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Periodic electric field as a biopolymer conformation switch: a possible mechanism

A. K. Vidybida

Institute for Theoretical Physics, Metrologicheskaya st., Kiev 252130, USSR
Temporary collective "Otklik"

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Abstract. A theoretical model is proposed to describe the influence of a periodic electric field (PEF) upon a biopolymer. The biopolymer is treated as a classical mechanical system consisting of subsystems (molecular groups) which interact with each other through potential forces. The PEF is treated as a periodic driving force applied to a molecular group. The energy dissipation is considered using the model of fluid (viscous) friction. Arguments for the non-linear character of the friction-velocity dependence caused by the non-Newtonian rheology of a viscous medium are formulated.

A forced molecular-group motion is investigated for the situation of a small driving-force period, with oscillations overdamped and a driving force consisting of more than one harmonic. As a result, it is established that the motion always gets to a terminal stage when only a small-scale vibration about some point, X^*, takes place. The terminal motion is preceded by a transient characterized by the presence of a directional velocity component and so by a drift along a potential profile. The drift goes on until a barrier is met which has a sufficiently large steepness (the barrier height is not important). As a result, the point X^* may happen to be remote from the conformation potential local minimum (conformational state). The physical reasons for the drift are described.

If we consider the small-scale vibration about X^* in the framework of the hierarchy of scales for intramolecular mobility, it can be regarded as an "equilibrium mobility", whereas the drift can be regarded as a functionally important motion, and X^* as a new conformational state which is realizable only in the presence of the PEF. It may be concluded, as the result of a consistent treatment and neglecting the small-scale vibration, that the conformational potential is modified by adding a linear term (in the one-dimensional case). In this connection, the set of conformational states can both deform (deviation of the positions of minima and their relative depth) and rearrange qualitatively (some minima can vanish and/or new minima can appear). In particular, the transition from one conformation to another one may happen due to rearrangement.

Key words: Intramolecular mobility, microviscosity, overdamping, non-Newtonian rheology, periodic electric field, hierarchy of scales, modified conformational potential

Introduction

At present a wide range of effects, diverse in their physiological and biochemical manifestations, generated by a periodic electric field (PEF) acting on bio-objects are known (Andreev et al. 1984; Adey and Lawrence 1983). It is natural to suppose, in view of the plurality of biological consequences produced by a minute PEF surface power, that the points of initial application are the mechanisms of communication and/or control. On the other hand, it is known that the functioning of the control (Koshland 1973; Changeux et al. 1984) and communication (Koshland 1973; Schramm and Selinger 1984) mechanisms on a molecular level is determined by the specificity of the spatial organization and dynamic conformational properties of biological macromolecules. That is, the factors which have an influence on biopolymer conformational states can, in principle, modify specific biochemical controlling actions.

In this paper, a theoretical model is proposed which explains the small-period PEF action on biopolymers through a rearrangement of their conformational properties. A biopolymer is treated as a classical mechanical system (Burkert and Allinger 1982), consisting of subsystems (microdomains or molecular groups), which are bound to each other by potential forces. The local minima of the mutual potential function correspond to conformational states. Certain mo-

lecular groups are charged (Hélène and Lancelot 1982), allowing the possibility of interaction with an external electric field. In addition, it should be noted that owing to the electrical properties of biological materials, an external low-frequency field, especially a constant one, is perfectly shielded, and does not permeate (Schwan 1983). Thus, the following mechanical problem arises: In what way is the potential function influenced by the external action of a periodic driving force without a constant component? A similar problem is known as a "Kapitza pendulum". For the Kapitza pendulum it is established that an external periodic action induces a potential function modification. Here a non-trivial modification occurs when the driving force amplitude is not constant with respect to a coordinate. In the case of biopolymers it could be postulated that the amplitude of an acting electric field is constant over the whole space. Nevertheless, if rotational mobility takes place with high rotation angle values, the angle should be taken as a configuration coordinate, and the moment of an electric force with respect to a rotation axis should be regarded as an acting force. In this case the dependence of the driving force amplitude on a (generalized) coordinate will be observed and the potential function (in large-scale terms) will be modified by an expression which is proportional to the squared driving force amplitude (Landau and Lifshitz 1976). In particular, if the pendulum fixed point is subjected to vibration, its upper rest position becomes stable. Concerning biopolymers in a rapidly oscillating electric field, the above mechanism will display a tendency for such an orientation of charged molecular groups which minimize the amplitude of a forced vibration.

Let us now consider a situation in which the microviscosity of a protein globule and its surroundings play an essential role. Here we shall not suppose any driving force dependence on a configurational coordinate (although such a dependence is possible). The mechanism mentioned above does not work then. Nevertheless, a modification of the potential function may occur in this situation as well. The crucial points which make the modification possible are the deviation of the dissipation law from a linear one and the non-trivial driving-force time dependence. In a one-dimensional case, the modifying effect of a periodic force results in adding a term linear with respect to a coordinate to an initial potential function. As a consequence, the conformational properties of a biopolymer may alter either quantitatively (changed position and relative depth of the conformational potential minima) or qualitatively (individual minima may disappear and/or new minima may appear). In particular, the transition from one minimum to another becomes possible owing to the modification i.e. the conformational switching.

Energy dissipation under intramolecular motion

When intramolecular motion in a globular protein is studied the energy dissipation is usually treated using the concept of viscous (fluid) friction (Gavish and Werber 1979; Beece et al. 1980; Shaitan and Rubin 1980; Goldanskii et al. 1983; McCammon 1984; Likhtenstein 1985). In this connection the Newtonian rheological model is normally used, this provides for the friction to be a linear function of the velocity (in accordance with Stokes Law). When studying the viscosity-induced decrease in the barrier crossing rate or the well oscillations deceleration, the variations in rheological models appear to be unimportant. In contrast, the difference between Newton's model and other (non-linear) models becomes fundamental when periodically driven oscillations are studied. In particular, if the medium is not subjected to Newton's model, a term non-linear with respect to velocity would appear in the equation of motion. It is well known that the presence of a term non-linear with respect to the coordinate X may provide for the solution $X(t)$ to have a zeroth harmonic (constant displacement). This, in particular, explains a thermal expansion phenomenon for solids. A (mathematically) similar mechanism would provide for the velocity to have a zeroth harmonic if a velocity-non-linear term is present. The direct component of the velocity causes a drift along the potential profile. The drift goes on until a barrier is met which has a sufficiently large steepness (the barrier height is not important). As a result, the molecular group can be displaced at a distance much greater than the forced oscillation amplitude (cf. an anharmonic case).

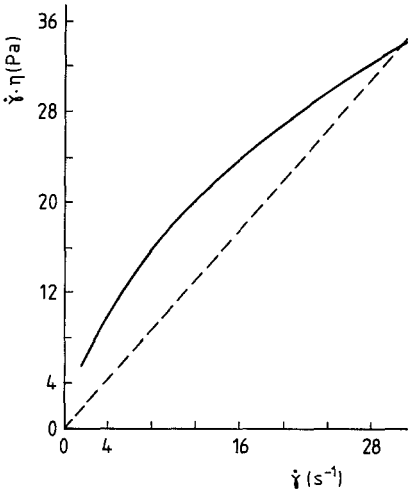

Fig. 1. $\eta\dot{\gamma}$ vs $\dot{\gamma}$ for the solution of 2.5 ml polymethylmetacrylate in 100 ml dimethylphtalate (Lodge 1964). Here η is the viscosity coefficient, $\dot{\gamma}$ is the shearing deformation velocity gradient. The $\dot{\gamma}$ value is proportional to the velocity when a body moves in a medium, $\eta\dot{\gamma}$ is proportional to the friction force. The non-linear pattern of the dependence shows the non-Newtonian rheology and the non-linearity of the friction-velocity dependence

At present the investigations for the energy dissipation law directly concerned with intramolecular mobility seem to be rather sparse. Nevertheless, the investigation of biological and similar materials (polymer solutions, liquid crystals) definitely prove that Newton's rheological model is not adequate in the context considered (Seifriz 1952; Lodge 1964; Barid 1978). As an example we consider the dependence of the product $\dot{\gamma}\eta$ (where $\dot{\gamma}$ is the deformation velocity gradient, η is the viscosity coefficient) on $\dot{\gamma}$, derived from data in (Lodge 1964) for a solution of polymethylmetacrylate in dimethylphthalate. ($\dot{\gamma}$ value is proportional to the velocity when a body moves in a medium, $\dot{\gamma}\eta$ is proportional to the friction force). It follows from the curve pattern (Fig. 1) that the friction depends on the velocity in a non-linear manner. In native conditions many biopolymers are integrated into a bimolecular lipid membrane, which represents a bilayer liquid crystalline smectic phase (Bouligand 1978). Globular protein as a material may also be considered as an aperiodic liquid crystal, having in mind its structural determincy and low activation energy for internal motions. However, the liquid crystals rheology is definitely not Newtonian (Barid 1978).

From the above it follows that a biopolymer operates in non-Newtonian rheological conditions. Let us make use, for a fluid medium, of a simple model different from the Newtonian one. This model is known as a "non-Newtonian fluid" (Reiner 1971). The only deviation from Newton's model here is that the viscosity coefficient depends on the velocity and as a consequence the friction force depends on the velocity in a non-linear manner.

Modification of the potential function caused by periodic action

We consider the simplest situation when for an internal motion in a biopolymer there is only one degree of freedom, X. The existence of a few conformational states is provided by a potential function which depends on X and has several minima (for example, as in Fig. 2). In this case the molecular-group motion under the action of an external periodic electric field is described by the following differential equation

$$m\ddot{X}(t) + \Lambda\dot{X}(t) - Eg(\dot{X}(t)/V_0) = F_0 f(t/T) - \Phi_0\varphi(X(t)/X_0), \quad (1)$$

where the following notation is used: $\dot{X}(t) = (\mathrm{d}/\mathrm{d}t)X(t)$ is the velocity, m is the mass of a molecular group; Λ is the coefficient of linear friction; E, V_0 and the non-dimensional function g characterize the non-linear friction component due to the deviation from Newtonian rheology; Φ_0, X_0 and the non-dimensional function φ characterize the force produced by a conformational potential; F_0, T and the non-dimensional function f characterize the driving force produced by PEF (of period T). Here f is periodic: $f(t\pm 1) = f(t)$, $|f(t)| \leq 1$, and has no constant component:

$$\int_0^1 f(t)\,\mathrm{d}t = 0. \quad (2)$$

The situation is thought to be natural when the well oscillations of a molecular group are overdamped (Shaitan and Rubin 1980; Morozov and Morozova 1983; McCammon 1984). For quantities occurring in (1) the overdamping means

$$m\varphi^*\Phi_0/(\Lambda^2 X_0) \ll 1, \quad (3)$$

where φ^* is the maximum value of the derivative of φ. The behaviour of the solution $X(t)$ for Eq. (1) is investigated under the condition (3) (Vidybida 1986; 1987).

When solutions for Eq. (1) are investigated the following condition is supposed to be valid, in addition to (3):

$$\Lambda T/m \ll 1. \quad (4)$$

It follows from a more precise consideration that (4) together with (3) may be replaced by

$$C(\Lambda T/m)\, m\varphi^*\Phi_0/(\Lambda^2 X_0) \ll 1, \quad (*)$$

where $C(\lambda) = \lambda(3-2\exp(-\lambda))/(1-\exp(-\lambda))$. When $\lambda = \Lambda T/m \ll 1$, $C(\lambda) \simeq 1$ and (*) coincides with (3). Conversely, when $\lambda \gg 1$, $C(\lambda) \simeq 3\lambda$ and (*) converts into the inequality

$$3T\varphi^*\Phi_0/(\Lambda X_0) \ll 1 \quad (**)$$

which should replace (3).

The physical meaning of inequalities (3) and (**) may easily be established when we draw an analogy with the harmonic potential situation. Choosing $PX^2/2$ as a potential function, we have $\Phi_0 = PX_0$, $\varphi^* = 1$ and (3) turns into $mP/\Lambda^2 \ll 1$, while (**) turns into $3PT/\Lambda \ll 1$ where T is a driving force period.

The final solution for Eq. (1) (when $t \gg T$ and the initial conditions are forgotten), as was established, represents small-scale oscillations of $X(t)$ about a certain point X^*. The final stage of motion is preceded by a transient when the directed drift takes place:

$$\frac{1}{T}\int_0^T \dot{X}(t)\,\mathrm{d}t = V^* \neq 0. \quad (5)$$

As a result, the point X^* which characterizes the final regime may be displaced from a potential local minimum at a distance much greater than the final oscillation amplitude (cf. an anharmonic case).

To interpret the described trajectory behaviour in terms of intramolecular mobility, it should be kept in mind that for biopolymers, especially for globular proteins, the hierarchy of scales for internal motion is

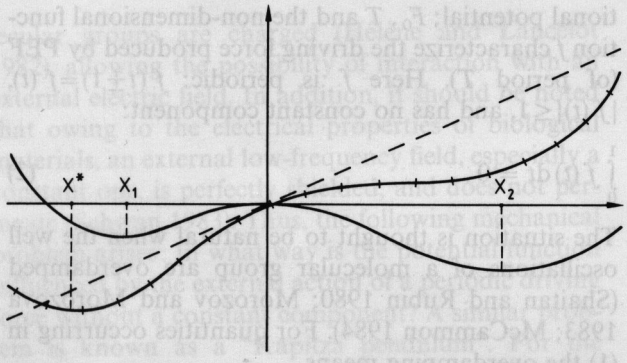

Fig. 2. Example of a conformational potential modification under periodic electric field action. Initial potential (———) and modified potential (– – –) differ in a term $D_0 X$, where D_0 is the stopping force. The final small-scale oscillation is performed in the neighbourhood of the coordinate, X^*

characteristic (Demchenko 1981; Ausari et al. 1985). The small-scale (short-period) motions do not alter the biopolymer functional state and may be ignored in this sense. Thus, as regards the biopolymer functioning the final trembling in the neighbourhood of X^* may be considered as its new state (conformation) characterized by X^* and realizable only under PEF action. When the PEF is removed, a biopolymer will restore one of its native conformations that does not necessarily coincide with the initial one. This PEF-induced transition from one native conformation to another is interpreted as conformational switching. In addition, the conformation X^* may happen to be a native one for a biopolymer having a different structure, with possible biochemical consequences.

To locate the state X^* for any external action $F_0(t/T)$, we introduce the "stopping force" idea (Vidybida 1986, 1987). Consider the following equation for the velocity $\dot{X}(t)$:

$$m\ddot{X} + \Lambda \dot{X}(t) - E g(\dot{X}(t)/V_0) = F_0 f(t/T) + D \qquad (6)$$

The stopping force D_0 is a value such that when $D = D_0$ in Eq. (6) the terminal (periodic) solution has no constant component:

$$\int_0^T \dot{X}(t)\,\mathrm{d}t = 0\,.$$

The non-zero value of D_0 is provided by the fact that the friction law is non-linear and the signal $F_0 f(t/T)$ is not sinusoidal. The point (points) X^* are the solutions for the following equation $-\Phi_0 \varphi(X^*/X_0) = D_0$.

Consequently, the PEF action manifests itself in an additional constant force $-D_0$ and so in a modification of the potential function, as is shown in Fig. 2. Here the question arises: what is the reason for the appearance of a constant force if the time-averaged force applied is equal to zero, or, equivalently, how does the simultaneous realization of conditions (2) and (5) match the momentum conservation law? The mathematical explanation of the phenomenon has been given in the previous section through the appearance of the velocity zeroth harmonic due to the non-linearity of the friction law. From the physical point of view the condition (2) implies that the time-averaged momentum transferred from an external field to a charged molecular group is equal to zero. However, the molecular-group movement due to external force $F_0 f(t/T)$ is executed so that the velocity grows (and falls) to the left in a tempo different than to the right. As a result, the absolute values of a momentum transferred to a viscous medium in the process of moving to the left or to the right appear as a rule to be unequal to each other (the friction law non-linearity is important here). The unsymmetrical loss of momentum is just the process imitating the appearance of an additional force in spite of Eq. (2). In more detail this mechanical phenomenon is considered for electrophoresis (Vidybida and Serikov 1984), where it is shown that for its appearance the presence of two harmonics in the signal $F_0 f(t/T)$ is sufficient.

Consider finally the effectiveness of the non-linear mechanism for an alternating force transforming into a constant one. Examples, especially for a dry friction show that the stopping force value may be as close to the driving force amplitude as desired (Vidybida 1986, 1987). In other words, the stopping force obeys the inequality $|D_0| < |F_0|$ which cannot be sharpened if the signal form $F_0 f(t/T)$ or the friction law are not specified.

Discussion

In the previous section a possible mechanism is considered for the functioning of biopolymers in the presence of a periodic electric field. For the given mechanism to operate, the non-linear dependence of the friction with respect to the velocity as well as the time dependence of the molecular group velocity when the PEF is acting are essential. In this context the temperature has not been taken into account, so one can state that the model is derived at zero temperature. It is possible to justify the application of this model to physiological temperatures if the forced-movement velocity is not very much distorted by Brownian motion. Given the maximum admissible distortion, it is possible to incorporate into a single inequality the quantities of Eq. (1) and the Brownian motion mean velocity for a given temperature. Such an inequality establishes the bounds for the applicability of a temperatureless approach in terms of, for example, F_0-value.

The requirement for the signal $F_0 f(t/T)$ to have more than one harmonic is another essential restric-

tion. At the same time the effectiveness of the simple harmonic signal is established experimentally (Adey and Lawrence 1983). Here it is natural to expect that because biological materials are essentially non-linear, the higher harmonics generation for a driving force is effected in the medium through electrical or acoustical mechanisms. It is also natural to suppose that an applied field can be amplified resonantly.

For a direct experimental testing of the theory presented one requires orientation control for a biopolymer with respect to the electric-field strength vector. As a result, a modification of conformationally dependent biochemical reactions may happen. A certain indirect experiment for a biopolymer in a solution is available. Namely, when exposed to PEF the solution will be heated, due to the electric field energy absorption. However some part of an external field energy will be accumulated as a conformational potential elastic energy (due to the modification). When PEF is removed this accumulated elastic energy will transform into a thermal one, so the solution temperature can be increased still further.

It should also be noted that the proposed mechanism for the action of the periodic electric field on biopolymers is not unique. An interesting mechanism for free energy transduction by enzymes from a periodic or noisy electric field has been proposed (Westerhoff et al. 1986; Astumian et al. 1987); here the nonlinearity with respect to the electric field strength is the important point. The mechanism proposed in the present paper may operate when the field period is much less than the duration of the enzyme operation cycle ($T<10^{-6}$ s), whereas the proposed free energy transduction seems to be effective in just the opposite situation: the presence of low-frequency harmonics is essential.

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