

## Feature article

# Long-distance electron tunneling in proteins

Alexei A. Stuchebrukhov

Department of Chemistry, University of California, Davis, CA 95616, USA e-mail: stuchebr@chem.ucdavis.edu

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**Abstract.** Long-distance tunneling is the major mechanism of electron transfer (ET) in proteins. For a number of years, a major question has been whether specific electron tunneling pathways exist. This question is still debated in the literature, because the pathways are not observed directly, and interpretation of experimental results on ET rates involves ambiguities. The extremely small tunneling interactions are difficult to calculate accurately. Recently, there has been remarkable progress in the area; however, some problems still remain unresolved. The accurate prediction of the absolute rates of long-distance ET reactions and other biological charge-transfer reactions is a particularly pressing issue. The current theoretical calculations indicate that the specific paths do exist in static protein structures. However, the protein motions can result in significant averaging of the spatial tunneling patterns, and it is not clear how accurately subtle quantum interference effects are described by the present theories. The key to resolving these issues is to perform accurate, first-principles calculations of electron tunneling that include the dynamics of the protein. This paper reviews some of theoretical issues of electron tunneling dynamics in inhomogeneous organic media.

**Keywords:** Electron transfer – Tunneling – Proteins

## 1 Introduction

The most remarkable aspect of electron transfer (ET) in proteins is that it occurs via quantum mechanical tunneling [1, 2, 3, 4, 5]. 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 states which result in the effective lowering of the tunneling barrier, and the exchange at physiological rates becomes possible [5]. It is remarkable that the whole biological energy transduction machin-

ery, of which electron transport is a major part [6, 7], is based on 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 exist in proteins [2, 3, 4, 5]. This question is still debated in the literature, because the pathways are not observed directly, and the interpretation of experimental results on ET rates involves ambiguities. The extremely small tunneling interactions (order of  $10^{-1}$ – $10^{-4}$  cm<sup>-1</sup>) are difficult to calculate accurately. Despite remarkable recent progress in the area [8, 9, 10, 11, 12, 13, 14], some important problems remain unresolved. The accurate prediction of the absolute rates of long-distance ET reactions and other biological charge-transfer reactions is a particularly pressing issue.

On the one hand, the current theoretical calculations are consistent with the idea of specific tunneling paths [8, 9, 14]; on the other hand, experimental studies have been reported that seem to indicate that the mutations of amino acids along the path do not significantly change the rates of ET. Adding to the puzzlement, the recently proposed [5] empirical relations for the rates of biological ETs, which are based on the averaged characteristics of the protein medium, such as local density, rather on the detailed structural data, are reported to agree well with the experimental data. An attempt to reconcile the two approaches has been presented recently [15]; however, the issue remains largely unresolved. In particular, the possible role of protein dynamics in averaging the paths is not completely understood yet [16, 17]. Since the tunneling amplitudes are not directly observed in experiments, many issues can only be resolved by performing accurate quantum calculations on realistic systems that involve the dynamics of the system. This is a challenging computational problem. The difficulties are not only purely technical/computational, however. In general, tunneling in many-electron systems is a nontrivial physical problem.

This paper reviews some of the theoretical issues of ET in proteins. We focus on what happens with an electron at

the transition state of an ET reaction, when it tunnels through the protein medium. Of our special interest is the many-electron nature of the phenomenon. The key approach to be discussed is the method of tunneling currents [14] developed by the author. Reviews of other approaches, and topics not covered here can be found in Refs. [8, 9, 10, 11, 12, 13].<sup>1</sup> Two classic reviews in Refs. [10, 11] discuss in detail earlier theoretical and experimental work in the field.

Before we begin the tunneling discussion, it should be mentioned that electron tunneling is not the only possible mechanism of ET. In some cases, the hopping mechanism or a combination of tunneling and hopping is responsible for transfer over long distances. This occurs when sufficient energy is available for direct excitation of an electron/hole to the band of the excited states. One example of such a mechanism is ET in DNA, discussed extensively in recent years [13, 19, 20, 21, 22].

## 2 Tunneling matrix element and tunneling pathways

The majority of ET reactions in proteins are nonadiabatic owing to the weakness of interaction between 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, 11]. This matrix element and the associated tunneling process are the main focus of the present paper.

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 BO approximations are made (or tacitly assumed). The first approximation assumes independence of the transfer matrix element of the medium nuclear configuration – practically it means that if we calculated  $T_{DA}$  at a nuclear configuration which is not exactly the transition state, we assume that the transfer matrix element at the transition state will be approximately the same. The deviation from the Condon approximation are briefly discussed in Sect. 5.

The BO approximation (for donor and acceptor states D and A) practically means independence of the transfer matrix element  $T_{DA}$  of the vibrational state of the medium at which the tunneling transition is taking place. In other words, in this approximation the electronic coupling is calculated at a specific fixed nuclear configuration of the system, disregarding the actual nuclear motion. The dependence of the rate (but not the matrix element!) on the vibrational state enters into theory in this case only in the form of the Franck–Condon vibrational factors.

<sup>1</sup>In this review we do not cover issues related to activation of the ET reaction, i.e. how the protein medium reorganizes to achieve a configuration at which electron tunneling takes place. Among important aspects here are the nature of the protein medium reorganization and the entropy of activation, the role of quantum modes of the medium, control of the reaction by protein dynamics, and the distance dependence of the reorganization energy and driving force. We also do not consider in great detail all the medium dynamic effects, which include both non-Condon and non-Born–Oppenheimer (BO) effects [18].

In the BO approximation, the wave function of the system (in the initial state D, or the final state A) is the product of the electronic and vibrational wave functions, and the distribution of total energy between electronic and vibrational degrees of freedom is fixed. Thus, 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 Ref. [18]) 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 vibrational and electronic degrees of freedom is no longer fixed and will depend 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 [18]. In this review, we assume the BO approximation and treat the tunneling coupling  $T_{DA}$  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 [23, 24]. The equivalence of superexchange and tunneling is discussed, for example, in Refs. [11, 25, 26, 27]. Based on the superexchange model, several methods for calculation of the electronic tunneling matrix element have been developed [11, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46].

We begin with a brief review of these methods and then move on to discuss the method of tunneling currents, the main subject of the paper. For a more detailed discussion of the superexchange methods, and a more complete reference list of the early work, the reader is referred to a comprehensive review of the subject by Newton [11].

### 2.1 Direct method

In this method the matrix element is calculated directly [11]. 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 – 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,  $S_{DA}$  is very small and therefore can be neglected in the denominator. Equation (2.1) can be used in both one-electron and many-electron formulations of the problem. This method has been used in the past for relatively strongly coupled D–B–A systems, [11, 46].

For long-distance tunneling, the potential problems with the previously described 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 involving donor and acceptor wave functions 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 Eq. (2.1), the very small matrix element is evaluated as the 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 Avoided crossing

In some cases, it is possible to calculate directly the energy difference between the two adiabatic (i.e. exact) states. Usually these are the ground state and the first excited state in the system, which are some mixtures of diabatic  $|D\rangle$  and  $|A\rangle$  states owing to their (unknown) coupling  $T_{DA}$ . To extract  $T_{DA}$  in this method the parameters of the system, such as external charges, are varied in such a way that the two adiabatic states experience an avoided crossing, and the minimum-energy distance between the states is determined. This distance is twice the magnitude of the matrix element  $T_{DA}$ .

For long-distance tunneling, the couplings are typically of the order  $10^{-1}$ – $10^{-2}$  cm $^{-1}$  or less. To find the avoided crossing point with such accuracy is not easy, at best. (This “needle in a haystack” problem is discussed in Ref. [44].) Moreover, the excited-state energy of a large many-electron system needs to be calculated with impractical accuracy. The method, however, can be used for calculations of some not very large one-electron systems [44]. In particular, for relatively small symmetric D–B–A systems, the calculation of the energy splitting can be carried out at various levels of ab initio theory [28, 29, 30]. For symmetric D–B–A systems, the transition state is well defined by symmetry, which makes these type of calculations particularly suitable.

## 2.3 Application of Koopmans’ theorem

At the SCF level, to determine the splitting of two adiabatic states, one can rely on Koopmans’ theorem [11, 28, 29, 30]. In this case, one assumes that there is no electronic relaxation of the “core” orbitals, and the only difference in the initial and final electronic state is the orbital of a single transferring electron. Thus, for example, for a system with an odd number of electrons,  $N$ , the initial and final (many-electron) states represented by one Slater determinant will be  $|D\rangle = |(\text{core})\phi_d\rangle$  and

$|A\rangle = |(\text{core})\phi_a\rangle$ , and the two adiabatic states are  $|\psi_+\rangle = |(\text{core})\phi_+\rangle$  and  $|\psi_-\rangle = |(\text{core})\phi_-\rangle$ , where

$$\phi_{\pm} = (\phi_d \pm \phi_a)/\sqrt{2} . \quad (2.2)$$

The  $N - 1$  core orbitals are assumed to be the same. Then, it is an easy matter to show that the splitting of two adiabatic states  $|\psi_{\pm}\rangle$ , i.e. the total electronic energy difference between the two states,

$$\Delta = (E_- - E_+) , \quad (2.3)$$

is the same as the distance between the energies of one-electron HOMO and HOMO-1 orbitals (Eq. 2.2) for a triplet state of a  $N + 1$  electron system,  $|(\text{core})\phi_+\phi_-\rangle$ . A nontrivial fact is that to find the energy splitting of an  $N$ -electron system, one performs (one Self-Consistent-Field, SCF) calculation on an  $N + 1$  electron system. This clever method is limited to symmetric systems, and is as accurate as Koopmans’ theory is. The method has been reported to produce reliable results for not very small electronic couplings, typically greater than 10–100 cm $^{-1}$ . The importance of electron relaxation effects has been examined by comparing the results based on Koopmans’ theorem and those from direct SCF evaluations of the energy splittings between adiabatic states [28, 29, 30].

In the following sections, we describe an approach to treat tunneling with the method of tunneling currents, in which an approximation based on the “frozen core” and one tunneling electron picture, similar to that assumed in Koopmans’ theory, is utilized.

## 2.4 Generalized Mulliken–Hush method

Recently, Cave and Newton [32] proposed the following method. For some configuration of the system, which is not necessarily that of the transition state, two adiabatic states – the ground state and the first excited state – are calculated. (Any of the available many-electron methods, including correlated ones, can be used.) In addition, the dipole moment matrix,  $\mu_{ij}$ , is calculated using these adiabatic states. They assumed then that the diagonalization of the matrix  $\mu_{ij}$  is associated with the same transformation as that which mixes diabatic states into adiabatic ones. The former is easily found, and the coupling  $T_{DA}$  can then be determined. The method can be justified using a perturbation theory argument. Assuming that the system is far from the crossing point, the adiabatic states are

$$|\Psi_1\rangle = |a\rangle + \frac{T_{DA}}{\Delta E_{ab}} |b\rangle \quad (2.4)$$

$$|\Psi_2\rangle = |b\rangle - \frac{T_{DA}}{\Delta E_{ab}} |a\rangle , \quad (2.5)$$

where  $|a\rangle$  and  $|b\rangle$  are corresponding diabatic states, and  $\Delta E_{ab}$  is their energies’ difference. An assumption has been made that the overlap between  $|a\rangle$  and  $|b\rangle$  is zero (see later). With these states the transition dipole moment  $\mu_{12}$  is evaluated. If now an additional assump-

tion is made that the matrix element between diabatic states  $\mu_{ab}$  is zero, the following relation between  $T_{DA}$  and  $\mu_{12}$  is found:

$$T_{DA} = \frac{\mu_{12}}{\Delta\mu_{ab}} \Delta E_{ab} \quad (2.6)$$

where  $\Delta\mu_{ab} = \mu_{bb} - \mu_{aa}$  is the difference of dipole moments in two diabatic states. This difference is roughly  $eR_{ab}$ , where  $R_{ab}$  is the distance between the donor and acceptor sites, or can be evaluated more accurately using  $\Delta\mu_{ab} \simeq \Delta\mu_{12}$ . This method has a nice feature that the system does not need to be brought into resonance to evaluate the coupling. A number of interesting applications of the generalized Mulliken–Hush (GMH) method have been reported recently [33, 34, 35].

For long-distance tunneling, both assumptions  $S_{ab} = \langle a|b \rangle = 0$  and  $\mu_{ab} = 0$  are not necessarily valid. However, a generalization of the Cave–Newton GMH method can be used which avoids these assumptions. In this scheme, three calculations at slightly different configurations are made, and three pairs of functions are found:  $|\Psi_i^{(n)}\rangle$ ,  $n = 1, 2, 3$ ,  $i = 1, 2$ . Each of the functions is approximately

$$|\Psi_1^{(n)}\rangle = |a\rangle + \frac{H_{ab} - E_a^{(n)} S_{ab}}{\Delta E_{ab}^{(n)}} |b\rangle \quad (2.7)$$

$$|\Psi_2^{(n)}\rangle = |b\rangle - \frac{H_{ab} - E_b^{(n)} S_{ab}}{\Delta E_{ab}^{(n)}} |a\rangle \quad (2.8)$$

With these functions, three transition dipole moments are calculated:

$$\mu_{12}^{(n)} = \mu_{ab} + \mu_{aa} \frac{H_{ab} - E_b^{(n)} S_{ab}}{\Delta E_{ab}^{(n)}} - \mu_{bb} \frac{H_{ab} - E_a^{(n)} S_{ab}}{\Delta E_{ab}^{(n)}} \quad (2.9)$$

for  $n = 1, 2, 3$ . From these three equations, three unknowns  $H_{ab}$ ,  $S_{ab}$ , and  $\mu_{ab}$  are determined and then the transfer matrix element  $T_{DA}$  is evaluated using Eq. (2.1). For reliability, more than three points can be examined. The tunneling energy  $E_0$  entering Eq. (2.1) is found approximately by extrapolating the external parameter, at which three pairs of energies ( $E_a^{(n)}$ ,  $E_b^{(n)}$ ) were determined, to a point where the energies  $E_a$  and  $E_b$  cross, as described, for example, in Ref. [44].

As seen, in this method one avoids the direct evaluation of the matrix elements entering into Eq. (2.1) by finding them from the calculated transition matrix elements of the dipole operator. The remarks made earlier about the potential problems with the evaluation of Eq. (2.1) apply here as well. In addition, here we rely upon the accuracy of the evaluation of the adiabatic states, and assume that the extremely small admixture of the second diabatic state, which is proportional to  $T_{DA}$ , is accurately represented in our states. These admixed components, however, appear only in the far tail of the adiabatic states. It is not clear, a priori, how accurately this extremely small admixture will be captured by the usual variational procedures employed in the evaluation of the adiabatic states, in particularly of the excited state.

## 2.5 The propagator method

In a one-electron description, a method which is based on perturbation theory treatment can be used. This technique grew out of the early work of Larsson [24] and Siddarth and Marcus [36] and was first applied in Refs. [37, 38, 39, 40]. In principle, the method can be generalized to many-electron systems as well [8], but for large biological systems such treatment becomes impractical. In the one-electron description, however, the method can be applied for treatment of very large systems, such as entire proteins.

The problem is cast in terms of weakly coupled D–B–A complexes. The donor and acceptor are redox groups in the protein, and the bridge is the protein itself. The key property to be evaluated is the electronic propagator or Green's function of the protein. The matrix element has been shown to have the form

$$T_{DA}^{(0)} = \sum_{ij} V_{di} G_{ij}(E) V_{ja} \quad (2.10)$$

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,

$$G_{ij}(E) = \langle i | (H_B - E)^{-1} | j \rangle \quad (2.11)$$

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 nonorthogonality of the atomic orbitals has been addressed in Refs. [41], where modifications of Eq. (2.11) were obtained.

To evaluate Eq. (2.10) for  $T_{DA}$ , and to avoid diagonalization or inversion of big matrices, the system can be rewritten as a system of linear equations with a sparse matrix  $(H_B - E)_{ji}$  and solved iteratively [40]. This procedure can be applied to very large systems, which can include as many as  $10^6$  atomic orbitals.

The smallness of the coupling  $V$  is related to a sensible partitioning of the problem into D–B–A complexes, and a correct choice of donor and acceptor states [42]. The partitioning, however, is not unique, and the smallness of the coupling is not obvious, in particular when the coupling between the D–B–A complexes is covalent. What makes the perturbation theory applicable is that the donor and acceptor orbitals are always delocalized over several atoms of their respective redox complexes. If both the partitioning and the zeroth order donor and acceptor orbitals  $|d\rangle$  and  $|a\rangle$  are chosen correctly, the terms  $V_{di}$  and  $V_{aj}$  then represent the coupling of the atomic orbitals of the bridge to delocalized molecular orbitals. That is,  $V$ s are not just nearest-neighbor interatomic interactions, but those multiplied by the small coefficients of expansion of  $|d\rangle$  and  $|a\rangle$  in the atomic basis set of the complex. Thus, for the perturbation theory to be applicable it is essential that the donor and acceptor complexes contain several atoms [42].

The tunneling problem is equivalent to that of scattering between two localized states  $|d\rangle$  and  $|a\rangle$ , and Eq. (2.10) is the lowest (“Born”) perturbation theory expression for the scattering amplitude [43]. 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, it is either a single low-order term or an infinite number of terms that makes a difference.)

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

$$T = V + VGV + VGVGV + VGVGVGV + \dots \quad (2.12)$$

In applications to the tunneling problem, one can think that the “scattering” occurs between the initial and final localized states  $|d\rangle$  and  $|a\rangle$  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. (2.11). Since typically there is no direct coupling between initial and final states, the odd terms in Eq. (2.12) disappear ( $V$  then is equivalent to that in Eq. 2.10).

The summation of all important terms in Eq. (2.12) results in the following expression for the transfer matrix element [44]:

$$T_{DA} = \frac{T_{DA}^{(0)}}{\sqrt{(1 - \Sigma'_{aa})(1 - \Sigma'_{dd})}}, \quad (2.13)$$

where  $T_{DA}^{(0)} = \Sigma_{da}$  is the lowest-order expression given previously, and  $\Sigma_{aa}$  and  $\Sigma_{dd}$  are the 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 Eq. (2.13) account for the delocalization of the diabatic donor and acceptor states in the protein medium. The expressions for self-energies  $\Sigma_{aa}$  and  $\Sigma_{dd}$  have the same structure as  $T_{DA}^{(0)} = \Sigma_{da}$  and can be computed using the same technique of sparse matrices as for  $T_{DA}^{(0)}$ . Calculations on Ru-modified proteins [2] showed that the new 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 a combination of both [11]. 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 Ref. [40]. The method treats the previous expressions for complex tunneling energies, and uses analytical properties of the tunneling amplitudes.

The success of the methods described is determined by the quality of the effective one-electron Hamiltonians used in the calculation. In practice, semiempirical extended-Hückel or tight-binding Hamiltonians are often used, which are simple and efficient, but not very accurate. Kurnikov and Beratan [45] have explored construction of more accurate effective Hamiltonians for proteins based on ab initio calculations.

## 2.6 Protein pruning

For the biological ET problem, it is not necessary to do sophisticated first-principles calculations on whole proteins. The tunneling nature of electronic communication between redox sites makes the size of the protein region involved in propagating the transferring electron relatively small, i.e. the problem is local. A natural approach, therefore, is to perform calculations in two stages: first to examine the whole protein with approximate one-electron methods, to identify the most important parts of the protein in order to simplify the system – the procedure that we call protein pruning [47]; then to proceed with more accurate many-electron ab initio treatments.

Protein pruning is the method to identify those amino acids of the protein that are involved in propagation of the tunneling electron. Several similar strategies have been proposed to achieve this goal [8, 48, 49, 50, 51]. The idea is to probe the sensitivity of the electronic coupling to computer-induced changes in the protein and to eliminated groups that are not important. A similar idea of computerized search (artificial intelligence search) was developed by Siddarth and Marcus [36]. The method relies upon the efficiency of a one-electron evaluation of the tunneling matrix element. Such calculations have been performed on several systems [52, 53, 54, 55, 56]. 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.

## 2.7 Tunneling pathways

From the biological perspective, it is important to know exactly how and where in the protein electron tunneling occurs [57]. There are two possibilities. If the tunneling electron is delocalized on a scale larger than a typical dimension of the protein’s amino acids, (i.e. the scale, or wavelength, on which the wave function of the tunneling electron decays, is greater than size of the 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 [4, 5].

However, if the wavelength (i.e. the characteristic decay length) of the tunneling electron is small, then the

detailed structure of the protein medium intervening between redox centers becomes important, the pathways do exist [2, 57] and a number of fundamental questions about the role of tunneling pathways in biological function and their molecular evolution arise [52, 53].

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 paper, and an interested reader is referred to recent reviews of the topic [2, 3, 4, 5, 8, 9]. Qualitatively, the wavelength of the tunneling electron turns out to be of atomic size (i.e. about 1Å), and the tunneling paths are certainly localized in frozen protein structures. However, protein dynamics can significantly reduce the structural effects (see later). This may explain the reported success of empirical relations for ET rates in proteins, which ignore the detailed chemical structure of the protein, yet account for its density inhomogeneity [5]. Also, the existence of these paths may not necessarily indicate their importance for biological function, provided ET is not the rate-limiting step [5].

From the theoretical perspective, the nature of the long-distance electron tunneling process in structured organic media, such as proteins, and in particular its many-electron aspect, is interesting regardless of its biological implications.

The first model of the tunneling pathways, which viewed them as specific sequences of atoms along which electron tunneling occurs, was developed by Beratan and Onuchic [57]. 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 the neglect of interference effects. The development of this simple and practically useful model, which now includes both interferences and multiple paths, has been recently reviewed by the authors [8, 9].

### 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, 58]. The general idea of the approach is to examine the dynamics of charge redistribution in a system which is artificially “clamped” at the transition state, when donor and acceptor states are degenerate.<sup>2</sup>

<sup>2</sup>To find the transition state, one can use external charges to simulate a fluctuating electric field within the protein, as described in Refs. [11,59]. These fields shift the redox potentials of donor and acceptor complexes and bring them occasionally to resonance, at which point electron tunneling occurs. The transition state of ET, i.e. the resonance condition, is obviously not unique

The tunneling dynamics is described by the following time-dependent wave function:

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

where  $|D\rangle$  and  $|A\rangle$  are diabatic donor and acceptor states, and  $T_{\text{DA}}$  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-electron 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. It is this tunneling current that we are focusing on in this method.

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

$$\frac{\partial \hat{\rho}}{\partial t} = -\text{div} \hat{\vec{j}}, \quad (3.2)$$

which for the tunneling state (Eq. 3.1) yields

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

As expected, the periodic variation of charge distribution is associated with a periodic time-dependent current,  $\vec{j}(\vec{r}, t)$ . The spatial distribution of current  $\vec{J}(\vec{r})$ , however, remains the same during the dynamic process. Given also the form of  $\vec{J}(\vec{r})$ , one concludes that  $\vec{J}(\vec{r})$  is not related to the 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  $\vec{J}(r)$  represent the whole manifold of quantum Bohmian trajectories, which received attention in the literature recently [60]. The tunneling transition therefore can be characterized by the current  $\vec{J}(\vec{r})$ .

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

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

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 interatomic currents  $J_{ab}$  and current density  $\vec{J}(\vec{r})$  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. The previous general relations are valid for both a one-electron and a many-electron description of the system.

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

$$\vec{J}(\vec{r}) = \frac{\hbar}{2m} (\psi_D \nabla \psi_A - \psi_A \nabla \psi_D), \quad (3.5)$$

where  $\psi_D$  and  $\psi_A$  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 two atomic orbitals on atoms  $a$  and  $b$ ,  $\mathbf{H}$  and  $\mathbf{S}$  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 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 the 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 over positive contributions  $J_{ab}$ , which describe the tunneling current from various atoms  $b$  to atom  $a$ . Both the interatomic 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 [53].

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, i.e. begin from a donor atom,  $d$  and find an atom  $b1$  to which the current  $J_{b1,d}$  is a maximum, then go to atom  $b1$ , repeat the procedure and find atom  $b2$ , etc., until the acceptor atom  $a$  is reached. The sequence of atoms  $d, b1, b2, \dots, bn, a$  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  $\vec{J}(\vec{r})$  and  $J_{ab}$  turn out to be related to the tunneling matrix element:

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

In Eq. (3.8)  $\Omega_D$  is the volume of space that comprises the donor complex, and  $\partial \Omega_D$  is its surface. These relations were obtained using the conservation of charge [58a,b].

In the methods for computing tunneling matrix elements reviewed earlier, 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 previous 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. Qualitatively, this is similar to the transition-state theory, where the rate is evaluated on the surface dividing reactants and products [61]. Using this technique, extremely small tunneling matrix elements can be evaluated (Fig. 1).

### 3.2 Many-electron picture

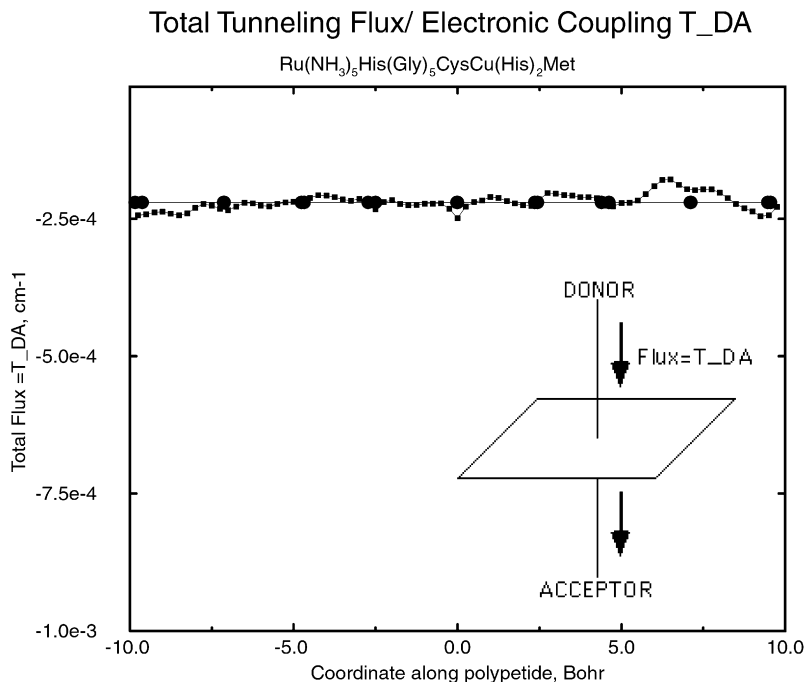
In a many-electron formulation of the problem, the main results cited earlier remain unchanged, except that now the diabatic states  $|D\rangle$  and  $|A\rangle$  should be understood as many-electron states, and the operators which act on them should be written in many-electron form. The detailed derivations can be found in the original papers [58], and in a recent review of the method [14]. In the following we summarize the key ideas.

#### 3.2.1 Calculation of current density. Hartree–Fock approximation

To calculate the spatial distribution of the tunneling current  $J(\vec{r})$  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), in which the current density operator is

$$\hat{j}(\vec{r}) = \frac{\hbar}{2mi} \sum_{i=1}^N \left[ \delta(\vec{r} - \vec{r}_i) \frac{\partial}{\partial \vec{r}_i} - \frac{\partial^+}{\partial \vec{r}_i} \delta(\vec{r} - \vec{r}_i) \right]. \quad (3.9)$$

Here the summation is over all electrons in the system, and the Hermitian operator should be understood as one acting on the function on the left-hand side. The states  $|D\rangle$  and  $|A\rangle$  can be represented by one or many Slater determinants, depending on the level of approximation used. The derivatives of the above operator act on the molecular orbitals that make up the Slater determinants.



**Fig. 1.** Transfer tunneling matrix element calculated as total flux by Eq. (3.8) for the Ru<sup>2+/3+</sup>-(Gly)<sub>5</sub>-Cu<sup>2+/1+</sup> system – two metal complexes connected by a peptide chain [59]. The distance between donor and acceptor is about 30 Å. The total flux is shown as a function of the position of the dividing surface oriented perpendicular to the Ru–Cu axis

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  $\sigma$  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 [62], one can evaluate the expression for the current  $\vec{J}$ , Eq. (3.3). The final expressions, however, are much simplified and some important physical insights are gained if the molecular orbitals  $\varphi_{i\sigma}^A$  and  $\varphi_{i\sigma}^D$  are made biorthogonal [63, 64, 65], by 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,

$$\langle \varphi_{i\sigma}^A | \varphi_{j\sigma}^D \rangle = \delta_{ij} \delta_{i\sigma}^{\sigma} . \quad (3.10)$$

Such orbitals are also known as corresponding orbitals, and have been utilized in the ET problem by Newton [66], Friesher [46], and Goddard [67] and their co-workers in the past.

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

$$\begin{aligned} \vec{J}(\vec{r}) = & -\frac{\hbar}{2m} \langle A | D \rangle \\ & \times \sum_{i,\sigma} \frac{1}{s_i^\sigma} [\varphi_{i\sigma}^A(\vec{r}) \nabla \varphi_{i\sigma}^D(\vec{r}) - \varphi_{i\sigma}^D(\vec{r}) \nabla \varphi_{i\sigma}^A(\vec{r})] , \end{aligned} \quad (3.11)$$

where

$$\langle A | D \rangle = \prod_i^p s_i^\alpha \prod_j^q s_j^\beta . \quad (3.12)$$

The total current in the system is given as a 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  $s_i^\sigma$  between 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 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 corresponding orbitals, which describe the tunneling electron. For such a pair the overlap ( $s_i$  in the denominator of Eq. 3.11) would be much smaller than for other pairs of corresponding orbitals<sup>3</sup>. The orbitals of other (“core”) electrons just shift slightly, owing 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 by Newton, who arrived at this picture in his corresponding orbitals analysis of the tunneling splittings [11, 66].

The shift of the core orbitals in donor and acceptor states does not appear to be significant, i.e. their Franck–Condon factor is of the order of unity. This is a surprising result since the canonical orbitals of the core electrons change significantly in donor and acceptor

<sup>3</sup>For example, for the (His)<sub>2</sub>Cu<sup>+1/+2</sup>-Cys-(Glu)<sub>5</sub>-(His)Ru<sup>+3/+2</sup> system, studied in Ref. [59], the overlap for one pair of tunneling orbitals is of the order 10<sup>-8</sup>, while for other pairs of corresponding orbitals the overlaps are in the range 0.9–1.0



states [11, 66], which is in line with a significant redistribution of charge in donor and acceptor complexes upon ET.

In practice, the currents are calculated in terms of the atomic basis functions. The molecular orbitals  $\varphi$  are found as linear combinations of these functions, and tunneling currents are calculated according to final formulas given in Refs. [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  $\phi_v(x)$ ,  $v = 1, \dots, K$ , be any particular atomic set that is chosen for electronic structure calculation, and  $|v\sigma\rangle$ ,  $|\mu\sigma'\rangle \dots$  etc. are corresponding atomic spin orbitals. The states belonging to different electrons will be distinguished by an additional index  $a$ ,  $|v\sigma(a)\rangle$ . In terms of these states, for the  $a$ th electron the population operator is written as

$$\hat{P}_{v\sigma}(a) = \frac{1}{2} \sum_{\mu=1}^K \left( |v\sigma(a)\rangle S_{v\mu}^{-1} \langle \mu\sigma(a)| + |\mu\sigma(a)\rangle S_{\mu v}^{-1} \langle v\sigma(a)| \right) . \quad (3.13)$$

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

$$\hat{P}_{v\sigma} = \sum_{a=1}^N \hat{P}_{v\sigma}(a) . \quad (3.14)$$

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

Using the population operators, one can now describe the 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  $|v\sigma\rangle$  at time  $t$  during the tunneling transition is given by

$$\bar{P}_{v\sigma}(t) = \langle \Psi(t) | \hat{P}_{v\sigma} | \Psi(t) \rangle , \quad (3.15)$$

and the rate of change of the population is

$$\frac{d\bar{P}_{v\sigma}(t)}{dt} = -\frac{T_{DA}}{\hbar} (\langle D | \hat{P}_{v\sigma} | D \rangle - \langle A | \hat{P}_{v\sigma} | A \rangle) \sin 2T_{DA}t/\hbar . \quad (3.16)$$

One can also evaluate  $d\bar{P}_{v\sigma}/dt$  in a different way. For this purpose, the velocity operator  $\hat{P}_{v\sigma}$  is introduced:

$$\hat{P}_{v\sigma} = \frac{i}{\hbar} [\hat{H}, \hat{P}_{v\sigma}] . \quad (3.17)$$

Calculating the average of the right-hand side of Eq. (3.17) over  $|\Psi(t)\rangle$  should give the same result as  $d\bar{P}_{v\sigma}/dt$  given by Eq. (3.16). One can easily check that

$$\begin{aligned} \langle \Psi(t) | \hat{P}_{v\sigma} | \Psi(t) \rangle &= \frac{d\bar{P}_{v\sigma}(t)}{dt} \\ &= -\frac{1}{\hbar} \langle A | [\hat{H}, \hat{P}_{v\sigma}] | D \rangle \sin 2T_{DA}t/\hbar . \end{aligned} \quad (3.18)$$

Now combining Eqs. (3.16) and (3.18), the kinetic equations can be cast in the desired form,

$$\frac{d\bar{P}_{v\sigma}}{dt} = \sum_{\mu} j_{v\sigma,\mu\sigma} , \quad (3.19)$$

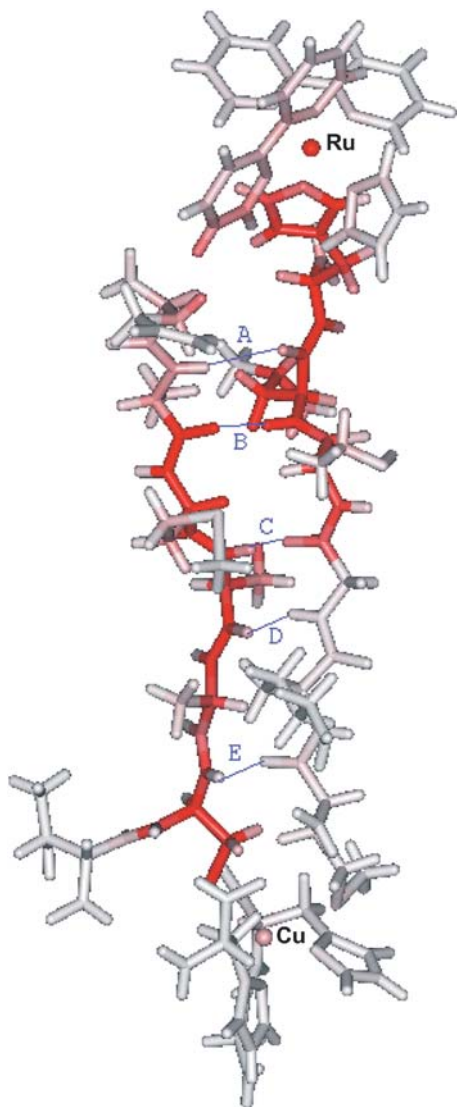
where kinetic coefficients  $j_{v\sigma,\mu\sigma}$  have the meaning of interatomic exchange currents. Summation over all orbitals of a given atom results in a kinetic equation of the form of Eq. (3.4).

The calculations of all matrix elements entering into the equations is described in Ref. [68], 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 found. 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 molecular orbitals of donor and acceptor states were obtained in Ref. [68]. These expressions, in the case of a nonorthogonal 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 Hartree–Fock expressions for interatomic currents, the proper tunneling current contributions are mixed with the local polarization currents of the core orbitals. While the significance of the latter has not been clarified, this mixing rendered the interatomic current formulation complicated, and was a major obstacle in practical implementation of ab initio interatomic currents. A significant simplification can be achieved, however, if the one tunneling electron approximation (see later) is used. In the one tunneling electron approximation, we neglect the polarization currents, assuming the core orbitals do not change at all, thereby simplifying the formalism [69].

One interesting example of the application of the interatomic tunneling currents [70] is shown in Fig. 2. The many-electron SCF implementation of the one tunneling electron approximation is utilized here to study electron tunneling in a Ru-modified protein, the system in which an electron needs to tunnel between two strands of the protein via hydrogen bonds. The details of the implementation of the one tunneling electron approximation can be found in Refs. [69, 70].

Practically, the concept of interatomic currents is a most useful one in describing tunneling in such complex systems as proteins. One should keep in mind, however, that this concept is as unambiguous as the concept of individual atoms in the protein is. As is well known,



**Fig. 2.** Distribution of interatomic tunneling currents in a (His126) Ru-modified azurin [3] system. The donor ( $\text{Cu}^{1+}$ ) and acceptor ( $\text{Ru}^{3+}$ ) 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 [70]

because of the overlaps of atomic orbitals, the separation of individual atoms in a molecule is not uniquely defined. Within this ambiguity, the interatomic currents are not uniquely defined as well. Here we presented a description that is based on the Mulliken separation technique, which allows a complete theory to be developed [68]. Obviously, other separation procedures would result in slightly different interatomic currents. (The degree of variations due to this ambiguity has not been carefully examined yet. To a large extent, this is a purely theoretical issue, since the individual currents, as well as individual tunneling paths, are not directly observed or quantified.) What remains unique, however, is the total current through the system, which according to Eq. (3.8) is equal to the tunneling matrix element, a unique quantity for a given system, and a given transition. Thus, the tunneling matrix element calculated by the technique

of interatomic currents does not depend on the separation scheme used to define interatomic currents; however, the currents themselves can vary (we expect slightly) with the separation technique.

#### 4 Many-electron aspects

A number of interesting issues are related to the many-electron nature of the problem [11]. 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. The electronic relaxation effects are not taken into account in this picture. We showed that in fact if such a pair of orbitals exists, it should be found in a specific (biorthogonalization) procedure, and the resulting orbitals are corresponding orbitals rather than the usual canonical ones. This picture is valid, however, only in the Hartree–Fock approximation. Can the tunneling event (i.e. tunneling dynamics of the many-electron system) be correctly described by Hartree–Fock wave functions? The tunneling charge can polarize the background electrons as it moves through the background of other electrons of the protein. Thus, the tunneling should be more properly described in terms of a “polaron-like” structure. To account for these (correlation) effects, one needs to go beyond Hartree–Fock methods.

##### 4.1 One tunneling electron approximation and polarization effects

The total current in Eq. (3.11), is a sum of the current due to tunneling charge per se, and 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, owing 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 [66] in the expression for the tunneling electron current, as explained in more detail later.

The relative stability of the core orbitals suggests a simple approximation in which only one pair of tunneling orbitals and a corresponding one tunneling electron (or hole) is considered, while the rest of the orbitals is assumed to be frozen. In this approximation, the two redox states have the form

$$|D\rangle = |\varphi_0^D, \text{core}^D\rangle |A\rangle = |\varphi_0^A, \text{core}^A\rangle, \quad (4.1)$$

where  $|\varphi_0^D\rangle$  and  $|\varphi_0^A\rangle$  is a pair of tunneling orbitals, and the  $|\text{core}\rangle$  represent the rest of the biorthogonal orbitals, which remain practically unchanged in the transition. In the context of the calculation of tunneling splittings, such a picture has also been considered by Newton and coworkers [11, 66].

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

$$\vec{J}(\vec{r}) = -\frac{\hbar}{2m} \langle D|A \rangle^{(0)} [\varphi_0^A(\vec{r}) \nabla \varphi_0^D(\vec{r}) - \varphi_0^D(\vec{r}) \nabla \varphi_0^A(\vec{r})] , \quad (4.2)$$

where

$$\langle D|A \rangle^{(0)} = \langle \text{core}^D | \text{core}^A \rangle = \prod_{i \neq 0} s_i . \quad (4.3)$$

Rigorously speaking, in the one tunneling electron approximation the core part of the wave functions should be considered unchanged, or frozen, and therefore the overlap should be exactly equal to unity. We, however, will use both the rigorous form and a “semi-rigorous” form of one tunneling electron approximation, where the overlap  $\langle \text{core}^D | \text{core}^A \rangle$  is allowed to be less than 1. The reason for this is discussed later.

The individual pairs of the 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 the 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 individual core orbitals Eq. (4.3). Each overlap  $s_i$  in Eq. (4.3) 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 0.8 to 1. We do not exclude, however, that in some cases the core overlap could be significantly smaller.

The considerations presented suggest that the one tunneling electron approximation can be used in long-distance tunneling calculations. There is also a more fundamental argument in favor of such an approximation, as described later.

#### 4.2 The limitation of the SCF description of many-electron tunneling

The expression for currents, and therefore for the matrix element  $T_{DA}$ , Eq. (3.8), is given by the sum over pairs of corresponding orbitals,  $i = 0, \dots, N$ . Each of the terms has the following structure:

$$J_i = \langle D|A \rangle^{(i)} \langle \varphi_i^D | \hat{J} | \varphi_i^A \rangle , \quad (4.4)$$

where the first factor is the product of pairwise overlaps of all orbitals except for the  $i$ th one, and the second factor is the matrix element taken over the  $i$ th pair of orbitals. As is seen, the first factor is an electronic analog of the Frank–Condon overlap, which is given here by

$$\langle D|A \rangle^{(i)} = \prod_{j \neq i} \langle \varphi_j^D | \varphi_j^A \rangle . \quad (4.5)$$

For this form of the matrix element to be correct, a specific separation of dynamic timescales should exist in

the system. Namely, as Eq. (4.4) suggests, the interaction associated with the mixing of the  $i$ th pair of orbitals should be much weaker (and therefore slower) than that of other orbitals. Such is the case, for example, in nonadiabatic proton transfer, where the transfer matrix element has exactly the same form [72]:

$$T_{DA} = \langle \chi_f | \chi_i \rangle \langle f | V | i \rangle . \quad (4.6)$$

Here the first term is the overlap of vibrational functions, and the second term is the matrix element of electronic interaction  $V$  between two electronic states. Equation (4.6) is obtained only for a weak (nonadiabatic) electronic interaction, i.e. for small  $V$  [71]. The mixing of two vibrational states  $\chi_i$  and  $\chi_f$  in the same electronic state would occur on a much shorter timescale, compared to that of the weak interaction  $V$ . That is the dynamics of mixing by  $V$  is slow.

Taking this analogy literally, one has to assume that in Eq. (4.4), the mixing of the  $i$ th pair of orbitals  $|\varphi_i^D\rangle$  and  $|\varphi_i^A\rangle$  should be much slower than that of the other orbitals. In the Hartree–Fock SCF picture, however, all orbitals are equivalent, and in the general SCF expression for current (Eq. 3.11) all enter on an equal footing, or in a symmetric fashion. The symmetric form of (Eq. 3.11) makes it impossible that the requirement of timescale separation be satisfied for all pairs of orbitals  $i$ . This is obviously a general limitation of the SCF procedure. The only possibility for the SCF expression Eq. (3.11) to be correct is to have only one specific term numerically dominating the others. In this case, the small terms would formally violate the requirement of timescale separation, but they will be small anyway.

In our case, there is one special pair of tunneling orbitals which indeed has a timescale of mixing much different from (much slower than) the rest of the system. Only one pair of orbitals,  $|\varphi_0^D\rangle$  and  $|\varphi_0^A\rangle$ , corresponds to a significant redistribution of charge in the system and therefore has a small overlap, and therefore weak interaction (an equivalent to term  $\langle f | V | i \rangle$  in Eq. 4.6). The rest of the orbitals, which we call the core orbitals, experience only weak polarization shifts upon charge transfer in the system, they have close to unity overlaps, and therefore have very a short timescale of mixing (which is equivalent to the  $\langle \chi_f | \chi_i \rangle$  term in Eq. 4.6). For the tunneling pair of orbitals the requirement of timescale separation is satisfied, and the contribution has the expected form of Eq. (4.6):

$$J_0 = \langle D|A \rangle^{(0)} \langle \varphi_0^D | \hat{J} | \varphi_0^A \rangle . \quad (4.7)$$

For all other pairs of orbitals, the separation of timescales is not satisfied. On this basis, it is proposed that all other terms in the current expression (Eq. 3.11) should simply be dropped. And if they cannot be dropped, because their contribution happened to be large, the Hartree–Fock description is not applicable at all in this case.

In the numerical examples considered, we saw that indeed there is one pair of orbitals that mostly contributes to the currents; however, the contribution of other orbitals is not always completely negligible. Since the accurate calculation of tunneling orbitals is a numerical

challenge, we cannot rigorously prove that the dominance of one pair of orbitals is always a rule. However, on the basis of the timescale separation argument, and taking into account the results of calculations on model systems [59], the approximation based on Eq. (4.7), in which only one pair of orbitals contributes to the tunneling transition and the rest experience only a weak polarization shift, appears to be the most reasonable form of theory.

In this case, one can think that only one electron (or hole) is transferring, and the other electrons respond via polarization. The tunneling electron contribution to the overall transfer matrix element is given by the  $\langle \varphi_0^D | \hat{J} | \varphi_0^A \rangle$  term and the polarization by the  $\langle D | A \rangle^{(0)}$  term in Eq. (4.7). It is this approximation that we refer to as the one tunneling electron approximation. If the core orbitals are completely fixed, then their overlap is unity, and the states that we are dealing with are similar to those assumed in Koopmans' theory (Sect. 2.3).

#### 4.3 Correlation effects. Polarization cloud dynamics. Beyond Hartree–Fock methods

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: the polarization of the background electrons by the tunneling electron. The energy of the tunneling electron, its tunneling velocity, and tunneling timescale [27, 71] are not much different from those of the valence electrons of the medium. This means that reorganization of these electrons will be quick enough to dynamically respond to a moving tunneling charge. Hence, as the tunneling electron moves through the protein, there is an electron polarization cloud that moves together with the tunneling charge. The compound nature of this tunneling quasiparticle object is rather complex. The virtual inseparability of the tunneling electron from those in the polarization cloud owing to the electron exchange effect (i.e. tunneling electron, as it passes an atom of the medium, can exchange with the electrons of that atom) adds to the complexity of the phenomenon. 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 electrons in the system, 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 relevant excited states that correspond to a tunneling electron/hole localized on the intermediate atoms of the medium, with other electrons adjusted to it. (Notice that these are not the usual virtual states for superexchange coupling between donor and acceptor. Most of these interactions are already included in the Hartree–Fock treatment of  $|D\rangle$  and  $|A\rangle$  states!) The idea of what needs to be done can be demonstrated

in a model which has one “linear” tunneling path, and schematically can be described as  $D-b_1-b_2-b_3-\dots-b_n-A$ , such as the peptide model  $(\text{bpy})_2\text{Ru(III)His}-(\text{Gly})_n-\text{CysCu(I)His}_2\text{Met}$  studied in Ref. [59].

The Hartree–Fock calculation deals with two diabatic SCF (single-determinant) states:  $|D\rangle$  and  $|A\rangle$  in which the charge is localized on the donor and the acceptor, respectively. The deficiency of this description is that in these states there are no configurations present that correspond to a tunneling electron/hole being localized on the bridge elements  $b(i)$  with all other electrons tuned to it. Obviously a one-determinant description of  $|D\rangle$  and  $|A\rangle$  states is not sufficient if the previously described picture of the polarization cloud is to be included in the calculations. Thus one needs to go beyond the single-determinant Hartree–Fock description of  $|D\rangle$  and  $|A\rangle$ .

The relevant additional states (or rather additional Slater configurations) can be found in standard SCF ground-state calculations by placing an external charge in the vicinity of each of the bridge elements  $b(i)$ , which will localize a tunneling electron on the bridge elements  $b(i)$ . The configurations determined in this way represent, of course, excited states, which will only virtually be present in the dynamics. What is needed is not the exact knowledge or specification of these excited states, but rather relevant configurations, which will be included in the description of the correct diabatic donor and acceptor states. Details of how these configurations are obtained are not important, since they are going to be used just as the basis function for the description. What is important is that this basis spans the whole physically important space.

For each bridge element  $b(i)$ , a corresponding SCF state  $|b(i)\rangle$  can be determined. Thus in addition to the usual SCF states  $|D\rangle$  and  $|A\rangle$  one has states  $|b(i)\rangle$ ,  $i = 1, \dots, n$ . (In the case of the  $\text{Ru}(\text{Gly})_5\text{Cu}$  peptide system  $n$  is about 20.) These are relevant one-determinant configurations that now need to be combined to obtain correct (multideterminant) diabatic states for donor and acceptor. These correct diabatic states will be called  $|\mathcal{D}\rangle$  and  $|\mathcal{A}\rangle$ , respectively (in contrast to their one-determinant SCF approximations  $|D\rangle$  and  $|A\rangle$ ). The appropriate combinations (i.e. coefficients of expansion)

$$|\mathcal{D}\rangle = C_D^D |D\rangle + \sum_i C_i^D |b(i)\rangle \quad (4.8)$$

$$|\mathcal{A}\rangle = C_A^A |A\rangle + \sum_i C_i^A |b(i)\rangle \quad (4.9)$$

can be found by diagonalizing the corresponding Hamiltonian matrix, that results from the usual variational procedure. All  $C_i^{D/A}$  coefficients are expected to be very small, of course.

After finding corrected donor and acceptor states, the calculations can proceed in a standard way. The object of the calculation is the tunneling current,

$$J(r) = -i \langle \mathcal{A} | \hat{j}(r) | \mathcal{D} \rangle, \quad (4.10)$$

where  $\hat{j}(r)$  is the tunneling current operator (Eq. 3.9). In a Hartree–Fock calculation one would have the matrix element calculated between states  $|D\rangle$  and  $|A\rangle$ . Now, the

tunneling current is reduced to a sum of pairwise currents between states  $D, b(1) \dots b(n)$ , and  $A$  of the type

$$J_{kl} = C_k^D C_l^A \langle b(k) | \hat{j}(r) | b(l) \rangle . \quad (4.11)$$

It is expected that the largest contribution will come from sequentially coupled states, i.e.  $D \rightarrow b1 \rightarrow b2 \rightarrow \dots \rightarrow bn \rightarrow A$ . This should compete with the direct and largest tunneling current from donor to acceptor. Having the tunneling current, the coupling matrix element is evaluated by Eq. (3.8), as described in Ref. [14].

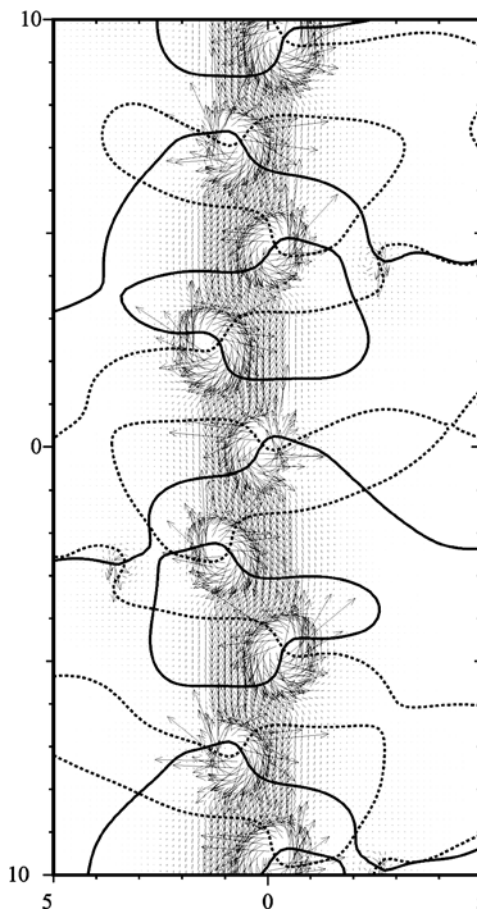
This procedure is a sort of configuration interaction calculation, in which only the most important, physically motivated states are included. The basis set used to construct multideterminant  $|\mathcal{D}\rangle$  and  $|\mathcal{A}\rangle$  states describes the continuous shift of the charge along the chain  $D \rightarrow b1 \rightarrow \dots \rightarrow bn \rightarrow A$ . When the number of states,  $n$ , is large, one can think of a continuous approximation,  $|b(s)\rangle$ , where  $s$  is a coordinate along the bridge. In this case our basis set in some sense is equivalent to a coherent states basis.

The dynamic correlation effects described for long-distance tunneling are certainly very interesting, but the actual magnitude of these effects in protein systems is not known at present. Efforts to implement the previously described scheme are underway in this group. In a different context, the electron correlation effects on the coupling matrix element  $T_{DA}$  have been examined recently by Cave and coworkers [32]. These authors investigated the formal sensitivity of the transfer matrix element calculated with their GMH approach to the level of theory used to describe the initial and final wave functions (Sect. 2.4). Although this approach does not directly probe the effects described, in both cases the electron correlations are reflected in the quality of the wave functions of the tunneling electron, and as such should formally yield similar results for the transfer matrix element.

By explicitly specifying the configuration interaction configurations that modify the tail (or bridge) region of the tunneling wave functions, and using the tunneling current method for evaluation of  $T_{DA}$ , Eq. (3.8), which deals specifically with the wave function tails, the previous scheme should be able to describe explicitly the dynamic response of the valence electrons in the protein medium to the tunneling charge.

#### 4.4 Quantum interference effects. Quantized vortices

The wave nature of the transferring electron manifests itself not only in the electron's ability to penetrate classically forbidden barriers, but also in interference effects. If the electronic coupling is due to several tunneling paths [28], each of them associated with an amplitude – a positive or a negative number – then the total tunneling amplitude, which is the sum of the partial amplitudes, can be enhanced (constructive interference) or diminished (destructive interference) depending on the relative signs of the amplitudes of the individual paths. Thus, for example, two coupling paths are not necessarily better than one, in case of destructive



**Fig. 3.** Vortex structure of the tunneling flow along the polypeptide molecular wire in the  $(\text{His})_2\text{Cu}^{+1/+2}-\text{Cys}-(\text{Glu})_5-(\text{His})\text{Ru}^{+3/+2}$  system studied in Ref. [59]. The vortices originate at points where nodal lines of donor and acceptor orbitals intersect

interference [17, 72]. This counterintuitive 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 [16].

Another interesting manifestation of the interference effects is the quantized vortices observed in the tunneling fluxes [73]. The distribution of the tunneling current in the peptide chain in the  $\text{Ru}^{2+/3+}-(\text{Gly})_n-\text{Cu}^{2+/1+}$  system [59] is shown in Fig. 3. The prominent feature in the flow is the presence of vortices. It turns out these vortices are of the same nature as those observed in superfluid helium [74, 75], and in many other quantum systems – superconductors, plasma, spin systems, wave fronts, and others [76, 77, 78].

The mathematical nature of these vortices is related to the nodes of complex wave functions. The phenomenon was first described by Dirac [79] in his famous monopole paper. If we have a complex wave function, which can be written as

$$\psi = \rho^{1/2} e^{i\phi} , \quad (4.12)$$

the current density is related to the gradient of the phase  $\phi$ ,

$$\vec{J}(\vec{r}) = \rho(\vec{r}) \left( \frac{\hbar}{m} \right) \nabla \phi(\vec{r}) . \quad (4.13)$$

If complex  $\psi$  happens to be zero at some point, the phase  $\phi$  is not defined, and the quantum flux has a vortex structure at such a point. The vortices are “quantized”, as explained in Ref. [74].

In the tunneling problem, the wave function of the tunneling particle can be written in the form (cf. Eq. 3.1),  $\psi(\vec{r}) = [\varphi_0^D(\vec{r}) + i\varphi_0^A(\vec{r})]/2^{1/2}$ , where  $\varphi_0^D(\vec{r})$  and  $\varphi_0^A(\vec{r})$  are donor and acceptor orbitals. Both  $\varphi_0^D(\vec{r})$  and  $\varphi_0^A(\vec{r})$  have nodes, because they are excited states of the Hartree–Fock Hamiltonian. The nodes of donor and acceptor orbitals are surfaces in three-dimensional space. Intersection of these surfaces with the  $xy$  plane are 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. The stream lines of the tunneling flow in Fig. 3 are the so-called Bohmian trajectories. The whole ensemble of such trajectories forming the flow presents a picture according to Bohm’s hydrodynamic interpretation of quantum mechanics [60]. For further discussion of the vortices the reader is referred to Ref. [14].

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 then also resembles quantum percolation.

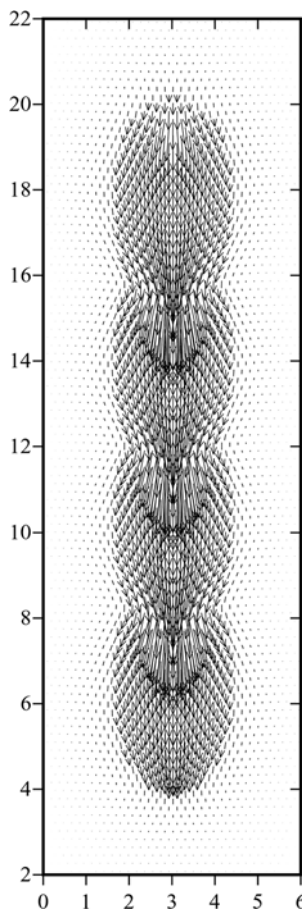
#### 4.5 ET or hole transfer? Exchange effects

ET is associated with 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 electron is present. Of course a combination of ET and hole transfer is also possible – a process in which virtual states of both types are involved [11].

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 is actually operating in real systems.

An interesting example that provides some insights into the 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 [81].

The spatial distribution of the tunneling current along the molecular axis is displayed in Fig. 4. Notice in Fig. 4 that electron tunneling occurs through the centers of He atoms. At first sight, this is counterintuitive, 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 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 be also interpreted as a hole transfer.



**Fig. 4.** The distribution of tunneling current in the  $\text{H}-(\text{He}-\text{He}-\text{He}-\text{H}^+)-\text{H}^+-(\text{He}-\text{He}-\text{He}-\text{H})-\text{H}$  transition. Electron tunneling occurs through centers of He atoms, and involves exchange with He  $1s$  electrons. The process can also be interpreted as hole transfer. This many-electron effect is incorporated in the one tunneling orbital description [80]

This calculation also indicates that any kind of substance is likely to be better than a 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 [34, 35, 53].

## 5 Dynamical aspects

We finally briefly mention an interesting issue related to the effects of the dynamics of the protein structure on electron tunneling [16, 17, 81]. 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 timescale (order of femto seconds 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  $|T_{\text{DA}}|^2$  over thermal configurations of the protein and to examine the 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 [5]. These are static or inhomogeneous effects.

The second effect is of dynamical nature, and is somewhat surprising at first sight. Since the tunneling jump occurs on such a short timescale, 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 [16, 81]. Although the protein structure is fixed on the timescale of tunneling, owing 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 short "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 direct observation of the tunneling paths.

Quantitatively, inelastic tunneling is described by the probability,  $P(\epsilon)$ , that the tunneling electron will exchange energy,  $\epsilon$ , 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.  $P(\epsilon)$  can be obtained from molecular simulations of the protein dynamics [81].

There is no doubt that the dynamic effects should be formally included in the description of electron tunneling in proteins. The key question, however, is how important they are in real proteins. This is a question of practical significance for those who are interested in absolute rates of ET reactions. At present there is no consensus on how important the effects described are, and work is in progress to do both accurate electronic structure calculations of electronic coupling and dynamical simulations of realistic models required to understand these effects. The inelastic tunneling manifests itself in the dependence of the tunneling matrix element  $T_{\text{DA}}$  on the configuration of the system [59, 81].

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 would provide support of Dutton's concept of the unstructured, effective dielectric protein medium [5]. The negative answer would lend more support to Gray's pathways model [2]. Although it is clear that the answer will depend on the system, it would be interesting to study individual cases and clearly show the existence of these two limits. The issue of the sensitivity of the tunneling paths is related to the most fundamental biological question, namely whether or not there are specific, evolutionary optimized tunneling routes between redox centers in proteins. Future work will provide an answer to this and other intriguing questions in this exciting area.

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