DNA, a molecular wire or not – The debate continues

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The structure of DNA, with its π-electron system of base pairs stacked in the core through the length of the molecule, is reminiscent of an 'electric wire'. The questions whether DNA is a molecular wire and can be used for transferring electrons through its π-stalk are being investigated through various approaches. An overview of the findings with emphasis on the recent direct measurement of conductivity of DNA filaments is given here. The answers are ambiguous, but support DNA-mediated electron transfer for correction of damages at the G and T sites.

THE possibility of long-range electron transfer through a DNA molecule has intrigued many researchers since a long time. Radiation biologists had invoked this concept almost 40 years ago to account for what was considered unusually high conductivity of DNA[1,2]. Later studies, however, showed this to be a consequence of 'ice particles' present due to water in the medium or of the charge mobility due to ions outside the duplex[3,4]. While studies based on electron spin resonance and luminescence methods provided support for long-range electron tunnelling[5,6], those based on the pulse radiolysis technique indicated that electron tunnelling is restricted to about five base pairs[7]. Other investigators searched in vain for soliton effects[8].

Interest in this field had been rekindled by Barton and co-workers[9] during the late nineties. They reported that long-range electron tunnelling occurred between intercalated reagents separated by > 40 Å. Remarkably, their experiments indicated a weak dependence of the electron transfer rates within the DNA on the number of interspersed bases[10–15]. Contemporary experimental observations concerning electron transfer through DNA are not consistent with these conclusions. According to other research workers, DNA is an appropriate medium for fast electron tunnelling when limited to a few base pairs[16–23]. Elegant experiments on the direct measurements of electrical conductivity of DNA have been carried out during the last two years in order to understand DNA-mediated electron/hole conduction. The purpose of this article is to summarize the background of the existing controversy and to evaluate the results of new experiments.

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Some basic principles

Before we take up issues concerning the charge migration within the DNA duplex, it is instructive to examine the necessary basic principles pertaining to the long-range electron transfer processes.

Marcus theory

According to Rudy Marcus – recipient of the Nobel Prize for his pioneering work in electron transfer chemistry[24,25] – the rate constant for electron transfer between the donor and acceptor species, k_{et}, is given by

$$k_{et} = \kappa(r) Z \exp(-\Delta G^*/RT), \quad (1)$$

where $\kappa(r)$ is the probability for the electron transfer normalized to the number of times the molecular assembly acquires the correct configuration to pass through the intersection of the potential energy surfaces of the reactant and product and Z is either the collision frequency in a bimolecular reaction or the vibrational frequency in an intramolecular reaction. ΔG^* is the free energy of activation for the process and, according to the Marcus theory, it bears quadratic dependence on ΔG^0 – the Gibbs free energy change associated with the electron transfer. In eq. (1), at large values of r (the donor–acceptor distance), κ depends exponentially on r. Thus, the distance dependence of electron transfer in a medium can be expressed by eq. (2):

$$\ln k_{et} \propto -\beta \Delta r, \quad (2)$$

where β is the damping factor (or the attenuation factor) exerted by the medium. Large values of β indicate higher 'resistance' exerted by the medium for the electron to pass through from the donor to the acceptor site. The 'medium' here refers to solvent, surface etc. in the case of an intermolecular electron transfer and to the intervening bonds (covalent/non-covalent) between the donor and the acceptor in an intramolecular situation.

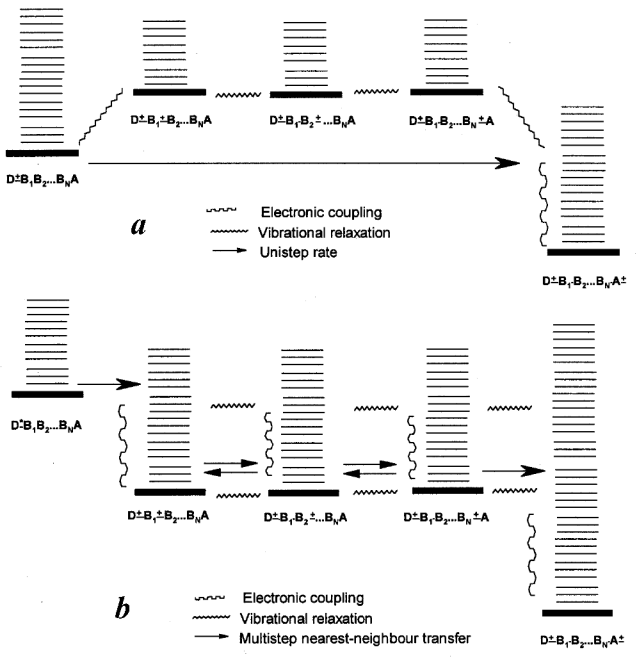


Figure 1. Super-exchange (*a*) and hopping (*b*) models of long-range electron transfer.

Super-exchange and hopping models

Recent electron transfer theories consider the generic example of separation of an electron–hole pair[26–29]. In these theories, the same approach will account for both electron and hole migration, and when applied to charge migration within the DNA, the migration pattern can be described using eq. (3):

$$\begin{aligned} D\,B_1B_2\ldots B_NA &\leftrightarrow D^{+/-}B_1{}^{-/+}B_2\ldots B_NA \\ &\leftrightarrow D^{+/-}B_1B_2{}^{-/+}\ldots B_NA \leftrightarrow D^{+/-}B_1\,B_2\ldots B_N{}^{-/+}A \\ &\leftrightarrow D^{+/-}B_1B_2\ldots B_NA^{-/+}, \end{aligned} \tag{3}$$

where D is the electron donor, A is the electron acceptor and $\{B_i\} \equiv B_1,B_2\ldots B_N$ are the intervening, adjacent base pairs. Two distinct charge separation mechanisms will be referred in this report. Electrons and holes can migrate from the locus of formation to trap sites through either a single-step 'super-exchange' mechanism (Figure 1 *a*) or a multi-step 'hopping' mechanism (Figure 1 *b*)[27]. These two models can be understood if one considers that the fundamental mechanism of molecular electron transfer requires an electronic interaction between the initial (D---A) and the final ($D^{+/-}$---$A^{-/+}$) states.

In most intramolecular or intermolecular electron transfer reactions, the charge is localized only on the first and the last sites. It is assumed to move between these two sites in a single coherent jump by the super-exchange mechanism. But, when the states that lie between the first and the last are sufficiently low in energy, the overall trajectory of the migrating charge follows the hopping model – like that of a wandering drunk. The coherent transfer processes cannot obviously get very far at room temperature, because the orbitals in which the electron density is found do not extend effectively over long distances. So, if the 'bridging states' (i.e. the intervening base pairs in DNA) are high in energy compared to the initial and final states (see Figure 1 *a*), one should anticipate a super-exchange pathway, characterized by a rapid exponential decay of the electron transfer rate or yield as a function of distance (eq. (2)). On the other hand, if the intermediate bridging states are comparable (or slightly lower) in energy than the initial state (see Figure 1 *b*), then one expects to see an incoherent, hopping behaviour that decays only slowly with distance. Intuitively, this latter type of mechanism involving the diffusive motion is responsible for the ordinary conductivity of metals.

Conductivity of metals and semiconductors – The band theory

The conductivities of insulators, semiconductors and metals are typically in the range 10^{-22}–10^{-14}, 10^{-9}–10^{3} and 10^{5}–10^{6} S cm^{-1}, respectively (S = Siemens or Ω^{-1}). The conductivity of metals decreases on increasing the temperature, but in semiconductors it increases. Such aspects are usually explained by the band theory of solids. Just as atomic orbitals combine to form molecular orbitals in molecules, in solids they combine to form a very large number of states. The energy levels corresponding to the states formed from a given type of orbital can be treated as a continuous band of energy. Since the atomic orbitals are discrete levels with energy gaps in between, the energy bands formed from the different atomic orbitals leave regions of energy in between where the entry of electrons is forbidden. Packing of available electrons from the lowest energy upwards, leads to the final band containing electrons to be partially filled; the highest level occupied by electrons is called the Fermi level. This allows unactivated electron transport and is characteristic of metals. When metals are heated the resistance increases because of increased lattice vibrations which impede electron flow. Packing of available electrons from the lowest energy upwards in a band structure can also end up with a completely filled band (valence band) and a higher energy empty band (conduction band), the two being separated by an energy gap. This situation leads to thermally activated conduction, characteristic of semiconductors. Heating causes increased lattice vibrations in semiconductors as well, however, it simultaneously leads to higher population of charge carriers in the conduction band and hence increase in conductivity.

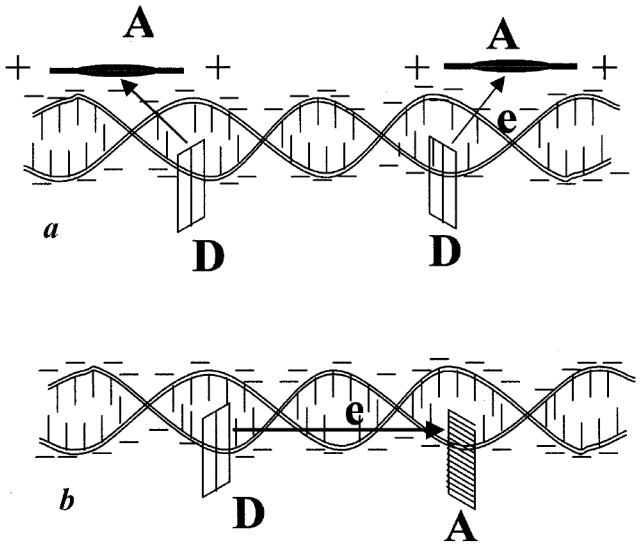


Figure 2. Interfacial (*a*) and through-stack (*b*) electron transfer through DNA.

Early work on DNA as a conductor

Electron transfer reactions occurring within a DNA duplex can be categorized according to mutual positioning of the redox partners. The simplest case concerns interfacial electron transfer from an intercalated donor (*D*, usually a dye) molecule to an electron acceptor (*A*) (Figure 2 *a*). The second case concerns electron transfer between intercalated donor–acceptor pairs separated by several base pairs (Figure 2 *b*).

Interfacial electron transfer

The first report on DNA helix enhancing electron transfer rates between the donors and acceptors associated with it appeared in 1986 and it concerns the interfacial electron transfer[30]. 'Double doping' of DNA resulted in the so-called 'coat/core' structure as shown in Figure 2 *a*, with the coat being dipositively charged 4,4'-dimethyl 2,2'-bipyridine (methyl viologen) and the core – the well known intercalator – ethidium bromide. By observing the quenching of fluorescence due to the electron donor (ethidium bromide) by the electron–acceptor (methyl viologen) and assigning it to the 'intermolecular electron transfer' within this donor–acceptor pair, Fromherz and Rieger[30] showed enhancement of the rate for this electron transfer by half a million on addition of DNA in the medium. Harriman[31] had further demonstrated such rate enhancement for many other 'coat/core' type *D–A* pairs in the presence of DNA. Harriman's experiments have revealed that these electron transfer reactions are characterized by weak coupling between the donor–acceptor pairs and are in conformity with the Marcus equation for electron transfer (eq. (1)). This finding is hardly surprising considering the avid intercalating ability of ethidium bromide and the other donor molecules such as porphyrins, etc. employed in this study, as well as the strong Coulombic binding of methyl viologen and other dipositively-charged acceptors with the negatively-charged phosphate backbone of DNA. However, the finding that DNA can mediate fast intermolecular electron transfer across its interface is novel.

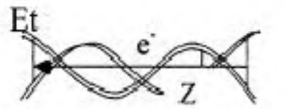
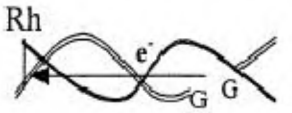
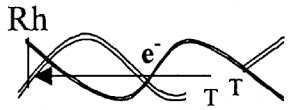
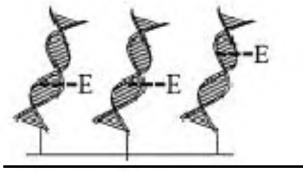
Through-stack electron transfer – Chemistry at a distance

The 'molecular wire' nature of DNA actually conjures up a vision of electron migration over long duplexes with several interspersed base pairs on the way – the through-stack electron transfer (Figure 2 *b*). It is in this second case, wherein the DNA has been compared to a 'live electric wire', the experimental evaluations seem contradictory. Most early experimental results that have indicated the 'wire' nature of DNA have come from photophysical measurements. We will give a brief overview of these findings in this report, as a number of reviews and commentaries on this topic have already appeared in the literature[9,32–35].

A strong proponent of 'long-range electron transfer' mediated through DNA base stack, Jacqueline Barton studied the problem by adopting two approaches[9–15,36–39]. In the first approach, the donor (*D* in Figure 2 *b*) and acceptor (*A* in Figure 2 *b*) molecules were fixed at known distances on the duplex via intercalation or covalent attachment, and photo-induced electron transfer between them was investigated. In the second approach, measurements were made of either the oxidative damage at the G (guanine) sites or repair at the dimerized TT (T = thymine) sites, both initiated usually by photoexcitation of a metal complex bound to DNA at a site far away from the damaged G or TT site (the so-called 'chemistry at a distance' approach[9–15,36–39]). These two approaches are illustrated and various experimental results are summarized in Table 1.

Emerging from the Barton experiments are two results relevant to our discussion here. These are (i) DNA can transport electrons over large distances (> 40 Å) using the core π-stack of its base pairs, called π-ways, and (ii) the value of β (eq. (2)) attributable to electron/hole mobility through the π-ways of stacked bases can, at times, be as low as 0.1 $Å^{-1}$. Initially, these observations appeared acceptable in view of the purported wire-like nature of DNA. However, almost all the subsequent studies employing similar approaches have come up with larger values of β, up to as high as > 1.0 $Å^{-1}$ (refs 16, 19, 22 and 23). Thus there is an

Table 1. Summary of early experiments on long range electron transfer mediated through DNA

Donor–acceptor assembly within DNA	Technique	Main result	Reference
	Fluorescence quenching (of Ru-complex (Ru) by Rh complex (Rh))	Efficient fluorescence quenching over 40 Å	10–12
	Fluorescence quenching (of ethidium bromide (Et) by Rh)	Ultra-fast electron over 17–36 Å with $\beta < 0.1$ Å^{-1}	13
	Fluorescence quenching (of Et by 7-deaza-guanine (Z))	Distance dependence (β = 0.2–0.4 Å^{-1}) is sensitive to stacking of reactants	14
	Gel electrophoresis and detection of fragments resulting from piperidine-treatment	Long-range oxidation of guanine doublets across 17–34 Å	36, 37
	Gel electrophoresis; Transient absorption spectroscopy (Ru^{ox} = oxidized Ru-complex)	Guanine doublets oxidized upon triggering from distances > 30 Å	38
	High performance liquid chromatography (HPLC)	Thymine dimer repaired by long-range electron transfer through the DNA helix	39
	Electrochemistry of ---E, intercalated/covalently linked electroactive species (methylene blue, daunamycin, etc.)	Efficient electron transfer over 40 Å to ---E. Detection of base mismatches based on charge transmission through DNA	9

on-going debate with regard to range, rate and mechanism of electron transfer in DNA[32–35]. It is possible that those contradictions are due to limitations of experiments in terms of the *D–A* pairs employed, the kind of oligos used and other components in the reactions. The value of β might just reflect the variants in the experiments rather than the true ability of DNA to transport charge.

Recent experimental efforts, especially those by Meggers *et al.*[29] and Harriman[31], have tried to resolve this problem as discussed below. A positive charge on a guanine base (designated as G^+ in Figure 3) created at a GC (C = cytosine) site on loss of an electron by a photochemical event in a DNA strand, in the experiment of Meggers *et al.*[29], was allowed to reach a target site (GGG site) separated by varying sequences. The energy of the hole when residing on the intervening adenine (A), cytosine or thymine bases is substantially higher than when on guanine. This is due to the differences in the redox potentials of these bases, with G having the lowest. Thus, the electron never stops, except on G bases, enroute to the target. By measuring the yields of fragments of DNA produced as a consequence of the electron-transfer event, they have actually measured the probabilities, and therefore the relative rates (k_{CT}(rel)) of hole transfer along the strand. As shown in Figure 3 *a* and *b*, there was a 100-fold reduction in the rate of the hole transfer from the G^+ site to the GGG triplet when the number of intervening AT pairs increased from two to four. Keeping the distance between the G^+ and the GGG sites in Figure 3 *c* and *d* the same as that in Figure 3 *b*, an intervening G–C pair enhanced the rate constants comparable to that in Figure 3 *a*.

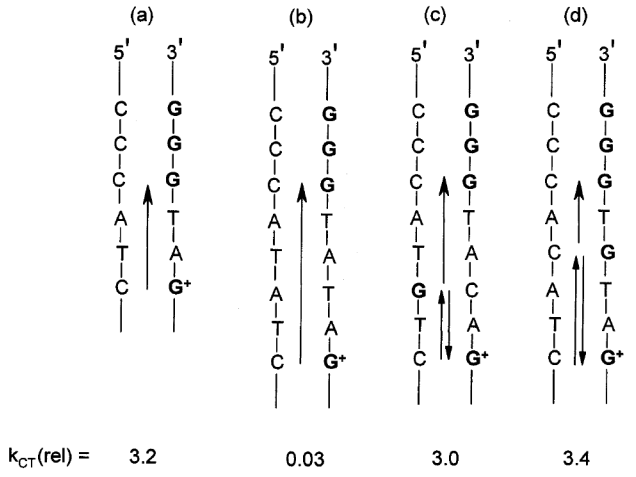


Figure 3. Relative rates (k_{CT}(rel)) of hole transfer between G^+ (donor) and GGG (acceptor) along the strand, consistent with the random walk model.

These results suggest that the hole does indeed hop incoherently among the G bases in a kind of random walk. However, the electron cannot stop in mid-journey when moving from one G base to the next, so that the electron transfer is a coherent super-exchange between two different G bases. This random walk model of the hole transfer within DNA sequences was validated by weak dependence on the donor–acceptor distance[40]. As noted above, the mechanism assumes that the long-range charge transport is facilitated by the charge transfer between DNA bases of similar redox potentials, (i.e. the G sites). In the case that every single hopping step occurs over the same distance, the hopping mechanism is described by eq. (4):

$$\ln k \propto -n \ln N, \tag{4}$$

where n is a proportionality factor which in the simplest case should be about 2 and N is the number of hopping sites. Applied to their data, this equation really yielded a value for n to be 1.7 ± 0.2, validating the application of the hopping mechanism to hole transfer.

Another result implicit in this study is that the base sequence plays a decisive role on the hole transfer. A very similar conclusion was arrived by Harriman who noticed that the rate of photo-induced electron transfer between the intercalated dye molecules is faster in poly[dAd*T*] oligos than in poly[dGd*C*][31]. The details of experimental procedures and interpretation of the results might be different in these two studies, but the discovery that the 'sequence plays a role' in charge migration through DNA in both studies is worth noticing.

Direct measurements of conductivity

Direct measurements of conductivity are expected to provide convincing evidence for charge migration through DNA. The focus of recent studies is indeed in this direction as summarized below.

Yes, DNA is a conducting wire

The recent work by Fink and Schonenberger[41] supports the molecular wire nature of DNA. Here, direct measurements of the electrical current as a function of the potential applied across a few DNA molecules aligned as single ropes have been carried out under ultra high vacuum (10^{-7} mbar) conditions. The experiment involves a low-energy electron point source (LEEPS) microscope developed by them. The measured resistivity is 1 mΩ cm, which includes a contribution due to finite contact resistance and hence constitutes an upper limit. The resistance attributed to DNA alone is still smaller and can be compared to the resistivities of conducting polymers, indicating that DNA transports electrical current like a good linear conductor. Measuring anisotropic electrical conductivity in an aligned DNA-cast film, a similar conclusion was reached by Okahata *et al.*[42].

Direct evidence for DNA-mediated electron transfer was also obtained with electrochemical experiments[9]. Gold surfaces were modified with DNA appended to an alkanethiol tether. Atomic force microscopic studies have revealed that such immobilized (due to gold–sulphur interaction) DNA duplexes are oriented at an angle of $\sim 45^0$ from the gold surface. Electroactive groups were then bound to the immobilized DNA, either non-covalently or by covalent connections (see last entry Table 1). Methylene blue was attached non-covalently (intercalation). Daunamycin was covalently connected in such a way that it intercalated within the base pairs situated at different distances from the electrode surface. Direct electrochemical studies carried out with these modified electrodes indicated that charge transport was required from the electrode to the electroactive species through the DNA lattice. Significantly, the measured rate constant for the reduction of methylene blue at the DNA-modified gold was of the same order of magnitude as that attached directly to the electrodes by aliphatic tethers of lengths similar to the thiol-terminated linkers used to bind DNA to the surface. Similarly, no qualitative differences of electrochemical responses were found for daunamycin covalently linked to DNA on varying the position of intercalator-binding sites up to 40 Å. In addition, C–T mismatches that were intentionally arranged in the electrode-bound duplex attenuated the electron transfer rates. This indicates that a DNA-mediated communication between the electroac-

tive species and the electrode surface indeed exists. Put together, these results seem to suggest that the long-range electron transfer for species intercalated within the base stack proceeds over exceptionally long distances at ultrafast time scales.

No, DNA is an insulator

In stark contrast to what is discussed above, results of two independent investigations provided evidence against DNA-mediated charge migration. In fact, both the studies are categorical in identifying DNA to be just an insulator! The initial aim of a recent study involving 'DNA wire' was not really to establish the insulating nature of DNA, but a control experiment gave this evidence. In their attempts to assemble a nanometer-scale electrical device, Braun *et al.*[43] employed DNA as a template to connect a 12 μm long, 100 nm wide conductive silver wire between two gold electrodes. They considered that construction of nanometer-scale electrical circuits has been rendered difficult largely owing to failure to achieve inter-element wiring and electrical interfacing to macroscopic electrodes. They were attracted by the idea that use of molecular recognition processes and the self-assembly of molecules into supramolecular structures involving DNA might help overcome these difficulties. A three-step chemical deposition process was adapted in this study for the construction of a circuit, which has two gold termini interspersed with a silver wire. In the first step, oligonucleotides with two different sequences (oligo A and oligo B in Figure 4) were attached to two gold electrodes (50 μm long). Then, these oligos were hybridized by λ-DNA containing two 'sticky ends' complementary to one of the two sequences attached to the gold electrodes. A DNA bridge between the electrodes is thus achieved. In the next step, silver ions were loaded onto this DNA bridge and were further converted to metallic silver by reduction (not shown in Figure 4). Remarkably, this micro-assembly containing a continuous, 'ultra-short' silver wire between the two gold electrodes was found to transport current. What is more interesting in the present context is the result of a control experiment. The λ-DNA bridge, in the absence of any silver ion deposition, was found to be practically insulating (resistance > 10^{13} Ω).

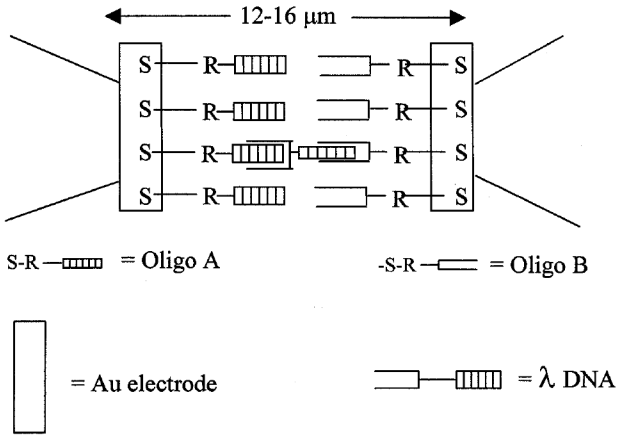


Figure 4. λ-DNA bridge constructed to devise a micro-assembly containing a continuous, ultra-short silver wire between two gold electrodes.

Debije *et al.*[44] used ionizing radiation (70 keV X-ray) to create electron–hole pairs within the oligodeoxynucleotides of varying lengths and base sequences and also within the calf-thymus DNA (thin films and lyophilized powder). Since the yield of trapped holes and electrons depends on the competition between electron–hole recombination and trapping reactions, it must also depend on electron transfer rate and distance. This situation is analogous to that employed by photochemical experiments described above, where a decreased yield in fluorescence was used to deduce a fast rate of electron transfer over a distance. The radical yields observed for calf-thymus DNA and for sequences d(CCTAGGG) and d(CTCGAG) were all high enough to conclude that there is no net charge migration within the duplex beyond 2–8 base pairs. Indeed, the yields within these duplexes were equal to those observed for crystals of α-methylmannoside, a lattice of sugar molecules that is an insulator, and are far different from those of conductors such as copper or graphite. Of additional interest in this regard is the fact that these experiments were conducted for samples at 4 K. If DNA had a metallic band structure, one should expect an increased conductivity at low temperatures. This phenomenon was not observed. In fact, the opposite was true!

Well, DNA is a semiconductor

This is the latest view based on the direct measurement of electrical conduction through DNA molecules[45]. In this study, direct measurement of electrical transport through a single, double-stranded 10.4 nm long, poly(G)–poly(C) DNA molecule connected between two platinum electrodes indicated large band-gap semiconducting behaviour (Figure 5). Deposition of a *single DNA molecule* across the two microelectrodes was achieved by a technique called 'electrostatic trapping' and was confirmed by scanning electron microscopic images. Nonlinear current–voltage curves that exhibit a voltage gap at low applied bias were obtained. This behaviour was true in both air and vacuum down to cryogenic temperatures. The voltage dependence of the differential conductance exhibited a peak structure. This is suggestive of the charge carrier transport being mediated by the molecular energy bands of DNA. However,

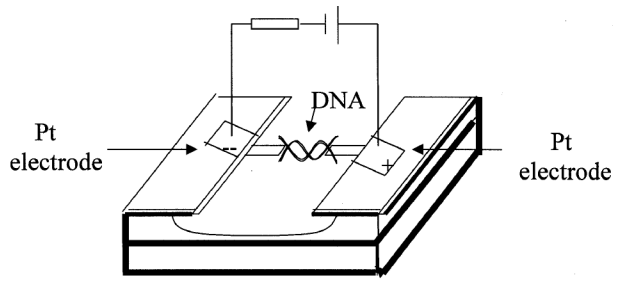


Figure 5. Schematic of the apparatus employed for the direct measurement of electrical transport through a single, double-stranded DNA molecule.

the nature of contact resistance between DNA and metal electrodes is not known. The contacts can be represented by tunnelling barriers in the absence of evidence for a good metallic contact. In the simplest hopping model, the DNA may be considered as a series of 30 very tiny (<3 Å) quantum dots (15 base pairs were used in a 10.4 nm long DNA wire). Each of these dots has a large charging energy and their series addition would lead to an even larger overall charging energy. This would lead to a Coulomb blockade voltage gap that is incompatible with the data. It was thus concluded that most of the observed gap probably originates from the offset between the Fermi level of the electrode and the molecular energy bands of the DNA molecule.

Conclusions

Is DNA a molecular wire? May be, may be not. It is still ambiguous. In our view, a more pertinent question to ask is, 'Is it necessary for DNA to be a molecular wire?'. The now well-known main biological roles of DNA involve information storage and transfer, and not electron transfer. There is no obvious biological function that requires DNA to be an effective conduit for long-range electron tunnelling. Indeed, X-ray structural data had already indicated that DNA repair photoenzymes, that rely on electron transfer mechanism, operate over short distances[46,47]. Nevertheless, it is important to note here that each experiment described above is an eye-opener for widening our knowledge about this ever-fascinating biomolecule. These experiments have also provided us novel molecular biological tools for cutting and repairing DNA. Sending in an electron through the molecule to the TT site rather than directly reaching this interior of the coiled DNA molecule is obviously a more feasible and desirable method. Similarly, the ability to cut a G site by photochemically triggering the scissoring action from a site far off from it, is equally appropriate. Other than these advantages, there seems to be no compelling need for DNA to act as a wire in its biological functions. On the other hand, experiments concerning DNA conductivity for use in abiological functions seem quite interesting. For example, these new experiments involving DNA ropes/single wires have yielded interesting templates for the fabrication of semiconducting micro/nano devices. The electrochemical studies involving DNA-modified electrodes have provided an opportunity to exploit the DNA-mediated electron transfer chemistry on a practical level in developing novel biosensors. It thus appears that the offshoots of this research area are more rewarding than its original objectives. And, that is the beauty of interdisciplinary science.

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