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Quantum processes in biological molecules. Enzyme catalysis

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Abstract. The oxidation – reduction enzymatic reaction is treated as a nonadiabatic multiquantum transition from the initial substrate – enzyme complex to a free product and free enzyme, taking into account the contribution of low-frequency (conformational) degrees of freedom of the enzyme molecule to the quantum transition described in terms of the reaction coordinate. It is demonstrated that the electromagnetic field has a marked effect on the enzymatic reaction rate by exciting low-frequency vibrations of enzyme molecules, a fact from which the nature of the so-called narrow biological resonances may be understood. A new mechanism giving rise to ultraviolet radiation from biological membranes is discussed. The theory can be used to explain the origin of ultraviolet radiation and dipole ordering of globular cell proteins.

1. Introduction

The impressive advances in quantum theory established and developed in the 20th century are widely known. Accordingly, the second half of this century witnessed the triumph of molecular biology either.

Hence, an important and justifiable question is: would it be possible to integrate this new knowledge into the quantum theory and would it be necessary?

This brings to mind the famous collection by N Bohr entitled *Quantum Physics and Biology* [I1], the well-known book by E Schrödinger *What is Life? The Physical Aspect of the Living Cell* [I2], and other publications to the same effect. Biological processes at the molecular level are extraordinarily complicated and sometimes difficult to interpret. A physicist has by necessity to seek an explanation in terms of physical ideas including quantum-mechanical theories, unless he resorts to theological models or the like.

The modern physics of solids with its fairly well developed electronic theory gives an example of the magnificent achievements in quantum mechanics including macroscopic quantum effects, such as ferromagnetism, superconductivity, etc.

Methods of solid-state physics can be fruitfully applied to the description of biological macromolecules and are thus conducive to understanding profound processes in living matter.

There is, however, one essential difference between the dynamic behavior of biological macromolecules and solid bodies. This is first and foremost the existence of a branched system of low-frequency conformational degrees of freedom which have a marked effect on electron – vibration processes in molecules. I would relate electron – nuclear interactions in

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biological macromolecules to 'soft-state physics' as opposed to the physics of solids.

Today, at the close of the 20th century, the extensive use of computational techniques has allowed the problem of the energy spectrum and wave functions of biological macromolecules to be practically resolved in the static approach. Suffice it to mention the well-known data obtained in quantum chemistry and quantum biochemistry (see the excellent monograph of B Pullman and A Pullman [I3] and also Refs [I4, I5]).

At the same time, dynamic processes in biological macromolecules await further studies, in fact the problem needs to be fully formulated.

During the last decade, the author and his co-workers have been developing physical models of enzymatic catalysis, based on the interpretation of the oxidation – reduction enzymatic reaction as a nonadiabatic electron – nuclear process. Such an approach permitted full advantage of the theory of nonadiabatic multiphonon transitions (known from solid-state physics and the theory of absolute reaction rates [I6, I7]) to be taken for the description of electron – nuclear interactions in biological macromolecules taking into consideration, however, the contribution of low-frequency (conformational) degrees of freedom to the processes (see Refs [I8 – I10] for comprehensive investigations into this matter).

The idea of the 'conformon' was first suggested by M V Vol'kenshteĭn [I11] by analogy with the notion of the polaron [I12, I13].

For nonadiabatic reaction rates, the role of conformational degrees of freedom must be evaluated based on a consistent quantum-statistical theory. Indeed, a multiquantum (multiphonon) nonadiabatic transition between high-frequency vibrational modes corresponding to the reaction coordinates should be considered with due regard for Bose – Einstein statistics, since the corresponding vibrational frequencies $\hbar\omega \gg k_0 T$, where k_0 is the Boltzmann constant, and T is the characteristic temperature of the living structure. It is this fact that is taken into account when the temperature dependence of the enzymatic reaction rate is assessed based on the medium rearrangement energy and the effect of measuring vibrational frequencies during a quantum transition.

The microscopic theory of heat release constants allows for the consideration of the shape of the reaction potential barrier. Both the width and the height of the barrier show an explicit dependence on conformational degrees of freedom. In other words, there is peculiar 'mixing' between quantum and classical degrees of freedom, which are of special importance in the calculation of penetration coefficients for nonadiabatic reactions and the description of tunneling, coherent and squeezed states, and other kinetic effects beyond the scope of a simple classic description.

However, the present review is confined to those results obtained by the author which could not be explained only in terms of simple classical ideas. Specifically, it concerns radiationless charge transfer during oxidation – reduction reactions in the low-temperature range, the role of a polar environment in nonadiabatic reactions, the theory of immobilized enzymes on biological membranes, the behavior of enzymatic reactions in a strong pulsed electromagnetic field, the generation of higher optical harmonics upon collisions between fast protons and biological macromolecules, the Jahn – Teller pseudoeffect in hemoglobin molecules in an external electromagnetic field, etc.

The concluding section of this review is focused on selected implications of the proposed concept of the elementary act of enzymatic catalysis as a nonlinear process for the manifestation of synergetic (cooperative) phenomena in modern molecular genetics (including the role of allosteric effects in the regulation of expression of the so-called mobile genes of eucaryotes).

All the results obtained by the author and his co-workers have been published in scientific journals referred to in the section titles.

The objective of the present review is to illustrate the important role of quantum concepts for the description of biological phenomena leaning upon the elementary acts of oxidation – reduction enzymatic processes. Certainly, references are also made to some other works known to the author.

2. Multiphonon model of the oxidation – reduction enzymatic reaction [1]

An oxidation – reduction (OR) enzymatic reaction involves the participation of the enzyme in the electron transfer from the initial state of the substrate – enzyme complex 2 [SE] to the final state of the product – enzyme complex 1 [PE]. (In certain cases, a transition directly to the free product [P] and free enzyme [E] as the final state is considered, for simplicity.)

Such electron transfer is referred to as a nonadiabatic transition associated with vibrational motions along the reaction coordinate path, which result in the mixing of the [SE] adiabatic potential with the [PE] adiabatic potential (Fig. 1).

This approach is based on the well-known adiabatic approximation which separates rapid electron motions along the reaction coordinate Q from slow nuclear motions, with the nonadiabaticity operator playing the role of a disturbing operator usually taken into consideration in the framework of perturbation theory.

(A more detailed discussion of radiationless nonadiabatic electron transitions can be found in Refs [1 – 3].) In the so-called static model, the role of perturbation operator can be performed by the energy of interaction between the transferred electron and vibrational degrees of freedom q_ω disregarded in the choice of the reaction coordinate. In modern usage, the reaction coordinate Q is an accepting

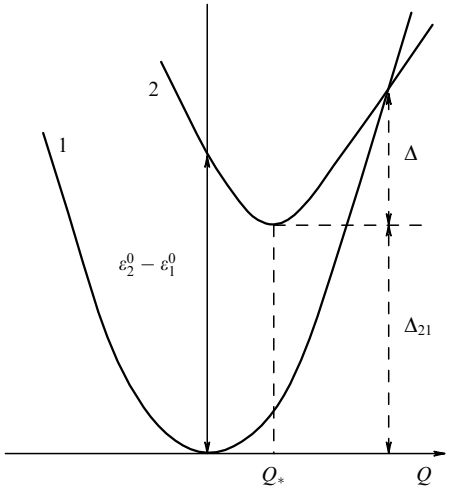

Figure 1. Adiabatic potentials of [SE] complex (2) and [PE] or [P] + [E] complexes (1) versus the reaction coordinate Q ($p_0 = (\varepsilon_2^0 - \varepsilon_1^0)/(\hbar\Omega)$).

mode, while the coordinates q_ω are promoting modes. The rate W_{21} of oxidation–reduction reaction (number of transitions per unit time: 2 → [SE], 1 → [PE]) is given by the expression

$$W_{21} = \frac{1}{\hbar^2} v_{21}^2 \int_{-\infty}^{+\infty} I_{21}(t)\,\mathrm{d}t\,, \tag{1}$$

where

$$I_{21}(t) = \left\langle \exp\left(\frac{\mathrm{i}}{\hbar} H_1 t\right) \exp\left(-\frac{\mathrm{i}}{\hbar} H_2 t\right) \right\rangle f(t)\,; \tag{2}$$

the angle bracket $\langle \ldots \rangle$ denotes averaging over the initial vibrational states of the [SE] complex:

$$\langle \ldots \rangle = \frac{\mathrm{Sp}\big(\ldots \exp\{-\beta H_2\}\big)}{\mathrm{Sp}\big(\exp\{-\beta H_2\}\big)}\,, \quad \beta \equiv \frac{1}{k_0 T}\,, \tag{3}$$

here $H_2(Q)$, $H_1(Q)$ are the vibrational Hamiltonians of the initial 2 and final 1 electronic states; v_{21} is the matrix element of electron–vibrational interactions for the promoting mode, which is built up on electron wave functions in [SE] and [PE] states, respectively; k_0 is the Boltzmann constant, and T is the temperature. For the sake of simplicity, a single promoting mode q_ω has been chosen, so that

$$f(t) = \bar{N}\exp(\mathrm{i}\omega t) + (\bar{N}+1)\exp(-\mathrm{i}\omega t)\,,$$
$$\bar{N} = [\exp(\beta\hbar\omega) - 1]^{-1}\,. \tag{4}$$

Normally, the approximation of a harmonic oscillator in state 2 at frequency Ω_2 is adopted for the reaction coordinate Q, and the harmonic approximation with oscillator frequency Ω_1 for the description of nuclear motions in state 1; the equilibrium position of the oscillator in electronic state 1 is assumed to be shifted by Q_* relative to that of the oscillator in electronic state 2.

A frequently employed simplest model is the so-called basic model or the model of 'shifted parabolas' in which the vibrational frequencies of the initial and final states coincide, i.e. $\Omega_2 = \Omega_1 = \Omega$. In this model, the radiationless transition rate is calculated by the methods known from the theory of multiphonon processes [1]. Hence, one obtains

$$W_{21} = \frac{v_{21}^2}{\hbar^2\Omega}\left\{\bar{N}R_{[p+\omega/\Omega]}(z_0) + (\bar{N}+1)R_{[p-\omega/\Omega]}(z_0)\right\}, \tag{5}$$

$$z_0 = a_0\sqrt{\bar{n}(\bar{n}+1)}\,, \quad \bar{n} = \big(\exp(\beta\hbar\Omega) - 1\big)^{-1}\,, \quad p = \frac{\Delta_{21}}{\hbar\Omega}\,, \tag{6}$$

where Δ_{21} is the difference between the adiabatic potential minima in the initial and final electronic states, and [A] is the integral part of A.

Parameter a_0 (Stokes constant) is given by the formula

$$a_0 = \left(\frac{V_{11} - V_{22}}{\hbar\Omega}\right)^2 = \frac{M\Omega Q_*^2}{\hbar}\,. \tag{7}$$

Here V_{11}, V_{22} are the matrix elements of electron–vibrational interactions in states 1 and 2 for the accepting mode, which determine the relative Q_* shift of the parabolas.

Function $R_{[p\pm\omega/\Omega]}(z)$ is given by the formula

$$R_s(z) = \left(1 + \frac{1}{\bar{n}}\right)^{s/2} \exp\left[-a_0\left(\bar{n} + \frac{1}{2}\right)\right] I_s(z)\,, \tag{8}$$

where $I_s(z)$ is a Bessel function of an imaginary argument.

In the asymptotic limit of high temperatures $\hbar\Omega/(k_0T) \ll 1$, $\bar{n} \approx k_0T/(\hbar\Omega) \gg 1$, the above formulas lead to the Arrhenius law for the temperature dependence of the enzymatic reaction rate:

$$W_{21} \sim \exp\left\{\frac{-(p - \omega/\Omega - a_0/2)^2}{2a_0}\,\frac{\hbar\Omega}{k_0T}\right\}. \tag{9}$$

At low temperatures, $\hbar\Omega/(k_0T) \gg 1$, W_{21} shows a weak temperature dependence.

In the low temperature case, the above formulas lead to the known expression for the tunnel enzymatic reaction rate (see, for instance, Ref. [4]).

The expression for the enzymatic reaction rate in a more general model taking into account the so-called frequency effect $\Omega_1 \neq \Omega_2$ has been considered in an earlier work by the author and his co-workers [5] and need not be written here.

Therefore, I confine myself to the basic model and the high-temperature limit for OR enzymatic reaction rates. However, in the forthcoming discussion, the contributions of low-frequency vibrational degrees of freedom to the OR enzymatic reaction rate will be more consistently taken into account by including the contribution to the zero-order Hamiltonian [6].

3. Kinetic model of deformation energy recuperation in conformational degrees of freedom of enzyme molecules [6]

The high activity of enzyme molecules is frequently accounted for by partial recuperation of energy (liberated during a chemical reaction) in enzyme intramolecular degrees of freedom. The most plausible mechanism of this process appears to be related to the energy storage in low-frequency (deformational) degrees of freedom because in this case the dissipation rate of the stored energy is reduced to a minimum. The electron transfer in an oxidation–reduction enzymatic reaction normally involves high-frequency molecular vibrations (reaction coordinates) of the active center, which form the potential barriers of the reaction. In the course of each electron transition event, the equilibrium positions of the degrees of freedom undergo rearrangement and new ones are established. This process conditionally proceeds in two steps. Firstly, the high-frequency degrees of freedom of the active center undergo rearrangement while the configuration of the low-frequency degrees of freedom remains unaltered. After that, slow rearrangement of the low-frequency degrees of freedom leads to complete equilibrium in a given electronic state. If, however, the system's lifetime in a given electronic state, determined by kinetic processes, is significantly shorter than the reciprocal characteristic frequencies of the slow subsystem, then the stationary configuration of the latter subsystem is attained in the course of multiple electron transitions. Therefore, the configuration of the low-frequency degrees of freedom of an enzyme molecule, unlike that of high-frequency degrees of freedom, is controlled by the average rather than the instantaneous state of the electronic subsystem. Deformation of a macromolecule in the course of continuous electron transitions (in a stationary chemical reaction) can, in turn, affect the rate of electron processes and thus distort barriers along the reaction coordinate.

An example is provided by the above model of [SE] complex (see Section 2) undergoing a single high-frequency vibration which corresponds to the reaction coordinate Q.

It will be recalled that our system can exist in two states: state 2 ([SE] complex) and state 1 ([PE] complex). Assume also that the frequencies Ω of vibration Q do not depend on the electronic state while equilibrium positions in states 1 and 2 are different. In this model, the Hamiltonian of the substrate-enzyme complex has the following form

$$H = H_e + H_q + H_Q + H_{eQ} + H_{qQ}\,, \tag{10}$$

where

$$\begin{aligned} &H_e = \varepsilon_2\hat{n}_2 + \varepsilon_1\hat{n}_1\,, \quad \hat{n}_2 = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}, \quad \hat{n}_1 = \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix}, \\ &H_q = \sum_{\varkappa}\left(-\frac{\hbar^2}{2m_\varkappa}\frac{\partial^2}{\partial q_\varkappa^2} + \frac{m_\varkappa\omega_\varkappa^2 q_\varkappa^2}{2}\right), \\ &H_Q = -\frac{\hbar^2}{2M}\,\frac{\partial^2}{\partial Q^2} + \frac{M\Omega^2 Q^2}{2} \end{aligned} \tag{11}$$

($m_\varkappa$ and M are the reduced masses); in addition, one obtains

$$\begin{aligned} &H_{eQ} = \hat{n}_2 A_2 Q + \hat{r}^+ V_{12} + \hat{r}^- V_{21}\,, \\ &\hat{r}^+ = \begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix}, \quad \hat{r}^- = \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix}, \\ &H_{qQ} = \Big(\sum_{\varkappa}\hat{n}_2 B_{2\varkappa} q_\varkappa\Big) Q\,. \end{aligned} \tag{12}$$

Here, H_e, H_q, and H_Q are the Hamiltonians of the electronic, low- and high-frequency vibrational subsystems, respectively; H_{eQ} describes the interaction between the electron and the high-frequency mode (terms proportional to V_{21} secure the transition from the substrate – enzyme state to the product – enzyme state); the term H_{qQ} characterizes the intermode interaction of low-frequency vibrations with the reaction coordinate (this interaction is different in different electronic states).

The Heisenberg equations of motion for the Q and q coordinates take the form

$$\ddot{Q} + \Omega^2 Q = -\frac{1}{M}\Big(A_2 + \sum_{\varkappa} B_{2\varkappa} q_\varkappa\Big)\hat{n}_2\,, \tag{13}$$

$$\ddot{q}_\varkappa + \omega_\varkappa^2 q_\varkappa = -\frac{1}{m_\varkappa}\,B_{2\varkappa} Q\hat{n}_2\,. \tag{14}$$

Suppose that the probabilities of electron transitions $2 \to 1$ and the rates of other kinetic processes sk_s, k_{-s}, k_p are significantly higher than the frequencies $\omega_\varkappa$ (sk_s is the production rate of substrate – enzyme complexes; s is the substrate concentration; k_{-s} is the disintegration rate of these complexes, and k_p is the disintegration rate of the product – enzyme complex into the free product and the free enzyme). Using this assumption, let us average Eqns (13, 14) over the time scale $\Delta t \ll \omega_\varkappa^{-1}$ which is significantly greater than both Ω^{-1} and characteristic times of the above kinetic processes. The expression for the averaged quantity takes the form

$$\ddot{\tilde{q}}_\varkappa + \omega_\varkappa^2\tilde{q}_\varkappa = -\frac{n_2}{m_\varkappa}\,B_{2\varkappa} Q_*\,, \tag{15}$$

where

$$Q_* = -\frac{1}{M\Omega^2}\Big(A_2 + \sum_{\varkappa'} B_{2\varkappa'}\tilde{q}_{\varkappa'}\Big)\,,$$

and $n_2 = \langle\hat{n}_2\rangle$. Therefore, the low-frequency coordinates satisfy the system of equations for coupled oscillators whose frequencies and equilibrium positions depend on the population of electronic state 2.

The kinetic equations for the populations n_2 and n_1 have the form

$$\dot{n}_2 = sk_s(1 - n_1 - n_2) - k_{-s}n_2 - W_{21}n_2\,, \tag{16}$$

$$\dot{n}_1 = -k_p n_1 + W_{21}n_2\,. \tag{17}$$

Here, the quantity W_{21} stands for the radiationless transition probability from state 2 to state 1 with the emission of hard vibrational quanta Q. It has been shown in Section 2 that this quantity has the form of Eqn (5).

Assuming that the displacement in equilibrium positions of vibrations $q_\varkappa$ is significantly greater than the amplitude of their equilibrium thermal vibrations, one obtains from Eqns (13), (15), (7)

$$a = \frac{A_2^2}{M\hbar\Omega^3}\left[1 - \frac{n_2}{M\Omega^2}\sum_{\varkappa}\frac{B_{2\varkappa}^2}{m_\varkappa\omega_\varkappa^2}\right]^{-2} \tag{18}$$

[for simplicity, this expression was derived neglecting renormalization of vibrational frequencies $q_\varkappa$]. By this means, the transition rate W_{21} shows a nonlinear dependence on the average population n_2.

The stationary populations n_1 and n_2 satisfy the equations

$$n_1 = \frac{W_{21}(n_2)}{k_p}\,n_2\,, \tag{19}$$

$$n_2\left\{(k_{-s} + sk_s) + W_{21}(n_2)\left(1 + \frac{sk_s}{k_p}\right)\right\} = sk_s\,. \tag{20}$$

The product yield per unit time is

$$K = k_p n_1 = n_2 W_{21}(n_2)\,. \tag{21}$$

According to the transcendental Eqn (20), when $W_{21} \ll k_{-s}$, sk_s, k_p, one obtains

$$n_2 = \frac{sk_s}{k_{-s} + sk_s}\,. \tag{22}$$

Using the high-temperature approximation, $k_0 T \gg \hbar\Omega$, for W_{21}, one arrives at

$$K = \frac{2\pi|V_{12}|^2 n_2}{\hbar\alpha_2(1 + n_2\beta_2)\sqrt{2\pi\hbar\Omega k_0 T}}\exp\left[-\frac{\Delta(n_2)}{k_0 T}\right], \tag{23}$$

$$\begin{aligned} &\Delta(n_2) = \frac{\hbar\Omega}{2\alpha_2^2(1 - n_2\beta_2)^{-2}}\left[p_0 - \alpha_2^2(1 - n_2\beta_2)^{-2}\right]^2, \\ &\beta_2 = \sum_{\varkappa}\frac{B_{2\varkappa}^2}{m_\varkappa^2 M\omega_\varkappa^2\Omega^2}\,, \quad \alpha_2 = \left(\frac{A_2^2}{M\hbar\Omega^3}\right)^{1/2}. \end{aligned}$$

It follows from Eqn (23) that the reaction rate K nonmonotonically depends on n_2 and reaches a maximum at $n_2 \approx 1/\beta_2(1 - \alpha_2/\sqrt{p_0})$. Since sk_s and k_{-s} increase monotonically with temperature, the reaction rate must show a reversible nonmonotone temperature dependence. Such maxima in temperature dependences have been observed in experiment [I11].

If W_{21} is of the same order of magnitude as the rates of the remaining kinetic processes, it is easy to demonstrate that Eqn

(20) can have three stationary solutions $n_2^{(1)} < n_2^{(2)} < n_2^{(3)}$ by virtue of the nonmonotone dependence $W_{21}(n_2)$. Analysis of time-dependent equations indicates that only two solutions ($n_2^{(1)}$, $n_2^{(3)}$) are stable. At certain values of the parameters, the system can reside in one of the two stable states characterized by significantly different enzymatic reaction rates. The transition from one state to the other occurs at a jump under continuous changes of (s, T) parameters. The reverse transition also occurs in a jump although at different threshold parameters. In other words, the dependence of reaction rate on s and T has a hysteretic character.

It is also interesting to consider the case in which the probability of the [ES] complex disintegration into the free substrate and free enzyme is rather small, so that the characteristic time of an enzymatic reaction is determined only by the nonadiabatic transition rate W_{21} (i.e. the rate of conversion of the substrate–enzyme complex into the product–enzyme complex).

This reaction rate is subject to substantial changes due to the contribution of low-frequency vibrational degrees of freedom to the process. It implies that the reaction coordinate Q undergoes mixing with the low-frequency vibrational degrees of freedom q of the enzyme molecule as a result of an anharmonic interaction.

Let us consider, for simplicity, the interaction between the reaction coordinate Q and a single low-frequency coordinate q of frequency ω. The interaction energy $\widehat{V}$ may be presented in the simplest form as $\widehat{V} = VQq$.

This type of interaction means that an additional force Vq appears in the equation of motion of the Q-oscillator. It leads to a slow ($\omega \ll \Omega$) shift in the Q-oscillator equilibrium position by the value $Vq/(M\Omega^2)$.

Let us assume that the $Q-q$ interaction constant is different in various electronic states: $V_1 \neq V_2$. Then, the positions of minima of adiabatic potentials $\varepsilon_2(Q)$ and $\varepsilon_1(Q)$ depend on the $Q-q$ interaction. Hence, an oscillatory contribution to the heat release constant yields

$$a = \frac{M\Omega}{\hbar}\left[Q_* - \alpha q(t)\right]^2 = a_0\left[1 - \frac{\alpha q(t)}{Q_*}\right]^2, \quad \alpha = \frac{V_2 - V_1}{M\Omega^2} \tag{24}$$

[see formula (7) for a_0].

If the electron transition time τ is much shorter than the vibration period of the low-frequency q-mode, the electron transition occurs at a fixed q coordinate.

If there is no correlation between chemical reaction phases in a molecular ensemble (this requirement is not mandatory under special experimental conditions), the reaction yield can be estimated by averaging the expression for the transition rate at a fixed coordinate $q = q_0 \cos\varphi$ (where q_0 is the vibrational amplitude corresponding to the amplitude of an [ES] complex), namely

$$\bar{W} = \frac{A}{2\pi}\int_{-\pi}^{\pi} \mathrm{d}\varphi \exp\left\{-\frac{\hbar\Omega}{k_0 T}\,\frac{[p_0 - a_0(1-(\alpha q_0/Q_*)\cos\varphi)^2]^2}{2a_0(1-(\alpha/Q_*)q_0\cos\varphi)^2}\right\}. \tag{25}$$

The integral in formula (25) can be estimated by the saddle-point method. If the αq_0 value is so large that the equation

$$p_0 - a_0\left(1 - \frac{\alpha}{Q_*}q_0\cos\varphi\right)^2 = 0 \tag{26}$$

has a solution at real values of the variable φ and if

$$\alpha q_0 > Q_*\left(\sqrt{\frac{p_0}{a_0}} - 1\right),$$

then this value of φ will give the largest contribution to the integral in formula (25).

We find that

$$\bar{W} \approx A\sqrt{\frac{2k_0 T}{\pi\alpha^2\Omega^2 q_0^2}}\left\{1 - \frac{\hbar a_0}{M\Omega\alpha^2 q_0^2}\left(\sqrt{\frac{p_0}{a_0}} - 1\right)^2\right\}^{-1/2}. \tag{27}$$

Thus, the activation temperature dependence of the reaction rate vanishes, and the transition probability increases exponentially.

This finding is qualitatively consistent with the results obtained by direct calculations and with conclusions pertaining to the processes of proton transfer in the catalytic reaction involving lysozyme [7].

The disappearance of the activation dependence of the enzymatic reaction is a result of the action of low-frequency q-vibration on the reaction barrier parameters.

It is important to emphasize that the energy stored by the q-vibration does not dissipate within the time span of an enzymatic reaction. But if αq_0 is not too large, Eqn (26) may have no real roots.

For $\alpha q_0 < Q_*(\sqrt{p_0/a_0} - 1)$, the main contribution to the integral (25) is made by the points $\varphi = \pm\pi$.

Using the saddle-point method, it is easy to estimate the contribution of this region of integration to the mean $\bar{W}$:

$$\bar{W} = \frac{A}{2\pi}\sqrt{\frac{2\pi a_0(1+z)^3}{z(p_0^2 - a_0^2(1+z)^4)}}\exp\left\{-\frac{\hbar\Omega}{k_0 T}\,\frac{(p_0 - a_0(1+z)^2)^2}{2a_0(1+z)^2}\right\}, \tag{28}$$

where

$$z = \left|\frac{\alpha q_0}{Q_*}\right| = |\alpha q_0|\sqrt{\frac{M\Omega}{\hbar a_0}}.$$

In this case, the activation type of dependence of the transition rate remains unaltered, whereas the activation energy decreases considerably.

In conclusion, it should be noted that a polar solvent in which reacting molecules are embedded can also play the role of a low-frequency subsystem.

The following section is focused on a radiationless transition model taking into consideration the fluctuation effect of ambient polar medium on the transition rate. By way of example we shall consider a tunneling charge transfer in biological systems.

4. Fluctuation effect of ambient polar medium on the radiationless electron transfer in biomolecules. Application of the theory to oxidation of low-potential cytochrome [8]

The phenomenon of electron charge transfer in biological molecules has been extensively studied over the last two decades. Since the well-known experimental data on the oxidation of low-potential cytochrome were obtained [9], this problem has been considered by several theorists [10–12] who have tried to explain temperature dependence of the

electron transfer rate in terms of the theory of multiphonon radiationless electron transitions in molecules and solids (see, for instance, Ref. [1]).

A most surprising result of the experiment reported in Ref. [9] amounts to revealing the temperature dependence of electron transfer over a range of relatively low temperatures. Because the vibrational frequency Ω corresponding to the reaction coordinate satisfies the inequality $\hbar\Omega \gg k_0 T$, theoretical models suggest consideration of the tunneling mechanism of electron transfer, the rate of which must be independent of temperature. To spare readers the trouble of detailed analysis of various approaches to the improvement of previously proposed calculation methods, suffice it to emphasize the important role of an ambient polar medium having a marked effect on the radiationless electron transfer rate in biological molecules.

For the so-called 'basic model' (see Section 2), this problem was considered in Ref. [13]. This study demonstrated that radiationless tunneling electron transfer may show a temperature dependence due to the influence of the classical environment on the shape of the reaction potential barrier. However, the basic model has a highly limited application. I therefore consider here a more realistic model of radiationless tunneling transition taking into account changes in the vibrational frequencies of the reaction coordinate during this process. This new model may be useful for the explanation of experimental data [9]. Formulas for electron transfer rates thus obtained can be used to describe other radiationless processes including oxidation–reduction enzymatic reactions, the rate of which is influenced by the molecular environment.

Let us consider a model of electron transfer from the initial state 1 to the final state 2 in a two-term molecule, which arises from the interaction between an electron and a high-frequency vibration Q (reaction coordinate) which, in turn, interacts with low-frequency fluctuations of the ambient polar medium (at frequency $\bar{\omega}$).

Let us assume for the sake of simplicity that this interaction involves an excited electronic state 2 and simulate the effect of the ambient medium on the reaction coordinate by a stochastic Gauss–Markov process $f(t)$ with the correlation function

$$\langle f(t)f(t')\rangle = B(t,t') = B_0^2(T)\exp\left(-\frac{|t-t'|}{\tau_c}\right). \qquad (29)$$

Here, $B_0^2(T)$ is the noise intensity, T is the temperature, and $\tau_c = 1/\gamma$ is the correlation time.

Then, the vibrational Hamiltonians in electronic states 1 and 2 will have the form

$$H_{1,2} = -\frac{\hbar^2}{2M}\frac{\partial^2}{\partial Q^2} + U_{1,2}(Q), \qquad (30)$$

$$U_1(Q) = \frac{1}{2}M\Omega_1^2 Q^2,$$

$$U_2(Q) = U_2(Q_0) - v_0(Q-Q_0) - f(t)Q,$$

where Q_0 is the point of intersection of the electronic terms $U_1(Q_0) = U_2(Q_0)$ (here, the consideration is confined to the linear term approximation).

Considering the transition from the ground vibrational state $\Phi_0(Q)$ of term 1 and taking into account the stationarity of the random process $f(t)$, one finds by known methods of the theory of multiquantum processes (see Ref. [1] for details) that

$$W_{12} = \frac{2V_{12}^2}{\hbar^2}\,\mathrm{Re}\int_0^\infty \mathrm{d}\tau \exp\left(\frac{\mathrm{i}\varepsilon_0\tau}{\hbar}\right)J_{12}(\tau), \qquad (31)$$

$$J_{12}(\tau) = \iint \mathrm{d}Q\,\mathrm{d}Q'\,\Phi_0(Q)\langle K(Q,\tau/Q',0)\rangle_f \Phi_0(Q'). \qquad (32)$$

The following notation is used in these equations:

$$\varepsilon_0 = U_2(Q_0) + v_0 Q_0,$$

$$K(Q,\tau/Q',0) = \langle Q|S_2(\tau)|Q'\rangle,$$

where the operator $S_2(\tau)$ is defined by Hamiltonian H_2, and $\langle\ldots\rangle_f$ stands for averaging over realizations of the random process $f(t)$.

Let us write down the Green's function $K(Q,\tau/Q',0)$ as a functional integral

$$K(Q,\tau/Q',0) = \int DQ(t)\exp\left\{\frac{\mathrm{i}}{\hbar}S(Q,\tau/Q',0)\right\}. \qquad (33)$$

Here, S stands for a classical action

$$S(Q,\tau/Q',0) = \int_0^\tau \mathrm{d}t L(Q,\dot{Q},t). \qquad (34)$$

The integral in (33) is taken over trajectories which satisfy the boundary conditions

$$Q(0) = Q', \quad Q(\tau) = Q. \qquad (35)$$

The extremal trajectory is found by a standard method. In so doing the boundary conditions are used.

We shall confine ourselves to the case of slow fluctuations $\bar{\omega}\tau_c \gg 1$ (quasi-static limit).

The parabolic term for the reaction coordinate near the point of intersection $Q = Q_0[U_1(Q_0) = U_2(Q_0)]$ is substituted by the linear term $v_0(Q-Q_0)$ (see Fig. 2).

The resultant expression for the characteristic function takes the form

$$J_{12}(\tau) = \left(\frac{1-\mathrm{i}bx^3/6}{1+\mathrm{i}x/6}\right)^{1/2}\frac{1}{\sqrt{1+(bx^2/2)(1+\mathrm{i}x/6)}} \times \exp\left\{-\frac{V_0^2}{4}x^2\frac{1+\mathrm{i}x/6}{1+(bx^2/2)(1+\mathrm{i}x/6)}\right\}. \qquad (36)$$

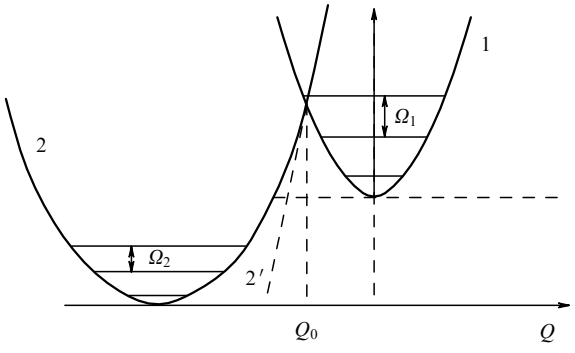

Figure 2. Adiabatic potentials of reduced (1) and oxidized (2) cytochromes. The dashed line 2′ corresponds to the linear term approximation to state 2.

The following notation was used when writing out the above expression:

$$x = \Omega_1 \tau\,, \quad V_0^2 = \frac{v_0^2}{\hbar M \Omega_1^3}\,, \quad b = \frac{B_0^2}{\hbar M \Omega_1^3}\,. \tag{37}$$

The rate of charge transfer from state 1 to state 2 can be calculated using formula (31) and the above expression for the generating function (32).

Figure 3 shows the dependence of the rate of charge transfer on the intensity of ambient medium fluctuations.

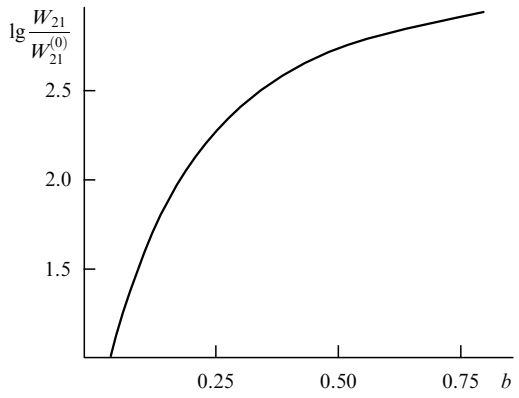

Figure 3. Plot of the probability of tunneling radiationless transition W_{21} versus parameter b ($W_{21}^{(0)}$ — the tunneling probability in the absence of external forces: $W_{21}^{(0)} = W_{21}(b=0) = 0.0138 \times 10^{-5}$).

The choice of the transfer reaction barrier in the form shown in Fig. 2 practically eliminates the problem of vibrational level resonance for the initial 1 and final 2 electronic states due to the continuous spectrum of nuclear motions in a uniform field. Such a model allows the temperature dependence of the transfer rate in low-potential cytochrome to be explained [9].

For a classical ambient medium one can suppose that $k_0 T \gg \hbar\bar{\omega}$, hence the parameter $B_0^2 \sim T$. In this case, the dependence of the electron transfer rate on B_0^2 determines its temperature dependence. The theoretical and experimental dependences coincide when

$$W_{12} \sim \exp\left(\frac{T}{T_0}\right), \quad T_0 = 43\,\mathrm{K} \tag{38}$$

(see Refs [14, 8] for details). It should be noted that expression (38) is different from the ordinary Arrhenius law $W_{12} \sim \exp[-\Delta/(k_0 T)]$ used in the majority of theoretical models. The difference of Eqn (38) from the Arrhenius law is due to the fact that expression (38) takes into consideration the effect of fluctuations of classical forces of the ambient medium on the shape of the reaction barrier, hence on the tunneling transfer rate.

5. Enzymatic reaction in an external electromagnetic field [5, 15]

At present, there is a wealth of experimental data showing the influence of external electromagnetic fields on the rate of biological processes including enzymatic reactions.

A well-known monograph [16] cites a number of experimental studies which investigated the effect of microwave radiation on the rate of various enzymatic reactions. Also, many other studies were concerned with the effect of laser radiation on the enzymatic reaction rate (see Ref. [5] for the results obtained by the author and his colleagues). Of special interest is the analysis of the well-known Fröhlich model simulating nonequilibrium vibrational states in biological membranes, which are produced by resonant swinging of these vibrations under the action of external electromagnetic radiation. Moreover, low-frequency vibrations are known to 'be coupled' to the enzymatic reaction coordinate. Taken together, these findings provide a unique opportunity for the resonance-mediated control of the rate of enzymatic catalysis and thus for the explanation of 'narrow' biological resonances. This problem is discussed below at greater length.

Let us first consider a simple model of an oxidation–reduction enzymatic reaction beyond the framework of the basic model, assuming that the vibrational frequencies Ω_2 and Ω_1 of [SE] and [PE] complexes, respectively, are different, whereas the equilibrium positions with respect to the reaction coordinate in the two complexes are identical. In this case, the nonadiabatic transition rate in the high-temperature limit is described by the Arrhenius exponent with the activation energy Δ given by the expression

$$\Delta = \frac{(J_2 - J_1)\Omega_2^2}{\Omega_1^2 - \Omega_2^2}\,, \tag{39}$$

where J_1, J_2 are the adiabatic potential minima in states 1 and 2.

Provided the interaction between the reaction coordinate Q and the low-frequency vibrational mode q is taken into account in the form

$$\widehat{V} = \frac{1}{2}\,\widetilde{V} q Q^2\,,$$

the activation energy of the enzymatic reaction for the slowly changing coordinate $q = q_0 \cos\varphi$ (q_0 is the vibration amplitude, φ is the random phase) will be described by formula (39) in which Ω_1^2 and Ω_2^2 should be substituted, respectively, by

$$\widetilde{\Omega}_{1,2}^2 = \Omega_{1,2}^2 + \frac{\widetilde{V} q_0}{M}\cos\varphi\,. \tag{40}$$

The nonadiabatic reaction rate is determined (the same as in Section 2) by means of averaging the Arrhenius exponent over the random phase of low-frequency vibration q; in other words, the transition rate W_{21} is given by the formula

$$W_{21} = W_{21}^0 \int_{-\pi}^{+\pi} \mathrm{d}\varphi \exp\left\{-\frac{J_2 - J_1}{k_o T}\,\frac{[\Omega_2^2 + (\widetilde{V}/M) q_0 \cos\varphi]}{\Omega_1^2 - \Omega_2^2}\right\}. \tag{41}$$

The main contribution to the integral over $\mathrm{d}\varphi$ is made by the saddle point $\varphi = \pm\pi$. In this case, the activation type of dependence of the transition probability remains unaltered, while the activation energy decreases by $\delta \sim q_0$. The quantity q_0 constitutes, in turn, the vibration amplitude of the soft mode subject to resonant swinging by external electromagnetic radiation. In the simplest case, one obtains

$$q_0 \sim F_0 \frac{1}{\nu^2 - \omega^2}\,,$$

where F_0 and ν are the strength and the frequency of the external electromagnetic wave.

δ grows sharply near the resonance.

It follows from the above that the enzymatic reaction rate is found to be an important function of external electromagnetic wave characteristics. Moreover, this rate may

undergo a sharp rise when the wave frequency approximates the frequency of the soft mode 'coupled' to the enzymatic reaction coordinate. This probably accounts for the existence of 'narrow' biological resonances, when some biological effects of a living system are markedly enhanced as the frequency of the external electromagnetic radiation approximates a certain threshold value. This approach can serve as a basis for explaining narrow biological resonances.

The phenomenon of a Bose – Einstein phonon condensation in biological systems first postulated by H Fröhlich (see, for instance, Ref. [17]) offers another aspect of the action of electromagnetic radiation on biological objects. According to this author, dipole-active vibrations of biological membranes in the frequency range from 10^{11} to 10^{12} Hz can be excited by external pumping and give rise to nonequilibrium vibrations. This phenomenon is in many respects analogous to Bose – Einstein condensation and has stimulated the interest of many researchers.

Critical comments on Fröhlich's ideas were published by M Lifshits [18, 19].

This problem was also discussed in a series of papers by T Wu and S Austin [20], R Mills [17], and several other authors.

Collectively, these studies allowed the applicability limits of Frohlich's model to be established. Moreover, they clarified the possibility of interpreting the results of Webb's spectroscopic experiments on biological objects (see, for instance, the monograph by A S Davydov [I13] for details).

The occurrence of high-intensity nonequilibrium long-wave vibrations predicted by Fröhlich's model is of special interest because the model suggests an interaction with the reaction coordinate of enzymatic catalysis (in full agreement with the dependence of the enzymatic reaction rate on the amplitude of low-frequency conformational vibrations).

This has led to the conclusion that Fröhlich's mechanism of Bose – Einstein condensation may be apparent upon a rise in enzymatic catalysis rates and is thus related to the entire spectrum of concomitant biological effects [21].

Elucidation of the role of squeezed vibrational states in quantum transitions, including enzymatic catalysis, appears to be of special interest [15]. A definition of squeezed states of an oscillator was offered in several reviews (see, for instance, Ref. [22]). Squeezed vibrational states and their role in optical quantum transitions were also discussed in Ref. [23].

It was shown earlier that overbarrier radiationless transitions are initiated by thermal fluctuations of oscillator vibration amplitudes (reaction coordinates). This usually leads to the Arrhenius law for the transition rate. Then the quantity $k_0T \equiv D_T^2$ stands for the dispersion of thermal fluctuations; it is normally small for biological structures.

The super-Poissonian distribution of oscillator amplitudes for squeezed vibrational states accounts, in case of a sufficiently high compression coefficient, for a large value of vibration amplitude dispersion D_s^2. So that the condition $D_s^2 > D_T^2$ is fulfilled. The latter condition may lead to a sharp exponential rise in the enzymatic reaction rate.

There are two main approaches to the formation of squeezed vibrational states of an oscillator: one is made by ultrashort laser pulses, the other by parametric swinging of an oscillator [22]. Further discussion is focused on the latter method.

In the quantum case, parametric resonance leads to an oscillator wave function in the form of a squeezed state wave function.

The compression coefficient for such a state (which determines the dispersion D_s) grows exponentially with time in accordance with the law $\exp\{(1/4)\alpha_0\omega_2 t\}$ (here, α_0 is the dimensionless coupling constant of two parametrically interacting vibrations, and ω_2 is the frequency of a hard valence vibration, e.g., for a CO_2 molecule).

In a simple case of CO_2-like molecules, the harder valence vibration of frequency $2\omega_2$ swings a deformation vibration of frequency ω_2 due to an anharmonic interaction between them.

In such cases $D_s^2 \gg D_T^2$ and the activation temperature dependence of the enzymatic catalysis rate can vanish. It is worthwhile to emphasize that a collision between the substrate and enzyme molecules, leading to the formation of a nonequilibrium substrate – enzyme complex, must be regarded as the starting point of enzymatic reaction. Naturally, an anomalous rise in the enzymatic catalysis rate will take place only when the reaction coordinate for the disintegration of the substrate – enzyme complex into the free product and the free enzyme coincides with the squeezed vibration coordinate. In this case, vibrations are excited by the energy released upon a collision between the substrate and enzyme molecules.

The breaking of the peptide bond in a formamide molecule upon its collision with an OH^- molecule was examined in Ref. [15]. It was shown to produce a resonance of a CO-vibration overtone with the fundamental tone of a CH-vibration. Swinging of the CO-vibration on account of the energy stored by the hard CH-vibration led to the modification of the reaction coordinate for the hydrogen bond breaking and facilitated rapid formation of the free products in the reaction, i.e. NH_3 and $COOH^-$.

6. Hemoglobin molecules in an external electromagnetic field [14]

Let us now try to explain the effect of external electromagnetic (EM) field on the rate of oxygen fixation by hemoglobin.

Hemoglobin is a blood protein which reversibly fixes oxygen and provides a good model of allosteric enzyme action. Strictly speaking, hemoglobin is not an enzyme, but it is well known that its saturation with oxygen depends on the oxygen partial pressure and is described by an S-shaped curve. A similar sigmoid curve describes the substrate saturation of allosteric enzymes [I11].

Alternatively, myoglobin saturation with oxygen is described by a hyperbolic curve, i.e. characterized by classical Michaelis – Menten kinetics [I11].

It is worth reminding that a hemoglobin molecule contains four hem-groups (iron-containing porphyrin) and four polypeptide chains, whereas each myoglobin molecule is made up of one hem-group and one polypeptide chain. This implies the existence of cooperative effects in a hemoglobin molecule, absent in myoglobin.

There are several well-known kinetic models explaining the sigmoid character of hemoglobin saturation with oxygen by cooperative effects in the system (for example, Perutz's model, Monod – Whyman – Changeu (MWC) model, Rabin's model). Some of these models are based on the assumption that the hemoglobin molecule undergoes reversible disintegration into two dimers each containing two hem-groups and α- and β-polypeptide chains [I11]. α- and β-dimers are considered to be functional subunits of hemoglobin. Binding of the very first substrate molecule to one of the

subunits of the regulatory enzyme (hemoglobin) is believed to facilitate the binding of the second molecule to the other subunit because the accompanying conformational changes in the former subunit are imparted, either mechanically or sterically, to the latter [I11].

In the previous section, the electron – vibrational model of enzyme-catalyzed processes as a radiationless transition from an initial substrate – enzyme complex [SE] to the final product and the free enzyme ([P] + [E]) was used to theoretically describe oxidation – reduction enzymatic reactions in an external EM field. It was also shown that an EM field may control radiationless transitions in an enzymatic system.

Both hemoglobin oxygenation and enzymatic reaction as a whole are known to proceed along several lines, say, through optical transition and radiationless transition channels, via collisions in chemical kinetics. The radiationless transition channel is practically closed in the case of hemoglobin oxygenation and an EM field opens it. A hem-group (iron-containing porphyrin) serves as an analog of the enzyme-active center in hemoglobin.

In deoxyhemoglobin, the coordination site is unoccupied and iron escapes from the porphyrin ring plane towards the histidine imidazole. In oxyhemoglobin, iron remains in the plane of the porphyrin ring. It is worthwhile to emphasize that the A_{2u} vibration related to the iron emergence from the porphyrin ring plane mixes up a_{1g} and a_{2u} electronic states of deoxyhemoglobin, separated by an energy gap of the order of 1 eV (in the case of oxyhemoglobin, the gap is almost 3 eV) [24]. Strong electron – vibrational interactions in deoxyhemoglobin are responsible for the marked Jahn – Teller pseudoeffect which leads, in terms of adiabatic potentials, to the narrowing of the upper sheet of the adiabatic potential and softening of its lower sheet. In addition, the lower sheet of the adiabatic potential passes from a parabola to a two-minimum potential.

The new vibronic (electron – vibrational) energy levels have the form

$$E_{\pm} = \frac{1}{2} m\omega^2 q^2 \pm \sqrt{\frac{\Delta^2}{4} + V^2 q^2}\,,$$

where Δ is the energy gap, V is the electron – vibrational coupling constant, and ω is the frequency of vibrational mode q.

In the case of oxyhemoglobin, there occurs a weak Jahn – Teller pseudoeffect corresponding to the softening of the lower sheet of the adiabatic potential in the absence of two potential minima.

In order to describe hemoglobin oxygenation kinetics in an external EM field, it is important to consider transitions from the lower sheet of the deoxyhemoglobin adiabatic potential to the lower sheet of the oxyhemoglobin adiabatic potential (via the excited state of oxyhemoglobin). In this case, the system will have a nonzero average dipole moment $\mathbf{d}_1 = \mathbf{d} \neq 0$ in the initial state of the process, and a zero average dipole moment $\mathbf{d}_2$ in the final state.

The interaction energy of a system [deoxyhemoglobin/EM field $\mathbf{F} = \mathbf{F}_0 \sin \nu t$] has the form $(\mathbf{d} \cdot \mathbf{F})$ (ν, $\mathbf{F}_0$ being the frequency and amplitude of the EM wave, respectively).

It is found from a known expansion

$$\exp(\mathrm{i}\rho \sin \nu t) = \sum_{n=-\infty}^{+\infty} J_n(\rho) \exp(\mathrm{i}n\nu t)$$

(where $J_n(\rho)$ is Bessel function of a real argument) that the quasi-energy harmonics separated by quantum $\hbar\nu$ have weights $J_n^2[(\mathbf{d} \cdot \mathbf{F}_0)/\hbar\nu]$ (see Ref. [1] for details) subject to the condition

$$\varepsilon_{1n} = \varepsilon_1 + n\hbar\nu\,, \quad n = 0, 1, 2, \ldots$$

Figure 4 shows only the first photonic satellite of a state corresponding to the deoxy-form of hemoglobin. It follows from this figure that radiationless transition from the photonic satellite is allowed but is less likely from a deoxy-form itself.

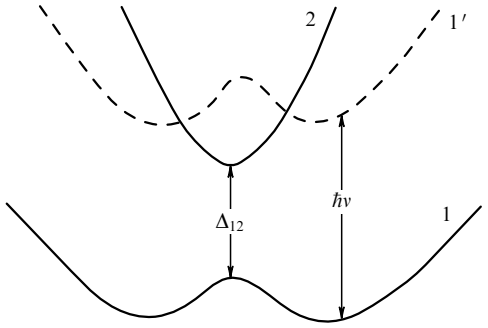

Figure 4. Adiabatic potentials of oxyhemoglobin (2) and deoxyhemoglobin (1) (these potentials have no points of intersection). The dashed line corresponds to the first photonic satellite 1′.

7. Multiquantum processes in enzyme molecules immobilized on biological membranes [25]

It is known that enzymes immobilized on biological membranes show enhanced activity. In this section, I wish to relate this enhanced activity to the influence of the membrane electric field on the rate of oxidation – reduction enzymatic reactions. The membrane potential in due course is a sensitive function of the external electromagnetic field (e.g., the capacity of the membrane may change with changing dielectric constant). Therefore, it should be expected that the enzymatic reaction rate also depends on the electromagnetic field.

Let us consider a model representing an immobilized enzyme as an electron – vibrational system, with the low-frequency mode being dipole-active and interacting with the membrane electric field $\mathbf{F}_0$.

The dipole moment of a polar molecule in the ith electronic state is given by

$$\mathbf{d}_i = \mathbf{d}_i^{(0)} + \mathbf{d}_i^{(1)} q\,, \quad i = 1, 2\,. \tag{42}$$

Here, $\mathbf{d}_i^{(0)}$ is the electronic part of the polar molecule dipole moment, $\mathbf{d}_i^{(1)} q$ is the dipole moment of a q-vibration ($\mathbf{d}_i^{(1)}$ also comprises a $\sqrt{\hbar/(m\omega)}$ factor having the dimension of length; m is the mass of an oscillator with frequency ω, and q is a dimensionless constant). In the simplest case, q-vibrations are described by the formula

$$q = q_0 \cos(\omega t + \varphi)\,. \tag{43}$$

Formula (43) corresponds to classical nuclear motion ($\hbar\omega < k_0 T$).

Therefore, the energy of interaction H_i' between a dipole moment $\mathbf{d}_i$ and an electric field $\mathbf{F}_0$ has the form

$$H_i' = \mathbf{d}_i^{(0)}\mathbf{F}_0 + \mathbf{d}_i^{(1)}\mathbf{F}_0 q_0 \cos(\omega t + \varphi)\,. \tag{44}$$

It follows from (44) that the second term of this formula has the same form as the energy of interaction between a constant dipole moment $\mathbf{d}_i^{(1)} q_0$ and an alternating electric field of intensity

$$\mathbf{F} = \mathbf{F}_0 \cos(\omega t + \varphi)\,. \tag{45}$$

Because the theory of multiquantum transitions under the action of alternating electric fields is fairly well developed [1] (see also Ref. [7] for multiquantum processes in biological molecules), the basic consequences of this theory can be used for the classical description of vibrations.

Hereinafter, our attention will be focused on the theory of multiquantum transitions from state 1 to state 2, which are illustrated in Fig. 5.

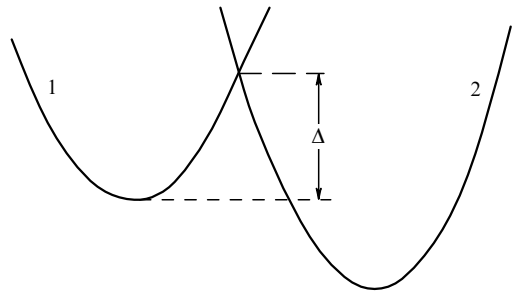

Figure 5. Adiabatic potentials (along the reaction coordinate Q) of [SE] complex (1) and free product/free enzyme ([P] + [E]) complex (2); Δ is the activation energy of radiationless transition $1 \to 2$.

Assume that the reaction coordinate Q in the initial state 1 has the frequency Ω ($\hbar\Omega \gg k_0 T$). For the sake of simplicity, the Q and q coordinates in the final electronic state 2 describe free motion in the potentials $VQ + V_0$ and $Uq + U_0$, respectively (the dipole-active asynchronous q-vibration corresponds, for instance, to the motion of substrate charged groups relative to oppositely charged groups of the enzyme; the Q coordinate may not have a dipole moment; the q coordinate in electronic state 2 does not interact with $\mathbf{F}_0$ either, because it describes free motion far from the membrane). V and V_0 constants define the reaction barrier and the thermal effect of the reaction, respectively. $U \equiv U_{22}$ and $V \equiv -V_{22}$ are the matrix elements of electron – vibrational interactions in electronic state 2. Constant U_0 may be assumed to equal zero, without compromising calculations.

The nondiagonal part of the electron/q-vibration interaction is taken as a perturbation operator producing a $1 \to 2$ transition:

$$\hat{H}_{12} = U_{12}\hat{q}\,. \tag{46}$$

Here, U_{12} is the electronic matrix element of the electron – vibrational interaction mixing the initial and final electronic states.

The expression for the rate of multiquantum transition W_{12} from state 1 to state 2 can be obtained by means of averaging the transition probability over the Gaussian distribution of q_0 amplitudes and over the phase φ uniformly distributed in the $[0; 2\pi]$ interval.

The transition rate is calculated exactly as in Section 2, taking into consideration the quantum description of the high-frequency Q-vibration. The resulting equation takes the form (see Ref. [25] for details):

$$W_{12} = \sum_{s=0}^{s_{\max}} W_{12}^{(s)}\,, \quad s_{\max} = \left[\frac{\tilde{\Delta}}{\hbar\omega}\right] + 1\,, \tag{47}$$

$$W_{12}^{(s)} = BU_{12}^2\,\frac{\Phi_0^{(s)}}{\hbar^2\Omega}\,\Phi_1^{(s)}\Phi_2^{(s)}\,, \tag{48}$$

$$\Phi_0^{(s)} = I_s\left(\frac{k_0 T}{2\hbar\omega}\,\rho^2\right)\exp\left\{-\frac{k_0 T}{2\hbar\omega}\,\rho^2\right\}, \tag{49}$$

$$\Phi_1^{(s)} = \exp\left\{-2\left(\frac{\tilde{\Delta} - s\hbar\omega}{\hbar\Omega}\right)\right\}, \tag{50}$$

$$\Phi_2^{(s)} = \exp\left\{-\frac{4\sqrt{2}}{3|\bar{V}|}\left(\frac{\tilde{\Delta} - s\hbar\omega}{\hbar\Omega}\right)^{3/2}\right\}, \tag{51}$$

$$\bar{V} = \frac{V}{\hbar\Omega}\,, \quad \rho = \frac{1}{\hbar\omega}\,\mathbf{d}_1^{(1)}\mathbf{F}_0\,. \tag{52}$$

Here, $[A]$ is the integral part of A; B is the dimensionless multiplier showing weak dependence on the system's parameters, and $\tilde{\Delta}$ is the activation energy of the process, including Stark shifts of the levels. Because the dipole moments $d_1^{(0)}$ and $d_2^{(0)}$ are largely formed by the enzyme, their values are very similar. Therefore, the Stark shifts are about the same, and the difference between Δ (see Fig. 5) and $\tilde{\Delta}$ is rather small. However, in each particular case, the correction for the Stark shifts must be taken into account. The $U_{12}^2\Phi_0^{(s)}$ factor is proportional to the probability of system excitation to the sth vibrational level of the q-oscillator. $\Phi_1^{(s)}$ is the probability of tunneling from the initial sth level of the system to the final state at point b (see Fig. 6), and $\Phi_2^{(s)}$ is the probability of tunneling through the triangular barrier abc. It follows from formula (48) for the transition rate that $W_{12}^{(s)}$ is a nonmonotone function of s.

At room temperature, there is a very small probability of tunneling from the ground state of the q-oscillator. For large parameters $\rho(\mathbf{F}_0\mathbf{d}_1^{(1)} \gg \hbar\omega)$, the main contribution to the transition probability is made by the term $W_{12}^{(s_{\max})}$, which corresponds to an overbarrier transition. This probability is

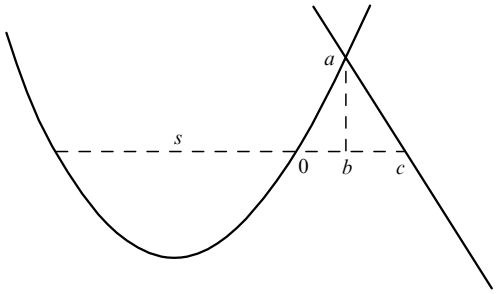

Figure 6. Tunnel decay of the sth vibrational level of q-oscillator through the reaction barrier $0ac$.

proportional to the Arrhenius exponential function $\exp[-(1/k_0T)\tilde{\Delta}]$.

However, an overbarrier transition for real parameters of biological systems $F_0 \lesssim 10^7\ \mathrm{V\,cm^{-1}}$, $d_1^{(1)} \lesssim 1\ \mathrm{D}$, $\omega \approx 100\ \mathrm{cm^{-1}}$, $\rho \sim 1$ appears unlikely. For the field intensity $F_0 (F_0 \sim \hbar\omega/d_1^{(1)})$ and a given temperature T, there is an optimal transition rate $W_{12}^{(s_{\mathrm{opt}})}$ through tunneling from the s_{opt} level. The value of s_{opt} can be determined using the approximation

$$\Phi_0^{(s)} \sim \exp\left\{-\frac{s^2\hbar\omega}{\rho^2 k_0 T}\right\}, \quad \frac{k_0 T}{2\hbar\omega}\rho^2 > s \tag{53}$$

and the condition

$$\frac{\tilde{\Delta}}{k_0 T} = \frac{s^2\hbar\omega}{\rho^2 k_0 T} + \frac{2(\tilde{\Delta} - s\hbar\omega)}{\hbar\Omega} + \frac{4\sqrt{2}}{3|\bar{V}|}\left(\frac{\tilde{\Delta} - s\hbar\omega}{\hbar\Omega}\right)^{3/2}. \tag{54}$$

It is easy to show that

$$s_{\mathrm{opt}} = \frac{1 + (1/|\bar{V}|)\sqrt{2\tilde{\Delta}/(\hbar\Omega)}}{\hbar\Omega/(k_0T)(1/\rho^2) + (1/|\bar{V}|)[\hbar\omega/(2\tilde{\Delta})]\sqrt{2\tilde{\Delta}/(\hbar\Omega)}}. \tag{55}$$

Quantitative assessment of typical parameters for biological membranes yields

$$\begin{aligned} &F_0 = 10^7\,\frac{\mathrm{V}}{\mathrm{cm}}, \quad d_1^{(1)} = 1\,\mathrm{D}, \quad \omega = 50\ \mathrm{cm^{-1}}, \\ &\tilde{\Delta} = 0.5\ \mathrm{eV}, \quad k_0T = 0.025\ \mathrm{eV}, \\ &\hbar\Omega = 0.1\ \mathrm{eV}, \quad |\bar{V}| = 3, \end{aligned} \tag{56}$$

hence,

$$s_{\mathrm{opt}} = 5. \tag{57}$$

This means that excitation to the $s = 5$ level of the 'soft' mode q makes tunneling more likely than a direct overbarrier transition.

Taken together, these results indicate that the enzymatic reaction rate for an immobilized enzyme is higher than that for a free enzyme by virtue of the influence which the membrane electric field exerts on the transition probability. This effect of the electric field leads to a change in both the height and the width of the reaction barrier due to the preliminary excitation of the system to the sth vibrational level of the q-oscillator.

The enzymatic reaction rate exponentially increases with the growing strength of the membrane electric field. Because the membrane potential is known to change under the action of external chemical and physical factors, the rate of OR reactions involving an immobilized enzyme is also subject to changes. It may be conjectured that the nonselective action of low-intensity laser radiation on biological objects is due to altered membrane potentials (sometimes enhanced rather than diminished). In this case, immobilized enzymes undergo activation and produce the resulting biological effect.

By way of example, let us examine cytochrome P-450 oxidation, which is involved in the conversion of inactive molecular oxygen into its active forms [26]. The Q coordinate corresponds to the motion of oxygen atoms in an O_2 molecule which is activated by two electrons. These electrons appear as a result of interaction between a NADH molecule and a cytochrome P-450 molecule. The q coordinate corresponds to the dipole-active vibration of an O_2^{2-} molecule relative to the positively charged Fe^{3+} group.

The frequency ratio $\omega/\Omega = 0.1-0.2$. Active oxygen oxidizes a variety of substrates in well-known reactions [27–29].

To conclude this section, active oxygen production depends on the membrane potential. The yield of active (atomic) oxygen is related to the rate of enzymatic reaction involving P-450 cytochrome and varies according to the intensity of laser radiation incident on the membrane. This is believed to account for the nonselective action of laser radiation on biological objects.

8. Generation of short-wave ultraviolet radiation in cells under the action of ultrashort pulses of intense visible light [30]

French researchers have recently reported a new physical phenomenon relating to the generation of highest-order optical harmonics (in the X-ray range) under the action of ultrashort power laser pulses of visible light [31]. For systems with a nonzero average dipole moment, this phenomenon was discussed by the author and co-workers in Refs [32, 33]. Because certain biological macromolecules possess high dipole moments [34], they can be used as effective objects for the generation of higher optical harmonics. In this case, it is important that in the excited electronic state of the biological macromolecule a new conformation may be realized with a dipole moment $\mathbf{d}_2$ differing from the dipole moment $\mathbf{d}_1$ of a molecule in the ground electronic state.

The intensity $I^{(s)}$ of the sth harmonic of laser radiation with frequency ν is described, as shown in Refs [32, 33, 35], by the expression

$$\begin{aligned} I^{(s)} &= C\left(\frac{V_{12}}{\hbar\nu}\right)^4 \left\{\frac{1}{\sin\pi a_+} J_{a_+}(\rho) J_{s-a_+}(\rho) \right. \\ &\quad \left. + \frac{1}{\sin\pi a_-} J_{a_-}(\rho) J_{s-a_-}(\rho)\right\}^2, \\ \rho &= \frac{(\mathbf{d}_1 - \mathbf{d}_2)}{\hbar\nu}\mathbf{F}_0, \quad a_\pm = \frac{\varepsilon_2 - \varepsilon_1 \pm \hbar\nu}{\hbar\nu}, \quad a_\pm \neq [a_\pm]. \end{aligned} \tag{58}$$

Here $[a]$ is the integral part of a, C is a constant, V_{12} is the matrix element of the dipole $1 \to 2$ transition, $J_\mu(\rho)$ is the Bessel function of a real argument, ε_1, ε_2 are the energies in electronic states 1 and 2, and $\mathbf{F}_0$ is the amplitude of the laser radiation field. Expression (58) follows from results produced in Ref. [32] using the formula

$$\sum_{m=-\infty}^{+\infty} \frac{J_m(x) J_{s+m}(x)}{a+m} = \frac{\pi J_a(x) J_{s-a}(x)}{\sin a\pi}, \qquad a \neq [a]. \tag{59}$$

It is clear from formula (58) that the intensity of the sth harmonic changes slowly with increasing harmonic number provided that

$$s \cong \rho + a_\pm. \tag{60}$$

A protein molecule can have rather a large dipole moment. For example, it is approximately 1,000 D for γ-globulin [34]. In order to reach a short-wave range of harmonic generation at $|\mathbf{d}_1 - \mathbf{d}_2| \sim 100$ D, it is necessary to induce a field of intensity $F_0 \sim 10^7\ \mathrm{V\,cm^{-1}}$.

For this purpose, GW laser pulses should be employed. It is known that ultrashort (picosecond) pulsed fields of such intensity fail to destroy biological objects. Also, it is worthwhile to emphasize that the photoexcitation of a protein molecule in the absorption range of $S = S_0$ bonds (i.e. via cysteine amino acid) results in changes of protein conformation and a molecular dipole moment.

Following the line of reasoning in a paper by the author and co-workers [30], the conversion of picosecond pulses of green radiation into ultraviolet (UV) radiation is of special interest in the context of thymine dimerization in DNA under the action of visible light. The importance of this process is emphasized by the high penetrating power of visible light, which can penetrates as distinct from UV radiation into plant generative organs.

The possibility of thymine dimerization under the action of picosecond laser pulses of visible light was verified using the E.coli strain K12 AB2480 uvr$^-$recA$^-$ kindly provided by professor G B Zavil'gel'skiĭ. This strain is highly sensitive to far UV radiation because it lacks the mechanism for dark reparation of thymine dimers which thus can undergo monomerization only due to photoreactivation with light having a wavelength of 0.390 μm or more.

Thymine dimerization was unequivocally documented in experiments designed to expose bacterial suspensions to picosecond pulses of green light. The viability of the irradiated bacteria turned out to be almost an order of magnitude higher than prior to photoreactivation (Fig. 7).

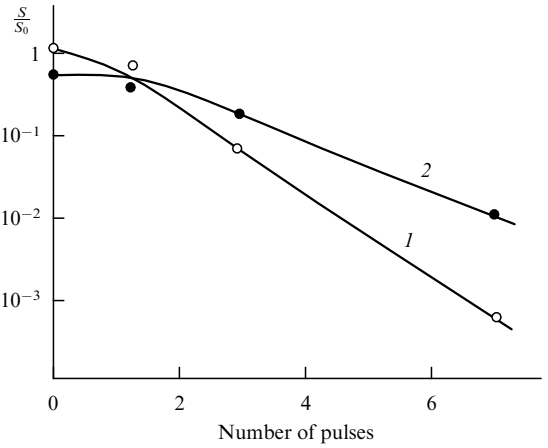

Figure 7. Survival of E.coli strain K12 AB2480 uvr$^-$recA$^-$ irradiated by picosecond pulses of visible light ($\lambda = 0.53$ μm): *1* — without photoreactivation; 2 — photoreactivation for 20 min at 37 °C ($\lambda \geqslant 0.390$ μm); pulse energy $E_i \approx 3$ mJ.

This experiment confirmed the possibility of generating ultraviolet harmonics of optical radiation through the mechanism discussed above in connection with the derivation of formula (58).

Thymine dimerization in DNA gives evidence of the appearance of ultraviolet radiation in the cell volume.

9. Generation of higher optical harmonics on biological membranes. Application to problems of mitogenesis and oncogenesis [36]

The discovery of the generation of higher optical harmonics under the action of pulsed optical radiation on quantum systems has stimulated numerous theoretical and experimental studies (see, for instance, Ref. [31]).

The use of a GW laser as the source of pulsed radiation to generate the highest-order optical harmonics in biological systems was discussed in Section 8.

Higher optical harmonics can be also induced by collisions with protons [37]. It will be shown below that this mechanism may be triggered using fast protons accelerated on biological membrane potentials. This specific method for the endogenic generation of optical harmonics is based on the possibility of exciting coherent vibrational wave packets (the existence of nonequilibrium vibrations in living cells has been confirmed experimentally [21] by the analysis of laser-Raman scattering spectra). Electrons, in turn, are able to accumulate the energy of many vibrational transitions, owing to electron – vibrational interactions, and thereafter release it in a flash of short-wave electromagnetic radiation. It will be shown below that such radiation promotes electromagnetic cell linkage, i.e. it can, along with other factors, underlie cellular cooperative effects and play a role in such important biological processes as mitogenesis and oncogenesis (see also a very interesting paper on oncogenesis by M Cooper [38]).

9.1 Excitation of coherent vibrations in protein molecules on the biological membrane

The kinetic energy of a proton travelling along an ion channel of a biological membrane is

$$E_{\text{kin}} = \frac{1}{2}\,\mu_0 v^2 \approx e\varphi\,. \tag{61}$$

Here, μ_0 is the proton mass, v is the proton velocity, and $e\varphi$ is the potential energy related to the action of the membrane potential φ ($e\varphi \sim 0.1-0.2$ eV). This energy is spent to synthesize ATP molecules with a certain probability of reaction yield η. A major part of the proton stream energy covers vibrational excitation of the surrounding protein molecules.

Let us consider a model of proton collision with an 'effective diatomic' molecule. For the membrane potential φ we get $e\varphi = 0.2$ eV, and the proton velocity is $v \cong 10^6$ cm s^{-1}. This energy is sufficient to produce a wave packet of approximately 10 vibrations of frequency $\omega \cong 200$ cm^{-1}.

The wave function of the vibrational packet is derived from the exact equation

$$\psi(q,t) = \int\int G(q,t;q',t')\,W(q',t')\psi(q',t')\,\mathrm{d}q'\,\mathrm{d}t'\,. \tag{62}$$

Here, $G(q,t;q',t')$ is a Green's function of the ω-oscillator, $W(q',t')$ is the interaction energy between an incident proton and ω-vibration. The collision time $t \sim \alpha_0/v$, where α_0 is the characteristic distance for the retarding potential (usually $\alpha_0 \sim 1$ A [39], hence $t \sim 10^{-14}$ s). Such a short collision time allows the calculation with formula (62) to be simplified. In this case, $\psi(q',t')$ should be substituted by $\psi(q,0)$ and the interaction term $W(q',t')$ chosen in the form [40, 41]

$$W(q',t') = -F(t')\left(1 + \frac{\lambda q'}{\alpha_0}\right), \tag{63}$$

where

$$F(t') = \frac{\mu_1 v^2}{2}\ \mathrm{sch}\ \frac{vt'}{2\alpha_0}\,, \quad \lambda = \frac{m_{\text{B}}}{m_{\text{A}} + m_{\text{B}}}\,,$$

q' is the deviation of the vibrational coordinate from equilibrium, μ_1 is the reduced mass of the oscillator and the

incident proton, m_A and m_B are the masses of atoms in the 'effective diatomic' molecule AB.

The wave function $\psi(q,0)$ is the eigenfunction of the Hamiltonian

$$H = H_{osc} + W(q,0)\,. \tag{64}$$

The oscillator is assumed to be initially unexcited ($\hbar\omega \gg k_0 T$), so that

$$\psi(q,0) = \left(\frac{1}{\pi}\right)^{1/4} \frac{1}{\sqrt{\sigma}} \exp\left\{-\frac{(q-\xi_0)^2}{\sigma^2}\right\}, \tag{65}$$

$$\xi_0 = \frac{v^2\lambda}{2\alpha_0\omega^2}\,, \quad \sigma^2 = \frac{\hbar}{\mu_1\omega}\,.$$

The evaluation of integral (62), taking into consideration the above observations, yields

$$\psi(q,t) = \left(\frac{1}{\pi}\right)^{1/4} \frac{1}{\sqrt{\sigma}} \exp\left(-\frac{i\omega t}{2}\right) \exp\left[-\frac{(q-\xi_0\cos\omega t)^2}{\sigma^2}\right]. \tag{66}$$

The function $|\psi(q,t)|^2$ describes the wave packet undergoing harmonic vibrations.

9.2 Oscillatory mechanism of higher optical harmonic excitation in protein molecules

Let us suppose that the vibratory protein groups located close to the ion channel's outlet undergo excitation by protons, which results in the induction of vibrational wave packets (see Subsection 9.1).

Construction of the ion channel in the form of a cavity with walls of parallel α-spiral protein fragments [12] allows fast protons to fly not only through the channel but also through the cavities of the α-spiral fragments. A proton accelerated by the membrane potential to the velocity $\sim 10^6$ cm s^{-1} needs approximately 10^{-12} s to fly through a 30–100 A long channel of a biological membrane. Notice that the damping time of amide group vibrations in a protein molecule can be rather prolonged [42]. (The mechanism responsible for a weak damping is frequently associated with the possibility of exciting solitons [I13]). For amide-VII vibrations we get $\omega = 200$ cm^{-1}, and the condition that the damping time of vibrations is much longer than 10^{-12} s can be fulfilled.

Therefore, an electron bound in a protein molecule acquires an additional energy $V(\mathbf{r},\mathbf{q})$ produced by the electron–vibrational interaction

$$V(\mathbf{r},q) = \sum_{i=1}^{s_0} V_i(\mathbf{r}) q_i\,. \tag{67}$$

Here, $\mathbf{r}$ is the electron's radius vector, q_i is the vibrational coordinate of the ith group, s_0 is the number of vibratory groups (near the outlet of proton channels) excited by proton impacts, and $V_i(\mathbf{r})$ characterizes the electron interaction with the ith group.

The mean value of $V(\mathbf{r},q)$ in the adiabatic approximation takes the form

$$\bar{V}(q) = \sum_{i=1}^{s_0} \bar{V}_i q_i\,, \tag{68}$$

$$\bar{V}_i = \int |\psi_e(\mathbf{r})|^2 V_i(\mathbf{r})\,d\mathbf{r}\,.$$

Here, $\psi_e(\mathbf{r})$ is the wave function of an electron located (close to the outlet of proton channels) in an amino acid residue of a protein molecule.

The state of an electron in the highest filled amino acid orbital has the characteristic radius r_0. It interacts with vibrational packets within a radius of 10–15 A, which corresponds to the specific size of a polaron (conformon) in macromolecules [43]. In our case, such long-wave optical vibrations are represented by oscillations of neighboring groups of amide-VII or more precisely by their 'longitudinal components'.

The potential $\bar{V}(q)$ can be written in the form

$$\bar{V}(q) = \sum_{i=1}^{s_0} \bar{V}_i q_{0i} \cos(\omega t + \varphi_i)\,. \tag{69}$$

Here, φ_i is the initial phase determined by the instant of proton collision with the ith vibrational group, and q_{0i} is the amplitude of classical vibration of the ith group ($q_{0i} \equiv \xi_0$, see Subsection 9.1).

In other words, the electron is influenced by the effective electric field of the surrounding groups, induced by the electron–vibrational interaction $\bar{V}(q)$. The potential $\bar{V}(q)$ is in a way analogous to the interaction energy between an electron and the electric field s_0 of asynchronous laser modes of frequency ω in a resonator [44]. If the number of modes $s_0 > 10$, the interaction potential (69) may be represented as

$$\bar{V} = \mathcal{F} D^* \cos\omega t\,, \tag{70}$$

where $D^* = er_0$ (D^* is the dipole moment of an amino acid located near the outlet of proton channels).

The strength of the effective electric field $\mathcal{F}$ is distributed with the Gaussian weight function $g(\mathcal{F})$:

$$g(\mathcal{F}) = \frac{1}{\mathcal{F}_0^2} \exp\left\{-\frac{\mathcal{F}^2}{\mathcal{F}_0^2}\right\}. \tag{71}$$

Here, $\mathcal{F}_0^2$ is the mean square of the effective electric field strength.

The variance $\mathcal{F}_0^2$ of the Gaussian distribution is characterized by the mean vibrational energy $\bar{V}(q)$. The distribution function $g(\mathcal{F})$ reflects changes in the $\mathcal{F}$ amplitude due to the random distribution of φ_i phases in the $[-\pi;\pi]$ interval.

Let us consider the generation of optical harmonics during the interaction of a classical alternating electric field $\mathcal{F}\cos\omega t$ with a two-level electronic system simulating quantum transitions in protein molecules. Such a system can be made up of the electron ground state 1 and the excited state 2 corresponding to the highest filled and the lowest unfilled amino acid orbitals in a protein molecule, respectively (the amino acid being located near the outlet of membranous proton channels).

Suppose, for the sake of simplicity, that the excited electron does not interact with vibrations of the nearest groups (or is involved in weaker interactions than in the ground state; true, this constraint is unessential and easy to take into consideration). The intensity of the nth optical harmonic at frequency $\nu = n\omega$ can be computed in the same way as in Refs [30, 31] [see Eqn (58)]:

$$P(\mathcal{F};\nu) \sim \mathcal{F}^2 \left(\frac{V_{12}}{\hbar\omega}\right)^4 \left(\frac{J_{a_+}(\rho)J_{n-a_+}(\rho)}{\sin\pi a_+} + \frac{J_{a_-}(\rho)J_{n-a_-}(\rho)}{\sin\pi a_-}\right)^2, \tag{72}$$

where

$$\rho = \frac{\mathcal{F}D^*}{\hbar\omega}\,, \quad a_\pm = a_0 \pm 1\,, \quad a_0 = \frac{\Delta}{\hbar\omega}\,, \quad \Delta = \varepsilon_2 - \varepsilon_1\,,$$

and a_0 must not be an integer; $J_\mu(\rho)$ is the Bessel function of a real argument ρ, Δ is the energy gap between the ground 1 and excited 2 electron states, V_{12} is the matrix element of dipole transition from the electron state 1 to electron state 2. The observed intensity of the nth harmonic of optical radiation can be obtained from formula (72) by averaging the latter with the series involving distribution function $g(\mathcal{F})$:

$$\bar{P}(v) = \int_0^\infty g(\mathcal{F})P(\mathcal{F}; v)\,\mathrm{d}\mathcal{F}^2\,. \tag{73}$$

Only numerical integration of Eqn (73) written in the general form is possible. However, an approximate analytical expression can be obtained with a sufficient degree of accuracy. In a polaron (conformon) model [43], the energy of electron localization ($\cong \Delta$) is of the same order of magnitude as the additional vibrational energy $\bar{V}(q)$ of an electron, i.e. $a_0 \cong \rho_0$, $\rho_0 = \mathcal{F}_0 D^*/(\hbar\omega)$. The main contribution to the integral (73) comes from ρ of the order of ρ_0. In this case, the Bessel functions $J_{a_+}(\rho)$ and $J_{a_-}(\rho)$ are smoothly and slowly varying functions and one can factor them outside the integral sign. Further integration is carried out exactly and leads, taking account of all necessary constants for $\bar{P}(v)$, to

$$\bar{P}(v) \cong \frac{e^4 v^4 \hbar^2 f_{12}^2 \mathcal{F}_0^2}{3m_e^2 c^3 \Delta^2 \omega^2} \frac{2(n-a_0)^2\pi^2}{(\sin\pi a_0)^2} J_{a_0}^2(\rho_0) \times \exp\left(-\frac{\rho_0^2}{2}\right) I_{n-a_0}\left(\frac{\rho_0^2}{2}\right). \tag{74}$$

Here, f_{12} is the oscillator strength, m_e is the electron mass, and $I_{n-a_0}(\rho_0^2/2)$ is the modified Bessel function.

For typical values of the system parameters $\omega \cong 200$ cm^{-1}, $\Delta = 3$ eV, $f_{12} \cong 0.5$, and $r_0 \cong 2$ A, we get for the optical harmonic intensity at frequency v ($\hbar v = 6$ eV): $\bar{P} \approx 50$ erg s^{-1}.

9.3 Electromagnetic cell linkage. Implications for mitogenesis and oncogenesis

Cell–cell interactions are of special interest because they allow for the consideration of cooperative effects such as mitotic cell division in the processes of cell differentiation. Mitogenic radiation is a well-known phenomenon [45, 46]. It is worthwhile to note that the ultraviolet radiation we generally associate with mitogenic rays is detected by a biological receiver at a rate of 10–40 UV photons per cell having a surface area of $\cong 1000$ μm^2 [47]. The intensity of radiation from a single channel has been calculated in Subsection 9.2. In a cell having on average 10 channels simultaneously open to let protons pass, the radiation intensity is $\bar{P} \sim 500$ erg s^{-1}.

This accounts for the maintenance of instantaneous electromagnetic linkage of a given cell with a group of cells as opposed to the slow chemical diffusive linkage.

A current concept has it that UV radiation initiates cell division, i.e. mitosis, acting via lipid peroxidation [48]. In this sense, endogenic ultraviolet radiation is conducive to the maintenance of communication channels through which information-bearing signals are transmitted from one cell to another. It thus supports cooperative effects and promotes the growth of sister-cells specific for a given biological process.

This line of reasoning leads to an important conclusion concerning the development of malignant tumors. Indeed, a break of electromagnetic cell linkage results in the loss of the cooperative effects underlying reproductive processes and cell specialization. Genetic aspects of malignancy remain a matter of numerous studies (see, for instance, Section 11 for a review of models for the triggering mechanism of action of a sarcoma-producing oncogene). What may be the cause of broken electromagnetic links between cells supported by UV harmonic generation? It is, in the first place, an enhanced utilization of intracellular ATP molecules (a characteristic feature of fast-proliferating cancerous cells) and a concurrent decrease of the proton fraction capable of exciting vibrational packets in amide groups, resulting in an essential weakening of UV harmonic intensity. These lead in turn to the breakage of electromagnetic intercell links and promote the autonomous behavior of individual cells with respect to their remaining stock. Energy expenditure to support membrane potentials substantially increases and cooperative effects give room for chaotic piling up of undifferentiated cells.

A developed model of UV radiation by cells also offers a plausible explanation of the so-called distance paradox observed in mitogenic ray experiments [45, 49]. This paradox consists in that the effect of cell division in the receiver (i.e. mitogenic effect) is heightened with increasing distance between the inductor (cells producing ultraviolet radiation) and the receiver (cells undergoing division under the influence of UV radiation emitted by the inductor), when the radiation is modulated with the aid of an UV-nontransparent disk having a small (~ 1 mm^2) hole and rotating with an angular velocity of approximately 1000 revolutions per minute. Based on the above considerations, this paradox can be interpreted in the following way. The intensity distribution of the electromagnetic field produced by an isolated emitter obeys the radiation law for a single dipole (see Fig. 8). The maximum radiation intensity is perpendicular to the emitting dipole vector, while the minimal intensity (which equals zero) coincides with the dipole axis. In other words, with increasing distance, the radiation from a separate emitter spreads over a larger area of the receiver which harbours a greater number of isolated cells absorbing radiation.

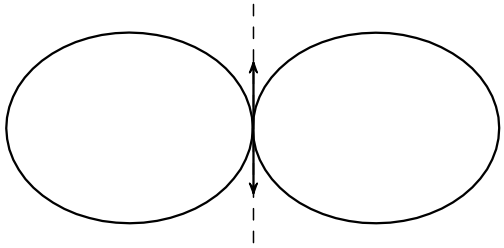

Figure 8. Angular distribution of electric dipole radiation intensity in the plane across the dipole axis.

It has been shown that the radiation intensity decreases as the distance increases. However, if the radiation dose remains sufficiently large to induce cell division, the overall mitogenic effect increases due to the larger number of radiation-absorbing cells.

Why then is this effect observed only in the case of radiation modulation and inapparent in the absence of a

holed disk? When the inductor and the receiver are at a large distance from each other and the shield is absent, the electromagnetic fields of many individual and chaotic emitters add up to give a net electromagnetic radiation incident on the receiver cells. Naturally, the resultant radiation falls off essentially and its intensity may be lower than the threshold intensity necessary to trigger cell division.

The rotating disk with a hole allows the radiation of a single emitter to be separated from that of many others. The above conjecture of an increased number of receiver cells absorbing radiation from the inductor is fully applicable to this situation. Given the said rotational frequency of the disk, the exposure is long enough to exceed the generation and action times of UV harmonics.

10. Dipole ordering of globular proteins in cells. Electromagnetic field as a morphogenetic factor [1]

Globular protein fractions have been reported to have enormously large constant dipole moments. For example, the dipole moment of γ-globulin is 1,000 D [34]. Large dipole moments are intrinsic in many proteins having domains of β-form polypeptide chains in their structure. It is this property of globular proteins that makes them a valuable object for examining the effects of external electromagnetic fields on the nonlinear optical characteristics of biological systems [30]. At the same time, endogenic (internal) electromagnetic radiation can also influence the orientation of animal cells during mitotic division, as was first shown in a well-known work [50]. Since the cytoskeleton of animal cells is essentially formed by actinic filaments [51] which largely contain globular proteins, it would be interesting to elucidate the nature of endogenic electromagnetic radiation and its role in the dipole ordering of globular proteins.

In the experiments reported in Ref. [50], confluent animal cell layers were plated on the opposite surfaces of thin glass films. One layer (inductor) produced electromagnetic radiation; the other was the receiver. Evidence of nonequilibrium electromagnetic radiation emitted in the infrared range of the spectrum ($\lambda = 800-900$ nm) which was obtained in Ref. [50] can be understood in the light of ideas developed by the author of this review with respect to the role of electron–vibrational processes in the generation of higher optical harmonics by macromolecules. In the context of the present study, the induction of coherent vibrations of frequency $\omega \cong 200$ cm^{-1} may be due to the excitation of an amide group (e.g., amide-VII) by fast protons.

Based on the results presented in Section 9, it is possible to compute the total field of infrared harmonics ($\hbar v \cong 1$ eV) generated by the inductor and acting on the receiver. Due to the dipolar nature of radiation, electromagnetic waves of individual emitters located in a given filamentous cell layer parallel to the glass surface combine, in accordance with Huygens' principle, and give rise to a plane wave front. Because each cell contains k filaments (k is of the order of a few hundred) excited by fast protons near the outlet of intracellular membrane channels (e.g., in mitochondrial membranes, membranes of endoplasmic reticulum), it is evident that the intensity of radiation emitted by a single inductor cell (for a given frequency $v = n\omega$) is k times that of an individual filament. Moreover, there are $\varkappa$ contacts of one filament with proton channels ($\varkappa$ is a number between 10 and 100). Therefore, the total radiation intensity transferred from one inductor cell is given by

$$P_0(v) = k\varkappa \bar{P}(v) .$$

An area of 1 cm^2 gives home for χ cells ($\cong 10^6$), so that the final radiation intensity from 1 cm^2 at a frequency $v = n\omega$ is $I(v) = \chi P_0(v)$.

Accordingly, the strength of the electric field at the receiver surface is

$$F_R = \sqrt{\frac{4\pi}{c} I(v)} ,$$

where c is the velocity of light.

The energy of interaction between a growing filament in the receiver and this field is given by the formula

$$E = D_f F_R \cos\theta .$$

Here, D_f is the dipole moment of a growing filament, and θ is the angle between the intensity vector F_R and the average direction of filament axes in the receiver (the initial growth direction in the receiver is approximately similar for all growing filaments). Because in a real system θ is not exactly equal to 90°, then $\cos\theta \neq 0$. The number of receiver cells in the experiment [50] being much smaller than that of inductor cells, the action of the receiver on the inductor may be neglected.

In the experiments reported in Ref. [50], the filament axes in the inductor cell layer were parallel to the partition (glass) plane. Inductor cells emitted linearly polarized waves, and the intensity vector of their electric fields was parallel to the filament axis. Receiver cells on the other side of the glass film were initially oriented in such a way that their filament axes lay at an arbitrary angle to the filament axes of inductor cells. Dividing receiver cells were continuously affected by the plane front of electromagnetic waves produced by inductor cells. The electric field of these electromagnetic waves tended to align the dipole moments of globular proteins, and the receiver filaments for that matter, along its own intensity vector or, after all, parallel to the inductor filaments. This accounted for the effect of electromagnetic radiation on the spatial orientation of the receiver cells observed in Ref. [50]. Naturally, the binding energy of individual proteins inside a filament is supposed to be higher than the mean thermal energy $k_0 T$, for instance, on account of hydrogen bonds.

Dipolar protein structures are known to play an important role in shaping cellular architectonics, i.e. the morphological characteristics of the cell. It is therefore appropriate to speak about the morphogenic function of endogenic electromagnetic fields and consider them as morphogenes, along with chemical gradients and other factors acting to the same effect [52].

11. Synergetic models based on enzymatic processes in molecular biology. Mobile genetic elements

The model of oxidation–reduction enzymatic reactions developed in previous sections is based on the concept of the multiphonon mechanism of elementary catalytic acts and can

[1] This section is an extention of a previous work [36] and was written jointly with B S Filip and E Yu Kanarovskiĭ.

be extended to other nonadiabatic enzymatic reactions. The nonlinear dependences on substrate concentration and temperature discussed earlier in this review can be used to describe nonlinear processes in molecule-genetic triggering systems. As a rule, the description must take into account feedback processes such as those listed below.

(1) Regulation of the rec*A* genorecombination expression by a lex*A*-coded repressor protein in procaryotes. This process was first described by E M Witkin [53] (see also [54]).

(2) Expression of eucaryotic genes (a genetic trigger similar to the Jacob – Monod trigger [55]).

(3) The mechanism triggering Src-oncogene incorporation in Georgiev's model [56] (see also [57]).

(4) The mechanism triggering a switch of phage λ suggested by M Ptashne [58] (see also [59]).

The auto-oscillatory process is exemplified by wave mutagenesis comprehensively investigated by N P Dubinin [60] (see also [61]).

One of the mechanisms triggering gene (Src-oncogene) expression is discussed in the following subsection based on the results of an earlier study [57]. The kinetic scheme which characterizes the triggering potency of this gene is applicable with slight modifications to the description of other processes listed above.

11.1 Mechanism triggering a temperature switch of TS-mutants of the Src-oncogene in Georgiev's model

The product of Src-oncogene is known to be necessary for the transformation of normal cells into the cancerous ones. This phosphoprotein, $pp60^{Src}$, has a proteinkinase activity capable of phosphorylating cellular proteins (via tyrosine amino acid) essential for the malignant transformation of cells by sarcoma virus [62, 63]. Infected cells remain normal at 41 °C but undergo transformation to cancerous ones at 35 °C.

According to the promoter model proposed by G P Georgiev [56, 64], carcinogenesis is initiated after some of the genes in an eucaryotic cell fall under control of the promoter and virus genome regulatory system, and the cell genome is cut off from its own control sequences. The existence of TS-mutants in a narrow temperature range calls for an explanation. A trigger model for the regulation of the virus genome taken up by an eucaryotic cell has been constructed in Ref. [57]. The regulatory system for procaryotes was discussed by the author of this review in an earlier paper with special reference to the effect of the newly-synthesized enzyme on its own repressor through a feedback mechanism [54]. As a result, a trigger model of this process has been developed to allow for a possible temperature switch between its regimes.

The principal idea of Ref. [54] used in the study was that the reaction rate controlled by regulatory enzymes is related to the substrate concentration through a sigmoid dependence (see Monod's works in Ref. [65]). This accounts for the nonlinearity of the process and its triggering potential. Also, it was assumed that the virus promoter P_2 exerts control over gene G coding for a protease-active E_{PA} enzyme capable of derepressing the R repressor of the P_2 promoter. This enzyme could just as well be a direct product of Src-gene expression having phosphorylating activity. The simplest oncogene switch triggering model for a polycystron was constructed and is presented in Fig. 9.

Sigmoid kinetics are known to be usually realized for regulatory enzymes due to their allosteric nature [65 – 67].

Account was also taken of the temperature maximum for the rate $K_0(T)$ (see Section 3).

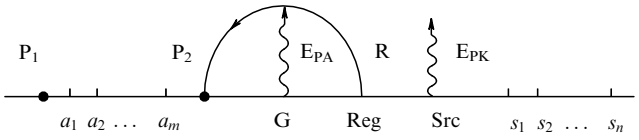

Figure 9. Process of oncogene trigger switching.

It was assumed that the temperature optimum of enzyme E is below the temperature at which normal cells undergo transformation to cancerous ones (35 °C). Such an assumption allowed a small temperature difference between the switching regimes (bistability, triggering effect) to be explained. At temperatures in excess of the temperature optimum, one finds

$$K_0(T) \simeq \frac{B}{A} \exp\left(\frac{\Delta_0}{\varkappa_0 T}\right), \tag{75}$$

where $\Delta_0 \equiv \Delta_2 - \Delta_1$.

The hysteretic temperature dependence of oncogene activity predicts the coexistence of active and inactive forms of the oncogene in a narrow temperature range (35 – 41 °C); the quantitative expression can be obtained by means of the Fokker – Planck probability density formalism [54]. Moreover, effect of the high-temperature regime (41 °C) favoring oncogene 'silence' (the 'healthy' state) must persist after the temperature falls to 35 °C, at least for a period shorter than the time needed for a spontaneous switch from the 'healthy' state to the 'ill' one and back. This prediction admits experimental verification. For example, the mathematical expectation of such a switch for $\sim 1.5 - 2$ eV barriers is $\sim 10^6$ s. Therefore, the promoter model of Georgiev for a TS-mutant of Src-oncogene is useful for the explanation of a narrow temperature range in which a switch of oncogene from the normal to carcinogenic state and back occurs. The explanation is possible on the assumption of sigmoid kinetics of the regulatory enzyme and its temperature optimum below 35 °C.

11.2 Elementary quantum processes in biological macromolecules and gene expression

It has been shown in a preceding section that kinetic coefficients governing gene expression are related to elementary quantum processes, such as repressor protein binding to and detachment from operator segments of genomic DNA molecules. Initiation of transcription depends on the interaction between polymerase and activator sequences in the promoter region.

The activation process itself includes the generation of low-frequency vibrations of activator sequences which bind to negatively charged phosphate groups of operator regions in DNA molecules via their own positively charged ε-groups.

It follows from the above models that polar low-frequency vibrations can be 'coupled' to the reaction coordinate and cause activation of polymerase-dependent enzymatic processes.

Worthy of note are the pioneer experiments of the Soviet biochemist A V Blagoveshchenskiĭ [70] dating back to the 1930s, which demonstrated the possibility of enhancement of certain enzymatic activities during phylogeny. Specifically, it was shown that the turnover rate of a catalytic enzyme, i.e. its

activity, in cultivated plants is higher than in their wild forms. This finding has important implications bearing in mind that crosses between cultivated and wild varieties are normally dominated by the latter. A dominance transcription model for the genetic trigger was constructed by the author of this review and A V Profir [55]. The results of Blagoveshchenskiĭ can probably be explained by the effect of soft low-frequency vibrations 'coupled' to the enzymatic reaction coordinate. Such vibrations can in turn arise as the protein structure becomes more complicated (tertiary and quaternary structures).

Another possible mechanism of enhancement of enzymatic activity may be related to the altered isoenzyme composition. The number of isoenzymes varies in the course of evolution, and the most active one may eventually prevail (see, for instance, Ref. [71]).

It may be expected that further success of genetic experiments will to a large extent depend on the knowledge of the effects of various physical and chemical factors on the enzymatic catalysis rates *in vivo* and their role in gene expression. Also, it should be remembered that cell's proteins escape proteolysis by regulator gene products because they undergo specific methylation to be protected from decomposition. This problem is however beyond the scope of the present review.

11.3 Enzymatic allosteric mechanism for the regulation of mobile gene expression

The objective of the present section is to show that the enzymatic catalysis model developed in Section 3 and supplemented by the allosteric model described in Ref. [15] can be employed to explain the action of the so-called mobile eucaryote genes [72].

It is known that in eucaryotic cells of certain plant organisms, gene expression is governed by genetic elements capable of travelling along chromosomes. Such active mobile elements A_s (activators) can break chromosome fibres in trans-positions occupied by inactive D_s elements (dissociators) unable to cut DNA strands in the absence of an activator.

Pairs of such mobile genetic elements were first discovered and described in ZEAMAYS plants by B McKlintock [73].

Recent studies have demonstrated that a dissociator can be regarded as an activator that lost part of the genetic information as a result of a deletion and thus the ability to move unless activated.

According to a model proposed in Ref. [74], an appropriate enzyme (polymerase) involved in reading genetic information is instructed to bind to the promoter sequence if the adjacent operator site is bound to a protein P_0 produced by the activator gene A_c on the sister chromosome. In other words, the complex of the transcriptional polymerase P_t and the promoter sequence I is formed only in the presence of protein P_0 in the operator region II.

Let us consider how polymerase works in the kinetic model developed in Section 3. The presence of the second binding centre II for protein P_0 introduces certain changes in the calculations described in Section 3. Suppose that the presence of protein P_0 leads to low-frequency vibrations between P_t and P_0 due to their motion relative to each other. Denote the appropriate vibrational coordinate as q, the reduced mass as m, the frequency as v, and the production rate of P_0 molecules by activator A_c as q_c. Then, in the simplest case, the mean concentration of protein P_0 complexes at the binding center II is given by the formula

$$n^{\mathrm{II}} = \frac{q_c}{W^{\mathrm{II}}} ,$$

where W^{II} is the complex II disintegration rate per unit time.

The mean concentration of polymerase complexes at the center I can be found from a kinetic equation of the form (16). In the simplest case of Michaelis–Menten kinetics, the mean concentration of the complexes in bound orbitals of the center I (n_2^{I}) can be obtained from formula (22).

The expression for the mean value of the $\tilde{q}$ vibration amplitude can be derived following the same scheme as was used in Section 3:

$$\tilde{q} = \frac{1}{mv^2} \sum_{i=\mathrm{I,II}} \frac{B^i A_2^i n_2^i}{M^i \omega_{\mathrm{I}}^2} \left[1 - \frac{1}{mv^2} \sum_{j=\mathrm{I,II}} \frac{B^{j^2} n_2^j}{M_j \omega_j^2} \right] . \tag{76}$$

Here, the following notation is used: B^j is the coupling constant relating the low-frequency vibration q and the reaction coordinate Q^j at $j = \mathrm{I}$ and $j = \mathrm{I, II}$ centers, respectively; M^j and ω^j, by analogy, are the mass and the Q^j ($j = \mathrm{I, II}$) reaction coordinate frequency, respectively; A_2^i is the constant for the electron interaction with Q^j vibration in the bound orbital of center $j = \mathrm{I, II}$, and n_2^i is defined above.

At $n_2^{\mathrm{II}} = 0$, formula (76) exactly goes over to the results presented in Section 3. Consider the simplest symmetric model of I and II centers; in other words, assume that $A_2^{\mathrm{I}} = A_2^{\mathrm{II}} = A$; $B^{\mathrm{I}} = B^{\mathrm{II}} = B$; $M^{\mathrm{I}} = M^{\mathrm{II}} = M$, and $\omega^{\mathrm{I}} = \omega^{\mathrm{II}} = \omega$. For center I, however, it is important to take into account the possibility of transition from the initial state I to II, i.e. disintegration of the substrate–enzyme complex.

For the complex localized at center II, there is no decay of state 2 because protein P_0 is devoid of enzymatic activity. Therefore, the following equation can be obtained for the symmetric model:

$$\tilde{q} = \frac{1}{mv^2} \; BA_2(n_2^{\mathrm{I}} + n_2^{\mathrm{II}}) .$$

The ratio of the heat release constant a_{10} (the first index denotes the occupation of center I, and the second the unoccupied state of center II) to constant a_{11} (both centers I and II are occupied) is written as

$$\frac{a_{10}}{a_{11}} = \left(1 - \frac{\xi n_2^{\mathrm{II}}}{1 - \xi n_2^{\mathrm{I}}} \right)^2 , \tag{77}$$

where

$$\xi = \frac{\hbar^2}{mv^2 M\omega^2} .$$

For the parameter $\xi = 0.1$, we get $a_{11} > a_{10}$.

The growth of the heat release constant due to the occupation of center II appears to reflect the effect of allostericity because the corresponding activation energy of the enzymatic reaction at center I decreases, which leads to an enhanced reaction rate. Thus, this model explains how the activator gene A_c influences the expression of gene D_s.

The allosteric effect being related to the reduced mass m and frequency v of the q oscillator, an isotopic effect is equally possible. Indeed, protein P_0 deuteration is accompanied by a change in the mass m and hence in the polymerase reaction rate. This change is apparent at the phenotypic level, e.g., in the grain colour patterns of ZEAMAYS.

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