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From Genes to Machines: DNA Nanomechanical Devices

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Abstract

The structural properties that enable DNA to serve so effectively as genetic material can also be utilized for other purposes. The complementarity that leads to the pairing of the strands of the DNA double helix can be exploited to assemble more complex motifs, based on branched structures. These structures have been used as the basis of larger constructions in 2D and 3D. In addition, they have been used to make nanomechanical devices. These devices range from DNA-based shape-shifting structures to gears and walkers, a DNA stress-gauge, and even a translation device. The devices are activated by mechanisms as diverse as small molecules, proteins, and, most intriguingly, other molecules of DNA.

Keywords

Structural DNA Nanotechnology; Unusual DNA Motifs; Nanomechanical Motion; Activation of Devices; Nanorobotics

Introduction

The half-century since the publication of the Watson-Crick model for DNA structure has seen ramifications of this advance in areas as diverse as medicine, forensics and basic biology, culminating in the sequencing of the human genome. The use of the DNA structure has largely been as a paradigm in understanding fundamental processes in genetics, and exploiting that understanding in practical applications. However, another activity involving DNA has been growing for over 20 years, based on the idea that objects, arrays, and devices could be made from DNA molecules. This effort started from the recognition that stable branched DNA motifs could be made from synthetic strands of DNA with carefully designed sequences, and that these motifs could be made to assemble via sticky-ended cohesion [1]. The effort to exploit this approach to building matter with nanoscale features and details is termed ‘structural DNA nanotechnology.’ It is useful to recall that the DNA double helix is a nanoscale object, whose diameter is roughly 2 nm, with a double helical repeat around 3.5 nm.

The initial endeavors in structural DNA nanotechnology were directed at constructing DNA objects, such as a cube [2] or a truncated octahedron [3]. Once suitably rigid motifs were developed, it was possible to build 2D arrays with programmable features [4-10]. The original impetus for building arrays came from the hope of improving macromolecular crystallization [1], but early goals also included organizing nanoelectronics [11], and DNA-based computation [12]. Winfree’s observation that branched DNA molecules with sticky ends could provide the means for implementing computation by Wang tiles on the molecular level spurred a lot of activity in the algorithmic assembly of branched nucleic acid

Teaser: Fifty years after Watson and Crick, DNA is being used as the basis for motors on the nanometer scale.

molecules [12]. Further discussion of DNA objects and arrays can be found in references [13, 14].

DNA polyhedra and arrays are static objects representing an approach to controlling nanoscale structure. However, a key aspect of controlling the structure of matter is the ability to make it change its shape. In principle, things that change their shapes in response to an external stimulus are capable of functional utility, i.e., they can act as machines. Given the ease with which it is possible to control the structures of DNA nanoconstructs, it makes sense to see if it is possible to get them to do some work. The last six years have seen an explosion of activity in the area of nucleic acid-based nanomachines. They work on a number of different principles, and their movements have been demonstrated using a variety of physical techniques. We restrict ourselves to systems that involve nanomechanical motion, and exclude molecular beacons [15,16]. This article is organized around different types of systems: These include the exploitation of DNA structural transitions, Watson-Crick and non-Watson-Crick DNA hybridization, protein binding and autonomous devices.

DNA Devices Involving DNA Structural Transitions

The first attempt to control DNA structure was a not-very successful effort to change the position of the branch point of a DNA cruciform [17]. This device is shown in Figure 1a. It consists of a DNA circle that contains a cruciform whose four central base pairs are capable of branch migration. The device exploits the fact that a cruciform will be extruded under conditions of negative supercoiling, and that it will be re-absorbed when the circle is relaxed. The addition and removal of ethidium was used to demonstrate direct control of double stranded DNA branch migration, but this system was cumbersome, its structure was not very well-defined, and its scale was huge. The action of the device was demonstrated by restriction combined with hydroxyl radical autofootprinting. Niemeyer and colleagues have reported another DNA system on this large scale [18]. It is based on a structural transition between two states in superhelical DNA that is induced by divalent cations; the transition is induced by increasing the concentration of Mg^{2+}. The transition is demonstrated convincingly by atomic force microscopy (AFM).

The first device that had a well-defined structure was based on the transition from right-handed B-DNA to left-handed Z-DNA [19]. Although originally conceived in the 1980's, the robust structural basis for demonstrating this device awaited the advent of rigid structural motifs, such as the double crossover (DX) motif [20]. The DX motif consists of two DNA double helices linked in two different places. These molecules are related to intermediates in genetic recombination, but the linkages are between strands of opposite polarity, rather than the same polarity. Figure 1b shows that the device consists of two DX molecules linked by a shaft of double helical DNA. The B-Z transition has two requirements, sequences prone to form Z-DNA (typically $(CG)_n$), and solution conditions that promote the transition [21]; the sequence requirement enables control of the transition in space, i.e., how much of the DNA will undergo it, and the need for Z-promoting conditions permits control in time. The 20 yellow nucleotide pairs on the connecting shaft fulfill the sequence requirement. and they form Z-DNA in the presence of $Co(NH_3)^{3+}_6$. The filled circles represent a pair of dyes that are used in a fluorescent resonance energy transfer (FRET) experiment that reports their separation: When the solution is in B-promoting conditions, the dyes are close together, but in Z-promoting conditions, they are further apart. Although quite successful, this device lacks one of the key features desirable in a DNA-based nanomechanical device, it is controlled by the addition of a small molecule to the solution, meaning that (within the limits of some chemical nuance [xx) only two mechanical states are available to any combination of devices. However, this problem was soon solved.

Devices Controlled by Nucleic Acid Hybridization

The key reason to use DNA-based devices is to take advantage of the sequence specificity associated with DNA hybridization. This approach to establishing the states of DNA devices leads to all of the diversity associated with different DNA sequences. Thus, sequence-dependent devices open a vast array of opportunities for simultaneous control in the same environment, perhaps in the same construct. The first hybridization-based device was a DNA tweezers built by Yurke *et al.* [22]. The method of controlling hybridization introduced by these workers has been used in all other DNA-duplex-based devices subsequently. The idea is very simple: First, put the DNA construct into a particular state using a 'set' strand that contains a 'toehold' on one end that makes it eight bases longer than necessary to pair with the rest of the motif; second, remove the set strand with an 'unset' strand complementary to the entire length of the set strand, leaving the motif free to pair with another set strand in the next cycle of operation. The unset strand is a better pairing partner for the set strand than the motif, because there are more base pairs between it and the set strand than there are between the motif and the set strand. The toehold dangles freely in solution when the set strand is paired with the motif. However, when the unset strand is added to the solution, it serves as an initiation point for it to remove the set strand; once bound to the set strand, it can invade the motif via single-stranded branch migration until it has removed the set strand completely. The unset strand can be thought of as the fuel that runs the device, and the set strand-unset strand duplex is the waste generated by the device. The efficacy of the tweezers was demonstrated by FRET.

The initial Yurke *et al.* device lacked robustness [22], because dimers sometimes formed between machine cycles, although later variants from that group including an actuator [23] and a 3-state device [24] were well behaved. The first robust device based on hybridization topology was the PX-JX_2 device [25]. The machine cycle of this device is shown in Figure 2a. The structure on the left is a motif called PX-DNA, wherein two double helices exchange strands of the same polarity at every possible position [26]. The motif on the right is called JX_2, which lacks two of these crossovers, resulting in the bottom of the device being rotated a half-turn relative to the PX conformation; this can be seen in the reversal of the red and blue colors. The conformation of the motif is established by two set strands, which are shown as green for the PX state and pink for the JX_2 state. In step I, the green set strands are removed by the addition of biotinylated unset strands that can the be removed with magnetic streptavidin beads. The resulting naked frame (top center) can be converted to the JX_2 conformation by the addition of the pink set strands (step II). Steps III and IV restore the structure to the PX state.

The robustness and effectiveness of this device were established by gel electrophoresis, but the most convincing evidence for its operation derived from AFM data. A series of DNA trapezoids formed from edge-sharing DNA triangles [27] are connected by the device, as shown in Figure 2b. In the PX state, the trapezoids are all parallel to each other, whereas in the JX_2 state successive trapezoids are oriented oppositely. Figure 2c illustrates AFM images of these arrays in each state, showing clearly that the device is able to effect these conversions.

The strength of hybridization-based DNA nanomachines is that devices that respond to different DNA signals can be designed easily just by changing the sequence in the region to which the set strands bind. An example of this approach is shown in Figure 2d, which contains the essential features of a DNA-based nanomechanical translation device [28]. This prototype apparatus consists of a DNA diamond (two fused triangles), and a pair of double diamonds connected by two different PX-JX_2 devices. In response to the set strands, the orientations of the double diamonds are determined. In the example shown, the left device is

in the PX state, so that the red half of the central double diamond is on the same side as the single diamond; however, the right device is in the JX_2 state, so that the blue half of the right double diamond is on this side. The diamonds all contain sticky ends that are numbered with Arabic numerals. As a result of the state of the machine, two DX molecules whose sticky ends complement these positions are selected to bind the device from a group of six in solution; DX2 and DX5 have been selected in the example shown. These DX molecules are ligated to each other and to an initiator DX (not shown), and the continuous strand that results is sequenced. For all four possible states, the correct molecule results. This is a translational device, because the coding between the sequences of the set strands and the final product is arbitrary.

There have been a fairly large number of devices based on the Yurke *et al.* [22] strategy. Prominent among them are walking devices [29,30], wherein a walker 'nanorobot' takes steps on a sidewalk. One of these devices [29] is illustrated in Figure 3a. The first panel of this drawing shows a blue sidewalk with three double helical domains at the bottom, and a walker with two brown double helical domains on the top. Both the sidewalk and the walker are tailed in single-stranded strands; a set strand connects the walker to the sidewalk at the left two positions. The domains of the sidewalk are adjacent to each other, but the domains of the walker are attached by a flexible linker. In the second and third panels, an unset strand removes the set strand that attaches the right leg of the walker to the sidewalk. In the fourth panel, a new set strand attaches the right leg of the walker to the rightmost domain of the sidewalk. The fifth and sixth panels show the same steps involving the movement of the rear leg, so that at the end of the walk, the walker has moved one step to the right. The steps of this walk were followed by crosslinking aliquots of the system with psoralen [29], but FRET has also been used for this purpose [30]. Tian and Mao have used this same approach to make DNA-based gears [31]: They demonstrate by non-denaturing gel electrophoresis that removal and addition of strands to two linked circular molecules leads to their mutual rotation.

An exciting combination of 2D DNA crystals and hybridization-based nanodevices has been developed by Yan and his colleagues [32]. Those investigators have inserted a nanodevice into a DNA parallelogram array [6], so that they can change the dimensions of the crystalline repeat by operating the device. The system is illustrated in Figure 3b: A stem-loop in one of the parallelogram edges is stabilized by a removable strand that serves as the complement only to its base. When that strand is removed and replaces with a strand that is complementary to the entire stem-loop, the length of the edge is increased. Figure 3b illustrates this notion schematically, along with showing elegant AFM images that demonstrate the functioning of the system. It is worth noting that this is a purely translational motion.

Non-Watson-Crick Base-Paired Motifs

The double helix is the most prominent of the unbranched DNA structures, but it is not the only one. The G-quartet motif [33] has been used by a number of investigators as a component of a DNA-based device. The simplest devices, from the labs of Tan [34] and Mergny [35] are simple shape-shifting systems wherein a single-stranded G-quartet structure is eliminated by the addition of a molecule complementary to the strand; G-quartet-based devices are based on the notion that G-quartet-containing molecules are less stable than the same strands bound to their Watson-Crick complements. This approach has been developed by Simmel and colleagues [36] into a reversible thrombin-binding device. They. can release a G-quartet-containing DNA aptamer from thrombin, by binding a molecule that is largely complementary to the G-quartet forming region. The resulting duplex contains a toehold, however, so that the complementary strand can be removed, leaving the original aptamer

strand free to bind to thrombin again. In another approach to using G-quartet, Sen and his colleagues employed Sr^{2+} as an agent to produce a 'pinched duplex' within a conventional double stranded molecule that contained an interrupted strand of G's [37]. The oligo-C-based I-motif has been used by Liu and Balasubramanian [38] to construct another shape-shifting device. This motif, is dependent on the hemi-protonation of cytosine, so the states of the device can be controlled by protonation.

Another device based on non-Watson-Crick base pairing was developed by Mao and his colleagues [39]. This is based on the reversible formation of a DNA triple-helix based on an oligo-purine-pyrimidine sequence. The T-A-T triple helix forms readily at neutral pH on the major groove (Hoogsteen) face of adenine; by contrast, the C-G-C triple helical requires the protonation of the major groove C, so it only forms at acidic pH. By varying the pH, Mao *et al.* are able to form an ordered triple helix from a duplex and a disordered strand segment. The formation of the triple helix results in a nanomechanical motion monitored by FRET. The change in structure caused by the transition has been used to control chemical reactivity [40].

A DNA-Based Stress-Gauge for Proteins

The machines described above do not work against any specific load, except for those forces in solution that oppose their motion. A DNA-based molecular device has been developed to establish how much work a DNA-distorting protein can do when it binds to DNA [41]. It was prototyped using integration host factor (IHF), a device that bends DNA 160° [42]. This device is illustrated in the top portion Figure 4a. The device is similar to the B-Z device, except that it contains three-domain planar motifs, termed TX [7]. The top shaft connecting the two TX portions of the device contains an IHF binding site. In addition, the bottom domain is connected by a pair of sticky ends. For IHF to bind, it must break the sticky ends. This concept is illustrated in the bottom part of Figure 4a, where a smaller bending angle is used for clarity. The bending is reported by a pair of dyes, via a FRET measurement. By increasing the strength of the sticky end, one can arrive at a point where the ability to do work is less than that necessary to break the cohesion of the sticky ends. The free energy associated with each sticky end is calculated from data obtained by SantaLucia's laboratory [43].

Autonomous Devices

All of the devices described above are clocked devices: The experimenter changes something about the environment of the device and some structural feature of the device itself is altered. It is evident that it would be desirable to create machines that run without experimenter intervention. This has now been done in a few instances. In one case, Mao and colleagues have built a device based on a DNAzyme that cleaves RNA [44, 45]. The advanced version of this device is shown in Figure 4b. In the open state (upper left), the device binds a strand of RNA and it opens. When the RNA is cleaved (upper right), the two cleavage products are sufficiently short that they dissociate from the device; when the products dissociate, the device closes. If there is another molecule of the substrate in the solution, it, too, can be bound, and the system can go through another round. The system shown in Figure 4b has another level of sophistication. A DNA brake that cannot be cleaved by the DNAzyme can be added to the solution, as shown at the bottom of the drawing. The machine can be activated by removing the brake, using the standard Yurke *et al.* [22] approach.

Reif, Turberfield and colleagues have demonstrated an autonomous walking device that is based on alternating cycles of ligation, followed by cleavage using type IIs restriction enzymes, followed by ligation [46]. The ends generated by the restriction enzyme are ligated

to form a substrate for a different enzyme. This strategy is closely related to the non-mechanical finite-state machines based on linear DNA and type IIs restriction enzymes developed by Shapiro and his colleagues [e.g. 47]. A cleavage-free strategy for free-running devices has been described by Turberfield and his colleagues [48]. It entails the invasion of loops by strands that are only barely able to do so in the absence of other strands that are 'catalytic' in freeing up the loops for hybridization. A cascade approach (called hybridization chain reaction), designed for sensors, more than devices, has been reported recently by Pierce [49]; once begun a system forms a long double helix based on preferential pairing.

Transcriptional control of nucleic acid devices sits between autonomous devices and clocked devices. In an exciting proof of principle, Dittmer and Simmel have used transcription of a designed sequence [50] to control the Yurke *et al.* [22] tweezers. They only close the tweezers with the RNA molecule that is transcribed, and need to open it by addition of an unset strand. Nevertheless, it is does not appear impossible to use cyclic systems to control nucleic acid nanodevices in a fashion similar to that used by Elowitz and Leibler [51] to control the color of cells.

Conclusions

The devices described above represent a remarkable toolbox for controlling the structural states of nucleic acid objects, and even of arrays. I suspect that the importance of the sequence selectivity (associated so far, only with the Yurke *et al.* [22] control method) is the key to future progress of this field. It will come to the fore even more than it has already when numerous robust devices are incorporated into fixed positions in periodic arrays and other structures, not only as done by Yan *et al.* [32], but also in systems where the devices do not modify the basic structure of the arrangement. Likewise, the extension of the Dittmer and Simmel [38] approach to complete autonomy will enable structural manifestations of logical circuits, produced perhaps by the techniques of DNA-based computation [e.g., 12]. The toolbox will no doubt continue to grow. However, what is needed now is for the DNA-nanodevices community to interact with other communities, ranging from materials science and nanoelectronics to biochemistry, genomics and molecular therapy. The value of the devices and approaches described above will be maximized when these diverse communities can help to establish goals for their use.

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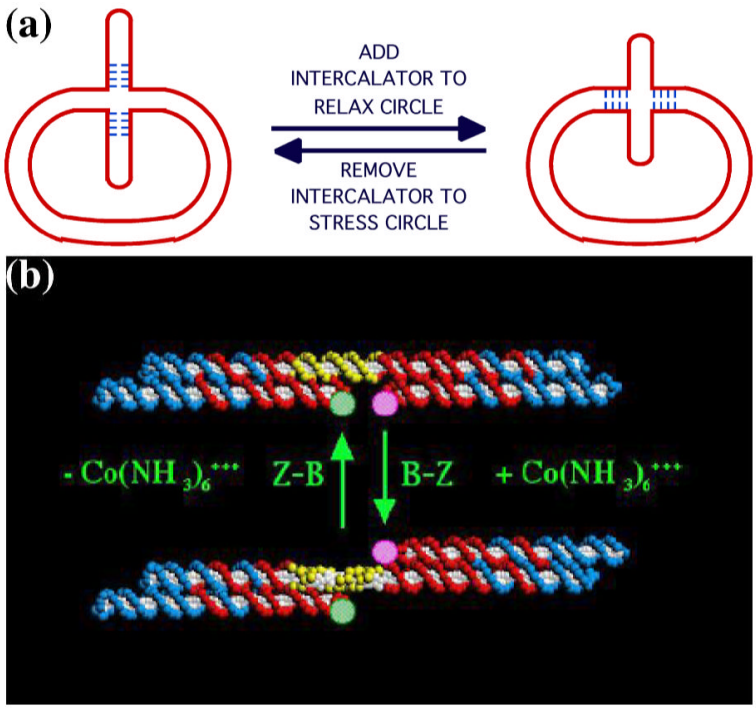

Figure 1. Early DNA Nanomechanical Devices

(a) A Device Based on DNA Supercoiling. The system consists of a small DNA circle that contains a permanent cruciform. The four nucleotide pairs at the base of the cruciform are capable of branch migration, because they are the same in both arms of the extruded cruciform (left). When the circle is relaxed by the addition of an intercalator, the mobile nucleotide pairs move to the circle. *(b) A Device Based on the B-Z Transition of DNA.* Two DX molecules (red and blue) are connected by a shaft that contains 20 nucleotide pairs (yellow) that are capable of undergoing the B-->Z transition. In the B-state, both domains are on the same side of the shaft (top), but when $Co(NH_3)^{3+}_6$ is added to the solution, the system switches to the Z-state, and the domains are on opposite sides of the shaft. The red and green circles represent a pair of dyes for a FRET measurement.

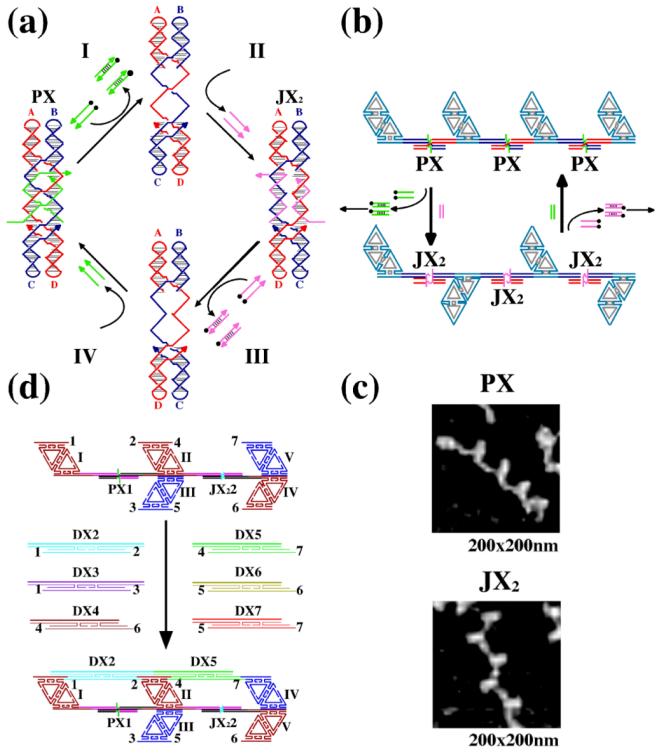

Figure 2. The PX-JX_2 Device and its Applications

(a) The Machine Cycle of the PX-JX_2 Device. The PX molecule (left) contains green set strands that are removed (process I) by unset strands that are biotinylated (black dots). The resulting naked frame (top) can be bound by pink set strands (process II) to put the device in the JX_2 state. Note that the bottoms have been rotated by a half-turn between the two states. Processes III and IV so that the same operations (with appropriate strands) can be used to restore the system to the PX state. (b) A System to Demonstrate the Motion of the PX-JX_2 Device. DNA trapezoids are connected by the device. When the system is in the PX state, all trapezoids point in the same direction, but they point in opposite directions in the JX_2 state. (c) Atomic Force Microscopy Images of the Molecules in (b). The PX and the JX_2 strings show the images expected from the schematics in *(b)*. (d) A Translation Device Based on the PX-JX_2 Device. A DNA diamond and two double diamonds are connected by two different PX-JX_2 devices; the one on the left is in the PX state, and the one on the right is in the JX_2 state. This arrangement establishes an order of Arabic numerals along the top of the device that will bind a particular pair of DX molecules; in this case, the molecules labeled DX2 and DX5 are selected for ligation. There is no transcriptional relationship between the set strands in the devices and the sequences in the product.

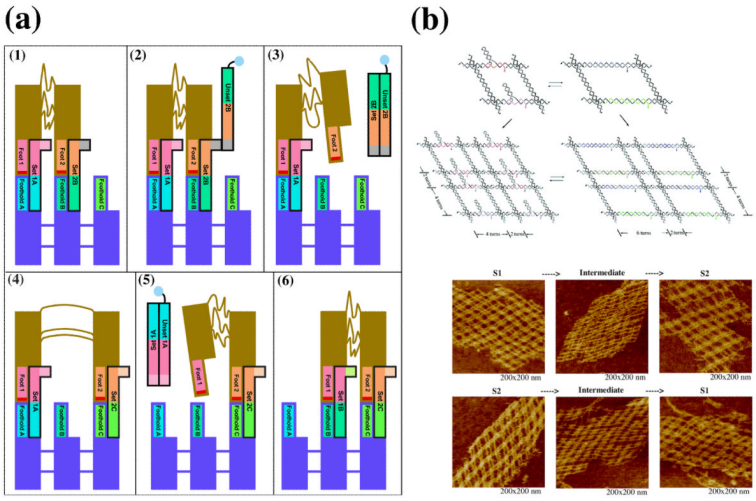

Figure 3. A DNA Walking Device and a DNA Array-Modifying Device

(a) A DNA Walking Robot. The device consists of brown double helices connected by a flexible linker. It is held to a blue sidewalk by set strands [1]. The rightmost set strand is removed [2] and [3]), and a new set strand attaches the right leg to a new position on the sidewalk. [4]. The same process is repeated in [5] and [6] so that at the end of the walk, the nanorobot has moved one step. The red mark at the bottom of each leg of the walker represents a psoralen molecule that crosslinks the walker to the sidewalk for analytical purposes. (b) A Two-Dimensional Array Capable of Changing Cavity Dimensions. The upper panel shows a schematic strand diagram of the tiles and their incorporation into arrays. The red and purple set strands correspond to a contracted state, while the blue and green set strands correspond to the expanded state. The lower panel shows AFM images that illustrate control of cavity size. The ‘before’ (left), ‘transition’ (center) and ‘after’ (right) states of the array are illustrated in both directions. Reproduced with permission.

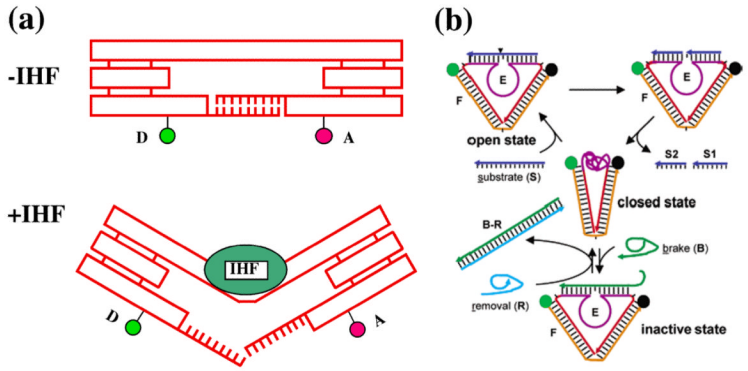

Figure 4. Advanced DNA Machines

(a) A DNA-Stress Gauge. A DNA-distorting protein (IHF in this case) binds to the upper domain of a DNA device. The central shaft, connects two three-domain double helical motifs (TX motifs), and it contains the binding site for IHF. When IHF binds, it distorts the upper helix. The TX motifs are also held together by sticky ends that must be disrupted for the protein to bind. By titrating the strength of the sticky ends, it is possible to estimate that amount of work that the protein can derive from binding to its recognition site. The green and red circles represent a pair of dyes to monitor the state of the system by FRET. *(b) An Autonomous DNA Machine.* The machine consists of a DNAzyme that can bind and cleave a piece of RNA; when it binds, the machine is in the open state (upper left). Following cleavage (upper right), the products dissociate from the device (middle). However, another RNA strand can bind and restore the machine to the open state. The state of the machine is monitored by FRET, using the dyes represented by filled circles. An additional sophistication to this device is the ability to apply a brake to the system. This is shown as the green strand, made of DNA, which can block the site, but which can be removed by a complementary strand (light blue). Reproduced with permission.