ANNUAL REVIEWS

Annual Review of Biomedical Engineering

Controlling Matter at the Molecular Scale with DNA Circuits

Dominic Scalise[1] and Rebecca Schulman[1,2]

[1]Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, Maryland 21218, USA

[2]Department of Computer Science, Johns Hopkins University, Baltimore, Maryland 21218, USA; email: rschulm3@jhu.edu

Annu. Rev. Biomed. Eng. 2019. 21:469–93

The *Annual Review of Biomedical Engineering* is online at bioeng.annualreviews.org

https://doi.org/10.1146/annurev-bioeng-060418-052357

Keywords

DNA strand displacement, structural DNA nanotechnology, synthetic biology, aptamers, chemical computing, programmable matter

Abstract

In recent years, a diverse set of mechanisms have been developed that allow DNA strands with specific sequences to sense information in their environment and to control material assembly, disassembly, and reconfiguration. These sequences could serve as the inputs and outputs for DNA computing circuits, enabling DNA circuits to act as chemical information processors to program complex behavior in chemical and material systems. This review describes processes that can be sensed and controlled within such a paradigm. Specifically, there are interfaces that can release strands of DNA in response to chemical signals, wavelengths of light, pH, or electrical signals, as well as DNA strands that can direct the self-assembly and dynamic reconfiguration of DNA nanostructures, regulate particle assemblies, control encapsulation, and manipulate materials including DNA crystals, hydrogels, and vesicles. These interfaces have the potential to enable chemical circuits to exert algorithmic control over responsive materials, which may ultimately lead to the development of materials that grow, heal, and interact dynamically with their environments.

Contents

1. INTRODUCTION

While publishing the world's first computer algorithm, Ada Lovelace remarked that computers "might act upon other things besides number" (1, p. 27). She noted that computer algorithms could manipulate anything that might be represented as digital information, which today includes numbers, music, images, and video. Now, nearly two centuries after Ada's insight, chemical circuits are enabling algorithms to operate outside of the traditional computer and directly manipulate the behavior of physical materials.

Electronic computers operate on information encoded in electronic voltages. Chemical computers (2), by contrast, are reaction networks that operate on information encoded in the concentrations of molecules. The outputs of these chemical computers are molecules, which can be designed to interface with materials. The use of chemical algorithms to direct the behavior of materials could eventually lead to the development of programmable matter in which chemical circuits control self-assembly, detect and heal damage, or adapt dynamically to signals sensed in the environment.

DNA circuits are a particularly promising means for computing within chemical systems. They are composed primarily of DNA oligonucleotides (i.e., short strands of DNA), but may also contain enzymes such as DNA polymerase or exonucleases (3–5). DNA circuits can perform the same fundamental operations as electronic transistor circuits, including Boolean logic and arithmetic (6–9), generation of oscillations and regulating time (10–13), and execution of interactive algorithms such as playing a game of tic-tac-toe (14).

The inputs to DNA circuits are strands of DNA with specific sequences that can convey information about a material or environment to the circuit. Likewise, the outputs from a DNA circuit

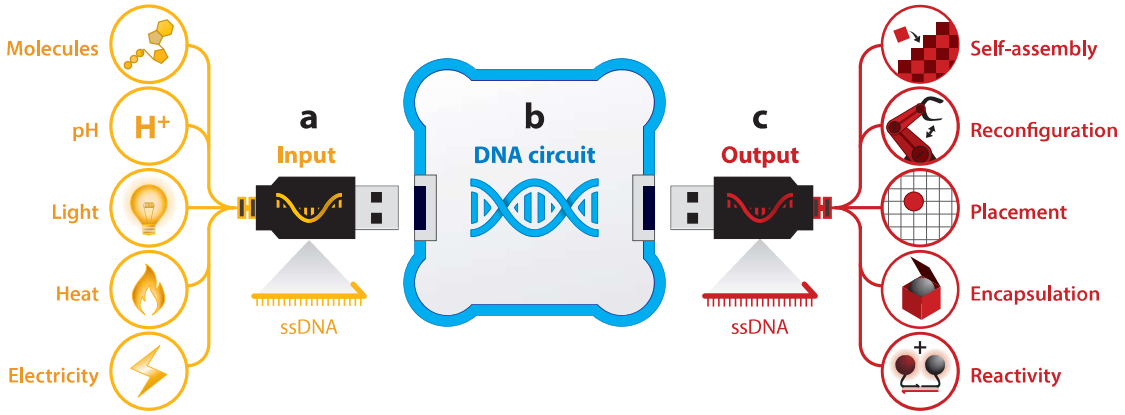


Figure 1

DNA circuit interfaces. (*a*) External stimuli are converted into single-stranded DNA (ssDNA), which serves as a standard interface between stimuli and the DNA circuit in a similar way to how a USB plug serves as a standard interface between peripheral devices and an electronic computer. (*b*) The DNA circuit reads the input strands, performs a programmed transformation, and releases output strands of ssDNA. (*c*) The output strands can direct downstream material processes, enabling the DNA circuit to program material behavior.

are strands that can control the states of downstream materials or molecules. The input/output strands for DNA circuits are thus analogous to USB ports for electronic computers, that is, a standard interface that allows the circuit to communicate with peripheral devices, in this case, molecules or materials (**Figure 1**). The use of modular input/output interfaces is a key design principle that allows the same types of circuits to interact with a diverse set of materials. An input sensor could, in principle, be exchanged for a different type of sensor to allow the same circuit to receive and process information about a different type of environmental stimulus. Similarly, output actuators could be exchanged to allow the same circuit to direct different material responses.

2. DNA CIRCUITS

DNA circuits can be conceptualized as black boxes that accept DNA strands as inputs, perform a programmed transformation, and release or synthesize strands of DNA as outputs. We collectively term the input and output strands the interface strands to distinguish them from the rest of the DNA circuit. The circuit elements within the conceptual black box can include (*a*) DNA strand-displacement reactions that rely solely on the base-pairing of DNA strands to sequester DNA strand inputs or release DNA outputs (**Figure 2*a***), (*b*) DNAzyme reactions that use the catalytic activity of DNA to make or break the covalent bonds of other strands of DNA (**Figure 2*b***), and (*c*) enzymatic circuits that utilize proteins such as DNA polymerase or exonuclease to synthesize, modify, or degrade strands of DNA (**Figure 2*c***). Circuits composed of these elements can perform many signal processing functions, including Boolean logic (**Figure 2*a*,*b***), neural network computation (15, 16), signal amplification (17, 18), the generation of oscillations and other time-dependent signals in the concentration of output molecules (**Figure 2*c***) (11–13), and the generation of spatially patterned signals wherein different outputs are released at different spatial locations (**Figure 2*d***) (11, 19, 20).

Designing modular interfaces between DNA circuits and materials often requires the circuit to be insulated from the material, and vice versa, so that the circuit does not irreversibly consume the input strands and the material does not irreversibly consume the output strands. In some cases in which this irreversible consumption (i.e., loading) cannot be avoided, an additional load driver mechanism may need to be inserted to fully insulate the circuit and material (21, 22). A similar

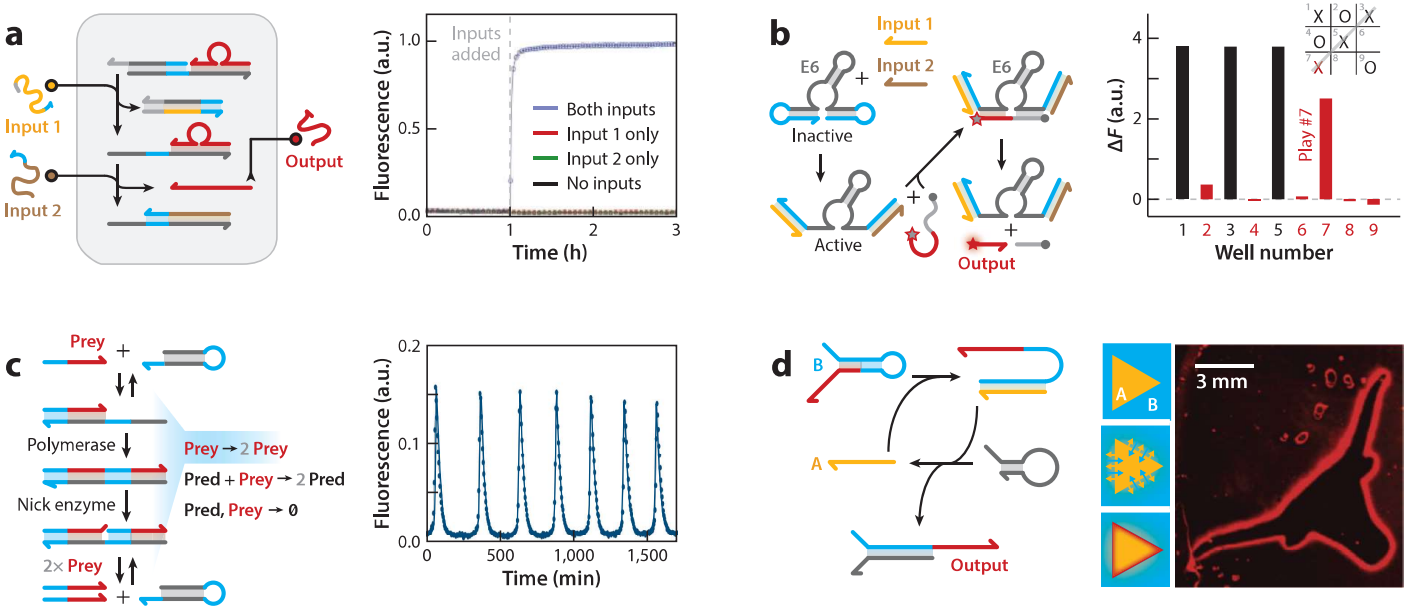


Figure 2

DNA circuits with DNA strand inputs (*yellow*, *tan*) and outputs (*red*). (*a*) A DNA strand-displacement circuit, which processes information via competitive DNA base-pairing. Here, a Boolean logic AND gate releases an output strand (*red*) from a complex only when both input strands (*yellow*, *tan*) are present (6). High fluorescence indicates a high concentration of the output strand. (*b*) (*Left*) A Boolean logic circuit built around the E6 DNAzyme (*dark gray*) (14) that cleaves a DNA strand, releasing an output strand (*red*) only when both input strands (*yellow*, *tan*) are present. A circuit composed of such gates can play tic-tac-toe if it receives input strands that encode information about the presence of X's played by the circuit and O's played by the human, and produces an output corresponding to the next move to be played. (*Right*) The final step of a game. The large red bar indicates the circuit's direction to play in the seventh cell of the game board to win the round. (*c*) A dynamic DNA circuit that produces an oscillatory output because of coupled DNA polymerization and nicking reactions, catalyzed by enzymes (11). This particular circuit is a signal generator and does not have a designated input strand. (*d*) A DNA edge-detection circuit. Two reactants, A and B, were initially present in different parts of the pattern. Photocleavage of reactants in certain areas allowed the reactants to diffuse and encounter one another. The resulting spatial computation process produces output strands only at edges where A is initially present on one side of the edge and B is initially present on the other side (19). Abbreviation: a.u., arbitrary units. Panel *a* adapted with permission from AAAS. Panel *b* adapted with permission from *Nature Biotechnology*. Copyright 2003, Nature. Panel *c* adapted with permission from *ACS Nano*. Copyright 2012, American Chemical Society. Panel *d* adapted with permission from *Nature Chemistry*. Copyright 2013, Nature.

challenge can arise if the material imposes conflicting constraints on the exact sequence or secondary structure of the interface strands. In principle, this sequence dependency can be addressed through the use of additional reactions to convert the input strands into entirely independent sequences before they interact with the circuit, and the output strands into different sequences before they interact with the material. This conversion step is generally called sequence translation (23). While useful for ensuring modularity, the use of load drivers and sequence translators often comes at the cost of additional circuit complexity.

For the remainder of this review, we focus on mechanisms that convert environmental stimuli, such as light and heat, to and from interface strands that can interact with DNA circuits. In this scope, we refrain from further discussing the internal workings of DNA circuit black boxes themselves, as they have been covered more extensively in other excellent reviews (3–5).

3. TRANSDUCING INFORMATION ENCODED IN DNA SEQUENCES TO AND FROM OTHER TYPES OF SIGNALS

Transduction is the conversion of information from one signal form to another. Information encoded in the concentration of a strand of DNA can be transduced from and to many other forms,

including the concentration of other molecules or ions or as pH, light, temperature, or electrical signals. In this section, we review methods for transducing these signals into interface strands of DNA, thus allowing DNA circuits to receive information about stimuli in the surrounding environment.

3.1. Molecular Inputs

DNA aptamers are sequences of DNA that can bind specifically to molecules such as ATP (24), cocaine (25), metal ions (26), proteins, and peptides (27–31). Aptaswitches are nucleic acid sequences or complexes that can bind to a target molecule and, in doing so, can further induce a conformational change of another part of the aptaswitch. In many cases, this conformational change can release a strand of DNA (32–35), which can then serve as a DNA circuit input. Aptaswitches can also expose a toehold domain in a DNA complex (36), which can allow a strand-displacement reaction to proceed. Aptaswitches can also displace domains that would otherwise inhibit other strands from binding to a DNA complex (37).

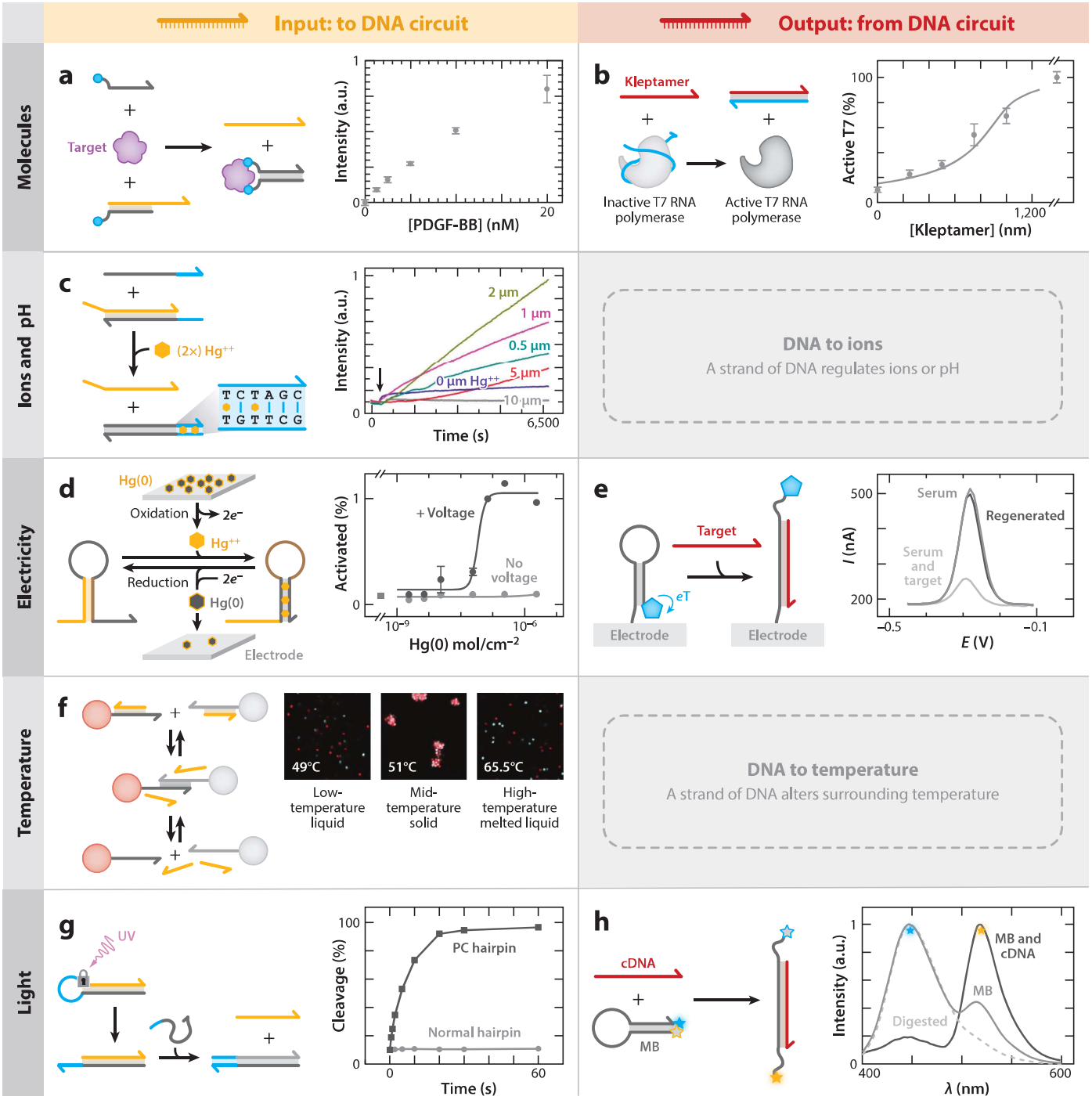
Output strands released by DNA circuits can also direct the capture or release of molecules from an aptamer by binding to the aptamer, thus changing the aptamer's binding affinity for its target. Bhadra & Ellington (38) modified the fluorescent RNA Spinach aptamer to fold into an inactive state in which it did not associate with its target molecule (DFHBI fluorophore). Hybridization with a trigger strand of DNA refolded the inactive aptamer into an active state in which it successfully bound its target (38). Lloyd et al. (39) used DNA strands complementary to aptamer sequences, called kleptamers, to bind to and displace aptamers from their targets. This technique was demonstrated with both a Broccoli aptamer, which binds to DFHBI, and an aptamer for a RNA polymerase, which prevents the RNA polymerase from transcribing while bound to the aptamer (**Figure 3*b***). Aptamers have also been integrated into reconfigurable DNA nanostructures. For example, they have been used as binding sites for target molecules at the end of DNA nanotweezers (40). When a trigger strand of DNA opens the tweezers, the two aptamer binding sites at the ends of the tweezers separate. Because binding of the target protein requires interaction with both binding sites, this conformational change releases the protein target. The tweezers nanostructure thus allows a strand of DNA that is not itself an aptamer binding sequence to direct the release of a target molecule.

3.2. Ions and pH

Strand-displacement reactions can be designed to release an interface strand of DNA only in the presence of target ions, which can then serve as an input strand to communicate the presence of the target ions to a DNA circuit. For example, Liu & Mao (41) used Hoogsteen triplex formation, in which CGC triplets form under acidic conditions where $[H^+]$ is high, to colocalize a strand of DNA to a complex and initiate a strand-displacement reaction. The release of the interface strand from this reaction thus signifies a high H^+ concentration. Amodio et al. (42) implemented a similar pH-responsive strand-displacement reaction that uses CGC triplets in a Hoogsteen triplex to stabilize both a clamp domain, which suppresses a DNA strand-displacement reaction, and a toehold domain, which initiates a strand-displacement reaction.

Tang et al. (43) split the sequences for a pH-dependent i-motif between an invading strand and a strand-displacement complex. At low pH, the formation of the complete i-motif colocalizes the strand to the complex, initiating a strand-displacement reaction that releases an interface strand of DNA. The authors also used a similar mechanism based on the G quadruplex motif, which formed upon the addition of strontium (Sr^{++}) ions to allow a strand-displacement reaction to occur only

in the presence of Sr^{++} ions. Ding et al. (44) developed a DNA strand-displacement reaction that is triggered by mercury (Hg^{++}) ions. The authors used a thymine–thymine (T-T) mismatch in the toehold domain of a strand-displacement complex to prevent an invading strand of DNA from binding to this toehold. However, when mercury ions are added, a non-Watson-Crick T-T base pair is stabilized between the invading strand and the complex, allowing the toehold domain to fully hybridize and initiate a strand-displacement reaction (**Figure 3*c***).



(Caption appears on following page)

Figure 3 (*Figure appears on preceding page*)

Transducing signals to and from DNA sequences. (*a*) An interface that converts the concentration of a target molecule, platelet-derived growth factor BB (PDGF-BB) (*purple*) into the concentration of an interface strand of DNA (*yellow*). Two aptamer sequences of DNA (*blue*) bind to the target molecule and displace the interface strand. A downstream fluorescent reporter complex tracks the concentration of the yellow strand (32). (*b*) A kleptamer (*red*) displaces an aptamer from T7 RNA polymerase. While T7 RNA polymerase is bound by the aptamer it cannot transcribe RNA (39). (*c*) An Hg^{++}-dependent DNA strand-displacement (DSD) reaction that releases the interface strand (*yellow*). A downstream fluorescent reporter tracks the concentration of the yellow strand over time. The black arrow in the graph marks the time when Hg^{++} ions were added (44). (*d*) A gold electrode is initially coated in Hg(0). When an oxidative potential is applied to the electrode, Hg(0) is oxidized into Hg^{++}, which can promote DNA hybridization using the same mechanism as in panel *c*. Application of a reductive potential reverses the process (45). (*e*) A hairpin (*dark gray*) modified with a methylene blue redox moiety (*blue pentagon*) is anchored on an electrode. Proximity of the methylene blue redox moiety to the electrode generates a Faradaic current. A complementary interface strand of DNA (cDNA) (*red*) opens the hairpin and prevents the methylene blue redox moiety from interacting with the electrode, suppressing the current. The data show high current for the initial state with no interface strand added (i.e., serum only), decreased current when the interface is added (i.e., serum + target), and high current again when the interface is removed by a washing regeneration step (i.e., is regenerated) (52). (*f*) A temperature-sensitive DSD reaction that directs DNA-modified (*dark and light gray*) particle assembly within a target temperature range. Below the target temperature, strands of DNA (*yellow*) bind to the linker strands and prevent assembly. At the target temperature, the particles bind to form a solid assembly and displace the yellow strands into solution. Above the target temperature, all strands are thermally dissociated (57). (*g*) A DNA hairpin with a photocleavable (PC) linker (*lock symbol*) presents a toehold domain (*blue*) after exposure to UV light, which allows a strand-displacement reaction to release the yellow strand (61). (*h*) A molecular beacon (MB) (*dark gray*) is a DNA hairpin with two different fluorophores at its ends. In the beacon's initial state, the fluorophores are close to each other, enabling fluorescence resonance energy transfer to excite the acceptor fluorophore via excitation of the donor fluorophore (coumarin). After a cDNA strand is added (*red*) that binds to and opens the hairpin, the two fluorophores are separated and the intensity of the acceptor fluorophore decreases significantly (64). Abbreviation: a.u., arbitrary units. Panel *a* adapted with permission from the *Journal of the American Chemical Society*. Copyright 2013, American Chemical Society. Panel *b* adapted with permission from *ACS Synthetic Biology*. Copyright 2017, American Chemical Society. Panel *c* adapted with permission from *Chemical Communications*. Copyright 2013, Royal Society of Chemistry. Panel *d* adapted from the Royal Society of Chemistry. Panel *e* adapted with permission from *Nature Protocols*. Copyright 2007, Nature. Panel *f* adapted with permission from *Soft Matter*. Copyright 2018, Royal Society of Chemistry. Panel *g* adapted with permission from the *Journal of the American Chemical Society*. Copyright 2013, American Chemical Society. Panel *h* adapted with permission from *Angewandte Chemie*. Copyright 2001, Wiley.

To the best of our knowledge, no experimental studies have reported the use of a DNA strand to directly trigger the release or sequestration of ions in quantities sufficient to significantly change free ion concentrations in solution (the converse of the use of ions to release specific DNA strands). Such a DNA-to-ion interface might allow DNA circuits to dynamically adjust the pH over time, or change pH suddenly in response to signals detected in the environment.

3.3. Electrical Signals

Electronic devices can provide inputs to DNA circuits through electrodes that release or activate interface strands of DNA. Ranallo et al. (45) developed four different mechanisms for activating DNA strand-displacement reactions by using voltage to release specific ions from gold electrodes. First, a gold electrode was coated with a thin film of mercury. When an oxidizing potential scan from 0.2 to 0.65 V was applied to the electrode, the mercury was released into solution as Hg^{++} ions. The released ions facilitated binding of target partially complementary DNA domains by stabilizing non-Watson-Crick T-T base pairs (**Figure 3*d***) (see also Section 3.2 on the ionic activation of DNA). Application of a reductive potential (−0.3 V) reversed the stabilization of the T-T base pairs by redepositing the mercury back onto the electrode. The other three mechanisms the authors used to electrically activate other DNA circuits involved releasing silver ions to facilitate non-Watson-Crick cysteine–cysteine (C-C) base pairs, releasing input strands of DNA initially bound to the electrode by thiol–gold bonds, and releasing copper ions to activate a copper-sensitive DNAzyme (45). These strategies might be used together to selectively activate or release different interface strands of DNA within the same solution. Other studies have electrochemically

controlled the activity of DNAzymes using ions other than copper (46, 47). Jeong et al. (48) used an entirely different technique to implement voltage-directed DNA strand activation by fabricating DNA-impregnated multilayer nanofilms on the surfaces of electrodes. Application of voltage to one such electrode reduced the nanofilm and released the impregnated strands of DNA into solution, where they interacted with a fluorescently labeled DNA beacon (48).

DNA strands can produce or regulate voltage or current by regulating the distance between an electrode and an electrically active molecular tag. The close proximity of the electrode to the tag generates a Faradaic current. Both Fan et al. (49) and Immoos et al. (50) demonstrated this technique using a redox ferrocene-labeled DNA hairpin immobilized on a gold electrode. When no other DNA strands were present, the DNA hairpin's lowest energy conformation kept the ferrocene close to the electrode, generating current. When a DNA strand with a sequence complementary to that of the hairpin was added, binding between this interface strand and the immobilized hairpin opened the immobilized hairpin, separating the ferrocene from the electrode and decreasing the measured current. Similar schemes involving electrodes with surface-immobilized DNA have used different labels to generate a current, including methylene blue (**Figure 3*e***) (51, 52), and conformational switches of DNA motifs other than hairpins (53). Electrochemical DNA sensors are further reviewed by Drummond et al. (54).

3.4. Temperature

Most current experimental studies involving DNA circuits tend to be designed to operate at a particular set temperature, rather than to respond to temperature as an input. However, some DNA hairpin structures have been designed to serve as temperature-responsive thermometers by tuning the strength, and thereby the melting temperature, of the stem domains that hold the hairpins closed (55, 56). When the stem melts, the hairpin opens into a single-stranded conformation. Manoharan and colleagues (57, 58) modified the temperature dependence of DNA-grafted colloids to program nonlinear aggregation and reentrant melting of the colloids, which suggests an alternative approach to programming temperature-sensitive DNA strand-displacement reactions. Specifically, these authors began with colloidal assemblies held together by DNA linkers between the colloids, and added complementary interface strands of DNA to bind to and displace the linkages from each other. At low temperatures, enthalpy favors disruption of the linkages and melting of the colloidal assemblies, because more total bonds can form when the competing strands sequester the linkages. At intermediate temperatures, entropy favors formation of the linkages, release of the interface strands, and stabilization of the colloidal assemblies, because two strands are displaced by every linkage formation. At high temperatures, complete thermal dissociation of DNA hybridization melts the linkages and the colloidal assemblies (**Figure 3*f***). This reaction system shows how DNA strands can be released or sequestered at a target temperature, which could be used to communicate information about the temperature of the environment to a downstream DNA circuit.

To the best of our knowledge, no studies have demonstrated how the presence of a specific DNA strand might directly alter the temperature of the surrounding solution. Such a DNA-to-temperature interface could be useful for creating programmable three-dimensional spatiotemporal temperature gradients within solutions. However, regulating temperature with DNA strands may prove difficult because the amount of energy that is required to heat water is large compared with the energy stored in DNA hybridization. Such a control system may thus need to harness an external energy supply, such as using light illumination plasmon resonance to generate heat from gold nanoparticles (59). With such a setup, interface strands of DNA might control where the gold nanoparticles are positioned to direct local heating.

3.5. Light

Light can direct the release of a specific DNA sequence by controlling the degradation or conformational change of reagents that initially block or sequester a DNA domain from participating in downstream reactions. Prokup et al. (60) created a photosensitive strand-displacement reaction by suppressing the ability of a strand to hybridize to its complement using four NPOM (6-nitropiperonyloxy-methylene)-caged thymidine groups evenly distributed along the strand. The authors found this photocaged strand did not react with a downstream strand-displacement circuit until UV irradiation at 365 nm removed the caging groups (60). Huang et al. (61) synthesized a DNA hairpin gate with a photocleavable linker in the hairpin backbone. On exposure to 365-nm light, the hairpin's backbone was cleaved, exposing a toehold domain within the hairpin loop. This exposed toehold allowed a strand with a complementary toehold to bind and initiate a strand-displacement reaction (**Figure 3*g***). Kou et al. (62) inserted *cis*-20,60-dimethylazobenzene (DMazo) into a strand of DNA, which favors duplex association in its *trans* state and dissociation in its *cis* state. By toggling the DMazo into its *trans* state with 475-nm light, the authors initiated a strand-displacement reaction. Toggling the DMazo back into its *cis* state by exposure to 365-nm light induced dissociation of DMazo strands from their complementary sequences, driving the strand-displacement reaction in the reverse direction (62). Nakamura et al. (63) used a photoinitiated cross-linker, 3-cyanovinylcarbazole (^{CNV}K), to form a covalent bond between an invading strand of DNA containing ^{CNV}K and a pyrimidine base in a complementary DNA complex, after exposure to light at a wavelength of 366 nm. This covalent bond made a strand-displacement reaction effectively irreversible and sped up its kinetics by a reported factor of 20-fold by inhibiting the backward branch-migration step (63).

A standard way to transduce a DNA hybridization event into a signal that alters the optical properties of the solution is to use a fluorescent molecule conjugated to the end of a strand of DNA to emit different intensities of light at a target wavelength, depending on the state of the conjugated DNA strand. Emission from the fluorophore can be quenched by a nearby quencher molecule or transferred by FRET (fluorescence resonance energy transfer) to a different fluorophore, which effectively changes the wavelength of the fluorescence output signal. An interface strand of DNA can change the distance between these different fluorophore and quencher modifications by opening a fluorophore-modified hairpin (**Figure 3*h***) (64), or displacing a fluorophore-modified strand from a complex (6). The kinetics of many of the devices described in this review are monitored by measuring changes in fluorescence from fluorescently modified DNA complexes.

4. USING DNA STRANDS TO CONTROL DNA NANOSTRUCTURE ASSEMBLY, DISASSEMBLY, OR REORGANIZATION

A strand of DNA that is an output of a DNA circuit can interact with DNA nanostructures by serving (*a*) directly as a building block in a self-assembly process, (*b*) as a trigger that activates one or more building blocks, or (*c*) as an agent that removes DNA strands or subassemblies from an initially assembled structure. Such interactions effectively use the sequence information encoded in a circuit's output strand to direct how an assembly should form or change shape.

4.1. Self-Assembly

DNA can self-assemble into arbitrary two- or three- dimensional shapes (65–68) up to several hundred nanometers in size (69), and into a diverse range of periodic lattices and crystals (70, 71). DNA nanostructures may be broadly classified into either scaffolded DNA origami nanostructures (65), in which short staple strands fold a long scaffold strand into a final shape, or unscaffolded

assemblies, in which DNA bricks (66) or tiles (72–73) self-assemble into ordered lattices via a crystal growth process. In both cases, the specific sequences of each strand determine which components may bind to which others and how strongly and, in turn, determine what final structures self-assemble.

In principle, DNA circuits could be used to direct the self-assembly of these structures by presenting outputs that control which strands are available to self-assemble (74). Dynamic control over the availability of different DNA strands might allow circuits to direct elaborate, hierarchical assembly protocols, or to incorporate feedback from the environment during assembly. One challenge to the design of such systems is that DNA nanostructures are generally formed by annealing: The temperature of the assembly mixture is first raised above the melting temperature of the DNA and then slowly cooled. Assembly occurs after the temperature drops below the nanostructure's melting temperature. Parameters other than temperature, such as denaturant concentration (75), have also been used for annealing. During an annealing process, most DNA circuits, which are held together by Watson–Crick base pairs, also melt and reform. Such melting and reformation of circuit components would interrupt the function of the many types of DNA circuits that are designed to begin operation in a metastable configuration and could denature enzymes or other cofactors needed for the operation of other DNA circuits. Because circuits are typically designed to operate isothermally, these circuits would need to be redesigned to operate during an annealing process.

An alternative approach to controlling self-assembly with DNA circuits is to develop mechanisms by which DNA nanostructures assemble isothermally. Isothermal nanostructure assembly processes are generally more difficult to design than assembly processes that use annealing because under isothermal conditions the component strands of DNA assemblies can easily become kinetically trapped in off-target intermediate structures. In principle, these kinetic traps could be avoided by using DNA circuits to control the pathway in which assembly components are made available.

4.1.1. DNA strand-directed activation of building blocks of DNA nanostructures. One strategy for controlling DNA nanostructure self-assembly is to use DNA strands to activate the building blocks of a target nanostructure. Zhang et al. (76) used DNA strand-displacement circuits to control the self-assembly of DNA nanotubes composed of DNA tiles. These authors constructed inactive tiles where two of the intertile sticky-end binding sites on each tile were covered by a DNA protector strand, which inhibited nanotube growth. A complementary interface strand, released by a DNA circuit, successfully removed the protection strand from the inactive tiles, thus activating the tiles and allowing nanotube assembly to occur (**Figure 4*a***). Franco and colleagues (77) demonstrated the reversible assembly and disassembly of similar DNA nanotubes by repeatedly protecting and deprotecting a tile's sticky end strands in response to changes in pH. Padilla et al. (78) created DNA tiles containing inactive binding domains, in which the binding of a sticky end on one side of these tiles partially displaced a cover strand of DNA. This cover strand could then activate a sticky end on the opposite end of the tile. A DNA circuit might presumably trigger a cascading assembly process involving such tiles by activating an initial tile, which then uses its newly activated sticky end to activate a chain of additional tiles. Zhang et al. (76) demonstrated an analogous sequential assembly cascade in which droplets, rather than tiles, are assembled into chains. Droplets were functionalized with two DNA attachment strands that were initially hybridized together. Interdroplet assembly was initiated by adding an interface strand of DNA that binds to one of the attachment strands via a single-stranded toehold, displacing the second attachment strand, which could then attach to another droplet (79).

Wang et al. (80) reversibly activated and deactivated larger DNA origami building blocks that could form different dimers depending on how they were activated (**Figure 4*b***). These authors reversibly assembled four different tile types (labeled A, B, C, and D) into different permutations

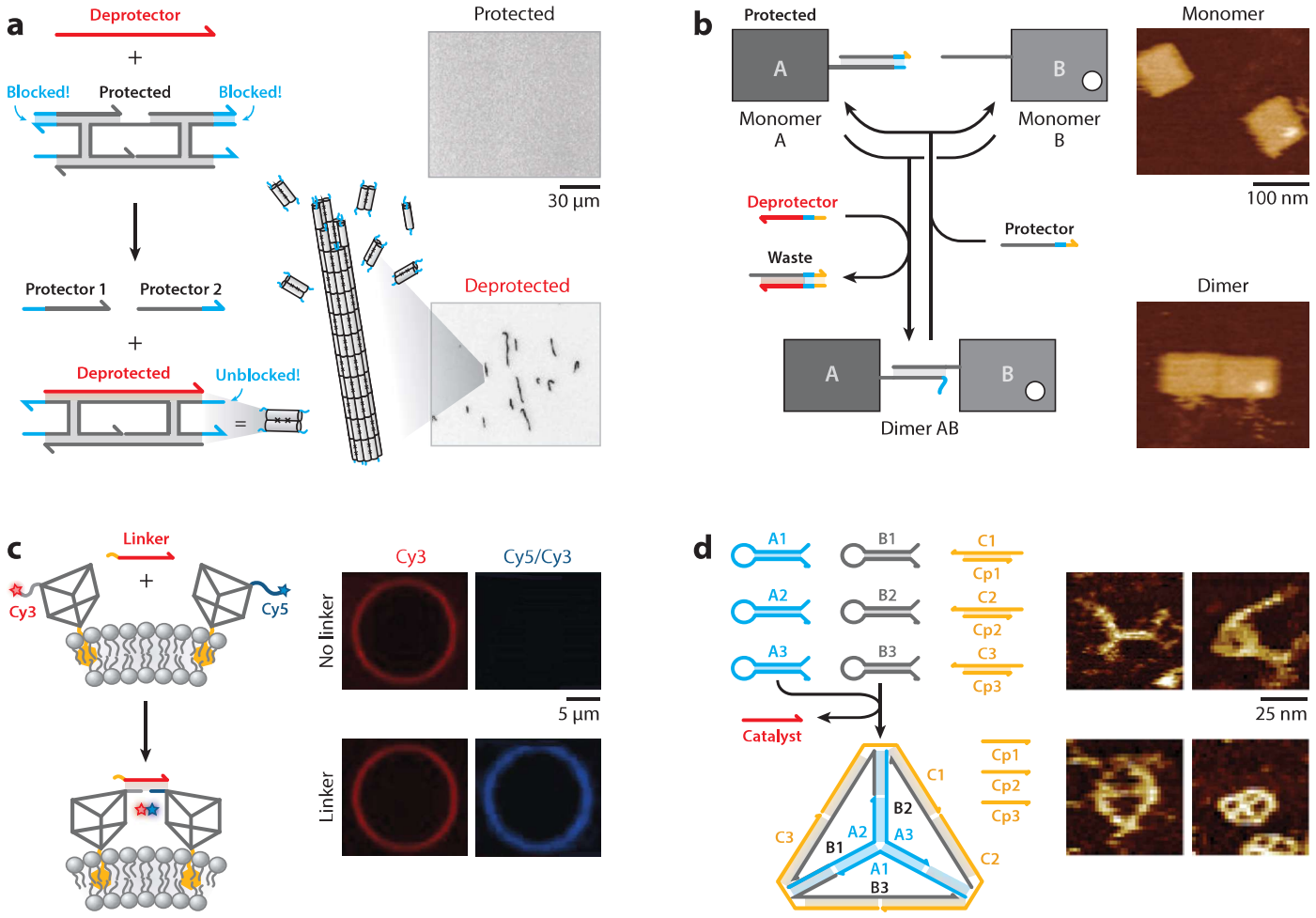


Figure 4

DNA strand-directed self-assembly. In each example, the red strand of DNA represents the interface strand, which could be the output of a DNA circuit, that directs the self-assembly of a nanostructure. (*a*) Activatable DNA tiles (76). Each tile starts in an inactive state in which two of its four self-complementary sticky ends (*blue*) are covered by protector strands of DNA. A deprotector strand (*red*) binds to a single-stranded toehold region at the center of the tile and displaces the protector strands, resulting in an active or deprotected tile. Deprotected tiles then proceed to self-assemble into nanotube structures. Total internal reflection fluorescence microscopy images show the tiles in (*top*) their protected state before deprotector strands were added, when no nanotubes are evident, and (*bottom*) their deprotected state after deprotector strands were added, where nanotubes have grown. (*b*) Scaffolded DNA origami tiles whose binding sites can be activated by DNA interface strands. A deprotector strand (*red*) binds to monomer A and removes its protector strand, creating a waste complex and allowing formation of a dimer AB. Introduction of a protector strand separates the monomers back into their initial state (80). Additional sequence-specific binding sites (not shown) facilitate different permutations of dimers. Atomic force microscopy (AFM) images show origami tiles in their monomer and dimer states. (*c*) Regulating self-assembly through the release of DNA linker strands that serve as bridges between two structures. Here, a linker strand (*red*) connects two DNA triangular prisms on a giant vesicle (81). (*d*) Catalytic assembly of a DNA tetrahedron. Initially, a solution was prepared that contained nine metastable hairpins or complexes (*blue*, *gray*, *yellow*), which constitute the parts of the tetrahedron. A catalyst strand (*red*) opens the A1 hairpin, initiating a cascade in which the tetrahedron forms via a series of reactions that follow a designed assembly pathway. AFM images show the intermediate structures: a three-arm junction, a closed triangle, two closed triangles, and the final tetrahedron (88). Panel *a* adapted from *Nature Communications*. Panel *b* adapted with permission from *Nano Letters*. Copyright 2018, American Chemical Society. Panel *c* adapted with permission from the *Journal of the American Chemical Society*. Copyright 2017, American Chemical Society. Panel *d* adapted from *ACS Nano*.

of dimers (AB, CD, AD, and BC) by adding different combinations of protector and deprotector strands to regulate different binding interfaces. They reported four cycles of reversible dimerization, with yields around 75%. DNA circuits might presumably direct assembly of origami tile with such interfaces into larger structures by releasing sequences of the relevant protector and deprotector strands.

4.1.2. Directing DNA nanostructure assembly by releasing linker strands for building blocks. DNA sequences can also direct the self-assembly of DNA nanostructures by acting as sequence-specific bridges between two other DNA structures. Unlike the use of interface strands to activate nanostructures described in the previous section, the use of interface strands as linkers helps separate structural building blocks from the sequences that determine connectivity, allowing the same building blocks to bind to different partners depending on which linker is activated.

Peng et al. (81) used linker strands of DNA to assemble multiple triangular wireframe DNA prisms anchored on vesicles into dimers (**Figure 4*c***). Displacement strands that were complementary to the linker strands were used to reverse the assembly process. Cao et al. (82) used different sequences of linker strands of DNA to selectively control the assembly of DNA-functionalized gold and silver–gold nanoparticles into aggregates, which were used as a two-color mechanism for detection of DNA. Yao et al. (83) used DNA strand-displacement circuits to control the self-assembly of DNA-functionalized gold nanoparticles by using output strands from a DNA circuit to link particles together. These authors further explored differences in reaction kinetics for strand-displacement reactions when the reactant strands were conjugated to gold nanoparticles, as opposed to standard strand-displacement kinetics without nanoparticle conjugations (84). For a more detailed discussion of how DNA strands can control the aggregation of DNA-functionalized nanoparticles, we refer the reader to a review by Thaxton et al. (85) and a perspective article by Cutler et al. (86).

4.1.3. Gated catalysts and nucleation sites. Single-stranded outputs from circuits have also been used to activate sites for nanostructure nucleation or catalysts for downstream self-assembly processes. This strategy for using DNA strands to control self-assembly effectively amplifies the signal, because each DNA input triggers multiple assembly steps. Yin et al. (87) developed a metastable hairpin assembly architecture in which a catalyst initiates a cascade of steps that assemble DNA hairpins into larger structures. Sadowski et al. (88) used this metastable hairpin architecture to assemble a tetrahedron in response to a catalyst trigger (**Figure 4*d***). Zhang et al. (89) used a DNA strand-displacement amplifier circuit to activate a metastable hairpin chain reaction process that triggered the assembly of a branched structure. Kishi et al. (90) developed isothermal primer exchange reaction (PER) cascades, in which DNA hairpins are templates on which DNA polymerase synthesizes strands of DNA. Each hairpin adds one short sequence domain to a growing strand in a programmed order so that the set of hairpins present controls what DNA strand is synthesized. Using this mechanism, these authors further created a PER hairpin that was initially inactivated by a protector strand blocking the hairpin's toehold. When an interface strand complementary to the protector strand was added, the hairpin's toehold was exposed and DNA synthesis proceeded.

4.2. Actuators

Beyond directing the self-assembly of structures and materials from components, DNA can also be used to change the shapes of nanostructures that have already been assembled. A common

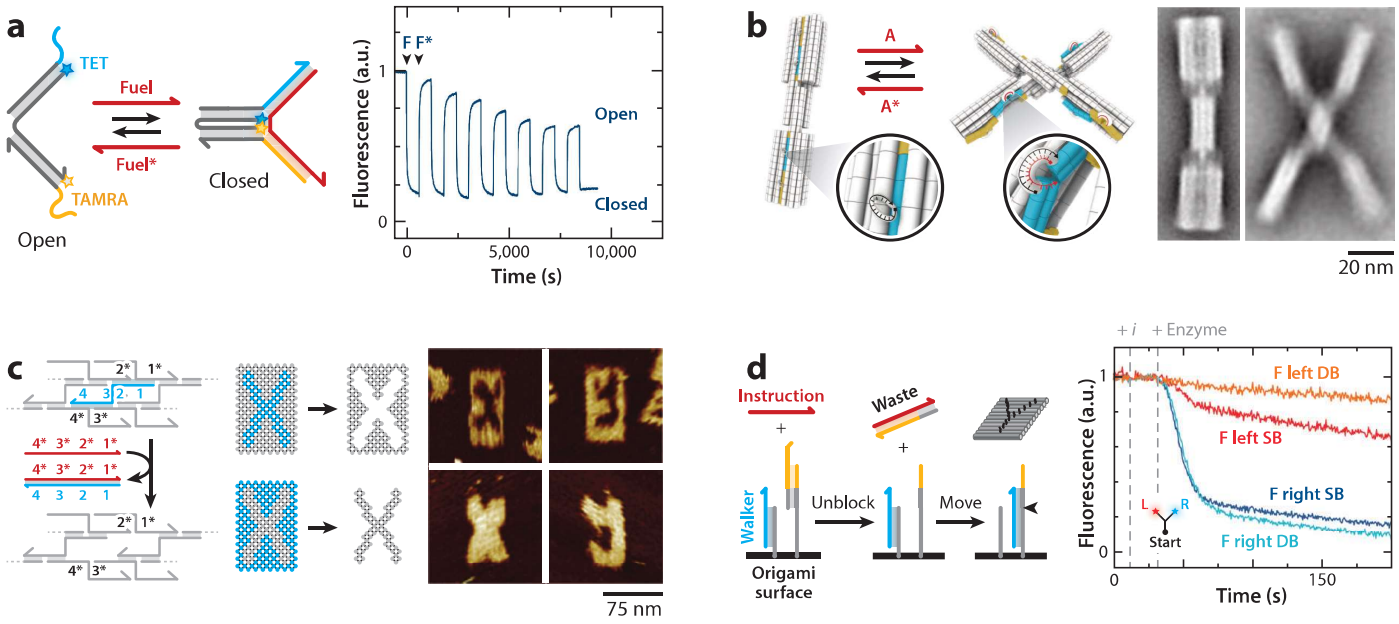


Figure 5

Reconfiguration of DNA nanostructures directed by DNA interface strands. In each example, the red strand of DNA is the interface strand that can facilitate communication between a circuit and a reconfiguring structure. (*a*) A pair of DNA tweezers (*gray*) with two different fluorophores at the ends (91). The tweezers are initialized in an open state where the TET fluorophore (*blue*) can be excited without fluorescence resonance energy transfer (FRET). A fuel strand of DNA (*red*) binds to and constrains the tweezers into a closed state, bringing the fluorescent ends of the tweezers close together and facilitating FRET between the TET and TAMRA (*yellow*) fluorophores. An antifuel strand (marked with an asterisk) displaces the fuel strand, returning the tweezers to an open state. Fluorescence intensity of TET emission shows multiple cycles of opening and closing the tweezers. (*b*) A rotary DNA origami actuator (100) driven by shape-complementary blunt-end stacking. Interface strand A (*red*) binds to complementary domains on the origami actuator to disrupt the blunt end stacking and open the actuator. Transmission electron microscopy images show the actuator in its closed and open states. (*c*) Subtractive modification of DNA brick structures. Targeted strands (*blue*) are removed from an initial blank canvas by corresponding subtraction interface strands (*red*). The addition of different sets of removal strands leads to different final shapes. Atomic force microscopy images show letter structures fabricated by this subtractive process (103). (*d*) A DNA walker (*blue*) on an origami surface (*black*) is blocked from traversing a target path by a blocker strand (*yellow*). An instruction strand (*red*) displaces the blocker strand from the origami, creating a pathway the walker can move across (106). Fluorescence monitoring shows a walker moving on a track with two gated pathways, after the right-hand pathway is activated by an instruction strand. The walker transports a quencher modification to a fluorophore at the end of the right-hand pathway, decreasing the fluorescence intensity. Abbreviations: a.u., arbitrary units; DB, double block; SB, single block. Panel *a* adapted with permission from *Nature Communications*. Copyright 2000, Nature. Panel *b* adapted with permission from AAAS. Panel *c* adapted with permission from *Angewandte Chemie*. Copyright 2014, Wiley. Panel *d* adapted with permission from *Nature Nanotechnology*. Copyright 2012, Nature.

mechanism of changing the shape of a DNA nanostructure is to add or remove strands of DNA that constrain the nanostructure in different configurations from a nanostructure. Yurke et al. (91) used this technique to repeatedly open and close a pair of DNA tweezers: adding a closing strand constrained the tweezers in a closed configuration, while an opening strand displaced the closing strand, thereby reopening the tweezers (**Figure 5*a***). The state of the tweezers was monitored by FRET between two fluorophores positioned at the ends of the tweezers. In a similar nanoactuator, an interface strand of DNA constrained the two ends of the device in an open state, rather than in a closed state (92). Feng et al. (93) constructed a linear actuator in which the two ends of the device are pushed away from each other along a straight track when an actuation strand is added. They then incorporated this device into a two-dimensional DNA lattice to actuate expansion of the lattice. Goodman et al. (94) used a similar linear actuator to reversibly change the length of a side of a DNA polyhedron, while Saccà et al. (95) used linear actuators to extend and contract

the edges of a cavity within a DNA origami tile. Chen et al. (96) developed a scheme in which linker strands bind along the edge of a DNA origami tile to direct the folding of the origami into a cylinder.

Several rotary devices have been developed in which an interface strand can direct a change in the relative angle between two parts of a nanostructure. Yan et al. (97) created an axial rotation device that reversibly rotates 180° between a paranemic crossover (PX) motif and its topoisomer (JX_2) in response to two sets of actuation strands. This motif was inserted as a modular component on a DNA array, which provided a fixed frame of reference for integrating multiple rotational actuators together into the same device (98). Marras et al. (99) developed a library of different DNA origami joints for both linear and rotational motion, and used interface strands of DNA to control the opening and closing of one of their composite devices. Gerling et al. (100) used DNA strand displacement to actuate the rotational movement of a four-armed DNA nanostructure, in which blunt-end stacking between shape-complementary components of the device provided the driving force for constraining the actuator with the arms either together or apart (**Figure 5*b***).

4.3. Subtractive Modification

Strands of DNA can also change the shape of a structure by removal or disassembly of targeted components. Han et al. (101) built a DNA origami Möbius strip and used strand-displacement processes by DNA interface strands to remove staple strands of DNA at target locations along the structure such that the removal of the staples acted akin to cutting. These authors first added DNA strands to "cut" along the centerline of the Möbius strip to create a longer loop with two full twists, and then added DNA strands to remove the staples along a line one-third of the width into the Möbius strip to create two interlocked loops. Zhang et al. (102) used strand displacement to both remove and replace staple strands in an origami structure, transforming a square structure into a quasifractal pattern of squares of decreasing size. Wei et al. (103) created regular square and cuboidal DNA brick canvases from which any component strand could be removed by adding a complementary strand (**Figure 5*c***). This technique allowed the authors to remove portions of a general-purpose square or cuboidal canvas to produce many shapes, including all 26 letters of the alphabet.

4.4. DNA Walkers and Molecular Transport

DNA walkers are mobile nanostructures that bind to and traverse a larger-frame-of-reference surface, such as a DNA origami tile surface. These types of devices can be used to transport cargo molecules to different locations on the origami surface (**Figure 6*a***) (104, 105). Walkers can be thought of as specific types of reconfigurable DNA nanostructures. DNA fuel strands can drive walker motion and can also act as decision making signals that indicate to the walker which path to take among a set of option branches by selectively removing blocker strands from the target pathway (**Figure 5*d***) (106). Numerous DNA walkers have been designed, and many walkers whose motion can be controlled by DNA strands are discussed in further detail in a review by Pan et al. (107).

5. DNA-DIRECTED CONTROL OF OTHER MATERIALS

DNA can also serve as a template for controlling many other molecules aside from DNA. In this section, we discuss interfaces that enable strands of DNA to control the placement of nanoparticles on larger structures and surfaces, encapsulation and release of payloads from origami boxes and

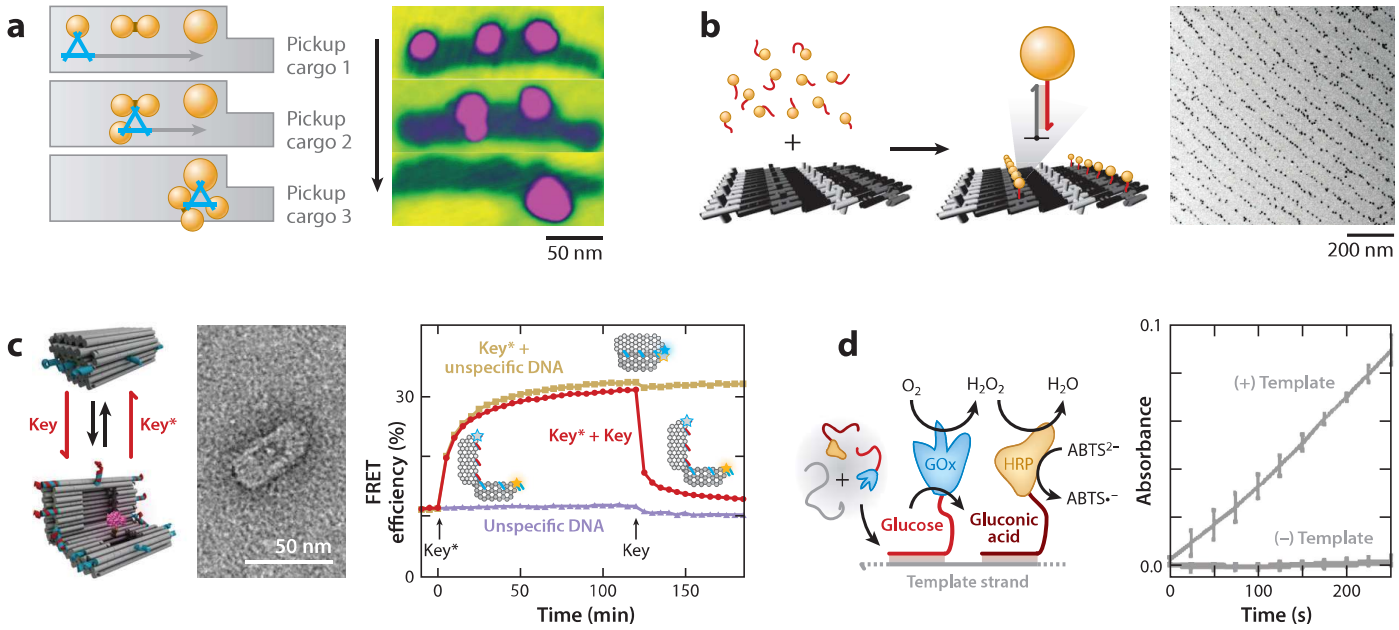


Figure 6

Positioning other molecules and particles. (*a*) A DNA walker (*blue*) on an origami surface (*gray*) picks up and colocalizes several gold nanoparticle cargos (*yellow*) (104). This type of cargo-manipulating walker could potentially be gated by a strand of DNA using a mechanism similar to that shown in **Figure 5*d***. (*Left*) Schematic and (*right*) atomic force micrograph of particles in different states during the movement process. (*b*) Gold nanoparticles (*yellow*) were positioned in a two-dimensional array by attaching them first to interface strands of DNA (*red*) that are complementary to attachment sites on a large preformed DNA scaffold (*gray*, *black*). (*Right*) Transmission electron microscopy image depicting the assembled array, where the gold nanoparticles are shown as black dots (115). (*c*) A DNA origami nanovault (123) with an enzyme (bovine α-chymotrypsin) (*pink*) attached to its inner cavity. The vault is held closed by lock domains of DNA (*blue*) along its outer edges. When complementary key strands of DNA (*red*) are introduced, they displace the locks and open the nanovault, exposing the encapsulated enzyme to substrate in the external medium. Fluorescence resonance energy transfer (FRET) between two different fluorophores positioned on the side of the nanovault indicates open and closed configurations of the nanovault. (*d*) A template strand (*gray*) assembles enzymes with DNA tags (*red*) into a local reaction cascade (128). Here, the cascade consists of glucose oxidase (GOx) (*blue*), which oxidized glucose to yield gluconic acid and hydrogen peroxide (H_2O_2), and horseradish peroxidase (HRP) (*yellow*), which used the generated H_2O_2 to oxidize $ABTS^{2-}$ into $ABTS^{\bullet-}$. Absorbance readings monitor the accumulation of the $ABTS^{\bullet-}$ product over time. A negative control that is missing the template strand shows no significant production. Panel *a* adapted with permission from *Nano Letters*. Copyright 2004, American Chemical Society. Panel *b* adapted with permission from *Nature*. Copyright 2010, Nature. Panel *c* adapted with permission from *Nature Communications*. Copyright 2017, Nature. Panel *d* adapted with permission from *Nano Letters*. Copyright 2009, American Chemical Society.

cages, templating of reactions between other molecules, and manipulation of bulk materials such as vesicles and hydrogels.

5.1. Particle Placement

In principle, any component that is conjugated to a strand of DNA, or bound by an aptamer sequence, might be positioned at a specific site on other DNA nanostructures via hybridization. Loweth et al. (108) modified gold nanoparticles with DNA tags, and exploited the sequence-specific binding of DNA to assemble these gold particles into dimers and trimers. Hazarika et al. (109) further demonstrated that nanoparticle assemblies could be reversibly disassembled with DNA strand-displacement reactions. Similar techniques have been used to assemble clusters of other DNA-functionalized components, including platinum–gold nanoparticles (110), quantum dots (111), and carbon nanotubes (112). Functionalization of cell surfaces by Staudinger ligation to phosphine-conjugated DNA strands has been used to direct the assembly of cell–cell contacts to

build three-dimensional microtissues with defined interconnectivities between cells (113). While in many of these studies the positions of DNA strands on their host particles were not specifically controlled, Kim et al. (114) developed a method for controlling the precise number and relative position of DNA strands on gold nanoparticles. Le et al. (115) formed larger two-dimensional arrays of gold nanoparticles using a DNA tile lattice as a template. Arrays were formed via the hybridization of DNA strands conjugated to gold nanoparticles to DNA strands on the lattice (**Figure 6*b***). A similar strategy of DNA tag hybridization to a DNA template has also been used to direct the assembly of proteins into arrays (116). Braun et al. (117) used DNA tags immobilized on the surfaces of gold electrodes to direct the attachment of a long double-stranded DNA between two electrodes separated by 12 μm. The double-stranded DNA was metallized with silver nanoparticles to create a conductive wire with differential resistances on the order of 7–30 MΩ (117). Hazani et al. (118) used similar gold electrode–immobilized oligonucleotides to direct the attachment of a DNA-modified carbon nanotube between two electrodes on a gold surface. Maune et al. (119) assembled two-dimensional cross-shaped junctions of carbon nanotubes on DNA origami, which they found exhibited field-effect transistor–like behavior.

Importantly, particles bound to DNA nanostructures can also move when the underlying nanostructure moves. Kuzyk et al. (120) demonstrated this by positioning gold nanorods on a rotating DNA origami actuator and using the actuator to dynamically tune the angle between the two rods. These authors used these devices as reconfigurable plasmonic metamolecules (120). For a more detailed overview of using DNA to position other nanoparticles, see the recent review by Rogers et al. (121).

5.2. Encapsulation and Drug Delivery

DNA nanostructures can be used as containers for other molecules. Andersen et al. (122) developed a DNA origami box measuring 42 × 36 × 36 nm^3, and used strands of DNA as sequence-specific keys to open the lid, although encapsulation of a payload within the box was not specifically demonstrated. Grossi et al. (123) created a DNA origami nanovault that contained an enzyme within a fully enclosed cavity, held closed by double-stranded DNA locks. Addition of key strands of DNA complementary to the lock domains opened the nanovault (**Figure 6*c***). In the closed state, the enzyme was inhibited by the nanovault from interacting with substrate molecules in solution; increased enzyme activity was measured when the nanovault was in an open state. Sun et al. (124) used DNA origami boxes as molds for growing metal nanostructures with defined geometries. They began with a hollow DNA origami barrel, added a strand of DNA that was conjugated to a metal nanoparticle to the inside of the box to act as a seed for growth, and then attached lids to the barrel. The metal seeds within the box were then grown in a mixture of silver nitrate and ascorbic acid until they conformed to the size and shape of their DNA barrel containers (124).

5.3. Templating Chemical Reactions

By controlling the effective local concentrations of reactive molecules conjugated to their component strands, DNA complexes and nanostructures can regulate the rates of some chemical reactions. Calderone et al. (125) conjugated different reactive groups, including maleimides, aldehydes, and amines, to DNA strands. These template strands were then mixed together in the same solution, with complementary strands of DNA binding together and initiating reactions between their attached reagent molecules. This technique allowed the authors to program different chemical reaction pathways within the same solution, which would otherwise have exhibited significant

cross-reactivity between the pathways (125). Kanan et al. (126) expanded on this technique for DNA-templated reaction discovery, testing 168 different possible reactions between 24 different reactants bound to template strands of DNA in a one-pot mixture. Usanov et al. (127) further expanded on this technique to produce a vast library of 256,000 different small-molecule macrocycles for insulin-degrading enzyme affinity.

Wilner et al. (128) used conjugated strands of DNA to place the enzymes glucose oxidase and horseradish peroxidase close together on a template strand of DNA, forming a biocatalytic cascade that produced $ABTS^{\bullet-}$ (**Figure 6*d***). Ke et al. (129) used a DNA origami tile to assemble two different enzyme reaction pathways on the same nanostructure, using "anchor" strands of DNA on the origami surface to position the enzymes, and then used strands of DNA to reversibly control which of the two pathways was activated at any one time by blocking or unblocking the anchor points. Several reviews exist that cover the topic of DNA templated reactions in further detail (130, 131).

5.4. Vesicles

Lipid vesicles can enclose small volumes of liquid and could be used to create artificial cells within which different DNA circuits operate. DNA nanostructures have been used as templates to control the static size, shape, and dispersity of vesicles (132–136). DNA origami nanopores have been added to vesicles to facilitate transport across their membranes (137–139). Zhang et al. (140) recently demonstrated that interface strands of DNA can change the shape of DNA-templated vesicles by reconfiguring their templating nanostructures (**Figure 7*a***). Sato et al. (141) used DNA interface strands to reversibly regulate the assembly of kinesin motors along the inner surfaces of vesicles to change the local curvatures of the vesicles (**Figure 7*b***).

5.5. DNA Hydrogels and Crystals

Hydrogels are materials composed of cross-linked polymer chains in water. By incorporating DNA into the hydrogel as cross-links (142), one can dynamically manipulate the material properties of the hydrogel by adding DNA strands to alter, break, or create cross-links. Lin et al. (143) developed DNA cross-links that could be reversibly dissociated by adding a strand complementary to one of the cross-link strands. Hydrogels with DNA cross-links can also be stiffened or softened by adding DNA that switches the conformation of cross-links between a double-stranded state or a partially single-stranded conformation (144) via DNA strand-displacement reactions. Lin et al. (143, 144) reported that these DNA cross-linked hydrogels had bulk elastic moduli ranging from tens of pascals to ~10 kPa, and that these hydrogels swelled upon softening, with volumetric swelling ratios up to ~25% between the stiff and soft states. Cangialosi et al. (145) used photolithographic patterning to form multidomain DNA-cross-linked hydrogels in which each domain could be swollen independently by the addition of different hairpin fuel strands of DNA to the surrounding medium; differential swelling of domains within the hydrogel causes bending or curling of the device, suggesting how such a system could be used for mechanical actuation. Cangialosi et al. incorporated a hybridization chain reaction, originally developed by Venkataraman et al. (146), into hydrogels to expand the size of the cross-links by incorporating many fuel strands of DNA into each cross-link to drive substantially higher swelling ratios than in previous research. Linear expansion due to swelling up to several hundred percent was reported (**Figure 7*b***) (145). DNA strand-displacement reactions have also been shown to operate within three-dimensional DNA crystals, for instance, by using strands of DNA with different fluorescent modifications to change the color of a crystal (**Figure 7*d***) (147).

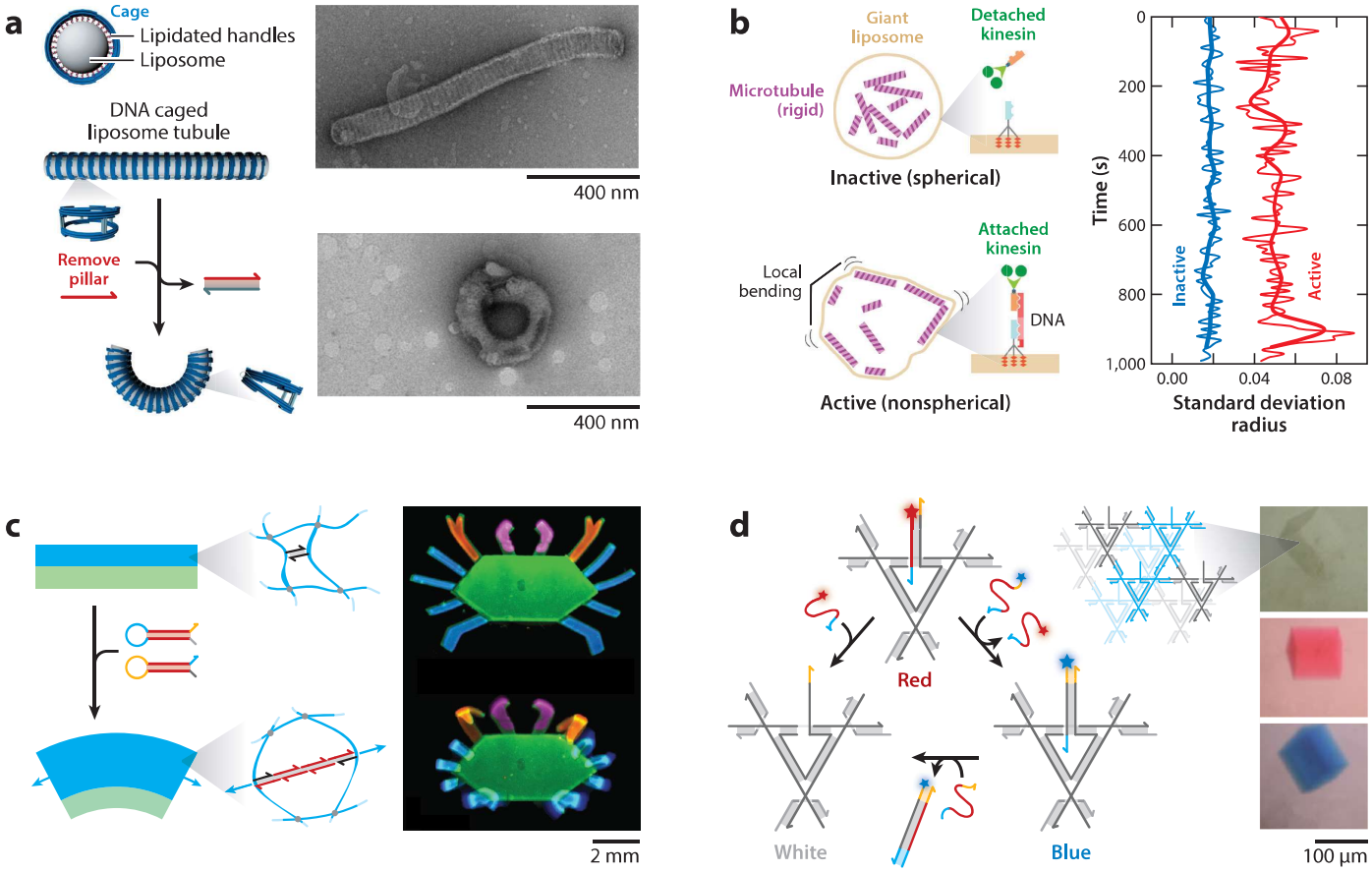


Figure 7

DNA-strand directed material change. (*a*) A DNA origami frame serves as a cage to control the size and shape of a liposome. (*Left*) Lipidated DNA handles immobilized on the inner surface of the origami frame serve as attachment points to position the liposome within the DNA frame. Here, the DNA frame directs the formation of a lipid tubule. Reconfiguring the frame structure by removing rigid pillars via an interface strand of DNA (*red*) changes the shape of the caged liposome. (*Right*) Electron micrographs of the caged liposome in the tubule and curled states (140). (*b*) (*Left*) A giant liposome in which the attachment of a kinesin motor by an interface strand of DNA (*red*) induces lipid surface microtubule transport, which in turn causes localized dynamic bending of the liposome (141). (*Right*) The standard deviations of the radius between the center of mass and the periphery of a liposome when kinesin motors are inactive versus active. (*c*) A DNA cross-linked hydrogel robot with components that swell in response to interface hairpin strands of DNA (*red*). Selective swelling of domains can induce actuation responses such as bending. Fluorescence micrographs with false color of a DNA cross-linked hydrogel crab in (*top*) initial and (*bottom*) actuated states (145). (*d*) Strand-displacement reactions within a three-dimensional DNA crystal (147) involving Cy3- and Cy5-modified DNA strands (*red*) can change what molecules are present within the crystal lattice, switching the color of the crystal between three states. Panel *a* adapted with permission from *Accounts of Chemical Research*. Copyright 2014, American Chemical Society. Panel *b* adapted with permission from *Nature Communications*. Copyright 2016, Nature. Panel *c* adapted with permission from AAAS. Panel *d* adapted with permission from *Nature Chemistry*. Copyright 2017, Nature.

6. DISCUSSION

In this review, we have explored mechanisms that allow DNA circuits to sense environmental stimuli and to control the assembly or reconfiguration of downstream materials. We define DNA circuits as black box information processing devices in which the inputs and outputs take the form of strands of DNA, which we define as the interface strands. In principle, these modular interfaces allow DNA circuits to be developed independently from the material systems they sense and control, analogously to how standardized electrical interfaces allow general-purpose electronic computers to interact with a diverse set of peripheral devices. Although we focus here on DNA,

a similar paradigm could apply to circuits composed of other nucleic acids, such as RNA, LNA (locked nucleic acid) (148), or PNA (peptide nucleic acid) (149). Through standardized interfaces, chemical circuits with different information processing functions could theoretically control a combinatorial variety of other materials and stimuli.

While exploring mechanisms by which interface strands of DNA could facilitate communication between materials and DNA circuits, we have identified several interesting unexplored directions for potential future research. First, if mechanisms were developed to allow interface strands of DNA to regulate local temperatures, DNA circuits could potentially be used to generate elaborate spatiotemporal temperature gradients in three dimensions. Second, mechanisms that allow output strands to regulate the concentration of ions could be useful for programming fluctuations in pH in response to events detected in the environment, such as the presence of a virus or bacteria. Third, regarding bulk materials, mechanisms that allow interface strands to regulate flux across membranes could facilitate communication between networks of isolated DNA circuits within neighboring vesicles, while mechanisms to initiate division of vesicles or hydrogels could be useful for creating synthetic materials that can replicate and evolve. Fourth, while there is a growing literature on the use of DNA interface strands to interact with soft macroscopic materials, interface mechanisms that allow DNA to regulate biomineralization processes could extend this control to harder or stiffer materials that have structural integrity at larger scales and under significant mechanical stresses. Finally, mechanisms that allow DNA circuits to dynamically control the state and position of DNA origami lithography masks (150, 151), potentially by reconfiguring DNA origami to fit shape-dependent surface attachment sites (152, 153), could enable DNA to assist in the fabrication of solid-state electronics.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors thank Phillip Dorsey, Joshua Fern, Naresh Dhanasekar, Moshe Rubanov, Samuel Schaffter, and Wenlu Wang for insightful conversations. The writing of this review was supported by grant DE-SC0010595 from the US Department of Energy, Basic Energy Sciences Division.

LITERATURE CITED

1. Isaacson W. 2014. *The Innovators: How a Group of Inventors, Hackers, Geniuses and Geeks Created the Digital Revolution*. New York: Simon & Schuster
2. De Silva AP, Uchiyama S. 2007. Molecular logic and computing. *Nat. Nanotechnol.* 2:399
3. Zhang DY, Seelig G. 2011. Dynamic DNA nanotechnology using strand-displacement reactions. *Nat. Chem.* 3:103
4. Baccouche A, Montagne K, Padirac A, Fujii T, Rondelez Y. 2014. Dynamic DNA-toolbox reaction circuits: a walkthrough. *Methods* 67:234–49
5. Willner I, Shlyahovsky B, Zayats M, Willner B. 2008. DNAzymes for sensing, nanobiotechnology and logic gate applications. *Chem. Soc. Rev.* 37:1153–65
6. Seelig G, Soloveichik D, Zhang DY, Winfree E. 2006. Enzyme-free nucleic acid logic circuits. *Science* 314:1585–88
7. Qian L, Winfree E. 2011. Scaling up digital circuit computation with DNA strand displacement cascades. *Science* 332:1196–201

8. Genot AJ, Bath J, Turberfield AJ. 2011. Reversible logic circuits made of DNA. *J. Am. Chem. Soc.* 133:20080–83
9. Zadorin AS, Rondelez Y, Galas JC, Estevez-Torres A. 2015. Synthesis of programmable reaction–diffusion fronts using DNA catalyzers. *Phys. Rev. Lett.* 114:068301
10. Franco E, Friedrichs E, Kim J, Jungmann R, Murray R, et al. 2011. Timing molecular motion and production with a synthetic transcriptional clock. *PNAS* 108:E784–93
11. Fujii T, Rondelez Y. 2012. Predator–prey molecular ecosystems. *ACS Nano* 7:27–34
12. Srinivas N, Parkin J, Seelig G, Winfree E, Soloveichik D. 2017. Enzyme-free nucleic acid dynamical systems. *Science* 358:eaal2052
13. Fern J, Scalise D, Cangialosi A, Howie D, Potters L, Schulman R. 2016. DNA strand-displacement timer circuits. *ACS Synth. Biol.* 6:190–93
14. Stojanovic MN, Stefanovic D. 2003. A deoxyribozyme-based molecular automaton. *Nat. Biotechnol.* 21:1069
15. Qian L, Winfree E, Bruck J. 2011. Neural network computation with DNA strand displacement cascades. *Nature* 475:368
16. Cherry KM, Qian L. 2018. Scaling up molecular pattern recognition with DNA-based winner-take-all neural networks. *Nature* 559:370–76
17. Zhang DY, Seelig G. 2010. DNA-based fixed gain amplifiers and linear classifier circuits. In *Proceedings of the 16th International Workshop on DNA-Based Computers*, pp. 176–86. Berlin/Heidelberg: Springer
18. Chen X, Briggs N, McLain JR, Ellington AD. 2013. Stacking nonenzymatic circuits for high signal gain. *PNAS* 110:5386–91
19. Chirieleison SM, Allen PB, Simpson ZB, Ellington AD, Chen X. 2013. Pattern transformation with DNA circuits. *Nat. Chem.* 5:1000
20. Zenk J, Scalise D, Wang K, Dorsey P, Fern J, et al. 2017. Stable DNA-based reaction–diffusion patterns. *RSC Adv.* 7:18032–40
21. Franco E, Del Vecchio D, Murray RM. 2009. Design of insulating devices for in vitro synthetic circuits. In *Proceedings of the 48th IEEE Conference on Decision and Control*, pp. 4584–89. Piscataway, NJ: IEEE
22. Jayanthi S, Nilgiriwala KS, Del Vecchio D. 2013. Retroactivity controls the temporal dynamics of gene transcription. *ACS Synth. Biol.* 2:431–41
23. Thachuk C, Winfree E, Soloveichik D. 2015. Leakless DNA strand displacement systems. In *Proceedings of the 21st International Workshop on DNA-Based Computers*, pp. 133–53. Cham, Switz.: Springer Int.
24. Huizenga DE, Szostak JW. 1995. A DNA aptamer that binds adenosine and ATP. *Biochemistry* 34:656–65
25. He JL, Wu ZS, Zhou H, Wang HQ, Jiang JH, et al. 2010. Fluorescence aptameric sensor for strand displacement amplification detection of cocaine. *Anal. Chem.* 82:1358–64
26. Zhou W, Saran R, Liu J. 2017. Metal sensing by DNA. *Chem. Rev.* 117:8272–325
27. Pendergrast PS, Marsh HN, Grate D, Healy JM, Stanton M. 2005. Nucleic acid aptamers for target validation and therapeutic applications. *J. Biomol. Tech.* 16:224–34
28. Tombelli S, Minunni M, Mascini M. 2005. Analytical applications of aptamers. *Biosens. Bioelectron.* 20:2424–34
29. Bunka DH, Platonova O, Stockley PG. 2010. Development of aptamer therapeutics. *Curr. Opin. Pharmacol.* 10:557–62
30. Ellington AD, Szostak JW. 1990. In vitro selection of RNA molecules that bind specific ligands. *Nature* 346:818–22
31. Tuerk C, Gold L. 1990. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. *Science* 249:505–10
32. Li F, Zhang H, Wang Z, Li X, Li XF, Le XC. 2013. Dynamic DNA assemblies mediated by binding-induced DNA strand displacement. *J. Am. Chem. Soc.* 135:2443–46
33. Picuri JM, Frezza BM, Ghadiri MR. 2009. Universal translators for nucleic acid diagnosis. *J. Am. Chem. Soc.* 131:9368–77
34. Zhu J, Zhang L, Zhou Z, Dong S, Wang E. 2013. Aptamer-based sensing platform using three-way DNA junction–driven strand displacement and its application in DNA logic circuit. *Anal. Chem.* 86:312–16

35. Niu S, Qu L, Zhang Q, Lin J. 2012. Fluorescence detection of thrombin using autocatalytic strand displacement cycle reaction and a dual-aptamer DNA sandwich assay. *Anal. Biochem.* 421:362–67
36. Xing Y, Yang Z, Liu D. 2011. A responsive hidden toehold to enable controllable DNA strand displacement reactions. *Angew. Chem. Int. Ed. Engl.* 50:11934–36
37. Wang H, Zheng J, Sun Y, Li T. 2018. Cellular environment–responsive intelligent DNA logic circuits for controllable molecular sensing. *Biosens. Bioelectron.* 117:729–35
38. Bhadra S, Ellington AD. 2014. A Spinach molecular beacon triggered by strand displacement. *RNA* 20:1183–94
39. Lloyd J, Tran CH, Wadhwani K, Cuba Samaniego C, Subramanian HK, Franco E. 2017. Dynamic control of aptamer–ligand activity using strand displacement reactions. *ACS Synth. Biol.* 7:30–37
40. Zhou C, Yang Z, Liu D. 2012. Reversible regulation of protein binding affinity by a DNA machine. *J. Am. Chem. Soc.* 134:1416–18
41. Liu Z, Mao C. 2014. Reporting transient molecular events by DNA strand displacement. *Chem. Commun.* 50:8239–41
42. Amodio A, Zhao B, Porchetta A, Idili A, Castronovo M, et al. 2014. Rational design of pH-controlled DNA strand displacement. *J. Am. Chem. Soc.* 136:16469–72
43. Tang W, Wang H, Wang D, Zhao Y, Li N, Liu F. 2013. DNA tetraplexes–based toehold activation for controllable DNA strand displacement reactions. *J. Am. Chem. Soc.* 135:13628–31
44. Ding W, Deng W, Zhu H, Liang H. 2013. Metallo-toeholds: controlling DNA strand displacement driven by Hg(II) ions. *Chem. Commun.* 49:9953–55
45. Ranallo S, Amodio A, Idili A, Porchetta A, Ricci F. 2016. Electronic control of DNA-based nanoswitches and nanodevices. *Chem. Sci.* 7:66–71
46. Frasconi M, Tel-Vered R, Elbaz J, Willner I. 2010. Electrochemically stimulated pH changes: a route to control chemical reactivity. *J. Am. Chem. Soc.* 132:2029–36
47. Freage L, Trifonov A, Tel-Vered R, Golub E, Wang F, et al. 2015. Addressing, amplifying and switching DNAzyme functions by electrochemically-triggered release of metal ions. *Chem. Sci.* 6:3544–49
48. Jeong H, Ranallo S, Rossetti M, Heo J, Shin J, et al. 2016. Electronic activation of a DNA nanodevice using a multilayer nanofilm. *Small* 12:5572–78
49. Fan C, Plaxco KW, Heeger AJ. 2003. Electrochemical interrogation of conformational changes as a reagentless method for the sequence-specific detection of DNA. *PNAS* 100:9134–37
50. Immoos CE, Lee SJ, Grinstaff MW. 2004. Conformationally gated electrochemical gene detection. *ChemBioChem* 5:1100–3
51. Xiao Y, Lubin AA, Baker BR, Plaxco KW, Heeger AJ. 2006. Single-step electronic detection of femtomolar DNA by target-induced strand displacement in an electrode-bound duplex. *PNAS* 103:16677–80
52. Xiao Y, Lai RY, Plaxco KW. 2007. Preparation of electrode-immobilized, redox-modified oligonucleotides for electrochemical DNA and aptamer-based sensing. *Nat. Protoc.* 2:2875
53. Immoos CE, Lee SJ, Grinstaff MW. 2004. DNA–PEG–DNA triblock macromolecules for reagentless DNA detection. *J. Am. Chem. Soc.* 126:10814–15
54. Drummond TG, Hill MG, Barton JK. 2003. Electrochemical DNA sensors. *Nat. Biotechnol.* 21:1192
55. Jonstrup AT, Fredsøe J, Andersen AH. 2013. DNA hairpins as temperature switches, thermometers and ionic detectors. *Sensors* 13:5937–44
56. Gareau D, Desrosiers A, Vallée-Bélisle A. 2016. Programmable quantitative DNA nanothermometers. *Nano Lett.* 16:3976–81
57. Gehrels EW, Rogers W, Manoharan VN. 2018. Using DNA strand displacement to control interactions in DNA-grafted colloids. *Soft Matter* 14:969–84
58. Rogers WB, Manoharan VN. 2015. Programming colloidal phase transitions with DNA strand displacement. *Science* 347:639–42
59. Govorov AO, Zhang W, Skeini T, Richardson H, Lee J, Kotov NA. 2006. Gold nanoparticle ensembles as heaters and actuators: melting and collective plasmon resonances. *Nanoscale Res. Lett.* 1:84
60. Prokup A, Hemphill J, Deiters A. 2012. DNA computation: a photochemically controlled AND gate. *J. Am. Chem. Soc.* 134:3810–15

61. Huang F, You M, Han D, Xiong X, Liang H, Tan W. 2013. DNA branch migration reactions through photocontrollable toehold formation. *J. Am. Chem. Soc.* 135:7967–73
62. Kou B, Zhang J, Huai X, Liang X, Xiao SJ. 2015. Light-driven reversible strand displacement using glycerol azobenzene inserted DNA. *RSC Adv.* 5:5055–58
63. Nakamura S, Hashimoto H, Kobayashi S, Fujimoto K. 2017. Photochemical acceleration of DNA strand displacement by using ultrafast DNA photo-crosslinking. *ChemBioChem* 18:1984–89
64. Zhang P, Beck T, Tan W. 2001. Design of a molecular beacon DNA probe with two fluorophores. *Angew. Chem. Int. Ed. Engl.* 113:416–19
65. Rothemund PW. 2006. Folding DNA to create nanoscale shapes and patterns. *Nature* 440:297–302
66. Ke Y, Ong LL, Shih WM, Yin P. 2012. Three-dimensional structures self-assembled from DNA bricks. *Science* 338:1177–83
67. Nummelin S, Kommeri J, Kostiainen MA, Linko V. 2018. Evolution of structural DNA nanotechnology. *Adv. Mater.* 30:1703721
68. Tørring T, Voigt NV, Nangreave J, Yan H, Gothelf KV. 2011. DNA origami: a quantum leap for self-assembly of complex structures. *Chem. Soc. Rev.* 40:5636–46
69. Wagenbauer KF, Sigl C, Dietz H. 2017. Gigadalton-scale shape-programmable DNA assemblies. *Nature* 552:78–83
70. Zheng J, Birktoft JJ, Chen Y, Wang T, Sha R, et al. 2009. From molecular to macroscopic via the rational design of a self-assembled 3D DNA crystal. *Nature* 461:74–77
71. Schulman R, Winfree E. 2007. Synthesis of crystals with a programmable kinetic barrier to nucleation. *PNAS* 104:15236–41
72. Fu TJ, Seeman NC. 1993. DNA double-crossover molecules. *Biochemistry* 32:3211–20
73. Winfree E, Liu F, Wenzler LA, Seeman NC. 1998. Design and self-assembly of two-dimensional DNA crystals. *Nature* 394:539–44
74. Lo PK, Karam P, Aldaye FA, McLaughlin CK, Hamblin GD, et al. 2010. Loading and selective release of cargo in DNA nanotubes with longitudinal variation. *Nat. Chem.* 2:319
75. Jungmann R, Liedl T, Sobey TL, Shih W, Simmel FC. 2008. Isothermal assembly of DNA origami structures using denaturing agents. *J. Am. Chem. Soc.* 130:10062–63
76. Zhang DY, Hariadi RF, Choi HM, Winfree E. 2013. Integrating DNA strand-displacement circuitry with DNA tile self-assembly. *Nat. Commun.* 4:1965
77. Amodio A, Adedeji AF, Castronovo M, Franco E, Ricci F. 2016. pH-controlled assembly of DNA tiles. *J. Am. Chem. Soc.* 138:12735–38
78. Padilla JE, Sha R, Kristiansen M, Chen J, Jonoska N, Seeman NC. 2015. A signal-passing DNA-strand-exchange mechanism for active self-assembly of DNA nanostructures. *Angew. Chem. Int. Ed. Engl.* 54:5939–42
79. Zhang Y, McMullen A, Pontani LL, He X, Sha R, et al. 2017. Sequential self-assembly of DNA functionalized droplets. *Nat. Commun.* 8:21
80. Wang J, Zhou Z, Yue L, Wang S, Willner I. 2018. Switchable triggered interconversion and reconfiguration of DNA origami dimers and their use for programmed catalysis. *Nano Lett.* 18:2718–24
81. Peng R, Wang H, Lyu Y, Xu L, Liu H, et al. 2017. Facile assembly/disassembly of DNA nanostructures anchored on cell-mimicking giant vesicles. *J. Am. Chem. Soc.* 139:12410–13
82. Cao YC, Jin R, Thaxton CS, Mirkin CA. 2005. A two-color-change, nanoparticle-based method for DNA detection. *Talanta* 67:449–55
83. Yao D, Song T, Sun X, Xiao S, Huang F, Liang H. 2015. Integrating DNA-strand-displacement circuitry with self-assembly of spherical nucleic acids. *J. Am. Chem. Soc.* 137:14107–13
84. Yao D, Wang B, Xiao S, Song T, Huang F, Liang H. 2015. What controls the "off/on switch" in the toehold-mediated strand displacement reaction on DNA conjugated gold nanoparticles? *Langmuir* 31:7055–61
85. Thaxton CS, Georganopoulou DG, Mirkin CA. 2006. Gold nanoparticle probes for the detection of nucleic acid targets. *Clin. Chim. Acta* 363:120–26
86. Cutler JI, Auyeung E, Mirkin CA. 2012. Spherical nucleic acids. *J. Am. Chem. Soc.* 134:1376–91

87. Yin P, Choi HM, Calvert CR, Pierce NA. 2008. Programming biomolecular self-assembly pathways. *Nature* 451:318–22
88. Sadowski JP, Calvert CR, Zhang DY, Pierce NA, Yin P. 2014. Developmental self-assembly of a DNA tetrahedron. *ACS Nano* 8:3251–59
89. Zhang Z, Fan TW, Hsing IM. 2017. Integrating DNA strand displacement circuitry to the nonlinear hybridization chain reaction. *Nanoscale* 9:2748–54
90. Kishi JY, Schaus TE, Gopalkrishnan N, Xuan F, Yin P. 2018. Programmable autonomous synthesis of single-stranded DNA. *Nat. Chem.* 10:155
91. Yurke B, Turberfield AJ, Mills AP Jr., Simmel FC, Neumann JL. 2000. A DNA-fuelled molecular machine made of DNA. *Nature* 406:605–8
92. Simmel FC, Yurke B. 2001. Using DNA to construct and power a nanoactuator. *Phys. Rev. E* 63:041913
93. Feng L, Park SH, Reif JH, Yan H. 2003. A two-state DNA lattice switched by DNA nanoactuator. *Angew. Chem. Int. Ed. Engl.* 115:4478–82
94. Goodman RP, Heilemann M, Doose S, Erben CM, Kapanidis AN, Turberfield AJ. 2008. Reconfigurable, braced, three-dimensional DNA nanostructures. *Nat. Nanotechnol.* 3:93
95. Saccà B, Ishitsuka Y, Meyer R, Sprengel A, Schöneweiß EC, et al. 2015. Reversible reconfiguration of DNA origami nanochambers monitored by single-molecule FRET. *Angew. Chem. Int. Ed. Engl.* 54:3592–97
96. Chen H, Weng TW, Riccitelli MM, Cui Y, Irudayaraj J, Choi JH. 2014. Understanding the mechanical properties of DNA origami tiles and controlling the kinetics of their folding and unfolding reconfiguration. *J. Am. Chem. Soc.* 136:6995–7005
97. Yan H, Zhang X, Shen Z, Seeman NC. 2002. A robust DNA mechanical device controlled by hybridization topology. *Nature* 415:62–65
98. Ding B, Seeman NC. 2006. Operation of a DNA robot arm inserted into a 2D DNA crystalline substrate. *Science* 314:1583–85
99. Marras AE, Zhou L, Su HJ, Castro CE. 2015. Programmable motion of DNA origami mechanisms. *PNAS* 112:713–18
100. Gerling T, Wagenbauer KF, Neuner AM, Dietz H. 2015. Dynamic DNA devices and assemblies formed by shape-complementary, non–base pairing 3D components. *Science* 347:1446–52
101. Han D, Pal S, Liu Y, Yan H. 2010. Folding and cutting DNA into reconfigurable topological nanostructures. *Nat. Nanotechnol.* 5:712
102. Zhang F, Nangreave J, Liu Y, Yan H. 2012. Reconfigurable DNA origami to generate quasifractal patterns. *Nano Lett.* 12:3290–95
103. Wei B, Ong LL, Chen J, Jaffe AS, Yin P. 2014. Complex reconfiguration of DNA nanostructures. *Angew. Chem. Int. Ed. Engl.* 126:7605–9
104. Gu H, Chao J, Xiao SJ, Seeman NC. 2010. A proximity-based programmable DNA nanoscale assembly line. *Nature* 465:202–5
105. Thubagere AJ, Li W, Johnson RF, Chen Z, Doroudi S, et al. 2017. A cargo-sorting DNA robot. *Science* 357:eaan6558
106. Wickham SF, Bath J, Katsuda Y, Endo M, Hidaka K, et al. 2012. A DNA-based molecular motor that can navigate a network of tracks. *Nat. Nanotechnol.* 7:169
107. Pan J, Li F, Cha TG, Chen H, Choi JH. 2015. Recent progress on DNA based walkers. *Curr. Opin. Biotechnol.* 34:56–64
108. Loweth CJ, Caldwell WB, Peng X, Alivisatos AP, Schultz PG. 1999. DNA-based assembly of gold nanocrystals. *Angew. Chem. Int. Ed. Engl.* 38:1808–12
109. Hazarika P, Ceyhan B, Niemeyer CM. 2004. Reversible switching of DNA–gold nanoparticle aggregation. *Angew. Chem. Int. Ed. Engl.* 116:6631–33
110. Li Y, Zheng Y, Gong M, Deng Z. 2012. Pt nanoparticles decorated with a discrete number of DNA molecules for programmable assembly of Au–Pt bimetallic superstructures. *Chem. Commun.* 48:3727–29
111. He X, Li Z, Chen M, Ma N. 2014. DNA-programmed dynamic assembly of quantum dots for molecular computation. *Angew. Chem. Int. Ed. Engl.* 53:14447–50

112. Li Y, Han X, Deng Z. 2007. Grafting single-walled carbon nanotubes with highly hybridizable DNA sequences: potential building blocks for DNA-programmed material assembly. *Angew. Chem. Int. Ed. Engl.* 46:7481–84
113. Gartner ZJ, Bertozzi CR. 2009. Programmed assembly of 3-dimensional microtissues with defined cellular connectivity. *PNAS* 106:4606–10
114. Kim JW, Kim JH, Deaton R. 2011. DNA-linked nanoparticle building blocks for programmable matter. *Angew. Chem. Int. Ed. Engl.* 50:9185–90
115. Le JD, Pinto Y, Seeman NC, Musier-Forsyth K, Taton TA, Kiehl RA. 2004. DNA-templated self-assembly of metallic nanocomponent arrays on a surface. *Nano Lett.* 4:2343–47
116. Liu Y, Lin C, Li H, Yan H. 2005. Aptamer-directed self-assembly of protein arrays on a DNA nanostructure. *Angew. Chem. Int. Ed. Engl.* 117:4407–12
117. Braun E, Eichen Y, Sivan U, Ben-Yoseph G. 1998. DNA-templated assembly and electrode attachment of a conducting silver wire. *Nature* 391:775–78
118. Hazani M, Hennrich F, Kappes M, Naaman R, Peled D, et al. 2004. DNA-mediated self-assembly of carbon nanotube–based electronic devices. *Chem. Phys. Lett.* 391:389–92
119. Maune HT, Han SP, Barish RD, Bockrath M, Goddard WA III, et al. 2010. Self-assembly of carbon nanotubes into two-dimensional geometries using DNA origami templates. *Nat. Nanotechnol.* 5:61
120. Kuzyk A, Schreiber R, Zhang H, Govorov AO, Liedl T, Liu N. 2014. Reconfigurable 3D plasmonic metamolecules. *Nat. Mater.* 13:862
121. Rogers WB, Shih WM, Manoharan VN. 2016. Using DNA to program the self-assembly of colloidal nanoparticles and microparticles. *Nat. Rev. Mater.* 1:16008
122. Andersen ES, Dong M, Nielsen MM, Jahn K, Subramani R, et al. 2009. Self-assembly of a nanoscale DNA box with a controllable lid. *Nature* 459:73–76
123. Grossi G, Jepsen MDE, Kjems J, Andersen ES. 2017. Control of enzyme reactions by a reconfigurable DNA nanovault. *Nat. Commun.* 8:992
124. Sun W, Boulais E, Hakobyan Y, Wang WL, Guan A, et al. 2014. Casting inorganic structures with DNA molds. *Science* 346:1258361
125. Calderone CT, Puckett JW, Gartner ZJ, Liu DR. 2002. Directing otherwise incompatible reactions in a single solution by using DNA-templated organic synthesis. *Angew. Chem. Int. Ed. Engl.* 41:4104–8
126. Kanan MW, Rozenman MM, Sakurai K, Snyder TM, Liu DR. 2004. Reaction discovery enabled by DNA-templated synthesis and in vitro selection. *Nature* 431:545–49
127. Usanov DL, Chan AI, Maianti JP, Liu DR. 2018. Second-generation DNA-templated macrocycle libraries for the discovery of bioactive small molecules. *Nat. Chem.* 10:704–14
128. Wilner OI, Shimron S, Weizmann Y, Wang ZG, Willner I. 2009. Self-assembly of enzymes on DNA scaffolds: en route to biocatalytic cascades and the synthesis of metallic nanowires. *Nano Lett.* 9:2040–43
129. Ke G, Liu M, Jiang S, Qi X, Yang YR, et al. 2016. Directional regulation of enzyme pathways through the control of substrate channeling on a DNA origami scaffold. *Angew. Chem. Int. Ed. Engl.* 55:7483–86
130. Li X, Liu DR. 2004. DNA-templated organic synthesis: Nature's strategy for controlling chemical reactivity applied to synthetic molecules. *Angew. Chem. Int. Ed. Engl.* 43:4848–70
131. Rajendran A, Nakata E, Nakano S, Morii T. 2017. Nucleic-acid-templated enzyme cascades. *ChemBioChem* 18:696–716
132. Perrault SD, Shih WM. 2014. Virus-inspired membrane encapsulation of DNA nanostructures to achieve in vivo stability. *ACS Nano* 8:5132–40
133. Dong Y, Sun Y, Wang L, Wang D, Zhou T, et al. 2014. Frame-guided assembly of vesicles with programmed geometry and dimensions. *Angew. Chem. Int. Ed. Engl.* 126:2645–48
134. Dong Y, Yang Z, Liu D. 2015. Using small molecules to prepare vesicles with designable shapes and sizes via frame-guided assembly strategy. *Small* 11:3768–71
135. Dong Y, Yang YR, Zhang Y, Wang D, Wei X, et al. 2017. Cuboid vesicles formed by frame-guided assembly on DNA origami scaffolds. *Angew. Chem. Int. Ed. Engl.* 56:1586–89
136. Yang Y, Wang J, Shigematsu H, Xu W, Shih WM, et al. 2016. Self-assembly of size-controlled liposomes on DNA nanotemplates. *Nat. Chem.* 8:476

137. Langecker M, Arnaut V, Martin TG, List J, Renner S, et al. 2012. Synthetic lipid membrane channels formed by designed DNA nanostructures. *Science* 338:932–36
138. Krishnan S, Ziegler D, Arnaut V, Martin TG, Kapsner K, et al. 2016. Molecular transport through large-diameter DNA nanopores. *Nat. Commun.* 7:12787
139. Langecker M, Arnaut V, List J, Simmel FC. 2014. DNA nanostructures interacting with lipid bilayer membranes. *Acc. Chem. Res.* 47:1807–15
140. Zhang Z, Yang Y, Pincet F, Llaguno MC, Lin C. 2017. Placing and shaping liposomes with reconfigurable DNA nanocages. *Nat. Chem.* 9:653
141. Sato Y, Hiratsuka Y, Kawamata I, Murata S, Shin-ichiro MN. 2017. Micrometer-sized molecular robot changes its shape in response to signal molecules. *Sci. Robot.* 2:eaal3735
142. Nagahara S, Matsuda T. 1996. Hydrogel formation via hybridization of oligonucleotides derivatized in water-soluble vinyl polymers. *Polym. Gels Netw.* 4:111–27
143. Lin DC, Yurke B, Langrana NA. 2004. Mechanical properties of a reversible, DNA-crosslinked polyacrylamide hydrogel. *J. Biomech. Eng.* 126:104–10
144. Lin DC, Yurke B, Langrana NA. 2005. Inducing reversible stiffness changes in DNA-crosslinked gels. *J. Mater. Res.* 20:1456–64
145. Venkataraman S, Dirks RM, Rothemund PW, Winfree E, Pierce NA. 2007. An autonomous polymerization motor powered by DNA hybridization. *Nat. Nanotechnol.* 2:490
146. Cangialosi A, Yoon C, Liu J, Huang Q, Guo J, et al. 2017. DNA sequence–directed shape change of photopatterned hydrogels via high-degree swelling. *Science* 357:1126–30
147. Hao Y, Kristiansen M, Sha R, Birktoft JJ, Hernandez C, et al. 2017. A device that operates within a self-assembled 3D DNA crystal. *Nat. Chem.* 9:824
148. Olson X, Kotani S, Yurke B, Graugnard E, Hughes WL. 2017. Kinetics of DNA strand displacement systems with locked nucleic acids. *J. Phys. Chem. B* 121:2594–602
149. Kabza AM, Young BE, Sczepanski JT. 2017. Heterochiral DNA strand-displacement circuits. *J. Am. Chem. Soc.* 139:17715–18
150. Diagne CT, Brun C, Gasparutto D, Baillin X, Tiron R. 2016. DNA origami mask for sub-ten-nanometer lithography. *ACS Nano* 10:6458–63
151. Surwade SP, Zhou F, Wei B, Sun W, Powell A, et al. 2013. Nanoscale growth and patterning of inorganic oxides using DNA nanostructure templates. *J. Am. Chem. Soc.* 135:6778–81
152. Kershner RJ, Bozano LD, Micheel CM, Hung AM, Fornof AR, et al. 2009. Placement and orientation of individual DNA shapes on lithographically patterned surfaces. *Nat. Nanotechnol.* 4:557
153. Gopinath A, Miyazono E, Faraon A, Rothemund PW. 2016. Engineering and mapping nanocavity emission via precision placement of DNA origami. *Nature* 535:401–5

Annual Review of Biomedical Engineering

Volume 21, 2019

Contents

Errata

An online log of corrections to *Annual Review of Biomedical Engineering* articles may be found at http://www.annualreviews.org/errata/bioeng