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Long-Distance Electron Tunneling in Proteins: A New Challenge for Time-Resolved Spectroscopy¹

A. A. Stuchebrukhov

Department of Chemistry, University of California, Davis, CA 95616 USA

Abstract

Long-distance electron tunneling is a fundamental process which is involved in energy generation in cells. The tunneling occurs between the metal centers in the respiratory enzymes, typically over distances up to 20 or 30 Å. For such distances, the tunneling time—i.e., the time during which an electron passes through the body of the protein molecule from one metal center to another—is of the order of 10 fs. Here the process of electron tunneling in proteins is reviewed, and a possibility of experimental observation of real-time electron tunneling in a single protein molecule is discussed.

1. INTRODUCTION

Most of the energy in aerobic cells is generated through oxidative phosphorylation, a process in which electrons are passed along a series of redox enzymes located in the mitochondrial (or bacterial) membrane to molecular oxygen, which is reduced with the addition of electrons and protons to water. The electron transport chain consists of three major enzymes—NADH dehydrogenase, bcl, and cytochrome c oxidase. Each of the complexes involves several metal redox sites, which form a continuous chain along which electrons eventually get to molecular oxygen. Each of these complexes works as a proton pump, which utilizes the free energy of oxygen reduction to push protons across the membrane. The proton gradient created in the process subsequently drives synthesis of ATP [1, 2].

The most remarkable aspect of electron transfer (ET) in these enzymes is that it occurs via quantum mechanical tunneling [3-8]. Typically, redox centers that exchange an electron are separated by distances of the order of 15–30 Å. In vacuum, tunneling over such long distances would be impossible. In proteins, the intervening organic medium facilitates tunneling by providing low lying virtual quantum states which result in the effective lowering of the tunneling barrier, and the exchange at physiological rates becomes possible [8]. It is remarkable that the whole biological energy transduction machinery is based on

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stuchebr@chem.ucdavis.edu.

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such a subtle quantum mechanical phenomenon, given that most of biology does not require quantum mechanics at all.

For a number of years, a major question has been whether specific electron tunneling pathways in proteins exist [5-8]. This question is still debated in the literature, because the pathways are not observed directly, and the interpretation of experimental results involves ambiguities. The extremely small tunneling interactions (order of 10^{-1} to 10^{-4} cm⁻¹) are difficult to calculate accurately. Despite the remarkable recent progress in the area [9-12], some important problems remain unresolved. The accurate prediction of the absolute rates of long-distance electron transfer reactions, and other biological charge transfer reactions including proton coupled reactions [13], still remains a challenging theoretical and computational problem.

Here I will review some of the theoretical aspects of electron transfer in proteins. We will focus on what is happening with an electron at the transition state of an ET reaction, when it tunnels through the protein medium. Of special interest is the many-electron aspect of the phenomenon. The key approach to be discussed is the method of tunneling currents [14] developed by the author. I will also discuss the elusive concept of tunneling time, and a new challenge for time resolved laser spectroscopy to trace a tunneling electron in a single protein molecule.

2. ELECTRONIC COUPLING AND TUNNELING PATHWAYS

Electron transfer (ET) in proteins occurs via thermally assisted tunneling, which means the following: at any given instance of time, and given nuclear configuration of the system, the electronic energies of the donor and acceptor states are different, and the electron is localized on the state of lowest energy (initially on the donor); in the course of nuclear thermal fluctuations, however, the energies of the donor and acceptor states are constantly changing, and from time to time the two states are brought into resonance. At the moment of level crossing, the Landau-Zener (LZ) transition occurs, in which an electron makes a tunneling jump from the donor to acceptor site. The nuclear configuration at which the transition occurs is called the transition state of the ET reaction. The overall rate of electron transfer is proportional to the number of level crossings per second, times the Landau-Zener probability that the transition does take place.

The majority of ET reactions in proteins are nonadiabatic (Landau limit of LZ theory) owing to the weakness of interaction between the redox sites. In this limit, the rate of ET is proportional to the square of the electronic coupling matrix element T_{DA} that connects distant redox sites [10, 15]. This matrix element and the associated tunneling process are the main focus of the following discussion.

The matrix element T_{DA} is a pure electronic quantity. Usually, in order to express the rate of ET in terms of the electronic coupling, both Condon and Born-Oppenheimer (BO) approximations are made (or tacitly assumed). The Condon approximation assumes that the transfer matrix element is independent of the medium nuclear configuration.

The BO approximation assumes that the transfer matrix element T_{DA} is also independent of the vibrational state of the medium in which the tunneling transition is taking place. The dependence of the rate (but not of the matrix element) on the vibrational state enters into theory only in the form of the Franck–Condon vibrational factors.

In the BO approximation, the wave function of the system is the product of the electronic and vibrational wave functions, and the distribution of total energy between the electronic and vibrational degrees of freedom is fixed. Therefore one can define the energy of the tunneling electron and the corresponding height of the tunneling barrier. As the distance between donor and acceptor increases beyond some characteristic distance L_{BO} (L_{BO} is 10–15 Å according to the estimate in [16]) the BO approximation breaks down. When this happens, the energy of the tunneling electron is no longer a well-defined quantity. The total energy, electronic plus vibrational, of the quantum state from which the transition occurs is fixed, of course, but the distribution of energy between the vibrational and electronic degrees of freedom is no longer fixed and depends on the tunneling distance. In this case, the theory of the rate takes a more complicated form, in which the electronic coupling depends on the vibrational state of the system. Here we will assume that the BO approximation holds and treat the tunneling coupling element T_{DA} as a pure electronic quantity which is calculated at some fixed nuclear configuration of the system.

Technically, the tunneling coupling in Donor–Bridge–Acceptor (D–B–A) systems is often described in terms of the superexchange model, following the steps of McConnell and Larsson’s early treatment of the problem [17, 18]. The equivalence of superexchange and tunneling is discussed, e.g., in [15, 19–21]. Based on the superexchange model, several methods for the calculation of the electronic tunneling matrix element (ME) have been developed. Below we give a brief review of these methods and then move on to discuss the method of tunneling currents, the main subject of this paper.

2.1. Direct Method

In principle, the coupling matrix element can be calculated as follows [15]. Suppose we know two diabatic states $|D\rangle$ and $|A\rangle$ that correspond to two redox states of the system—electron on the donor and on the acceptor, respectively—and the configuration of the system is that of the transition state, i.e., the states have the same energy E_0 . Then the transfer matrix element is

$$T_{DA} = \frac{H_{DA} - E_0 S_{DA}}{1 - S_{DA}^2}, \quad (2.1)$$

where H is the Hamiltonian of the system (at the transition state configuration), $H_{DA} = \langle D|H|A\rangle$, $E_0 = \langle A|H|A\rangle = \langle D|H|D\rangle$ is the tunneling energy, and $S_{DA} = \langle A|D\rangle$ is the overlap integral. Typically for long-distance ET, the overlap S_{DA} is very small and therefore can be neglected in the denominator. There are above expression can be used in both one- and many-electron formulations of the problem. This method is applicable for relatively strongly coupled D–B–A systems, see, e.g., [15, 22]. There are a number of variations of the above direct approach, such as the method of avoided crossing [23–25], a method based on application of Koopmans’ theorem [15, 23, 24], and others [26, 27].

For long-distance tunneling, the potential problems with the above approach are as follows. First, the diabatic states, in practice, are well-defined only in the region of their localization and perhaps in the barrier region adjacent to it, and are poorly defined in the region of the other redox site, where the other function is admixed. In other words, the “tails” of the diabatic states are not well-defined. Therefore, in the region where $|D\rangle$ is well-defined, $|A\rangle$ is poorly defined, and vice versa. Both H_{DA} and S_{DA} , which are integrals over the whole space, are not well-defined then, because of the contribution of the regions around donor and acceptor complexes where either one or the other function is not well-defined. Second, the tunneling energy E_0 can be determined only approximately. If so, in the above formulation, the very small matrix element is evaluated as a difference of two large numbers (notice that E_0 is the total energy of the system), each of which can be evaluated only approximately.

2.2. The Propagator Method

The smallness of the electronic tunneling coupling causing a problem for the direct methods is turned into advantage in the perturbation theory treatment. This technique grew out of the early work of Larsson [18, 28], and Marcus with co-workers [29] and was first applied in [30-33]. In principle, the method can be generalized to many-electron systems [9], but for large biological systems such treatment becomes impractical. In the one-electron approximation, however, the method can be applied for treatment of very large systems, such as entire proteins.

Here the problem is cast in terms of weakly coupled Donor–Bridge–Acceptor complexes: the Donor and Acceptor are the redox groups, and the Bridge is the protein itself. The key property to be evaluated is the electronic propagator or Green’s Function (GF) of the protein. The matrix element has been shown to have the form:

$$T_{DA}^{(0)} = \sum_{ij} V_{di} G_{ij}(E) V_{ja}, \quad (2.2)$$

where V_{di} and V_{ja} are the coupling matrix elements of the donor and acceptor orbitals to the nearest atomic orbitals of the protein, and $G_{ij}(E)$ is the electronic propagator between the $|i\rangle$ -th and $|j\rangle$ -th atomic orbitals of the protein,

$$G_{ij}(E) = \langle i | (H_B - E)^{-1} | j \rangle, \quad (2.3)$$

where H_B is the protein/bridge Hamiltonian, i.e., part of the protein that excludes the donor and acceptor complexes, and E is the tunneling energy. The problem of non-orthogonality of the atomic orbitals has been addressed in [34], where modifications of the above expression have been obtained.

To evaluate the expression (2.2) for T_{DA} , and to avoid diagonalization or inversion of big matrices, the expressions can be re-written as a system of linear equations with a sparse matrix $(H_B - E)_{ij}$ and solved iteratively [33]. This procedure can be applied to very large systems, which can include as many as 10^6 atomic orbitals.

The tunneling problem is equivalent to that of scattering between two localized states $|D\rangle$ and $|A\rangle$, and the above Eq. (2.2) is the lowest (Born) perturbation theory term for the scattering amplitude [35]. Naturally, the expression can be generalized and higher order terms in V can be included. In practice, however, the inclusion of such higher terms becomes sensible only if an infinite number of them can be summed up. (As is usually the case with perturbation theory, either a single low order term is sufficient or an infinite number of perturbation terms need to be taken into account.)

As in the scattering theory, the complete series for the transfer amplitude has the form

$$T = V + VGV + VGVGV + VGVGVGV + \dots \quad (2.4)$$

In application to tunneling problems, one can think that the “scattering” occurs between the initial and final localized states of the tunneling electron by the atoms of the protein. The operator V represents the coupling of the initial and final states and their coupling to the bridge, whereas G is the propagator in the bridge, Eq. (2.3). Since typically there is no direct coupling between the initial and final states, the odd terms in Eq. (2.4) disappear, and V then is equivalent to similar terms in Eq. (2.2).

The summation of *all* important terms of Eq. (2.4) results in the following expression for the transfer matrix element [36]:

$$T_{DA} = \frac{T_{DA}^{(0)}}{\sqrt{\left(1 - \sum'_{aa}\right)\left(1 - \sum'_{dd}\right)}}, \quad (2.5)$$

where $T_{DA}^{(0)} = \sum_{da}$ is the lowest order expression given previously, Eq. (2.2), and Σ_{aa} and Σ_{dd} are the so-called self-energies of the Green functions for the tunneling electron in the donor and acceptor states, respectively, and the prime denotes a derivative in energy. The corrections captured in the above expression account for the delocalization of the diabatic donor and acceptor states in the protein medium. The expressions for self-energies Σ_{aa} and Σ_{dd} have the same structure as $T_{DA}^{(0)} = \sum_{da}$ and can be computed using the same technique of sparse matrices as for $T_{DA}^{(0)}$. Calculations on Ru-modified proteins [6] showed that the above expression gives results which are nearly identical to those obtained with exact diagonalization of the Hamiltonian matrix, even when intermediate resonances are present in the medium (in contrast to $T_{DA}^{(0)}$, which diverges for such cases). The advantage of the former method, of course, is that it can be applied to systems that may be too large for a direct diagonalization.

In proteins, charge transfer can occur via electron or hole transfer or combination of both [15]. The relative contribution of different channels is an important characteristic of the tunneling coupling. The separate contributions of hole and electron transfer to the total amplitude T_{DA} , without explicit calculation of molecular orbitals of the protein, and without diagonalization of the Hamiltonian matrix, can be obtained with a method described in [33].

The method treats the above expressions for *complex* tunneling energies, and uses analytical properties of the tunneling amplitudes.

The success of the described methods is determined by the quality of the effective one-electron Hamiltonians used in the calculation. In practice, semi-empirical extended Huckel or tight-binding Hamiltonians are often used, which are simple and efficient, but not very accurate. Some authors have explored construction of more accurate effective Hamiltonians for proteins based on ab initio calculations [37].

Further simplification in practical calculations can be achieved by reducing the number of atoms considered using a procedure known as protein pruning [38]. This can be done because the tunneling process is local. The pruning procedure naturally leaves intact donor and acceptor complexes and identifies a number of amino acids that make up the tunneling bridge between them. Typically the pruned molecule contains 10–20 amino acids and redox complexes.

2.3. Tunneling Pathways

From the biological perspective, it is important to know exactly how and where in the protein electron tunneling occurs [39]. There are two possibilities. If the tunneling electron is delocalized on a scale larger than a typical dimension of the protein's amino-acids, then, as far as electronic coupling between redox centers is concerned, the detailed structure of the protein is not important for its biological function. The protein matrix can be viewed in this case as an effective medium, perhaps not totally homogeneous, but lacking detailed structure, whose only purpose is to lower the tunneling barrier, and to make long-distance electronic communication between redox sites possible [7, 8].

However, if the wavelength of the tunneling electron is small, then the detailed structure of the protein medium intervening between redox centers becomes important, and pathways do exist. In this case a number of fundamental questions about the role of tunneling pathways in biological function and their molecular evolution arise [40, 41].

The question of whether or not tunneling paths exist in proteins is still debated in the literature. This question is beyond the scope of the present review, and an interested reader is referred to recent discussions of the topic [5-8]. Qualitatively, the wave-length of the tunneling electron turns out to be of an atomic size, and the tunneling paths are certainly localized in the “frozen” protein structures. However, protein dynamics can significantly reduce the structural effects (see below). This may explain reported success of empirical relations for electron transfer rates in proteins, which ignore detailed chemical structure of the protein, yet account for its density inhomogeneity [8]. Also, the existence of these paths may not necessarily indicate their importance for biological function, provided electron transfer is not the rate limiting step [8].

The first model of tunneling pathways, which viewed them as specific sequences of atoms along which electron tunneling occurs, was developed by Beratan and Onuchic [39]. Each path in this model is associated with a weight, which is calculated as a product of three different empirical factors—for each transfer through a covalent bond, hydrogen bond, and

van der Waals contact between atoms along the path. The tunneling path (or paths) is the sequence of atoms with the largest weight. The motivation of this approach stems from the exponential decay of tunneling wave functions. Each pathway can be regarded as a Feynman path, and the weight factors can be understood as absolute values of their quantum amplitudes. The neglect of the sign of the amplitude is equivalent to neglect of the interference effects.

3. THE METHOD OF TUNNELING CURRENTS

3.1. General Relations

Detailed information about the tunneling process can be obtained with the method of tunneling currents [14]. The general idea of the approach is to examine the dynamics of charge redistribution in a system which is artificially “frozen” at the transition state, when donor and acceptor states are degenerate. To find the transition state, one can simulate the fluctuating electric field within the protein [42]. The fluctuating field shifts redox potentials of donor and acceptor complexes and bring them to resonance, at which point electron tunneling occurs. The transition state of ET, i.e., the resonance condition, is obviously not unique. The relation of the transfer matrix element obtained in this section to the actual rate of ET reaction will be discussed in Section 7.

The tunneling dynamics (at the *frozen* transition state) is described by the following time-dependent wave function:

$$|\Psi(t)\rangle = \cos\left(\frac{T_{DA}t}{\hbar}\right)|D\rangle - i\sin\left(\frac{T_{DA}t}{\hbar}\right)|A\rangle, \quad (3.1)$$

where $|D\rangle$ and $|A\rangle$ are diabatic donor and acceptor states, and T_{DA} is the transfer matrix element. The diabatic states are localized on their respective complexes, but their exponentially small tunneling tails extend over the whole protein. In both one- and many-electron formulations of the problem the time-dependence of the wave function is the same. The periodic change of the wave function from donor to acceptor state (the wave function *perestroika*) results in periodic variations of charge distribution in the system. The redistribution of charge is associated with current. This tunneling current is the focus of the method.

The redistribution of charge in the system during the tunneling transition can be described in terms of current density $\mathbf{j}(\mathbf{r}, t)$ and its spatial distribution $\mathbf{J}(\mathbf{r})$. The appropriate expressions for these quantities are obtained from the continuity equation,

$$\frac{\partial \hat{\rho}}{\partial t} = -\nabla \cdot \hat{\mathbf{j}}, \quad (3.2)$$

which for the tunneling state Eq. (3.1) yields

$$\mathbf{j}(\mathbf{r}, t) = -\mathbf{J}(\mathbf{r}) \sin\frac{2T_{DA}t}{\hbar}, \quad \mathbf{J}(\mathbf{r}) = -i\langle A|\hat{\mathbf{j}}(\mathbf{r})|D\rangle. \quad (3.3)$$

As expected, the periodic variation of charge distribution is associated with a periodic time-dependent current $\mathbf{j}(\mathbf{r}, t)$. The spatial distribution of current $\mathbf{J}(\mathbf{r})$, however, remains the same during the dynamic process. Given also the form of $\mathbf{J}(\mathbf{r})$, one concludes that $\mathbf{J}(\mathbf{r})$ is not related to specific periodic time-dependence of the wave function Eq. (3.1), but rather is a more general characteristic of the quantum transition between states $|D\rangle$ and $|A\rangle$. The streamlines of the current $\mathbf{J}(\mathbf{r})$ represent the so-called quantum Bohmian trajectories [43]. The tunneling transition therefore can be characterized by the current $\mathbf{J}(\mathbf{r})$.

Alternatively, one can introduce atomic populations P_a , and corresponding *interatomic* currents J_{ab} as:

$$\frac{dP_a}{dt} = \sum_b j_{ab}, \quad j_{ab} = -J_{ab} \sin \frac{2T_{DA}t}{\hbar}. \quad (3.4)$$

The spatial distribution of the tunneling current is described here in terms of the matrix J_{ab} . In this approach, the total current through an atom is proportional to the probability that the tunneling electron will pass through this atom during the tunneling jump.

Both inter-atomic currents J_{ab} and current density $\mathbf{J}(\mathbf{r})$ provide full information about the tunneling process and, in particular, about the distribution of the tunneling current in space, i.e., about the tunneling pathways.

In the one-electron approximation, the expressions for tunneling currents have the following form:

$$\mathbf{J}(\mathbf{r}) = \frac{\hbar}{2m} (\Psi_D \nabla \Psi_A - \Psi_A \nabla \Psi_D), \quad (3.5)$$

where Ψ_D and Ψ_A are donor and acceptor diabatic states, and

$$J_{ai,bj} = \frac{1}{\hbar} (H_{ai,bj} - E_0 S_{ai,bj}) (C_{ai}^D C_{bj}^A - C_{ai}^A C_{bj}^D), \quad (3.6)$$

where ai and bj are indices of the atomic orbitals on atoms a and b , H and S are the Hamiltonian and overlap matrices, and C^D and C^A are the coefficients of expansion for states $|D\rangle$ and $|A\rangle$ in the atomic basis set of the system. The total interatomic current between two atoms, J_{ab} , is a sum of $J_{ai,bj}$ over all orbitals of these atoms.

The sign of the current is associated with its direction—a positive J_{ab} , for example, corresponds to current from atom b to atom a . But most importantly, the sign reflects the quantum nature of currents. Since basis functions of the stationary states $|D\rangle$ and $|A\rangle$ can be chosen to be real, all information about quantum mechanical phases, and interferences, is contained in the sign of quantum amplitudes. Addition of positive and negative amplitudes, for example, results in destructive interference. Tunneling currents, by their meaning, are quantum amplitudes, and therefore their signs contain information about interferences in the tunneling process.

The total current through a given atom is proportional to probability that a tunneling electron will pass through this atom during the tunneling jump. The total atomic current is given by the sum:

$$J_a^+ = \sum_{b'} J_{ab}, \quad (3.7)$$

where the summation is restricted to positive contributions J_{ab} , which describe tunneling current from various atoms b to atom a . Both the inter-atomic currents J_{ab} and the total atomic currents J_a^+ can be utilized for visualization of the tunneling process and tunneling pathways. For example, the magnitude of J_a^+ can be taken as an indicator that the atom is involved in the tunneling process, see, e.g., [41], and Fig. 2, below.

The information about all tunneling paths and their interferences is contained in matrix J_{ab} , which describes the total tunneling flow in an atomic representation. The analysis of the tunneling flow gives a rigorous description of where electronic paths are localized in space. For example, if a specific atomic path exists, one can find it using the method of steepest descent, that is: begin from a donor atom d and find an atom b_1 to which the current $J_{b_1, d}$ is maximum, then go to atom b_1 , repeat the procedure and find atom b_2 , etc., until the acceptor atom a is reached. The sequence of atoms: $d, b_1, b_2, \dots, b_m, a$ is the tunneling path. Of course, this procedure will work only if a single atomic path exists. Usually, the structure of the tunneling flow is more complicated and many interfering paths exist simultaneously. A more careful analysis of J_{ab} is required in this case.

Remarkably, both $\mathbf{J}(\mathbf{r})$ and J_{ab} turn out to be related to the tunneling matrix element:

$$T_{DA} = -\hbar \sum_{a \in \Omega_D, b \notin \Omega_D} J_{ab} = -\hbar \int_{\partial \Omega_D} (d\mathbf{s} \cdot \mathbf{J}). \quad (3.8)$$

In the above formula Ω_D is the volume of space that comprises the donor complex, and $\partial \Omega_D$ is its surface. These relations for electron transfer reactions were first derived in [44-46] using the conservation of charge argument. Similar relations of the coupling matrix element to tunneling current were derived in the solid state physics context by Bardeen [47].

In the methods for computing tunneling matrix elements reviewed in Subsection 2.1, the most significant problem is that the diabatic states, by their nature, are well-defined only in the regions of the localization of the charge, and perhaps in the tunneling barrier, but not in the far region of the other site. As a result, in a volume integral, representing the matrix elements such as $\langle A|H|D \rangle$ over states D and A , there are major regions (around donor and acceptor) where one function is well-defined, but the other is not. This can potentially lead to numerical errors. To avoid this problem, in the calculation one would somehow need to use the region of the barrier only, where both functions D and A are well-defined. This is exactly what the Tunneling Current Method accomplishes. The above expressions for the matrix element involve only the surface in the region of the barrier, where both $|D \rangle$ and $|A \rangle$ are well-defined. This is similar to the transition state theory, where the rate is evaluated on the surface dividing reactants and products. Using this technique, extremely small tunneling matrix elements can be evaluated, see Fig. 1.

3.2. Many-Electron Aspect

In the many-electron formulation of the problem, the main results cited earlier remain unchanged, except that now the diabatic states $|D\rangle$ and $|A\rangle$ should be understood as many-electron states, and the operators which act on them should be written in many-electron form. The detailed derivations can be found in the original papers [46, 48], and in a detailed review of the method [14].

3.2.1. Hartree-Fock approximation. Tunneling current density—To calculate the spatial distribution of the tunneling current $J(\mathbf{r})$ one needs first to determine diabatic donor and acceptor states $|D\rangle$ and $|A\rangle$, and then to evaluate the many-electron matrix element given by Eq. (3.3) for an appropriate many-electron current density operator.

Suppose states $|D\rangle$ and $|A\rangle$ are single-determinant many-electron functions, which are written in terms of (real) canonical molecular orbitals $\varphi_{i\sigma}^D$ and $\varphi_{i\sigma}^A$, where σ is the spin index, $\sigma = \alpha, \beta$. These are the optimized orbitals obtained from Hartree-Fock calculations of states $|D\rangle$ and $|A\rangle$. Using standard rules for matrix elements of one-electron operators [49], one can evaluate the expression for the current $\mathbf{J}$, Eq. (3.3). The final expressions, however, are much simplified, and some important physical insights are gained if the molecular orbitals $\varphi_{i\sigma}^D$ and $\varphi_{i\sigma}^A$ are made biorthogonal [50], by a rotation of these orbitals, one with respect to the other, in the Hilbert space. In this case, the overlap matrix of states $|A\rangle$ and $|D\rangle$ becomes diagonal,

$$\langle \varphi_{i\sigma}^A | \varphi_{j\sigma}^D \rangle = \delta_{ij} s_i^\sigma. \quad (3.9)$$

Such orbitals are also known as corresponding orbitals, and have been utilized in the ET problem by Newton [51], Friesner [22], and Goddard [52] and their co-workers in the past.

If now $|D\rangle$ and $|A\rangle$ are two such biorthogonalized states, with p orbitals in α -spin and q orbitals in β -spin, the expression for currents takes the form:

$$\mathbf{J}(\mathbf{r}) = -\frac{\hbar}{2m} \langle A|D \rangle \times \sum_{i,\sigma} \frac{1}{s_i^\sigma} \left[\varphi_{i\sigma}^A(\mathbf{r}) \nabla \varphi_{i\sigma}^D(\mathbf{r}) - \varphi_{i\sigma}^D(\mathbf{r}) \nabla \varphi_{i\sigma}^A(\mathbf{r}) \right], \quad (3.10)$$

where

$$\langle A|D \rangle = \prod_i^p s_i^\alpha \prod_j^q s_j^\beta. \quad (3.11)$$

The total current in the system is given by the sum of contributions from the corresponding orbitals of donor and acceptor states.

This expression is an obvious generalization of the one-electron picture. Now, different pairs of corresponding (overlapping) orbitals of donor and acceptor states contribute to the current density. The smaller the overlap between the corresponding orbitals in donor and acceptor

wave functions, i.e., the greater the change of an orbital between the $|D\rangle$ and $|A\rangle$ states, the greater is the contribution of a given pair of orbitals to the current.

Typically, the major contribution to the current is due to one particular pair of external orbitals, which describes the tunneling electron. The orbitals of other (“core”) electrons just shift slightly, due to polarization effects. Their contribution enters as an electronic Franck–Condon factor in the expression for the tunneling electron current. This factor (product of overlaps of individual core orbitals) is the overlap of the wave functions of the core electrons in the donor and acceptor states. The idea that the description of the tunneling process can be reduced to a “Franck-Condon dressed” one-electron picture was introduced first by Newton in his analysis of the tunneling splitting [15, 51, 53].

In practice, the currents are calculated in terms of the atomic basis functions. The molecular orbitals are found as linear combinations of these functions, and tunneling currents are calculated according to formulas given in [14]. The tunneling matrix element is evaluated as a surface integral of the current, Eq. (3.8), Fig. 1.

3.2.2. Interatomic tunneling currents—The many-electron atomic formalism is developed in a similar way to that of current density. The idea is to derive kinetic equations for atomic populations that describe the charge redistribution in the system during the tunneling transition, Eq. (3.4). The major steps in the formalism leading to these equations are as follows.

First of all, one needs an operator of the total atomic population that would correspond to P_a . For this purpose, the Mulliken population operators are used. Let a set of real functions $\phi_\nu(x)$, $\nu = 1, \dots, K$, be any particular atomic set that is chosen for the electronic structure calculation, and $|\nu\sigma\rangle$, $|\mu\sigma^*\rangle$, ..., etc., are corresponding atomic spin orbitals. The states describing different electrons will be distinguished by an additional index a , $|\nu\sigma(a)\rangle$. In terms of these states, for the a -th electron the population operator is written as:

$$\hat{p}_{\nu\sigma}(a) = \frac{1}{2} \sum_{\mu=1}^K (|\nu\sigma(a)\rangle S_{\nu\mu}^{-1} \langle\mu\sigma(a)| + |\mu\sigma(a)\rangle S_{\mu\nu}^{-1} \langle\nu\sigma(a)|). \quad (3.12)$$

The operator of the total population of the state $|\nu\sigma\rangle$, $\hat{P}_{\nu\sigma}$, is the sum of the above operators over all electrons in the system:

$$\hat{P}_{\nu\sigma} = \sum_{a=1}^N \hat{p}_{\nu\sigma}(a). \quad (3.13)$$

The atomic populations are found by summing the contributions of all orbitals of a given atom.

Using the above population operators, one can now describe dynamics of the atomic populations. The time evolution of the system is described by Eq. (3.1). The average value of the population of any atomic state $|\nu\sigma\rangle$ at time t during the tunneling transition is given by

$$\bar{P}_{\nu\sigma}(t) = \langle \Psi(t) | \hat{P}_{\nu\sigma} | \Psi(t) \rangle \quad (3.14)$$

and the rate of change of the population is

$$\frac{d\bar{P}_{\nu\sigma}(t)}{dt} = -\frac{T_{DA}}{\hbar} \left(\langle D | \hat{P}_{\nu\sigma} | D \rangle - \langle A | \hat{P}_{\nu\sigma} | A \rangle \right) \times \sin(2T_{DA}t/\hbar). \quad (3.15)$$

The above kinetic equation can be cast in the following form,

$$\frac{d\bar{P}_{\nu\sigma}}{dt} = \sum_{\mu} j_{\nu\sigma,\mu\sigma}, \quad (3.16)$$

where the kinetic coefficients $j_{\nu\sigma,\mu\sigma}$ have the meaning of interatomic exchange currents. Summation over all orbitals of a given atom results in a kinetic equation of the form of Eq. (3.4).

The calculations of all matrix elements entering into the above equations is described in [48], where the explicit expressions for interatomic currents J_{ab} in terms of the molecular orbitals of the diabatic states $|D\rangle$ and $|A\rangle$ are given. Thus, the interatomic current J_{ab} , can be obtained from first principles calculations. When the matrix J_{ab} is known, the analysis of the tunneling pathways, and the calculation of the transfer matrix element T_{DA} can be carried out as described in the previous section.

In the Hartree–Fock approximation, the expressions for interatomic tunneling currents J_{ab} in terms of the MO's of donor and acceptor states were obtained in [48]. These expressions, in the case of a non-orthogonal atomic basis, although straightforward for numerical implementation, are quite complicated, and therefore are difficult to deal with practically. The main problem is that in the formally exact HF expressions for interatomic currents, the proper tunneling current contributions are mixed with the local polarization currents of the core orbitals. A simplification can be achieved, however, if the One Tunneling Orbital approximation (OTO, see below) is used [54]. One interesting example of calculation of OTO interatomic currents is shown in Fig. 2. The shown system is a model for electron tunneling in a Ru-modified protein azurin. Interestingly, in this system electron tunnels simultaneously along two strands of the protein [55].

3.2.3. One tunneling orbital (OTO) approximation and polarization effects—A number of interesting issues are related to the many-electron nature of the tunneling problem in electron transfer reactions [15]. Can one specific orbital represent a tunneling charge, and if so, how is such an orbital found? A naive guess, based on Koopmans' approximation, is that it is the canonical HOMO of the system. We showed that in fact if such a pair of orbitals exists, it should be found in a special (biorthogonalization) procedure, and the resulting orbitals are the corresponding orbitals rather than the usual canonical ones.

The total current in Eq. (3.10), is a sum of the current due to tunneling charge per se, and current due to polarization effects. In the Hartree-Fock approach, all electrons in the systems are treated on equal footing and, therefore, the expressions for both tunneling and

polarization currents are similar in structure. The major contribution to the current however is due to one particular pair of orbitals, which describes the tunneling electron. The orbitals of other (“core”) electrons just shift slightly, due to the polarization interaction with the tunneling charge, and their contribution to total current can be neglected. The net core orbitals’ contribution therefore enters only as the electronic Franck–Condon factor [51, 53] in the expression for the tunneling electron current, as explained in more detail below.

The relative stability of the core orbitals suggests a simple approximation in which only one pair of tunneling orbitals is considered, while the rest is assumed to be frozen. This is the One Tunneling Orbital (OTO) approximation. In this approximation, the two redox states have the form:

$$|D\rangle = |\varphi_0^D, \text{core}^D\rangle, \quad |A\rangle = |\varphi_0^A, \text{core}^A\rangle, \quad (3.17)$$

where $|\varphi_0^D\rangle$ and $|\varphi_0^A\rangle$ are a pair of tunneling orbitals, and the $|\text{core}\rangle$ represent the rest of the biorthogonal orbitals, which remain practically unchanged in the transition.

If such an approximation is adopted, the tunneling current density takes the form:

$$\mathbf{J}(\mathbf{r}) = -\frac{\hbar}{2m} \langle D|A\rangle^{(0)} \times \left[\varphi_0^A(\mathbf{r}) \nabla \varphi_0^D(\mathbf{r}) - \varphi_0^D(\mathbf{r}) \nabla \varphi_0^A(\mathbf{r}) \right], \quad (3.18)$$

where

$$\langle D|A\rangle^{(0)} = \langle \text{core}^D | \text{core}^A \rangle = \prod_{i \neq 0} s_i. \quad (3.19)$$

Rigorously speaking, in OTO the core part of the wave functions should be considered unchanged, or frozen, and therefore the above overlap should be exactly equal to unity. We however, will use both the rigorous form, and a “semi-rigorous” form of OTO approximation, where the overlap $\langle D|A\rangle^{(0)}$ is allowed to be less than one. The reason for this is discussed later.

The individual pairs of core orbitals do not contribute to tunneling current density per se, because $|\varphi_i^D\rangle$ and $|\varphi_i^A\rangle$ ($i \neq 0$) are practically the same. Moreover, the core orbitals are localized, therefore the contribution to current is due to a small number of such orbitals. Yet, their overall indirect contribution to total current, in the form of electronic Frank–Condon factor, $\langle \text{core}^D | \text{core}^A \rangle$ may be substantial. Indeed, the total overlap of the two cores is a product of a large number of terms corresponding to overlaps of individual core orbitals Eq. (3.10). Each overlap s_i in Eq. (3.10) for $i \neq 0$ is close to unity; however, the product involves a large number of such terms, and therefore may differ substantially from unity. For example, in the examples that we considered, this term typically ranges from 0.6 to 0.8. We do not exclude, however, that in some cases the core overlap could be significantly smaller.

3.2.4. Correlation effects. Beyond Hartree–Fock methods—Can the tunneling event (i.e., tunneling dynamics of the many-electron system) be correctly described by HF wave functions?

When an electron tunnels through the protein medium, it moves in the sea of other electrons. The tunneling potential is, to a large extent, due to interaction of the tunneling electron with other electrons in the medium. There is also an opposite effect, of course, namely the polarization of the background electrons by the tunneling electron. The energy of the tunneling electron, its tunneling velocity, and tunneling time-scale [56] are not much different from those of the valence electrons of the medium. This means that the reaction of these background electrons to a moving tunneling charge will be quick enough to dynamically follow it. Therefore, as the tunneling electron moves through the protein, it drags with itself an electron polarization cloud of background electrons. The compound nature of this tunneling quasi-particle object is rather complex. An additional complication is due to a virtual inseparability of the tunneling electron from those in the polarization cloud because of the electron exchange effect. (A tunneling electron, as it passes an atom of the medium, can exchange with the electrons of that atom.) How can one quantitatively describe such a complex tunneling object?

At the SCF level of description of $|D\rangle$ and $|A\rangle$ states, the effect of the polarization cloud moving together with the tunneling charge is not captured. The latter is obviously due to dynamic correlation between the electrons in the systems, the effect which is not present at the SCF level.

To explore the significance of these correlation effects and to estimate the accuracy of Hartree–Fock calculations, one needs to modify the description of $|D\rangle$ and $|A\rangle$ states and to include some relevant excited states that correspond to the tunneling electron/hole localized on the intermediate atoms of the medium, with other electrons adjusted to it. These effects have not been explored to any extent yet.

4. QUANTUM INTERFERENCE EFFECTS. QUANTIZED VERTICES

The wave nature of the transferring electron manifests itself not only in the electron's ability to penetrate classically forbidden barriers, but also in the interference effects. If the electronic coupling is due to several tunneling paths, each of them associated with an amplitude—a positive or negative number, then the total tunneling amplitude, which is a sum of the partial amplitudes, can be enhanced (constructive interference) or diminished (destructive interference) depending on the relative signs of the individual paths' amplitudes. Thus, for example, two coupling paths are not necessarily better than one, in case of destructive interference [45]. This counter-intuitive effect is of pure quantum nature. Typically the quantum phases, i.e., the signs of the partial amplitudes, are sensitive to the nuclear configuration of the system, and therefore thermal motion of the system would result in averaging of these effects, on the one hand, and cause fluctuations of the coupling matrix element, on the other [57].

Another interesting manifestation of the interference effects is the presence of quantized vortices in the tunneling currents [58]. This feature of electron tunneling can be seen in Fig.

3, in which the distribution of tunneling current in the $\text{Ru}^{2+/3+}\text{-(Gly)}_n\text{-Cu}^{2+/1+}$ system is shown. The prominent feature in the tunneling current is the presence of vortices. These vortices are of the same nature as those observed in super-fluid helium, and in many other quantum systems—super-conductors, plasmas, spin systems, wave fronts, and others.

The mathematical nature of these vortices is related to the nodes of complex wave functions. The phenomenon was first described by Dirac. If we have a complex wave function, which can be written as

$$\Psi = \rho^{1/2} e^{i\phi} \quad (4.1)$$

the current density is related to the gradient of the phase ϕ ,

$$\mathbf{J}(\mathbf{r}) = \rho(\mathbf{r}) \left(\frac{\hbar}{m} \right) \nabla \phi(\mathbf{r}). \quad (4.2)$$

If complex ψ happens to be zero at some point, the phase ϕ is not defined, and the quantum flux has a vortex structure around such a point. The vortices are “quantized,” as explained in [58].

In the tunneling problem, the wave function of the tunneling particle is *complex* (cf. Eq.

(3.1)) $\Psi(\mathbf{r}) = [\varphi_0^D(\mathbf{r}) + i\varphi_0^A(\mathbf{r})] / \sqrt{2}$, where $\varphi_0^D(\mathbf{r})$ and $\varphi_0^A(\mathbf{r})$ are donor and acceptor orbitals. Both $\varphi_0^D(\mathbf{r})$ and $\varphi_0^A(\mathbf{r})$ have nodes, because they are excited states of the Hamiltonian. The nodes of donor and acceptor orbitals are some surfaces in 3D space. The intersections of these surfaces with the xy plane form lines, which are shown in Fig. 3. The crossing points of the nodal lines of donor and acceptor orbitals then point to the centers of vortices. In Fig. 3 they are shown as crossing points of solid and dotted lines, which indicate nodes of real and imaginary parts of the wave function of the tunneling electron, respectively.

The intricate structure of the tunneling flow provides information on how electron tunneling through molecular wires such as polypeptide chains actually occurs. This picture of the tunneling flow is a remarkable illustration to Bohmian hydrodynamic interpretation of quantum mechanics [43].

The analogy with quantum liquids suggests a qualitative picture of biological electron tunneling in which chains of atoms of the protein matrix form a network of molecular tubes connecting the donor and acceptor, over which the “quantum electron liquid” can flow. Electrons can tunnel in such tubes only when there is a fluctuational quantum mechanical resonance between the initial and final states [10], thus, although always connected, these tubes can be thought to open up only infrequently, allowing gradual (and incoherent) leakage of electrons from donor to acceptor. The overall process also resembles quantum percolation.

5. ELECTRON TRANSFER OR HOLE TRANSFER? EXCHANGE EFFECTS

Electron transfer is associated with a superexchange coupling via virtual states in which both donor and acceptor complexes are oxidized; the hole transfer is due to virtual excited states in which both donor and acceptor are reduced. In the latter case a (virtual) hole is present in the protein medium while in the former case an additional (virtual) electron is present. Of course a combination of electron and hole transfer is also possible—a process in which virtual states of both types are involved [15].

Experimentally these two cases are impossible to distinguish, because in both cases the initial and final states of the system are the same. Yet, it is interesting to know which case of coupling actually occurs in real systems.

An interesting example that provides some insights into the above issue and shows the effects of the many-electron nature of tunneling transitions, is a simple model system, $\text{H}-(\text{He}-\text{He}-\dots-\text{He}-\text{He})-\text{H}^+$, in which electron tunneling occurs between two protons, across a chain of three He atoms [59].

Figure 4 displays the spatial distribution of the tunneling current along the molecular axis. As can be seen in Fig. 4, the electron tunneling occurs right through the centers of He atoms. At first sight, this is counter-intuitive, because the $1s$ orbital of He is doubly occupied and the next available orbital for an additional (tunneling) electron lies above the vacuum level (electron affinity of He is negative). That would mean that direct tunneling through He atoms should be more difficult than through the vacuum, and therefore the tunneling electron should try to avoid He atoms. The stream lines of the current should then look like the lines of the magnetic field expelled from a superconducting sphere. Yet the calculation shows that electrons move right through the centers of the He atoms. What is actually happening is explained by the exchange of the tunneling electron and electrons with the same spin in $1s$ orbitals of He atoms. Such a process can also be interpreted as a hole transfer.

This calculation also indicates that any kind of substance is likely to be better than vacuum for electrons to tunnel through! Water in proteins, for example, can definitely facilitate the electronic coupling if cavities or gaps filled with water are present along the tunneling path [60].

6. DYNAMIC ASPECTS. TUNNELING PATHS DRESSED WITH PHONONS

We finally briefly mention an interesting issue related to the effects of the dynamics of the protein structure on electron tunneling [57, 61, 62]. Protein dynamics is an integral part of the transfer mechanism, and thermal motions are needed to bring the donor and acceptor states into resonance. There are however, other important implications of protein dynamics.

First of all the ET transition state is not unique, and the resonance at which tunneling occurs may be achieved at slightly different configurations of the protein matrix. The tunneling jump itself occurs on a time-scale (order of fs or less) much shorter than that of protein dynamics. Therefore tunneling in different molecules will occur through slightly different

instantaneous configurations of the protein. To take this effect into account in the rate, one needs to average $|T_{DA}|^2$ over thermal configurations of the protein and examine sensitivity of the pathways. This averaging, at least in some cases, can perhaps explain the success of phenomenological/empirical relations for rates of ET in proteins that take into account only local density of the protein medium but not their detailed structure [8]. These are static or inhomogeneous effects.

The second effect is of dynamical nature. Since the tunneling jump occurs on such a short time-scale, the protein structure can certainly be considered as fixed during the jump. Yet, protein dynamics can modify the tunneling event. This occurs via inelastic tunneling [57, 62]. Although the protein structure is fixed on the time-scale of tunneling, due to the elastic properties of the medium through which electron propagates, it can exchange energy with the medium by exciting a vibration or receiving energy from the medium. In other words, the tunneling occurs simultaneously with a vibrational transition of the protein medium.

One can think that the tunneling electron, as it jumps from atom to atom in the protein, will slightly change the momenta of these atoms by sharp “kicks,” without shifting them in space. Thus a tunneling electron can leave a trace of excitations along the path, and in principle this can allow for direct observation of the tunneling paths.

Quantitatively, inelastic tunneling is described by the probability $P(\varepsilon)$ that the tunneling electron will exchange energy ε with the protein when it makes the tunneling jump from donor to acceptor. The longer the distance between donor and acceptor, the larger the probability that such an energy exchange will occur. The function $P(\varepsilon)$ can be obtained from molecular simulations of the protein dynamics [62].

There is no doubt that the above dynamic effects are present in proteins; however it is not clear how strongly they modify the rate of electron transfer in real systems. At present there is no consensus on how important the described effects are, and work is in progress to do both the accurate electronic structure calculations of electronic coupling and the dynamical simulations of realistic models required to understand these effects. Both static and inelastic tunneling effects are reflected in the dependence of the tunneling matrix element T_{DA} on the configuration of the system [62].

Another interesting question is the sensitivity of the pathways to slow and large-amplitude configurational changes of the protein. The question is: does the (dynamic) inhomogeneity of the protein structure randomize the pathways to an extent that individual paths determined for a fixed configuration of the protein become meaningless?

The positive answer to the last question shifts the tunneling description toward Dutton's limit of the unstructured, effective dielectric protein medium [8]. The negative answer pushes the picture closer to Gray's limit of individual pathways [5]. It is understood however, that the actual picture is somewhere in between these two extremes. Of particular interest also are the cases when the tunneling electron is coupled to proton transfer [13]; in some of such reactions the proton transfer mediates the coupling and thereby localizes the tunneling electron to a specific pathway. The issue of the sensitivity of the tunneling paths is

related to a fundamental biological question, namely whether or not there are specific, evolutionary optimized tunneling routes between redox centers in proteins.

7. HOW LONG DOES IT TAKE FOR AN ELECTRON TO TUNNEL A DISTANCE OF 20 Å?

There are *four* different time-scales in a tunneling ET reaction. The first two time-scales are related to thermal motion of the protein and the solvent around it. For the transition between the two electronic states to occur, the two electronic states of donor and acceptor need to be brought into resonance. How often this happens is determined by the nuclear motions in the system. The other two time-scales are electronic. The interplay between these time-scales determines the overall rate of the reaction. The following provides a simple estimate of the time-scales involved.

The frequency at which two electronic states are brought into resonance is given by the transition state theory:

$$k_{nuc} = \nu_0 e^{-(\nabla G^0 + \lambda)^2 / 4kT\lambda}, \quad (7.1)$$

where G^0 is the standard Gibbs energy of the reaction, λ is reorganization energy, which is typically of the order of 0.5 eV in proteins, and $\nu_0 = kT/2\pi\hbar$ is the frequency factor of the order of 10^{12} – 10^{13} s⁻¹. The second time-scale is the time interval during which the two states “stay in resonance” upon single level-crossing (the time of level-crossing) is

$$\tau_x = \frac{2\pi T_{DA}}{\nu_0 \sqrt{4\pi kT\lambda}}. \quad (7.2)$$

The third time-scale is the electronic one: on this time-scale the donor and acceptor electronic states would be mixed if the system were frozen at the transition state,

$$\tau_{el} = \hbar / T_{DA}. \quad (7.3)$$

This process of mixing of donor and acceptor electronic states is what we called wave function *perestroika*.

Now, the ratio of level-crossing time, and the time of electronic mixing gives the Landau–Zener probability that the tunneling transition will occur,

$$P_{LZ} = \frac{2\pi T_{DA}^2}{\hbar \varepsilon} = \frac{\tau_x}{\tau_{el}}. \quad (7.4)$$

Finally, the overall rate of the electron transfer is the product of frequency of visiting the transition state and the LZ probability that the tunneling takes place:

$$k_{ET} = P_{LZ} k_{nuc} = \frac{2\pi}{\hbar} \frac{T_{DA}^2}{\sqrt{4\pi\lambda kT}} e^{-(\Delta G^0 + \lambda)^2 / 4\lambda kT}. \quad (7.5)$$

This is a well-known Marcus–Levich–Dogonadze expression for the rate of non-adiabatic electron transfer.

The fourth time-scale is present in the problem “behind the scenes.” This is the time that it takes for an electron to tunnel between donor and acceptor in a single protein molecule. The elusive concept of tunneling time has been discussed extensively in the past, most thoroughly by Landauer and Martin [63], and most recently by Nitzan et al. [21], and Georgievskii and Stuchebrukhov [56]. To formally measure this time one can use the dynamics of an internal coordinate of the tunneling particle, such as spin, assuming that the internal coordinate changes only when the particle is under the barrier. For tunneling time one can find the following expression:

$$\tau_{tun} = \hbar \partial \ln |T_{DA}(E)| / \partial E, \quad (7.6)$$

where E is the tunneling energy. In the semi-classical limit the above expression gives a well-known estimate ($m = 1$)

$$\tau_{tun} = \int \frac{dx}{\sqrt{2(V-E)}}. \quad (7.7)$$

Whereas in the quantum limit,

$$\tau_{tun} = N \frac{\hbar}{\Delta E}, \quad (7.8)$$

where N is the number of intermediate virtual states that the particle needs go over in the protein between donor and acceptor sites, and E is the energy of the virtual states with respect to initial and final states, i.e., height of the barrier. Typically the number of atoms that the tunneling electron is passing through in a protein is of the order of 20 or more, whereas the height of the barrier that it tunnels through $E \sim 1$ eV. The last estimate gives for electron tunneling time $\tau_{tun} \sim 10$ fs. Thus the time-scale on which an electron is tunneling through the body of a single protein molecule is within the reach for modern time-resolved spectroscopy. It would be interesting to probe such a process experimentally.

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Fig. 1.

Transfer tunneling matrix element calculated by Eq. (3.8) for the $\text{Ru}^{2+/3+}\text{-(Gly)}_5\text{-Cu}^{2+/1+}$ system—two metal complexes connected by a peptide chain [42]. Distance between donor and acceptor is about 30 Å. Total flux is shown as a function of the position of the dividing surface oriented perpendicular to the Ru–Cu axis.

Fig. 2. Distribution of interatomic tunneling currents in a (His126) Ru-modified azurin [6] system. The donor Cu^{1+} and acceptor Ru^{3+} are coupled by two protein strands, and an electron has to jump from one strand to the other in the reaction using hydrogen bonds between the strands. The identified pathway shows how this happens [55].

Fig. 3. Vortex structure of the tunneling current in a polypeptide molecular wire, such as shown in Fig. 1 (left). The vortices originate at points where nodal lines of donor and acceptor orbitals intersect.

Fig. 4.
The distribution of tunneling current in the $\text{H-He-He-He-H}^+ \rightarrow \text{H}^+-\text{He-He-He-H}$ transition. Electron tunneling occurs through centers of He atoms, and involves exchange with He 1s electrons [59].