DNA: insulator or wire?

David N Beratan[1], Satyam Priyadarshy[1] and Steven M Risser[2]

DNA-based electron transfer reactions are seen in processes such as biosynthesis and radiation damage/repair, but are poorly understood. What kinds of experiments might tell us how far and how fast electrons can travel in DNA? What does modern theory predict?

Addresses: [1]Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA and [2]Department of Physics, Texas A&M-Commerce, Commerce, TX 75429, USA.

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Electron transfer reactions involving DNA are clearly important in nucleic acid biosynthesis, regulation, damage, and repair. Studies of electron transfer between species bound covalently and noncovalently to DNA have given provocative results, and are at a similar stage to that reached several years ago by the protein electron transfer community [1–3]. Electron transfer has been shown to proceed over large distances (~15 to 40 Å) in DNA (see Figs 1,2), but no systematic distance dependence studies of the reaction rates have yet been forthcoming [4–11]. If these reactions proceed by the conventional bridge-mediated electron-tunneling mechanism familiar in proteins, in which the uncertainty principle allows leakage of the electron from donor to acceptor guided by the intervening medium, the rate of electron transfer would be expected to drop exponentially with distance, and the drop-off factor is expected to be substantial [12,13]. For example, electron transfer rates in proteins slow by about a factor of 10 for every ~2 Å increase in donor–acceptor distance.

The essential features to be determined are how strongly ribose phosphate chains and base pairs contribute to the transfer of electrons from donor to acceptor. At present, experimentalists hold widely varying views. Modern theoretical chemistry should help to focus attention on the reasons for these differences, and, perhaps, help to resolve them. Here, we give an overview of the current state of the DNA long-range electron transfer field, summarize theoretical predictions, and outline critical experiments for the future.

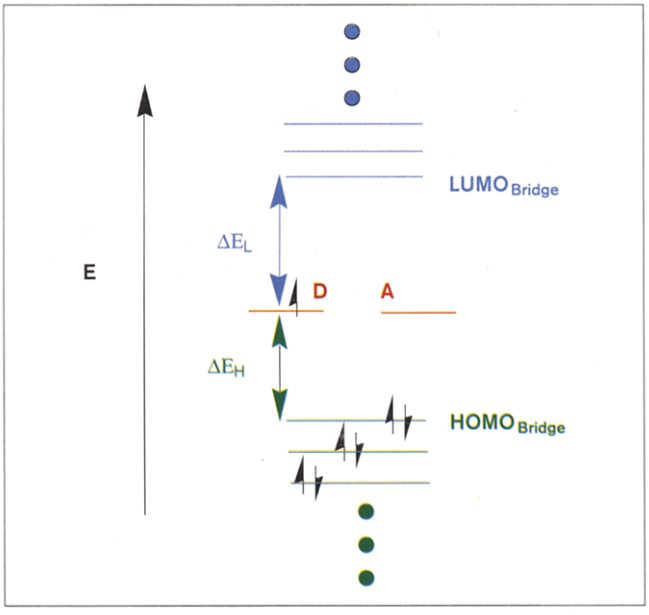
Electron transfer in proteins

Proteins are well known to facilitate electron transfer. Electrons flow between cofactors (hemes, chlorins, blue copper centers, flavins, etc.) that are embedded in proteins [1–3]. The redox-active species in proteins have a common characteristic: the donor and acceptor states are localized and their orbitals mix relatively weakly with those of the surrounding protein. Thus, the oxidizing or reducing potential of these cofactors is not sufficiently high to allow them to react with the protein, which is relatively inert. Electron transport occurs only because electron tunneling allows 'leakage' over distances as large as tens of Ångstroms through regions that are classically forbidden [14]. Proteins have evolved to take advantage of this fact, and the pathway model of electron transfer allows the derivation of a relatively simple set of rules that describe how rapidly electronic amplitude decays across covalent, hydrogen bond, and van der Waals contacts in proteins [15–19]. Do redox reactions in DNA behave in a similar way?

Energetics of electron transfer in macromolecules

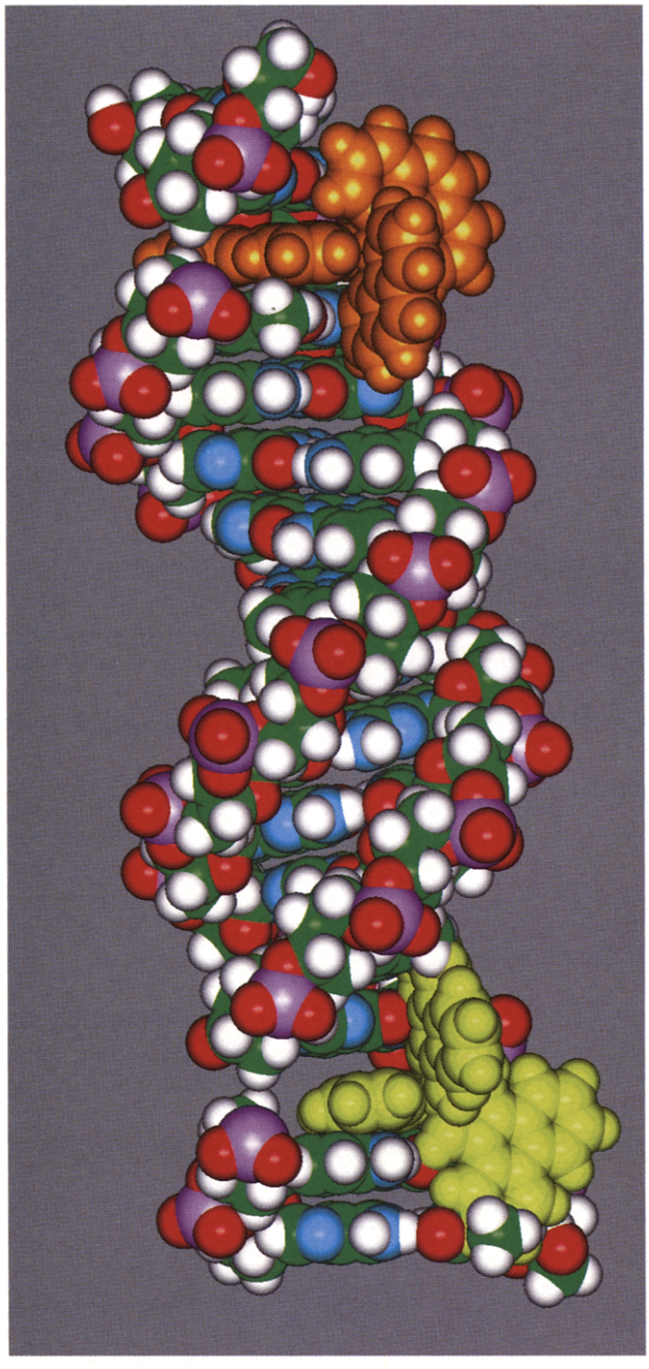
Electron amplitude leakage, or tunneling, between bound donors and acceptors in biomolecules occurs when the mobile electron is not sufficiently energetic to access unoccupied delocalized molecular orbitals of the bridge (Fig. 1). The barrier between the donor (D) and acceptor

Figure 1



Donor, acceptor, and bridge centered molecular orbital energy levels. Half-arrows represent electrons. The donor and acceptor localized electron transfer active states lie in the energy gap between the HOMO and LUMO of the DNA localized molecular orbitals. When ΔE_H and $\Delta E_L \gg k_BT$, electron transfer occurs via the tunneling mechanism $D^-BA \rightarrow DBA^-$. On the other hand, when ΔE_H or ΔE_L is comparable to k_BT, the reaction may proceed through real oxidized or reduced intermediates of the bridge: $D^-BA \rightarrow DB^-A \rightarrow DBA^-$ or $D^-BA \rightarrow D^-B^+A^- \rightarrow DBA^-$.

Figure 2



Modeled Barton structure [4] consisting of tethered and intercalated donor (orange ruthenium complex) and acceptor (light green rhodium complex). The covalent tethering linkage between the DNA and the metal complex is not shown.

(A) is~2 eV (electron volts) (or ~50 kcal per mole) high [14]. Thermal energies are of the order of Boltzmann's constant multiplied by the absolute temperature (k_BT), which is ~1/40 eV at room temperature, so passage over the barrier (by forming a state in which the bridge contains one more electron, or one less) is impossible. The only way that the electron can propagate across the barrier is quantum mechanical tunneling.

A second kind of electron transport mechanism may arise when donor and acceptor energies approach bridge molecular orbital energies, in which case it becomes possible to oxidize or reduce the bridge using thermally available energy, and transport may occur over very long ranges indeed (Fig. 1). This is how photoconductors function after photoexcitation.

A third transport mechanism can also be imagined. Consider a chain of N cofactors (as in the bacterial photosynthetic reaction center or in cytochrome *c* oxidase) forming a line from our initial donor to our final acceptor [1–3]. Now, imagine a sequence of short-range hops, from a state localized on D to a state on 1, from 1 to 2, 2 to 3, and finally N to A. In each step, the electron must tunnel over a much shorter distance than the overall D–A distance. The rate of a step is exponentially related to the distance tunneled, and so the series of short steps is far faster than one long range hop would be. In the photosynthetic reaction center, the multiple hops are exothermic, but it is also possible that endothermic reactions, uphill by about k_BT, could occur.

Electron transfer in proteins is forbidden by classical mechanics, but electron transfer in vacuum is even more unlikely. This is because virtual oxidized and reduced states of the intervening protein — which are allowed to exist through the uncertainty principle, though only for an infinitesimal time — guide the electrons from donor to acceptor. In vacuum, the only energy states available to the tunneling electrons to facilitate their propagation are the (ionized) free particle states, which are much more energetically removed from the state than the molecular orbitals of the electron transfer active protein. Throughout chemistry, mixing between orbitals of similar energies leads to enhanced coupling compared to species with disparate energetics. This is precisely the case in biological electron transfer (see below).

Where, then, do natural and synthetic D, A and bridge states lie in energy? For proteins the answer is relatively clear. The energies of the bridge frontier orbitals are related to the negative ionization potential (IP) and negative electron affinity (EA) of the protein. But since the virtual states of the bridge (B^{+} and B^{-}) are so very transient (they exist for less than the period of a typical chemical bond vibration), the relevant IPs and EAs are those of the state of the protein in which the nuclei are frozen in their equilibrium neutral state geometry. Typical theoretical estimates place the protein HOMO (highest occupied molecular orbital) level at a binding energy of about –7 eV [20,21].

The analysis of protein energetics described above suggests that the HOMO–LUMO (lowest unoccupied molecular orbital) gap in proteins is about 5–7 eV. This is a large gap indeed, and one that is somewhat larger than one might extrapolate from the photon energy needed to excite the π–π^* electronic transitions on amino acid side chains. (The IP/EA gap is larger than the optical gap because it reflects the energies of N+1 and N-1 electron virtual oxidized and reduced protein states, not just the pure N electron ground and excited states that participate in optical absorption processes). For thermally activated electron transfer through bridge localized states to occur, donor and acceptor cofactor-localized states would have to be within k_BT (only 1/40 eV at room temperature) of the HOMO or LUMO. Clearly this is not the case, which is fortunate as it would be a disaster for protein function. If the unoccupied bridge states were readily accessible, cofactors would not be able to localize the redox equivalents, the electrons that should be kept in the cofactor until needed would instead reduce amino acid side chains indiscriminately and the chemistry coupled to directed electron transfer would never occur. In this imaginary situation, photosynthetic reactions might form the basis for biological photoconductivity, not biosynthesis.

DNA electron transfer reactions

Are DNA and protein electron transfer qualitatively different? Perhaps so. After all, DNA consists of an extended π-electron stack, a sea of π-electrons. There are two key aspects to these interacting π-systems: the p–σ interaction through-space between stacked π-electron rings, and the in-plane p–π interaction. In the direction parallel to the carbon bond planes in graphite, the conductivity is several orders of magnitude smaller than that of copper. But in directions orthogonal to the carbon planes, the conductivity drops by an additional five orders of magnitude. Apparently, p–σ interactions in carbon do not facilitate conduction in graphite.

Is there any hint of particularly strong inter-base pair interactions in DNA? The signature of extended interactions between molecular units is splitting (or dispersion) of energy levels. For example, the HOMO–LUMO energy gap in butadiene is 75 % that of ethylene, while the gap in carotene is less than half that size. This dispersion in the energy of bonding and antibonding alkene states arises from p–π interactions, leading to a dramatic drop-off in the optical gap. When we compare the optical gap for a single base pair, double stranded DNA oligomers, and native double stranded DNA, however, no dramatic change in the π–π^* transitions is observed [22–24]. Nor does DNA display the optical signatures associated with a dramatically falling HOMO–LUMO gap as a function of chain length. Thus, it would seem that if conduction-like effects can be induced in DNA, they will arise from placing donor and acceptor states within k_BT of the frontier orbitals, and not from the dispersion of energy levels that might arise from the 3.4 Å p–σ through-space interactions between base pairs. Note too, that if the HOMO-LUMO gap in DNA were abnormally small, the donor excited state would itself be quenched by electron transfer. There is apparently no evidence for this kind of effect in the electron transfer systems described here. Indeed, it would be very helpful to know just how far typical excited state redox potentials are from the energy level required to oxidize or reduce the DNA.

Long-distance electron transfer in proteins and in DNA

To understand electron transfer rates in proteins or DNA we must understand how the orbitals of the bridging macromolecule guide the leakage of electrons between donor and acceptor. The tunneling pathway model for proteins predicts how through-bond and through-space decay balance, giving rise to predicted secondary and tertiary motif effects (which in fact occur as predicted) [15–19].

The predictions of the pathway model are testable thanks to the techniques developed by Gray and coworkers for tethering artificial redox species on protein surfaces [25–27]. These fixed species can donate or accept electrons at precise distances and, more importantly, with known bridge structure between donor and acceptor. Experiments show an average exponential decay constant of $\beta = 1.0$–1.5 Å^{-1} for protein electron transfer, where the electron transfer rate is $k_{ET} \propto \exp[-\beta R_{DA}]$ with R_{DA} equal to the donor–acceptor edge-to-edge distance. Before these tethered Ru complex experiments, the issue of distance dependence had not been resolved, although simple models had predicted that β would equal 1.4 Å^{-1} [14]. Without the tethering techniques, the interpretation of electron transfer rates in proteins was complicated by the uncertainties in distances to the point that the experiments could realistically only set modest bounds on the distance dependence.

Are aromatic amino acids more important than average in mediating protein electron transfer? Apparently not, according to a body of experiments and family of computations aimed at probing this issue [28–31]. In the simple pathway analysis, it is argued that the symmetry penalty for mixing onto and off of the π-electron system, and their limited spatial extent, offsets the enhanced coupling that might arise from the decrease in energy gap between the donor–acceptor orbital and the π-electron protein orbitals [15–19]. Because of the much larger density of π-electron units in DNA, this argument cannot be transferred directly to DNA electron transfer. More detailed theroretical analysis (see below) is essential.

The field of DNA electron transfer chemistry is undergoing the kind of rebirth that was experienced by protein electron transfer chemistry 15 years ago when transition

metal labeling of surface amino acids became possible. We can now ask how electron transfer rates in DNA depend on distance, and the sequence and conformation of DNA. Several labs are addressing this question using ground-state and excited-state electron transfer experiments on tethered/intercalated [4], simply intercalated [5–8], and tethered donor–acceptor species in DNA bridged electron transfer systems [9,10]. Experiments involving base pair oxidation or reduction provide complementary information. This new generation of experiments will provide the answers, just as the work on fixed-distance Ru-modified proteins resolved several puzzles in long-range protein electron transport [25–28].

Estimates of the important distance decay parameter β can now be made from data provided by four groups. The resulting values are ~0.2 $Å^{-1}$ for a tethered intercalated D–A system [4–6], ~0.9 $Å^{-1}$ for one randomly intercalated D–A system [7,8], ~1.0 $Å^{-1}$ for a second noncovalent intercalated D–A system [6] and, finally, a rate 'comparable' with that expected for protein-facilitated transfer over a similar distance (that is, β in the range 1.0–1.5 $Å^{-1}$) in a system with donor and acceptor bound to ribose rings [9,10]. How are these disparate results to be resolved?

DNA electron transfer: a theoretical view

Although single rate measurements such as those discussed above provide a first glimpse at electron transfer chemistry in DNA systems, what is really needed is a systematic study of transfer rates for donor–acceptor pairs intercalated or tethered to DNA at different known positions. But these studies require heroic efforts of both synthesis and spectroscopy. In the absence of such data, theory can be particularly productive in both challenging experimental interpretations and motivating experimental design. First, what distance dependence would we anticipate for DNA electron transfer reactions?

When D and A interact weakly, the rate of long distance electron transfer is expected to be proportional to the bridge-mediated coupling, T_{DA}, squared [1–3]:

$$k_{ET} \propto |T_{DA}|^2 \qquad \text{Equation 1}$$

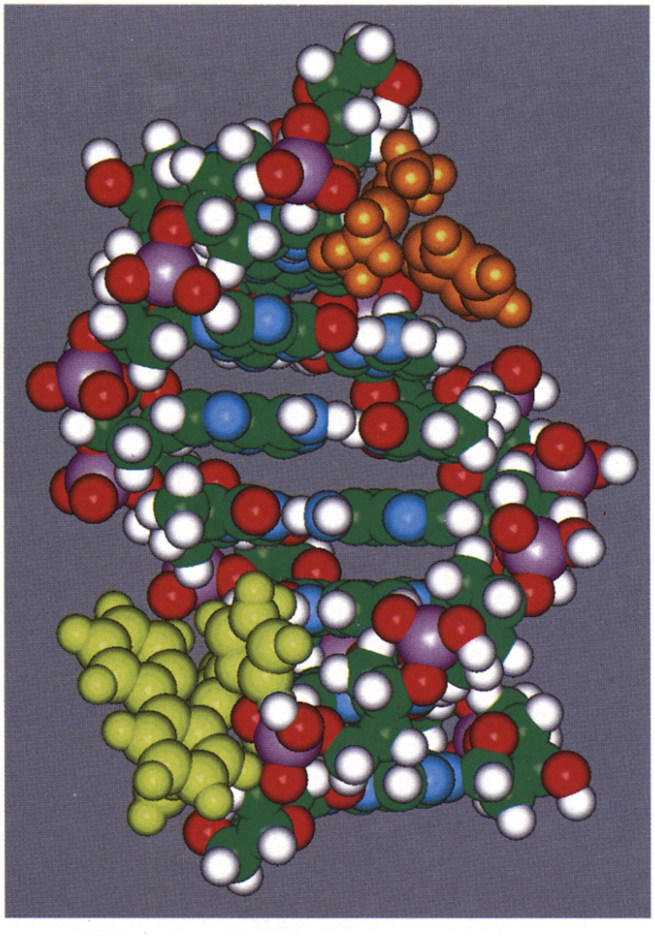
In a molecular orbital model based on an orthogonal set of localized atomic orbitals [32] we have:

$$T_{DA} = \sum_{d,i,j,a} \sum_{N} \frac{v_i^d C_i^{(N)*} C_j^{(N)} v_j^a}{E^{(N)} - E_{tun}} \qquad \text{Equation 2}$$

where $v_i^d (v_j^a)$ is the interaction between the donor atomic orbital d (acceptor atomic orbital a) and the i^{th} (j^{th}) atomic orbital of the bridge; E_{tun} is the electronic energy (the tunneling energy) of the donor and acceptor localized states in the activated complex; $C_j^{(N)}$ is the molecular orbital coefficient of the j^{th} atomic orbital in the N^{th} molecular orbital of the DNA; and $E^{(N)}$ is the energy of the N^{th} DNA molecular orbital. The summation on N is carried out over all of the occupied and unoccupied molecular orbitals of the duplex DNA. The energy denominator $E^{(N)} - E_{tun}$ reflects the energy dependence of molecular orbital coupling discussed above.

We have computed T_{DA} by performing large scale self-consistent field calculations at the semi-empirical level on the DNA bridge [22–24]. In the case of the structure investigated by Barton and coworkers [4] (Fig. 2), the system consists of ~3300 valence orbitals. Modern computational resources allow these molecular orbitals to be computed directly. Calculating T_{DA} in this manner using equation 2 includes the influence of all possible tunneling pathways, and weights each with an appropriate strength and phase. The method also builds in the appropriate relatively large IP-EA gap discussed earlier. For the Meade and Kayyem structure [9] (Fig. 3), and Brun and Harriman structure [7,8], we compute β values of 1.2 and 1.6 $Å^{-1}$, respectively,

Figure 3



Modeled Meade& Kayyem structure [9] consisting of donor (orange) and acceptor (light green), both ruthenium complexes, attached covalently to deoxyribose rings.

in reasonably good agreement with the experimental data. While we cannot compute β from a single structure like the one of Barton and coworkers [4], we can say that our donor–acceptor coupling element predicts a rate about six orders of magnitude slower ($<3 \times 10^3\ s^{-1}$) than the one extracted from the experiments ($>10^9\ s^{-1}$). Barbara and coworkers [6] recently suggested that quenching of the excited state by processes other than long-range electron transfer might account for the remarkably small apparent β value in the system of Barton and coworkers [4].

Although these calculations are advanced, a number of potential pitfalls exist. Semi-empirical self-consistent field methods of the kind that we used to analyze DNA mediated donor–acceptor coupling probably underestimate the strength of nonbonded interactions, leading to an upper bound on the value of β. Also, the calculations neglect water of solvation, and assume an artificially 'neutralized' DNA structure. Fluctuations of the DNA away from the textbook geometry will probably cause the apparent value of β to drop as well. The positions of the donor and acceptor states in the HOMO–LUMO gap of the DNA are estimated on the basis of redox potentials; errors in these levels would affect β (although the dependence on E_{tun} is likely to be weak for these systems). Finally, the approximation that the coupling drops according to a single exponential decay law can break down at short distances depending upon the binding motif [24].

While all of the approximations used in these studies can be improved upon or removed in future work, there are two key predictions that are not expected to change. First, the long-range electron amplitude leakage (tunneling) in DNA is predicted to be protein-like (that is, $\beta \sim 1.0$–$1.5\ Å^{-1}$ for donor and acceptor species like those in the studies discussed here; see [33,34] for experiments that access true oxidized or reduced bridge intermediate species). The source of this large β is the through-space gap of 3.4 Å between stacked base pairs. Second, despite the gap between the bases, the base-pair π-systems dominate the tunneling process. The closeness of the bridge orbital energies to the electron tunneling energy and the long winding ribose-phosphate pathways determine this. It will be interesting to see whether the results of systematic distance dependence studies of electron transfer in DNA, and in model π-stacked bridge systems such as cyclophanes, support these conclusions.

Challenges in DNA electron transfer

After the distance dependence of electron transfer in DNA has been determined, what comes next? Measurements of the dependence of tunneling on base sequence will be challenging, but should be possible. As further experiments explore DNA oxidation and reduction, the question of how the transition from long-range tunneling to multi-state hopping (based on excess electron or hole injection) along a double helix will be particularly interesting. Current analysis of noncovalent DNA donor–acceptor systems indicates intriguing complications that arise from cooperative donor–acceptor binding motifs [6,35]. These observations are critical for further interpretation of electron-transfer data obtained from DNA systems with noncovalently bound intercalated donors and acceptors.

The very recent synthesis and characterization of a modified 11-mer and 14-mer (with donor and acceptor at well defined locations) by T.J. Meade and coworkers (personal communication) could lead to the first direct experimental measure of DNA electron transfer distance dependence. With this basic information in hand, we will be able to begin to apply the notion of DNA-mediated electron transfer to DNA damage and repair, electrochemical sensor design [36], and molecular scale devices [37].

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