Precise arrangement of individual photonic building blocks in space, including metal nanoparticles (NPs), quantum dots (QDs), nanodiamonds, fluorophores, etc., is crucial for creation of advanced nanophotonic systems with tailored optical properties and novel functionalities. Despite the remarkable advances in nanophotonics enabled by top-down nanofabrication techniques, critical limitations remain. For instance, realization of three-dimensional complex nanostructures, especially with structural reconfiguration as well as organization of nanoscale components of different species in close proximity, is still challenging.

Molecular self-assembly offers an alternative to circumvent these limitations. In particular, the DNA origami technique identifies a unique route for the realization of nanophotonic structures with hierarchical complexities. DNA origami can be created in almost any arbitrary shapes. Such origami structures can then serve as templates for assembly of a variety of functional components with nanoscale precision.

Figure 1 illustrates the workflow of the DNA origami fabrication. Long single-stranded DNA (ssDNA) with known sequence (called “scaffold” and derived from the single-stranded genome of the M13 bacteriophage) is mixed with a set of short synthetic ssDNA (called “staples” and usually purchased from oligonucleotide synthesis vendors) (Figure 1a).

Each “staple” strand possesses a unique sequence and binds the scaffold at specific positions. This makes DNA origami fully addressable. The staple strands fold the scaffold strand into a prespecified two- or three-dimensional shape (Figure 1b). ssDNA extensions (called capture strands) or chemical modifications, e.g., biotin and amino groups on origami, can serve as binding sites for the precise arrangement of nanoscale components including proteins,15–17 metal NPs,15–17 QDs,22–24 and nanodiamonds,25,26 which are functionalized with complementary binding modifications (Figure 1b). Fluorophores are often directly incorporated into the DNA “staple” strands for arrangement on DNA origami structures.27–32

Generally, the workflow of a DNA origami-templated nanophotonic system starts with identification of individual components of interest and their desired relative spatial arrangement. Subsequently, a DNA origami structure with certain geometry is conceived to template such an arrangement. The DNA origami structure is designed using computer-aided design (CAD) open source software, e.g., caDNA3033 (Figure 1c).
Figure 1. Principle of the DNA origami folding, design, and assembly. (a) DNA origami consists of long single-strand DNA ("scaffold") and several hundreds of short ssDNA strands ("staples"). (b) Upon thermal annealing, the "staples" fold the "scaffold" strands into two- or three-dimensional structures with predesigned shapes. DNA origami structures can be modified with ssDNA extensions that serve as binding sites for further assembly of different nanoscale components, including fluorophores, quantum dots, nanodiamonds, metal nanoparticles, proteins, etc., into almost arbitrary geometries with nanometer precision. (c) DNA origami structures are usually designed with caDNAno software. (d) Sequences of the "staple" strands required for the assembly are generated. (e) "Staple" strands are usually purchased in multiwall plates from commercial vendors specializing in automated DNA synthesis. Single-stranded phage DNA is typically used as scaffold for DNA origami structures. The scaffold strands can be produced by M13 phage amplification or purchased from several suppliers. Scaffold is mixed with "staple" strands (with a large excess), and the origami structures are assembled through thermal annealing. The structures are usually purified before being used as templates for further assembly. (f) Atomic force microscopy (AFM) and transmission electron microscopy (TEM) are often used to characterize two- and three-dimensional origami structures.

1c). As output, a set of DNA sequences for the staple strands (Figure 1d) is generated and sent to commercial vendors specializing in automated DNA synthesis (Figure 1e). The obtained staple strands are mixed with the scaffold strand of choice (produced by M13 phage amplification or purchased) followed by thermal annealing. The origami structures are then purified for structural characterizations (Figure 1f). Functionalization of individual components that can bind to the origami often utilizes conjugation with ssDNA strands, complementary to the capture strands. Another frequently used method relies on incorporation of biotin/streptavidin modifications for binding to the origami through streptavidin–biotin interactions. Less often used are alkyne, amino, and azido functional groups.

There are excellent reviews and perspectives that elucidate the technical aspects of the DNA origami technique, including designing, assembly, and characterization of DNA origami structures. Since its birth, the DNA origami technique has been widely used in a wealth of research fields for instance, drug delivery, artificial nanopores, single molecule studies, nanometry and macroscopy standards, etc. In this perspective, we will focus on the applications of DNA origami in nanophotonics. Particularly, we highlight several promising directions, along which the DNA origami technique may help to solve the present technological challenges and open new pathways to realizing nanophotonic systems with novel functionalities.

DNA ORIGAMI FOR NANOPLASMONICS

Localized surface plasmon resonances result from collective oscillations of the conduction electrons in metal NPs, when they interact with light. The plasmon resonances can be tuned by the compositions, shapes, and local surroundings of the metal NPs. Plasmons of metal NPs placed in close proximity can be coupled, mixed, and hybridized. Such coupling is very sensitive to the relative arrangement of the individual NPs in space. On one hand, this provides a unique opportunity to engineer near- and far-field optical properties of the constructed nanostructures. On the other hand, it poses many technical challenges to assemble metal NPs into well-defined configurations, especially in three dimensions.

At the end of the 20th century, DNA emerged as one of the most versatile construction materials at the nanoscale. Utilization of DNA for assembly of metal NPs into larger structures was first demonstrated by Alivisatos and Mirkin in 1996. Since then, DNA has been widely used for direct assembly of NPs into a variety of structures with increasing complexities. Impressive progress has been witnessed in DNA-based assembly of two- and three-dimensional periodic lattices. However, fabrication of well-defined plasmonic clusters composed of discrete numbers of interacting metal NPs remained challenging until the introduction of the DNA origami technique in 2006 by Rothemund. Inherent addressability of the DNA origami made it ideally suitable for templated assembly of plasmonic nanostructures. Nevertheless, several technical challenges had to be overcome in order to achieve plasmonic systems with distinct optical properties. The
The first advancement was the realization of high-yield assembly of NPs on DNA origami templates.\textsuperscript{15,82--84} (Figure 2a–d) Metal NPs fused together on DNA origami through electroless metal deposition.\textsuperscript{85} (Figure 2e–h) Sophisticated metal NP assemblies on three-dimensional complex origami templates.\textsuperscript{19,88--90} (Figure 2i) Metalization of DNA origami ring structures.\textsuperscript{91} (Figure 2j) DNA origami structures as molds for growth of metal colloids with defined morphologies.\textsuperscript{92} (Figure 2k) Chiral plasmonic assemblies with gold NRs.\textsuperscript{93} (Figure 2l) DNA origami-templated assembly of helical NP assemblies with strong plasmonic circular dichroism in the visible spectral range.\textsuperscript{94} (Figure 2m) DNA origami-templated assembly of helical NP assemblies with strong plasmonic circular dichroism in the visible spectral range.\textsuperscript{94} (Figure 2n) Chiral plasmonic assemblies with gold NRs.\textsuperscript{95} (Figure 2o) Plasmonic nanostructures with dynamically controlled optical responses enabled by stimulus-driven DNA origami templates.\textsuperscript{96--99} (Figure 2p) Plasmonic walker on DNA origami.\textsuperscript{100} Scale bars: (a–c) 100 nm, (d) 20 nm, (e) 100 nm, (f) 50 nm, (g) 30 nm, (h) 50 nm, (i,j) 100 nm, (m) 20 nm, (n,o) 50 nm.

Initially, single-layer DNA origami and spherical gold nanoparticles (AuNPs) were widely used due to the ease of design and fabrication. DNA conjugation with AuNPs was done through a gold–thiol bond.\textsuperscript{16,82,85} Soon after this, methods for assembly of silver spherical NPs\textsuperscript{84} and anisotropic gold nanorods (NRs)\textsuperscript{86} were developed. In addition, further advancement of the origami technique, for instance, extension into three dimensions\textsuperscript{4} and introduction of twisted and curved structures,\textsuperscript{87} enabled fabrication of DNA origami-templated assemblies of metal NPs\textsuperscript{19,88--90} with unprecedented complexities (Figures 2e–h).

Apart from the well-established approach to assemble metal NPs on DNA origami templates,\textsuperscript{15,82--84} (Figure 2a–d) there are also several other solutions. Attempts were made to metalize the entire origami structures\textsuperscript{92,93} (Figure 2i). For metallization, DNA templates were first seeded with small gold or silver clusters followed by electroless deposition of gold for further metal growth. Electroless metal deposition not only enlarged the size of the NPs\textsuperscript{84} but also could fuse the particles together\textsuperscript{95} (Figure 2j). DNA origami structures were also used as molds for growth of metal colloids with complex shapes.\textsuperscript{96,97} A small particle served as seed (Figure 2k), and the origami structure restricted the growth of the metal into a specific and predefined shape (Figure 2l). In addition, standard silicon etching and metal deposition techniques were used to transfer the shape of two-dimensional DNA origami objects into metal nanostructures.\textsuperscript{98,99}

The ability to arrange metal NPs on DNA origami templates with high yield and accuracy opened the pathway to construct plasmonic structures with novel optical properties. In 2012, Liedl and Ding used DNA origami to arrange metal NPs into helical assemblies,\textsuperscript{94,100} respectively (see Figure 2m), which exhibited strong plasmonic circular dichroism in the visible spectral range, originated from collective interactions of the metal NPs in the helical geometry.\textsuperscript{101} Since then, DNA origami has been widely used as templates for assembly of spherical NP\textsuperscript{85,90,102,103} and NRs\textsuperscript{104--108} (Figure 2n–p) into chiral plasmonic structures.\textsuperscript{109--111} Utilization of NRs provides an additional benefit for generating a stronger optical response compared to spherical NPs.\textsuperscript{112} However, assembly of NRs on
DNA origami is technically more challenging. Another example of origami-based plasmonic nanostructures with novel optical responses is a ring of NPs, which exhibited both electric and magnetic resonances at visible frequencies\(^8\) (Figure 2f). Other progresses have also been achieved in fabrication of NP-based waveguides for energy transfer.\(^11\)\(^3\)\(^-\)\(^1\)\(^1\)\(^5\)

Importantly, DNA origami-templated plasmonic nanostructures are not limited to static systems.\(^1\)\(^1\)\(^6\) The solution-based nature of DNA structures and dynamic DNA nanotechnology provides a unique way to actively manipulate both spatial and temporal arrangements of metal NPs, enabling reconfigurable plasmonic systems with dynamically controlled optical responses. The Liedl group demonstrated reversible plasmonic circular dichroism responses by orientation switching of the origami-templated chiral plasmonic assemblies on the surface.\(^1\)\(^1\)\(^9\) Reconfigurable plasmonic structures were also realized by assembly of metal NPs on dynamic DNA origami templates, which were switched among several configurations by external stimuli (Figure 2o). The spatial reconfiguration of the DNA origami templates resulted in rearrangement of the plasmonic NPs and therefore altered optical responses.\(^1\)\(^2\)\(^0\)\^-\(^1\)\(^2\)\(^3\)

There are various ways to control the configurations of the DNA origami templates.\(^1\)\(^1\)\(^6\) Probably the most versatile and thus widespread approach is based on the so-called "toehold-mediated strand displacement reaction", which utilizes DNA strands as fuel to regulate spatial configurations.\(^1\)\(^2\)\(^4\)\^-\(^1\)\(^2\)\(^5\) Also, photoresponsive molecules such as azobenzene can be employed through incorporation with DNA to activate responses upon light stimuli.\(^1\)\(^2\)\(^1\)\^-\(^1\)\(^2\)\(^4\) Recently, selective manipulation of DNA origami-based plasmonic structures has been demonstrated, taking the advantage of the pH sensitivity of the DNA triplexes.\(^1\)\(^2\)\(^5\)\^-\(^1\)\(^2\)\(^6\) More intriguing approaches could include reversible reconfiguration based on shape-complementarity or structural adaptions of aptamers to the presence of target molecules.\(^1\)\(^2\)\(^9\)\^-\(^1\)\(^3\)\(^1\) In addition to using reconfigurable DNA origami templates, it is also possible to rearrange metal NPs on static DNA origami templates (see Figure 2p). In this approach, NPs are either guided by the so-called molecular walkers or act as walkers themselves.

### DNA ORIGAMI FOR FLUORESCENCE IMAGING

Since its invention, DNA origami has found numerous applications in the field of fluorescence imaging,\(^1\)\(^3\)\(^5\) owing to its bottom-up self-assembly properties and the availability of dye-modified oligonucleotides. Especially, the combination of DNA origami nanostructures with single-molecule fluorescence imaging has been exploited to achieve nanoscale spatial resolution below the diffraction limit.\(^1\)\(^3\)\(^6\)\^-\(^1\)\(^3\)\(^7\) In this Perspective, we will focus on the recent advances in DNA origami-based super-resolution imaging, with an emphasis on DNA-PAINT and its variations.

**Figure 3.** DNA origami for fluorescence applications. (a) Super-resolution imaging by DNA-PAINT. Short dye-labeled oligonucleotides bind transiently to their complementary target on a DNA origami structure. The transient binding creates an apparent "blinking" used for stochastic super-resolution microscopy.\(^1\)\(^4\)\(^0\) (b) Tunnel-like DNA origami with DNA-PAINT docking strands at red-colored faces imaged using transmission electron microscopy, diffraction-limited microscopy, and DNA-PAINT super-resolution microscopy.\(^1\)\(^4\)\(^7\) (c) Exchange-PAINT enables spectrally unlimited super-resolution multiplexing. Distinct molecular targets are labeled with orthogonal docking strands. Subsequent imaging is performed sequentially with alternating washing and imaging rounds using the same color fluorophore for all rounds.\(^1\)\(^4\)\(^7\) (d) DNA-PAINT’s resistance to photobleaching in combination with intricate drift correction enables ultra-resolution imaging, resolving docking strands spaced 5 nm apart on DNA origami structures.\(^1\)\(^5\)\(^3\) (e) 3D-DNA-PAINT image of a DNA tetrahedron.\(^1\)\(^4\)\(^6\) (f) Origami’s precise control over spatial positioning and stoichiometry enables the construction of 124 ‘metall fluorophores’ for diffraction-limited barcoding applications using only three spectral colors and five prescribed intensity levels.\(^1\)\(^3\)\(^4\)
techniques is attractive due to origami’s unique spatial addressability on length scales ranging from a few to hundreds of nanometers combined with exquisite positioning accuracy. One of the first applications of DNA origami in single-molecule fluorescence was its combination with emerging super-resolution techniques to create nanoscopic rulers for resolution calibration. Stochastic super-resolution techniques circumvent the classical diffraction limit of light by “switching” fluorophores from the so-called dark- to bright-states and back, thus only activating and localizing the emission of a single dye molecule in a diffraction-limited area at every given point in time. Time-lapsed acquisition and repeated switching then eventually allow for complete reconstruction of all molecule positions, yielding a super-resolution image. While super-resolution techniques readily achieve spatial resolutions down to a few tens of nanometers, it is hard to precisely quantify their achievable spatial resolution due to the lack of versatile nanoscale rulers. However, DNA origami nanostructures are ideal calibration standards due to their high folding yield and subnanometer positioning accuracy.

DNA origami nanostructures are also ideally suited as test structures for the development of new imaging approaches. While stochastic super-resolution techniques such as stochastic reconstruction microscopy (STORM) or photoactivated localization microscopy (PALM) are already starting to transform the way we look at biology today, their experimental implementation—especially with regard to multiplexed detection, i.e. the imaging of multiple targets—is still challenging due to the necessity to carefully adjust buffer conditions for each fluorophore species. DNA Points Accumulation In Nanoscale Topography (DNA-PAINT) was developed to overcome some of the difficulties of incumbent super-resolution approaches. In DNA-PAINT, stochastic “blinking” of targets is achieved by the transient hybridization of short, dye-labeled oligonucleotides (called “imager” strands) to their complementary strands (called “docking” strands) on a target of interest. Unbound imager strands freely diffuse in solution, adding only minimal background when image acquisition is performed in total internal reflection or oblique illumination. As DNA-PAINT uses transient hybridization of short oligonucleotides to create the necessary blinking in stochastic

Figure 4. DNA origami for hybrid nanophotonic systems. (a) Directing light through FRET along fluorophores. A single fluorophore (depicted in green) is employed as “jumper”. (b) Sketch of a rectangular DNA origami structure with a single AuNP and fluorophore employed to study the distance dependence energy transfer. (c) Optical antenna dimer for fluorescence enhancement. (d) The incident light polarization is rotated to match the dimer orientation. (e) Optical antennas dimer for SERS applications. (f) Single molecule SERS signal obtained with gold dimer antenna covered with silver to further reduce the gap distance. (g) Sketch of a DNA origami structure with a single AuNP and a fluorophore pair for plasmonic enhanced FRET studies. (h) Plasmonic NPs-based optical waveguide for energy transfer over 50 nm. (i) Study of the emission coupling between single molecules and NPs using super resolution techniques. (j) Combination of DNA origami structures and lithographic plasmonic structures such as zero mode waveguides and (l) photonic crystal cavities. Scale bars: (j) 200 nm, (l) 250 nm (top), and 500 nm (bottom).
reconstruction microscopy, it is ideally suited to visualize DNA nanostructures. With obtainable spatial resolution on the nanometer scale, features such as the two faces of the DNA origami structure—spaced only 16 nm apart—are clearly resolvable (Figure 3b).

In DNA-PAINIT, imaging and labeling probes can actually be seen as DNA barcodes owing to their unique sequences of the DNA bases. Thus, multiplexing can be easily achieved by sequential imaging of different target molecules labeled with orthogonal docking strands (Figure 3c). In this approach, called Exchange-PAINT,147 the first target (e.g., P1) is imaged by the complementary strand (e.g., P1*, Figure 3c). Then a washing buffer is introduced to remove P1* from the sample, followed by the introduction of P2* imager strands to visualize the second target. This imaging and washing procedure is repeated until images for all targets are successfully acquired and pseudocolors were assigned. Exchange-PAINT now enables spectrally unlimited multiplexing, only restricted by the amount of orthogonal DNA sequences, which could easily reach hundreds under appropriate experimental conditions. Similar exchange strategies can be applied for other super-resolution approaches as well, using slightly more stable hybridization strategies.

Due to DNA-PAINIT’s resistance to photobleaching (imager strands are constantly replenished from solution), very high spatial resolutions are achievable by extracting the maximum number of photons from a dye-labeled strand before unbinding from its target. In combination with intricate drift correction,149 DNA-PAINIT achieves molecular-scale spatial resolutions of better than 5 nm, as demonstrated by imaging the MPI and LMU logo on DNA nanostructures shown in Figure 3d with single binding sites spaced 5 nm apart.153 3D super-resolution imaging of complex 3D DNA origami nanostructures is also straightforward to implement by using a cylindrical lens in the microscope imaging path to encode the 3D location in an elliptical point spread function.146 (Figure 3e).

Further applications of DNA-based super-resolution imaging have demonstrated quantitative target detection in vitro and in situ in single cells, allowing researchers to count integer numbers of biomolecules based on their kinetic signature without spatially resolving them,150 even allowing single nucleotide mismatch discrimination of RNA targets.151 Also, DNA origami is ideally suited for applications that do not require super-resolution. In a recent study, DNA origami structures have been used to enable the construction of novel fluorescent probes, termed “metafluorophores”, that enable diffraction-limited imaging with up to 124 distinct colors.154 This was achieved by using the exquisite spatial arrangement accuracy of origami to prepare objects with a defined number of dyes, thus allowing for the construction of intensity barcodes (Figure 3f).

## DNA ORIGAMI FOR HYBRID PHOTONIC STRUCTURES

One of the main advantages of the DNA origami technique lies in its capacity to self-assemble different species with precise stoichiometry control and nanometer precision. Perhaps one of the simplest examples of a hybrid photonic structure consists of a pair of fluorophores placed in close proximity. For distances typically below 10 nm, fluorescence resonance energy transfer (FRET) can occur between the fluorophores. The incorporation of fluorophores to DNA origami structures is straightforward. Staple strands labeled at a desired position with a palette of fluorophores across the visible range are commercially available. Most fluorophores are incorporated to the DNA sequences forming the staple strands through one linker. Although this approach guarantees a nanometer positioning of the fluorophore within the DNA origami structure, its orientation cannot be determined and will depend among other factors on the resulting fluorophore’s charge.

Figure 4a depicts a fluorophore system self-assembled onto rectangular DNA origami. The precise arrangement of the fluorophores enables light guiding via FRET155 with an energy path that can be controlled by the presence of a fluorophore acting as a “jumper”. Furthermore, the DNA origami technique has also been exploited to self-assemble fluorophore systems for fabrication of artificial light harvesting antennas.25,30,51

In addition to a combination of fluorophores,152 another type of widespread hybrid photonic structures comprises optical light sources coupled to optical antennas.156 Typical examples of the light sources include fluorophores and QDs, whereas optical antennas generally consist of nanometer-sized metal structures that exhibit localized surface plasmon resonances in the optical range. It is worth discussing the advantages of the DNA origami technique for the fabrication of this type of structures. Optical antennas have been successfully fabricated using ion or electron beam lithographic techniques.157 However, these top-down approaches have several shortcomings. First, fabrication is serial by nature and requires specialized and costly equipment. Second, they often yield rough surfaces and polycrystalline metals with grains, which hamper the properties of the designed structure and reduce the resonance quality.158 However, the most critical limitation of these techniques is that it is extremely challenging to position a single light source at the focus of an optical antenna.159 In one example, a demanding multistep lithographic procedure was employed to place a single QD at the focus of a Yagi-Uda antenna,160 whereas in another work an undefined number of fluorophores were immobilized with the aid of a polymer layer in a region including the focus of a bow-tie antenna.157 In contrast to the top-down approaches, the bottom-up DNA origami technique can overcome the aforementioned shortcomings. It is parallel in nature and capable of self-assembling colloidal crystalline metal NPs with higher quality resonances. Finally, both single light sources and optical antennas can be self-assembled with nanometer precision and stoichiometric control.

The first experiments in this direction are sketched in Figure 4b. The same rectangular DNA origami structure was used to study the distance dependent energy transfer between a single fluorophore and a single 10 nm AuNP161 (Figure 4c). This approach enabled a detailed study of the manipulation of fluorescence with plasmonic NPs at the single molecule level, including the polarization in near field excitation,162 the controlled increase in photostability,163,164 together with the determination of how fluorescence rates are affected in the vicinity of NPs.165 The flexibility of the DNA origami technique was also exploited to self-assemble dimer antennas (Figure 4d). Initial efforts were conducted toward fluorescence enhancement applications and included two AuNPs (with sizes up to 100 nm) and a single fluorophore at the hotspot self-assembled onto a 3D pillar shaped DNA origami structure.156 The resulting gap between the NPs was higher than 20 nm which limited the fluorescence enhancement to 2 orders of magnitude. Additional developments on the NPs incorporation
and origami design\(^{167}\) lead to a reduction of the gap to approximately 10 nm and an increase of the fluorescence enhancement over 3 orders of magnitude.\(^{168}\) Furthermore, with these results self-assembled optical antennas managed to outperform top-down lithographic antennas in terms of fluorescence enhancement and single molecule detection at elevated concentrations. Recently, dimer antennas based on colloidal silver NPs have been self-assembled using the DNA origami approach. These structures exhibit a broadband fluorescence enhancement throughout the visible spectral range.\(^{169}\) DNA origami based dimer antennas were also employed for surface-enhanced Raman spectroscopy (SERS) applications (Figure 4e). Initial experiments addressed an undefined number of molecules.\(^{170−172}\) Single molecule SERS (Figure 4f) resolution was later attained through a drastic reduction of the interparticle gap. Two different approaches were followed, a silver layer was grown onto the AuNPs\(^{173}\) (Figure 4g) or shrinking of the DNA origami structure was thermally induced, reaching a gap size of a few nanometers.\(^{174}\) Recently, strong SERS enhancement and single molecule detection were achieved using a bowtie antenna composed of two gold triangles on DNA origami.\(^{175}\) DNA origami structures have also been employed to study the influence of metal NPs on FRET processes\(^{176}\) (Figure 4h). These studies, which further demonstrate the DNA origami capabilities to self-assemble a pair of fluorophores and a metal NP in a precise geometry, showed that the energy transfer rate between the fluorophores can be moderately enhanced. Additionally, energy transfer along a plasmonic waveguide composed of five metal NPs bound to a DNA origami structure has also been demonstrated.\(^{114}\) In this work, the energy transfer along 50 nm could be reversibly switched by changing the position of the center particle (Figure 4i).

Not only the interaction of fluorophores and optical antennas consisting of metal NPs has been studied in terms of fluorescence enhancement, SERS, and FRET efficiency, but also the first steps toward the analysis of the effect of optical antennas on the emission properties of fluorophores were taken.\(^{177}\) Through a combination of DNA nanotechnology, plasmonics, and super-resolution microscopy, the quantitative study of the emission coupling of single molecules to optical nanoantennas revealed that it can lead to mislocalizations in far-field images (Figure 4j).

Another type of hybrid nanostructure includes the combination of DNA origami structures with the top-down lithographic photonic structures. The first efforts toward the fabrication of these types of hybrid nanostructures included the use of DNA origami structures as sizing units to increase the single occupancy of zero-mode waveguides (also termed nanoapartures)\(^{178}\) (Figure 4k). This development could in principle improve the performance of real-time DNA sequencing approaches.\(^{179}\) Recently, DNA origami structures have also been employed to control the coupling between fluorophores and photonic crystal cavities\(^{180}\) (Figure 4i). This approach enabled the mapping of the local density of states with subwavelength resolution.

Finally, although the DNA origami arises as the most promising technique to build complex hybrid nanostructures, for some photonic applications, for example in the field of metamaterials, functionality is reached through the combination of several nanostructures arranged in macroarrays. The first steps to creating an array of DNA origami structures were taken with nanoimprint techniques\(^{181}\) whereas other approaches such as optical printing\(^{182}\) or STED lithography\(^{183}\) have not been explored yet.

### Outlook and Future Directions

DNA origami-based fabrication of nanophotonic systems has advanced very rapidly in the past decade.\(^{135,184−186}\) It has become a well-established technique for assembly of metal NPs into well-defined clusters, 1D chains, 2D arrays, and 3D lattices.\(^{85,89,94,187−192}\) The ability to assemble various types of NPs into periodic lattices is very promising for discovery of novel cooperative optical effects. So far, broader applications of the DNA origami technique for plasmonic materials, and materials science in general, have been restricted by the cost of large-scale fabrication. However, very recently biotechnological methods have been successfully developed for mass-production of DNA origami structures, significantly decreasing the cost.\(^{193}\)

Incorporation of dynamic responses into DNA origami-based plasmonic structures affords extra functionalities. In addition, dynamic DNA origami-based plasmonic structures are excellent candidates for the generation of smart plasmonic probes for biochemistry and life sciences. One of the main advantages of such probes is the unprecedented level of programmability. Target–probe interactions, transduction mechanisms, and output signals are highly customizable and can be tailored to specific needs. Employment of such smart probes also for in vivo monitoring of cellular processes is an open challenge due to the poor stability of DNA origami structures under physiological salt conditions. Coating of DNA origami with proteins\(^{194}\) or peptides containing block copolymers\(^{195,196}\) has been shown to improve stability. Also, DNA objects based on the so-called wireframed design are intrinsically more stable at low salt concentrations compared to densely packed structures.\(^{197,198}\) In addition, recent developments in utilization of RNA as construction material\(^ {199–201}\) are expected to expand the category of templates available for assembly of functional photonics elements. RNA provides several benefits: the structures can be genetically encoded, can be expressed, and function inside cells. Furthermore, RNA can fold during transcription, which eliminates the need for thermal annealing.

In order to realize the full potential of the DNA origami technique and DNA-based imaging approaches in combination with single-molecule fluorescence for the biological and biomedical application, several key challenges have to be solved. One of the main roadblocks moving forward for in situ imaging inside cells will be labeling: How can one quantitatively (i.e., 1:1 stoichiometry) and efficiently (ideally 100% target coverage) label proteins inside cells using DNA molecules. DNA origami structures themselves will not be suitable as barcoded labeling probes, due to their extended size; however, they can provide a valuable programmable test platform to evaluate novel, orthogonal labeling approaches for proteins such as small molecule binders,\(^{202}\) nanobodies,\(^{203}\) or aptamers.\(^{204}\) Labeling probes such as the metallfluorophores for the intensity barcoding discussed above could be adapted to only assemble from small, monomeric units upon detection of a trigger sequence in situ inside a cell. In combination, novel labeling and imaging approaches using structural and dynamic DNA nanotechnology could bring Systems Biology to the single cell level, eventually allowing researchers to analyze network-wide interactions of a multitude of biomolecules in situ with highest spatial resolution.

The DNA origami technique enabled tremendous progress in the fabrication of hybrid structures for photonics
applications. Currently, dimer optical antennas based on metal NPs can reach single molecule SERS sensitivity and outperform lithographic antennas in terms of fluorescence enhancement. These developments render DNA origami based optical antennas promising devices for diagnostics, DNA sensing, and light harvesting applications. Further control of the gap of dimer optical antennas might be exploited for single molecule strong coupling studies, among other quantum effects. The coupling between fluorophores and optical antennas might be optimized by controlling the relative orientation. To this end, commercially available doubly linked fluorophores might lead to a much higher control of the fluorophores dipole moment within the DNA origami structure. Along this line, for many applications it would be desirable to replace organic fluorophores with more stable single light sources with improved photophysical properties. Recently, QDs, as well as fluorescent nanodiamonds, were successfully incorporated to DNA origami structures. However, nanodiamonds have not been so far combined with optical antennas. Another promising direction is related to fabrication of optical antennas based on high-index dielectric NPs using the DNA origami technique. These particles, of materials such as silicon or germanium among others, attracted considerable attention since they arise as candidates to circumvent one of the main shortcomings of metal NPs, which are Joule losses.

The DNA origami technique provides a flexible platform to meet future nanofabrication needs in nanophotonics. The origami fabrication process uses standard biochemistry lab equipment, e.g., thermocyclers, centrifuges, etc. Computer-aided design software (caDNAo) and structure predicting tools (CanDo) are intuitive and freely available. All these factors make this technique accessible to anybody with the basic knowledge of DNA. We anticipate that this technique will be more adopted by the general nanophotonic community and will help to complement the existing nanofabrication toolbox. Without a doubt, such adaptations will stimulate a plethora of new exciting research areas and real-life applications.

### ACKNOWLEDGMENTS

This work was supported by the Academy of Finland (grant 308992 (A.K.)), the European Research Council (Starting grants: Dynamic Nano (N.L.) and MolMap (R.J.)), the Volkswagen foundation (N.L.), the Alexander von Humboldt-Foundation through the Sofja Kovalevskaja grant (N.L.), the Deutsche Forschungsgesellschaft (AC 279/2-1 (G.P.A.), JU 2957/1-1 (R.J.), SFB 1032 (R.J.)), the state ministry for research of Lower Saxony in the frame of the “Quantum- and Nanometrology” (QUANOMET) (G.P.A.), the Max Planck Society (R.J., N.L.), the Max Planck Foundation (R.J.), and the Center for Nanoscience (CeNS) (R.J.).

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