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From DNA Nanotechnology to Material Systems Engineering

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In the past 35 years, DNA nanotechnology has grown to a highly innovative and vibrant field of research at the interface of chemistry, materials science, biotechnology, and nanotechnology. Herein, a short summary of the state of research in various subdisciplines of DNA nanotechnology, ranging from pure "structural DNA nanotechnology" over protein–DNA assemblies, nanoparticle-based DNA materials, and DNA polymers to DNA surface technology is given. The survey shows that these subdisciplines are growing ever closer together and suggests that this integration is essential in order to initiate the next phase of development. With the increasing implementation of machine-based approaches in microfluidics, robotics, and data-driven science, DNA-material systems will emerge that could be suitable for applications in sensor technology, photonics, as interfaces between technical systems and living organisms, or for biomimetic fabrication processes.

1. Introduction

Deoxyribonucleid acid (DNA) is made of monomeric nucleotide (nt) building blocks that are covalently linked to each other by phosphodiester bonds. According to Watson–Crick base pairing rules, the four different nucleotides, adenine (A), thymine (T), cytosine (C), and guanine (G), selectively form hydrogen bonded base pair (bp) dimers in a way that A and C exclusively pair with T and G, respectively, thereby giving rise to formation of the well-known DNA double helix.[1] In pioneering work, Nadrian Seeman proposed in 1982 to use DNA as a construction material for the assembly of geometrically defined objects with nanoscale features.[2] This rather unconventional and revolutionary concept sets the foundation of an emerging research field, nowadays termed as "structural DNA nanotechnology."[3] Taking advantage of the hybridization of sets of complementary oligonucleotides, a first phase of the development concerned the emergence of branched DNA-motifs which have sufficient mechanical stiffness to be suitable for the assembly of extended supramolecular networks. These developments have given rise to numerous so-called "DNA tiles" that can be used as building blocks for the assembly through sticky-end cohesion into discrete "finite" objects or periodic "infinite" 2D and 3D periodic lattices.[4] However, since the production of finite DNA nanostructures from DNA tiles remained complicated,[5] the development of the "scaffolded DNA origami" technique by Rothemund[6] is to be seen as an important milestone. Indeed, this method enabled the breakthrough of DNA nanotechology for the fabrication of finite, programmable, and addressable nanostructures, thereby initiating a second wave of innovation in the field.[7] As discussed in Section 2, this set the stage to address applications in the life sciences and materials research.

Also of great importance is the insight that DNA alone cannot fulfill the requirements of nanotechnology and materials science because nucleic acids offer only limited options, when it comes to electrical, optical, catalytic, or mechanical properties of nanostructured materials and devices.[8] To address this issue, early work on the modification of nucleic acid nanostructures concerning the integration of proteins[9] and nanoparticles[10] has been continuously expanded in order to exploit DNA nanostructures as scaffolds for the precise positioning of (bio) molecular (Section 2) and colloidal (Section 3) components.[11] This main stream of developments in DNA nanotechnology is flanked by the development in two additional areas, DNA polymer chemistry (Section 4)[12] and DNA surface technology (Section 5).[13] In this progress report, we will give a brief summary of the state of the art and highlight challenges in the subfields that have been overcome and still need to be resolved. In Section 6, we draw conclusions for possible perspectives of DNA-based material systems. We discuss that by convergence of the subfields and increasing implementation of machine-based approaches, DNA-material systems could emerge that enable advanced applications in life sciences, technology, and even biomimetic fabrication processes.

2. DNA Origami Nanostructures

Rothemund's "scaffolded DNA origami" technique[6] dramatically simplified the fabrication of finite DNA nanostructures. In a simple and fast "one-pot" reaction, hundreds of short oligonucleotides, referred to as "staple strands," are used to direct the folding path of a kilobase long circular single-stranded DNA (ssDNA) "scaffold" into an arbitrary shape held together

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by a periodic arrangement of antiparallel helices connected by periodic crossovers. Staple strands as well as the scaffold, often the genomic DNA of the bacteriophage M13mp18, can be purchased from commercial suppliers. Astonishingly high yields of the target structure (typically > 80%) are usually obtained, presumably due to the entropic advantage in using just a single long scaffold strand for folding. This enables cooperative binding processes and displacement of wrong or truncated sequences through exchange mechanisms and leads to substantial reduction of experimental errors and working time because the tight control over stoichiometry and purity of the oligonucleotides needed for tile-based assembly[4a,d] is no longer necessary. These advantages in practicability, together with the capability to generate nanoscaled objects with arbitrary shapes and dimensions, have made the scaffolded DNA origami technique to an extraordinary robust and powerful tool for the fabrication of DNA-based molecular architectures.[14]

2.1. Design Aspects

In his initial description,[6] Rothemund demonstrated the assembly of single-layered, planar origami structures, ranging from simple figures (triangles, squares, etc.) to more complex nongeometric structures, such as a smiley face (**Figure 1**A). As shown in Figure 1B,[6] two neighboring helices are held together by a number of periodic crossovers interspaced by 1.5 helical turns of about 16 bp, thereby forming single layer planar sheet of interconnected helices. These design rules also enable more complex 2D patterns, such as the shape of China[20] or dolphins,[21] and they also allow for fabrication of 3D origami nanostructures. For example, preformed planar DNA structures that were connected at specific angles by additional crossovers were folded stepwise into hollow 3D objects of different geometry, such as prisms,[22] closed polyhedral,[23] or a DNA box with a controllable lid.[24]

To overcome a major limitation of single-layer DNA origami, that is their relatively low mechanical stiffness, more rigid 3D DNA objects were developed by either packing multiple helices into a space-filling structure[15,25] or by implementation of tensegrity rules.[26] Multilayer DNA origami are densely packed arrays of antiparallel helices linked together by a 3D arrangement of crossovers, which determines the geometry of the basic building block[15] (Figure 1C). A more detailed overview of such multilayered structures has been given elsewhere.[11b] Latest design approaches rely on computer-based folding of arbitrary polygonal digital meshes of target objects[16] (Figure 1D) or representation of objects as closed surfaces that are rendered as polyhedral networks of parallel DNA double helices (Figure 1E).[17] Both methods lead to stable and monodisperse, high fidelity 3D structures.

2.2. Scaling up DNA Origami Structures

Many applications in life sciences and materials research require the availability of differently sized origami structures that can be manufactured in large quantities at reasonable cost. The size of DNA origami structures is determined by the length of the ssDNA scaffold (typically about 5–10 kb), leading to size dimensions in the 100 nm regime. Smaller particles can be produced by using short ssDNA circles as "mini scaffolds."[27] Larger particles are more difficult to obtain because of limitations occurring from bacterial machinery to produce large plasmids. To solve this problem, "superorigami" or "origami of origami" superstructures have been developed.[14] In this strategy, individual DNA building blocks, such as DNA tile motifs and origami structures are hybridized into assemblies of higher order.[28] Hence, each preformed DNA origami serves as an individual motif that is arranged, by programmable DNA interactions, inside a larger framework of the same or differently shaped origami structures.[29] The power of this approach has recently been demonstrated by the fractal assembly of micrometer-scaled 2D DNA origami arrays with arbitrary patterns[18] and the fabrication of gigadalton-scale shape-programmable 3D DNA assemblies (Figure 1F).[19]

Typical laboratory scale syntheses nowadays allow production of nanomol amounts of DNA origami structures for costs of about 1000 €. However, recent developments suggest that larger volumes and lower prices can be expected in the future. Solid phase DNA oligonucleotide synthesis based

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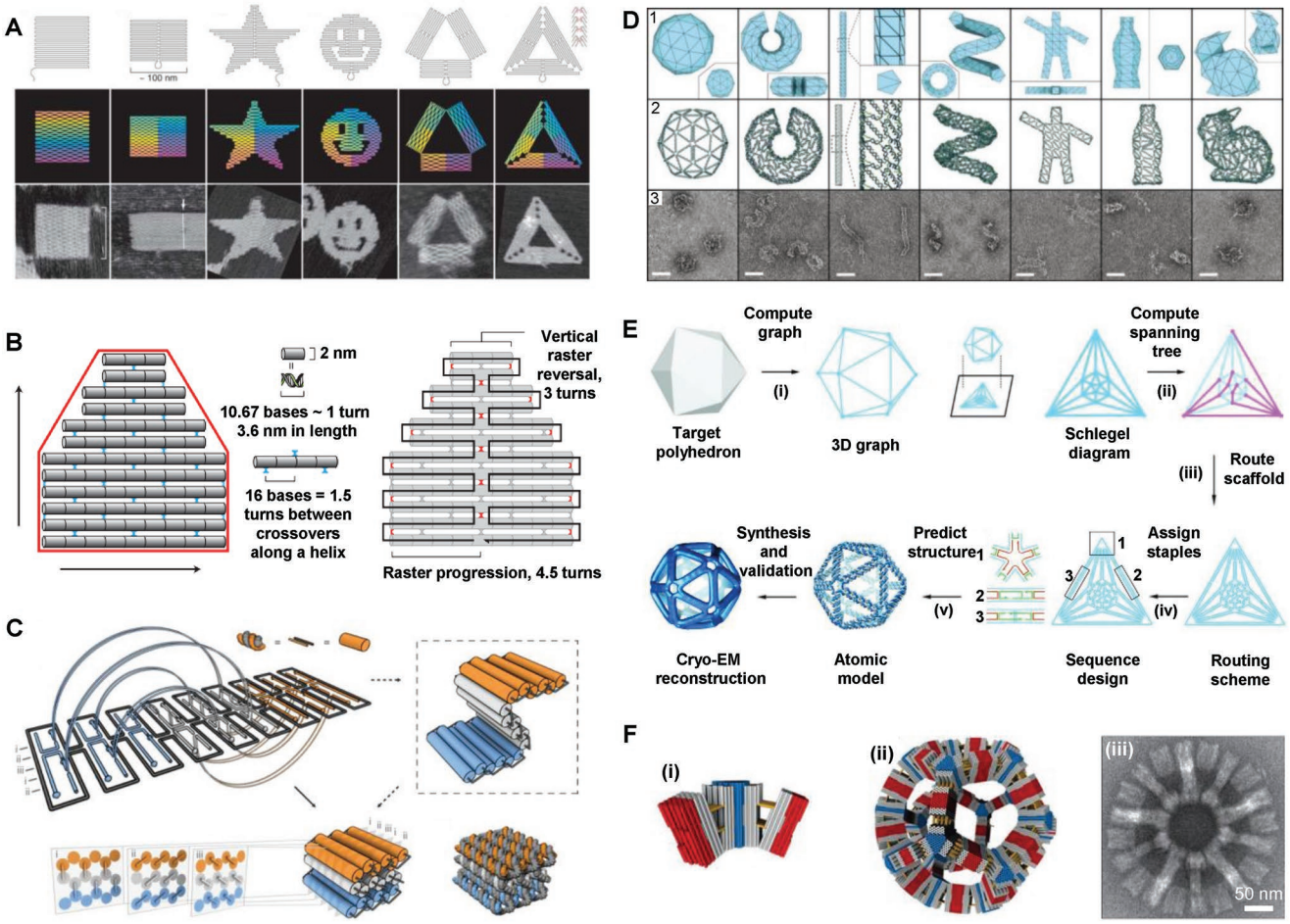

Figure 1. DNA origami structures. A) Single-layered DNA origami shapes and respective AFM (atomic force microscopy) images. B) Illustration of design rules: the shape (red) is approximated by parallel double helices joined by periodic crossovers (blue) which fold a scaffold (black) that runs through every helix overs (red). A,B) Reproduced with permission.[6] Copyright 2006, Nature Publishing Group. C) Design of multilayered DNA origami structures by packing multiple helices into a space-filling structure. Reproduced with permission.[15] Copyright 2009, Nature Publishing Group. D) 3D meshes rendered in DNA. Different views of the 3D meshes provided as starting points for the automated design process (1); front face of the complete DNA designs (2), and transmission electron microscopy (TEM) images of each structure (3). Scale bar: 50 nm. Reproduced with permission.[16] Copyright 2015, Nature Publishing Group. E) Specification of arbitrary target geometries based on a continuous, closed surface that is discretized with polyhedra. Reproduced with permission.[17] Copyright 2016, American Association for the Advancement of Science. F) Self-limiting self-assembly of hierarchical 3D origami structures. i) Cylinder model of reactive vertices designed for the self-limiting assembly of a dodecahedron (ii), and a representative TEM image of the final structure (iii). Reproduced with permission.[19] Copyright 2017, Nature Publishing Group.

on conventional controlled-porous glass columns or multiplexed microchip formats allow for large-scale and low-cost production of DNA oligomers.[30] Chip-based staple strand production can be combined with the use of both strands of bacterial plasmids to markedly increase the scale of DNA origami production.[31] Furthermore, biotechnological "mass production" of DNA origami has recently been demonstrated by using a scalable and cost-efficient method based on bacteriophages.[32] Hence, the above examples clearly indicate that in the next few years almost any particle size and sufficiently large amounts of DNA nanostructures will be accessible. To achieve this goal, however, it is necessary to transfer the current laboratory routines on an industrial scale to standard operation procedures with corresponding quality controls, as has been done, for example, in DNA synthesis and sequencing.[33]

2.3. Addressable Scaffolds for Organization of Non-Nucleic-Acid Components

It is of utmost importance to recall that DNA origami structures possess an addressable surface area of a few thousand nm^2 with a single "pixel" resolution of about 6 nm.[11b] Thus, a typical 100 × 80 nm origami structure can be used as a molecular pegboard with more than 200 "pixels," singularly addressable with a precision of only few nanometers. One of the first applications of this unique addressability utilized rectangular shaped origami, wherein staple strands at defined positions were capable to specifically bind RNA targets in homogeneous sample solutions. After depositing the structures on mica, bound RNA could be identified by AFM.[34] Despite this unprecedented addressability, materials comprised entirely of nucleic acids have only limited electrical,

optical, catalytic, or mechanical functionality. Therefore, applications of DNA materials usually require functionalization with non-nucleic acids.

Direct coupling of small molecules, such as dyes or redox active molecules,[35] with distinctive oligonucleotides through conventional phosphoramidite chemistry is the simplest way to achieve functionality. Numerous studies used this approach to generate well-defined nanoscale patterns of dyes, applicable for studies of basic principles of, e.g., Förster resonance energy transfer (FRET) or as nanorulers for traceable distance measurements and benchmarking of nanoscopy methods.[36] In case of 3D origami devices the positioning of the dyes can even be carried out with a resolution of less than the Bohr radius.[37] 3D origami structures equipped with FRET pairs can be harnessed as force sensors that allow for precise measurement of forces in biomolecular assemblies.[38] Furthermore, coupling of lipid molecules to selected staple strands can be exploited to assemble origami on lipid membranes[39] or to fabricate origami coats for membrane sculpting[40] and nanopore channels for membrane insertion.[41]

The assembly of proteins on DNA nanostructures is particularly promising because these biological macromolecules reveal intrinsic, evolutionary optimized functionality, such as specific binding to biomolecular targets or catalytic conversion of ligands and substrates.[42] In particular, arrangements of synthetic multienzyme cascades on DNA nanostructures are currently attracting much attention because they represent spatially interactive biomolecular networks.[43] Representative examples include a three-enzyme pathway built to facilitate efficient substrate transfer (**Figure 2**A)[44] or to demonstrate that enzyme pathways can be regulated in a directional fashion by the physical control of substrate channeling (Figure 2B).[45] Since the synthetic multienzymes can be steered by synthetic switches and are not limited in terms of the incorporated biocatalytic entities, they could be useful for synthetic biology and the next generation of industrial biocatalysis.[46] Furthermore,

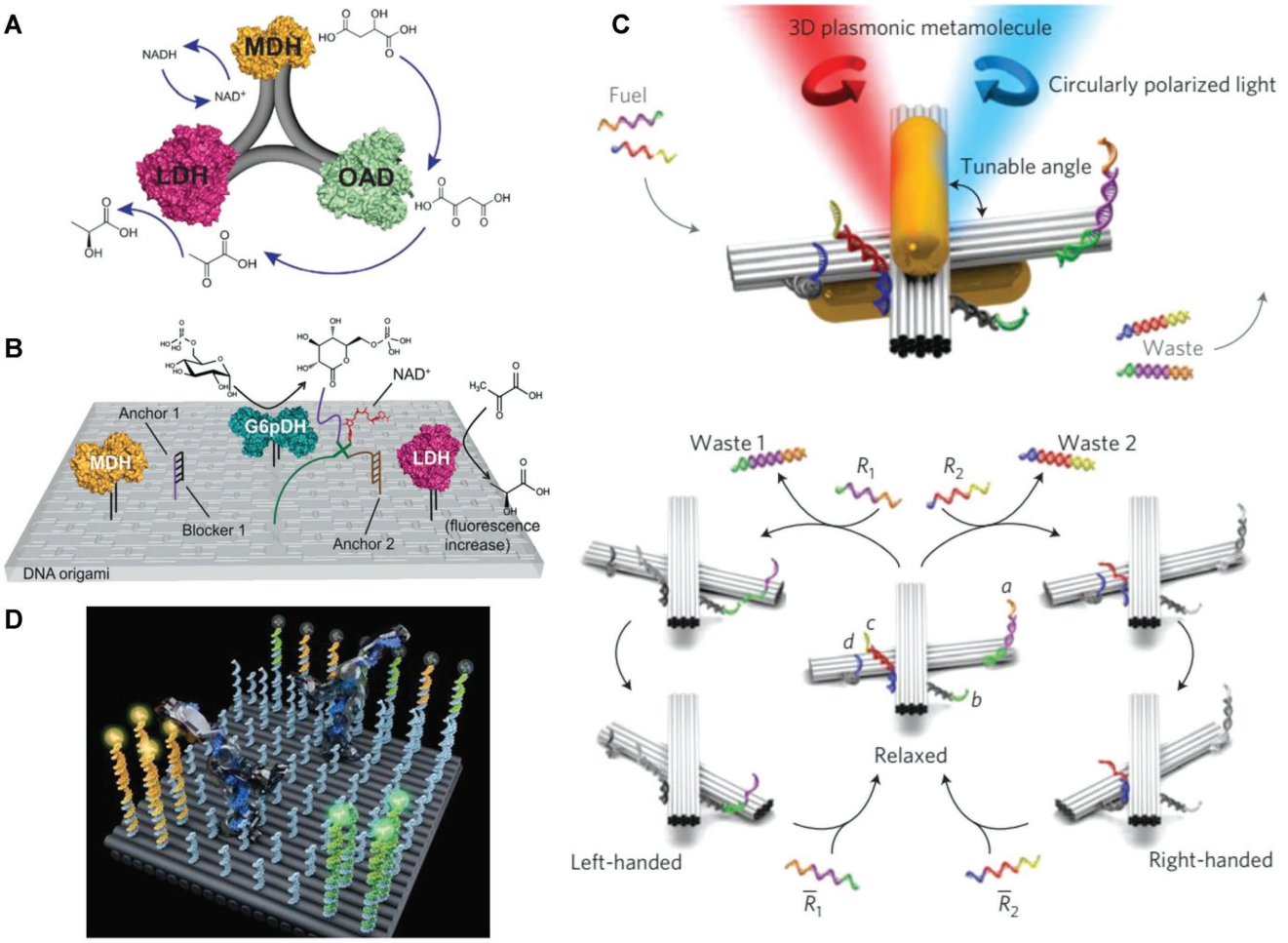

Figure 2. Functionalized DNA origami structures. A) Three-enzyme pathway composed of malate dehydrogenase (MDH), oxaloacetate decarboxylase (OAD), and lactate dehydrogenase (LDH) arranged on a triangular three-point star DNA nanoscaffold. Reproduced with permission.[44] Copyright 2016, Wiley-VCH. B) Three-enzyme pathway composed of MDH, glucose-6-phosphate dehydrogenase (G6pDH), and LDH arranged on a rectangular DNA origami platform. Reproduced with permission.[45] Copyright 2016, Wiley-VCH. C) Schematic representation of reconfigurable 3D plasmonic AuNR with switchable plasmonic properties. Reproduced with permission.[48] Copyright 2014, Nature Publishing Group. D) Artistic illustration of a DNA robot that can explore a 2D testing ground on the surface of DNA origami, pick up multiple cargos that are initially at unordered locations, and deliver them to specified destinations. Reproduced with permission.[49] Copyright 2017, American Association for the Advancement of Science.

protein-functionalized DNA nanostructures hold great potential for other applications in the life sciences, ranging from biosensing and drug delivery[14,42,43] to fabrication of bioinstructive materials and surfaces (discussed below, Sections 4 and 5) The survey of the respective literature clearly indicates that future applications of such DNA-scaffolded multiprotein complexes critically depend on means for their reproducible production, ideally at large scale under industrial standards. While it is evident that methods of recombinant protein technology along with tailored bioorthogonal coupling chemistries will make this possible,[42,47] it is also clear that it will be a long and rocky road to implement such complex molecular architectures into routine applications.

Inorganic nanoparticles are used for functionalization of DNA origami structures in order to develop new materials that can be used for applications, such as nanophotonics, plasmonics, and electronics. DNA-based plasmonic nanostructures are a hot topic in materials research because this approach allows to produce complex and hierarchical DNA hybrid structures in a highly controllable manner to yield static and dynamic molecular devices.[50] Representative examples include nanostructures with controlled chirality,[51] reconfigurable 3D plasmonic metamolecules (Figure 2C),[48] or plasmonic nanoantennas for surface-enhanced Raman spectroscopy.[52] As described below (Section 3), much of the ongoing work is focused on colloidal gold nanoparticles (AuNP) and gold nanorods (AuNR). However, the fabrication of functional devices often calls for the integration of nanoparticles made of other materials. Current state-of-the-art indicates that inorganic nanoparticles made of silver,[53] semiconductor quantum dots,[54] or carbon nanotubes[55] can as well be organized on DNA origami scaffolds. Furthermore, 3D origami nanostructures can also be used as templates and molds to encode the size and shape of inorganic nanoparticles.[56] As in the case of protein immobilization, robust chemical methods are also required here in order to enable production of the inorganic–organic hybrid structures with high reproducibility on a larger scale. This should make it possible to develop a comprehensive toolbox in the coming years to produce multicomponent hybrid structures for applications in physics and engineering.

2.4. Computational Science and Molecular Robotics

From its very beginning, the genesis of DNA nanotechnology was intrinsically tied to the development of mathematical models and computational algorithms,[3] be it to design complex DNA nanostructures using computer-aided methods[16,17,57] or to exploit DNA assembly and amplification in DNA computation to process information.[58] Both approaches include dynamic DNA systems, in which reversible transition mechanisms between various stable or metastable states, such as secondary structure conformations, are implemented by means of hybridization, strand-displacement, cleavage or other processes.[59] This can be utilized, on the one hand, for dynamic scaffolds, such as the reconfigurable plasmonic metamolecule, shown in Figure 2C. On the other hand, metastable origami structures can also be exploited for so-called "DNA walkers." These systems are latently mobile DNA motifs that follow a prescribed path through hybridization and strand displacement.[60] It was recently shown that this concept can be used for construction of autonomous DNA-based "robots" that can sort nanoparticle cargoes on their surface (Figure 2D)[49] or biohybrid rotor–stator nanoengines that move along predefined tracks.[61] This work gives rise to the hope that molecular machines made from DNA will one day be able to perform complex tasks, such as the controlled translocation of molecules across barriers,[62] the evaluation of the molecular composition of cell surfaces for therapeutic purposes,[63] or the assembly of tiny electrical and mechanical devices. Given that basic functions have been demonstrated in proof-of-concept studies, it seems reasonable that the next level of sophistication will be attainable by consequent implementation of molecular bottom-up assembly and top-down microengineering. This will make it possible both to analyze the basic functions of DNA machines at the single molecule level[64] and to maintain their operation,[65] preferably in the form of extended long-range ordered arrays on surfaces (see also Section 5.2).

3. DNA-Based Colloid Assemblies

The initial description of using DNA oligonucleotides to organize AuNP[10] in 1996 promised a novel approach that could readily deliver materials from arbitrary nanoparticles, which have novel, size-dependent properties, can be tailored in their 3D structure, might respond "intelligently" to external stimuli, and should open the door to a broad spectrum of applications ranging from sensing and catalysis to device fabrication.[8] Now, more than 20 years later, we are looking on roughly 15 000 scientific publications with the keywords "nanoparticle" and "DNA" and we can resume that some of these goals have actually been achieved. We here focus on state-of-the-art examples regarding the synthesis and assembly of DNA-based colloidal assemblies in various dimensions, explain interim problems and solutions and conclude that especially chemical and engineering methods will need further attention to open the door to the development of complex DNA material systems.

3.1. Preparative Synthesis Aspects

One of the major drivers that pushed forward the field of DNA-based nanoparticle assembly was the ease with which DNA-functionalized AuNP can be produced. Thiolated oligonucleotides are commercially available and they readily chemisorb on the surface of citrate-stabilized AuNP under formation of a stable covalent sulfur–gold bond. Mirkin and co-workers are certainly leading this field of research[66] that has triggered biomedical applications of oligonucleotide-functionalized AuNP, often dubbed as "spherical nucleic acids."[67] While thiol chemisorption is a possible means for DNA immobilization on silver colloids,[68] nanoparticles made of other materials, such as quantum dots,[69] iron oxide,[70] silica,[71] polymers,[72] or CNT[73] require more sophisticated chemical procedures that often lead to lower surface occupancies and stabilities of the nanoparticle–oligonucleotide hybrids. Hence, to achieve the goal of a comprehensive toolbox for the production of arbitrary

multicomponent hybrid structures for applications in physics and technology, robust chemical methods have to be developed to efficiently convert inorganic colloids into DNA conjugates.

3.2. Assembly in One and Two Dimensions

Depending on the nature of a DNA scaffold, oligonucleotide-modified particles can be assembled in various dimensions ranging from linear chains and wires of nanoparticles (1D) over planar arrays and sheets (2D) up to the arrangement in 3D space (**Figure 3**A). A relatively simple approach to 1D wire assemblies is based on the direct metallization of the DNA strand by reducing metal cations (e.g., Ag^+, Au^{3+}, Pd^{2+}, Pt^{2+}, etc.) bound to the negatively charged DNA backbone. Resulting nanowires usually have granular morphologies which can show conductive behavior,[74] however, high-quality structures are very difficult to prepare in a reproducible manner.[75] To better control 1D wire formation and even allow for precisely controlled interparticle spacing, the problems of metallization can be overcome through scaffold-assisted assembly of preformed nanoparticles.[76] An impressive demonstration of multicomponent hybrid structures has recently been given by the DNA origami-based 1D assembly of trimeric Au–Ag–Au nanoparticle constructs. These assemblies reveal hotspot-mediated nondissipative and ultrafast plasmon passage that could be important for applications in information technology.[53b] As demonstrated in various studies,[77] suitable templates for 2D nanoparticle arrays can be regular "infinite" arrays of DNA tiles (Figure 3A) or DNA origami structures (Figure 3B).[78] Since such arrays are highly important for development of 2D layered materials for optics and photonics, current and future work regards their implementation into extended long-range ordered surface arrays (see also Section 5.2).

3.3. Assembly in Space

Since oligonucleotide-modified nanoparticles contain thousands of ssDNA molecules on their surface, they are multivalent spheres—hence, Mirkin's term of "spherical nucleic acids"—and do assemble in three dimensions once the DNA strands are complementary. In case of noble metal nanoparticles, the DNA-mediated assembly leads to changes in the plasmon absorption, and this principle forms the basis of many diagnostic tests.[67] Since the "DNA bond"[1] is programmable and reversible by nature, variable bond strengths and particle spacings can be adjusted, predetermined heteroassemblies of different nanoparticles can be formed, and particle aggregates can be disassembled by thermal melting,[83] enzymatic cleavage, or strand-displacement.[84] However, since the 3D nanoparticle assemblies are usually obtained as amorphous aggregates, the challenge is to devise methodologies that allow for assembly of either finite "molecule-like" or infinite "crystal-like" nanoparticle assemblies.

One approach to the problem of better controlling the 3D assembly is to encapsulate the colloids with a DNA envelope. This breaks the symmetry of spherical nanoparticles and allows to control the number and position of oligonucleotides.[85] Hence, finite assemblies of nanoparticles can now be synthesized by solution-based methods to yield sophisticated architectures that resemble satellite- or molecule-like superstructures.[54b] The synthetic strategy usually includes several steps, which include the use of DNA templates to direct bonding geometries (Figure 3C,[80] and 3D[81]) and it provides access to even complex nontrivial shapes, such as a nanoparticle model of Leonardo da Vinci's Vitruvian Man.[86] Recently the strategy was exploited for fabrication of dynamic nanosystems consisting of a core nanoparticle surrounded by small nanoparticle satellites which can undergo conformational changes to alter their interactions with living cells.[87] As noted by the authors, such strategies could be used for navigating complex biological environments. It also seems possible that the implementation of such constructs in fluidic platforms could lead to new approaches for self-organized systems that control the growth and repair of DNA materials (discussed in Section 6).

Crystal-like assemblies of DNA–nanoparticles had long been proposed, however, first examples were described only more than 10 years later from Gang and co-workers[88] and Mirkin and co-workers.[89] This breakthrough opened the door to systematic exploration of the design rules for DNA-programmable colloidal crystallization, which nowadays allows to engineer AuNP superlattices with almost arbitrary crystal lattice geometries (Figure 3D).[82,90] It is important to realize that such AuNP superlattices have high water content. Hence they reveal materials properties more similar to hydrogels than to solid phase crystals. For example, they show dynamic behavior, which can be triggered by strand displacement and hybridization.[91] While these properties could be advantageous for biological applications or dynamic material systems (see above), the superlattices are prone to collapse or dissociate in deionized water, common organic solvents, at high temperatures, or under vacuum. In order to circumvent these disadvantageous properties for solid materials, methods need to be developed for mechanical stabilization. Current work suggests that this can be achieved, for instance, by encapsulation into mechanically supportive silica shells[92] or by stabilization of the particle-connecting DNA duplexes with Ag^+ ions.[93] Furthermore, since 3D origami lattices are well suited for site-specific hosting of nanoparticles,[94] the colloidal assemblies may also be stabilized by sequence-specific establishment of covalent bonds.[95] Importantly, the implementation of bottom-up colloidal assembly in top-down micropatterning processes[96] has recently been used to fabricate stable 2D crystal-like large-scale assemblies (see Section 5.2).

4. DNA-Based Polymer Materials

Polymers range from synthetic plastics, such as polystyrene, to natural macromolecules, such as DNA and proteins. They are composed of repeated subunits, which are coupled via polymerization of respective molecular building blocks (monomers). This leads to high molecular weight products. While some natural biopolymers (DNA, proteins, and some oligosaccharides) have a precisely determined molecular composition and weight, polymers are usually mixtures of differently sized macromolecules. Therefore, the here described

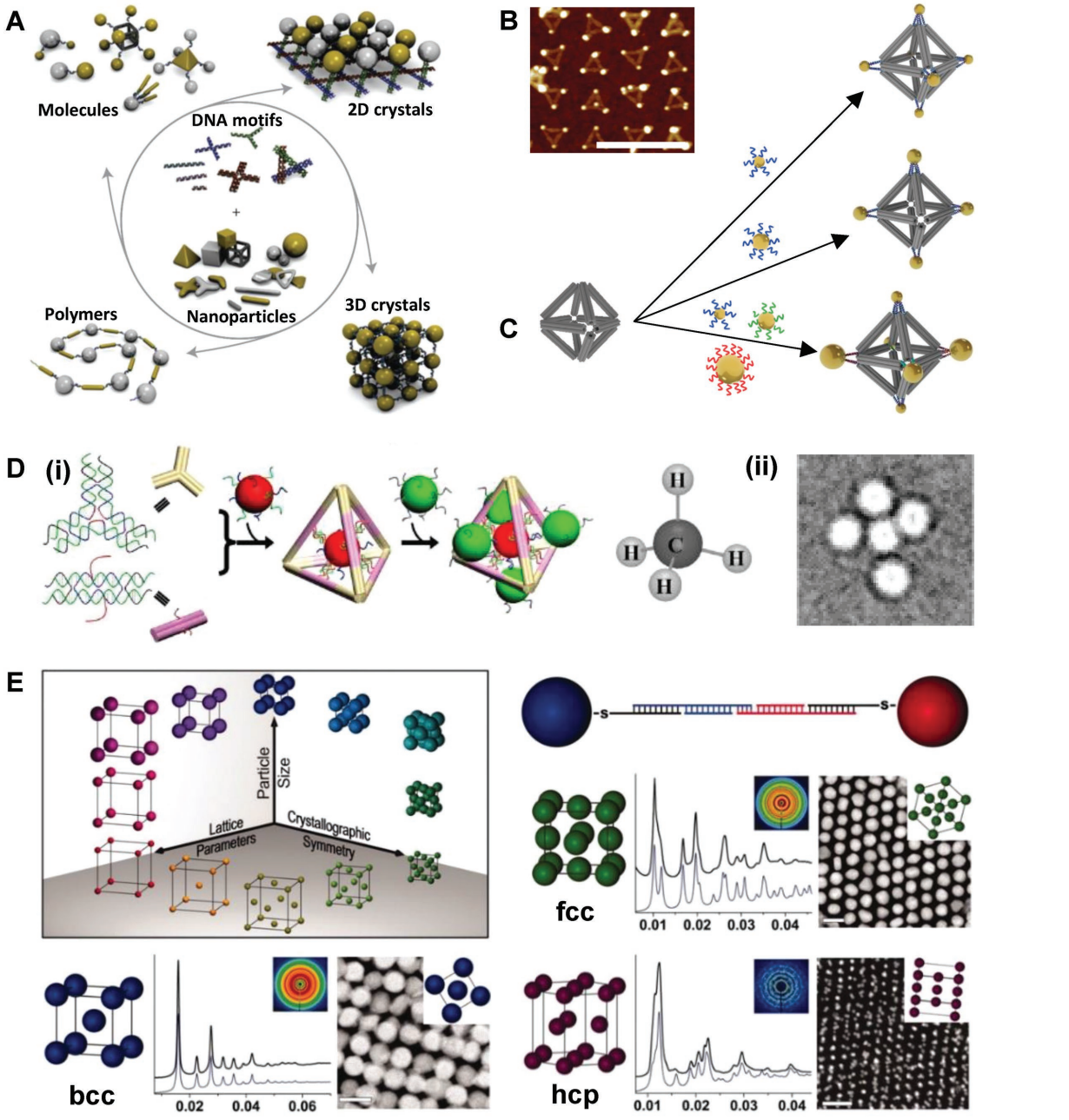

Figure 3. DNA-based colloid assemblies. A) Schematics of nanoparticle assembly by using various DNA motifs. Reproduced with permission.[79] Copyright 2011, Nature Publishing Group. B) 2D arrays of gold nanoparticles directed by lithographically confined DNA origami. Scale bar: 500 nm. Reproduced with permission.[78] Copyright 2010, Nature Publishing Group. C) Scheme of three designed clusters assembled from DNA-functionalized AuNP on correspondingly encoded vertices of octahedral DNA frames. Reproduced with permission.[80] Copyright 2015, Nature Publishing Group. D) Self-assembly of methane-like nanoparticle molecules; schematic illustration (i) and cryo-EM image (ii). Reproduced with permission.[81] Copyright 2015, American Chemical Society. E) Engineering of lattice parameters and crystallographic symmetry of nanoparticle superlattices through particle size and DNA spacer length. Representative examples: face-centered-cubic (fcc), body-centered-cubic (bcc), hexagonal close-packed (hcp) superlattices. From left to right, each panel shows a model unit cell (not to scale), 1D and 2D (inset) X-ray diffraction (SAXS) patterns, and a TEM image of resin-embedded superlattices. Scale bar: 50 nm. Reproduced with permission.[82] Copyright 2011, American Association for the Advancement of Science.

DNA-based polymer materials differ significantly from the aforementioned DNA origami nanostructures, which are monodisperse particles obtained from only a single well-defined DNA scaffold. The concept of fusing synthetic DNA molecules with organic polymers goes back to the strategy for altering polymer properties by combining different polymer segments within one polymer, known as block copolymers.[97] This usually leads to microphase separation of the individual polymer components, which results in formation of nanosized domains within the polymeric materials. As a consequence, novel materials

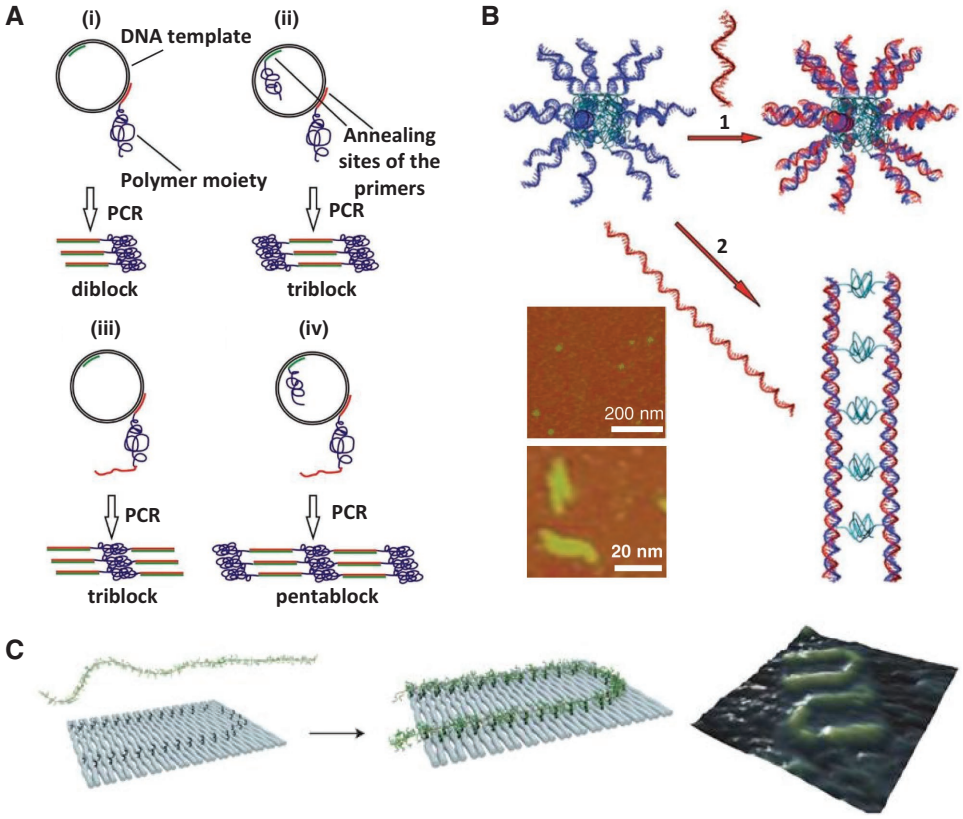

Figure 4. Synthesis of DNA block copolymers (DBCs). A) Synthesis of DBCs from organic polymers and variable numbers of DNA strands by using PCR. Reproduced with permission.[97] Copyright 2012, American Chemical Society. B) Hybridization of ssDNA-PPO micelles with short oligonucleotides yields micelles with a corona of dsDNA (1), whereas base pairing with a long ssDNA results in rod-like micelles (2). The insets are AFM images of spherical (top) and rod-like (bottom) micelles. Reproduced with permission.[106] Copyright 2007, Wiley-VCH. C) Routings of oligonucleotide-modified polymer chains on 2D DNA origami plates; schematic illustration (left) and AFM image of polymer-modified origami structures. Reproduced with permission.[114] Copyright 2015, Nature Publishing Group.

properties arise which can be exploited for applications in life sciences, organic electronics, and many other fields.

4.1. DNA Block Copolymers

DNA block copolymers (DBCs) are hybrids, comprised of synthetic organic polymers and DNA segments. They are known since the mid 1980s, when Lemaitre and co-workers grafted antisense DNA oligonucleotides onto a poly(L-lysine) backbone.[98] In the following, the field has made substantial advances with respect to variations in the organic building blocks, leading to DBCs with tunable physicochemical, mechanical, and biological properties.[97]

To synthesize DBCs, usually presynthesized oligonucleotides are grafted onto prepolymerized organic polymers. Covalent linkage is achieved by amidation, esterification, disulfide coupling, or, nowadays, bioorthogonal "click" chemistries, which are increasingly important for synthetic DNA modification.[99] Alternative strategies include continuous on-column syntheses using phosphoramidite[100] or *N*-hydroxysuccinimide[101] chemistry and biochemical methods based on polymerase chain reaction (PCR)[102] (**Figure 4**A) or enzymatic restriction/ligation.[103] For a more detailed assessment of DBC synthesis and applications in nanoscience and biomedicine, the survey of Schnitzler and Herrmann is recommended.[97]

DNA polymer hybrids are being used, for example, to explore fundamental principles of nanosciences because they offer new opportunities for studying amphiphilic properties of supramolecular polymer assemblies and electronic interactions therein.[104] Micellar nanostructures can be prepared by self-assembly from DBCs containing hydrophobic polymer moieties,[100b,105] and the structural properties can be engineered by hybridization with complementary DNA sequences (Figure 4B).[106] This gives rise to complex supramolecular architectures, such as pH-inducible morphology shifting polymers, coil–rod–coil triblock structures and DNA-dendron fibers.[104,107] Even geometrically challenging amphiphilic assemblies like cuboid and dumbbell-shaped heterovesicles can be obtained by aid of DNA origami scaffolds.[108] Likewise, liposomes can be encapsulated inside rigid DNA nanotemplates[109] or rendered to functionally programmed fusion cascades.[110] DNA-based approaches were also used to prepare sequence-defined polymers,[111] nanopatterned polymer sheets of various heights[112] or amphiphilic assemblies from semiconducting polymers as a means for creating soft optoelectronic nanostructures.[113] Along this line, to create molecular-scale electronic or optical wires in arbitrary geometries,

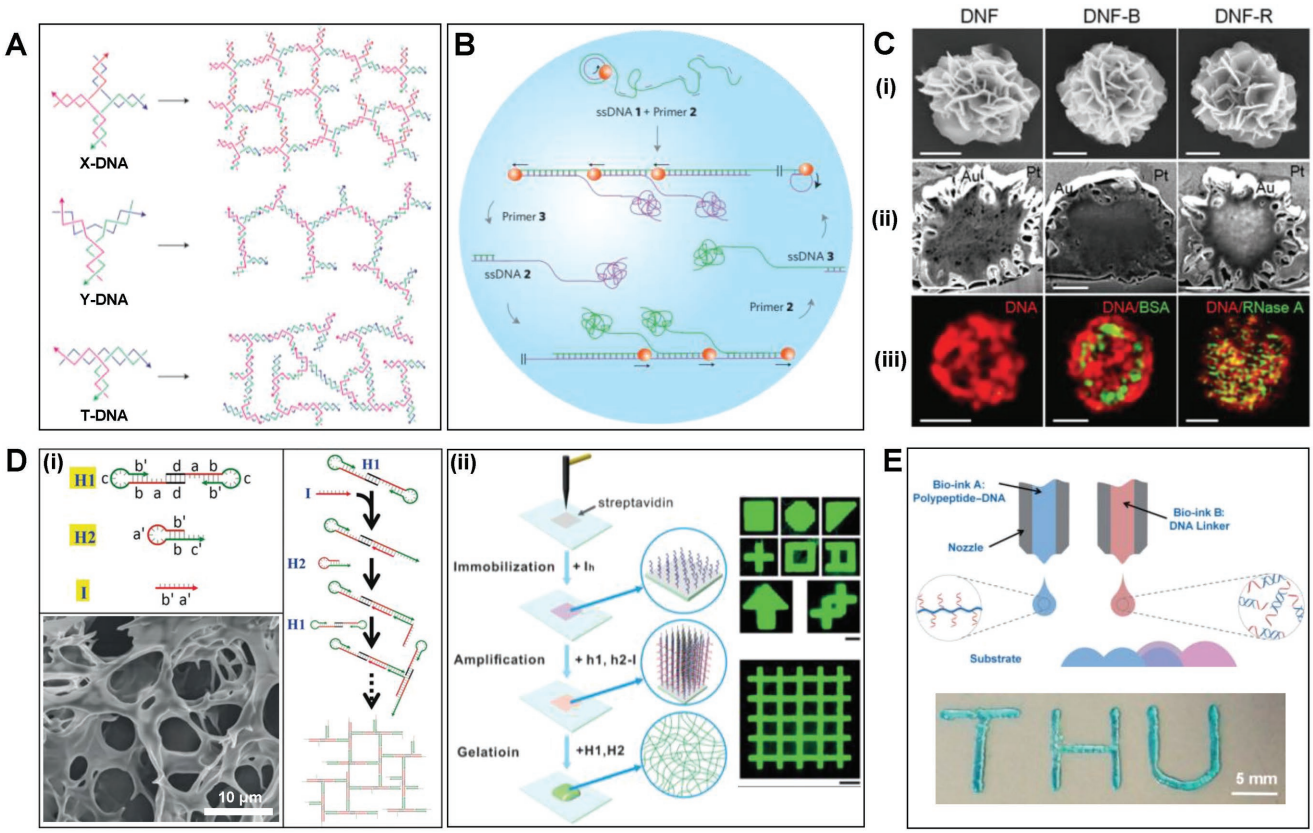

Figure 5. A,B) Synthesis of pure DNA hydrogels by hybridization/ligation of preassembled branched X-, Y-, and T-shaped oligonucleotide structures (A) or multiprimed rolling circle amplification (RCA) (B). A) Reproduced with permission.[118] Copyright 2006, Nature Publishing Group. B) Reproduced with permission.[119] Copyright 2012, Nature Publishing Group. C) Representative scanning electron microscopy (SEM) images (i), focused ion beam (FIB)-SEM images of orthogonal cross-sections (ii), and structured illumination microscopy (SIM) images (iii) of "DNA nanoflowers" composed of pure DNA (DNF) or endowed with bovine serum albumin (DNF-B) or RNase A (DNF-R). In the SIM images, DNA and proteins are shown in red or green, respectively. Scale bars: 500 nm (top and middle), 1 μm (bottom). Reproduced with permission.[134] Copyright 2017, Wiley-VCH. D) Mechanism of clamped hybridization chain reaction (i) and illustration of surface-initiated hydrogel formation and fluorescence images of printed polygon patterns (ii). Scale bars: 500 mm (top), 1 mm (bottom). Reproduced with permission.[121] Copyright 2017, Wiley-VCH. E) 3D bioprinting of two complementary DNA bioinks that hybridize to DNA–polypeptide hydrogels to yield arbitrarily designed 3D structures. Reproduced with permission.[133] Copyright 2015, Wiley-VCH.

synthetic polymer wires have been assembled into arbitrary routings on 2D DNA origami plates (Figure 4C),[114] and DBCs were used for assembly of field-effect transistor devices.[115] The latter examples in particular are interesting for realizing future perspectives with regard to self-growing and self-healing polymer materials for technical applications. Similar as discussed for nanoparticles, this requires improved (bio)chemical methodologies with which organic, inorganic and biological molecules can be selectively and efficiently appended.

4.2. Pure DNA Hydrogels

Instead of grafting onto synthetic organic polymers, DNA oligonucleotides can also be used to produce pure DNA hydrogels.[12a,116] Pure DNA hydrogels are prepared by two methods, either the hybridization/ligation of linear[117] and branched DNA oligonucleotide building blocks (**Figure 5**A),[118] or else by enzymatic extension of oligonucleotide primers, in particular through rolling circle amplification (RCA). The resulting DNA hydrogels are entangled networks that often reveal shape memory persistence[119] and can be grown enzymatically to mesoscopic structures with distinctive morphologies, often dubbed as "DNA nanoflowers" (Figure 5B,C)[120] Polymerization times range from days for enzymatic procedures, such as RCA, to only a few hours for hybridization-based methods, such as the recently developed "clamped hybridization chain reaction" (Figure 5D),[121] which can even be conducted on patterned surfaces. Owing to the availability of commercial DNA oligonucleotides, the gels can be prepared in macroscopic amounts. Because of their high (usually >90%) water content, DNA hydrogels are promising scaffold materials in tissue engineering. They are perfectly biocompatible and their 3D structure has tissue-like elastic properties that allow for effective permeation of oxygen and nutrients, which is crucial for cellular colonization.[122]

In addition to organic polymers, as in DBCs, DNA polymers can also be coupled with organic macromolecules, such as cucurbit[8]uril,[123] or grafted onto polypeptides[124] and even whole proteins.[125] The incorporation of light-sensitive synthetic groups, e.g., azobenzene moieties, into DNA hydrogels can be exploited for targeted delivery and controlled release of drugs[126] or for tumor photothermal immunotherapy.[127] Furthermore,

DNA polymer composite materials have been produced from inorganic materials, such as carbon dots,[128] graphene oxide,[129] carbon nanotubes,[130] semiconductor quantum dots,[131] or AuNP [126a,127] and magnetic nanoparticles.[132] The addition of nanoparticles adds functionality to the DNA hydrogels, whether be it mechanical stability,[123] optical traceability,[131] or remote controllability by external magnetic fields.[132] This broad spectrum of functionalization possibilities is particularly interesting for biological applications, ranging from bioinstructive materials for drug delivery and transfection over encapsulation of enzymes and cells to 3D bioprinting of cell populations by additive manufacturing processes (Figure 5E).[133] In this regard, methods would be useful for systematic and facile modification of the biological stability and manufacturability of such polymer materials. For example, this could be achieved by developing recombinant polymerases and other enzymes that can also process non-natural DNA analogues (see also Section 5.1).

4.3. DNA Polymer Materials can be Easily Programmed

DNA polymers are attracting so much attention because the genetic material allows for rational programming of these soft materials through integration of DNA motifs that can be recognized and processed by functional biological molecules and cells. For example, stimuli responsiveness can be easily introduced, e.g., by incorporation of pH-dependent folding motifs[135] or enzymatic restriction sites.[136] This enables on-demand dissolution of the gels,[136] which is useful to release embedded components, such as nanoparticles, enzymes, or cells.[137] Another example concerns aptamers, folded nucleic acid motifs that exhibit specific binding, that can be easily incorporated to engineer target-responsive[138] and logic gate materials.[139] These can be used for sensing[140] or capture of molecules[138] and ions for purification purposes.[141] Very importantly, because DNA can store genetic information, DNA polymer materials can be engineered to instruct biological systems. Indeed, this approach has been used to create protein-producing hydrogels. Such materials can instruct the enzymatic machinery of cell lysates in vitro to synthesize messenger RNA that is translated into functional proteins.[142] By implementation into microfluidic devices, these developments could lead to novel material systems for the production of a variety of complex molecules, such as protein or glycan conjugates. Hence, DNA polymers represent a very important class of materials that could be combined with the particular properties of nanoparticles and/or DNA origami structures in the future to create material systems that are applicable to both life sciences and technology (see also Section 6).

5. DNA Surface Technology

The advent of DNA microarray technology in the course of the human genome project in the 1980s led to the evolution of sophisticated DNA microarrays, which are nowadays routine tools for genotyping and expression profiling in fundamental and applied biomedical research.[143] Since DNA is an extraordinary stable molecule, industrial processes for large-scale production and use of DNA microarrays that contain up to millions of different ssDNA oligonucleotides are fully developed.[144] However, the scope of DNA surfaces goes far beyond applications in genomics and transcriptomics. The method of "DNA-directed immobilization" (DDI) of proteins, invented in the early 1990s,[9] opened up the DNA chip platform for the analysis of proteins and other non-nucleic acid molecules.[13,145] DDI takes advantage of surface-bound capture oligonucleotides to selectively bind sets of proteins tagged with complementary oligonucleotides (**Figure 6**A). It is a very mild process because surface microstructuring with DNA is fully separated from surface functionalization with delicate proteins. The latter can be conducted under chemically mild, physiological conditions, which do not harm the sensitive tertiary, and quaternary structures of proteins. Additional advantages of DDI include multiplexing capabilities,[146] high surface-coating density, and the option to regenerate the DNA surface by simple denaturation protocols.[147] In more than 20 years, hundreds of research papers have demonstrated the advantageous utility of the DDI method,[145] of which we here present selected examples that are related to the aspects of DNA-based materials described above.

5.1. Protein-Decorated DNA Surfaces

Solid substrates containing microarrays of proteins are of utmost importance for sensing, biomedical diagnostics, and proteome research.[149] DDI-based protein decoration is not limited to glass or polymer surfaces. It can also be used for silicon, gold and other materials. This enables plasmonic detection of small molecules,[150] electrochemical screening of enzymes[151] or the study of electron transfer processes in between proteins and metals.[152] For proteome research, DDI on conductive silicon substrates is used.[153] Importantly, as demonstrated in proteomic studies,[154] synthetic peptide nucleic acid (PNA) oligomers can as well be used for DDI. This draws attention to a generally important point: DNA-based materials are increasingly produced with synthetic DNA analogs, e.g., PNA[155] or locked nucleic acids (LNA),[156] in order to increase physical and biological stability.[157]

For future perspectives of DNA-based material systems, it is important to emphasize that the DDI method is fully compatible with microfluidic platforms. This enables (bio)functionalization of previously assembled, closed flow systems,[158] along with reduction of sample and reagent sizes, and improvements in assay stability and processing times. These advantages have been demonstrated for the analysis of biomarkers in lab-on-a-chip devices, point-of-care diagnostics, and compartmentalized biocatalytic systems.[46,159] Hence, the integration of DDI and microfluidics will play a crucial role in the future development of material systems (see also Section 6).

5.2. Nanomaterials on DNA Chips

The use of nucleic acid hybridization for functionalization of bulk materials is not limited to proteins but can be readily extended to small molecules, such as peptides,[154b] glycans,[160] or hormones[150] as well as to inorganic nanoparticles. The latter is of particular interest for the self-assembly of DNA-based materials. For example, groundbreaking work of Mirkin on the DDI

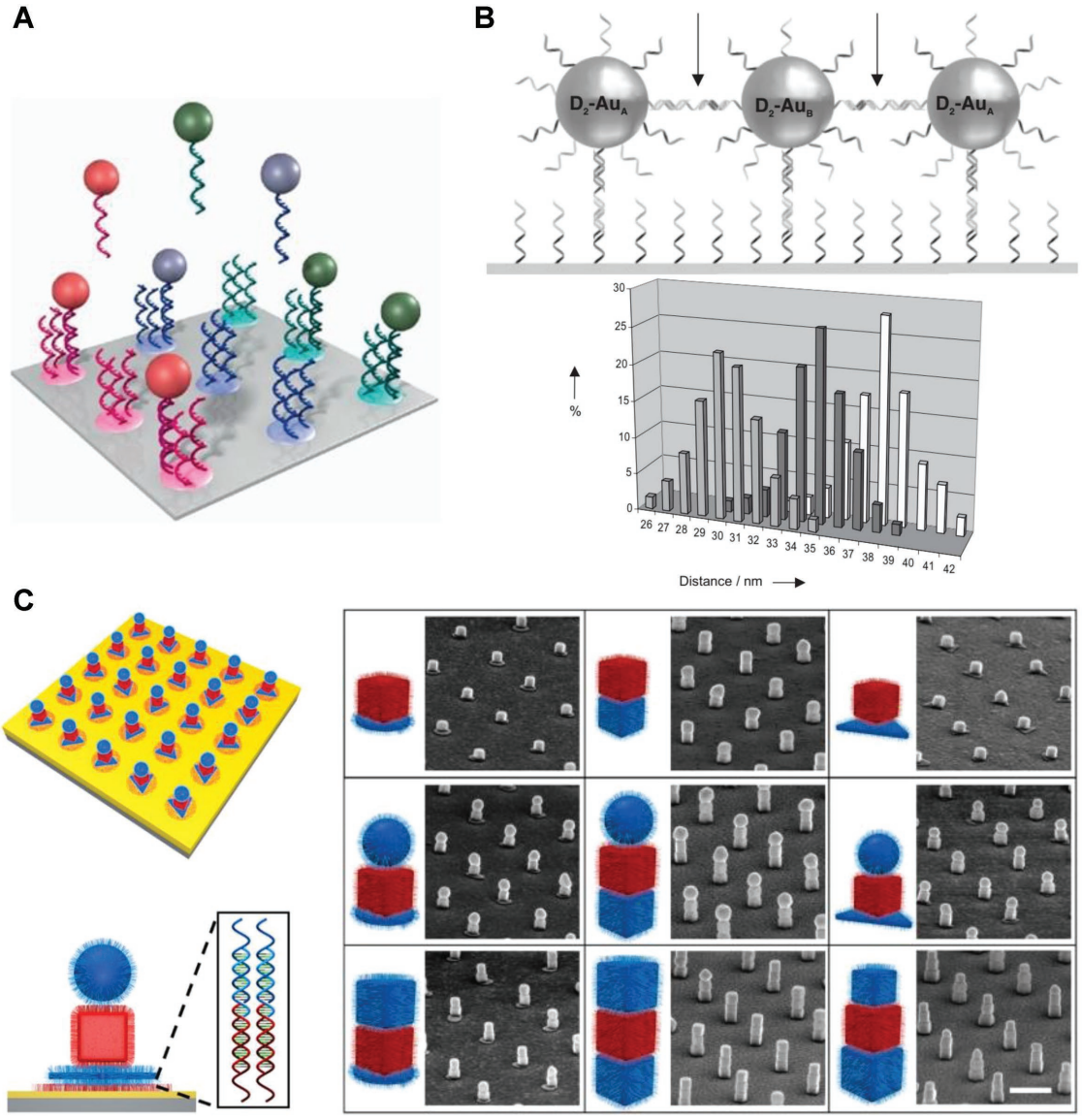

Figure 6. DNA surface technology. A) Schematic representation of DNA-directed immobilization (DDI). Reproduced with permission.[145] Copyright 2014, Elsevier Inc. B) DDI of bifunctional DNA-AuNP (D_2-Au) leads to crosslinked colloid layers in which the particle's center-to-center distances depend on the length of the crosslinking oligonucleotide (arrow). Reproduced with permission.[148] Copyright 2005, Wiley-VCH. C) Schematic illustration and SEM images of oriented superlattices of two and three-layer nanoparticle architectures prepared in microfabricated polymer pores. Scale bar, 300 nm. Reproduced with permission.[96] Copyright 2018, American Association for the Advancement of Science.

of AuNP[161] has led to a whole suite of bioanalytical assays for detection of nucleic acids and proteins.[67,162] Other nanoparticles, such as semiconductor quantum dots,[163] CNT,[164] or the broad variety of silica nanoparticles (SiNP),[71] are as well amenable to the DDI approach. For example, self-assembled 2D micropatterns of oligonucleotide-functionalized, fluorescent dye-encoded core/shell SiNP on glass substrates can be used for improved adhesion and guidance of eukaryotic cells on technical surfaces.[71]

In addition to applications in biomedical research, colloidal self-assembly on surfaces opens the door to materials and device fabrication.[165] The approach can be used to prepare electronic circuits, as demonstrated by selective hybridization of AuNP in electrode gaps. Subsequent electroless silver deposition on the AuNP bridges the gap and establishes electrically conductive contacts.[166] By using multifunctional DNA-AuNP bearing different oligonucleotide addresses (Figure 6B),[167] crosslinked 2D AuNP layers with adjustable interparticle distances can be assembled on surfaces.[148,168] The electrical properties of such layers then depend on interparticle spacing.[169]

Recent advances in DNA-directed colloid assembly on surfaces include methods for patterned deposition of nanomaterials on DNA surfaces to integrate self-assembly with top-down methodologies.[170] Many individual origami structures can be captured and aligned on patterned surfaces.[171] This allowed to produce large-area spatially ordered arrays of AuNP arranged on the lithographically confined DNA origami

patterns (Figure 3B).[78] The fabrication of large materials surfaces with highly defined long-range ordered nanoscaled objects can also be achieved by using top-down microfabricated polymer pores for the LNA-mediated bottom-up assembly of complex plasmonic nanoparticle architectures (Figure 6C).[96] These methodologies provide platforms for the systematic study of light–matter interaction in nanoparticle-based materials.

The above described works illustrate the potential of colloidal surface assembly for manufacturing of 2D layered materials. This class of materials displays a large anisotropy to their bonding, electrical and/or magnetic properties. Therefore, it is of tremendous interest for an enormous breadth of fields, ranging from semiconductor technology, electronics, and energy storage over photofunctional and catalytic devices to biomedical applications.[172]

5.3. DNA Surfaces for Cell Biology

The DDI method is particularly well suited for the patterning of living cells on solid surfaces. Such cell microarrays are important for tissue engineering, diagnostics, assays in drug development, and fundamental studies in cell biology.[173] To enable site-selective cell attachment onto DNA surfaces, short DNA oligonucleotides can be bound directly to the membrane of living cells by a variety of mild chemical methods.[145] Alternatively, arrays of ligands with specific affinity for receptors on the cell surface can be prepared by DDI, and the resulting patterns can be used for selective cell adhesion.[174] Furthermore, DNA-directed patterning of single cells can be achieved by using the atomic force microscope for top-down mechanical positioning of individual cells.[175] The DNA-based approaches have been exploited for electrochemical metabolic analysis of single mammalian cells on gold electrodes,[176] the analysis of intercellular signaling,[177] the multiplexed patterning of single cells for tissue engineering,[173a] the activation of natural killer cells,[178] or for switch-like, light-controlled perturbations inside living cells.[179]

Importantly, the potential of DNA-based surfaces goes far beyond patterning and assembly of single cells when ligand arrays with subcellular dimensions are prepared to enable precise functional manipulation of small regions inside living cells.[180] To this end, ligand arrays of <5 μm diameter feature size are fabricated by, e.g., combined dip-pen nanolithography printing and DDI assembly processes. The ligands specifically bind epitopes of transmembrane receptors in the plasma membrane of adhered cells. This leads to recruitment and concentration of the receptors on the micropatterned ligand arrays (**Figure 7**A). The approach has been used for the analysis of native transmembrane receptor signaling,[180a] as well as for the generation of protein-interaction arrays inside living cells that express synthetic bait-presenting artificial receptor constructs (Bait-PARCs, Figure 7B).[180b]

The power of DNA surfaces as tools for fundamental research in biomedicine can even be enhanced by implementation of DNA nanostructures. DNA-encoded surfaces can be used for site-specific immobilization and assembly of DNA double-crossover (DX) motifs, which are equipped with protruding arms that serve to anchor the resulting DNA lattices in a programmable orientation on the solid support.[181] Using DNA origami structures instead of the DX tiles, the approach was used to create a novel platform for analysis of the preorganization of cellular membrane receptors. These are frequently geometrically constrained, and they often organize in supramolecular assemblies before or as part of their response to ligand binding.[182] Investigation of these processes requires technologies for fabrication of ligand arrays with precisely defined nanoscale geometries. This can be achieved with multiscale origami structures as interface for cells (MOSAIC),[183] wherein ligand-decorated origami structures are immobilized on subcellular micropatterns (Figure 7C). In a proof-of-concept, the MOSAIC method was used to establish that the activation of epidermal growth factor (EGF) receptors in living cells is influenced by the nanoscale geometry of EGF ligands. Hence, this example nicely illustrates that by integration of top-down and bottom-up methods a full control over the number, stoichiometry, and precise nanoscale orientation of molecules on surfaces can be achieved. MOSAIC shows that, in contrast to material science applications (see Section 5.2), long range order is not required to achieve macroscopic effects in biological systems. Therefore, bioinstructive MOSAIC materials can be envisaged for applications in the life sciences that cannot be tackled by conventional technologies.

6. Discussion

"DNA in a material world"[3]—as illustrated above, this revolutionary idea of Seeman in the early 1980s has indeed become today's reality. We are looking at an impressive number of fundamental and application-based research works in this innovative field at the crossroads of materials science, biotechnology, and nanotechnology, where the original pure research on structural DNA nanotechnology had substantially gathered momentum by advancement of nucleic-acid-modified proteins and nanoparticles.[184] Spurred by complementary developments in DNA polymer chemistry and DNA surface technology, we are now observing a converging field of research that is generating a steadily growing number of applications through increasing coherence. We would like to emphasize here some points that we consider essential for the future prospects of the field.

6.1. Integration of Subdisciplines is Necessary for Applications

The merging of the subareas is already evident from many examples in this article, such as the use of tile-based assembly methods for the production of origami superstructures (Section 2.2), the exploitation of recombinant protein technology to enable functional DNA nanostructures for live science applications (Section 2.3), the use of DNA nanostructures for creating colloidal superstructures that in turn can be fine tuned and functionalized with proteins (Section 3), the implementation of functional nucleic acid motifs into polymeric materials (Section 4), or the integration of DNA-surfaces to enable efficient manufacture of heterogeneous superstructures applicable in biology and material sciences (Section 5). Based on

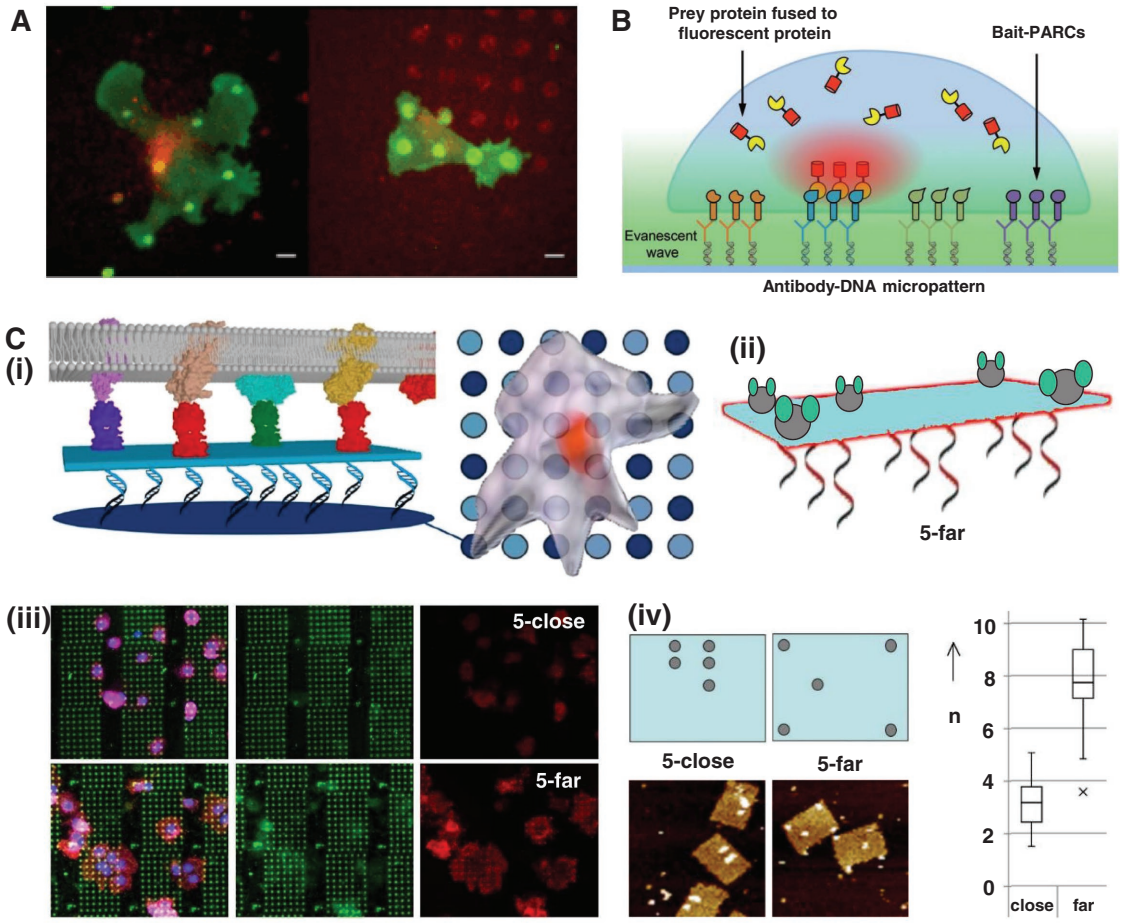

Figure 7. DNA surfaces for investigation of intracellular processes. A) Total internal reflection fluorescence microscopy (TIRFM) images indicate the colocalization of cellular epidermal growth factor (EGF) receptors (green) on micropatterns of DNA-immobilized EGF ligands (red). Scale bar, 10 µm). Reproduced with permission.[180a] Copyright 2013, Wiley-VCH. B) Bait-presenting artificial receptor constructs (Bait-PARCs) are used to transfer a surface-bound micropattern into living cells to enable analysis of the interaction with fluorescently labeled prey proteins. Reproduced with permission.[180b] Copyright 2013, Wiley-VCH. C) Multiscale origami structures as interface for cells (MOSAIC). i) General principle of MOSAIC wherein protein-decorated DNA origami nanostructures are site-specifically immobilized on DNA micropatterns (green in (iii)). EGF-modified DON constructs (such as 5-far in (ii,iv)) were used to establish EGFR activation depends on nanostructural features, as quantified by immunohistological staining (red spots in (iii)) and statistical evaluation of activated spots/cell (*n*) in (iv)). Reproduced with permission.[183] Copyright 2015, Wiley-VCH.

these examples, we have illustrated that research on DNA-based materials has already produced a first generation of applications in sensing and medicine[12a,67,185] and the second generation, is already emerging in the form of, e.g., advanced material surfaces, smart carriers, and robots for biomedicine[33] or devices for plasmonics.[50a,96] In order to open up these and other fields of application, the increasing implementation of engineering sciences is of great importance.

6.2. Microfluidics, Robotics, and Data-Driven Science

These are key areas of engineering, which are increasingly implemented in the production of DNA nanostructures, their manipulation, and application. Examples include machine-assisted production and analysis of DNA molecules[33] and nanoparticles,[186] or microfluidic platforms for manipulation of DNA nanostructures[187] and handling and analysis of DNA chips.[13,144b,145] Indeed, microfluidics should be regarded as a key enabling technology, because it offers an extraordinary high degree of control over temperature profiles and diffusion-based mixing[188] along with an excellent connectivity to high-throughput liquid handling, robotics, (in-line) analytics, and data acquisition.

The latter point is of great relevance because end-to-end automated technology platforms, covering the entire process from synthesis to functional analysis, are capable to deliver enormous amounts of data. This "big data" can be used, in a "data-driven science" approach,[189] to gain new insights into complex processes that are not accessible by experiment or simulation. At the moment, intensive work is being conducted on the development of end-to-end automated platforms for synthetic organic chemistry[190] and synthetic biology[191] as well as for biocatalysis[46] and materials research.[192] Taking into account that i) DNA-templated synthesis has emerged as an almost routine tool for materials discovery[193] and ii) DNA nanotechnology is intrinsically tied to data sciences (Section 2.4),[57,58c] it is the next logical step to develop technical platforms that can be

used for the automated development of customized DNA-based material systems. As explained below, such systems could, in the long run, lead to the development of better technical materials and more sustainable production processes.

6.3. Scale-Bridging Manufacturing and Compartmentalization will Open Up New Horizons

Nature shows impressively that systems of almost incredible complexity can be created with minimal energy consumption but maximal capabilities for programmable replication, repair, regulation, and environmental responsiveness. The living systems are hierarchically organized ranging in size from nanometers of molecules to meters of higher organisms. In order to equip these biosystems with their extraordinary complexity and functionality, nature has invented "compartments" as essential construction elements (e.g., supramolecules, organelles, cells, tissues, and organs). These hierarchical systems are based on cross-scale constructions that arise from self-organization under nonequilibrium conditions. With this strategy, even the integration of molecular quantum systems is possible.[194] In the case of technical systems, top-down microengineering gives access to numerous products with dimensions in the low micrometer range, however, to further reduce the size, manufacturing processes become much more complex, energy-demanding, and expensive. Therefore, it is of utmost importance for the future to develop material systems with which biological construction principles—scale-bridging construction from the sub-nanometer to the macroscopic range, compartmentalization, and self-organization—can be mimicked and implemented to devise new smart products and resource-saving manufacturing processes.

6.4. DNA-Based Material Systems are Suitable for this Daunting Task

Due to their chemical structure, DNA materials can undoubtedly be used to build scale-spanning structures ranging from the atomic regime of base pairs to the 100 nm regime of origami structures (Section 2). In a bottom-up approach, the rational design and addressability of nucleic acid nanostructures can be used for tailored mesoscopic polymer materials, which has already been demonstrated for shape and size control of amphiphilic assemblies (Section 4.1).[108,109] Furthermore, ongoing work is already focusing on the combination of top-down and bottom-up fabrication methods to integrate supramolecular DNA structures into micrometer-scale functional units (Section 5), and these scale-bridging approaches have led to first examples of novel sensors for the analysis of cells,[183] nanophotonic superlattices,[96,171b] or nanoscale robotics controlled by microelectronics.[65] Due to their scale bridging character and their excellent biocompatibility, DNA materials should also be useful for refined biointerfaces that intimately connect technical microdevices with the nanoscale circuitry of living organisms.[195] Last but not least, since DNA-based materials can be produced using nucleic acid-metabolizing and modifying processes, they should also be amenable for self-organization processes under nonequilibrium conditions. Therefore, and by taking advantage of the rapid developments of synthetic biology,[33] it seems possible that the further development of DNA-based material systems can even lead to biomimetic production processes with which complex functional goods can be manufactured.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

DNA-directed immobilization, DNA–nanoparticle conjugates, DNA nanostructures, DNA polymers, DNA–protein conjugates

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