THE THEORY OF COOPERATIVE PROCESSES AS THE FOUNDATION OF MOLECULAR BIOPHYSICS

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The application of the theory of information to the investigations of biological processes allows one to explain many questions, concerning fundamental biological phenomena, such as ontogenetic and phylogenetic development. The fundamental principles of regulation of biological processes in toto and in details proved to be the same as the general physical principles of cybernetics. The theory of information is but a phenomenological theory. The possibility of a mathematical description of biological processes established by cybernetics does not exhaust the content of theoretical biology and biophysics. On the contrary it shows especially clearly the necessity of constructing a molecular theory of biological processes.

The main difficulty met by a physicist starting the study of living matter consists in extreme complexity and in the great number of interacting processes and in their realization on the macroscopic overmolecular level. In other words, the systems responsible for the occurrence of biological processes are specific not only on account of the specific structure of the molecules contained but also on account of the peculiarity of the overmolecular structure. The biophysicist meets a situation, which does not exist in the physics of non-living matter. The problem of constructing molecular biophysics turns out to be very complicated. It does not mean however that such a problem is insoluble.

In his well known book "The physical foundations of biology" Elsasser (1) writes that the biological laws cannot be described by the language of usual physical ideas since they possess a specific "biotonic" character. Elsasser connects the non-physical features of biology with the Bohr complementarity principle. Having not the aim to analyze these philosophical questions, I wish to point out that the "epigenetic" concept of Elsasser is not based on the results of concrete biophysical studies. The limits of applicability of contemporary physical theory in biology cannot be settled in a speculative way and I doubt that their existence can be proved. In the discussion of Elsasser with Schrödinger, who claims that the stability of

genetic substance is determined by its molecular structure (2), Schrödinger's position seems to have better foundations. The overmolecular biological functioning system contains a greater amount of information than the molecules building this system. The storage of information is therefore non-additive. Its increase has an endogeneous character (Elsasser is right here (1), p. 176) but is possible only as a result of metabolism, owing to the increase in the entropy of the surrounding medium.

The increase of the information in the organism means the increase of order in a complicated aperiodic molecular and overmolecular structure. We may ask whether the contemporary molecular physics allows us to understand the nature of such processes of ordering without introducing the nature-philosophical considerations about the "biotonic" laws?

Evidently the description of biological processes by the language of information theory is not sufficient for their real physical understanding. The concrete molecular-physical and of course chemical analysis of the phenomena of life is necessary.

Taking into account the complexity of the overmolecular structure and its functionality we have first to investigate the molecular level of the biological phenomena. The division of chromosomes in mytosis is a macroscopical process. It is not a molecular transformation but is undoubtedly determined by them, in particular by the process of reduplication of the deoxiribonucleic acid (DNA) macromolecules.

The processes of ordering (and the reverse processes of disordering) in the non-living matter are well known in physics. The examples of such phenomena are the well studied processes of the condensation of gases and crystallization of liquids, the ordering in binary alloys, the transitions of some substances from paramagnetic into ferromagnetic state etc. It is to be emphasized that the increase of the amount of information in the case of a phase transition, e.g., in the case of crystallization, is also endogeneous. The specificity of the structure of molecules allows them to build up a crystalline lattice under definite thermodynamical conditions. The crystallization is accompanied by a decrease in the entropy of the substance and occurs in the non-isolated system owing to an increase in the entropy of a cooler. The condition for the transition is the equality of the thermodynamic potentials of the liquid and crystal. The thermodynamics itself cannot explain the mechanism of the ordering, of the phase transition. The break of the thermodynamical functions occurring at the phase transition point can be explained statistically if two conditions are fulfilled. Firstly the ensemble considered must contain a very large number of units and secondly these units must interact and their interaction must depend on the state of the whole system. Such an ensemble is called cooperative, the processes of ordering are principally cooperative. To use the cybernetical language, cooperativity means the existence of some feedback—the interaction of the ensemble units leads to the changes of its state, but the change in the state of he system changes the interaction. In this sense the cooperative process is autocatalytic. The treatment of

the cooperativity as a kind of feedback establishes the region of unification of molecular physics with the information theory.

We can now formulate the following general thesis. The biological processes are characterized by the changes of ordering. Such processes in the non-living nature are cooperative. Therefore the biological processes are cooperative too. Their molecular theory is the theory of cooperative phenomena (3). Let us try to argue this statement.

The fundamental biologically active substances in organisms are the biopolymers —proteins and nucleic acids. These are macromolecular substances, therefore molecular biophysics is first of all macromolecular biophysics. The macromolecularity of biological substances is by no means accidental. The linear polymeric structure of biomolecules plays the fundamental biological rôle, determined by the following factors (4).

1. The macromolecules possess a high level of individuality with the simultaneous conservation of the integrity and continuity of their structure. This level is determined by chemical and stereochemical distribution of the links in the polymeric chain and by multiformity of the configurations of the chain as a whole. In general the macromolecules do not submit to the law of the conservation of composition and structure.

2. The important changes in the structure of the links can occur without any disturbance of the structure of the chain as a whole.

3. The multiplicity of the primary, secondary etc. structures of the macromolecules determines the possibility of the storage of a large amount of information and of its transmission.

4. The macromolecules are characterized by a great variability of structure and properties on the overmolecular level. Here the big values of relaxation times in the macromolecular systems are important. Therefore the nonequilibrium structures are very stable in many cases.

5. The macromolecules possess the ability of transforming the chemical energy to mechanical work and vice versa and therefore determine the existence of mechanochemical systems working in isothermic and isobaric conditions. This ability is connected with the changes of charges in the side groups of the macromolecules (polyelectrolytes) or with chemical reactions in the chains (for example—the division of the double helix of DNA in the course of its reduplication (5)).

6. The macromolecules possess special possibilities of taking part in the irreversible processes, occurring in the open systems. These possibilities are connected with the large number of internal degrees of freedom, that is of the configurational lability of polymeric chains.

These factors were studied in (4) but the following should be added. A linear polymeric chain possessing configurational lability (flexibility) is able to change its

secondary structure in a cooperative way. The helix-coil transitions (the intramolecular melting, discovered by Doty in synthetic polypeptides and polynucleotides and also in proteins and nucleic acids (6)) are precisely this.

As it is shown by the configurational statistics of polymeric chains, they are cooperative rotational-isomeric systems (7). The flexibility of a macromolecule, which determines the secondary and tertiary structure, arises in consequence of the possibility of the existence of every link of the chain in a number of discrete positions with different energies. These positions differ by the angle of rotation around single bonds, i.e., they are rotational isomers. The internal rotations in the chain are cooperative—the realization of a definite conformation of a given link depends on the conformations of neighboring links. The theory of the physical properties of macromolecules confirmed by experiment is based on considerations of the cooperative rotational isomerism. In particular the stretching of the polymeric chain by the action of external force (the fundamental process in the physics of rubber elasticity and perhaps in the physics of muscular action too) occurs as a cooperative process of rotational isomerization (7).

A definite order is already contained in the molecule of a synthetic homopolymer in the sense of a fixed monotonous sequence of links. Such a macromolecule does not store any specific information analogous to the information stored in the primary structure of DNA, but the information in the macromolecule is higher than in the totality of the single monomers. The reaction of polymerization in a condensed phase proceeds in many cases as a typical cooperative process (8). One should think therefore that biosynthesis—the creation of a fixed primary structure of a biopolymer—has to be treated as a cooperative transition from the system of monomers in solution to the chains. Biosynthesis of proteins and nucleic acids proceeds on a template, which plays the role of a "cooperator" (3). Thus not only the transformations of the secondary structure, but the irreversible chemical synthesis of biopolymers also can be investigated on the basis of the theory of cooperative phenomena.

The mathematical modeling of cooperative processes is well developed now for statistical-thermodynamical problems of the physics of linear polymers. The model of Ising is used here introduced by him in 1925 for the constructing the theory of ferromagnetism (9). The Ising model did not lead to a decisive success in this field as the statistical description of ferromagnetic phenomena requires a three-dimensional model. The strict calculations in this case meet insurmountable mathematical difficulties (contemporary theory based on Ising's model is treated in (10, 11, 12)). On the contrary, the one-dimensional model is quite applicable in the theory of linear polymers and consequently we can use here very simple methods of calculation. Let us examine as an illustration the one-dimensional model of the ferromagnetic. Let us assume that we have a linear ensemble of spins, which can have only two orientations—to the right and to the left. The neighboring particles interact and

the energy of interaction of two antiparallel spins is ϵ and of two parallel spins $-\epsilon$. The energy is equal to

$$E_{ik} = -\epsilon\sigma_i\sigma_k\,\delta_{ki\,i+1} \tag{1}$$

$\sigma_i, \sigma_k = 1$ for the spins looking to the left and -1 for the spins looking to the right, $\sigma_{k,i+1}$ is Kronecker's symbol. If a magnetic field H acts on the particles then each of them will have additional energy $-\mu H\sigma_i$(μ is the magnetic momentum of the particle). The partition function of a system containing N particles in the magnetic field will be

$$Z = \sum_{\sigma_1=\pm 1} \cdots \sum_{\sigma_N=\pm 1} \exp\left\{\frac{\epsilon}{kT}\sum_{i=1}^{N-1}\sigma_i\sigma_{i+1} + \frac{\mu H}{kT}\sum_{i=1}^{N}\sigma_i\right\} \tag{2}$$

The cooperativity is described by the factors $\sigma_i\sigma_{i+1}$. Using the cyclic condition $\sigma_{N+1} = \sigma_1$ one can write (2) in the form

$$Z = \sum_{\sigma_1=\pm 1} \cdots \sum_{\sigma_N=\pm 1} \prod_{i=1}^{N} P(\sigma_i, \sigma_{i+1}) \tag{3}$$

where $P(\sigma_i, \sigma_{i+1})$ are the elements of a matrix of second rank

$$P(\sigma_i, \sigma_{i+1}) = \exp\left\{\frac{\epsilon}{kT}\sigma_i\sigma_{i+1} + \frac{\mu H}{kT}\sigma_i\right\} \tag{4}$$

The matrix is

$$\mathbf{P} = \begin{bmatrix} e^{a+b} & e^{-a+b} \\ e^{-a-b} & e^{a-b} \end{bmatrix} \tag{5}$$

where $a = \epsilon/kT$, $b = \mu H/kT$. It follows from (3)

$$Z = \text{spur}\,(\mathbf{P}^N) = \lambda_1{}^N + \lambda_2{}^N \tag{6}$$

where λ_1, λ_2 are the eigenvalues of the matrix. If $N \gg 1$ and $\lambda_1 > \lambda_2$, then

$$Z \cong \lambda_1{}^N \tag{7}$$

In this way the partition function can be written analytically by means of the maximal root of some matrix. Knowing Z we can determine the thermodynamical functions of the model.

We have to emphasize that the calculation of the one-dimensional model for the stretching of polymeric chain is wholly analogous to the above calculation. We have only to put instead of the field H the stretching force f and instead of μ the length of the link l. The quantity 2ϵ plays the role of the difference of the energies of two rotationed isomers (7).

In accordance with the statement of L. D. Landen (13) the one-dimensional model is not suitable for the description of the phase transitions. This model however corresponds to the behavior of linear polymers. Thermodynamical transformation of state of the macromolecule is not a real phase transition but in the case of a high degree of polymerization can be very sharp and practically indistinguishable

from the phase transition. The treatment of the macromolecular transformation is adequate with the application of the one-dimensional Ising model. This model was at first applied in the polymer physics in the development of the configurational statistics of macromolecules (7). Subsequently the same model was successfully used in the theory of helix-coil transitions of biopolymers and analogous synthetic substances (14, 15, 16, 17, 18). Finally the same one-dimensional model was applied to the description of a biosynthetic process, that of the reduplication of the double helix of DNA (19–23). The physical idea used in these works is the following one. The new DNA chains are built by means of polycondensation of the activated nucleotides onto a template consisting of the DNA chains arising by the division of the initial Watson-Crick's double helix. The division of the helix and the polycondensation are treated as a united process. The binding of the nucleotides to the template by means of hadrogen bords is not cooperative. The cooperativity of the process is expressed in the postulated possibility of polycondensation only in such cases when two neighboring units of the template are occupied by "suitable" nucleotides. The theory gives the conditions of reduplication and denaturation of DNA. Both processes proceed very sharply, similarly to a phase transition of the first kind, if the polymerization degree is of the order 10^3.

The methods of modeling and calculation based on the Ising's model are the simplest and strictest methods for investigations of problems connected with the synthesis and transformations of biopolymers. Other methods of treatment of the cooperative phenomena (e.g. the method of Bragg and Williams, of Kirkwood, etc. See (23)) give approximate results and are suitable mainly for the purposes of giving the obvious and qualitative description.

Let us consider now some new results obtained in the theoretical study of mechanochemical processes. Mechanochemistry is of fundamental importance in biology since every biological phenomenon is determined not only by the chemical synthesis of some structures, but also by their displacement in space. This displacement possess the character of directed and not of statistical thermical motion.

The general principle of polymer mechanochemistry consists in the dependence of the course of chemical reaction (particularly electrochemical) performed by the links of a polymeric chain (or by the particles absorbed on them) on the change of the spacial arrangement of the chain. Two types of models are now used to the theory of motility of muscles and cells.

Models of the first type are based on the assumption of uncoiling and coiling of polymeric chains (see, e.g. (24)); models of the second type on the relative translational motion of the chains (see, e.g. (25)). T. M. Birshtein, V. I. Vorobiev and O. B. Ptitsyn have shown (26) that the models of the first kind can operate only if they are cooperative systems. The shortening or the elongation of the chain alters the relative positions of the side groups of the chain or of the molecules and ions absorbed by them. If the chemical (or electrochemical) reactions between these

groups and the reagents of the medium depend on the relative positions of the groups, that is they are cooperative, then the equilibrium constant of the reaction will be changed in the course of shortening or elongation of the chain. On the other hand the length of the chain for the given force will depend in this case on the degree to which the chemical reaction has proceeded. It is to be emphasized that such a mechanism is possible only under the condition of the cooperativity of the chemical reaction mentioned above.

In the simplest case the cause of the mechano-chemical process can be the reaction consisting of the ionization of a polybase or of a polyacid. Kuhn, Katchalsky and Hargitay (27) and also other investigators have observed the change in the length of a loaded polyelectrolitic fibre in the course of changing the pH of the surrounding medium and Kuhn (see (28)) and Vorobiev (29) have observed the change of pH of the medium in the course of elongation of the fibre. The cause of these phenomena consists in the dependence of the dissociation constant of the ionizable groups which are near one to another on their mutual distances, which are changed by the elongation of the chain. It also follows from this dependence that the potentiometric titration curves of the polymer must deviate from the titration curves for the monomer. This question has been investigated both theoretically (30, 31, 32) and experimentally (33, 34).

The length of a polymeric chain stretched by the force f is equal to (7):

$$\bar{x} = \frac{f}{3_k T}\,\overline{h^2} \tag{8}$$

where $\overline{h^2}$ is the mean square length of the distance between the ends of the chain. As it was shown in (35) if the stretching force is not extremely small (not smaller than $kT/(\overline{h^2})^{1/2}$), the equation (8) contains only $\overline{h^2}$, calculated by taking into account only the interactions of the groups which are the nearest one to another along the chain. The change of pH of the medium and therefore the change of the degree of ionization can alter the value of $\overline{h^2}$ and $\bar{X}$ very strongly at the given force f.

On the other hand, as it was shown in the work (26), the change of pH during the elongation of the chain with a constant degree of ionization α is equal to

$$\Delta pH = -\tfrac{3}{2}\gamma^2 \frac{\overline{h_0^2}}{\overline{h^2}} \frac{d \ln \overline{h^2}}{d\alpha} \tag{9}$$

where γ is the ratio of $\bar{X}$ to the maximal length of the chain and h_0^2 is the mean square of the distance between the ends of a chain with free internal rotation. Here we have

$$\frac{d \ln \overline{h^2}}{d\alpha} \sim \frac{\Delta u_e}{_k T}\,\alpha \tag{10}$$

where ΔU_e is the difference of energies of the electrostatic interaction of charged groups in the stretched and coiled conformations of the monomeric units. In the absence of cooperativity $\Delta U_e = 0$ and $\Delta pH = 0$. If $\overline{h^2}$ increases as α increases, that

is the electrostatic repulsion of charged groups stabilizes the elongated conformations of monomeric units, the pH will decrease in the course of stretching; similarly if $\overline{h^2}$ decreases as α increases then the pH will increase. The equation (9) shows that $|\Delta pH|$ max $\sim \Delta pK$ (pK is the change of the dissociation constant of the ionizable group of the polymer brought about by the charging of the chain), that is the changes of pH can reach high values ($\sim$1).

All the above treated problems are related to the physical-mathematical modeling of the molecular biophysical processes with the aim to establish their statistical thermodynamical conditions. The study of the kinetics of cooperative biophysical phenomena is perhaps much more interesting. However the kinetics of cooperative phenomena are not yet as well developed as their statistical thermodynamics. The cooperativity must clearly bring about important deviations of the kinetic laws from the simple relations which are valid for non-interacting particles. In particular the equation of Arrhenius which is the fundamental relation in the case of the usual kinetics is not valid in the case of cooperative interactions. It must be emphasized that the sharpness of thermodynamical transitions in cooperative systems does not mean that such transitions must occur with an anomalously high rate analogous to an explosion. Thus, the rate of crystallization can be very small, depending on a series of factors, e.g., on the rate of supplying of crystallizable substance and on the rate of cooling etc.

In the works of Bogoliubov, Green, Kirkwood and other authors (see, e.g., (36, 37)) kinetic equations are treated which describe the transport phenomena in gases and liquids. These equations contain as the parameters of state the continuously changing coordinates and impluses of the interacting particles. In applications to the problem of the kinetics of biosynthesis on a template we can use simpler models without great mathematical difficulty. We can construct here models containing parameters of state which can have two or more discrete values (38).

Let us consider a system containing N units with correlated states. Such units can be for instance the sites of a template used for a chemical reaction. Let us assume that the probability of the change of state of every unit depends not only on its state but also on the states of the neighboring units. In the same time we assume that this probability does not depend on the transitions of the neighboring units, that is we consider only single transitions. The full distribution function of all the units over their states $F(\alpha_1, \alpha_2, \ldots \alpha_N) = F\{\alpha\}$ must satisfy the kinetic equation

$$\frac{dF\{\alpha\}}{dt} = -F\{\alpha\} \sum_j \sum_{\alpha_j' \neq \alpha_j} w_{\alpha_j \to \alpha_j'}(\{\alpha\}, \alpha_j') + \sum_j \sum_{\alpha_j' \neq \alpha_j} F(\alpha_1, \alpha_2, \cdots \alpha_{j-1}, \alpha_j', \alpha_{j+1}, \cdots \alpha_N) w_{\alpha_j' \to \alpha_j}(\{\alpha\}, \alpha_j') \qquad (11)$$

where $w_{\alpha_j \to \alpha_j'}(\{\alpha\}, \alpha_j')$, the probability of transition of the unit j from the state α_j; to the state α_j'; depends on α_j, α_j' and generally speaking on the states of the neigh-

boring units. Let us introduce the partial distribution functions of the n-th order, depending on the states of n units

$$F^{(n)}(\alpha_{i_1}, \alpha_{i_2} \cdots \alpha_{i_n}) = \sum_{(k \neq i_1, i_2 \cdots i_n)} \cdots \sum_{\alpha_k} F\{\alpha\} \tag{12}$$

The kinetic equations for the partial functions of distribution of different orders are obtained by the corresponding summations in the equation (11). We get a system of equations. The first equation of the system is

$$\frac{dF^{(1)}(\alpha_i)}{dt} = -\sum_{\alpha_{i_1} \cdots \alpha_{i_s}} F^{(s+1)}(\alpha_i, \alpha_{i_1} \cdots \alpha_{i_s}) \sum_{\alpha_i'} w_{\alpha_i \to \alpha_i'}(\alpha_i, \alpha_i', \alpha_{i_1} \cdots \alpha_{i_s})$$
$$+ \sum_{\alpha_{i_1} \cdots \alpha_{i_s}} \sum_{\alpha_i'} F^{(s+1)}(\alpha_i', \alpha_{i_1}, \cdots \alpha_{i_s}) w_{\alpha_i' \to \alpha_i}(\alpha_i', \alpha_i, \alpha_{i_1} \cdots \alpha_{i_s}) \tag{13}$$

Here z is the number of units interacting with the given one. For a linear cooperative system of type of a macromolecule $z = 2$ since only the neighboring units are interacting in this case. The equations for such a system are

$$\frac{dF^{(1)}(\alpha_i)}{dt} = -\sum_{\alpha_{i-1}, \alpha_{i+1}} F^{(3)}(\alpha_{i-1}, \alpha_i, \alpha_{i+1}) w_{\alpha_i \to \alpha_i'}(\alpha_{i-1}, \alpha_i, \alpha_i', \alpha_{i+1})$$
$$+ \sum_{\alpha_{i-1}, \alpha_{i+1}} F^{(3)}(\alpha_{i-1}, \alpha_i', \alpha_{i+1}) w_{\alpha_i' \to \alpha_i}(\alpha_{i-1}, \alpha_i', \alpha_i, \alpha_{i+1}) \tag{14}$$

$$\frac{dF^{(2)}(\alpha_i, \alpha_{i+1})}{dt} = -\sum_{\alpha_{i-1}} F^{(3)}(\alpha_{i-1}, \alpha_i, \alpha_{i+1}) w_{\alpha_i' \to \alpha_i}(\alpha_{i-1}, \alpha_i, \alpha_i', \alpha_{i+1})$$
$$- \sum_{\alpha_{i+2}} F^{(3)}(\alpha_i, \alpha_{i+1}, \alpha_{i+2}) w_{\alpha_{i+1} \to \alpha'_{i+1}}(\alpha_i, \alpha_{i+1}, \alpha'_{i+1}, \alpha_{i+2})$$
$$+ \sum_{\alpha_{i-1}} F^{(3)}(\alpha_{i-1}, \alpha_i', \alpha_{i+1}) w_{\alpha_i' \to \alpha_i}(\alpha_{i-1}, \alpha_i', \alpha_i, \alpha_{i+1})$$
$$+ \sum_{\alpha_{i+2}} F^{(3)}(\alpha_i, \alpha'_{i+1}, \alpha_{i+2}) w_{\alpha'_{i+1} \to \alpha_{i+1}}(\alpha_i, \alpha'_{i+1}, \alpha_{i+1}, \alpha_{i+2}) \tag{15}$$

etc.

We can solve such a system of equations using the method of successive approximations. The approximation of the order zero does not take the cooperativity into account. In the first approximation the function of the n-th order is expressed by the product of functions of the first order. To obtain the functions $F^{(1)}(\alpha)$ in the second approximation we have to put the functions $F^{(z)}$ of the first approximation into the initial system of equations and get $F^{(z+1)}$ in the second approximation. Putting the $F_2^{(z+1)}$ thus obtained into the equation for $F^{(1)}$ we get $F^{(1)}$ in the second approximation etc. Let us illustrate this method by the help of a model of biopolymer synthesis on a template. We assume that every site of the template can be in two states—in the free state α' and in the state occupied by a monomer α. The transition $\alpha' \to \alpha$, the absorption of a monomer, is considered as a non-cooperative process but the separation of monomer is considered impossible if one of the neigh-

boring sites of the template is also occupied by the monomer. We get in the first approximation.

$$\frac{d\nu_1}{dt} = -\nu_1[k - K\nu_1(1 - \nu_1)] \tag{16}$$

Here $\nu_1^{(1)}(\alpha')$ is the relative number of sites in the "excited" state α',

$$k = w_{\alpha_i'\to\alpha_i}(\alpha_{i-1}, \alpha_i', \alpha_i, \alpha_{i+1})$$

$$= w_{\alpha_i'\to\alpha_i}(\alpha'_{i-1}, \alpha_i', \alpha_i, \alpha_{i+1}) = w_{\alpha_i'\to\alpha_i}(\alpha'_{i-1}, \alpha_i', \alpha_i, \alpha'_{i+1})$$

$$K = w_{\alpha_i\to\alpha_i'}(\alpha_{i-1}, \alpha_i, \alpha_i', \alpha_{i+1})$$

Other probabilities of transitions are equal to zero.

In the second approximation

$$\frac{d\nu_2}{dt} = -k\nu_2 + KF_2^{(3)}(\alpha', \alpha, \alpha') \tag{17}$$

We obtain $F_2^{(3)}$ from the system of equations

$$\frac{dF^{(3)}(\alpha', \alpha, \alpha')}{dt} = -(K + 2k)F^{(3)}(\alpha', \alpha, \alpha') + kF^{(3)}(\alpha', \alpha', \alpha')$$

$$\frac{dF^{(3)}(\alpha', \alpha', \alpha')}{dt} = -3kF^{(3)}(\alpha', \alpha', \alpha') + KF^{(3)}(\alpha', \alpha, \alpha')$$

$$+ 2KF^{(4)}(\alpha', \alpha, \alpha', \alpha') \tag{18}$$

Putting into it $F^{(4)}(\alpha', \alpha, \alpha', \alpha')$ in the first approximation, that is

$$F_1^{(4)}(\alpha', \alpha, \alpha', \alpha') = F_1^{(1)}(\alpha)[F_1^{(1)}(\alpha')]^3 = \nu_1^3(1 - \nu_1) \tag{19}$$

If $k > K$, the second approximation is practically equivalent to the first one. However if $k << K$ the convergence of the method is much worse and we have to use the more exact superpositional approximation, in this case (36). For a linear cooperative system in the equilibrium state the condition fulfilled is

$$F^{(n)}(\alpha_1, \alpha_2, \cdots \alpha_n) = \frac{\prod_{i=1}^{n-1} F^{(2)}(\alpha_i, \alpha_{i+1})}{\prod_{i=2}^{n-1} F^{(1)}(\alpha_i)} \tag{20}$$

This gives us the possibility to look for the unequilibrium function in the same form.

The application of the method outlined here allowed us to model the kinetics of reduplication of DNA. The cooperativity considerably increases the rate of biosynthesis. In connection with this problem we have to investigate the following question. The rate of reduplication of DNA is limited by the time necessary for the division, that is the unwinding, of the DNA double helix. Kuhn (39) treated this process as a simple combination of rotational and translational diffusion while Longuet-Higgins and Zimm (40) proposed taking into account the gain of eutropy

due to the many configurations of the flexible chains of DNA becoming free. As a result the rotational torque is created which increases the rate of unwinding. However, the model considered in the work (40) suits the denaturation but not the reduplication of DNA. The torque produced by the reduplication is due to the gain of free energy in the process of synthesis of the new double helices. The general principle of the polymer mechanochemistry is realized here, according to which the chemical reaction in the chain can produce a mechanical motion, performed in the cooperative way, link after link. The calculation shows that a very small fraction of the free energy gained in the reduplication is sufficient to provide the necessary rate of the process.

The results of the theoretical study of some biophysical problems outlined here show that the theory of cooperative processes is particularly fruitful in this field of science. The results described have been obtained in the last few years and they are in general of a preliminary character. It is quite clear that the further development of the theory of cooperative processes is very important. It should be emphasized that these ideas are not adequately used enough in physics of non-living matter. Very general considerations show that any physical or chemical processes occurring in a condensed phase are cooperative. The contemporary theory of liquids and solids, the theory of chemical reactions in condensed phases (particularly polymerization (8)) barely consider the cooperativity and are therefore not-adequate to the reality. Evidently the development of the theory of cooperative processes represents the next task in the development of molecular physics.

The analogy between biosynthetic processes and the processes of the transformations of biologically-functioning substances on one hand and the phenomena of phase transitions on the other, is not superficial. Such an analogy has been used for a long time. Hourowitz, in introducing his hypothesis of the biosynthesis onto a template spoke about its similarity to crystallization (41). Hinshelwood used the same analogy in his treatment of the autocatalysis in an open biological system (42). In reality we have to speak not about an analogy but about the true unity of the corresponding mechanisms. Molecular physics allows us to understand the nature of fundamental biological phenomena occurring on the molecular level. At the same time the study of biological problems enriches the molecular physics and opens the way to a new approach to non-biological problems.

We can express confidence that the phenomena realized in biological systems on the overmolecular level can also in principle be studied based on the same general ideas.

The region of molecular biophysics treated here does not practically meet any quantum mechanical questions. We are concerned here with classical physics, which is natural enough since the biopolymers are systems, containing very large numbers of atoms and functioning at sufficiently high temperatures. Such systems do not manifest any quantum—mechanical effects in many of their properties.

Quantum mechanics is indispensable however if we investigate the specific chemical, optical or electromagnetic properties of a biological system or of its model, or if we investigate the problems of the energy migration etc.

The mathematical modeling of biophysical mechanisms is not an end in itself. Its aim is to elucidate the real nature of biological processes. We have seen that the methods of molecular physics are very fruitful here and it is clearly premature to speak about the limits of application of the usual, non-biological physics to biological problems.

SUMMARY

The theoretical methods of investigation of the molecular problems of biophysics are treated on the basis of the theory of cooperative processes. Biopolymers are cooperative rotational-isomeric systems and their structural transformations and biosynthesis onto a template can be studied by means of the one-dimensional Ising model. Examples of such a study are the processes of helix-coil transitions and of the DNA reduplication. The same ideas are successfully applied in the theory of mechanochemical polymer processes. A general method for the treatment of the kinetics of cooperative processes is described and illustrated by the kinetics of biosynthesis on a template. The analogy between biological processes on the molecular level and phase transitions represents the real nature of biological phenomena.

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