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Review

A 'tile' tale: Hierarchical self-assembly of DNA lattices

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ABSTRACT

DNA has been used as a material for the construction of complex nanostructures. Branched DNA molecules can be glued together by sticky end cohesion, providing a route to dictate hierarchical self-assembly of one-, two- and three-dimensional periodic lattices. DNA tiles provide site-specific attachment sites, and can lead to spatially positioned arrays of nanoparticles or macromolecules with nanometer-scale precision. This review discusses the origin and use of various DNA tiles in constructing higher order DNA lattices that can be used as scaffolds for hosting external guests. In addition, the development of DNA origami tiles and arrays is also discussed.

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Contents

1. Introduction

DNA is well known as the molecule involved in storing and transmitting genetic information. It has also been proven to be exceptional as an engineering material for the construction of micrometer-scale objects with nanometer-scale features [1,2]. DNA is useful for the 'bottom-up' construction of nanostructures for a variety of reasons: With a diameter of ~2 nm, helical pitch of ~3.4–3.6 nm and a persistence length of ~50 nm (150 base pairs), the DNA double helix is a nanoscale molecule that combines the properties needed for engineering scaffolds at the nanoscale with unparalleled precision, excellent predictability and easy programmability. Most importantly, DNA has a molecular recognition system: Watson–Crick base pairing allows for both control and programmability of structural assembly through simple manipulation of nucleic acid design.

Structural DNA nanotechnology exploits the distinct characteristics of DNA in the construction of higher-ordered geometric structures and periodic arrays through self-assembly. Numerous reports demonstrate the successful use of DNA as a structural building material to make a variety of architectures including periodically patterned structures [3–5], three-dimensional polyhedra [6,7], topological constructs [8,9], biosensors [10,11] and molecular computing systems [12–14]. The occurrence of different conformations of DNA [15–17] depending on the ionic environment has also been used to construct devices based on conformational changes [18–20]. Self-assembled two- [21–23] and three-dimensional lattices [24–32] created from DNA can be used as a template to organize nanoparticles [33–35] and macromolecules [36,37]. Such spatial positioning of guest molecules with precision and programmability can be achieved using appropriate attachment chemistries [38,39]. The advent of synthetic DNA oligonucleotides has fast-tracked the creation of these complexes [40]. Such platforms can be built using the molecular recognition properties of DNA with size ranges that are difficult to attain via conventional microstructuring or chemical approaches [41].

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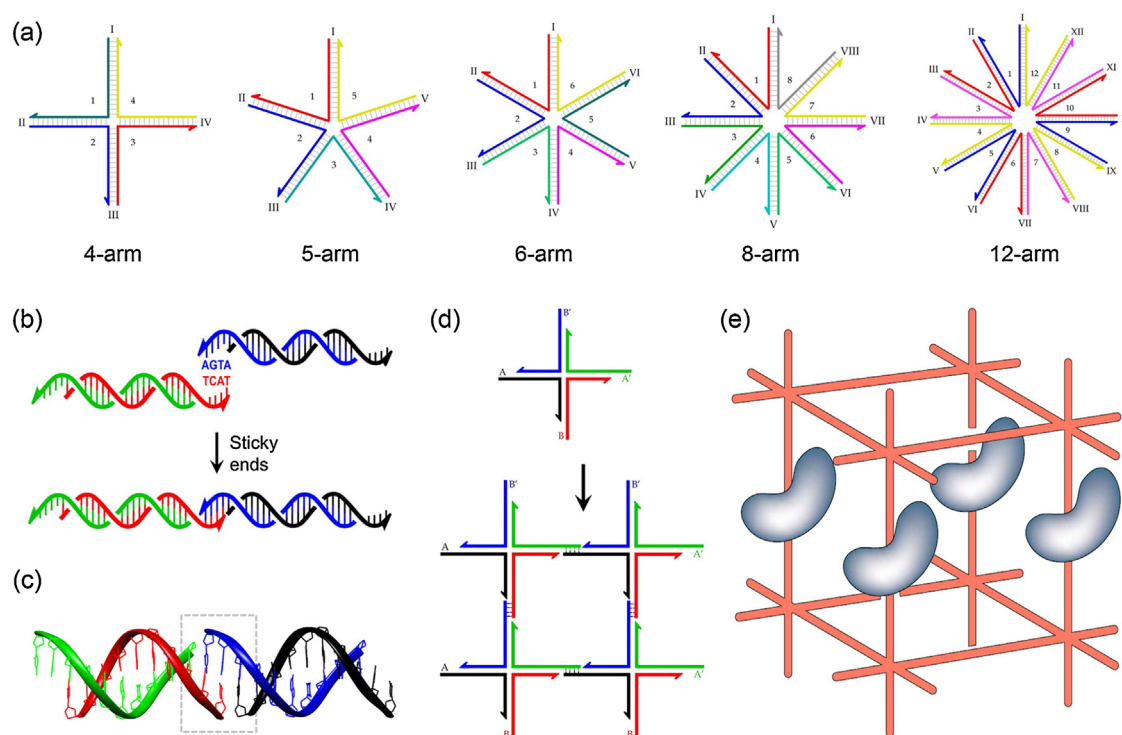   *E-mail address:* arunrichard@nyu.edu (A.R. Chandrasekaran).

Fig. 1. Nucleic acid junctions and lattices. (a) Branched DNA junctions with differing number of arms. Adapted from [46–48] with permission. Copyright 1983, Nature Publishing Group (NPG); Copyright 1991 and 2007, American Chemical Society (ACS), respectively. (b) Scheme of sticky end cohesion. Adapted from [2] with permission. Copyright 2010, Annual Reviews. (c) Predictable local geometry of sticky ended cohesion [49]. PDB ID: 309D. (d) Combining branched junctions and sticky ends to create lattices, in this case a quadrilateral. Adapted from [2] with permission. Copyright 2010, Annual Reviews. (e) The idea of using DNA lattices as a scaffold for crystallizing external guests. Reproduced from [1] with permission. Copyright 2003, NPG.

A variety of DNA motifs have been used to self-assemble periodic arrays in one-, two- and three-dimensions through tile-based methods [42]. DNA origami — in which a long single stranded 'scaffold' DNA is folded using hundreds of short 'staple' strands into nanoscale shapes — has been used in the construction of geometric and non-geometric two-dimensional shapes as well as 3D objects [43,44]. Tile-based self-assembly and DNA origami are directed by the specificity of binding and predictability of canonical Watson–Crick base pairing. This review discusses the design and use of various DNA tiles in the hierarchical self-assembly of two- and three-dimensional DNA arrays.

2. Hierarchical assembly: principles and design

DNA is inherently a linear molecule, and for hierarchical arrays to be produced, branched DNA motifs are required [45]. DNA motifs with 4-, 5-, 6-, 8- and 12-arms have been created (Fig. 1a) [46–48]. An additional feature is the self-assembly of designed DNA tiles based on sticky end cohesion [49]. A sticky end is a short overhang of single-stranded DNA on one strand of a duplex that can facilitate cohesion to a complementary overhang on another duplex (Fig. 1b). Molecular recognition properties in DNA allow for the use of sticky ends to direct the assembly of higher ordered nanostructures. This specific and directed strand cohesion is highly desirable for the construction of one-, two-, and three-dimensional arrays as it provides predictable local geometry in hierarchical assemblies (Fig. 1c) [49]. In addition, the sequences in these motifs are specifically designed with symmetry minimization [45]. This minimizes other possible conformations resulting from unintentional Watson–Crick associations. DNA molecules have been used in forming a variety of DNA motifs and tiles that serve as basic structural units for the construction of periodic arrays (Fig. 1d). The notion of using DNA as a material was to create DNA lattices that can act as a framework

for the periodic arrangement of external guests such as proteins for crystallization purposes (Fig. 1e).

3. Tile-based 2D DNA lattices

The discovery of rigid motifs formed the basis for tile-based self-assembly of periodic arrays. The simplest of these are DNA double crossover (DX) tiles. DX molecules are named as such because they have two crossover sites between helical domains [50]. DX molecules can either be parallel (P) or antiparallel (A), depending on the relative orientations of the two double helical domains. Next, DX molecules can either have an odd (DPO/DAO) or even (DPE/DAE) number of helical half-turns between the crossovers. The DX motif with antiparallel double helical domains containing even number of helical half-turns between the crossovers (DAE) has been shown to be approximately two-times as stiff as linear DNA duplexes [51]. This rigidity, in conjunction with sticky end overhangs on edges of the DNA motif, leads to the formation of large one- and two-dimensional periodic arrays.

DX molecules with programmed sticky ends were first shown to self-assemble into two-dimensional crystals (Fig. 2) [21]. Two DX tiles — A and B — with different sets of sticky ends were used to create a two-dimensional (2D) striped lattice. Antiparallel DX units DAO and DAE were used, and the sequences of DX molecules were designed under the principle of sequence symmetry minimization [45]. To test the robustness of the 2D lattice, tile B was modified topographically (Fig. 2a) with two hairpin-terminated bulged 3-arm junctions (hairpins are denoted by *). These protrusions in B* appear as vertical stripes in AFM images (Fig. 2b). Additionally, the periodicity of the crystal lattice could be doubled when using four unit tiles, creating a 4-tile DX system of ABCD* (Fig. 2c). Similar to B*, the D* tile was decorated with two hairpins so that it is visible as stripes under the AFM. The DX systems could self-assemble into
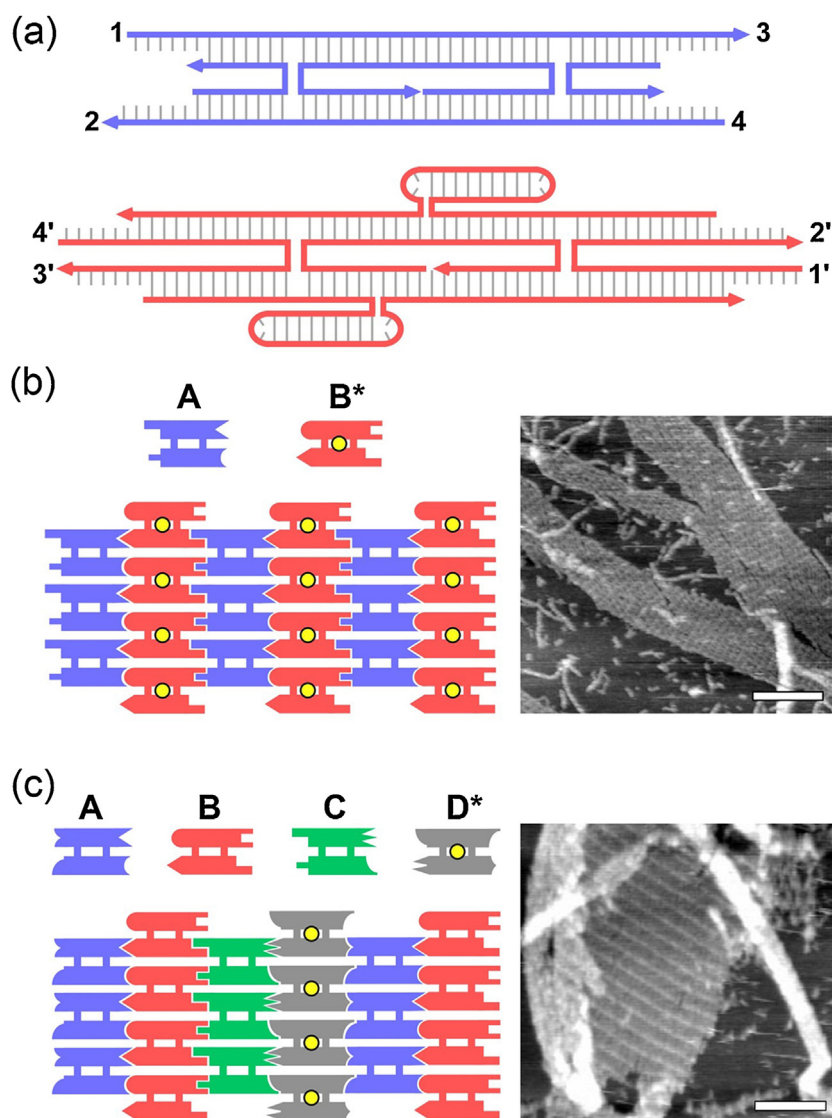
Fig. 2. Double-crossover (DX) motifs for 2D self-assembly. (a) The two DX tiles made from DNA double crossover molecules with Tile B having a hairpin marker (denoted as B*). Complementary sticky ends are denoted by n and n', arrows indicate the 3' ends of strands. (b and c) Scheme of the assembly and AFM results for 2D lattices consisting of two units and four units respectively. In the two-unit design, tile B contains the topological marker (B*) while tile D is modified (D*) in the four-unit design. Complementary sticky ends are shown as complementary shapes between the tiles. Scale bars: 300 nm. Adapted from [21] with permission. Copyright 1998, NPG.

well-defined periodic 2D crystals and provide a platform for the creation of complex patterns [52].

Another complex, the DNA triple crossover (TX) motif, has also been used to create self-assembled 2D crystals [22]. The TX molecule consists of four oligonucleotides, hybridized into three double-helices that are connected by four crossover points (Fig. 3a). In contrast to the DX molecule that consists of only two helical domains, the TX molecule consists of three helical domains that contain at least two crossover sites between each helical domain. Similar to the 2D DX arrays, this assembly consisted of a two-unit and four-unit self-assembly pattern. For the two-unit design, two different tiles were used: A is a normal TX molecule, and B* contains an extra pair of hairpins facing out of the plane of the central helix to produce a topographic pattern in AFM. The resulting AFM image shows a periodic pattern of stripes that are separated by ~28.6 nm, which is the expected distance based on the design (Fig. 3b). For the four-unit design, two additional tiles C and D were used. Tile C is a TX molecule with sticky ends only on the central helix that are complementary to tiles A and B on either side. On formation of the array, tile C is rotated 103° with respect to A and B; this rotated

tile is denoted as C' (Fig. 3c). Tile D is a normal duplex molecule, and is used to fill in the gaps in the array. The resulting 2D array formed from ABC'D is shown in Fig. 3c. The rotated C' tile provides a topographic marker, seen as stripes separated by ~35 nm.

A rhombus-like motif has also been used for self-assembly into 1D and 2D arrays [23]. This design consists of four six-turn double helices fused together by four junctions. The vertices of the rhombus are separated by four double helical turns. Through sticky end association, these DNA rhombus structures can form both 1D and 2D arrays (Fig. 4a). To form 1D arrays (Fig. 4b), sticky ends were placed on only two edges in one direction, and the remaining two edges were blunted. For 2D assembly, sticky ends were designed to be complementary in two directions such that the tile repeats to form the pattern shown in Fig. 4c. Expected distances between repeating units in AFM images confirmed that the 2D lattices were a result of the design of the motif.

The three-point star tile [53] can self-assemble into large, porous, hexagonal 2D arrays (Fig. 5a). This DNA motif has 3-fold rotational symmetry, where each of the three arms is a four-arm junction. The tiles connect via sticky ends on both arms in each
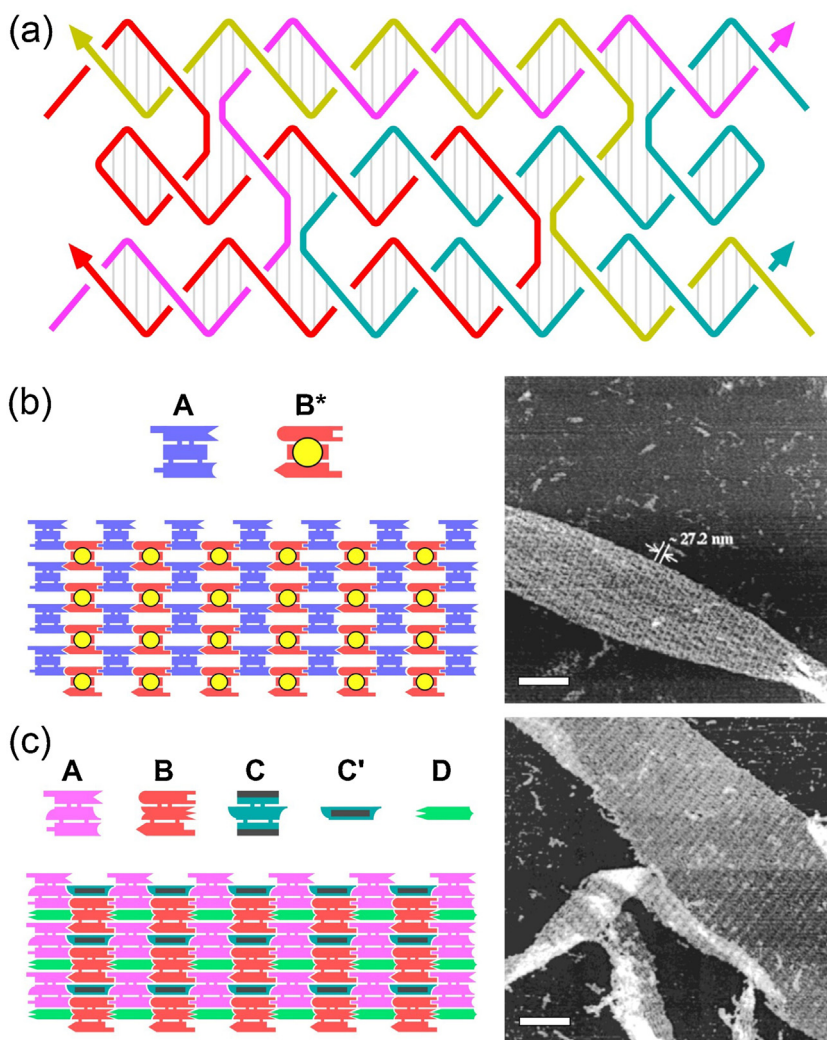
Fig. 3. Triplex-crossover (TX) motifs for 2D self-assembly. (a) The TX complex containing three helices, designed to have their axes coplanar. The molecule is composed of four strands shown in different colors, arrows indicate the 3′ ends of strands. (b and c) Schematics and AFM images of the 2D arrays formed by two-unit and four-unit self-assembly respectively. Scale bars: 200 nm. Adapted from [22] with permission. Copyright 2000, ACS.

direction to yield a 2D array (Fig. 5a, right). Another motif is the symmetric "cross" motif, which consists of 9 strands but only 3 different sequences [54]. All four arms are identical in sequence, and this sequence symmetry prevents unwanted curvatures in the self-assembly of 2D arrays. Through corrugation and sticky ends, 2D lattices were self-assembled from the cross-tiles (Fig. 5b). The resulting AFM images show that well-ordered lattices successfully formed with the expected repeat distance (Fig. 5b, right). The DNA six-pointed-star motif is a similar motif that demonstrates periodic self-assembly of two-dimensional lattices [55]. This tile design allows for more connectivity in that each star motif connects to six other star motifs. The six-pointed-star motif is 6-fold rotationally symmetric, where each arm is a four-arm junction (Fig. 5c). There are 13 strands: a central black strand, six identical blue strands, and six identical red strands. Six T4 loops in the center prevent stacking so that the 2D lattice formed is flat. The resulting 2D crystals were imaged under AFM and showed the expected periodic pattern (Fig. 5c, right).

Double stranded (ds) DNA bridges have been used to connect pre-formed lattice pieces [56]. The 2D lattice was formed by two cross-shaped tiles, A and B (Fig. 6a). Self-assembled DNA nanotracks (NTs) can be formed from two different sized dsDNA nanobridges, short (16 bases) and long (26 bases). AFM images of the NTs without

dsDNA bridges is shown in Fig. 6b and arrays with shorter dsDNA bridges (Fig. 6c) and longer bridges (Fig. 6d) showed distances that correspond to the design. The DNA tensegrity triangle is another rigid motif with flexible junctions that can readily form periodic arrays in one- and two-dimensions [57]. The DNA tensegrity triangle combines both tense and integrity with rigid struts and flexible tendons. The motif consists of three helices spanning three-space that are connected pairwise by four-arm junctions that form each vertex of the triangle. As with the other arrays mentioned earlier, the addition of sticky end overhangs to edges of the triangle directs the formation of arrays in both one- and two-dimensions. AFM imaging of the arrays confirm the formation of arrays with a controlled distance between repeating subunits in 1D and 2D (Fig. 7).

Another motif design that utilizes tile-based assembly is the double-decker tile [58] that was developed from the already established 4 × 4 cross-tile [36]. The design consists of two 4 × 4 cross-tiles stacked on top of each other, linked together by two crossovers in each arm (Fig. 8a). The arms are symmetric with the same sequence composition, and contain four double helices each. Sticky end cohesion can be used to guide the self-assembly of both two-dimensional and three-dimensional lattices from the double-decker tile. Large two-dimensional lattices were formed
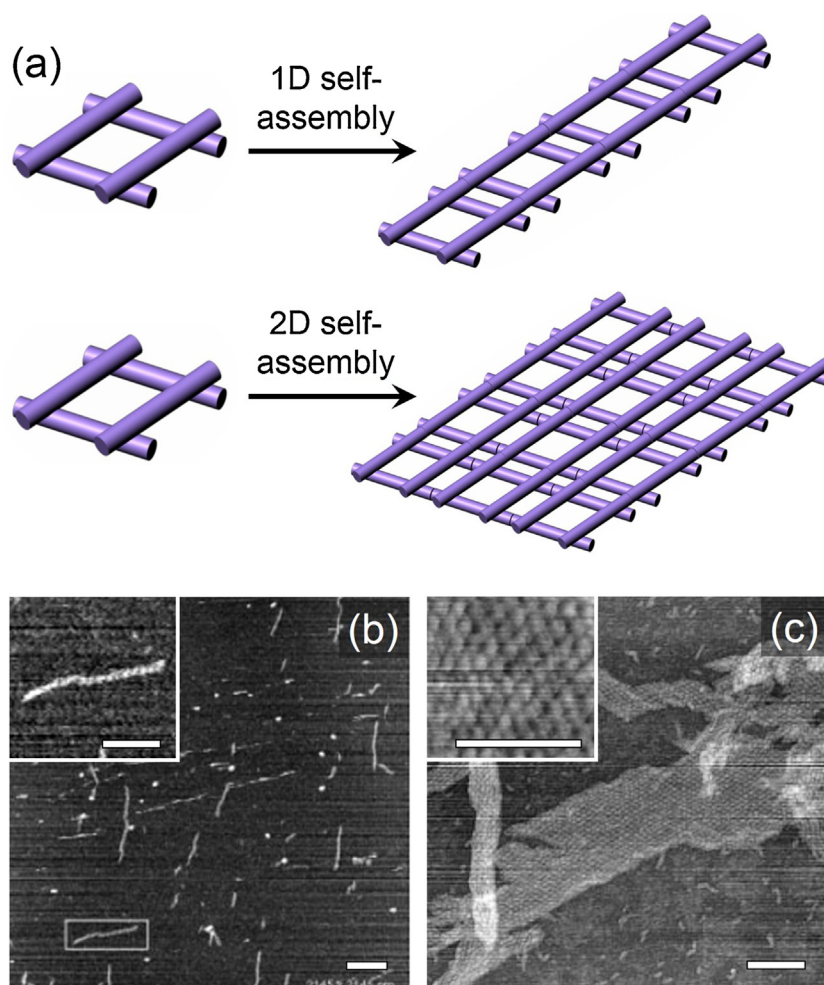
Fig. 4. Holliday junction arrays based on a rhombus-like motif. (a) One- and two-dimensional self-assembly of the rhombus-like motif into an array. 1D self-assembly is shown to produce a railroad-track-like arrangement (b), while 2D self-assembly produces a latticework of DNA (c). Scale bars: 200 nm. Adapted from [23] with permission. Copyright 1999, ACS.

using corrugation, in which adjacent tiles (15 helical half-turns apart from center to center) are flipped. AFM imaging demonstrated successful formation of the 3.4 nm high 2D lattice (Fig. 8a, right). By modifying the sticky ends, three-dimensional lattices with a cavity size of ~60 nm can theoretically be formed from the double-decker tile. This will be useful for the insertion of a guest molecule in 3D space.

In contrast to ideally infinite 2D-DNA superlattices which are assembled from DNA tiles by sticky-end hybridization, there is also a great interest in generating finite quasi-2D DNA superstructures. Using rational DNA design, it is possible to control in how many dimensions a growing lattice assembles, and whether this growth is potentially infinite or terminated. Finite assemblies have been created by replacing specific sticky ends in some tiles by blunt ends or hairpin loops. This approach has been applied to assemble finite nanoarrays from cross-shaped tiles [36], which were used to precisely position individual streptavidin molecules, much like a molecular pegboard (Fig. 8b) [59]. Each tile had unique seven nucleotide sticky ends, chosen to hybridize with only one other tile at each side. The outer edge of each of the outer tiles had TTT overhangs that terminated further self-assembly into any larger arrays. In addition, each tile contained a small double helical stub from which protrudes a 16 base single-stranded probe that is unique to the tile. Even these small (3 × 3) arrays can be useful for probing cooperative effects in ligand binding. Such a small-scale addressable array may also find applications in investigating proximity effect between proteins or other macromolecules.

Another triangle motif used to create 2D arrays is the DX triangle [35]. The design of this motif is based on the tensegrity triangle [57] but contains DX molecules instead of single helices in each of its three domains (Fig. 8c). Each triangle has eight double helical turns of DNA on each edge. This motif was designed and built to have alternating even and odd separations between crossovers. Two such DX triangles were used to form a two-component 2D array. The organizational power of this system has previously been demonstrated in a well-positioned alternating 2D array of 5 and 10 nm gold nanoparticles [35].

4. Tile-based 3D DNA lattices

A motif based on the tensegrity triangle was used to create the first self-assembled macroscopic 3D DNA crystals [24]. The formation of periodic 3D arrays through self-assembly has been a major goal in structural DNA nanotechnology because of its potential to serve as a scaffold to host external moieties such as functional molecules or proteins. The DNA tensegrity triangle was already shown to be capable of self-assembling into periodic 1D and 2D arrays. The tensegrity triangle motif used was 3-fold symmetric, and all three helices were designed to contain 2-nucleotide sticky ends in a symmetric fashion (Fig. 9a). Each triangle can associate
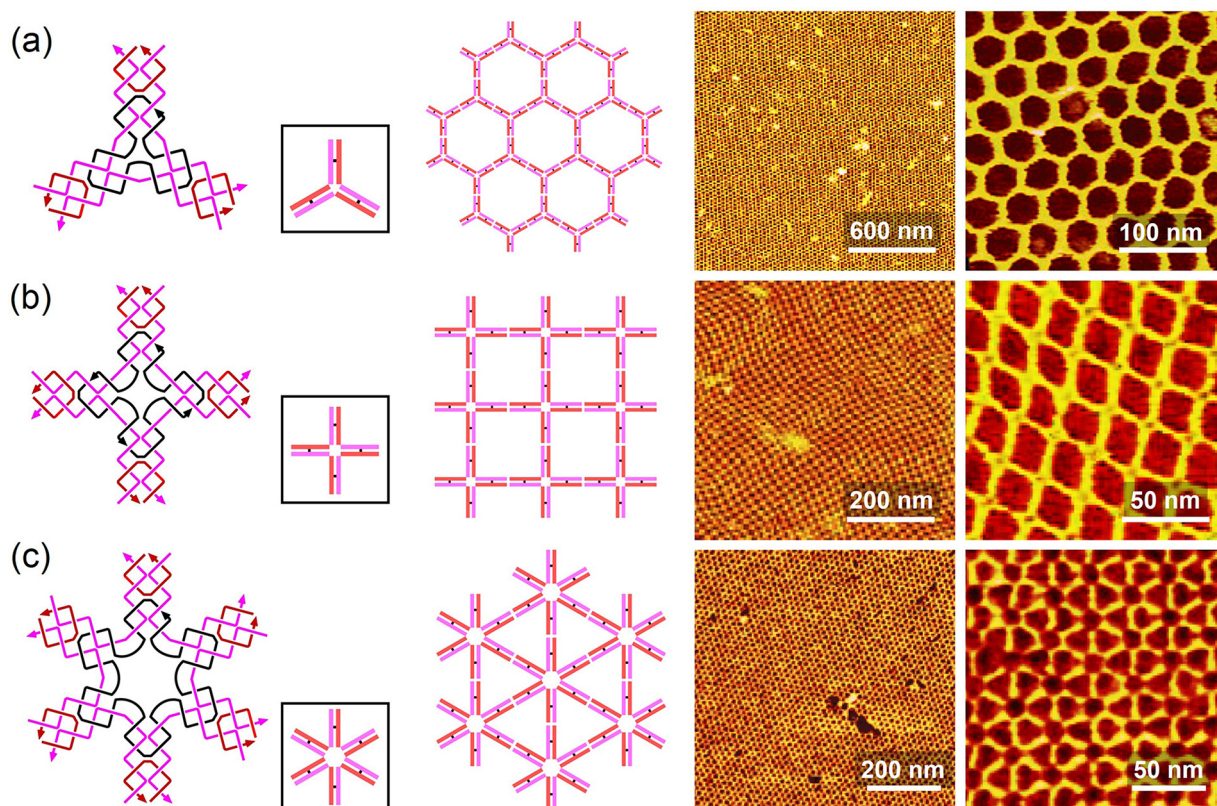
Fig. 5. DNA star-motifs for 2D self-assembly. (a) Three-point-star DNA motif and the extended, hexagonal 2D DNA array. Adapted from [53] with permission. Copyright 2005, ACS. (b) A symmetric cross-shaped motif and the corrugated self-assembly in two dimensions. Adapted from [54] with permission. Copyright 2005, Wiley-VCH. (c) DNA six-pointed-star motif and its extended, periodic array. Adapted from [55] with permission. Copyright 2006, ACS. Corresponding AFM images of the 2D arrays are shown on the right. (For interpretation of the references to color in this figure citation, the reader is referred to the web version of this article.)
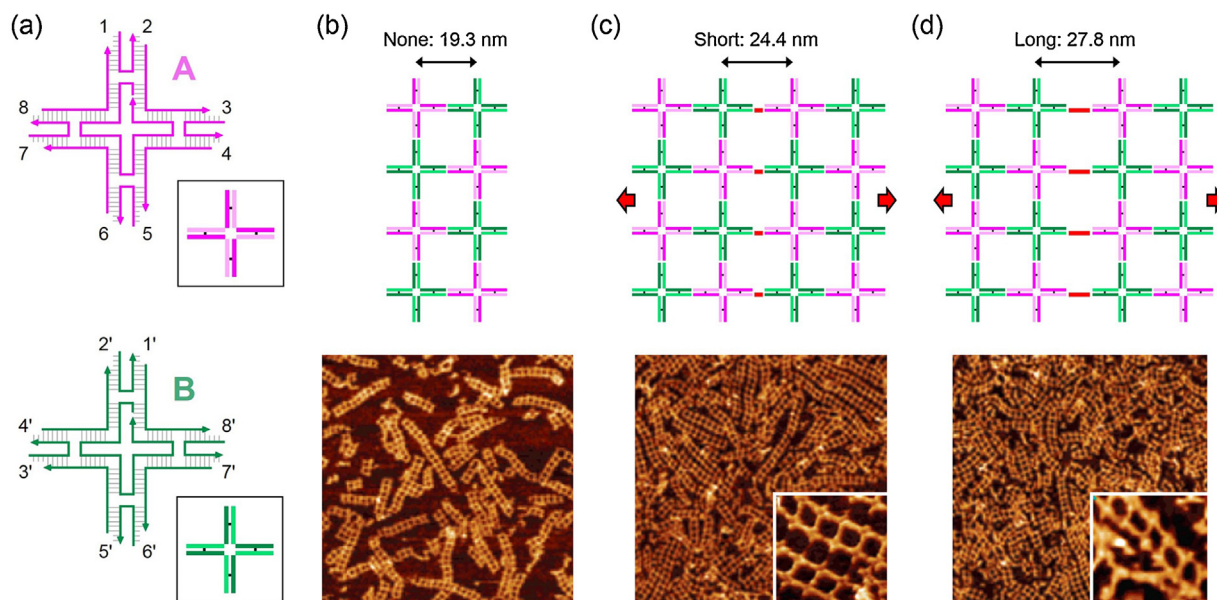

Fig. 6. DNA nanotracks (NT) with double stranded bridges. (a) Drawings of A and B cross-tiles. Schematic and AFM images of (b) NT without bridges, (c) NT with short bridges, and (d) NT with long-bridges. Red arrows indicate growth-directions towards additional dsDNA bridges. AFM images are 800 nm × 800 nm, insets 100 nm × 100 nm. Adapted from [56] with permission. Copyright 2008, ACS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with six other triangles in three orientations to produce the lattice (Fig. 9c and d). The resulting 3D crystals (Fig. 9b) diffracted to ~4 Å resolution [24]. Triangle motifs lacking this three-fold symmetry produced crystals that diffracted to a slightly lower resolution. The unit cells of these crystals contain a rhombohedral cavity that

can accommodate external guests (Fig. 9d). This periodic crystalline lattice can be used to host external guests for crystallographic structure determination and also to potentially host nanomechanical devices for programmed molecule capture. A similar 3D DNA crystal was designed to contain two different triangles in an asymmetric
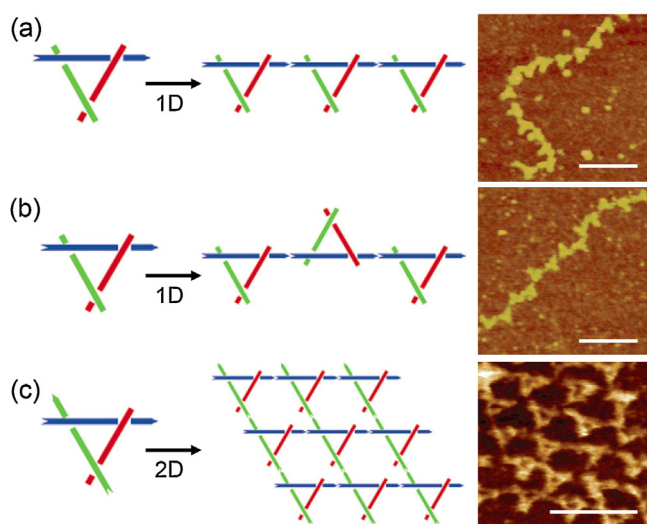
Fig. 7. The DNA tensegrity triangle. The motif contains three DNA duplexes, shown as rods with different colors. (a and b) 1D self-assembly of DNA triangles in a linear or zigzag pattern. (c) 2D self-assembly of DNA triangles. Sticky end complementarity is represented by geometric complementarity. Corresponding AFM images are shown on the right. Scale bars: 100 nm. Adapted from [57] with permission. Copyright 2004, ACS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 8. Tile-based 2D lattices. (a) Double-decker tile and self-assembly into two-dimensional lattices. Inset scale: 200 nm. Adapted from [58] with permission. Copyright 2011, ACS. (b) Assembly of a finite-size, chemically addressable DNA nanoarray from cross-shaped DNA tiles. Inset scale: 100 nm. Adapted from [59] with permission. Copyright 2005, ACS. (c) DX triangle motif with double stranded helices shown as cylindrical rods around which the individual strands are wrapped. The three DX domains are not planar but span three directions. Schematic and AFM image of a two-component array are shown on the right. Adapted from [35] with permission. Copyright 2006, ACS.

unit [25]. In this case, the two triangles alternated throughout the lattice (Fig. 9e and f). This design showed the ability to control the asymmetric unit of the rationally designed 3D crystal, and allows for the positioning of unique guests in the DNA framework.

5. DNA origami-based tile assembly

A wide variety of DNA nanostructures have been successfully constructed through tile-based assembly. In tile-based assembly, structures had to be designed based on individual DNA strands, and DNA of the desired sequence needed to be synthesized. Because these structures were designed from scratch, they were generally limited to a maximum length of 150 base pairs. Another major
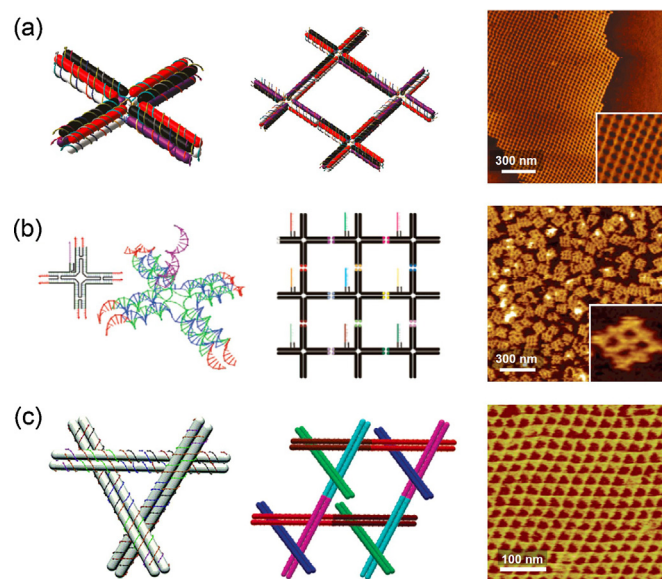
method of self-assembly is DNA origami (Fig. 10a) [43]. In this strategy, a long single-stranded scaffold is folded using multiple complementary staple strands into various complex patterns, structures, and even 3D objects. The scaffold strand is usually naturally occurring, for example, viral genome M13 (7249 nucleotides), for which the exact sequence was known. DNA origami allows for the creation of geometric and arbitrary shapes with holes or patterns from a designed folding path with a spatial resolution of ∼6 nm. This process provides precision, and immensely broadens
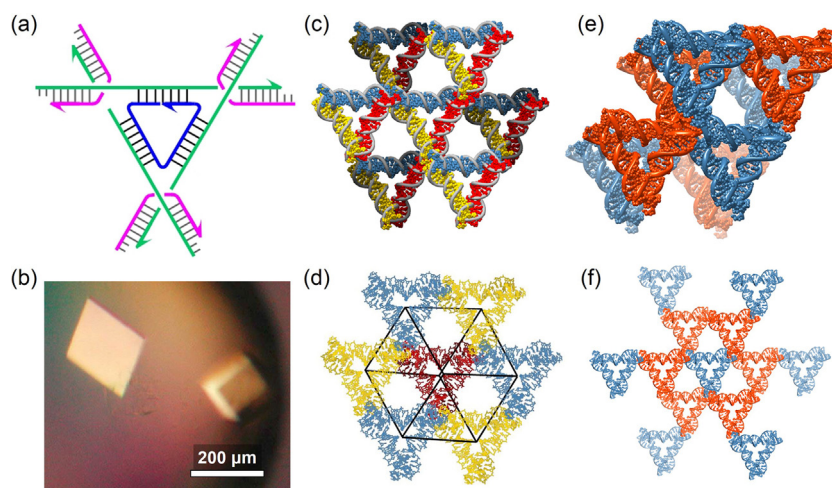

Fig. 9. Rationally designed 3D DNA lattices. (a) Schematic of the tensegrity triangle. The three unique strands are shown in magenta (strands restricted to a single junction), green (strands that extend over each edge of the tensegrity triangle) and dark blue (one unique nicked strand at the center passing through all three junctions). Arrowheads indicate the 3′ ends of strands. (b) An optical image of crystals of the tensegrity triangle. (c) This image distinguishes the three independent directions by base-pair color. The central triangle is flanked by six other triangles. (d) This image shows seven of the eight triangles that comprise the corners of the rhombohedral cavity. The cavity outline is drawn in black. The rear red triangle connects through one edge each to the three yellow triangles in a plane closer to the viewer. The yellow triangles are connected through two edges, each to two different blue triangles that are even nearer to the viewer. (e and f) Spatial arrangement of the alternating triangle units in a 3D crystal with two triangles (shown in blue and red) in the asymmetric unit. (a–d) Adapted from [24] with permission. Copyright 2009, NPG. (e–f) Adapted from [25] with permission. Copyright 2010, ACS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
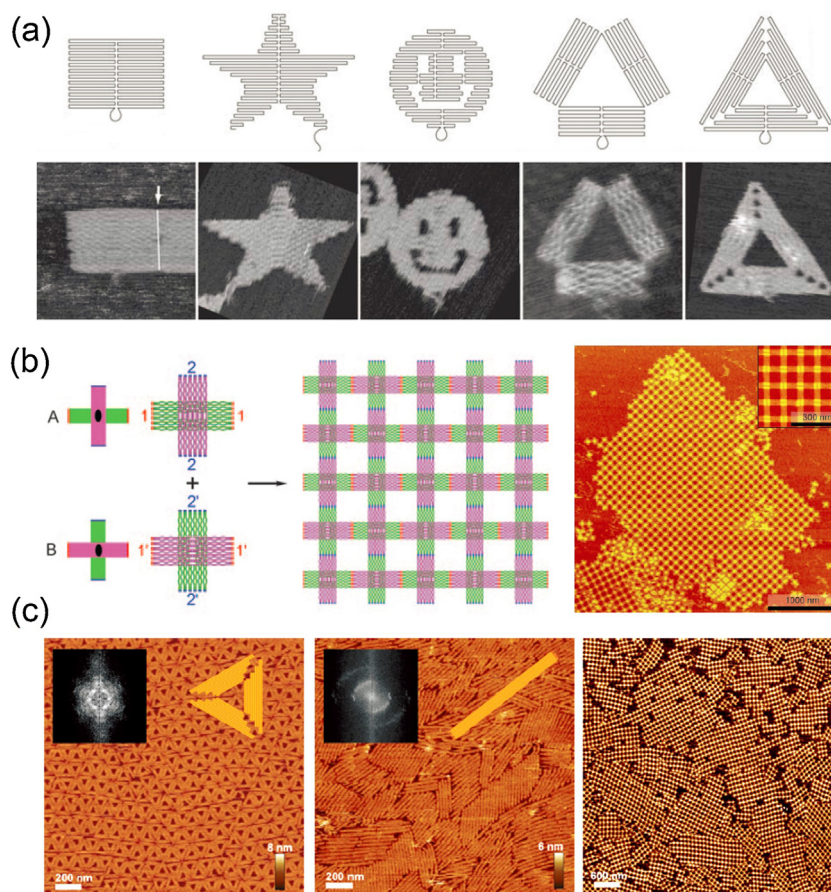
Fig. 10. DNA origami tiles and arrays. (a) Folding paths and AFM images of a rectangle, star, smiley face, triangle with rectangular domains and sharp triangle with trapezoidal domains. AFM images are 165 nm × 165 nm. Reproduced from [43] with permission. Copyright 2006, NPG. (b) Two cross-shaped DNA origami tiles designed to form a crystalline 2D array by sticky end cohesion. Adapted from [60] with permission. Copyright 2011, Wiley-VCH. (c) Surface assisted stacking of DNA origami tiles of different shapes: a sharp triangle, a DNA rod and cross-shaped tiles shown in (b). Adapted from [63] with permission. Copyright 2014, Wiley-VCH.

the number of possible array patterns that can be formed. Unlike tile-based self-assembly, DNA origami does not require highly pure strands, sequence optimization, or very precise stoichiometry of component strands. DNA origami extends beyond the construction of 2D structures to large 3D structures by means of raster fill method. It has been shown to be relatively easy to use, cheaper, and produces high yield of the desired result [43].

DNA origami tiles have been used to create micrometer-scale 2D lattices via sticky end hybridization [60]. This strategy involved an origami tile whose helix axes propagates in two independent directions; two such tiles designed to cohere to each other via sticky ends resulted in large, ordered 2D arrays (Fig. 10b). Surface-assisted assembly [61,62] has also been used to create large arrays of DNA origami structures using improved surface mobility on the addition of monovalent salts. Large ordered origami lattices were created by a combination of blunt-end stacking interactions and surface diffusion of origami tiles of different shapes (Fig. 10c) [63]. This lattice was also used for the ordered arrangement of proteins.

6. Conclusion

The self-assembly of periodic DNA arrays has long been utilized in DNA nanotechnology. The construction of nanostructures in one-, two-, and three-dimensions has diverse applications, and therefore has been studied intensively for the past few decades. Self-assembled lattices created from DNA can be used as a template for the organization of other functionalized molecules. For example, DNA-protein hybrids combine the structure-directing properties of DNA with the functionality of proteins such as molecular

recognition, catalysis, energy conversion, and membrane translocation. Furthermore, the DNA lattice may contain an arbitrary number of different tiles if necessary, so that the conjugate binding to the guest molecule (e.g.: aptamers) can be placed at desired locations with varied spacing between them. Notably, various tiles within the lattice may potentially be engineered to display different guests at defined positions and orientations by virtue of the different possible combinations of aptamers and target ligands. The scope of such assemblies is ever expanding and design parameters have been improved in recent years. For tile-based assembly, the formation of stable, rigid motifs have led to the successful formation of 3D crystalline lattices. DNA origami allows for the precise creation of various patterns and shapes in 2D and objects in 3D. Newer approaches to self-assembly aim to decrease the errors and limitations of tile-based methods and DNA origami.

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