Mini-review for *Surface Science* John T. Yates Jr. special issue

DNA charge transport: Moving beyond 1D

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Abstract

Charge transport across novel DNA junctions has been studied for several decades. From early attempts to move charge across DNA double crossover junctions to recent studies on DNA three-way junctions and G4 motifs, it is becoming clear that efficient cross-junction charge migration requires strong base-to-base electronic coupling at the junction, facilitated by favorable pi-stacking. We review recent progress toward the goal of manipulating and controlling charge transport through DNA junctions.

Introduction

The determination of DNA's double helical structure enabled a profound appreciation for some of the molecular underpinnings of life [1]. In addition to the biological role of DNA, this remarkable molecule has been recruited to serve as a framework to create self-assembling, programmable nanoscale structures [2]. Indeed, the ability to exploit the logic of Watson-Crick base pairing sets the stage for the imaginative engineering of functional nanostructures and nanomachines. The aim of this mini-review is to describe recent progress toward controlling the flow of charge through three-dimensional constructs based on nucleic acids.

A cubic structure built from DNA was first reported in 1991 [3]. Around this time, synthetic and photophysical studies focused on DNA charge transport systems based on donor-bridge-acceptor motifs with π -stacked bases [4-7]. 25 years later, strategies are emerging to direct charge flow through branched DNA nanostructures. This mini-review focuses on selected recent discoveries in charge transfer through the kinds of DNA junctions that arise in the complex assemblies derived from DNA. We begin by describing early attempts to direct charge through DNA double crossover (DX) junctions and we also describe recent progress based on DNA three-way junctions (TWJ) and G-quadruplexes (G4).

It is well established that charge can move through DNA by superexchange [8], incoherent hopping [9-11], ballistic transport [12; 13], and intermediate mechanisms. Intermediate regimes include polaronic hopping [14; 15], flickering resonance (conformationally-gated resonant transport) [16], hopping with incomplete relaxation of the hopping intermediates [17], and multi-range hopping [18] (see Fig. 1). Single-step

superexchange is associated with bridge-mediated tunneling that displays rates with decay exponents of $\sim 1 \text{ \AA}^{-1}$. In contrast, multi-step hopping produces very weak distance dependent rates that drop approximately inversely with chain length. Fig. 1 summarizes some of these mechanisms.

Fig. 1. Three mechanisms relevant to DNA charge transport include (1) coherent bridge-mediated superexchange (SE) with very limited population of the transiting electron or hole on the bridge, (2) incoherent multi-step hopping with population of the charge carrier on the bridge, and (3) flickering resonance, with transient bridge electronic state energy alignment that allows coherent charge transit during the lifetime of the multi-state resonance.

Many well-characterized charge-transport (CT) experiments employ hole transport through DNA. In this regime, positive charge (holes) mixes dominantly onto purine nucleobases (guanines and adenines) [10; 19], producing real (hopping or FR) or virtual

(tunneling) transport. Since guanine and adenine are more readily oxidized than the pyrimidines, purines are believed to dominate hole-transport. Electron transport through reduced (real or virtual) states is thought to be mediated by pyrimidine nucleobases (cytosines and thymines). Thus, sequences can be designed to direct electron and/or hole flow [7; 20; 21].

Hopping mechanism hole transport has attracted attention in the context of multi-strand and cross-strand DNA CT junctions. In systems of this kind, the cross-junction interaction may establish the overall rate-limiting step. Thus, research on this family of structures has relied largely on attempts to increase the electronic coupling through the junctions.

DX Junctions

Double-crossover (DX) junctions (Fig. 2) attracted early interest in DNA charge transport [22-25]. This junction architecture consists of backbone crossovers between two DNA helices, separated by an integral number of DNA turns [19]. The DX junctions cause pairs of DNA helices to run roughly parallel to one another, and these junctions are used to assemble 2D and 3D DNA nanostructures [18,20].

The electronic properties of the DX junction are of considerable interest in the context of DNA electronics. In 2000, Barton et al. explored the ability of charge to flow between two DNA helices joined by DX junctions [26]. Their experiment injected a hole into one of the helices, while a second helix contained a triple guanine (GGG) hole trap. Hole trapping at guanine is detectable through the chemical conversion of the G into 8-oxo-G. No G to 8-oxo-G conversion was found in the target helix, indicating that charge transfer to

that helix did not take place with high yield. That is, the two helices joined by the DX junction were electronically isolated.

We recently simulated the DX structures studied by the Barton group [26] and related systems. An idealized all-atom model of the DX junction was built (Fig. 2), and analysis of the base-to-base distances in the model found that the placement of the GG/GGG hole hopping sites dictated by the experimental requirements of ref. [26] likely disfavors hole hopping between the sites because of weak electronic coupling between the sites. We hypothesize that the GG sites in the charge-injection helix and the GGG sites in the target helix could have been placed in closer proximity to enhance hole transport. Room-temperature molecular dynamics (MD) simulations were conducted to test this hypothesis. One simulation included the DX junction with the sequence from the earlier study (“Caltech” structure, Fig. 2), and an alternative theoretical sequence that has a shortened distance between the GG and GGG hole trap sites (“Duke” structure, Fig. 2).

10ns-long classical molecular dynamics simulations found a significant degree of conformational fluctuations in the “wings” of the DX junctions for both sequences (Fig. 2). The root-mean square deviation (RMSD) of the wings from their initial geometry was in the range of 4-8 Å, while the RMSD of the stable DX junction core, located between the two backbone crossover sites, was found to be about 1.5 Å. Thus, no charge transport between the GG/GGG sites placed in the DX junction wings would be expected since the conformational changes exhibited by the wings results in a significant separation between the GG and GGG sites.

Fig. 2. Simulations of structural dynamics for the DX junction structures. Left: the idealized molecular structure at the start of the MD simulation. Center panels: the root mean square deviation (RMSD) of the different portions of the DX junction from the initial structure for the two simulated sequences. The colors of the DX core and the two wings are indicated in the inset. Right: The structures of the DX junction with the “Caltech” and “Duke” sequences after 10ns of MD simulation. The guanine bases are shown in red, and the adenine bases are shown in blue. The larger spheres indicate nucleobases with an electronic coupling computed to the bases on the other helix of the DX junction above a minimal cutoff value.

The distance between the GG and GGG sites located near the core of the DX junction in both sequences remained relatively stable throughout the simulations. The inter-helix electronic couplings for each pair of purine nucleobases, between both guanines and adenines, in the two helices were calculated using the INDO/s method as implemented in the CNDO software [27; 28]. The coupling between the hole states on the two nucleobases was approximated by the HOMO-HOMO coupling, calculated from the cross-terms of the

Fock matrix as described in ref. [29]. The cross-terms decreased approximately exponentially with distance and fell below the numerical precision of CNDO output for interatomic distances greater than 15-16 Å. Such couplings were considered inconsequential.

Throughout our MD trajectories, only a few purine-purine pairs yielded consequential inter-helical couplings. In the “Caltech” structure, 4 purine-purine pairs showed significant couplings for less than 8% of the simulation time. The maximum computed coupling was 2.4×10^{-7} eV (*cf.* Table 1). None of these consequential couplings were between G bases. The “Duke” sequence had 13 purine-purine pairs with consequential inter-helical couplings up to 11% of the time. The largest computed coupling was 17.5×10^{-7} eV (*cf.* Table 1). Half of those couplings were between G bases belonging to the designed GG/GGG sites.

The DX DNA sequence	$N_{V>0}$	$V_{max},$ $\times 10^{-7}$ eV	$V_{ave},$ $\times 10^{-8}$ eV	$\delta V,$ $\times 10^{-8}$ eV	$P_V, \%$
‘Caltech’	4	2.4	0.1 – 1.1	1.0 – 3.4	0.5 – 8.5
‘Duke’	13	17.5	0.4 – 4.4	0.4 – 4.2	0.4 – 11.3

Table 1. Statistics for the helix-to-helix electronic couplings calculated in the “Duke” and “Caltech” DX simulations. The columns show: $N_{V>0}$, the number of pairs of purine bases that exhibited consequential electronic coupling in the simulation; V_{max} , the maximum inter-helical electronic coupling computed in the simulations, V_{ave} and δV , the mean square

magnitudes and standard deviation of the inter-helical electronic coupling. P_V is the percentage of time during which a purine-purine nucleobase pair exhibited a consequential electronic coupling. For V_{ave} , δV , and P_V , the data correspond to the ranges of values computed for the different purine-purine pairs in the two simulations;

The increased values of the electronic coupling in the “Duke” structure agree with the smaller purine-purine distances, compared to the “Caltech” structure. That is, the MD-average distances between the G bases with consequential inter-helical couplings were in the range of 14.5-15.5 Å for the “Duke” structure, while the average distance between the G bases of the only G-G pair with consequential inter-helical coupling in the “Caltech” structure was 16.5 Å.

Thus, our analysis indicates that the electronic couplings and, hence, the expected rate of charge hopping, between the DX helices in the “Caltech” structures could be increased by sequence redesign. However, the predicted increase in electronic coupling should be put into perspective. The strongest couplings found in both structures are on the order of 10^{-7} eV which is 5-6 orders of magnitude less than the nearest-neighbor base-to-base coupling in B-DNA ($\sim 10^{-2} - 10^{-1}$ eV [30]). Certainly, our calculations could underestimate the inter-helical coupling values, given the approximate nature of the semiempirical methods in this very weak coupling regime, as well as the simplification of the nucleobase environment in the analysis (lacking the DNA backbone and the solvent). Indeed, accounting for the environment could increase the calculated coupling by values

[31]. Nonetheless, the inter-helical couplings are expected to remain several orders of magnitude smaller than the intra-helical interactions.

Based on the above analysis, charge transport within the same DNA helix seems to be much more likely than inter-helical charge transfer, and the inter-helical current through the DX junctions is likely to be negligible under most conditions, regardless of sequence. Other DNA constructs, like the three-way junctions and the G4 motifs discussed below, may be better suited for applications that require charge flow from one DNA strand to another.

DNA TWJs

The appeal of the DX structures explored above is that they could enable the control of charge flow in two and three dimensions. Establishing motifs that direct charge in higher dimensions could enable the future development of novel charge combiners, splitters, switches and gates.

Radical cation transport in three-way junctions (TWJs) was studied by Schuster and coworkers a decade ago [32]. Anthraquinone (AQ) oxidants were linked to the terminus of one arm in a TWJ, and strand cleavage was found in all three arms. Related experiments found that the radical cation was not able to migrate across a DX junction, suggesting that cross-junction migration requires pi-stacking (or at least transient pi-stacking) at the junction. Recent experimental and theoretical studies support the viability of engineering pi-stacking to facilitate charge flow in DNA TWJs [33; 34].

Lewis, Wasielewski and co-workers recently showed that charge can transfer through DNA 3-way junctions (Fig. 3) [33; 34]. A hole donor stilbene (Sa) on the lower branch of a DNA TWJ junction is photoexcited and this species can transfer a hole via the nucleobase stack to a hole acceptor stilbene (Sd) on the upper branch. By engineering an extended guanine pathway, charge can be guided either to the left (for **1a** and **1c**) or the right (for **1b** and **1d**) branch of the TWJ. Charge separation times and quantum yields were measured using transient absorption spectroscopy. The quantum yields for these DNA TWJs are relatively low compared to double-stranded DNA with similar sequences and donor-acceptor distances, while the charge transfer time is of the same order of magnitude. The charge transfer is not completed in 7 ns, suggesting that electron transfer (ET) is gated, possibly by conformational fluctuations.

Fig. 3. Structures of DNA TWJs. (**1a,1b**) DNA TWJs with one extended guanine pathway and no polyethylene glycol (PEG) linking group. (**1c,1d**) DNA TWJs with one extended guanine pathway with one PEG linking group.

Theoretical studies of the TWJ structures find that conformational gating controls the charge flow [34]. Molecular dynamics (MD) simulations indeed found that the junctions undergo large-scale conformational changes on the nanosecond time scale. The

simulations found that two of the three DNA strands can form a B-DNA like stack, while the third branch is located nearly perpendicular to the stack, thus forming a “T” structure, see Fig. 4 [34].

Fig. 4. (a) Structure of a DNA TWJ (**1d**) with a PEG linker (**X**). (b) Typical snapshot of a T-shaped conformation. Backbones, linking group, and hydrogens are removed for clarity. (c) Upper: Coupling between Gs at the junctions (labeling as in (a)). Once the π -stacked geometries form, the cross-junction coupling is strongly enhanced. Bottom: Time evolution

of the angles between the three DNA branches is shown with colors as in (a). This structure is locked in the T-shaped geometry after ~ 2 ns. Figure and caption adapted from [34].

For TWJ structures without polyethylene glycol (PEG) “extenders” (**1a** and **1b**), the junction region is too constrained sterically to accommodate stable “T”-configuration base stacking [35-37]. Transient “T” stacking enhances the cross-junction coupling by one order of magnitude, with absolute value averaging to $\sim 10^{-4}$ eV, three orders of magnitude less than the nearest-neighbor coupling in B-DNA. Adding a PEG linker to the junction in structures **1c** and **1d**, relieves the stress and enables the formation (in our simulations) of a “T” conformation. This conformation can persist for more than 25ns, as nucleobase stacking stabilizes the conformation. For structures with PEG linkers, the cross-junction coupling in a “T” conformation is around 0.1 eV, similar to the nearest-neighbor coupling in B-DNA. Peak couplings several fold larger than the average were computed (cf. Fig. 4c), corresponding to rare conformations where swinging motion of the branches brings the bases at the junction to a shorter distance than would be expected in B-DNA. These simulations and experiments point to a significant role for conformational fluctuations and pathway switching in DNA 3WJs.

G4 motifs

G-rich DNA strands can associate to form G-quadruplexes (G4) [38-40], which are stabilized by ions surrounded by the DNA bases. The strand directions (5'-3') in G4 can be parallel or antiparallel. Different combinations of strand directions establish specific G4 constructs [41]. G4 appears in both telomeric and non-telomeric DNA, playing an

important role in biological function [42-44]. G4 is thermally more stable [45] and more conductive than DNA duplexes because the inter-strand interactions in G4 provide more charge transport pathways [46]. Increasing attention has focused recently on assembling molecular electronic devices based on G4 and modified-G4 motifs because of their stability, programmability, and conductivity. Porath et al. measured currents through 30-70 nm long G4 (all parallel strands) with voltage biases ranging from -5 V to +5 V [47]. They observed small currents (2pA) for voltage biases less than 3-4 V, but the current jumps to tens of pA for bias beyond ± 5 V, and the current depends weakly on the G4 length. Similar measurements were conducted on dsDNA, and no current was found for voltages up to ± 8 V at similar lengths, suggesting G4 motifs are more conductive than dsDNA. Sen and coworkers designed branched nucleic acid structures by extending the G4 ends with DNA duplexes [48; 49] (see Fig. 5). Holes were injected into one branch (UV irradiated AQ, see Fig. 5 (b)) and moved to other branches via the G4 block. Hole conductance in each direction was monitored by G oxidation in each duplex branch (G_{AQ} , G_X , G_Y , G_Z in Fig. 5 (b)). This kind of charge splitter/combiner moves beyond the linear design motifs in most DNA and G4 charge transfer experiments and serves as a possible building block for future molecular charge transfer structures. As indicated in Fig. 5 (a), the presence and removal of the K^+ and Sr^{2+} ions reversibly controls the formation and dissociation of the quadruple helix in the middle G-rich region. Without K^+ and Sr^{2+} ions, the central G-rich region consists of four loose single strands with weak G pi-stacking, preventing holes from transporting to other branches. Adding K^+ and Sr^{2+} creates well-stacked G-tetrads, which are effective hole conductors. Indeed, G oxidation was observed on the X, Y, Z branches of the structures. K^+

and Sr^{2+} ions are the control elements in this electronic structure to enable switching between the “on” and “off” states.

Fig. 5. Design of twDNA [43]. (a) Design and conception of a prototypical twDNA. Four single-stranded DNAs, a, b, c, and d, self-assemble to give twDNA, made up of a guanine-rich core and four duplex arms: AQ, X, Y, and Z. In the absence of K^+ or Sr^{2+} ions (left), the four strands of the core are expected to have a loose single-stranded character. In the presence of K^+ or Sr^{2+} ions, however (right), the guanine-rich core should twist to form a quadruple-helical (right-handed) G-quadruplex, stabilized by K^+ or Sr^{2+} ions bound to the cavities between successive quartets. (b) The specific twDNA used in this study. Altogether, five single-stranded DNA oligomers are used, with the base-pairing complementarities shown. A short DNA strand (AQ-P) derivatized with anthraquinone at its 5' terminus forms a portion of the AQ arm. Strand a has two sets of specifically positioned GG dinucleotide “reporters”; the guanines closest to the 5' end of these GG sequences are labeled G_{AQ} and G_{X} . Likewise, strand c has two reporters, with the guanines closest to the 5' end labeled G_{Y}

and G_Z. (Adapted from Ref. [48])

Studies of G4 pi-stacking indicate that the motif can be more effective than duplex DNA for conducting current. G4 layers can be extended by attaching duplexes, creating multi-branched structures that could establish charge splitter/combiner style function with function switched by the presence of specific counter-ions.

Conclusions and perspectives

The rich self-assembly chemistry of DNA enables the creation of junctions with a diversity of function and control beyond the possibilities offered by linear motifs. Tremendous effort has been invested into developing wires, charge splitters/combiners and charge switches, based on DNA chemistry, and an impressive level of structural diversity and functional richness is emerging.

Early lessons learned in DX junctions have exploited in DNA TWJ and G4 motifs. The idea of using DNA base stacking to establish electronic conduits among G or multi-G hole hopping sites continues to provide a useful design paradigm. Recent studies of DNA TWJs indicate that charge flow through the junction is conformationally gated; conformational flexibility needs to be engineered into the junctions to enable the conformational assembly of strong base-to-base electronic interactions pathways. Moreover, designing specific purine pathways allows one to guide holes through the junctions. These concepts have led to the recent demonstrations of charge splitter/combiners prototypes based upon DNA architectures. Progress in charge transfer through G4 layers and 4-way G4 junctions (Fig. 5) may one day lead toward self-assembling circuit elements.

Acknowledgment and Dedication.

This paper is dedicated to the memory John T. Yates, Jr., our joyous colleague, collaborator, and friend of many decades who went to great lengths to engage with our team in all manner of scientific discussion, collaboration, and global adventures. This research is supported by ONR Grant N00014-11-1-0729 and by NSF Grant DMR-1413257.

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