

DNA 自组装技术的研究进展及难点

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摘 要 近年来,DNA 自组装成为 DNA 计算及纳米材料科学等领域研究的热点,它关系着 DNA 计算机的发展。DNA 分子如何组装已成为许多学者关注的焦点。为此,文中主要围绕着 DNA 分子组装成的初级元件的类型:一条长的 DNA 单链、多条短寡核苷酸链和自组装单元,重点从自组装的初级元件形成的一维、二维及三维结构上讨论 DNA 自组装技术与方法。文中讨论了这些技术的原理及应用的研究进展,并且分析了 DNA 自组装应用于 DNA 计算的主要难点及解决方案。首先,编码的好坏决定着实验是否能实施;其次,DNA 单链之间组装的角度及初级原件之间的连接是影响自组装体产量的关键因素;从具体的实验操作上看,每条 DNA 单链的浓度比例及退火温度则决定着自组装的成败。随着学科之间的高度交叉,DNA 自组装将是材料学、信息学、生物学等领域的重要研究方向,也是推动 DNA 计算机发展的重要手段。

关键词 DNA 自组装;初级元件;组装技术;二维平面;三维立体结构

中图法分类号 TP301

Progress and Difficulty in DNA Self-Assembly Technology

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Abstract DNA self-assembly, widely developed in the fields of DNA computing and nanotechnology, is related to the development of DNA computer. How DNA molecules assemble has become the focus of scientific fields. This paper mainly discusses the DNA self-assembly technology of one-dimension, two-dimension and three-dimension structure. DNA self-assembly units are divided into three types: a long DNA single-strand, several short DNA single-strands and primary units of DNA self-assembly. In the meantime, the principle and research progress of DNA self-assembly are discussed. On the other hand, the main obstacles and solutions of the application on DNA computing are also analyzed. Firstly, coding is the most difficult problem, as it decides whether the experiment can be implemented. Secondly, the assembled angle between DNA single-strands and the connections among motifs. In addition, from the experiment operation, whether the self-assembly structure can be achieved is decided by the concentration proportion of each DNA single-strand and the anneal temperature. With the rapid developing of science and technology and combination of multi-disciplinary science, DNA self-assembly has become the important research direction in the fields of material, informatics and biology, and will also be the critical instrument that promotes the development of DNA computer.

Keywords DNA self-assembly; primary motifs; assembled technology; two dimensional array; three dimensional polyhedra

1 Introductory

DNA had been selected as the genetic material long before, as DNA was the distinct double-helical structure and carried all genetic information. As the huge memory ability of DNA, it becomes the important study materials in the fields of biology, computer and nanotechnology. In 1994, Adleman firstly constructed the computing model with DNA^[1]. From then on, many researchers also established different DNA computing models, such as Ouyang's DNA solution of the maximum clique problem^[2], sticker DNA computing model of Roweis^[3], and DNA self-assembly structures of Winfree's group^[4]. Up to now, DNA computing had been developed at a high speed no matter in constructing theoretic models or in applying the biological operations.

In recent years, there are some main computing models as follows: DNA self-assembly models^[5-6], DNA computation models on surface^[7-9], computational model imitating Turing^[10]. Based on the types of solving problems, these models can be divided into the three categories: DNA computing models for solving graph theory^[11-14], Boolean circuits^[15-16], and decipher codes^[17]. Based on the formed structure of DNA self-assembly, DNA models are divided into one-, two-, and three-dimensional structures. In 1960s, Wang used DNA single-strands to assemble tiles as the computing instrument^[18]. In 1998, Winfree used Wang's tile to form 2D crystal^[19]. In addition, other researchers also contributed tremendous fruits on DNA self-assembly. In 2008, Mao applied several single-strands to further assemble into different complex polyhedra^[20]. Here, we introduce the development of molecular self-assembly these years, summarize the study results, and present the prospect of DNA self-assembly.

2 Progress in DNA Self-Assembly Technology

DNA self-assembly is a method that exploits the specificity of base-pairing to form polyhedron or supermolecular structure. This is a complex progress from simple to complicated, from disordered to well-regulated. In 1960s, Wang's tile, constructed by DNA single-strands, opened a new door^[18] for DNA self-assembly. In 1990s, Seeman improved the tile and constructed many kinds of complex DNA polyhedra such as quadrangle, loop, knot, etc^[21-23]. Though it still has a lot of disadvantages for these self-assembly structures such as

the lower yields and difficult to be picked up, this method is a huge milestone for DNA computation.

2.1 One Dimension Structure and Application of DNA Self-Assembly

In 1994, Adleman firstly applied DNA self-assembly to solve a Hamiltonian Path Problem. Since then, the method was used by lots of researchers to solve logical computation, simple addition computation and graph theory problems. In 2002, Seeman published an article in PNAS. He pointed out that a one-dimensional example using DNA tiles had been used in logical computation and could also be viewed as a circuit that realized the parity of the input elements^[24]. Besides, lots of researchers also applied a one-dimensional structure of DNA self-assembly to carry out addition computation such as the insert-delete method of Qiu and Lu^[25] and the binary arithmetic of Barua^[26]. In a word, the main idea is that the experiment steps will linearly increase with bits of addition increasing.

2.2 Two-Dimensional Array and Application of DNA Self-Assembly

It is not good enough to use one dimensional structure of DNA molecules to compute. Lots of researchers, based on a great deal of experiments, make DNA molecules assemble into more complex two-dimensional array and carry on computation. At present, the idea of the self-assembled tile starts from the Wang's tile that imitates the operation of Turing. However, it has more advantages than Wang's tile, because it can implement computation not only using simple structure, but also more complicated structure such as 2D and 3D DNA structure. In these complex structures, there are three main basic elements: a long DNA single strand^[27-28], self-assembled unit (consisted of several DNA strands and had sticky ends) and multiple short DNA strands^[29-31]. The self-assembled unit includes Double-crossover (DX) molecules^[32], Triple-crossover (TX) molecules^[33], and several-point-star DNA motifs (three-point-star^[20,34], four-point-star^[35-36], and six-point-star^[37]).

DX molecules, as a self-assembled unit, consisted of two side-by-side double-stranded helices. The double-stranded helices contain four DNA single-strands, linking at two crossover junctions. In 1999, LaBean improved the DX structure and developed TX molecules, which was composed of three side-by-side double-stranded helices and linked at four immobile crossover points. Besides, several-point-star DNA motifs are more complex

than DX and TX. They are consisted of three kinds of DNA single-strand: a central loop-strand, several shell-strands and several arm-strands. For different point-star DNA motifs, the number of required DNA strands is different.

At present, a long DNA single strand is selected from M13, which is the member of filamentous bacteriophage family and is a DNA single-strand with 6400 bases. M13 is a very important material in DNA self-assembly area. There are three main reasons. (i) M13 is a stable single-stranded DNA. Compared with double-stranded DNA, it can freely hybridize and is more flexible to be folded or assembled. In the past DNA self-assembly structure, self-assembled unit is constituted of some short DNA single-strands, so it is strict to control the concentration of each strand, and finally these strands form to integrate self-assembly structure. In addition, using several short DNA single-strands to construct complex structure is gradually created by several-step assembly, so the yield of DNA self-assembly structure is not much high. (ii) Its length is much proper, which can decide the size of self-assembly structure. The

longer DNA strand is, the larger and more elaborate self-assembly structure is. M13 satisfy the requirement properly, and the gene of M13 has been known clearly by scientists, thus, M13 is an inherent material as the motif of self-assembly structure. (iii) The cost of obtaining the M13 sequence is much low, because the price of synthesized long DNA sequence such as M13 is quite high, but it only costs little money to clone the M13 gene from bacteriophage.

In 2006, Rothemund presented a novel method for using a 7kb single-strand of M13 and over 200 short oligonucleotide staple strands to fold into desired shapes such as squares, triangles and five pointed stars etc^[27]. These six different shapes were successfully detected by using AFM and STM surface manipulation (Fig. 1). In addition, according to the basic desired shapes, he also assembled the structures that could be created with arbitrarily shaped holes or various patterns such as letters, snowflake, and map. These patterns would be higher than that of any previously self-assembled shapes, so they could be observed by AFM and STM (Fig. 2).

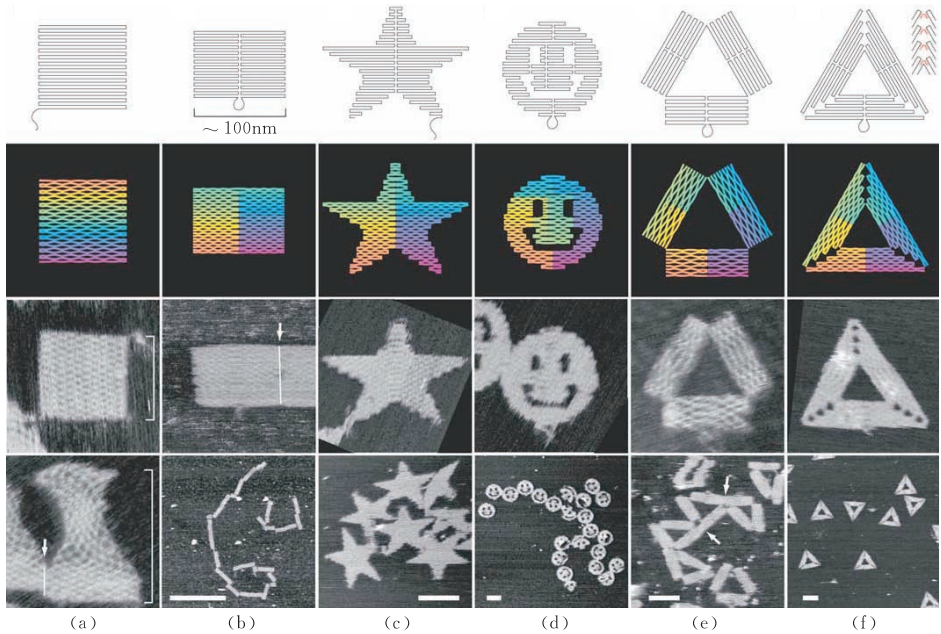


Fig. 1 DNA origami shapes and AFM images

Applied the same method, the research group from Shanghai Jiaotong University used a 7kb single-strand of M13mp18 and over 200 short staple strands to fold into the pattern of China map that were roughly 150nm in diameter. And the China map was detected by using AFM^[28].

Self-assembled unit is another familiar motif, and DX molecule is one of these motifs in DNA

self-assembly. In 1998, according to the theory of Wang's tiles, Winfree designed DX molecules which acting as Wang's tiles could implement desired computations by molecular self-assembly^[32]. During these processes, five enough rigid DX motifs were successfully constructed, but only DAO and DAE motifs are stable (Fig. 3). DAO motif, consisting of four DNA strands, each of which

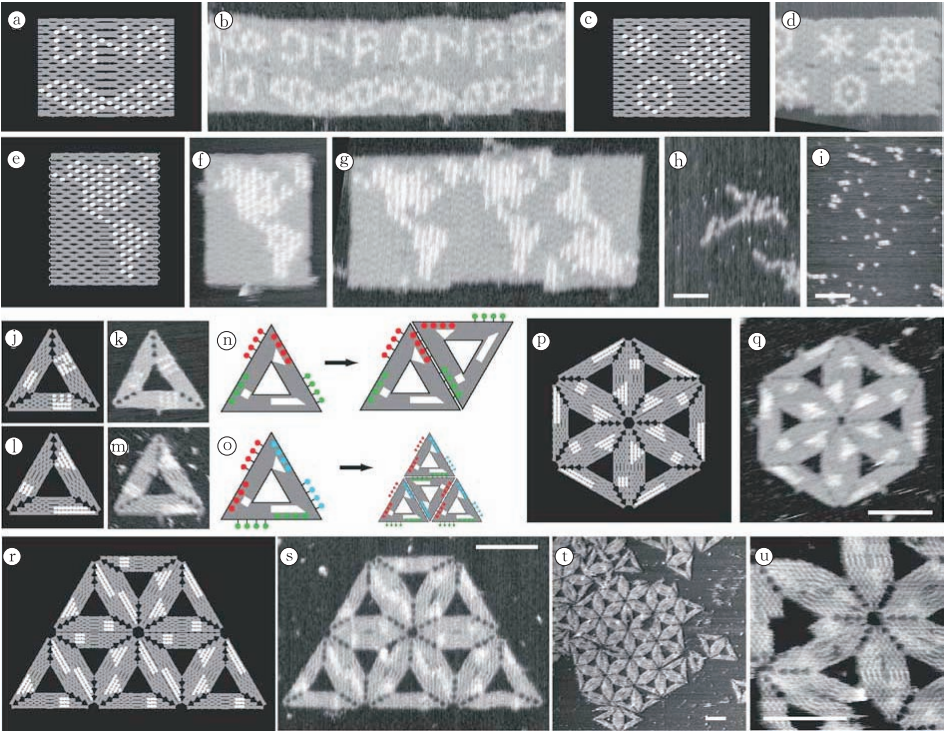


Fig. 2 Patterning of DNA origami and AFM images

joined in two helices, had double crossover and spacing. By comparison, DAE molecules, a little different from DAO, consisted of five strands, three of which participated in both helices. And another two strands did not form into crossover. Each motif of DX unit had a sticky end with a 4bp unique sequence which could control the assembly between DX units by Watson-Crick complementarity. Each of DX unit was combined by recognizing the sticky ends into two dimensional (2-D) lattices. Using DAO and DAE units, two various lattices were obtained. One, consisting of DAO units, was called DAO-E, and the other was called DAE-O which consisted of DAE units. Here, we take the DAO-E for example to introduce the self-assembly process of DAO units. In this 2D lattice,

there were two kinds of motifs, two DAO and one DAE. One of DAO, on the left, was marked “A” and the other was marked “B”. Additionally, one DAE unit was an alternative form B^{\wedge} that could replace B. In fact, B^{\wedge} belonged to DAE unit, but it contained two hairpin-terminated bulged 3-arm junctions. In this way, B^{\wedge} increased the height of the 2D lattice so that it produced the light and shade stripes by AFM imaging. The upper sticky end on the right of “A” unit bonded to the sticky end below on the left of “B” unit, and one below on the right of “A” unit bonded to the upper sticky end on the left of “B” unit, and vice versa. In this way, the 2D lattice was formed. Finally, DAO-E and DAE-O were detected by AFM imaging (Fig. 4).

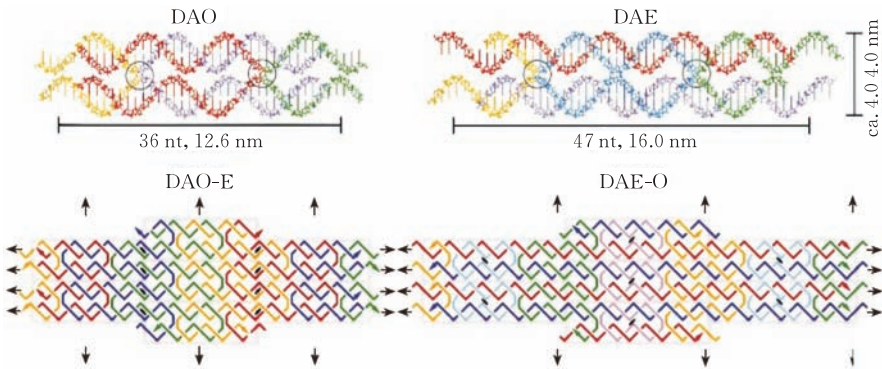


Fig. 3 Models for DAO and DAE tiles and the lattice topologies consisting of DAO and DAE tiles

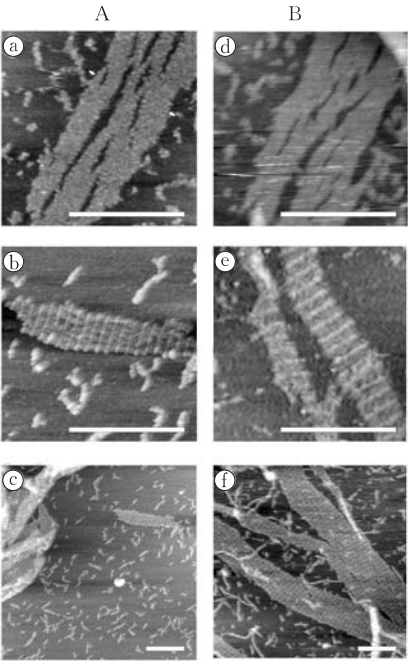


Fig. 4 The AFM images of two tiles lattice; DAO-E AB, DAO-E AB⁻ and DAE-O AB, DAE-O AB⁻

DX unit has more advantages than primary tiles. It not only surpasses the simple one-dimension structure, but also can combine into 2D and 3D structure. This provides the new module to perform DNA computation. However, DX unit has still a lot of flaws such as lacking of reporter strands and smaller space between single strands. Thus, it is very important to synthesize more perfect and stable motifs in the fields of nanotechnology and DNA computing. To achieve this goal, LaBean, founding on structure of DX unit, constructed TX module that was more excellent than DX unit^[33]. He designed four oligonucleotides (Fig. 5), which formed three DNA helices by four immobile crossover points. The three antiparallel double-stranded DNA helices finally formed to TX unit in a plane and had four sticky ends. In TX units, DNA single-strands, participating in three helices, could act as reporter strands and implement the output of computing result. In the meantime, the 2D structure consisting of TX units was filled with some space that provided gaps for other molecules. Some different TX units were designed by LaBean. A and B, two of TX units, contain four sticky ends. The sticky ends of A were designed to be complementary with that of B to develop the AB array (Fig. 6). Besides, C, C' and D were other three TX units. C consisted of three helices, but contained only a pair of sticky ends in the central helix which paired with those of A and

B respectively. When C was rotated about 103°, it would become another unit "C'", which formed the raised stripes on the surface of 2D array. D was a common double-stranded helix, filling the gaps existing in the array. By recognizing the various sticky ends, these TX units produced the ABC'D array, detected by AFM image. Since then, TX module was applied to DNA computing such as Boolean calculation and addition operation.



Fig. 5 Schematic drawing of TX motif

In recent years, point-star DNA motifs attract more researchers' attention. Its structure is more complex than those of DX and TX motifs. In the structure of point-star DNA motifs, there are three types of DNA single-strands: central strand, identical medium strands and identical peripheral strands. The number of DNA single-strands is a little different for different point-star motifs. In 2003, Hao et al. published a paper in Science that presented a novel cross-shaped DNA module (four-point-star motif), and formed square gridding structure^[35].

In 2007, Park improved its structure to construct two distinct two-dimensional superstructures in controlled ways, basing on the four-point-star motif. One was finite-size lattice 2×2 nanoarrays (NAs) and dsDNA bridges, and the other was extended lattices nanotracks (NTs) and dsDNA bridges^[36]. These two superstructures were formed from A-tiles (Fig. 7 ㉔) and B-tiles (Fig. 7 ㉕). Both of them consisted of three kinds of strands; a central loop-strand, four shell strands, and four arm-strands. The difference between A-tile and B-tile was the opposite direction of sticky ends at both 5'- and 3'-ends. As shown in Fig. 7, one 1×2 and two forms of 2×2 NAs were assembled by Watson-Crick complementary sticky-ends. One 2×2 NAs had no arm-strands (Fig. 7 ㉖), and

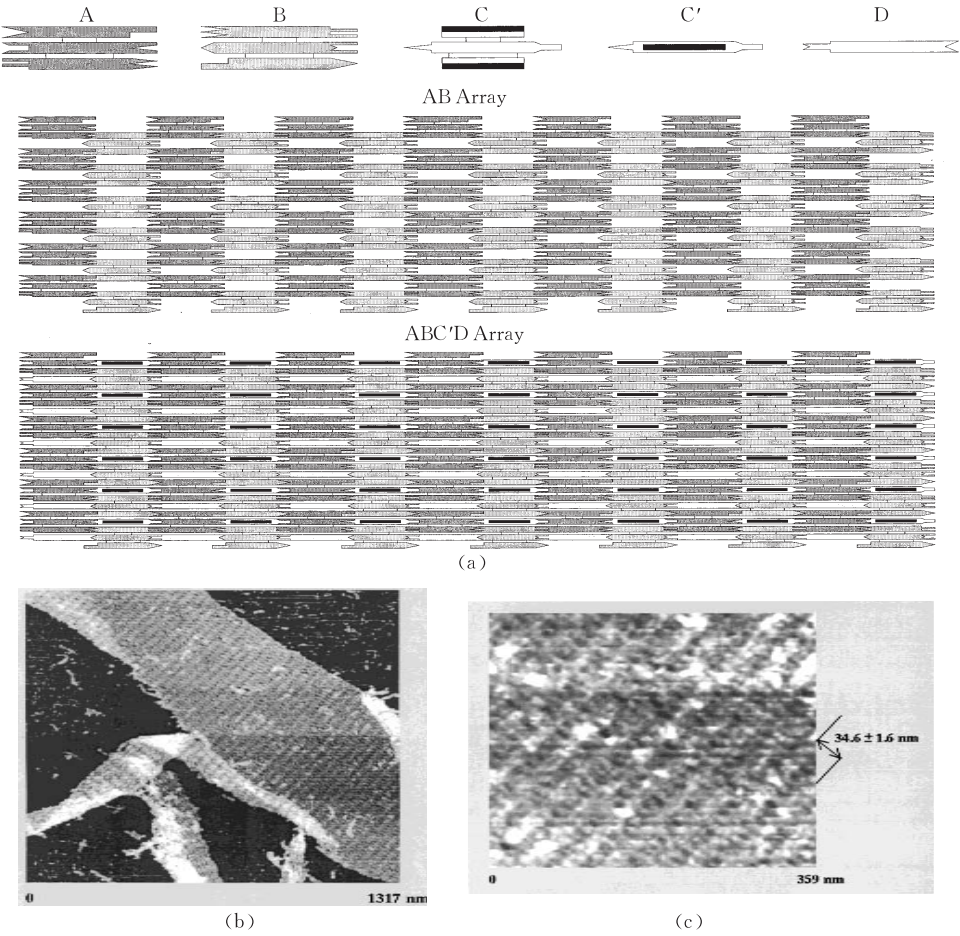


Fig. 6 2D array consisting of TX motifs: A, B, C, C' and D (a common double stranded molecule)

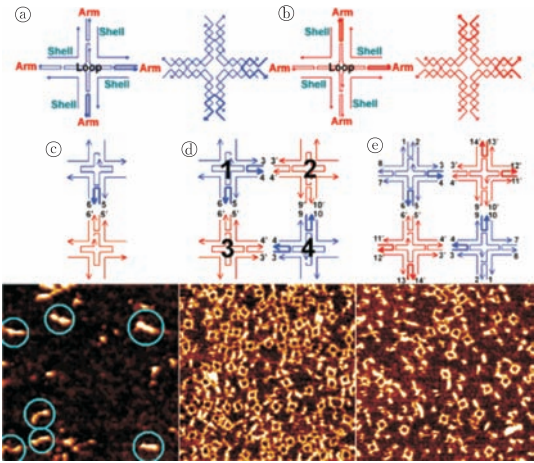


Fig. 7 AFM images of basic tiles and NAs without dsDNA bridges

the other had noncomplementary sticky ends on the outer arm-strands (Fig. 7(c)). Among these superstructures, with the assembled structure becoming complex, the yield decreased accordingly. Next, dsDNA bridge was designed. It was connected with NAs and NTs respectively to assemble limited 2D lattice and extended 2D lattice structures (Fig. 8, Fig. 9). When constructing extended 2D lattice

structure, A-tiles and B-tiles were linked to form NTs. Then dsDNA bridges with various lengths (5.1 nm and 8.5 nm) were connected with NTs. Finally, they obtained the extended 2D lattice structure and detected by AFM images (Fig. 9).

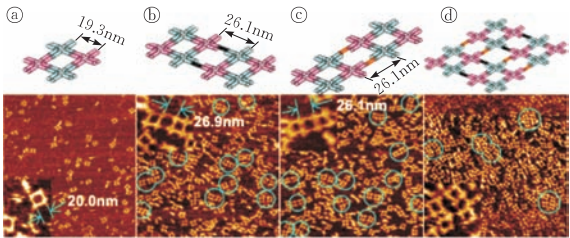


Fig. 8 AFM images of 2×2 NAs and dsDNA bridges

Except the four-point-star motif, He constructed six-point-star motif, which was the highest connectivity in DNA two dimensional arrays reported so far^[37]. The motif was 6-fold rotational symmetry, formed from thirteen DNA single-strands: a central strand, six shell-strands and six arm-strands (Fig. 10). At the center of the six-point-star motif, a central strand was twisted to a loop, which connected the six shell-strands and

avoided forming of the helices between shell-strands.

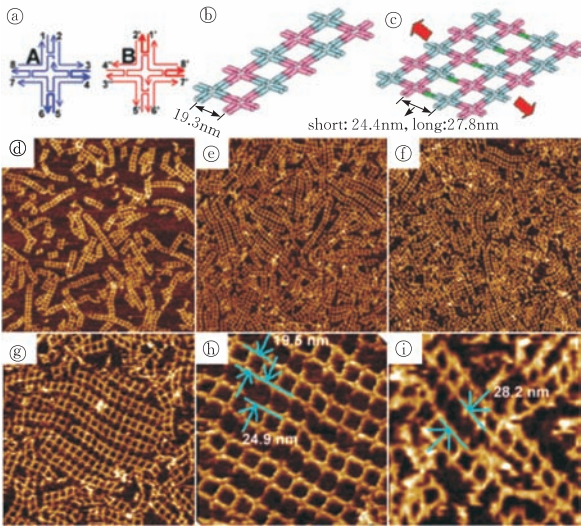


Fig. 9 A- and B-tiles, NTs with dsDNA bridges and without dsDNA bridges

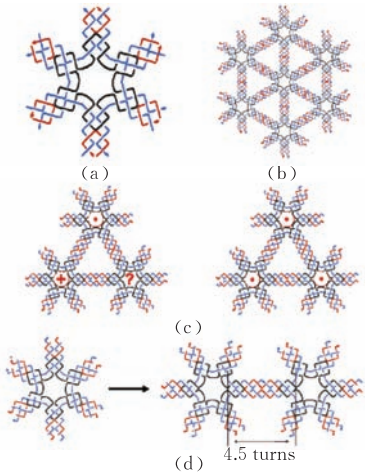


Fig. 10 Schematic drawings of six-point-star motif and assembled extended 2D array

At the end of shell-strands, arm-strands combined with them and produced six sticky ends. To further assemble into 2D array, all six-point-star motifs had to be connected by sticky ends with face-to-face sides of the array plane. For common motifs (such as three-point-star motif), when all motifs in an array are associated by means of face to opposite sides, degree of curvature become larger, and the 2D array structure also become more compact, and vice versa. However, six-point-star motif is different from the common motifs, because the motifs are not connected by using corrugation strategy above to increase degree of curvature. Instead, all motifs have to face to the same side to assemble into 2D array. As shown in the picture of AFM imaging (Fig. 11 (a), (b), (c)), the regular and

periodic structures were observed. This 2D array was isotropic, and could be observed by staining with a fluorescence dye YOYO-1 under the fluorescence microscope (Fig. 11 (d)).

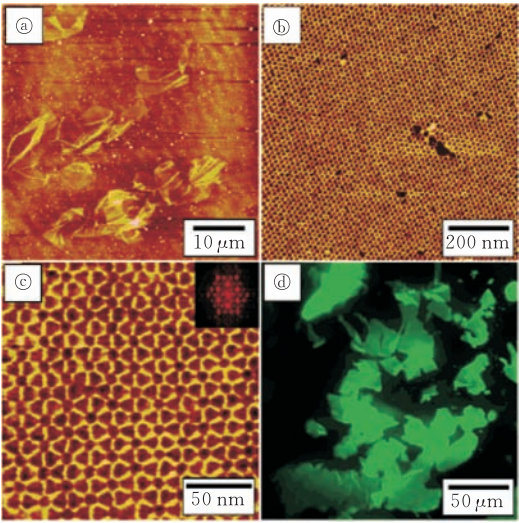


Fig. 11 AFM and FM images of 2D array

2.3 Three-Dimensional Polyhedra and Application of DNA Self-Assembly

Three-point-star motif, different from four- and six-point-star, is another significant tile in DNA self-assembly motifs. In 2005, a three-point-star DNA motif (Fig. 12) had been reported by He, and it could assemble into two-dimensional arrays^[34]. These motifs above can not only form into 2D array, but also assemble more complex 3D DNA structures.

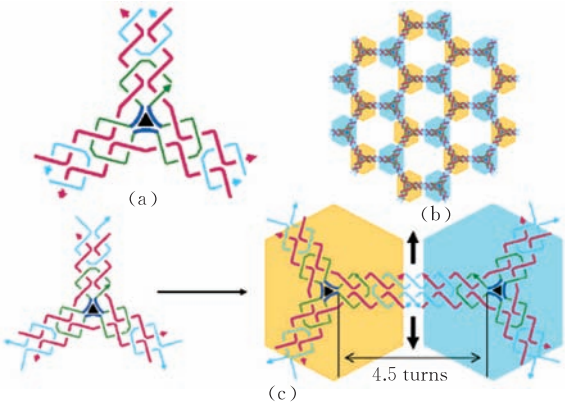


Fig. 12 Three-point-star and schematic drawings of 2D array

In 2008, Mao applied three-point-star motifs to further assemble into tetrahedron, dodecahedron and buckyball^[20]. The three-point-star motif consisted of three types of DNA single-strands: a long central strand (strand L or L'), three identical medium strands (strand M), and three identical peripheral strands (strand S). At the center of the

motif, the loop, forming from the long central strand, decided the flexibility and retractility of the motif. The flexibility of the motif could be changed with the adjustment of loop length. Each termini of the motif had four-base-long sticky ends. The motifs assembled into the polyhedra by complementary sticky ends (Fig. 13). Here, we take the tetrahedron for example to explain the assembled process (Fig. 14). A tetrahedron was constituted by using four three-point-star motifs, each of which located at a vertex of the tetrahedron. Two neighbouring motifs were connected by complementary sticky ends to form the edge of the tetrahedron.

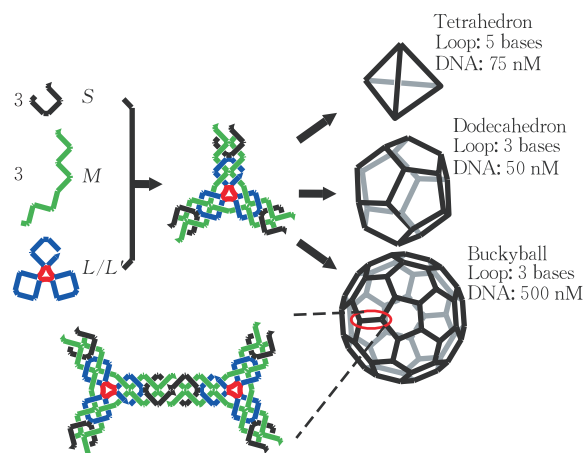


Fig. 13 Self-assembly of DNA polyhedra

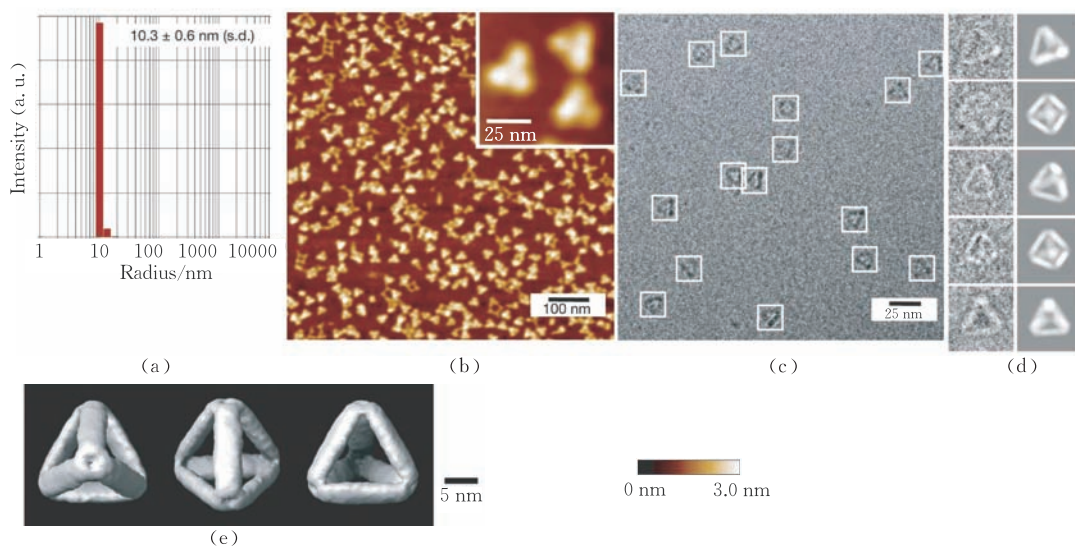


Fig. 14 DLS, AFM and Cryo-EM images of DNA tetrahedron

Because the tetrahedron was three-dimensional structure, four motifs were no more planar, and needed to be significantly bent. Thus, the three-point-star motif was required to be flexible enough. To increase the flexible of the motifs, the loop length was added to be five bases long. In the same way, dodecahedron and icosahedron were assembled too, but there were some difference among them. Dodecahedron consisted of 20 three-point-star motifs, which formed 12 faces and 30 edges; icosahedron consisted of 60 three-point-star motifs, 32 faces and 90 edges. Compared with tetrahedron, dodecahedra were less curved between faces, so the curvature degree of the motifs was smaller and the central loop did not need to be much flexible. Thus, the length of the central loop was designed to three bases long. Besides, icosahedron was another closed symmetrical congeries, because it was least curved, and the flexibility of the central strand was also lowest among the three

types of polyhedra. The results demonstrated that the more motifs were required, the more difficult polyhedra structure assembled.

The short oligonucleotides strands are a distinct motif, which can self assemble into three-dimensional structures. It has two advantages. (i) The price of synthesizing short DNA strands is much lower, and the accuracy is very high. For long DNA strands, bases easily mutate, so the accuracy is not higher than short DNA strands. (ii) Complex secondary structures were easily assembled. Compared with self-assembled motifs, the angle between motifs need not be considered by using short oligonucleotides strands, and secondary structures are easier to be formed. In fact, the coding of short oligonucleotides strands is required to be significantly strict. In 2008, Goodman used four short DNA strands (Fig. 15(a)) as primary motifs to assemble into a reconfigurable tetrahedron^[29]. Each strand was constituted of three segments,

each of which formed one edge of tetrahedron. Six complementary domains of four strands hybridized to six edges of tetrahedron. 5' and 3' ends of each strand met at the center of the edge. In the tetrahedron, five edges consisted of 20-base-pair DNA double helices, but the sixth edge was a little different with the other edges, which contained 10bp double helix and a hairpin loop with a 4bp neck and a 12nt loop. This hairpin-loop structure determined the flexibility of tetrahedron. When adding the “fuel” strand, the edge could be extended, because the “fuel” strand was complementary to the hairpin-loop structure. Of course, the edge could also be contracted, when adding the “antifuel” hairpin. This process fulfilled the switch between two states. In addition, this research group also constructed the tetrahedron with two reconfigurable edges, but the codes of two hairpin-loop strands were different from each other. The switch among four states would be achieved by the changes of two open and closed edges independently. Finally, four different states of the tetrahedron were detected by polyacrylamide gel electrophoresis (Fig. 16).

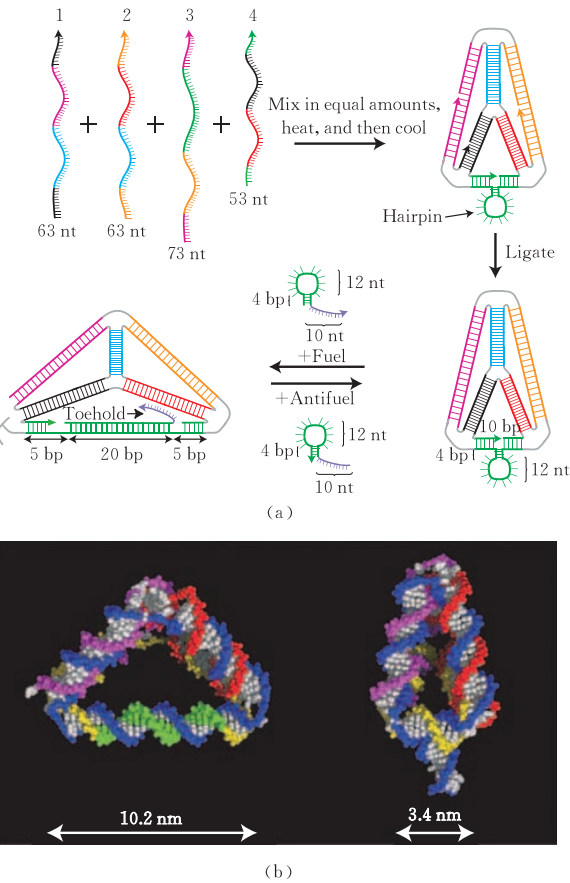


Fig. 15 DNA tetrahedron with one reconfigurable edge

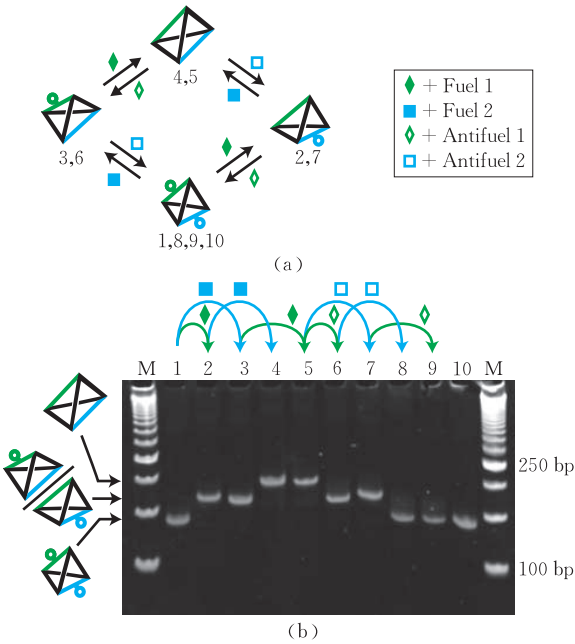


Fig. 16 Electrophoresis of a tetrahedron with two reconfigurable edges

3 Difficulty and Prospect

DNA self-assembly technology has been applied not only in DNA computing, but also in nano-material area. However, there are many difficulties in applying DNA self-assembly to DNA computing. Firstly, coding is the most difficult problem, as it decides whether the experiment can be implemented. Secondly, there are two significant keys to effect on the yield of self-assembly structure: the assembled angle between DNA single-strands and the connections among motifs. In addition, from the experiment operation, whether the self-assembly structure can be achieved is decided by the concentration proportion of each DNA single-strand and the anneal temperature.

(1) Coding. The coding is a very difficult problem in any type of DNA computing. To solve this problem, we should not only consider the following theoretic factors as (G + C)%, hybridization between primers and false pairing, but also consider the specific model. Besides, we should examine whether the coding can make the experiment successfully carry on. Sometimes, from the view of basic restrict conditions, coding is good enough to carry on experiment, but in fact, biochemical reactions can not be fulfilled. The reason is that there is different anneal temperatures between various coding, and extreme difference will lead to the problem that DNA strands can not be

linked. Thus, how to obtain the best coding has a greatly effect on DNA self-assembly and other areas of DNA computing.

(2) Angles and connection between the motifs. The angle between primary motifs is another crucial ingredient in DNA self-assembly. Before secondary structure is formed, researchers have to calculate the folding angle of single-strands in all types of DNA tiles or motifs. As demonstrated in recent research results, with the angle between peripheral strands increasing large, curvature degree of the formed faces will decrease. Thus, according to different assembled structure, the designed angle between primary motifs should be changed. Moreover, the connection between primary motifs is another important factor that controls the fulfillment of secondary structure. The angle between primary motifs directly effect on the assembled degree of congeries. When two motifs are combined by face to face, the curvature degree between them will increase correspondingly, and secondary structure will become more closed. On the contrary, the curvature degree between them will decrease by face to opposite way, and the formed congeries will be much looser. Thus, the motifs, consisting of tubular structure, should be connected by the means of face to face; reversely, the motifs, forming from planar structure, have to be combined in the way of face to opposite.

(3) Concentration of DNA single-strands. In different types of DNA self-assembly structures, required DNA single-strand concentrations are much different. Usually, with the concentration increasing, the assembled structure (such as 2D array) becomes larger, and vice versa. However, in biological operations, it is important to consider the concentration proportion of each DNA single-strand. Generally speaking, the concentration of long strands is higher than that of short strands, for instance, the concentration of long strands is 100 times higher than that of short strands in constructing the China map.

Although DNA self-assembly still has its disadvantages in computation, lots of researchers used DNA self-assembly to solve simple Boolean calculation and addition operation. However, the self-assembly frames are immobile, so it will not extend, cut and react with enzymes freely to carry on such bio-operations as PCR etc. If DNA self-assembled structure can be moved like DNA molecules, and enzymes can be controllably moved on self-assembled structure, their future in DNA

computing looks bright as well.

In summary, it is a significant key for developing DNA self-assembly to overcome the difficulties above. If we can connect it to carbon nanotubes and fluorescence label, the prospect of DNA self-assembly will be exciting. With the rapid developing of science and technology and combination of multi-disciplinary science, DNA self-assembly will become the important research direction in the fields of material, informatics and biology, and will also be the critical instrument that promotes the development of DNA computer.

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