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On the Concept of the Nonequilibrium Conformon (Self-Organization of a Selected Degree of Freedom in Biomolecular Systems)

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Abstract. A concept of the conformon as a dynamical bound state formed by a flux of particles interacting with conformational degrees of freedom is proposed. The correlation of variables of the subsystems composing such a formation are considered.

Key words: Electron(ion)-conformational interactions, chains of biological transport, biomolecular machines, correlations in hierarchical systems, nonequilibrium phase transitions in molecular objects, molecular synergetics.

Recently, the point of view on nonlinear processes referred to as 'synergetics' has come in for wider use in biophysics. At the macroscopic level, this approach may be regarded as universally accepted, although failing to avoid excessive claims (evidently provoking criticism of the weak constructive basis of the dissipative structure notion in biology, e.g. Blumenfeld [1]). Nowadays, synergetic ideology has started penetrating the area of molecular organization, because a more adequate approach to the understanding of the functioning of molecular machines seems hardly possible. In view of this, biomolecular processes of enzymatic catalysis, the function of the charge transport chain, and the phosphorylation processes associated with it are of vital interest and importance. In all such processes, the enzymatic function (regarded in a general sense) is essentially carried out by protein macromolecules, containing, apart from the active center, a large high-molecular portion (globule) whose role is far from passive. Its main feature consists of conformational lability (in a figure of speech, a protein is 'a sack of conformations').

Numerous and effective experimental investigations removed all doubts that it is this property which determines the unique functioning efficacy of protein com-

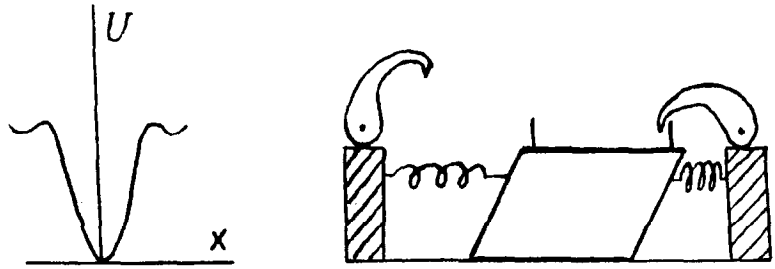

Fig. 1. Typical shape of the conformational potential and mechanical analogy to the 'protein-machine' concept [3].

plexes. Attempts to develop general principles and to determine physical mechanisms by which conformational degrees of freedom participate in this function (models of induced structural correspondence, rack model, energy recuperation hypothesis, etc. [1]), have been known for a long time.

Gradually, these qualitative ideas were shaped into a hypothesis on the presence in protein-enzyme of the so-called selected degree of freedom of a mechanical nature, having a key role in the processes of energy accumulation and utilization during the transformations in an enzyme-substrate complex [2]. It was postulated that all the multiplicity of protein conformational transformation may be schematically reduced to a one-dimensional mechanical process with a nonlinear potential along the reaction coordinate, which is, in fact, represented by a generalize conformational coordinate assumed to be weakly dissipative. In this case, the protein-enzyme function is similar to the function of a construction with one degree of freedom – a machine with detaining barriers etc. (the' protein-machine' concept [1–3]) (see Figure 1).

Further development of these ideas naturally advanced towards specifying the emergence of such potential profiles and the initiation of motion in them at the expense of electron-conformational (mainly for transport chains) or enzyme-substrate interactions. This resulted in the emergence of the model of the functioning of the molecular carrier-'transformer' [3–5] and in the relaxation concept of the elementary act in enzymatic catalysis [1,4] being conceptually very close. The 'transformer' scheme of functioning is clear from Figure 2.

The energy taken from the electron and accumulated in the elastic deformation (conformation) of the macromolecule, is spent in the coupled endoergic process (ATP synthesis, active transport, etc.) at, say, stage IV. Here, it performs the role of a primary macroerg, i.e. as a universal energy portion used in bioenergetics. While these patterns were under discussion, the problem arose of the characteristics of the formation initiated by a charge coming to a molecule and being essentially a

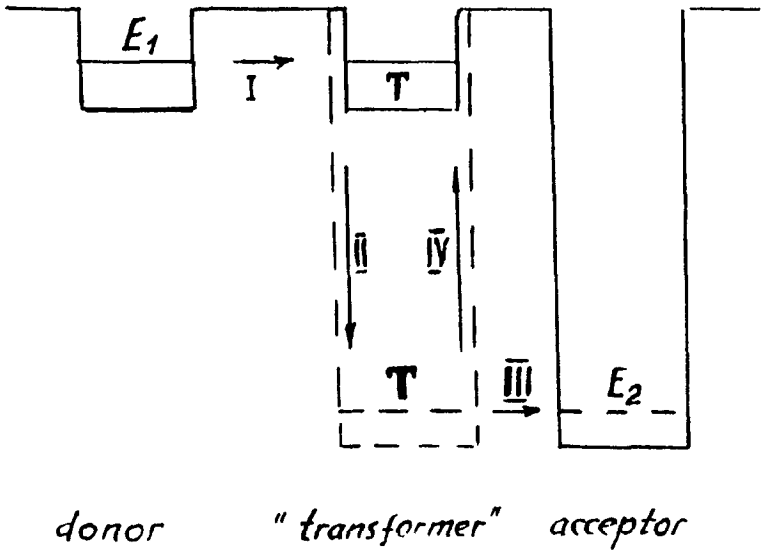

Fig. 2. 'Four-step' performance regime of carrier-transformer T [3]. $T°$, T^- states describe the 'initial', and $\mathbf{T}^-$, $\mathbf{T}°$ – the 'final' conformations ($\mathbf{T}°$ and T^- are metastable). Electron transitions I, III may be of a tunnel-like nature.

polaron on a macromolecule scale. Indeed, such a 'conformon' ([6], see also [7,8]), i.e. a local conformational transformation of a functional nature, may (as estimated in [3]) accumulate and utilize the energy of ~ 0.5 eV, with dimensions of ~ 20 Å and more, and characteristic frequencies in the EHF range, etc.

The above models are useful in interpreting the fundamental role of charge (substrate)-conformational interactions in the biochemical elementary act. At the same time, they immediately suggest many questions on kinetics (the conjugation of rapid processes of charge transport and slow conformational motions, the necessity for special dissipation mechanisms, and so on), hindering both their acceptance and utilization. For this reason, the following explanation may be suggested. Although the authors emphasize (see, e.g., extensive remarks given in the context of relaxation model in Section 6.5 of [1]) the necessity of essentially nonequilibrium conditions for the functioning of the suggested mechanisms, nevertheless, in their models, nonequilibrity is mostly of a relaxation nature, and does not represent a creative factor. It may be possible to eliminate this drawback, noticeable as it is, by a more modern formulation of the problem.

Along this line, we want to introduce one of the first examples of that kind, namely a recently suggested nonlinear model of a self-organized system of charge transport [9]. Although developed for the description of the peculiarities of ion current through the potential-dependent membrane channels, it admits a broader interpretation. Its distinctive feature consists of explicitly accounting for the influence of the density of charges passing through the transport system upon the formation

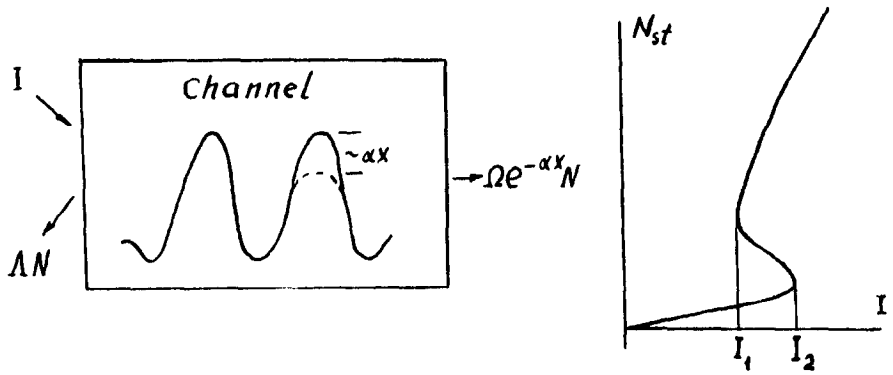

Fig. 3. (*left*) I-particle flux ('pumping') supplied to the system. ΛN – withdrawal of particles that have not passed through the channel. $\Omega e^{-\alpha x} N$ – the flux that has passed. The channel is presented by the double-barrier model with population N and the height of one of the barriers depending on the conformational coordinate x. (*right*) The bifurcation curve at $\Omega/\Lambda > e^2$.

of this system (e.g., upon the conformation of channel molecular groups, in turn, determining the conditions of passing through the channel). Such self-consistency can be illustrated by two equations (1) with a single nonlinear coupling (see also Figure 3)

$$\begin{aligned} \frac{dN}{dt} &= I - (\Lambda + \Omega\, e^{-\alpha x})\, N\,, \\ \frac{dx}{dt} &= -kx + \chi N\,, \end{aligned} \tag{1}$$

where x is a conformational coordinate (overdamped oscillator) coupled to an average number N of particles in the channel. Λ, Ω, and k are the corresponding kinetic rate constants and α, χ the constants of coupling. If $\Omega/\Lambda > e^2$, stationary solutions of the system (1) exhibit a bistable behaviour within a certain area of values of the control parameter (pumping I).

In this case, the magnitude of channel-passing current may greatly vary (channel self-blocking, operation by the yes-no principle, etc.). Relative probabilities of the realization of 'closed' and 'open' states can be found if we extend the slaving principle [10] to the adiabatic elimination of variable $N(t)$ (assuming it to be quickly altered as compared to $x(t)$, which has a physical justification [9]).

Hereafter, the second of Equations (1) reflects the motion in a self-consistent potential

$$\Psi(x) = kx^2/2 + \chi I \int_0^x dy(\Lambda + \Omega\, e^{-\alpha y})^{-1}\,,$$

acquiring the second minimum with the growth of pumping I and further transforming into a ground state from a metastable one (Figure 4). The picture is typical for the nonequilibrium phase transition of the first kind and, in explicit form, we

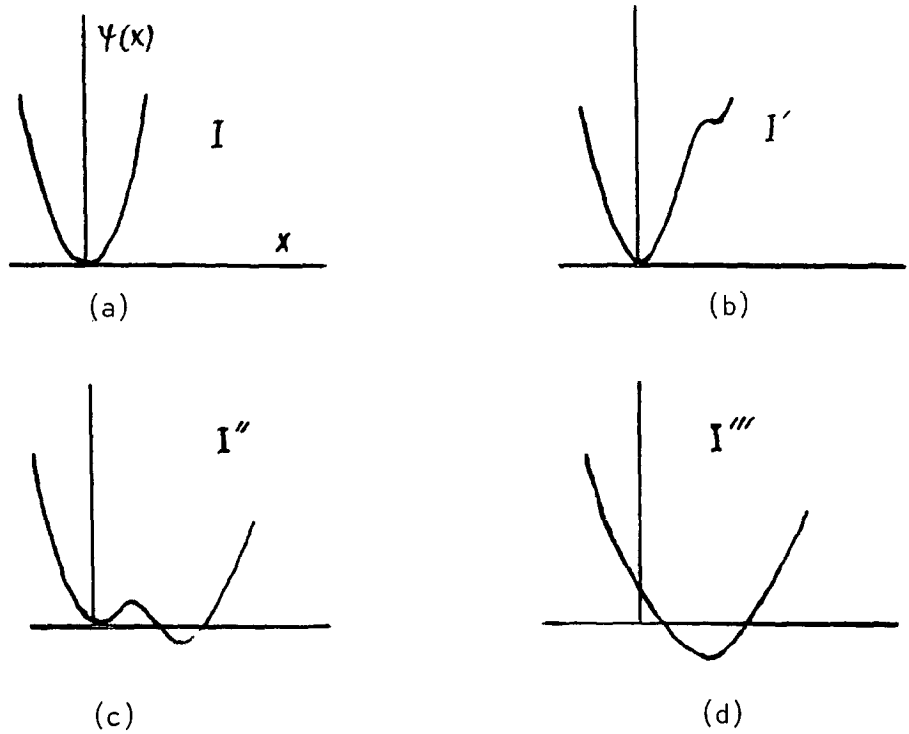

Fig. 4. (a) $I < I_1$; (b) $I_1 < I' < I_2$; (c) $I_1 < I' < I'' < I_2$; (d) $I_2 < I'''$.

trace the formation of the order parameter (the selected degree of freedom) represented, in this case, by the conformational subsystem, as well as the development of a nonlinear potential, 'catches', etc., postulated in the 'protein-machine' concept. Thus, removing the stress from the flux characteristics to the conformational one in the model discussed, we see that the functional role of the conformational characteristics may fully comply with all the demands imposed upon the selected degree of freedom (conformon) in the above model. A particular development of such ideas of a conformon demands special investigation (one interesting possibility is to be found in the closure of the conformational coordinate on the second (e.g., flux) variable, which would greatly enlarge the application aspect of the model).

Thus, in the above sense, the conformon represents a coherent self-organized formation (a form of dynamic bound state), created under nonequilibrium conditions due to the interaction between two subsystems of different natures (frequently hierarchically separated in time). Though such a definition is in full agreement with the terminology assumed in synergetics, we would like to dwell on certain aspects in more detail, namely on the meaning of the notions 'self-organized' and 'coherent'. The first term is as intuitively clear as it is difficult to be formalized. In the long run, in view of this, situations emerge when, say, the self-organization direction may be determined with accuracy to the opposite one and in cases which are

standard enough (see, e.g., the discussion of the degree of organization of laminary and turbulent flows in [11, 12]). The efforts undertaken to establish the quantitative criteria of self-organization by entropy characteristics [11] have not yet offered reliable results (see [12, 13]). The term 'coherent' seems better defined, however. When used in biology, it often acquires a qualitative sense only, i.e. determines the relation between different parts of the system. Meanwhile, strictly speaking, it would be reasonable to form a judgement on coherence only when the processes of its destruction are taken into account. The corresponding procedures and statistical quantitative characteristics are well known. From this standpoint, the model under study, in the simplest case based upon Equations (1), will be considered.

Thus, introducing Langevin-type stochastic forces in dynamic equations

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= I - (\Lambda + \Omega\, \mathrm{e}^{-\alpha x})\, N + f_{LN}\,, \\ \frac{\mathrm{d}x}{\mathrm{d}t} &= -kx + \chi N + f_{Lx}\,, \end{aligned} \tag{2}$$

we intend to reveal the behaviour of the statistical characteristics depending on the control parameter represented again by pumping I. The stationary function of the correlation of fluctuations of variables $\langle \Delta x\, \Delta n \rangle$ is the most trivial of these characteristics; when divided by mean-square deviations, it presents a mutual correlation coefficient, or the 'degree of coherence' $K(I)$ we are interested in

$$K = \frac{\langle \Delta x\, \Delta n \rangle}{[\langle (\Delta x)^2 \rangle\, \langle (\Delta N)^2 \rangle]^{1/2}}\,, \tag{3}$$

whose modulus is in the segment from 0 (complete independence of variables) to 1 (complete 'coherence').

In the general case, the solution of both stochastic equations (2) and the Fokker–Planck equation corresponding to them, is rather difficult. However, our prime interest is in a particular case of temporal hierarchy in the system expressed by the inequality $\Lambda \gg k$ (slow rate of conformational coordinate changes as compared to the rate of change in the flux). If it is fulfilled, the system behaves as predicted from the point of view of self-organization as interpreted by Haken ([10], Chapt. 7). However, Haken's slaving principle, based on the possibility of adiabatic elimination of the fast variable (in this case $N(t)$) should be used with caution [13] for our purposes. As is shown by analysis, the simplest and the most informative variant of correlation investigations is associated with the system (2), where $f_{Lx} = 0$ and f_{LN} is a white noise (pumping fluctuations) of intensity D:

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= I - (\Lambda + \Omega\, \mathrm{e}^{-\alpha x})\, N + \sqrt{D}\, \xi(t)\,, \\ \frac{\mathrm{d}x}{\mathrm{d}t} &= -kx + \chi N\,, \quad \Lambda \gg k\,, \end{aligned} \tag{4}$$

$$\langle \xi(t) \rangle = 0\,, \quad \langle \xi(t)\, \xi(t') \rangle = \delta(t - t')\,. \tag{5}$$

Even in this case, it is hardly possible to write down an exact solution of the statistical problem. Therefore, one has to resort to the method of adiabatic elimination of the fast variable in the corresponding Fokker–Planck equation, though not in Haken's variant [10] where the investigation of the case (4) is impossible, but in one of the modifications of the 'noisy slaving' variant (i.e. the study of 'eliminated' variable noise [14], see also [15]). Such a procedure results in authentic qualitative results for the k value, improving with the approach to system instability and enhancement of inequality $\Lambda \gg k$ [13].

Thus, we seek a stationary distribution function $p(x, N)$ as a solution of the Fokker–Planck equation

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x}\left[(-kx + \chi N)\, p\right] - \\ -\frac{\partial}{\partial N}\left[(I - (\Lambda + \Omega\, \mathrm{e}^{-\alpha x})\, N)\, p\right] + \\ +\frac{D}{2}\,\frac{\partial^2 p}{\partial N^2} \tag{6}$$

corresponding to the system of stochastic differential equation (4), in the form of

$$p(x, N) = g(x)\; h(N/x)\,, \tag{7}$$

with normalizing conditions

$$\int g(x)\,\mathrm{d}x = 1\,, \quad \int h(N/x)\,\mathrm{d}N = 1\,. \tag{8}$$

Then, the averages of arbitrary function $\phi(x, N)$ look like

$$\langle \phi(x, N) \rangle = \int g(x)\,\mathrm{d}x \int \mathrm{d}N\, \phi(x, N)\; h(N/x) = \int g(x)\, \langle \phi \rangle_x\, \mathrm{d}x\,, \tag{9}$$

where $\langle \phi \rangle_x$ is a partial average. In the $h(N/x)$ function, due to the $\Lambda \gg k$ hierarchy, a slow variable x is considered as a fixed parameter. In this case, in order to find $h(N/x)$, Equation (6) may be reduced to the Fokker–Planck equation, corresponding to the first of Equations (4), with x taken as a parameter. Its (stationary) solution is*

$$h(N/x) = \frac{\mu(x)}{\sqrt{\pi D}}\, \exp\left[-\frac{\mu^2(x)}{D}\,\left(N - \frac{I}{\mu^2(x)}\right)^2\right]\,, \tag{10}$$

where $\mu^2(x) = \Lambda + \Omega\, \mathrm{e}^{-\alpha x}$. As it is seen from the detailed analysis [13–15], the equation for $g(x)$ in the adiabatic approximation can be obtained assuming

* For the sake of simplicity, we use 'natural' boundary conditions on both variables for h and g functions.

$\mathrm{d}N/\mathrm{d}t = 0$ in the first of Equations (4) and expressing $N(t)$ through $x(t)$ and $\xi(t)$ in the second of Equations (4). This results in a stochastic differential equation with multiplicative noise or in the Fokker– Planck equation

$$\frac{\partial g}{\partial t} = -\frac{\partial}{\partial x}\left[\mathcal{A}(x)\, g(x)\right] + \tfrac{1}{2}\,\frac{\partial^2}{\partial x^2}\left[\mathcal{B}(x)\, g(x)\right]$$

with stationary solution

$$g(x) = \frac{\mathcal{N}}{\mathcal{B}(x)}\,\exp\left\{2\int^{x}\left[\mathcal{A}(x')/\mathcal{B}(x')\right]\mathrm{d}x'\right\}. \tag{11}$$

Here

$$\mathcal{A}(x) = -kx + \frac{\chi I}{\Lambda + \Omega\,\mathrm{e}^{-\alpha x}}\,; \qquad \mathcal{B}(x) = \frac{\chi^2 D}{(\Lambda + \Omega\,\mathrm{e}^{-\alpha x})^2}\,.$$

In (11), the integral is expressed in elementary functions, but it has rather a bulky 'transcendent' form which is inconvenient for analysis. We shall return to this later. The character of $g(x)$ and k, which changes with the increase of pumping, can be traced in rough approximation. Judging from Figures 3 and 4, we can distinguish three areas of I variation from 0 to ∞: of very small and very large I, where the system is evidently monostable, i.e. $g(x)$ has one distinct maximum* at $x = \bar{x}_i$ ($i = 1$ when $I \Rightarrow 0$ and $i = 2$ when $I \Rightarrow \infty$), and transition area $I_1 < I < I_2$ (shifted at the expense of noise multiplicity) with the bimodal form of the $g(x)$ function. To begin with, we first examine two areas, where $g(x)$, at sufficiently small D, will be presented in the form of the simple Gaussian

$$g_i(x) = \sqrt{k/\pi D_i}\,\exp\left[-\frac{k}{D_i}\,(x - \bar{x}_i)^2\right]. \tag{12}$$

It is easy to see that, in this case,

$$\bar{x}_1 \simeq \frac{\chi I}{\Omega k}\,, \qquad D_1 \simeq \frac{\chi^2}{\Omega^2}\,D\,, \quad I \Rightarrow 0\,,$$

$$\bar{x}_2 \simeq \frac{\chi I}{\Lambda k}\,, \qquad D_2 \simeq \frac{\chi^2}{\Lambda^2}\,D\,, \quad I \Rightarrow \infty\,.$$

When calculating the statistical values entering into expression (3) for $K(I)$ by (10), (12), (9) for sufficiently small D, we shall confine ourselves to the first two terms of the expansion

$$\langle\phi(x)\rangle i = \int \phi(x)\, g(x)\,\mathrm{d}x \simeq \phi(\bar{x}_i) + \frac{D_i}{4k}\,\phi''(\bar{x}_i)\,,$$

Ultimately, in the above-mentioned limit areas, we receive

* The more distinct, the less the intensity of noise D is; noise multiplicity is not essential in this case.

$$K_i(I) = \left. \frac{I(\mathrm{d}\mu/\mathrm{d}x)}{\sqrt{I^2(\mathrm{d}\mu/\mathrm{d}x)^2 + k\mu^4(D/4D_i)}} \right|_{x=\bar{x}_i},$$

i.e., the degree of coherence

$$K(I) \simeq \begin{cases} I\alpha\chi/\sqrt{k\Omega^3}\ , & I \Rightarrow 0\,, \\ \dfrac{2\chi\alpha\Omega}{\Lambda^2 k}\, I\, \exp[-I(\alpha\chi/\Lambda k)]\ , & I \Rightarrow \infty \end{cases} \tag{13}$$

is decreasing to zero when moving further away from the area of nonequilibrium phase transition. A similar result would be obtained if we examined the small fluctuations around the stationary monostable solutions and linearized stochastic equations, i.e. reduced them to the two-dimensional Ornstein–Uhlenbeck process (see [13]).

In the area of function $g(x)$ bimodality (i.e. in transition area) for small D, we can present the latter in a purely illustrative approximation as a discrete set

$$g(x) = \begin{cases} P_1\ , & x = X_1\,, \\ & P_1 + P_2 = 1\,, \\ P_2\ , & x = X_2\,, \end{cases} \tag{14}$$

where X_1, X_2 are the locations of the peaks of real $g(x)$ in the bistability area. According to (14),

$$\langle x^2\rangle = P_1X_1^2 + P_2X_2^2\,, \quad \langle(\Delta x)^2\rangle = P_1P_2(X_1 - X_2)^2\,,$$

$$\langle N\rangle = P_1\langle N\rangle X_1 + P_2\langle N\rangle_{X_2}\,, \text{ etc.}$$

Then K, after altering P from 0 to 1 (transition from one to another bifurcation curve branch, i.e. 'nonequilibrium phase transition') assumes the form of

$$K = \frac{\sqrt{P_1P_2}\,(\langle N\rangle_{X_1} - \langle N\rangle_{X_2})}{\sqrt{\dfrac{D}{2}\left(\dfrac{P_1}{\mu^2(X_1)} + \dfrac{P_2}{\mu^2(X_2)}\right) + P_1P_2\,(\langle N\rangle_{X_1} - \langle N\rangle_{X_2})^2}} \tag{15}$$

witnessing the fact that, at small D, it may assume the values of the order of one.

Thus, the degree of coherence can be qualitatively characterized with an increase in pumping as acquiring a maximum of the order of unity in the area of transitive pumpings and decreasing to zero beyond the boundaries of this area. Such behaviour of $K(I)$ will be more pronounced when the temporal hierarchy is more distinct in the system (cf. [13]). One may try to quantitatively refine this result using the explicit form of the function (11):

$$g(x) = \frac{\mathcal{N}}{(\Lambda + \Omega\,\mathrm{e}^{-\alpha x})^2} \exp\frac{2}{D\chi^2}\left\{-\frac{k\Lambda^2}{2}\left(x - \frac{\chi I}{k\Lambda}\right)^2 + \right.$$

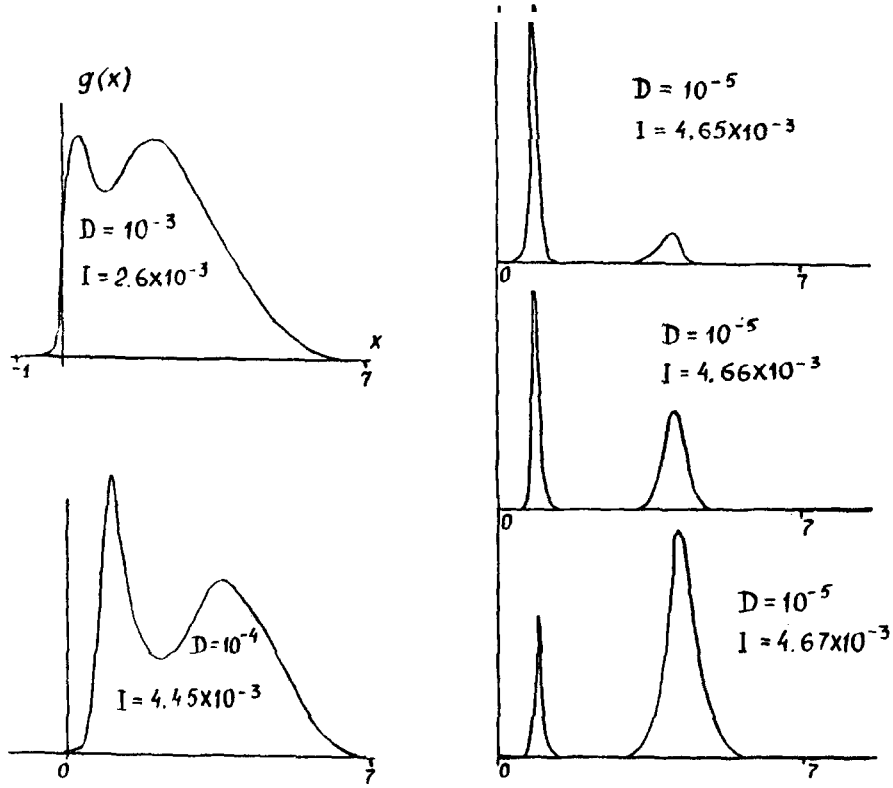

Fig. 5. Function $g(x)$ (relative units). $\Omega = \alpha = \chi = 1$, $\Lambda = 0.1$, $k = 0.01$; changes of D and I are shown.

$$+\frac{2\Lambda\Omega k}{\alpha}\,\mathrm{e}^{-\alpha x}\left(x+\frac{1}{\alpha}-\frac{\chi I}{2\Lambda k}\right)+\frac{k\Omega^2}{2\alpha}\,\mathrm{e}^{-2\alpha x}\left(x+\frac{1}{2\alpha}\right)\Bigg\} \quad (16)$$

in expression (3), assuming, with respect to (7), the form of

$$K(I)=\left\{\int\frac{xg(x)\,\mathrm{d}x}{\Lambda+\Omega\,\mathrm{e}^{-\alpha x}}-\left(\int xg(x)\,\mathrm{d}x\right)\int\frac{g(x)\,\mathrm{d}x}{\Lambda+\Omega\,\mathrm{e}^{-\alpha x}}\right\}\times$$

$$\times\left\{\left[\int x^2\,g(x)\,\mathrm{d}x-\left(\int xg(x)\,\mathrm{d}x\right)^2\right]\left[\int\frac{g(x)\,\mathrm{d}x}{\Lambda+\Omega\,\mathrm{e}^{-\alpha x}}\times\right.\right.$$

$$\left.\left.\times\left(\frac{I^2}{\Lambda+\Omega\mathrm{e}^{-\alpha x}}+\frac{D}{2}\right)-I^2\left(\int\frac{g(x)\,\mathrm{d}x}{\Lambda+\Omega\,\mathrm{e}^{-\alpha x}}\right)^2\right]\right\}^{-1/2} \quad (17)$$

Calculations by formulae (16) and (17), using a computer, supports the qualitative conclusions on the behaviour of $K(I)$ (Fig. 5,6). The parameters' values used here are illustrative and ensure the existence of a bistability area only. As for

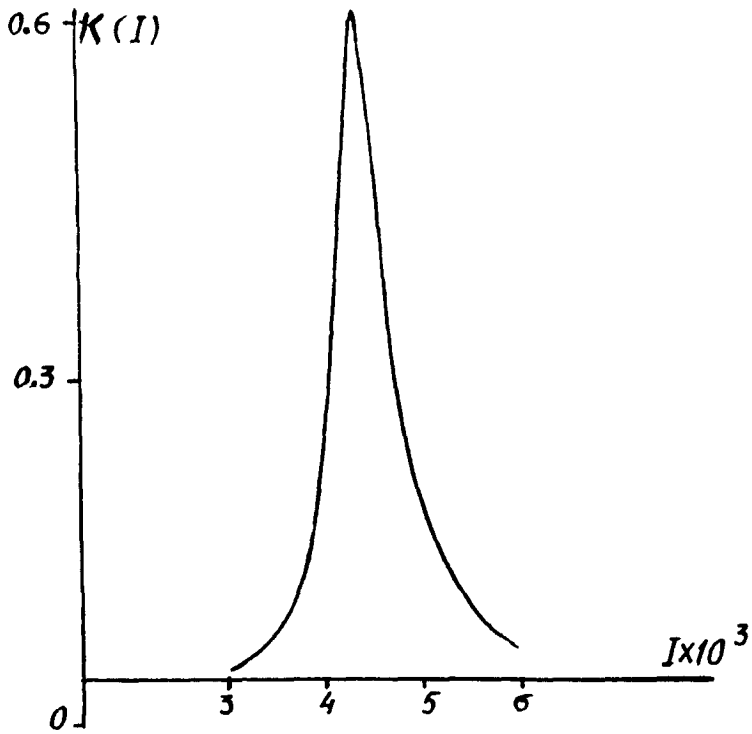

Fig. 6. The degree of coherence as a function of pumping intensity. $D = 10^{-4}$. Other parameters are the same as in Figure 5.

biological reality, we may note that the very similar values for sodium channels do not contradict the picture described above [7].

Conclusion

A short summary of this paper is given below.

At the beginning we discussed in detail the key role played in biomolecular processes by the conformational state of the corresponding components of a system and modern interpretations of charge-conformational interaction, and the conformon problem in particular. By way of an example of a model of a self-organized system of biological charge transport, we demonstrated that the emergence of a functionally selected degree of freedom of conformations seems to be more natural (and rather preferable in the kinetic sense) in nonequilibrium flux conditions which are widespread in biochemical processes. A proposed concept of a 'nonequilibrium conformon' originates from the idea of its being one of the 'projections' of a bound charge-conformation state of the dynamic type, whose very existence and func-

tional activity are regulated by the intensity of charge flux. From our viewpoint, such concept is more convenient for the description of the coupling of biological fluxes of a different nature.

In the model under study, a nonequilibrium conformon serves, literally speaking, as an example of a coherent product of the internal interactions of subsystems constituting a biomolecular transport system. As we have shown, the corresponding correlation characteristics of subsystem fluctuations created by noise have a noticeable increase in the functional self-organization area (it is interesting that the growth is taking place in the area of nonequilibrium phase transition of the first kind). It seems possible that it may serve as one of the suitable quantitative estimates of manifestations of the effects that are assumed to be denoted by the word 'self-organization'. As it takes place, the dynamics of discrete state emergence in the simple two-component dissipative system is demonstrated. It seems to pave the way to understanding the initiation mechanism of integral macroscopic quantum systems, the concept of which allows us to explain the differential stability of living systems [16].

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