simplified model of a protein molecule, is a quite distinctive statistical system.

However, a real protein globule is incomparably more complex. Its spatial structure is determined by the fixed sequence in the chain of different amino-acid residues interacting with one another. These links are relatively exactly localized in space; the globule is an "aperiodic crystal" (see[4]) and a dynamically organized system. A protein molecule is a sort of machine that works by virtue of exactly coordinated behavior of all its parts. Although the nature of the forces acting in the globule is evident, we are yet far from constructing a physical theory for it. Thus, the problem has not yet been solved of establishing the spatial structure of a globule from the known sequence of amino-acid residues in the chain. A physical theory to explain the functioning of protein molecules faces even greater difficulties.

The functions of proteins and nucleic acids are chemical in nature. Thus, enzyme proteins serve as catalysts for any of the chemical processes in the cell, and nucleic acids are indispensable participants in the biosynthesis of protein. At the same time, the major role in these processes is played by conformational rearrangements of biopolymer molecules that depend on the flexibility of the polymer chains, i.e., their capacity for rotational isomerization.

The interactions of biopolymers with one another and with small molecules that determine the processes of molecular recognition are created by relatively weak intermolecular forces and they are cooperative in nature. Conformational rearrangements optimize these interactions.

Modern views of the nature of enzymatic activity start with the idea of induced structural fit of the enzyme and the substrate (reagent) that is realized by means of these rearrangements. This idea was first advanced by D. Koshland (see[37]).

The macromolecules of proteins and nucleic acids have no specific electronic properties as whole systems. In this sense they resemble dielectrics, rather than semiconductors or ferromagnetic materials. The features of the electronic, i.e. chemical, behavior of biopolymers involve their conformational lability. The chemical electronic process is governed by the conformational transitions. Conversely, an electronic influence acting on a biopolymer gives rise to these transitions. Correspondingly, the fundamental problem of the modern physical theory of biopolymers consists in theoretical and experimental study of electronic-conformational interactions (ECI).[38]

It is proper to ask ourselves whether we can separate a complex process into motion of electrons and conformational motion. This is possible for the same reasons as when one separates electronic and vibrational transitions in molecular spectra (the Born-Oppenheimer theorem). Conformational motion is the motion of nuclei, and it occurs many times more slowly than the rearrangement of the electronic structure. The theory of ECI naturally applies quantum mechanics to studying the properties of biopolymers. The first attempts have been made to construct physical models for enzymatic activity[39] and for the functioning of bioenergetic membranes.[40]

The theory of biological macromolecules and supermolecular biological systems (membranes, etc.) is developing on the basis of advances in theoretical solid state physics. It seems promising to work with the concept of a conformon—a provisional quasiparticle that represents a displacement of the electron density and the local conformational rearrangements caused by it in a biological molecule or supermolecular structure.[41] One must develop a theory of the conformon, which differs in a number of features from the polaron and the deformon.

An important study by Kuhn[42] has recently appeared that proposes a reasonable model for prebiological and biological evolution starting with short chains of RNA. This model is free from the defect in Eigen's model discussed on p. 212. The value of the information contained in RNA is determined by the coiling of its chains into a tertiary structure.

8. Biological macromolecules, the cell organoids, the cell, and the organism are all complex, dynamic but not random, chemical machines characterized by heterogeneity and extreme individualization of structure. On all levels of structure, we encounter very exact and definite regulation of the behavior of the system in space and time. Naturally, the new branches of science (cybernetics, information theory, and theory of automatic regulation) are effectively applied in biology. The fundamental difference between a biological system and the machines that man currently knows how to invent consists primarily in the nature of signalization. In the cell and in the organism, the signals are molecules, and their sources, converters, and receptors are also molecular structures. Thus, we must consider an enzyme molecule to be a converter of a signal—of the substrate molecule (the reagent) into a molecule of the product. It is not by chance that the phenomenological description of complex enzymatic processes uses the methods that are customary in electro- and radiotechnology (graph theory, see[37]).

Even on the molecular level, we encounter the nonrandom nature of biological systems. As I have stated, studying them apparently requires further development of the ideas of solid state physics, including study of states of partial equilibrium characterized by the existence of memory and/or topological restrictions. In such partial-equilibrium systems, distinctive critical situa-

tions can appear that lead to self-organization of spatial structures that are ultimately macroscopic. Such systems can evolve. I. M. Lifshitz has begun studies along these lines.

"Biological machines" arise from disordered systems. The fundamental difficulty of the theory consists in a quantitative, physically meaningful solution of the "chance-necessity" problem, i.e., the problem of the relationship between the stochastic, fluctuating behavior of a system and its regular resultant properties in space and time. This problem has been posed in a natural-philosophical study by the Nobel Prize winner Monod.[43] This author introduces the concept of "teleonomy," i.e., the existence of a programmed plan of development of a biosystem. However, Monod cannot solve the posed problem while remaining within the framework of purely biological treatment. Eigen's ideas have incomparably greater content. We can suppose that taking account of stochastics will permit us to explain a number of the properties of those systems whose behavior is now treated as being completely deterministic: enzyme molecules, membranes, and other supermolecular structures.

The extreme complexity and distinctiveness of biological systems is obvious. The physics of living nature is in its initial stage of development. Its major advances as yet belong mainly to the molecular level of organization. However, advance has begun in recent decades along pathways that undoubtedly will lead to the goal—to knowing whole biological systems as material objects amenable to physical study.

All that has been attained by molecular biology, physics, and cybernetics indicates no boundaries in biology for application of contemporary physics. Apparently, the further development of biophysics will not face the necessity of constructing a "new physics." Introduction of new concepts is unavoidable, e.g., value of information, but knowledge of living nature leads to no contradictions with the fundamentals of physics: thermodynamics, statistics, kinetics, quantum mechanics, etc. In this sense, biophysics does not exist as a special, separate science. There is a unified physics, which now turns to studying living nature, owing to grandiose advances in biology.

We expect much from these studies.

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