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Invited Review
DNA-mediated artificial nanobiostructures: state of the art and future directions

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DNA (deoxyribonucleic acid)-mediated assembly of nanometer and micrometer scale structures can have a profound impact in the fields of nanoelectronics and nanotechnology. Such structures can also find applications in microelectromechanical systems, hybrid bio-sensors, and the potential to continue the scaling of Moore's law beyond the 50 nm node. While engineers and scientists have been long aspiring to controllably and specifically manipulate structures at the micrometer and nanometer scale, nature has been performing these tasks and assembling structures with great accuracy and high efficiency using highly specific biological molecules such as DNA and proteins. This paper describes the motivations and fundamentals behind these assembly concepts, with a focus on DNA hybridization-mediated assembly, and presents the state of the art in this field. In addition, new ideas and directions for future research on DNA-mediated assembly of active devices and DNA-based molecular devices are also presented.

Key words: DNA hybridization, self-assembly, nanobiotechnology, DNA-mediated self-assembly.

1. Motivation for bio-inspired self-assembly

Since the invention of the junction transistor in 1947 and the subsequent invention of the integrated circuit, the complexity of microelectronic integrated circuits and devices have increased exponentially. Figure 1 shows the trends in miniaturization and complexity using silicon CMOS technology. The minimum feature size has decreased from 2 um in 1980 to 0.18 μm in 1999 in volume production [1]. In research labs, the minimum features sizes, which are a factor of 5–10 smaller, have been demonstrated. It is, however, becoming increasingly difficult to continue to downscale due to real physical limitations including size of atoms, wavelengths of radiation used for lithography, interconnect schemes, etc. However, no known solutions currently exist for many of these problems [2, 3]. The SIA (Semiconductor Industry Association) roadmap projects that these trends will continue for another 15–20 years, which is being received with skepticism by industry and researchers alike.

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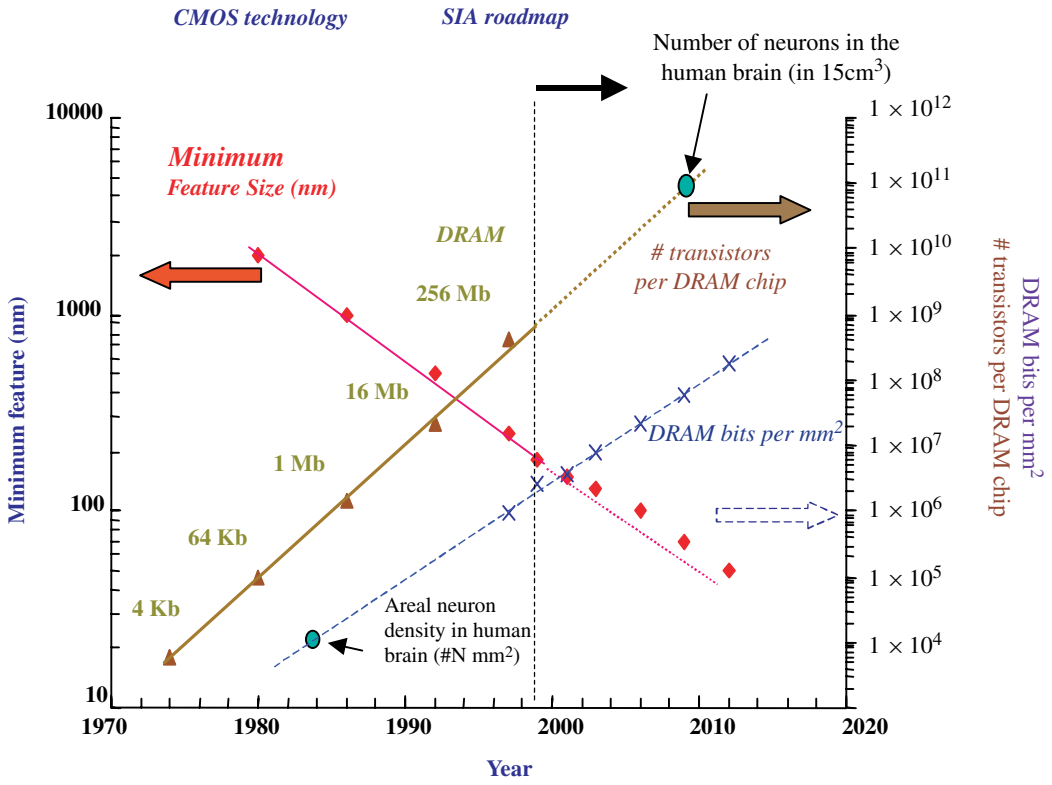

Fig. 1. Trends in miniaturization of integrated circuits in the last 25 years.

As the construction of artificial computational systems, i.e. integrated circuits, continues to become insurmountably difficult, more and more engineers and scientists are turning towards nature for answers. A variety of extremely sophisticated and complicated molecular systems occur in nature that vary in density, are self-assembled, sense and relay information, and perform complex computational tasks. Two examples can be considered, i.e. that of the human brain and that of genomic DNA in the nucleus of the cell. There are about 10^{11} neurons in the human brain in a volume of about 15 cm^3 [4]. The total number of transistors on a two-dimensional chip will actually reach the number of neurons in the human brain by about year 2010. The area density of the neurons was actually surpassed in the mid 1980s but, as is postulated, the three-dimensional nature and interconnections of the neurons is what makes the exquisite functions of the brain possible. So even though humans have achieved or will soon achieve a similar density of basic computational elements to that of the brain, the replication of brain functions are far from reality. Similarly, the case of DNA is also far-reaching and intriguing. Human DNA is about 6 mm long, has about 2×10^8 nucleotides and is tightly packed in a volume of 500 μm^3 [4]. If a set of three nucleotides can be assumed to be analogous to a byte (since a 3 codon set from mRNA is used to produce an amino acid), then these numbers represents about 1 Kb μm^{-1} (linear density) or about 1.2 Mb μm^{-3} (volume density). These numbers are not truly quantitative but can give an appreciation of how densely stored information is in the DNA molecules. Certainly, a memory chip based on DNA as the active elements could have extremely high density!

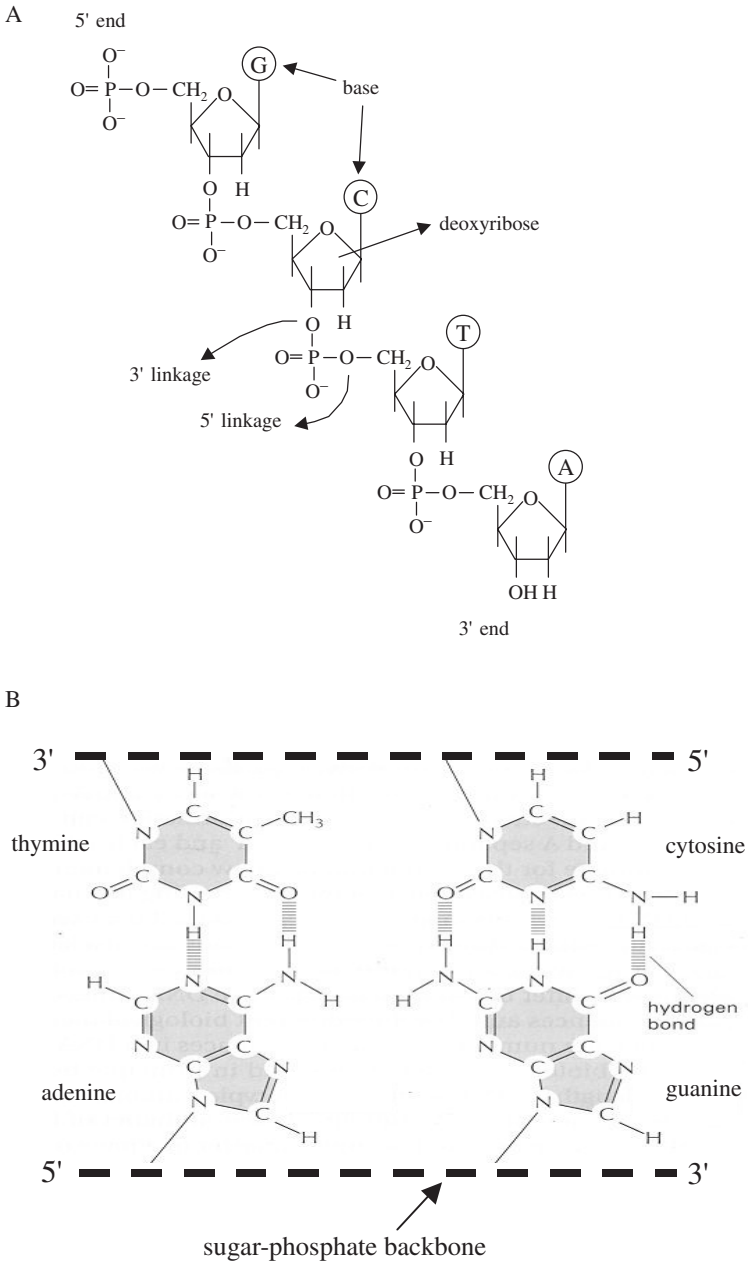

Fig. 2. A, Sugar-phosphate backbone of DNA; B, the four bases of DNA showing their complementary binding properties (redrawn from [3]).

This paper takes a look at the current and possible future applications of the DNA molecules for the fabrication of artificial nanostructures and devices. The use of DNA molecules can be for the assembly of devices/computational elements, for the assembly of interconnects, or the use as the device element itself. The text below presents the fundamental properties of DNA and discusses its applications in the above-listed categories. New ideas and directions of research are also presented.

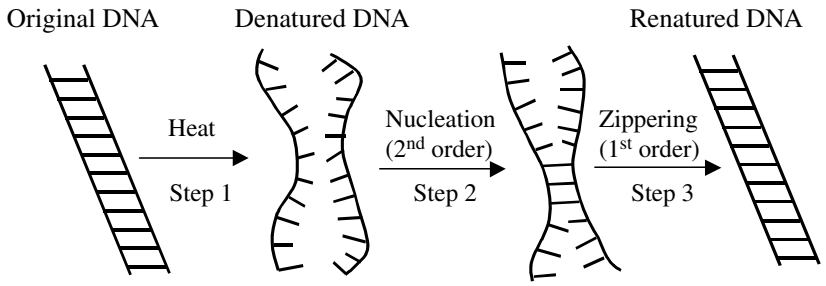

Fig. 3. Schematic showing denaturing and hybridization of DNA.

2. DNA fundamentals

DNA is the basic building block of life. Hereditary information is encoded in the chemical language of DNA and reproduced in all cells of living organisms. The double-stranded helical structure of the DNA is key to its use in self-assembly applications. Each strand of the DNA is about 2 nm wide and composed of a linear chain of four possible bases (adenine, cytosine, guanine, thymine) on a backbone of alternating sugar molecules and phosphate ions (see Fig. 2). Each unit of a phosphate, a sugar molecule, and base is called a nucleotide and each nucleotide is about 0.34 nm long. The specific binding through hydrogen bonds between adenine and thymine, and cytosine and guanine as shown in Fig. 2B can result in the joining of two complementary single-stranded (ss) DNA to form a double-stranded (ds) DNA. The phosphate ion carries a negative charge in the DNA molecule, a property used in the drift of the molecule under an electric field, e.g. in electrophoresis applications. The negative charges result in electrostatic repulsion of the two strands and hence to keep the two strands together, positive ions need to be present in the ambient to keep the negative charges neutralized. The joining of two ssDNA through hydrogen bonding to form a dsDNA is called 'hybridization'. Hence two single strands of DNA can be designed to have complementary sequences and made to join under appropriate conditions. If a double-stranded DNA is heated above a certain temperature, called the melting temperature T_{m}, the two strands will separate into single strands. The melting temperature is a function of temperature, ion concentration of the ambient, and the G–C content in the sequence. When the temperature is reduced, the two strands will eventually come together by diffusion and 'rehybridize' or 'renature' to form the double-stranded structure as shown in Fig. 3. These properties of the DNA can be utilized in the ordering and assembly of artificial structures if these structures can be attached to ssDNA. It should also be pointed out that the sequence of the DNA can be chosen and the molecules can be obtained from a variety of commercial sources [5].

3. Attachment of DNA to gold surfaces

It is now important to review the methodology to attach DNA molecules to surfaces. The most widely used attachment scheme utilizes the covalent bond between sulfur and gold [6–18]. The formation of long chain ω-substituted dialkyldisulfide molecules on a gold substrate was first reported in 1983 [6]. Films of better quality were formed and reported by the adsorption of alkyl thiols [7–13]. Bain and Whitesides [7, 8] presented a model system consisting of long-chain thiols, $\mathrm{HS(CH_2)}_n\mathrm{X}$ (where X is the end group) that adsorb from a solution onto gold and form densely packed, oriented monolayers. The schematic of the Au–S bond is shown in Fig. 4 [9]. The bonding of the sulfur head group to the gold substrate is in the form of a metal thiolate, which is a very strong bond ($\sim$44 kcal mol^{-1}) and hence the resulting films are quite stable and very suitable for surface attachment of functional groups. For example, the DNA molecule can be functionalized with a thiol (S–H) or a disulfide (S–S) group at the 3′ or 5′ end. Upon immersion of clean gold surfaces in

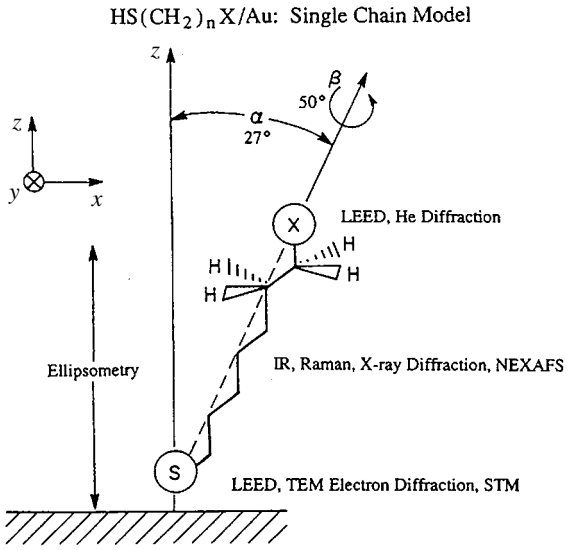

Fig. 4. Schematic of a long-chain thiol molecule on a gold surface (from [9]). Reprinted, with permission, from the Annual Review of Physical Chemistry, Vol 43, © 1992 by Annual Reviews, www.AnnualReviews.org.

solutions of thiol-derivatized oligonucleotides, the sulfur adsorbs on the gold surfaces forming a single layer of molecules as schematically shown in Fig. 4, where the hydrocarbon is now replaced with a ssDNA or a dsDNA molecule [16–19]. Hickman *et al*. [10] also demonstrated the selective and orthogonal self-assembly of disulfide with gold and isocyanide with platinum. This work can be important in the orientation-dependent self-assembly of structures that have both a platinum and gold surface exposed for functionalization. Hence, the thiol-based chemistry has served as the fundamental attachment scheme for DNA and oligonucleotides for the self-assembly of artificial nanostructures.

4. DNA-inspired self-assembly and construction of nanostructures

There has been a tremendous interest in recent years to develop concepts and approaches for self-assembled systems for electronic and optical applications. Material self-assembly has been demonstrated in a variety of semiconductor materials (GaAs, InSb, SiGe, etc.) using Stranksi–Krastanov strain-dependent growth of lattice mismatch epitaxial films [19–22]. Periodic structures with useful optical properties have been demonstrated but no reports of actual electronic functions can be found in literature using these lattice strain-dependent growth and assembly. While significant work continues along that direction, it has also been recognized by engineers, chemists, and life scientists that the exquisite molecular recognition of various natural biological materials can also be used to form a complex network of potentially useful particles for a variety of optical, electronic, and sensing applications. This approach can be considered a ‘bottom-up’ approach rather than the ‘top-down’ approach of conventional scaling and much work has been reported towards this front.

4.1. Nanostructures by DNA itself

Pioneering research extending over a period of more than 15 years by N. C. Seeman [23–27] has laid a foundation for the construction of structures using DNA as scaffolds, which may ultimately serve as frameworks for the construction of nanoelectronic devices. In that work, branched DNA was used to form stick

figures by properly choosing the sequence of the complementary strands. Macrocycles, DNA quadrilateral, DNA knots, Holliday junctions, and other structures were designed. Figure 5A shows a stable branched DNA junction made by DNA molecules. The hydrogen bonding is indicated by dots between the nucleotides. It is also possible to take this structure and devise a two-dimensional lattice as shown in Fig. 5B if hybridization regions ('sticky ends') are provided in region B. It was also pointed out that it was easier to synthesize these structures but more difficult to validate the synthesis. The same group also reported on the design and observation, via AFM, of two-dimensional crystalline forms of DNA double cross-over molecules that are programmed to self-assemble by the complementary binding of the 'sticky ends' of the DNA molecules [26]. Single domain crystal sizes, which were as large as 2 μm$\times$8 μm were shown by AFM images. These lattices can also serve as scaffolding material for other biological materials. It should be noted that in this work, the 2 nm wide stiff DNA molecules themselves are used to form the two- and three-dimensional structures.

4.2. DNA-mediated assembly of nanostructures

Among roles envisioned for nucleic acids in nanoelectronic devices, the self-assembly of DNA-conjugated nanoparticles have received the most attention in recent literature. Mirkin *et al*. and Alivisatos *et al*. were the first to describe self-assembly of gold nanoclusters into periodic structures using DNA. Mirkin *et al*. [28] described a method of assembling colloidal gold nanoparticles into macroscopic aggregates using DNA as linking elements. The method involved attaching noncomplementary DNA oligonucleotides to the surfaces of two batches of 13 nm gold particles capped with thiol groups, which bind to gold. When another oligonucleotide duplex with ends which are complementary to the grafted sequence is introduced, the nanoparticles self-assemble into aggregates. The process flow is shown in Fig. 6 and this process could also be reversed when the temperature was increased due to the denaturation of the DNA oligonucleotides. Closed packed assemblies of aggregates with uniform particle separations of about 60 Å were demonstrated in this study as shown in Fig. 7A.

In the same journal issue, Alivisatos *et al*. [29] also reported techniques where discrete numbers of gold nanocrystals are organized into spatially defined structures based on DNA base pair matching. Gold particles, 1.4 nm in size, were attached to either the 3′ or 5′ end of 19 nucleotide long single-stranded DNA 'codon' molecules through the well-known thiol attachment scheme. Then, 37 nucleotide long single-stranded DNA 'template' molecules were added to the solution containing the gold nanoparticles functionalized with ssDNA. The authors showed that the nanocrystals could be assembled into dimers (parallel and antiparallel) and trimers upon hybridization of the codon molecules with that of the template molecule. Due to the ability to choose the number of nucleotides, the gold particles can be placed at defined positions from each other as schematically shown in Fig. 8. TEM results showed that the distance between the parallel and antiparallel dimers were 2.9–10 nm and 2.0–6.3 nm, respectively. These structures could potentially be used for applications such as chemical sensors, spectroscopic enhancers, nanostructure fabrication, etc. These techniques have been used to devise sensitive calorimetric schemes for the detection of polynucleotides based on distance dependent optical properties of aggregated gold particles in solutions [30].

Mucic *et al*. [31] have also described the construction of binary nanoparticle networks composed of 9 nm particles and 31 nm particles, both composed of citrate-stabilized colloidal gold. These 9 ($\pm$1) and 31 ($\pm$3) nm particles were coated with different 12-mer oligonucleotides via a thiol bond. When a third DNA sequence (24-mer), which was complementary to the oligonucleotides on both particles was added, hybridization led to the association of particles. When a ratio of 9 nm to 31 nm particles was large, the assembly illustrated in Fig. 7B was formed (redrawn from [31]). Loweth *et al*. [32] have presented further details of the formation of the hetero-dimeric and hetero-trimeric nonperiodic nanocluster molecules based upon earlier work of Alivisatos. The authors showed exquisite control of the placement of 5 nm and 10 nm gold nanoclusters which were derivatized with ssDNA. Various schemes of hetero-dimers and hetero-trimers

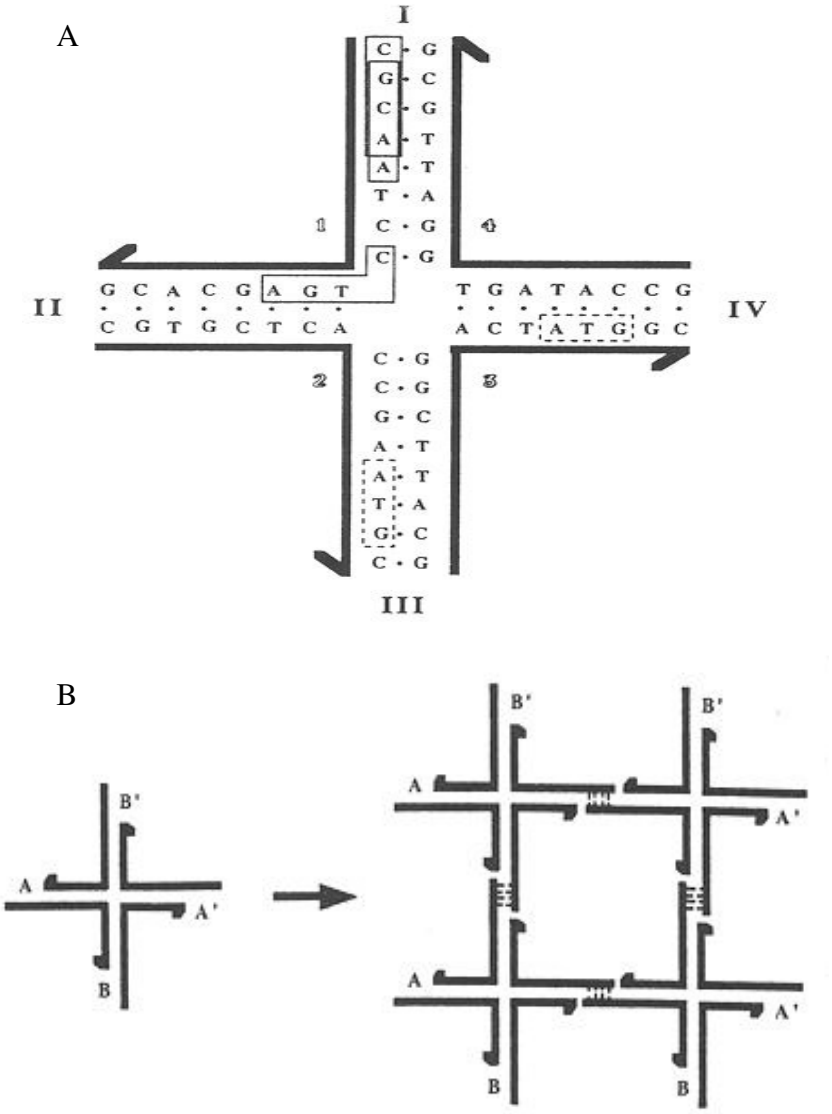

Fig. 5. A, A four-armed stable branched junction made from DNA molecules; B, use of the branched junction to form periodic crystals (from [24]). Reprinted, with permission, from Nanotechnology, © 1991, p. 149. IOP Publishing Ltd, and with permission from N. C. Seeman.

were designed and demonstrated using TEM images. Reviews on these topics have also been recently published and can provide additional information than presented here [33–35].

4.3. DNA-directed nanowires

The concepts of DNA-mediated self-assembly of gold nanostructures has recently been extended to metallic nanowires/rods [36–38]. The concept, though feasible, has not yet been completely demonstrated. The basic idea behind this work is to fabricate gold and/or platinum metal wires, functionalize these wires with

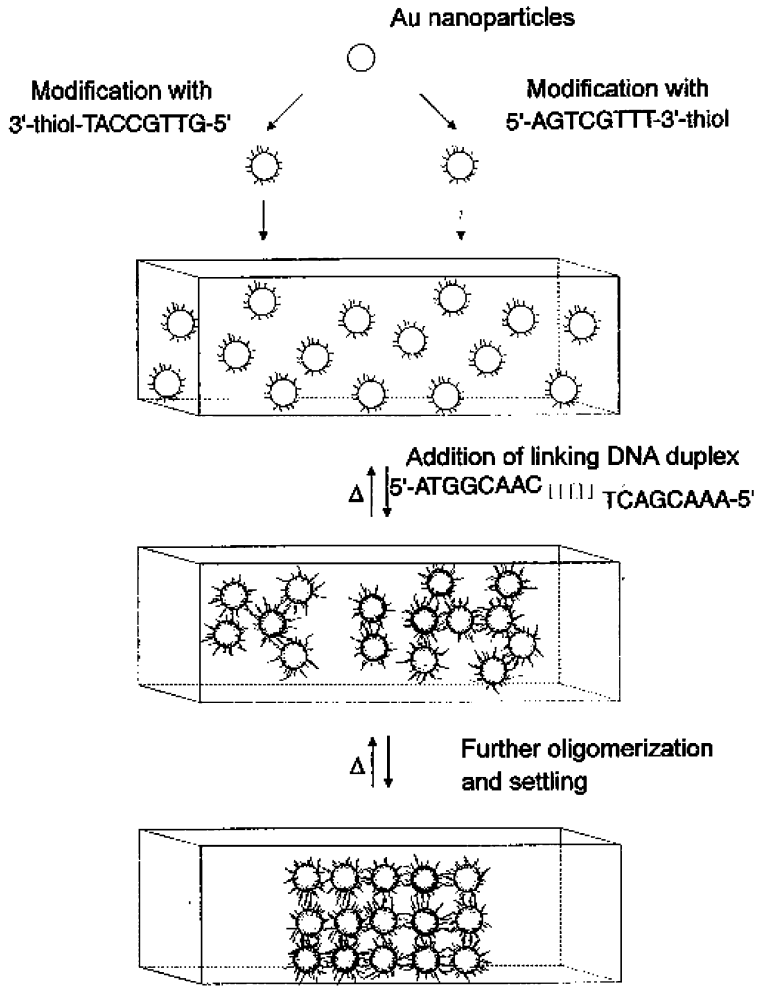

Fig. 6. Fabrication process for the aggregated assembly of DNA conjugated gold nanoparticles (from [28]). Reprinted, with permission, from Nature, Vol. 382, 15th August, 1996, p. 607. Macmillan Magazines Ltd and with permission from C. Mirkin.

ssDNA, and assemble them on substrates which have the complementary ssDNA molecules attached at specific sites. Thus, self-assembly of interconnects and wires can be made possible. The metallic wires are formed by electroplating in porous alumina membranes with pores sizes of about 200 nm [37] (The processes for the formation of alumina films with nanohole arrays has been developed and demonstrated by many authors [39, 40].) Metallic rods, ranging from 1–6 μm in length were produced, depending on the electroplating conditions. The goal of the work would be to form Pt rods with Au at the ends or vice versa. Then, selective attachment of thiol to Au and isocyanide to Pt can be used [10] to assemble these interconnects in specific orientations.

The use of DNA as a template for the fabrication of nanowires has been demonstrated through a very interesting process by Braun *et al*. [41–43]. The authors formed a DNA bridge between two gold electrodes, again using thiol attachment. Once a DNA bridge is formed between the 12–16 μm spacing of the electrodes, a chemical deposition process is used to vectorially deposit silver ions along the DNA through Ag^+/Na^+ ion

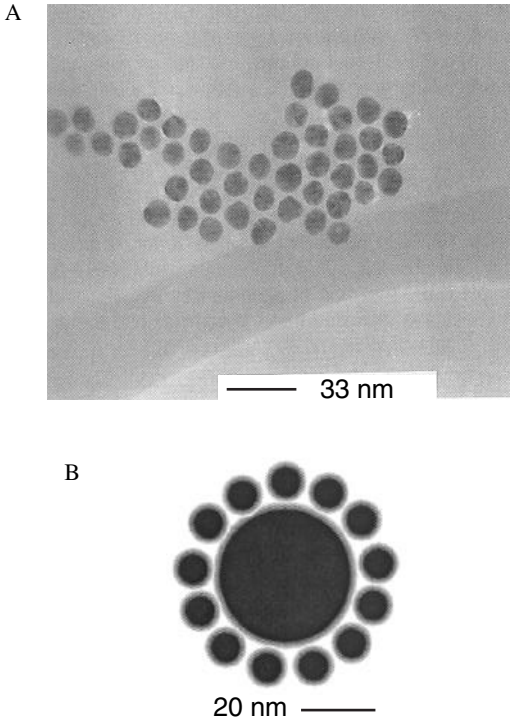

Fig. 7. A, TEM image of the aggregated DNA/Au colloidal particles (from [28]); B, TEM image of a nanoparticle satellite constructed via DNA-mediated docking of 9 nm gold particles onto a 31 nm gold particle (redrawn from [31]). Reprinted, with permission, from J. Am. Chem. Soc. Vol. 120, p. 12674, © 1998, American Chemical Society, and with permission from C. Mirkin.

exchange and formation of complexes between the gold and the DNA bases (see Fig. 9). The result is a silver nanowire which is formed using the DNA as a template or skeleton. Current–voltage characteristics were measured to demonstrate the possible use of these nanowires. The authors also reported the formation of luminescent self-assembled poly (*p*-phenylene vinylene) wires for possible optical applications [42]. The work has a lot of potential and much room for further research to control the wire width, the contact resistances between the gold electrode and the silver wires, and use of other metals and materials.

5. Future directions

5.1. DNA-based 'active' device assembly

A lot has been accomplished in the last 10 years towards the DNA-mediated assembly of artificial nanostructures. Nevertheless, a great deal remains to be done to bridge the gap between the electronic devices that will be constructed on a 50–100 nm scale within the next 10 years and molecules of a few nm or less in size. While one of the goals for the nanotechnologists certainly remains to extend the current CMOS device scaling roadmaps, it is also important to view the DNA-mediated self-assembly technology as an enabling technology that can also be applied towards different applications. All current work done to date focuses on the basic demonstration and assembly of passive components and devices (gold clusters, metal rods, etc.). While these activities are of paramount interest, one needs to also look at the processes for self-assembly of active devices such as transistors, etc. The entire foot-print of a current CMOS transistors in production,

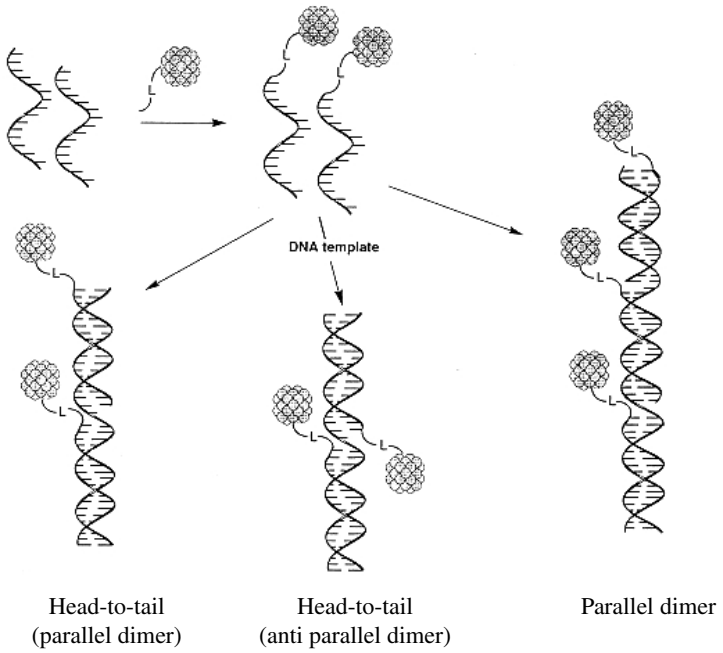

Fig. 8. Assembly of nanocrystals to form dimers and trimers based on DNA hybridization (from [29, 32]). Reprinted, with permission, from Nature, Vol. 382, p. 60, 15th August, © 1996, Macmillan Magazines Ltd and with permission from A. P. Alivisatos.

with $W/L = 1\ \mu\text{m}/0.18\ \mu\text{m}$, is less than 1.4 μm on a side. These device sizes are smaller, in many cases, than many biological organisms such as human red blood cells, bacteria, etc. DNA-inspired self-assembly of active devices has been proposed by Heller and co-workers [44] for assembling optical and optoelectronic components onto a host substrate; however, the basic concept has not yet been demonstrated. Some of the questions to be asked to guide future research in these directions include;

> Can active devices of such sizes be assembled in two and three dimensions using DNA-mediated assembly? Doing so can potentially reduce the cost of fabrication of microelectronic systems and circuits. Such processes can also provide truly reconfigurable circuits by the physical movement of the devices.
>
> Can DNA-mediated self-assembly be used to assemble and position such devices onto different materials, i.e. obtain heterogenous integration of materials? Can silicon devices be positioned on specific locations on glass or polymer substrates, making it possible to make high performance LCDs or displays on foldable plastic substrates? Similarly, it should be possible to place compound semiconductor devices on silicon, and vice versa, using these approaches.
>
> Can sub-systems and small circuit elements be fabricated and be used as markers for specific sites in the body for diagnostics or therapeutic applications? Imagine tiny radio transmitters which self-assembly and dock on a specific site determined by the recognition properties of the molecules that functionalize these devices.

These and other quests are not too far from reality, given the rate of progress in the field of nanotechnology and nanobiotechnology. Current work going on in our laboratory is focusing on developing the basic technology for such applications by demonstrating the feasibility of self-assembly of useful microscale active

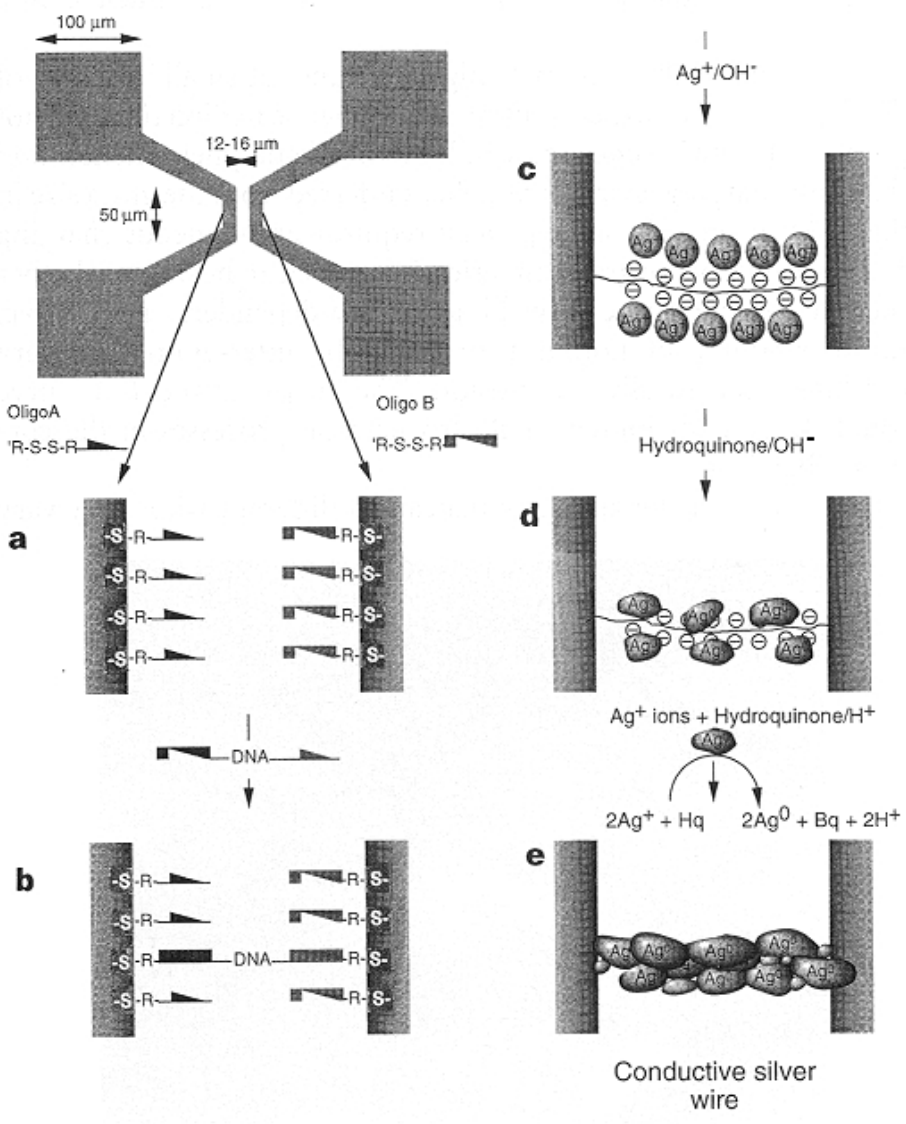

Fig. 9. The process flow for the formation of DNA-directed silver nanowires (from [41]). Reprinted, in part, with permission, from Nature, Vol. 391, p. 775, February, © 1998, Macmillan Magazines Ltd and with permission from E. Braun.

silicon devices using hybridization and specificity of DNA molecules. The microscale silicon devices are fabricated using silicon-on-insulator (SOI) technology, a well-developed wafer fabrication process, in such a way that they can be 'released' from their host substrate into a surrounding medium. Figure 10 shows the process flow for the fabrication and release of such devices. Figure 11 demonstrates some preliminary results showing the fabricated silicon device islands which have also been released and collected on another substrate. Work continues to attach ssDNA at specific locations on these devices using a flexible polyethylene glycol linkage. Meanwhile, a substrate will be prepared with 2D (3D in future work) interconnect layers.

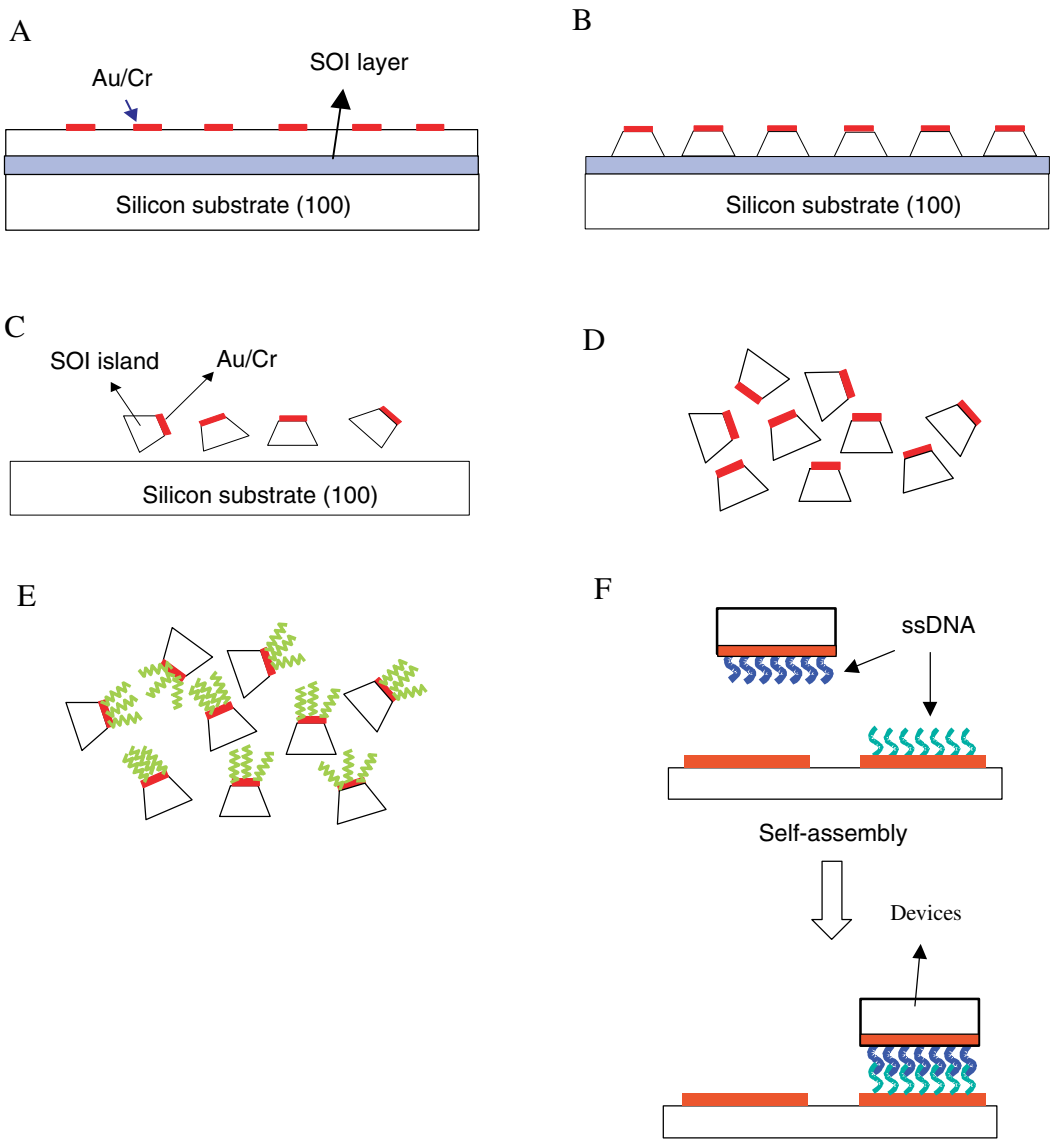

Fig. 10. Process flow for the proposed active device fabrication, release and self-assembly. A, Define patterns of Au contacts on an SOI wafer; B, etch the silicon down to the buried oxide using potassium hydroxide, Au acts as a mask for the silicon etch; C, etch off the buried oxide using hydrofluoric acid; D, collect and concentrate (using centrifuge) the devices in a test-tube; E, functionalize the devices with ssDNA having a thiol either 3′ or 5′ end; F, assembly of the devices on another surface with the complementary ssDNA.

These layers will also be functionalized with single-stranded oligonucleotides. The free-floating active devices will be released onto the patterned and functionalized substrate along with oligonucleotides that will complementarily bind and connect the two molecules on the substrate and the device. These silicon devices will thus self-assemble onto the interconnect layers, as dictated by the hybridization of the complementary strands of DNA. Conceptually the process can be repeated multiple times, making many layers of devices, which can be assembled to make three-dimensional ICs. These processes can also provide heterogenous in-

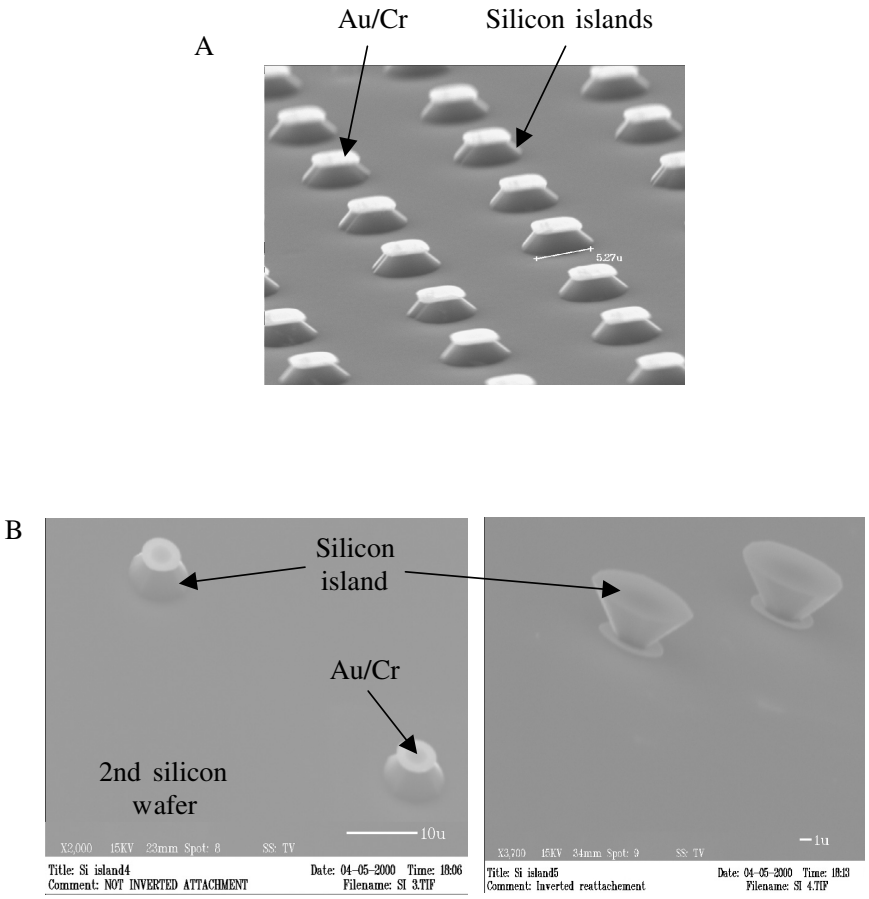

Fig. 11. A, SEM pictures of the fabricated devices; B, verification of device release and collection on another substrate.

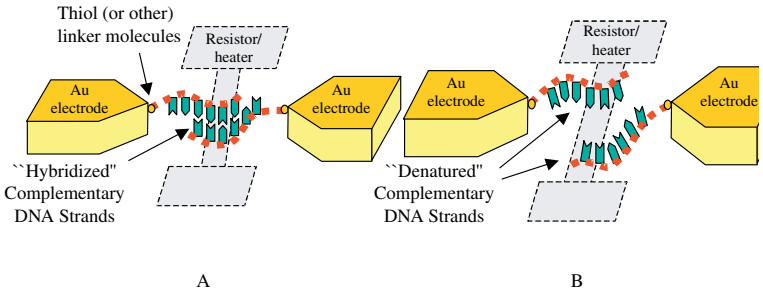

Fig. 12. A, Single-stranded DNA attached to each electrode using a linker molecule; B, if $I > I_{\text{critical}}$, joule heating will result in $T > T_{\text{m}}$ (DNA), which will denature the DNA and the current flow will stop flowing. Alternatively, the temperature around the DNA strand can also be increased above T_{m} by a metal heater/resistor.

tegration of materials, for example, to place silicon on glass or polymer substrates for display applications, GaAs on silicon for optoelectronic applications, etc.

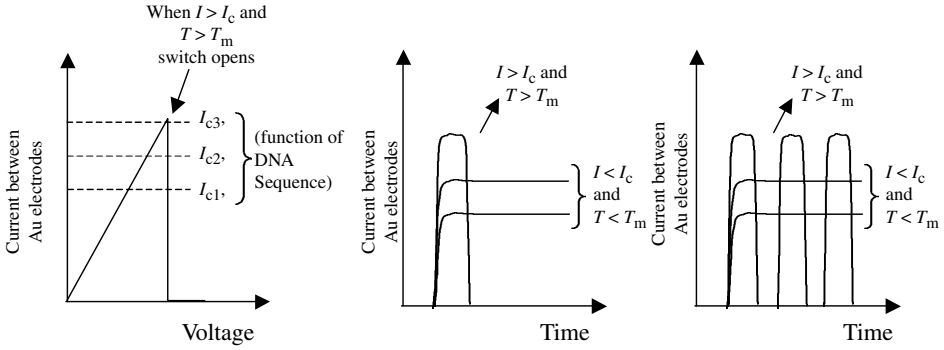

Fig. 13. A, Expected current versus voltage; B, current versus time; C, oscillatory current–time plots for the DNA-based molecular switch device shown in Fig. 12.

5.2. DNA-based 2 and 3 terminal switch and oscillator

As the search for molecular devices continues, DNA could also provide possible solutions towards this front. There have been no reports of active device concepts using the DNA molecule itself; however, the electronic properties of DNA have been under intense study in recent years. Even though there have been contradictory measurements in the literature with regard to DNA conductivity [45], recent reports have demonstrated that the conductivity of the DNA molecule measured between two electrodes behaves like a large band-gap semiconductor [46]. The resistance of the molecules in the conductive regime was reported to be on the order of $40 \times 10^9/100$ Å long molecule. The ideas presented below assume that DNA behaves as a conductor in specific voltage/current regimes. The specificity of the Watson–Crick base pairing is a very interesting and useful property that can be exploited to propose novel DNA-based interconnect functionalities and devices. Two complementary strands of DNA can be made to denature by increasing the temperature of the molecule above a characteristic 'melting temperature' (T_m), as briefly discussed on Section 2. This concept can be used to make a DNA-based switch as shown in Fig. 12. Two Au electrodes can be defined and thiol-derivatized ssDNA can be attached to each electrode such that parts of these strands have a complementary sequence. Once the two molecules have hybridized, current can be passed between the two electrodes. This current will result in joule heating of the molecule and as the temperature increased beyond T_m, the strands would denature and the current would stop flowing. The temperature increase can be directly from the current flow through the molecule or from an external heater lithographically defined in the region under the two Au electrodes (as shown in the figure). The hybridization can be direct as shown in the Fig. 12, or indirect where a third DNA strand is used to connect the first two strands.

The denaturing phenomenon, which is illustrated in Fig. 12, also provides the basis to realize DNA-based devices with characteristics that may be suitable as functional elements. If the heating was due to the current flow through the DNA strands, a negative differential resistance device may be possible. As illustrated in Fig. 13, such a device could also be used to form an oscillator. Once the two strands have denatured upon internal or external heating of the molecule, they would rejoin due to diffusion in a certain time, given some thermal energy. Thus the strands would denature due to heating, cool due to no current flow, and then hybridize again since they are in close proximity of each other. The re-hybridization might be slow at first examination since it is controlled by diffusion. However, since the molecules are in such close proximity to each other, the time for rehybridization might not be as low as expected.

6. Conclusions

The field of nanotechnology has emerged as one of the most important area of research in the future and DNA-mediated self-assembly has the potential to profoundly impact this field. The ability to choose the sequence of nucleotides and hence provide addressability during the self-assembly processes makes DNA an ideal molecule for these applications. This paper presented a review on the state of the art of DNA-mediated self-assembly, also describing the fundamentals of DNA, and its attachment to gold surfaces via the established thiol (S–H) chemistry. The assembly of structures using DNA alone, the assembly of gold nanoclusters using DNA as the linking molecule, and the formation of nanowires using DNA was reviewed. In addition, new ideas related to self-assembly and positioning of active devices using DNA were also presented. Finally, active device elements using the hybridization properties of the DNA were also proposed.

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