Energy Transfer Logic on DNA Nanostructures: Enabling Molecular-Scale Amorphous Computing

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Abstract

Molecular-scale amorphous computing may enable novel biological applications. However, current silicon-based fabrication techniques are unlikely to scale to the sizes required for compatibility at the cellular level. Therefore, significant technological advances are necessary to deliver on the potential of this new computing paradigm. This paper presents our initial steps toward developing a technology that can achieve molecular-scale amorphous computing. The theoretical foundation of our proposed technology is resonance energy transfer (RET) between small fluorescent molecules. For RET to occur these molecules must be placed 1nm-10nm apart. DNA self-assembly provides a low-cost, scalable fabrication method that is compatible with spacing and sizes required by molecular-scale computing. We experimentally demonstrate the fabrication and operation of a resonance energy transfer based OR-gate. This first step is encouraging, but many obstacles remain. Therefore, this paper also discusses the overall prospects for this approach to become a complete technology.

1. Introduction

The concept of amorphous computing [1] is predicated on the existence of large numbers of inexpensive nodes with limited computational ability, limited memory capacity, and limited communication range. The set of potential applications for amorphous computing is vast, ranging from smart paint to *in vivo* computation for biological applications.

Biological applications require nodes on sizes compatible with molecules or cells. Unfortunately, creating such devices using conventional top-down fabrication techniques is costly and increasingly complex. Creating sophisticated circuits by placing individual atoms requires more energy and time than exploiting chemical self-assembly techniques. Furthermore, self-assembly enables fabrication through composition and hierarchies.

Different types of molecules can be fabricated independently using the most cost-effective method for each type of molecule. Larger molecular motifs can then be created through the composition of heterogeneous molecules. The final step for cost-effective fabrication is to employ hierarchical methods.

A scalable, cost-effective molecular-scale fabrication technique is necessary, but not sufficient to achieve molecular-scale computing. The fabrication method must be accompanied by the appropriate molecular-scale devices that enable computation. These devices must meet certain requirements to provide the appropriate abstractions for computing. The requirements include, but are not limited to: 1.) gates: nonlinear modulation of signals, 2.) wires: linear signals, 3.) insulators, 4.) signal restoration: energy supply, 5.) circuits with feedback, and 6.) input/output.

The goal of this paper is to map out one potential path toward achieving molecular-scale computing. The specific fabrication method we exploit is DNA-based self-assembly and presented in Section 2. The theoretical basis for our active devices is Resonance Energy Transfer (RET), and described in Section 3. Preliminary results for an OR-gate are presented in Section 4 and we describe the prospects for these technologies in Section 5 before concluding.

2. DNA Self-Assembly

DNA is an attractive substrate to investigate for applications in molecular-scale amorphous computing. The precise binding rules of DNA enable the creation of nanostructures with minimum pitch on the order of a few nanometers. These nanostructures can be used to place and interconnect nanoscale components with molecular-scale precision. Thus, DNA self-assembly is an enabling technology for new computing paradigms.

The challenge in creating DNA nanostructures is to specify the appropriate DNA sequences such that the desired structure (geometry) forms and is thermodynamically stable. To meet this challenge, DNA self-assembly can exploit the common technique of composing a small set of relatively simple pieces to create more sophisticated structures. The structure is composed through a hierarchical assembly of motifs. Ultimately, the final assembly step combines all motifs to form a grid structure.

2.1. Nucleotides, Oligos, and the Helix

DNA is widely studied in the context of molecular genetics. However, we are concerned primarily with DNA as a substrate for fabricating nanostructures, and thus provide a brief review in this context.

DNA's basic building blocks—called a nucleotide (nt)— contain nucleobases. The common bases are adenine (A), guanine (G), thymine (T) and cytosine (C) and are arrayed to create the so-called single-stranded DNA molecule. Single strands can wrap around each other to form double strands in the well-known helical structure, or double helix.

The double stranded DNA structure is stable when the pairwise nucleobase interactions (or base pairs) are "complementary", i.e., if A pairs with T and G pairs with C. Under these conditions (in the "B-form" helix) each base pair (bp) is approximately 2 nm wide (diameter of the helix) and on average 0.34 nm away from adjacent bases. The helical twist of the two strands is such that a full turn occurs between every 10th and 11th base. Further, the stability of this interaction is only approximately linear per base and depends on neighboring mismatch or complementary interactions [2]. The stability and exact dimensions, orientation, and form of the nucleobase interactions depend on several factors including the pH of the solution and microenvironment of the DNA.

Thermodynamics

The central theme in the use of self-assembly for nanoscale fabrication is the application of external control over an otherwise spontaneous reaction to direct its outcome [3]. This control directs the assembly of materials into structures that are interesting and relevant to a target design problem. In the context of computer system fabrication the self-assembly is used to direct the formation of switching devices (e.g., transistors and wires) to create logic circuitry, memory, and I/O interfaces. The temperature of the reaction volume (i.e., the solution) is a simple control in DNA self-assembly. The melting temperature (T_m) of a DNA strand is the temperature at which exactly 50% of the single strands in solution are bound to their complements. The T_m of two strands is dependent on their sequences and the degree to which they are complementary. This simple picture is complicated by the introduction of multiple sequences in solution. Further, the time evolving dynamics of these interactions are still under study [4].

Sequence Design

A strand of DNA obeys certain thermodynamic behavior, most importantly that double strands form at temperatures below the T_m of the constituent single strands, and this interaction can be complex if multiple unique (sequences) DNA strands are in solution. Specification of the strand sequences provides external control over the self-assembly process (through temperature control) and determines the formation of structures (through complementarity).

Sequence design is important because it determines many aspects of the target DNA nanostructure (e.g., geometry and stability). Therefore it is critical to have good methods for choosing sequences. One approach is to use abstractions to create increasingly sophisticated structures.

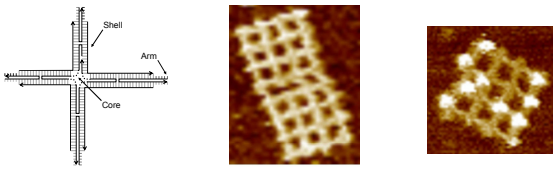
2.2. DNA Motifs

Complex designs are often created using a relatively small set of common building blocks—called motifs. DNA self-assembly can exploit this same design principle to hierarchically create more sophisticated aperiodic structures. For DNA there are many possible motifs, however we focus on only a few in the context of our energy transfer logic. Motifs include junctions that enable three or more double stranded helices of DNA to interact and thus form specific structures (e.g., a triangle, a corner, etc.) Another important motif is a single strand of DNA protruding from a double stranded helix—called a sticky-end.

Two motifs with complementary sequences on their sticky-ends will bind to form a composite motif. These composite motifs may also have embedded sticky-end motifs and thus can also bind with other composite motifs to form another, larger, composite motif. This results in a hierarchical structure for motifs.

The cruciform motif is composed from three smaller motifs: a core, four shells, and four arms (each arm contains two 5-nt sticky-ends). Figure 1 shows: (a) a schematic of the cruciform motif, (b) an AFM image of a hierarchical 8x4 grid, and (c) a

protein-patterned nanostructure each developed in our laboratory using methods described elsewhere [5].



(a) (b) (c)

Figure 1 – (a) Schematic of a cruciform motif, (b) an 8x4 grid, and (c) a protein-patterned grid. Each cavity is 20nm on a side.

Although motifs provide an easy abstraction for reasoning about DNA nanostructures, there are many potential issues related to sequence dependent physical (and structural) properties. For example, the above cruciform motif has a slight curvature in three-space, thus composite motifs formed with this motif must account for this curvature to ensure the desired final geometry is formed. Furthermore, the structural properties of DNA sequences can create strain in the final structure which can prohibit proper formation.

Related DNA Nanostructures

DNA and RNA have gained popularity as a material system for creating complex, aperiodic nanostructures due to the ease with which these materials can be synthesized and controlled [5-10]. The pioneering development of the DNA crossover enables the rational design and synthesis of structurally rigid molecular complexes from DNA [11-16]. Such methods rely on the programmability of oligonucleotide interactions and leverage the control that complementary nucleotide sequences exert over the thermodynamics of the assembly process. Recent advances in this field have produced many examples of periodic planar DNA lattice [15, 17-20]. However, to form aperiodic 2D structures these methods require the number of unique DNA sequences (and therefore cost) to scale with the area of the structure or the development of algorithmic self-assembly [21, 22]. To overcome such limitations a low-cost hierarchical method to fabricate large molecular weight, aperiodic structures by DNA self-assembly must be employed [23].

Hierarchical DNA self-assembly provides the fabrication characteristics (low-cost, nm resolution) necessary for molecular-scale computation. However, this fabrication substrate must be complemented by suitable molecular-scale devices. The following section describes the theoretical foundation for one potential set of optical devices.

3. Resonance Energy Transfer

One of the more important challenges for molecular scale devices is interaction with the external macroscale. We propose using photon-molecule interactions to create logic systems. Photons routinely interact with molecules many times smaller than their wavelengths. The chlorophyll in every plant absorbs photons from the sun and transfers that energy into the cell. Beyond the potential for harvesting solar energy, energy transfer can be used to convey information along well defined pathways. Resonance energy transfer (RET) is the underlying mechanism that couples energy from a source (donor) to its destination (acceptor). The donor and acceptor are molecules—*called chromophores*—and, by analogy, resemble the current rectification of a PN diode when undergoing energy transfer since the excited-state energy of the donor transfers to the acceptor but not vice versa. RET is extremely sensitive to the separation between donor and acceptor and requires distances of 1-10nm between chromophores. To understand the sensitivity of RET to distance we begin by defining the process. Fluorescence resonance energy transfer (FRET) which can probe molecular scale phenomena that indirectly change the distance between the donor and acceptor is described by

$$D + A \xrightarrow{h\upsilon_1} D^* + A \xrightarrow{RET} D + A^* \longrightarrow D + A + h\upsilon_2$$

The donor (D) is first excited by the absorption of a photon with energy $h\nu_1$ denoted by D*. The exited-state donor energy is transferred to the acceptor (A), which becomes exited (A*) through RET and by spontaneous decay of the excited-state A* to A emits a photon with lower energy $h\nu_2$. The transition energy diagram for this process is shown in Figure 2. Absorbed energy (1) can decay radiatively (2) or non-radiatively (2a) to produce a photon (2b) by FRET.

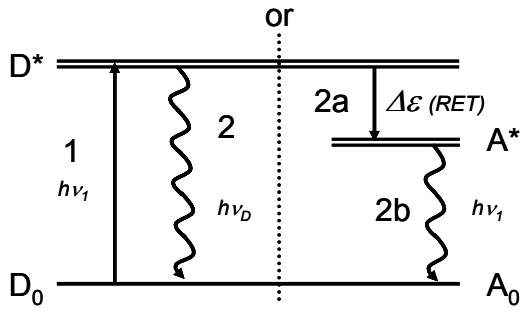


Figure 2 – Transition energy diagram for FRET.

The rate of energy conversion from $h\nu_1$ to $h\nu_2$ is directly proportional to the strength of the RET

coupling between the chromophores. The rate constant for this process was first derived by Förster based on classical charge dipole-dipole coupling and quantum mechanics, shown in equation 1 [24].

$$k_{RET} = k_D \left(\frac{R_0}{r} \right)^6 \qquad (1)$$

where k_D is the emission rate for the donor without RET to the acceptor, r is the distance between the acceptor and donor, and R_0 is the Förster radius, or distance at which RET occurs with 50% efficiency.

The Förster radius is a given for a pair of chromophores (due to their molecular structures and orientation) and dependent on the spectral overlap between the emission and absorption bands of the donor and acceptor, respectively. E.g., pairs with little spectral overlap will have small Förster radii. The efficiency of the energy transfer between donor and accepter (Φ_T) can be defined and when combined with equation 1 yields

$$\Phi_{T_{D \to A}} = \frac{k_{RET}}{k_D + k_{RET}} = \frac{{R_0}^6}{r^6 + {R_0}^6} \qquad (2)$$

This transfer efficiency is typically <100% because several mechanisms compete for the relaxation of the donor's excited-state energy. Radiative decay, or simple fluorescence, is the re-emission of the absorbed energy, typically at a lower energy. The excited-state energy may undergo inter-system crossing and decay through any number of slower processes that will not couple to the acceptor. Non-radiative thermalization of the excited-state energy will lead to simple local heating with no energy transfer to the acceptor. Despite theses degenerate pathways, Φ_T can approach 100% at separations where $r << R_0$ due to the strong (r^{-6}) dependence of k_{RET}.

To be useful for the transfer of information in circuits, RET must permit energy to transfer between multiple pairs of donors and acceptors across long distances. Since Φ_T is the per step transfer efficiency, a cascade of n chromophores will have a total efficiency described by equation 3.

$$\Phi_{T_n} = \prod_{i=1}^{n} \Phi_{T_{D_{i-1} \to A_i}} \qquad (3)$$

Clearly, when each donor-acceptor pair has identical transfer efficiency the total cascade efficiency is simply Φ_T^n, which scales poorly in the length of the cascade, n.

Fortunately, energy migration (EM) observed between ensembles of donors has no impact on the probability of radiative or non-radiative decay if the donors are sufficiently close. Thus, the excited-state energy of a donor can diffuse within the ensemble with the same probability of de-excitation as an individual donor until it finds an acceptor. The implication is that EM along arrays of identical chromophores can extend the distances over which RET may take place well beyond the limits of the Förster radius. The combination of RET with EM serves as the foundation on which to build molecular devices for computing.

In theory, RET and EM alone are sufficient to implement wires, OR-gates (akin to a wired-OR), or possibly AND-gates. However, they are not sufficient to restore signals from losses, to invert signals, or to generate feedback from the end of a cascade to its beginning. These challenges have been addressed by a number of studies aiming to demonstrate non-linear optical phenomena outside of the context of computer systems.

4. Preliminary Results

This section presents the current status of our ongoing efforts to fabricate molecular-scale amorphous computing nodes. We provide experimental results that demonstrate progress toward scalable manufacturing using DNA self-assembly, energy transfer wires and OR-gates.

4.1. Scalable molecular manufacturing: DNA self-assembly.

We extend our prior work for creating aperiodic DNA self-assembled nanostructures [5, 8]. Since each motif is assembled from five common and four unique oligonucleotides in an individual vessel, each grid can be independently modified and can create arbitrary patterns as shown in Figure 3.

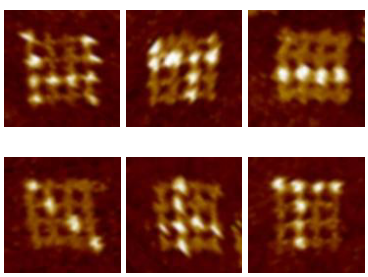


Figure 3 – AFM images of streptavidin patterned 4x4 DNA grids.

The grids are selectively functionalized with streptavidin by using a biotin-functionalized core-oligo during the annealing of the component motifs and introducing free streptavidin afterward.

The cost of our technique scales with the number of unique oligos in the final nanostructure (e.g., 69 oligos in this case). The origami method [10, 25] suffers from this scaling law as well but in principle could use the methods outlined here to reduce the cost of larger multi-shape structures.

Regardless of the method employed to assemble the basic motif we must bypass the requirement of a unique set of sticky-ends required to assemble a structure unambiguously and reuse strands to decouple the cost of a structure from the linear dependence on its area. Thus, such a method is scalable in terms of the size of the nanostructure that can be fabricated from a finite DNA sequence space. In the limit, a single oligonucleotide sequence might be used to form large supramolecular structures [26]. However, to retain maximal programmability we use multi-strand designs with a variable degree of re-use. Strand reuse is exploited to some extent in both methods [5, 10, 25] but had not previously been demonstrated as a viable alternative for assembling large aperiodic structures.

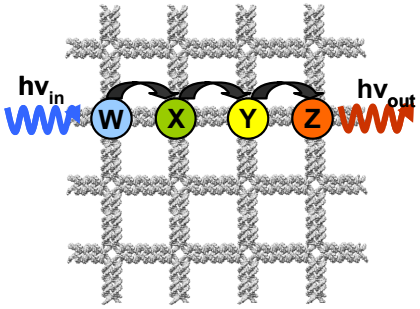


Figure 4 – Schematic of a RET wire on a DNA grid. A photon with energy hv_{in} excites W and is transferred through the wire to Z which emits a photon with energy hv_{out}.

4.2. Energy transfer wires

One-dimensional multi-chromophore cascades have been demonstrated to carry excited-state energy over distances ~13nm with >90% efficiency on linear DNA [27]. DNA nanostructures present the unique opportunity to go beyond 1D structures and organize 2D or 3D wires.

Figure 4 illustrates a possible 2D energy transfer wire. Chromophore W (the donor) can be excited by a photon from the far-field and, through RET, couple the energy to X, then to Y, then Z, and ultimately lead to an emitted photon with energy hv_{out}.

Figure 5 is the transition energy diagram for the four chromophore cascade from Figure 4.

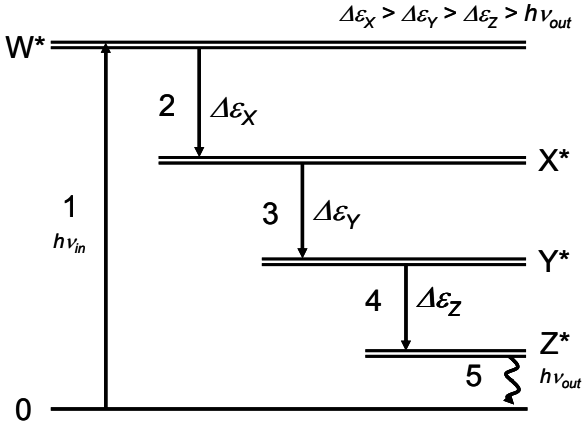


Figure 5 – Transition energy diagram for a four chromophore cascade. Each chromophore begins in the ground state (0) and is sequentially excited (1-4) until a photon is emitted by Z^* (5).

The difference in excited-state energies between the chromophores must obey the inequality

$$\Delta\varepsilon_X > \Delta\varepsilon_Y > \Delta\varepsilon_Z > h\upsilon_{out}$$

This inequality ensures that the input energy will eventually be transferred to the end of the wire. The same competing mechanisms for RET have influence during each stage in the wire and will result in "leakage" of the energy in the form of prematurely emitted photons and thus a source of signal loss.

While photonic wires are useful in transferring information, they do not provide computation. The next section details our progress in assembling energy transfer logic gates that can perform computation on information delivered by energy transfer wires.

4.3. Energy transfer OR-gate

We use access points on the DNA scaffold to construct an energy transfer OR-gate. There are three chromophores, two for the input signals (OG and PO) and one for the output signal (RR) attached to the scaffold as shown in Figure 6.

OG's absorbance peak is at 488 nm, which we use as the excitation for the first input. PO's absorbance peak is at 400 nm which we use as the excitation for the second input.

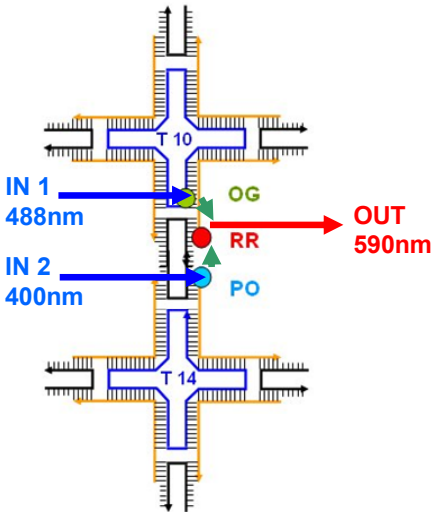


Figure 6. Schematic of the energy transfer OR-gate.

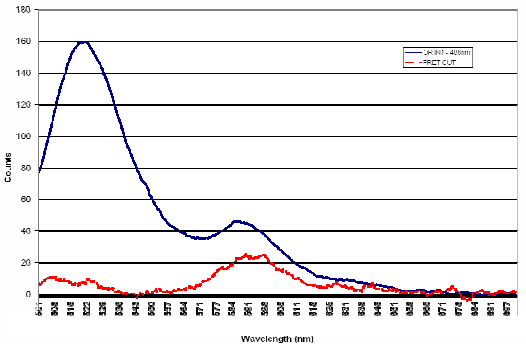


Figure 7: Observed output from the OR-gate under 488 nm excitation (IN 1). Solid line is uncorrected data, dashed line is corrected.

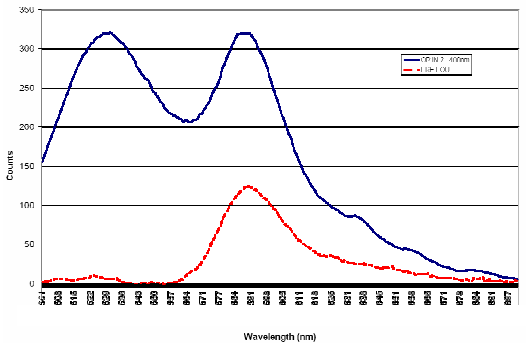


Figure 8: Observed output from the OR-gate under 400 nm excitation (IN 2). Solid line is uncorrected data, dashed line is corrected.

We experimentally assembled scaffolds with the attached OR-gates as described above. A fluorometer measured the output of the assembly in the 300-800 nm range under various input conditions. Input excitation was generated by a custom dual-beam excitation source. We estimate that the sample contained ~10^{12} gates and the raw spectral response for 488 nm (IN 1) and 400 nm (IN 2) excitation is shown in Figure 8 and Figure 7 (continuous line), respectively. We separate the specific contribution of the RR chromophore due to FRET from the excited input dye using the method in [28] (dotted line). This is necessary since our unprocessed spectra also include background fluorescence, mostly from the input chromophores decaying through a degenerate radiative pathway.

These results show the capability of the assembled gate to transfer excited-state energy from either of two distinct inputs to the same output, characteristic of an OR-gate. Future work will investigate the impact of simultaneous input excitation to characterize the linearity of the RET process.

5. Prospects for Energy Transfer Logic

The preliminary work described in the previous section provides encouragement for further investigations. However, to develop a complete energy transfer logic set further research is necessary to optimize the wires and OR-gate, develop an inverter, nonlinear signal modulation, signal restoration, insulators, internal circuit feedback, and input/output.

5.1. Optimized wires and OR-gate

The efficiency of RET on the grid is highly dependent on the distance between neighboring chromophores. Techniques in DNA motif design can be used to decrease the spacing between chromophores and improve transfer efficiencies.

There are also experimental and theoretical data showing that the RET range can be extended by nearby noble metal islands or films. Since DNA grids can be metallized with noble metals [18], we can expect selective grid metallization to improve the efficiency and/or range of grid-bound RET wires.

Unlike insulated metal wires, energy transfer wires may leak, where chromophores internal to the wire fluoresce and emit a photon instead of transferring the energy down the wire. This leakage can be minimized by controlling the distance and dipole orientation of the chromophores so that for each chromophore pair the probability of resonance transfer is much higher than that of fluorescence.

Another potential difficulty with RET is photo-bleaching of chromophores which can lead to permanent failure. The rate of photo-bleaching can be significantly reduced by controlling the environment (especially by removing oxygen) as well as by selecting chromophores that are more chemically stable.

5.2. Non-linear modulation of signals

The so-called molecular photoswitches are promising candidates for nonlinear signal modulation. The potential of such molecular switches as optical memory has been noted before [29] and recent work has demonstrated reliable optical switching in a Green Fluorescent Protein (GFP) mutant named Dronpa [30]. This molecule can be switched between a bright state (in which it fluoresces) and a dark, state (with no fluorescence). Further, recent work [31] shows that compound structures made of single chromophores bound to gold nanoparticles exhibit transfer properties that can be modulated by weak electric fields. All of these are promising candidates for optical gating and power restoration within the context of energy transfer logic.

5.3. Insulators

A critical aspect of any dense computational technology is the prevention of signal interference between independent devices and wires. In conventional CMOS, oxide and minimum physical separation are used to prevent crosstalk. Our system can employ a similar physical separation by placing molecules at fixed distances from one another. Specifically, since RET degrades as $\sim r^{-6}$ the coupling between independent RET wires can be reduced to negligible levels by a separation of $\sim 10 \cdot R_0$.

5.4. Signal restoration and feedback

The transition energy diagram in Figure 5 illustrates the discrete steps in transition energies along a RET wire. Each step proceeds downhill in energy and at the end of a cascade the last chromophore can only emit a photon. However, a complete technology requires feedback from outputs to inputs to implement cross-coupled logic gates or finite state machines.

Signal restoration from long wavelengths (low energy) to short wavelengths (high energy) requires additional energy. For RET this extra (restorative) energy can come from an external supply that blankets the system with infrared (IR) photons of the necessary energy to excite Z* *energetically backward* to an adjacent chromophore. The specific energy of the IR photons depends on the detailed band structure of the two chromophores but in principal should be in the near- to mid-IR range.

5.5. Input/Output

Energy transfer logic does not necessarily require direct addressing of individual components. That is, input signals can be sent into the system and absorbed by any (or all) input chromophores simultaneously. Similarly, output chromophores can be observed by ensemble measurements. This method requires strict wavelength division multiplexing on the inputs, the internal RET wires, and the output chromophores to disambiguate control and output signals. The design challenge is to find instances of chromophores (i.e., real molecular structures) that can satisfy the wavelength and spectral overlap requirements for inputs, wires, gates, and outputs. Our demonstration of the OR-gate is a small step toward this goal.

6. Conclusions

This paper outlines one potential path toward achieving molecular-scale computation through DNA self-assembly of electron donor-acceptor molecule pairs. DNA self-assembly provides a scalable fabrication technology that enables placement of molecules at distances in the 1nm-10nm (or larger) range. This provides the spacing necessary for certain molecules, called chromophores, to undergo resonance energy transfer, the theoretical foundation for our proposed molecular-scale logic system.

We provide preliminary experimental results that demonstrate the first steps toward fabrication and operation of energy transfer based logic systems. Specifically, we show 1) that DNA provides a cost-effective and scalable fabrication technique and 2) the operation of an energy transfer based OR-gate fabricated using DNA self-assembly. Although these preliminary results are encouraging, many challenges remain before a complete energy transfer based technology can be mass produced. Nonetheless, we identify candidate techniques for overcoming these challenges and delivering on the promise of molecular-scale computing.

7. Acknowledgements

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