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Wireframe and Tensegrity DNA Nanostructures

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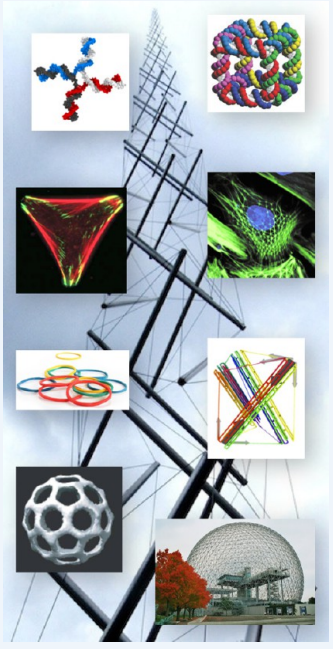
CONSPECTUS: Not only can triangulated wireframe network and tensegrity design be found in architecture, but it is also essential for the stability and organization of biological matter. Whether the scaffolding material is metal as in Buckminster Fuller's geodesic domes and Kenneth Snelson's floating compression sculptures or proteins like actin or spectrin making up the cytoskeleton of biological cells, wireframe and tensegrity construction can provide great stability while minimizing the material required.

Given the mechanical properties of single- and double-stranded DNA, it is not surprising to find many variants of wireframe and tensegrity constructions in the emerging field of DNA nanotechnology, in which structures of almost arbitrary shape can be built with nanometer precision. The success of DNA self-assembly relies on the well-controlled hybridization of complementary DNA strands. Consequently, understanding the fundamental physical properties of these molecules is essential. Many experiments have shown that double-stranded DNA (in its most commonly occurring helical form, the B-form) behaves in a first approximation like a relatively stiff cylindrical beam with a persistence length of many times the length of its building blocks, the base pairs. However, it is harder to assign a persistence length to single-stranded DNA. Here, normally the Kuhn length is given, a measure that describes the length of individual rigid segments in a freely jointed chain. This length is on the order of a few nucleotides. Two immediate and important consequences arise from this high flexibility: single-stranded DNA is almost always present in a coiled conformation, and it behaves, just like all flexible polymers in solution, as an entropic spring.

In this Account, we review the relation between the mechanical properties of DNA and design considerations for wireframe and tensegrity structures built from DNA. We illustrate various aspects of the successful evolution of DNA nanotechnology starting with the construction of four-way junctions and then allude to simple geometric objects such as the wireframe cube presented by Nadrian Seeman along with a variety of triangulated wireframe constructions. We examine DNA tensegrity triangles that self-assemble into crystals with sizes of several hundred micrometers as well as prestressed DNA origami tensegrity architecture, which uses single-stranded DNA with its entropic spring behavior as tension bearing components to organize stiff multihelix bundles in three dimensions. Finally, we discuss emerging applications of the aforementioned design principles in diverse fields such as diagnostics, drug delivery, or crystallography. Despite great advances in related research fields like protein and RNA engineering, DNA self-assembly is currently the most accessible technique to organize matter on the nanoscale, and we expect many more exciting applications to emerge.



■ INTRODUCTION

In the struggle for survival, efficient use of resources provides evolutionary advantage for all living organisms. Over millions of years, Nature has therefore optimized the concept of providing high resilience and at the same time adaptability to external influences and forces while employing minimal energy and reducing material costs.

The cytoskeleton of biological cells is an instructive example for efficient and flexible architecture. Its skeletal structure ensures stability but also high permeability and flexibility. Next to many other stabilizing elements such as stiff microtubules or stretchable intermediate filaments, actin is an important structural protein found in all eukaryotic cells. Actin monomers polymerize into linear polarized microfilaments of several micrometers in length with a tightly wound, helical conformation,[1] resulting in a semiflexible filament with a persistence length of about 10 μm.[2] Among many other tasks, actin helps to maintain cell shape and the individual filaments, often organized in bundles,[3] are able to withstand tensions of up to 600 pN.[4]

The cellular membrane also provides tensile stability. A major constituent of its stabilizing meshwork is spectrin, a long, flexible, rod-like protein, lining the cytoplasmic side.[5] The spectrin mesh is tightly coupled to the actin network: a protein complex of short actin bundles and other components acts as a vertex, binding the ends of five or six spectrins and thus leading to triangulated scaffolding.[6] The resulting stable, yet flexible membranes can be found, for example, in red blood cells. Along with many other molecules, spectrin and actin form the

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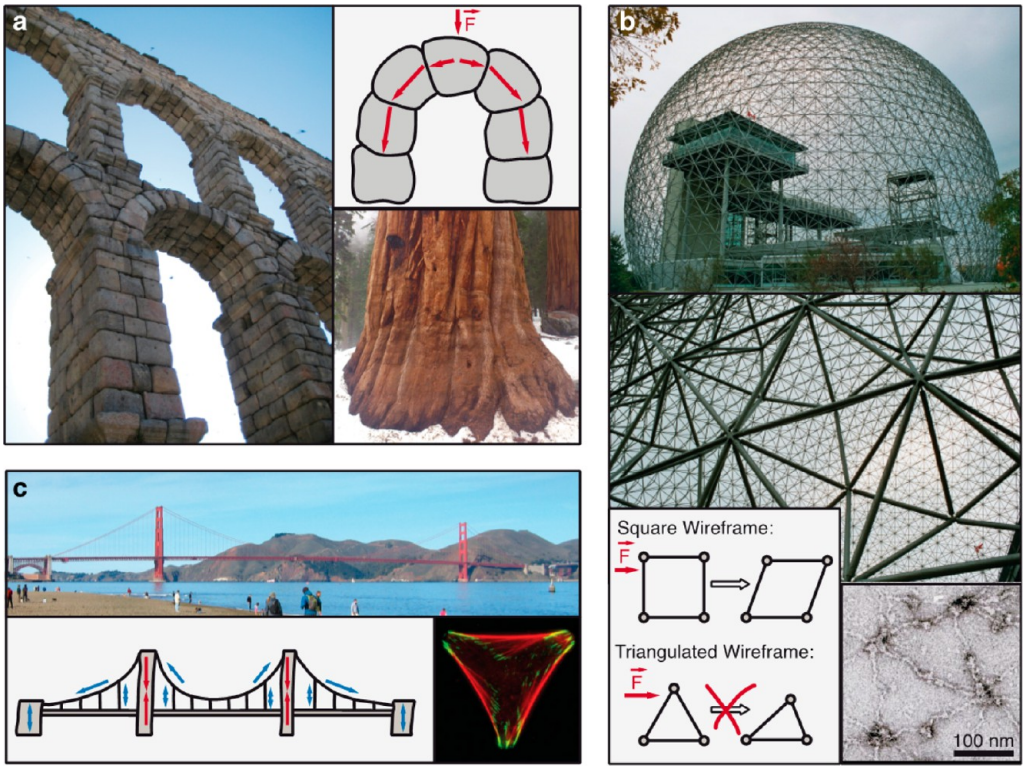

Figure 1. Building concepts in architecture and nature. (a) Aqueduct in Segovia. Pressure is distributed from the keystone in the apex to the adjacent stones. (bottom right) Sequoia tree trunk. (b) Fuller's Biosphère in Montreal. Triangulation yields high stability because it prevents shearing. (bottom right) Spectrin meshwork in a cell membrane.[6] (c) Golden Gate Bridge in San Francisco. Compression-resistant pillars support tension-bearing cables. (bottom right) Actin filaments under stress.[3] Panel b reprinted with permission from ref 6. Copyright 2001 APS. Panel c reprinted with permission from ref 3. Copyright 2006 Wiley-Liss.

cytoskeleton, a highly dynamic three-dimensional protein network.[7,8]

■ WIREFRAME ARCHITECTURE

In architecture, in contrast, stability often is achieved through compact construction techniques, which require large amounts of building material.

Many ancient buildings and monuments still standing today were built of massive limestones. Striking examples can be found in cyclopean masonry and Roman architecture. No mortar was needed for construction; stability was provided by the sheer shape and weight of the boulders, a building principle that can also be referred to as "continuous compression". A famous construction dating from this time is the Arkadiko Bridge in Greece. Built ca. 1300−1200 BC, it is one of the oldest bridges still in use. Roman aqueducts, a heritage of the Roman Empire found all across Europe, are a more sophisticated example for stone bridges supported by arcades (Figure 1a), and also the ancient pyramids in Egypt or Latin America rely on compression. Even today, conventional buildings and private homes in Europe are often built by the bricks-and-mortar method, which guarantees high stability at low expense, albeit at high volume of materials.

The emergence of new building materials enabled architects to develop new lightweight construction techniques. Gustave Eiffel's iron lattice tower, inaugurated in Paris in 1889, quickly became a global icon.

In the 1950s, architect Buckminster Fuller achieved fame for his geodesic domes, giant triangulated spheres with surfaces subdivided into tetrahedral and icosahedral patterns.[9] One of his best-known constructions is the "Biosphère" in Montreal (Figure 1b). Artist Kenneth Snelson, a former student of Fuller, creates so-called floating-compression sculptures made of compressed struts and prestressed cables. For these lightweight yet stable buildings and structures, Fuller coined the expression "Tensegrity", fusing the words "tension" and "integrity". Munich's 1972 Olympic Stadium, for example, relies on this interplay of tension and compression, and many outdoor tents being sold today are based on the geodesic building principle.

In suspension bridges, stability and flexibility is provided by wire cables suspended on pillars, examples being the Golden Gate Bridge in San Francisco, CA, USA (Figure 1c), or the Kurilpa Bridge, recently inaugurated in Brisbane, Australia.

■ DNA NANOTECHNOLOGY

The emergence and rapid evolution of DNA nanotechnology made it possible to design and build complex structures with the same dimensions and similar mechanical properties as biological building blocks and cellular components. Nadrian Seeman proposed DNA as building material more than three decades ago because of its characteristic chemical and biological properties, namely, the molecular recognition of complementary strands based on Watson−Crick base pairing and the ability to form Holliday and other multiway junctions.[10,11]

In 1991, Seeman presented a cube made of six DNA strands with determined mutually complementary sequences.[12] This simple but iconic structure inspired many other researchers to work on DNA-based self-assembly. In 2006, Paul Rothemund demonstrated a new technique he termed DNA origami, where

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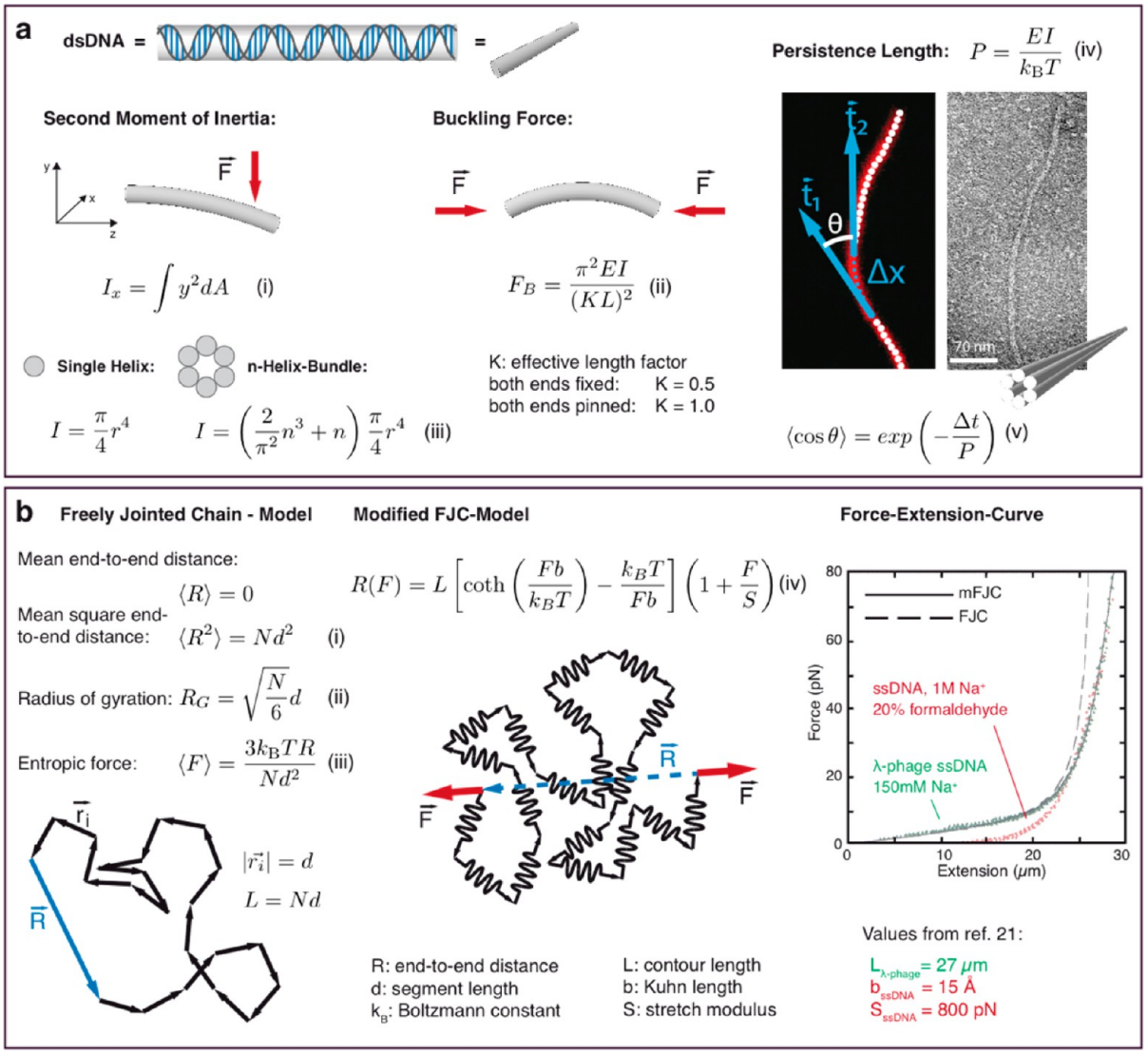

Figure 2. Mechanical characteristics. (a) Second moment of inertia and buckling force of dsDNA. (b) The (m)FJC model can be used to predict the flexibility of ssDNA. Panel b reprinted with permission from ref 22. Copyright 1996 AAAS.

a viral circular DNA "scaffold" strand is folded into arbitrary shapes by hundreds of oligonucleotides called "staples".[13,14]

Since then and with the arrival of simple computer-aided design tools and simulation methods,[15−21] structural DNA nanotechnology has become a popular and widespread scientific field.

Here, we will review the advances of DNA-based construction focusing on wireframe, triangulated, and pre-stressed designs and discuss the wide variety of DNA structures realized by utilizing the building principles introduced above based on triangulation, compression, and tension and give examples of successful applications.

■ MECHANICAL PROPERTIES OF DNA

We will first recapitulate the well-studied mechanical characteristics of DNA, because a good intuition for its behavior will provide insight into the opportunities and limitations that this building material implies. Single-stranded and double-stranded DNA differ considerably in their physical properties. Double-stranded DNA (dsDNA) can be regarded as rather stiff over a range of tens of nanometers, which implies the applicability of beam mechanics and physical parameters such as persistence length and Euler buckling force. Single-stranded DNA (ssDNA) in contrast behaves like a flexible and coiled polymer even on the scale of a few nanometers. Due to this behavior, ssDNA can be approximated successfully by a "modified freely jointed chain (mFJC) model".

With its double helical structure, dsDNA resembles a long, elastic rod whose flexibility can be described by the persistence length P. This parameter gives the typical distance along the contour of the rod after which the averaged angular correlation between two tangential vectors is lost (see eq v in Figure 2a). For dsDNA in physiological buffer, values for P between 40 and 50 nm are generally accepted;[22−24] for short duplexes, however, higher flexibility has been observed.[25,26] Due to the thermal nature of the conformational fluctuations of DNA in solution, P can be related to the thermal energy, $k_B T$, the dsDNA's Young's modulus, E (0.25 ± 0.1 GPa), and second moment of area I (see eq iv in Figure 2a). As I grows with the fourth power of the radius of a cylindrical object, the bending stability of DNA structures can be strongly improved by arranging multiple double strands in parallel bundles.[27] The experimentally observed values of P of such bundles are in very good

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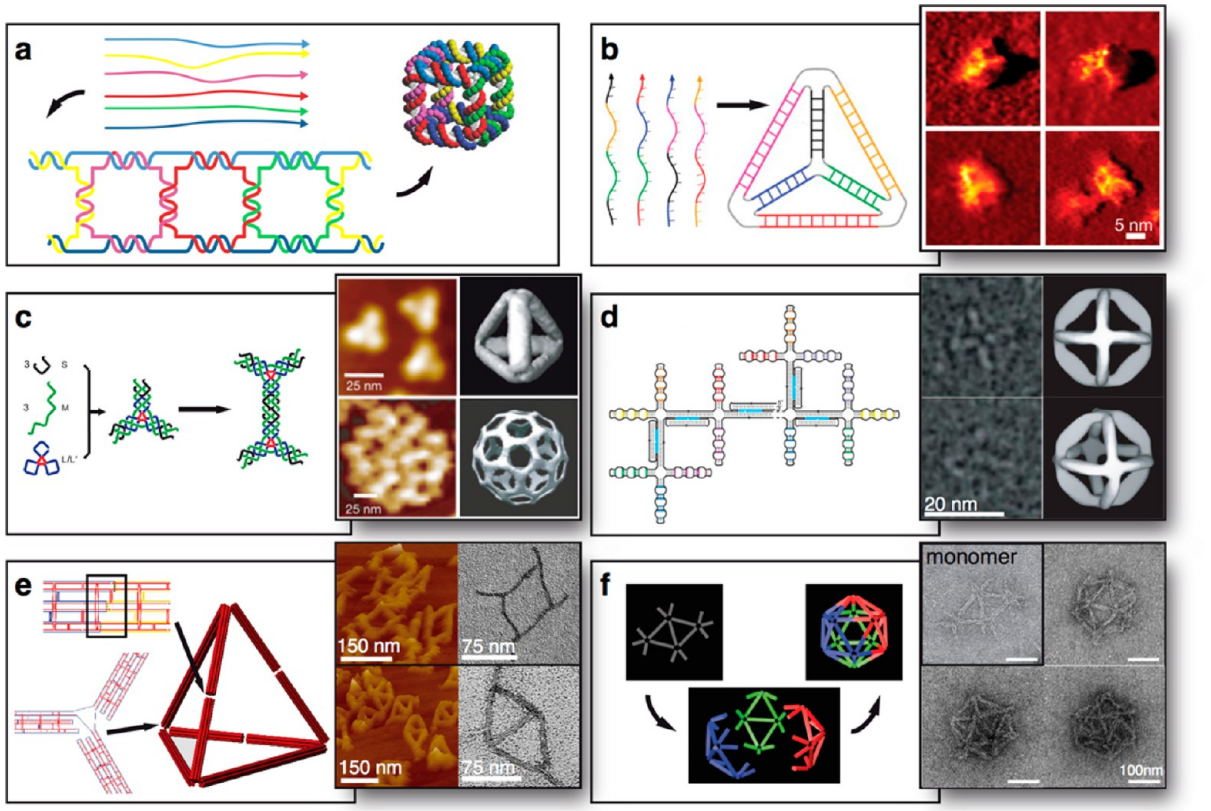

Figure 3. DNA wireframe structures. (a) Wireframe cube. Reprinted with permission from ref 40. Copyright 1991 and 2003 Nature Publishing Group. (b) Four-strand tetrahedron. Reprinted with permission from ref 31. Copyright 2005 AAAS. (c) Polyhedra assembled from three-point star motif tiles. Reprinted with permission from ref 41. Copyright 2008 Nature Publishing Group. (d) Octahedron assembled from a 1.7 kb DNA strand and five oligonucleotides. Reprinted with permission from ref 32. Copyright 2004 Nature Publishing Group. (e) Flattened DNA origami tetrahedron. Reprinted in part from ref 42. (f) Icosahedron assembled from three DNA origami tiles. Reprinted with permission from ref 33. Copyright 2009 Nature Publishing Group.

agreement with calculated values (see eqs iii in Figure 2a).[28−30] For torsional movements, however, the rigidity appears to grow only linearly with the number of helices in one bundle.[12,17,28,30−33]

Another important parameter when evaluating the stability of a column is the buckling force, F_B. It denotes the critical force that a beam can withstand along its axis, which can also be understood as the vertical load that causes a beam to buckle. It is described by Euler's formula (see eq ii in Figure 2a), which depends on E and I but also on the length of the beam L and a factor K characterizing its boundary conditions (e.g., K = 1 for two hinged ends and K = 0.5 for two fixed ends). Buckling of DNA struts has been experimentally observed for both individual DNA helices[31] and DNA bundles.[34]

Single-stranded DNA, on the other hand, is a chain-like molecule connected through single covalent bonds, which is reflected in its high flexibility and elasticity. In the following, we will ignore secondary structure and hairpin formation and only focus on polymer behavior. While it is impractical to describe the exact conformation of a polymer in solution, its overall shape (random coil) and size (see eqs i and ii in Figure 2b) can be approximated with the FJC model,[35] which assumes completely random orientation of each chain element (Kuhn length of ssDNA = 1.5 nm) and neglects self-avoidance (Figure 2b).

Next to the structural appearance, this model also allows prediction of the entropic forces a polymer can exert (see eq iii in Figure 2b). This can be understood with a simple statistical argument: a fully extended polymer implies only a single conformation of its chain elements, a straight line between the two ends. An end-to-end distance of zero at the other extreme allows for a large number of possible paths between the ends. It is hence on average more likely to encounter the polymer in a coiled state, translating into an entropic force pulling the ends together.[36,37] Bustamante et al. investigated long DNA strands under small and high tensions and found that for higher forces the FJC-model requires a modification taking into account the stretch modulus of DNA. This allows precise predictions of the end-to-end distance and forces observed for ssDNA (Figure 2b)[22,38] and the design of prestressed tensegrity.[34]

Taken together, it is no surprise that individual double helices provide enough stability for the DNA structures like Mao's tensegrity triangle[39] or Turberfield's tetrahedra[31] with only a few nanometers in size.[31] In contrast, intermediate constructs exhibit designs with pairs of double helices as beams,[32] and DNA origami structures, which span up to several hundred nanometers, are built of multihelix bundles.[17,33]

■ WIREFRAME DNA OBJECTS

With the nanomechanical properties of DNA duplexes resembling sturdy wires and ssDNA resembling flexible threads, wireframe construction consequently dominates DNA nanoarchitecture. Typically, flexible DNA branches act as joints or vertices connecting stiff double-stranded regions. Over the last

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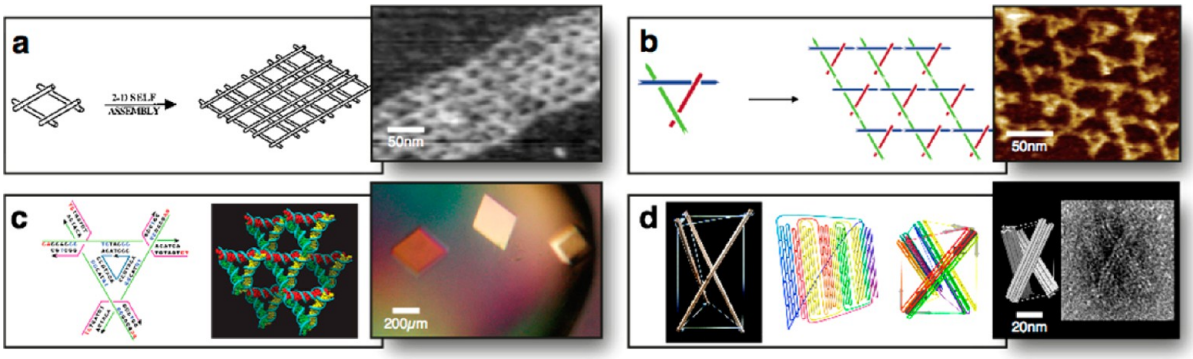

Figure 4. DNA tensegrity structures. (a) Rhombus-like motif from four Holliday junctions. Reprinted with permission from ref 54. Copyright 1999 American Chemical Society. (b) DNA tensegrity triangle and 2D array. Reprinted with permission from ref 39. Copyright 2004 American Chemical Society. (c) Tensegrity 3D crystal. Reprinted with permission from ref 55. Copyright 2009 Nature Publishing Group. (d) Prestressed DNA origami tensegrity. Reprinted with permission from ref 34. Copyright 2010 Nature Publishing Group.

two decades, designs "evolved" from Seeman's cube[12] to complex polyhedra and buckyball-like structures.

Seeman's cube was composed of six oligonucleotides, each framing one face of the structure (Figure 3a). The single-stranded, complementary segments of adjacent sides base-paired to form the cube's double-helical framework. Based on the same assembly strategy, later a truncated octahedron made of 14 oligonucleotides was designed.[43] Shih, Quispe, and Joyce followed a different approach in 2004 in their design of a clonable octahedron (Figure 3d). Anticipating the DNA origami method, the structure consisted of one 1.7 kilobase long single strand "stapled" together by five oligonucleotides.[32]

In 2005, Turberfield and co-workers presented tetrahedral structures that featured simple design, quick assembly, and optimal yield (Figure 3b).[31]

Later, Mao et al. developed a family of polyhedral structures using a three-point-star motif, based on a technique used previously for two-dimensional lattices (Figure 3c).[41,44,45] One short, one medium, and one long oligonucleotide, combined in 3:3:1 stoichiometry, make up one tile. In the same reaction, the tiles hybridize, resulting in tetrahedra, dodecahedra, or buckyballs, depending on the length of the single-stranded loop of the motif's vertex and the DNA concentration during assembly. Subsequently, the family of polyhedra was extended by using star-point motifs with three to six arms.[46,47] With this library of geometric wireframe objects at hand, Mao and co-workers investigated the conformational flexibility, symmetry, and chirality of polyhedra.[48−50]

Yan et al. presented two different approaches to assemble tetrahedral structures: a wireframe tetrahedron synthesized *in vivo* from a single ssDNA strand[51] and a tetrahedral container with closed faces based on the DNA origami techique.[52] The latter building principle was also used for a wireframe tetrahedron with a strut length of 75 nm (Figure 3e)[42] and a wireframe icosahedron assembled from three origami units with a diameter of about 100 nm (Figure 3f).[33] Only recently, Yan et al. reported two- and three-dimensional gridiron wireframe structures based on an origami technique with a crossover instead of a parallel layout of the scaffold strand.[53]

■ DNA TENSEGRITY

After Mao, Sun, and Seeman investigated the torsion of Holliday junction analogues in two-dimensional DNA crystals (Figure 4a),[54] the first successful application of tensegrity principles in DNA nanotechnology was a triangle made up of five oligonucleotides, designed by Mao et al. (Figure 4b).[39]

Such a triangle consists of three struts with overlapping ends connected by flexible (single-stranded) hinges. At each of these vertices, a four-arm-junction[56] is formed, and the resulting flexibility allows the structure to relax into an equilateral triangular conformation with three internal angles of 60°. Mao and co-workers showed that by adding sticky ends to one or two struts, the triangles formed one-dimensional arrays or two-dimensional grids, respectively.

Seeman, Mao, and co-workers expanded the concept of a tensegrity triangle to the third dimension.[55] With only three different oligonucleotide types, they were able to assemble 3D DNA crystals almost on the millimeter scale that diffracted with a resolution of 4 Å (Figure 4c). These crystals have the potential to act as scaffolds for biological molecules in crystallographic experiments, as envisioned by Seeman earlier. However, the cavities of the present design are not yet large enough to "accommodate" larger proteins. Mao, Seeman, and co-workers were also able to grow crystals made of two triangle units[57] and to improve diffraction resolution by adding phosphates to the 5′ ends of each unit.[58] Shih, Högberg, and co-workers showed that diffracting DNA crystals can further be assembled from enzymatically fabricated oligonucleotides.[59]

These examples strikingly demonstrate how high structural rigidity can be achieved even when all connections between the individual struts are flexible.

One of the remarkable features of Snelson's floating-compression structures is that structural integrity is attained by the use of long cables under tension that are connected to the ends of struts resisting the resulting compressive forces (see cord and stick model in Figure 4d). The DNA origami method made it possible to realize such prestressed structures on the nanometer scale. Rigid struts of multihelix bundles are used as compression-bearing elements, while long sections of single-stranded scaffold DNA act as tension-bearing cables. Following this principle, prestressed kites and prisms with overall sizes of over 100 nm were assembled (Figure 4d).[34] The structural appearance can be predicted in a reliable fashion[60,61] by taking into account the mechanical properties of double- and single-stranded DNA introduced above.

■ EMERGING APPLICATIONS

Numerous applications of DNA wireframe and tensegrity nanostructures have been reported over the years. Two-

dimensional lattices were used to position molecules or particles of interest in a periodic fashion. Yan and co-workers used 4 × 4 tiles for the construction of two-dimensional protein and aptamer arrays with a tunable density and a barcode-like platform for multiplexed biosensing.[62,63] Seeman et al. used a tensegrity triangle motif to build a two-dimensional periodic nanoparticle array (Figure 5a).[64] The Turberfield group assembled a two-dimensional crystalline array using DNA four-arm junctions for the positioning of proteins to facilitate cryo-electron microscopy.[65]

Wireframe structures were also used for the three-dimensional arrangement of particles and the construction of various molecular cages for the encapsulation of molecules. With the goal to build chiral assemblies, Alivisatos and co-workers positioned gold nanoparticles of different sizes at the vertices of a DNA tetrahedron (Figure 5b).[66] Turberfield et al. used their DNA tetrahedron as a container for single cytochrome *c* molecules,[69] while the Krishnan group constructed a DNA icosahedron for the encapsulation of gold nanoparticles.[70] Mao and co-workers used their method of assembling different DNA polyhedra from the same star motif to decorate three-dimensional DNA nanostructures with RNA molecules and proteins at defined positions.[71]

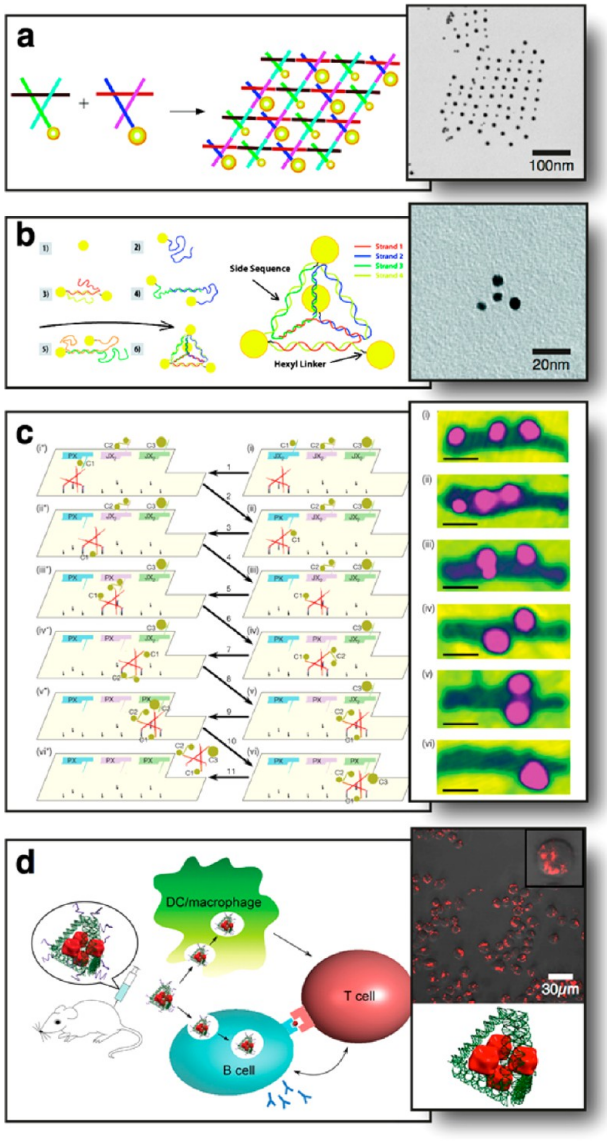

Figure 5. (a) Periodic arrangement of gold nanoparticles of different sizes. Reprinted with permission from ref 64. Copyright 2006 American Chemical Society. (b) 3D arrangement of gold nanoparticles using a DNA tetrahedron. Reprinted with permission from ref 66. Copyright 2009 American Chemical Society. (c) Programmable nanoscale assembly line. Reprinted with permission from ref 67. Copyright 2010 Nature Publishing Group. (d) DNA tetrahedron platform for vaccine development. Reprinted with permission from ref 68. Copyright 2012 American Chemical Society

Various groups demonstrated the controlled release of encapsulated cargos from DNA wireframe structures: Sleiman and co-workers showed the release of gold nanoparticles from triangular DNA nanotubes.[72] More recently DNA nanocages releasing their cargo in response to a chemical trigger or to a temperature change were demonstrated.[73,74] Reconfiguration of DNA wireframe assemblies was achieved by toehold mediated branch migration and other methods.[75,76] Seeman and co-workers constructed "DNA scissors": two double-crossovers connected by a flexible Holliday junction in the center and a duplex containing the binding site for a DNA repair protein. Binding of this protein results in contraction of the scissors, which can be monitored by FRET.[67] Sugiyama et al. used a DNA origami frame to accommodate duplex DNA under tension to study how structural flexibility of DNA duplexes containing a binding site for *Eco*RI methyltransferase regulates the enzyme's efficiency.[77−79]

In 2012, Anderson and co-workers claimed gene silencing via siRNA delivered to cells by folate decorated DNA tetrahedra.[80] Yan, Chang, and co-workers used the same DNA tetrahedron as a platform for vaccine development: the DNA structure serves as a scaffold to create adjuvant−antigen vaccine complexes, which induce B cell response and antibody production upon internalization by antigen-presenting cells (Figure 5d).[60,68,81]

The entropic spring behavior of ssDNA has been used to change the conformation of DNA nanoconstructs: Sleiman and co-workers observed that partially single-stranded square DNA nanotubes bend significantly compared with the fully double-stranded version.[82] In DNA origami-based tensegrity structures, forces of up to 14 pN were generated, and the built-in tension was further used to induce large conformational changes upon enzymatic cutting of prestressed elements.[34] The Seeman group presented a DNA tensegrity triangle walker to realize a programmable nanoscale assembly line (Figure 5c)[67] and Douglas et al. used single-stranded scaffold hinges as "springs" to assist the opening of two domains of a barrel to expose its payload.[83]

■ CONCLUSION AND OUTLOOK

Using DNA as a building material combined with wireframe and tensegrity design principles created a huge variety of triangulated and prestressed assemblies, in both two and three dimensions. The emerging use of these structures as scaffolds for the controlled positioning of molecules or the encapsulation and triggered release of drugs from cage-like objects might lead to exciting applications: porous DNA structures, either wireframe polyhedra or tensegrity structures, could be used as catalyst material and for drug delivery. For the latter, an essential question is the stability of the constructs in biological surroundings such as cell culture growth medium, blood serum, or intracellular environments. The Turberfield group reported that their DNA tetrahedron remained intact up to 48 h after

transfection into living mammalian cells.[78] Other studies reported much shorter survival times of DNA constructs.[60,81] Discrepancies are not surprising, because all studies investigated different systems under varying conditions. A thorough understanding of the involved degradation processes will hopefully emerge in the coming years. The survival time of such delivery capsules in biological environments might be drastically enhanced via chemical modifications of DNA itself, the decoration with molecules such as PEG as shielding agent, or the wrapping in lipid bilayers.[84] Mechanotransduction of prestressed tensegrity objects upon external stimuli could be used for sensing applications or the injection of cargo molecules to target cells. Networks of tensegrity objects might be used to build responsive hydrogels and cytoskeleton mimicking architectures. The periodic arrangement and orientational control of proteins in three dimensions using crystalline DNA arrays anticipated by Nadrian Seeman might enable the determination of a huge class of unsolved protein structures via both X-ray crystallography and cryo-electron microscopy.[11]

The astonishing and ongoing development of structural DNA nanotechnology will lead to many more applications not even envisioned today and will broaden the usage of DNA tools in science and technology.

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