

## Charge transport in DNA

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The base pair stack within double helical DNA provides an effective medium for charge transport. The DNA  $\pi$ -stack mediates oxidative DNA damage over long molecular distances in a reaction that is exquisitely sensitive to the sequence-dependent conformation and dynamics of DNA. A mixture of tunneling and hopping mechanisms have been proposed to account for this long-range chemistry, which is gated by dynamical variations within the stack. Electrochemical sensors have also been developed, based upon the sensitivity of DNA charge transport to base pair stacking, and these sensors provide a completely new approach to diagnosing single base mismatches in DNA and monitoring protein–DNA interactions electrically. DNA charge transport, furthermore, may play a role within the cell and, indeed, oxidative damage to DNA from a distance has been demonstrated in the cell nucleus. As a result, the biological consequences of and opportunities for DNA-mediated charge transport now require consideration.

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### Abbreviation

*M.HhaI* methyltransferase *HhaI*

### Introduction

Using a full range of physical and biochemical methods, studies have now established that double helical DNA is a medium for the efficient transport of electrons. As a result, the focus of the field has shifted from asking whether DNA can mediate long-range charge transport to questioning how it works. How do DNA structure and sequence affect this reaction, and is DNA-mediated charge transport physiologically important? In this review, we describe recent experiments in which charge transport through the  $\pi$ -stacked DNA base pairs has been demonstrated and through which critical parameters have been established. These experiments have underscored not only that the DNA base pair stack can mediate hole and electron transport chemistry but also the exquisite sensitivity of charge transport through the  $\pi$ -stack to DNA structure and dynamics.

A variety of experimental approaches have been used to probe DNA charge transport. The earliest studies involved physical measurements of current flow in DNA fibers and led to a mixture of conclusions, some suggesting high electron mobility through DNA, others indicating no conductivity [1,2]. Electron conductivity was clearly demonstrated in recent experiments on aligned DNA films; this conductivity was found only along the direction parallel

to the helical axis [3]. Sophisticated methods have also recently been used by physicists to examine electrical transport in single molecules or small collections of molecules at low temperatures [4,5\*]. In these experiments, DNA was found to have the characteristics of a semiconductor, but whether wide gap or narrow gap also varied with the experiment. In fact, one experiment even pointed to DNA as a superconductor [6]. These physical studies have not yet been reconciled with one another. The variations seen probably depend heavily upon the connections between the DNA and the electrodes used, as well as upon the integrity of the DNA itself in the absence of water and exposed to very high voltages.

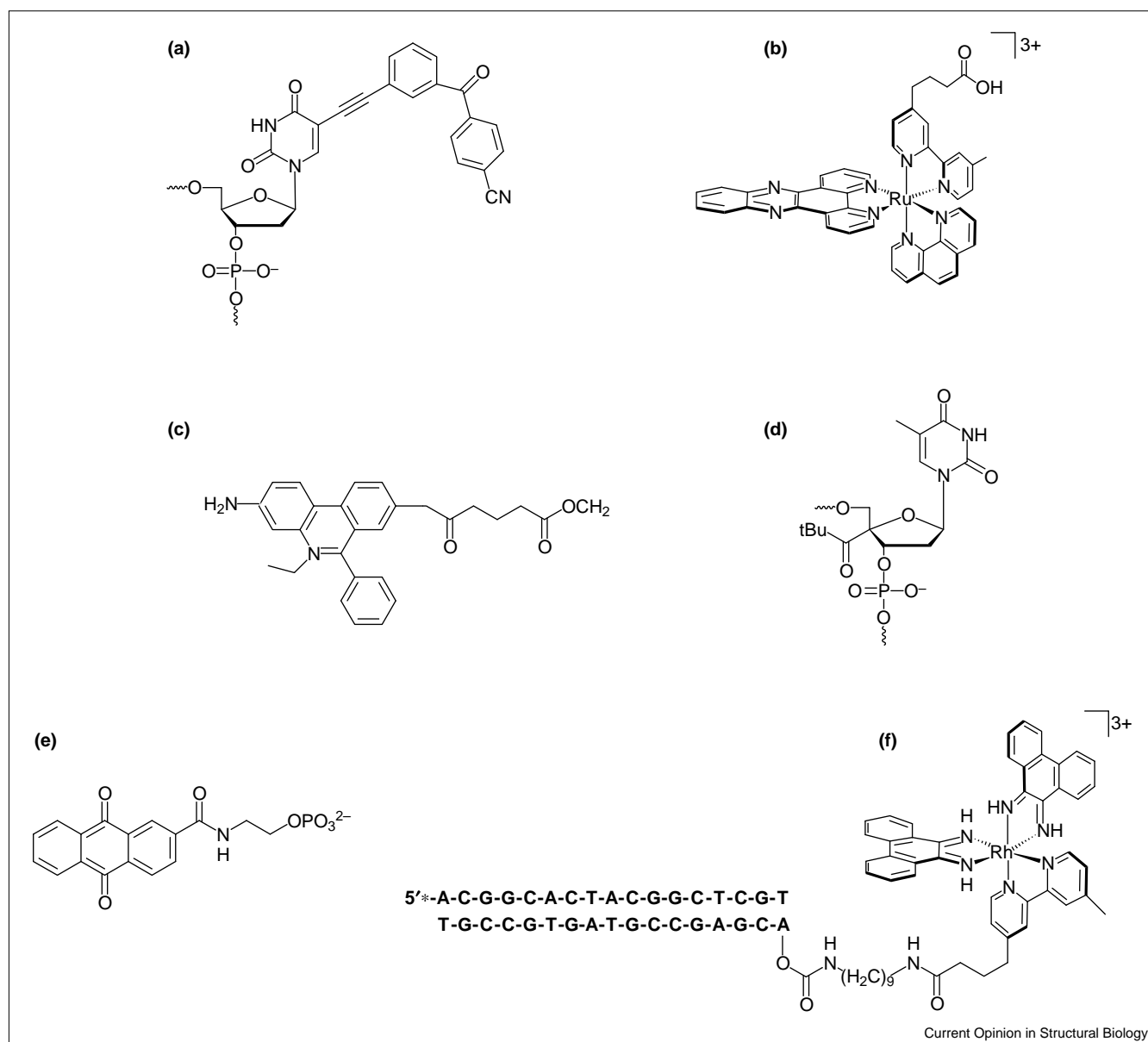
Chemists have instead focused primarily on photochemical and photophysical studies of well-defined oligonucleotide assemblies in solution. Assemblies were first prepared containing pendant electron donors and acceptors, and electron transfer was measured through fluorescence quenching as a function of distance [7–10]. These studies also yielded a mixture of conclusions and, again, this variation probably depends upon the connection, or coupling, of the donor and acceptor within the base pair stack. Effective quenching with a shallow distance dependence was seen with donors and acceptors that were well coupled with the base pair stack through intercalation.

Of the techniques described so far, biochemical studies of DNA charge transport have perhaps been most fruitful, first in identifying that DNA charge transport can proceed over long molecular distances ( $\sim 200$  Å) [11,12] and, second, in raising the possibility that such transport may be a factor leading to DNA damage within the cell [13]. In these studies, photooxidants were appended to a DNA duplex at a given site spatially separated from guanine doublet or triplet sites, which are the targets of oxidative damage. The yield of strand breaks resulting from oxidative damage was then analyzed using gel electrophoresis. Some examples of the different photooxidants used [12,14–18] are given in Figure 1. Also shown is the first assembly in which oxidative damage to DNA was demonstrated [14]. Using the pendant rhodium intercalator as the photooxidant, damage was observed at guanine doublet sites 17 Å and 34 Å away from the site of rhodium intercalation. These studies laid the foundation for much of the work that followed, in which variations in length, sequence and structure were explored, and through which mechanistic proposals were tested.

### Mechanistic considerations

Two theories ascribed to the mechanism by which charge is transported from donor to acceptor through DNA duplexes are superexchange, or tunneling, through the DNA bridge between the bound donor and acceptor, and

Figure 1



Chemical structures of some of the photooxidants that have been used in DNA charge transport studies: (a) cyanobenzene-modified deoxyuridine [17], (b)  $\text{Ru}(\text{phen})(\text{bpy})(\text{dppz})^{3+}$  [15], (c) ethidium functionalized for tethering to DNA [16], (d) 4'-pivaloyl-modified deoxythymine [18] and

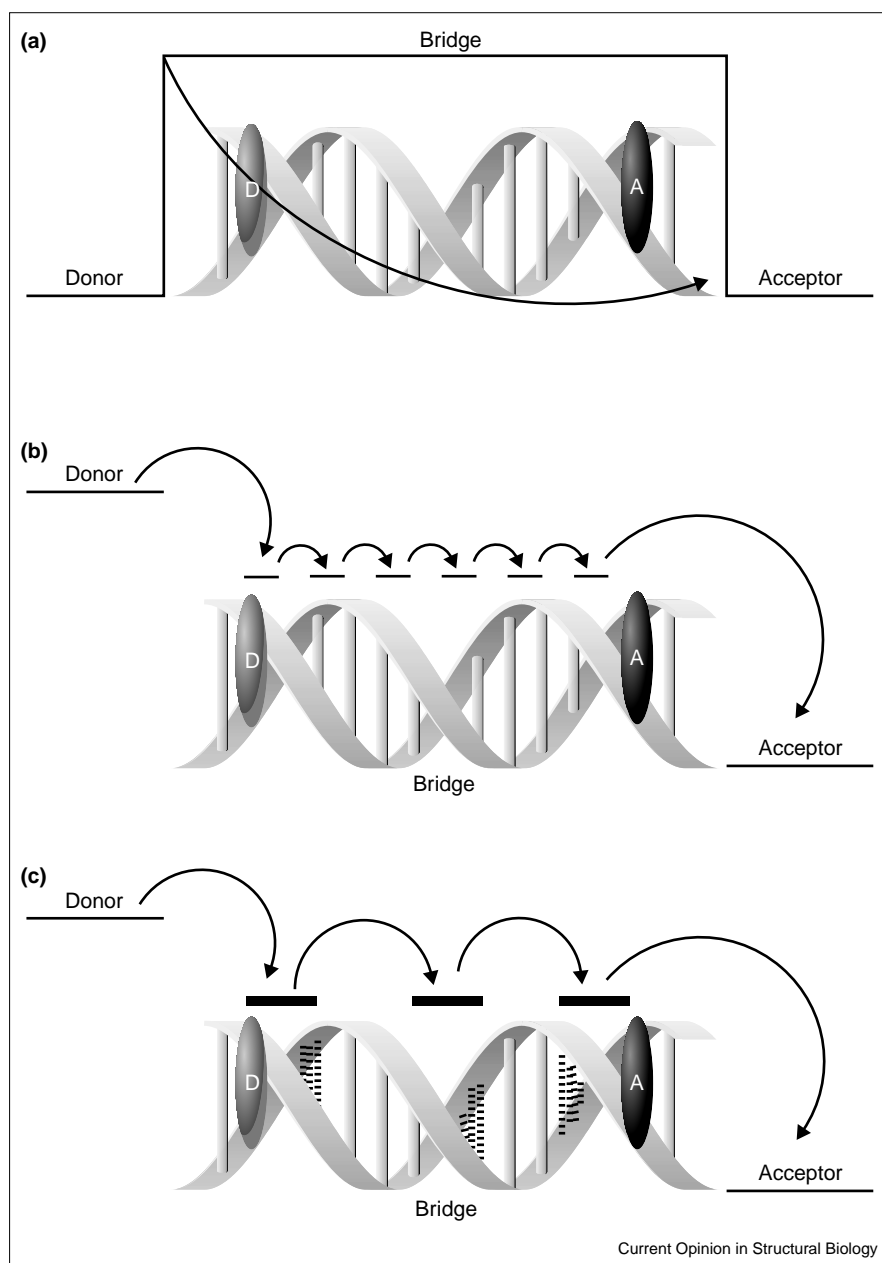
(e) modified anthraquinone [46]. (f) A typical assembly used to promote long-range guanine oxidation using  $\text{Rh}(\text{phen})(\text{bpy})^{3+}$  in our laboratory [14]. This is the first assembly in which oxidative damage to guanine bases was observed using an appended photooxidant.

charge hopping between discrete base orbitals (Figure 2). Tunneling mechanisms predict that the rate of charge transport will decrease exponentially with increasing distance between donor and acceptor, whereas, in an incoherent hopping mechanism, the distance dependence is expected to be much more shallow [19,20]. Experimentally, the rates of electron transfer were determined over short distances by measuring the extent of oxidative damage and a range of distance dependencies were observed [21–24,25\*,26]. Recent data have pointed generally to an intermediate distance dependence of charge transport

through DNA, which is more shallow than for proteins, but not sufficient for 'wire-like' behavior over a long range. Biochemical measurements of yields of oxidative damage have also been used indirectly to assign relative rates of charge transport and these studies have prompted most of the mechanistic proposals concerning long-range charge transport [27].

Based upon these seemingly contradictory data, theoretical proposals have sought to combine tunneling and hopping regimes in efforts to describe charge transport given

Figure 2



Schematic representations of three possible mechanisms for charge transport through DNA. **(a)** Superexchange: the charge tunnels from the donor (D) to the acceptor (A) through the bridge in a nonadiabatic process. An exponential decrease in the rate of charge transport with increasing length of bridge is predicted. **(b)** Hopping: charge occupies the bridge in travelling from donor to acceptor by hopping between discrete molecular orbitals on the bridge. If the rate of charge migration is faster than trapping, the charge should be able to migrate over long distances before getting trapped. **(c)** Domain hopping: charge occupies the bridge by delocalizing over several bases, or a domain. This domain hops along the bridge to travel from donor to acceptor. As in a pure hopping mechanism, the charge should be able to travel long distances before getting trapped.

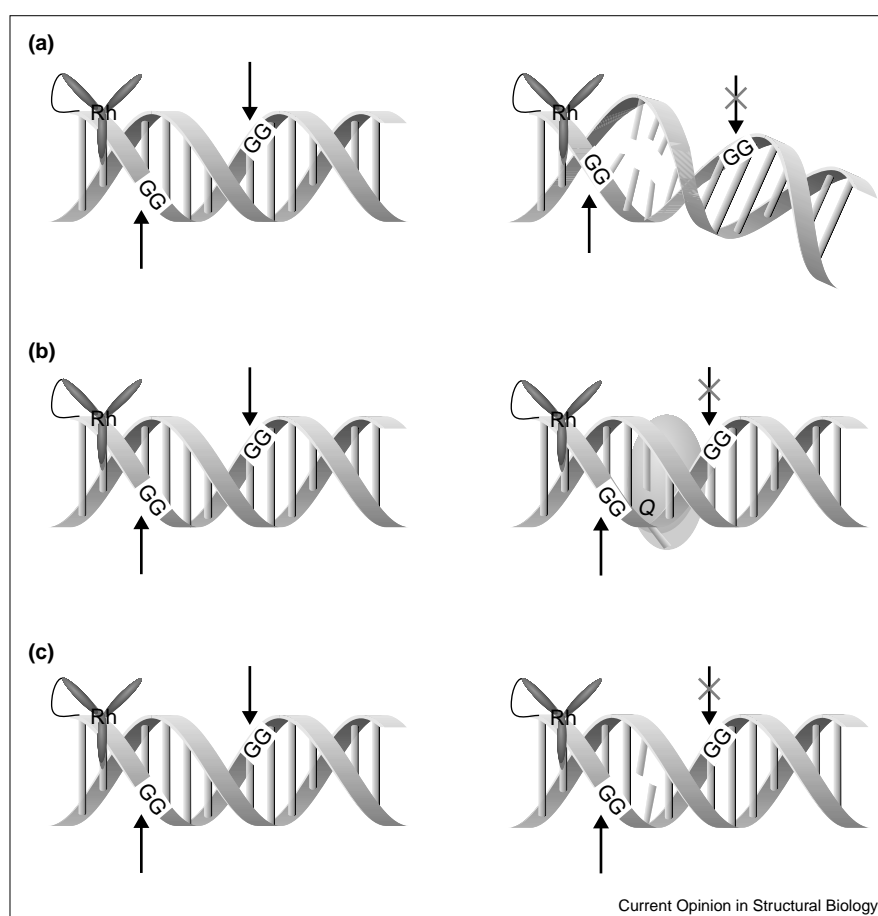
various distance and energetic constraints [28,29]. One interesting proposal focused on the sequence dependence of DNA charge transport [30]. It was proposed that charge transport occurs by hopping between guanine bases and tunneling through intervening TA steps. Giese and co-workers [30] observed that yields of guanine oxidation decrease dramatically with increasing separation of guanine 'stepping stones' by TA steps. However, 5'-TA-3' steps tend to be particularly flexible and this flexibility, in decreasing base pair coupling within the base stack, could also account for the results. To test the notion that tunneling, rather than hopping, occurs on AT tracts, we systematically varied the length of TT, AA and AT intervening segments during biochemical measurements of long-range oxidative

damage [31\*\*]. Guanine oxidation was observed over separations of up to ten TA steps with no loss of yield over that distance and, in fact, the introduction of a GC base pair within the ten base pair TA stretch decreased the oxidative damage yield. Thus, a simple guanine-hopping model was not sufficient to describe charge transport through long sequences of DNA.

More experiments were carried out particularly to reconcile the variations in observations for long- versus short-range charge transport. Experiments in which the radical cation was formed first on the sugar, followed by hole transport to a neighboring guanine, showed that the yield of guanine oxidation decreased steeply only if guanine stepping

Figure 3

Schematic illustrations of some of the base stacking perturbations that have been studied using guanine oxidation ratios: (a) base bulges, (b) protein-induced distortions and (c) single base mismatches. DNA-mediated charge transport chemistry is exquisitely sensitive to such stacking perturbations and, with a stacking perturbation intervening between two guanine doublets, the ratio of oxidation at the distal site versus the proximal site is significantly diminished (Rh, Rh[phi]<sub>2</sub>bpy<sup>3+</sup>).



stones were separated by less than three TA steps; if more bridging base pairs were present, oxidation yields exhibited a far more shallow distance dependence [32\*\*]. This change in damage yield was attributed to a shift in mechanism from superexchange at short distances (less than three base pairs) to a mechanism mediated by thermally induced hopping of charge between adenine bases at long distances.

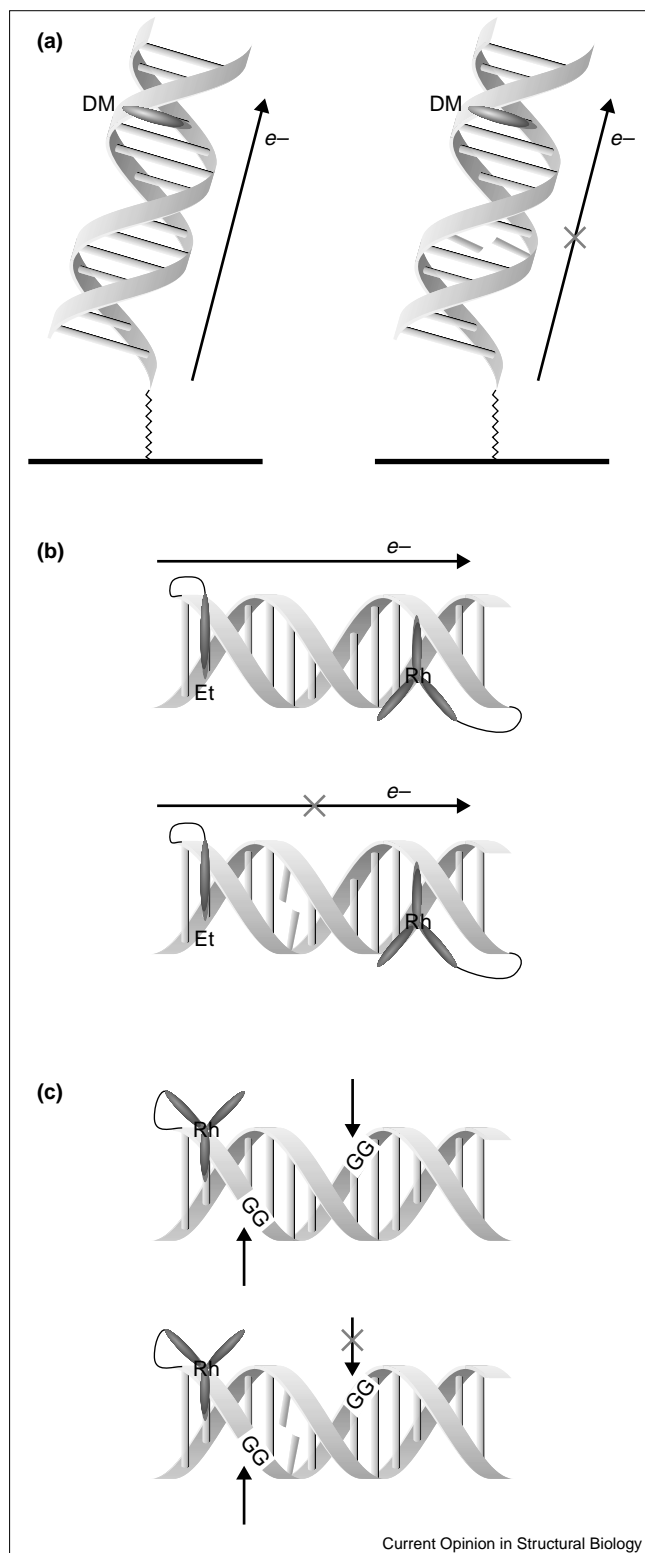
Schuster and co-workers [33] have proposed phonon-assisted polaron hopping between guanine residues as a mechanism for charge migration in DNA, also based on measurements of oxidative damage yields. In this model, upon hole injection, a transient polaron is formed and the sequence-dependent conformational dynamics of DNA are expected to aid charge transport of this polaron. Charge is then transported along the DNA by polaron hopping assisted by phonons. Polaron formation and propagation are expected to be sensitively modulated by the changing counterion distribution [34]. Charge transport was also seen to be quite sensitive to the placement of static charges, for example, the introduction of phosphate termini on the 3' or 5' ends of the oligomer [35]. From these experiments, a high longitudinal polarizability for DNA was inferred,

another characteristic that could enhance charge transport within the DNA interior [36].

The critical importance of DNA dynamics was underscored by ultrafast spectroscopy experiments [24] using tethered ethidium as the photoexcited DNA oxidant and 7-deazaguanine (Z) as the electron donor. Charge transport in these assemblies, which was observed with femtosecond resolution, was independent of ethidium and 7-deazaguanine separation, but the kinetics of the process had two time constants, a 5 ps and a 75 ps component. These components were assigned, respectively, as the inherent rate of charge transport and the motional time for the ethidium intercalator within its binding site to align in an orientation allowing charge transport. These data suggest that dynamical motions within the base pair assembly gate DNA-mediated charge transport. These data also suggest that hole injection into the DNA bridge is rate determining, which indicates that the DNA orbitals between the electron donor and acceptor participate in the reaction directly, not merely as a virtual bridge (as would be expected with superexchange).

On the basis of these and other results that reflect the high sensitivity of the reaction to sequence-dependent

Figure 4



Schematic illustrations of different experiments for single mismatch detection based on DNA charge transport. The diminution in efficiency of DNA-mediated charge transport chemistry upon introduction of a single mismatch into the intervening base stack can be detected using (a) electrochemistry through DNA films to an intercalator (DM, daunomycin), (b) fluorescence quenching and (c) guanine oxidation yield. These results illustrate both that base stacking is a general principle that governs charge flow in DNA and how remarkably sensitive this chemistry is even to very small structural perturbations, such as single base mismatches (Et, ethidium; Rh, Rh[ $\phi$ ]<sub>2</sub>bpy<sup>3+</sup>).

flexibility, allowing charge transport from one delocalized domain to the next.

### Sensitivity of charge transport to dynamical structure

Irrespective of the mechanisms used to describe the process, it has become apparent that these charge transport reactions are extremely sensitive to DNA base pair stacking [7,8,12,23,37–40,41\*,42–48]. Indeed, charge transport studies may be able to provide a measure of the sequence-dependent conformational dynamics of DNA. How the electron donor and acceptor bind to DNA, as well as the DNA base sequence, conformational dynamics and local flexibility all contribute to coupling within the base pair  $\pi$ -stacked array and, therefore, to the efficiency of the DNA-mediated charge transport reaction.

The importance of the stacking of the electron donor and acceptor within the DNA base stack has been highlighted in experiments measuring base–base electron transfer [37]. Charge transport between guanine and modified fluorescent adenine derivatives was measured in fluorescence quenching studies on DNA duplexes. Depending on how well the un-natural adenine base was stacked within the DNA duplex, the DNA helices displayed charge transport efficiencies ranging from insulating to ‘wire-like’. Measurements of base–base electron transfer also established that, in B-DNA duplexes, the rate of intrastrand electron transfer is approximately 100 times faster than the rate of interstrand transfer. The preference for intrastrand transfer is understandable given that intrastrand rather than interstrand base stacking occurs preferentially in B-DNA.

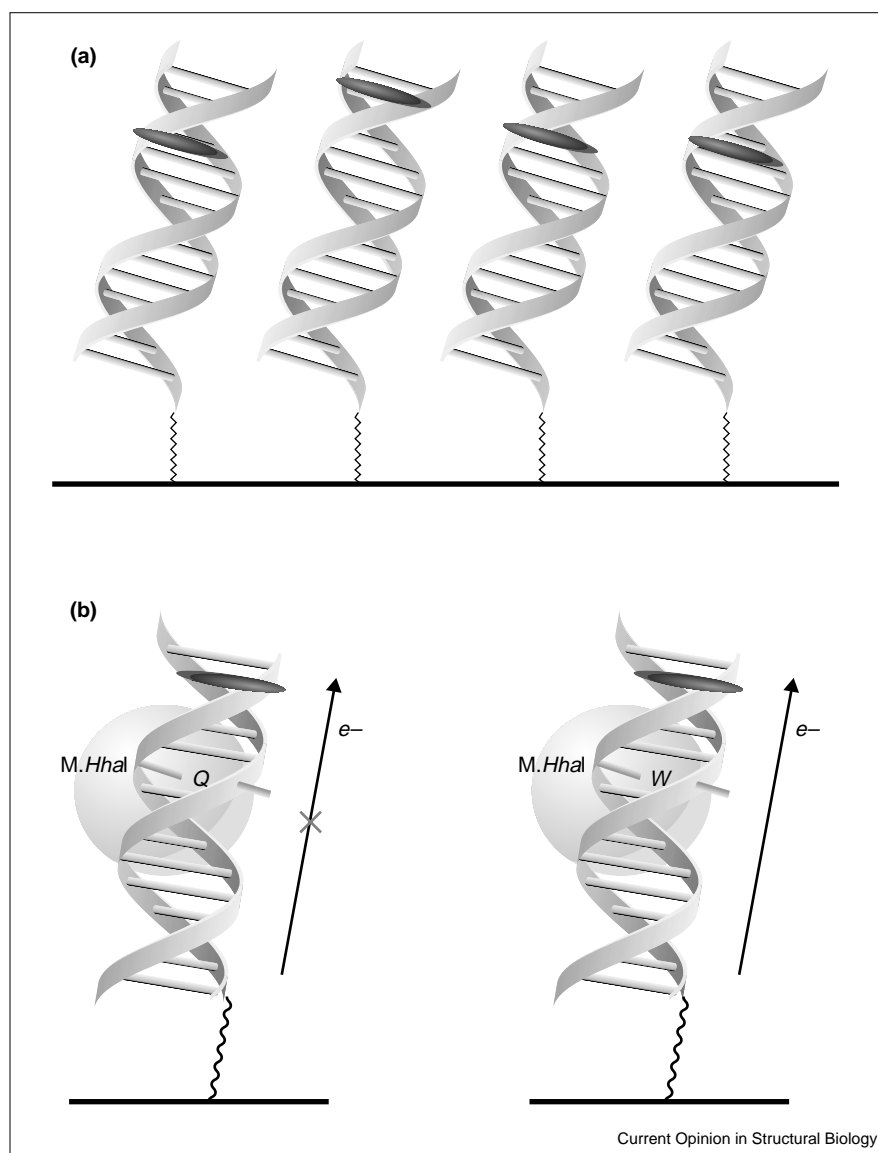
Biochemical experiments have also underscored the remarkable sensitivity of DNA-mediated charge transport to the stacking of the base pairs intervening between the donor and acceptor [7,8,12,23,37–39,41\*,42]. Base bulges [38], flexible sequences [11,31\*\*] and protein-induced distortions [40,41\*] all greatly influence the efficacy of long-range DNA-mediated electron transfer. Some of the distortions examined are illustrated in Figure 3. Long-range oxidative damage has also been examined in DNA–RNA hybrids [42,43], in DNA triplexes [44,45] and in multiple-stranded assemblies [39].

conformation, we have proposed [11,31\*\*] that charge transport over long molecular distances might best be considered as domain hopping, whereby charge is transiently delocalized over domains according to their sequence and dynamical motions. Charge hopping and propagation are gated by sequence-dependent DNA

In a DNA duplex, mismatches are generally stacked, but they undergo greater dynamical motion than Watson–Crick

Figure 5

Applications of DNA-mediated charge transport chemistry using DNA-based array technology. (a) DNA-mediated charge transport is monitored electrochemically at DNA-modified electrode surfaces using intercalators bound to the film as the redox probe. The efficiency of reduction of the intercalator bound near the top of the film provides a measure of the intervening DNA stack. (b) Such DNA films can also be used to monitor stacking perturbations associated with DNA-binding proteins.



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paired bases [49–51]. DNA charge transport was also found to be very sensitive to these motions (Figure 4). For example, a single CA mismatch inserted into a DNA duplex between a covalently attached photoinduced electron donor (ethidium) and a covalently attached intercalating acceptor ( $\text{Rh}[\text{phi}]_2\text{bpy}^{3+}$ ) significantly inhibits electron transfer, as can be seen from the results of fluorescence quenching experiments [8]. The ability of DNA duplexes to support charge transport through base mismatches was recently systematically examined in DNA assemblies using guanine oxidation ratios as a measurement of charge transport efficiency [52]. These results indicated that charge transport through a mismatch site is closely correlated to the base pair lifetime of that mismatch, as measured by  $^1\text{H}$  NMR imino proton exchange rates. These results again implicate base dynamics in modulating long-range charge transport through DNA.

Many proteins, in binding to the double helix, cause distortions in the base pair stack. Guanine oxidation ratios, as measures of charge transport efficiency, have also been used to probe DNA–protein interactions [40,41\*]. This methodology was used, for example, to examine base flipping by the methyltransferase *HhaI*. *In vivo*, *M.HhaI* methylates each cytosine in 5'-GCGC-3' sequences by flipping the cytosine into its active site pocket and inserting Gln237 in its place, effectively creating a hydrophobic plug within the base stack of the DNA. When the binding site for *M.HhaI* was placed between two guanine doublets and long-range hole transport from an appended rhodium photooxidant was determined, guanine oxidation at the site distal to protein binding was greatly diminished. In identical experiments using a mutant enzyme that inserts the aromatic, heterocyclic residue tryptophan instead of glutamine, distal damage was restored. Furthermore, using

the tryptophan mutant enzyme bound to DNA tethered to a ruthenium photooxidant, a transient tryptophan radical was observed in spectroscopic studies of DNA-mediated charge transport [53,54\*\*]. This protein-dependent charge transport was observed over 50 Å and, over this distance range, charge transport was not rate limiting, occurring at a rate  $\geq 10^7$  s<sup>-1</sup>.

### Applications in sensing

The sensitivity of DNA charge transport to base stacking provides the basis for sensor applications. In this effort, we have focused on electrochemistry experiments on DNA films [55–59,60\*\*]. In these experiments, DNA oligonucleotide duplexes containing a thiol linker are attached to a gold surface and the reduction of a redox-active intercalator bound to the close-packed DNA film is monitored (Figure 5). We first examined DNA films containing daunomycin covalently bound to guanine sites in the duplex and found that current flow to daunomycin was independent of its position in the film [58]. We then tested current flow in the presence of an intervening CA mismatch (Figure 4). Remarkably, the presence of this mismatch shut off the reduction of the daunomycin adduct. This experiment established again that the path of charge transport is through the base pair stack. Importantly, given the sensitivity of charge transport to base pair stacking, the experiment also established that a single base mismatch in DNA could be detected electrochemically.

Subsequent experiments established the sensitivity of the charge transport reaction to all intervening base mismatches in DNA. Interestingly, using noncovalent daunomycin as a redox reporter bound near the top of the densely packed film [59], results were found to correlate with the evidence from long-range oxidative damage studies on assemblies containing intervening mismatches [52]. Thus, sensitivity to structure was evident from both oxidation chemistry (of the DNA base) and reduction chemistry (of the DNA-bound daunomycin).

The ability to detect single base mismatches by DNA-mediated charge transport is now being exploited for mutational analysis in electrochemistry-based assays [60\*\*]. The assay has increased mismatch discrimination and signal:noise using electrocatalysis and, as a result, provides a completely new technology for the rapid detection of single nucleotide polymorphisms. DNA-modified electrodes are prepared by self-assembly of prehybridized duplexes. After dehybridization of the well-matched strand, target DNA can be hybridized to the DNA-modified electrode. The electrocatalytic reduction of methylene blue, a redox-active DNA intercalator, coupled to Fe(CN)<sub>6</sub><sup>3-</sup> is then monitored by chronocoulometry. Using this electrocatalytic assay, all single base mismatches, including GA and GT, are easily distinguished from Watson–Crick base-paired DNA. Base lesions such as oxo-A, hydro-T and abasic sites are also easily detected, underscoring the remarkable sensitivity of the reaction to variations in base

pair structure. The reaction, furthermore, is sequence independent, probably owing to the decreased flexibility of oligomers within the well-packed film. This technology was also found to be compatible with DNA-based chip platforms. As a result, this assay may offer significant advantages in accuracy and sensitivity over current technologies for DNA-based diagnosis.

We have most recently found that the electrochemical reduction of DNA-bound intercalators is also effective in developing an assay for protein-induced changes in DNA structure (Figure 5) [61\*]. Gold electrode surfaces modified with loosely packed DNA duplexes covalently cross-linked to daunomycin and containing the binding site for the test protein were constructed and charge transport through DNA as a function of protein binding was assayed. Substantial attenuation in current is seen in the presence of the base-flipping enzymes *M.HhaI* and uracil DNA glycosylase, as well as with the TATA-binding protein. Again, a restoration in current flow is seen upon binding the *M.HhaI* mutant containing tryptophan. No significant diminution in current flow is evident upon binding *PvuII*, an endonuclease containing the helix-turn-helix motif, to its methylated target, but, without target methylation, restriction by the enzyme can be monitored electrically. This novel probe of protein–DNA interactions could be particularly useful in screening for inhibitors of protein–DNA interaction and perhaps also in monitoring real-time perturbations in DNA structure associated with protein binding and reaction.

### Biological considerations

Experiments from many different laboratories have now confirmed that oxidative damage to DNA can proceed over long molecular distances and that the reaction is sensitive to sequence, as well as to sequence-dependent structure. These findings prompt the question of whether long-range charge transport similarly promotes chemistry at long range within the cell. Are some sites, for example, necessarily insulated from charge transport damage, whereas others represent hot spots to which damage is funneled? Given that both activation and inhibition of charge transport by DNA-binding proteins have been seen in the test tube, do DNA-binding proteins similarly modulate charge transport chemistry in the nucleus?

In considering these possibilities, it is important first to establish that DNA-mediated charge transport does proceed in the cell. Using photoactivated rhodium intercalators, DNA charge transport within cell nuclei has begun to be probed [62\*\*]. *HeLa* cell nuclei were incubated with the rhodium photooxidant, irradiated and then the genomic DNA was isolated and examined. The analysis revealed base damage preferentially at the 5'-guanine of 5'-GG-3' sites, a hallmark of base damage by DNA-mediated charge transfer chemistry. Moreover, for transcriptionally active DNA within the nucleus, oxidative damage was found at protein-bound sites that were inaccessible to rhodium, as

established by photofootprinting. Thus, within the nucleus, DNA-mediated charge transport can lead to base damage from a distance. Direct interaction of an oxidant is not necessary to generate a base lesion at a specific site.

Various proposals are now being made concerning the biological ramifications of this chemistry and how it may be exploited physiologically. It has been proposed, for example, that regions containing a disproportionate frequency of guanines, as found in CpG islands and telomeres, may represent hot spots for damage [63]. Our studies of long-range damage on restriction fragments [44] suggest that the physiological range of charge migration may be on the order of 100 base pairs, but probably not longer. This range does, however, represent the size range of nucleosomes, in which DNA is packaged within the cell; efficient oxidative damage from a distance has been demonstrated in the nucleosome core particle [64].

Furthermore, reactions on DNA through charge transport chemistry are not restricted to oxidative base damage. We have found that the repair of thymine dimers in DNA may be triggered oxidatively from a distance [65–67] and thymine dimer repair has also been demonstrated reductively with bound flavins [68,69]. Our electrochemistry experiments to sense mismatches and lesions in DNA also suggest that this chemistry might be valuable as a sensing device within the cell [13], although this application *in vivo* is yet to be demonstrated. Certainly, however, charge transport chemistry mediated by DNA offers opportunities to carry out a range of reactions from a distant position on the DNA helix.

## Conclusions

DNA charge transport chemistry is a remarkable characteristic of double helical DNA. Oxidative DNA damage mediated by the base pair stack can occur over 200 Å away from the position of the oxidant, in a reaction that is modulated by intervening sequence, structure and dynamics. Proteins, in binding to DNA, can also modulate long-range charge transport, both positively and negatively. Indeed, given the sensitivity of this chemistry to base pair stacking, DNA charge transport is being harnessed as a sensor of perturbations in the base pair stack. The applications of this chemistry, practically and perhaps also in the context of chemotherapy, are exciting to consider. More intriguing still, and a challenge for biochemists today, is the consideration of the consequences of and opportunities for charge transport through the DNA base pair stack within the cell.

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