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Title

Three-Dimensional DNA-Programmable Nanoparticle Superlattices

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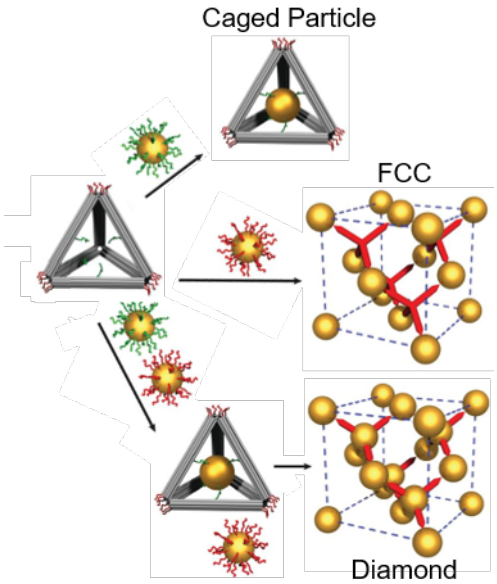
Abstract

In recent decades, there have been considerable efforts made in the design and synthesis of materials comprised of functional nanoscale particles. However, there is an increasing need to establish platform approaches for creating large-scale three-dimensional (3D) organizations from these particles, with the ability to control and prescribe ordered structures. The use of DNA, as a means of programming interactions between nanocomponents, provides powerful and tailorable means for the rational self-assembly of nanomaterials. The assembly pathway and assembled phases are highly dependent on both particle shape and interparticle interactions, governed by particle DNA coronas, binding modes, or linking mediators capable of complex topologies. This review highlights and discusses recent significant advancements in the field, as well as offers outlook towards future paths in the assembly of the DNA programmable three-dimensional nanoparticle superlattices.



Highlights:

- Tunable parameters and composition of DNA shells can be used to modulate the organization of isotropic nanoparticles
- Use of anisotropic geometries and anisotropic binding interactions of nanoscale objects can diversify assembled superlattices
- DNA origami can be used as complex linkers and cages to organize isotropic nanoparticles with designed interparticle topologies
- DNA origami can be used to scaffold a lattice, providing binding positions for particles to attach in a given organization
- DNA-based reactions provide capabilities to dynamically modulate the structure of three-dimensional assemblies

Introduction

DNA was first proposed as a structural material in the 1980's[1] and introduced as a means of establishing programmable bonds between colloidal nanoparticles (NPs) in the mid-1990's[2,3]. The approach of connecting nanoparticles using DNA consists of grafting chemically-modified, single-stranded DNA to the surface of NP sets, where these grafted DNA sequences form NP shells and can bind to complementary NP-grafted sets through hybridization based on Watson-Crick base pairing. Although the bonds between NPs can be readily formed using hybridization, the fundamental question for the field is how to utilize DNA programmable bonds for the creation of large-scale ordered materials from nanoscale building blocks, particularly in three-dimensions (3D), where creating nanostructured materials is a challenging task for conventional fabrication methods. The experimental realization of NP assembly of simple lattices was demonstrated by the groups of Gang[4,5] and Mirkin[6] about a decade ago, where it was shown that both the details of the DNA shell design and thermal pathway are important for the formation of periodic 3D organizations. While at the nanoscale particle size is comparable to the thickness of the DNA shell, micron-sized particles might inhabit different or similar regimes due to significant difference in the ratio between DNA shell size and of particles[7–9]. In fact, DNA-guided crystallization was first observed for such micron-scale particles by the Crocker group[7], and later expanded upon to include more complex assemblies and the examination of the kinetics of the assembly [9,10].

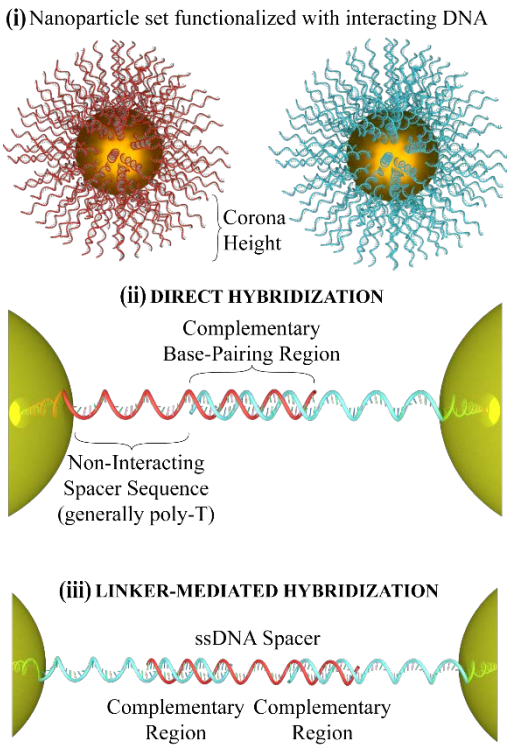


Figure 1: Common modes of DNA-based inter-particle bonds. (i) DNA-functionalized particles, with associated binding by (ii) direct hybridization or (iii) linker-mediated hybridization

To control the structure of DNA-guided NP assembly, it is necessary to mediate interparticle interactions; this can be done by controlling individual details of chain-chain hybridization and by modulating shell-shell interactions via shell design. For individual chains, there are several design strategies for realizing DNA bonds in order to link particles. The two most prevalent being either (a) Direct hybridization, whereby the DNA grafted to the particle surface is terminated by complementary ends, commonly referred to as "sticky ends"[4,6], or (b) Linker-mediated hybridization, whereby two non-complementary DNA shells are linked by a third DNA sequence that is partially complementary to both shells[5,11] (both modalities are illustrated in **Figure 1**). With respect to the DNA shells, the properties of shells are highly tunable through the choice of individual DNA motifs and grafting density, and this can be used as a means of exploring a wide range of self-assembled organizations. The complexity of hybridization between DNA chains from NP shells, and a need to arrange many bonds for NP lattice formation, requires a thermal annealing of an aggregated phase, without which

aggregates of NP remains amorphous with a structure locked in a meta-stable state along a complicated kinetic pathway[8,12].

Isotropic Nanoparticles

The various properties of the grafted DNA strands, including length, rigidity, sequence, and grafting density, can all be independently tuned to program inter-particle interactions, as well as the resultant assemblies[4,6,7,9,11,13–15]. It has been shown theoretically[13–15] and experimentally[4,6,7,9,11] that the tuning of the shells can affect the 3D ordering of NPs, phase diagram, and morphological appearance of crystallites. An example of this shell contribution is shown in **Figure 2A** and **2B**, where different spacer lengths in a direct binding form at[4] (**2A**) and a linker-mediated format (**2B**) [16] affect changes in the final organization. Multiple orthogonal DNA sequences can be grafted to the surface of a particle, allowing for tailoring shell composition and, consequently, for the precise tuning of attractive and repulsive inter-particle forces[12,15], as well as the capability to bind to other kinds of DNA-encoded particles[17,18].

The aforementioned self-assembly strategies were used to crystallize isotopically DNA grafted spherical NP's with close-packed crystal symmetries. Those with a singular shell type arrange in a face-centered-cubic phase (FCC), whereas a system with two particle shell types assembles with a body-centered-cubic phase (BCC)[4–6]. Combinations of nanoparticle shell height and particle size can be used to tune the crystallographic symmetries and lattice parameters of the assemblies of isotropic particles[16]. The grafting density is another tunable parameter of the DNA shell and can be used to drive the formation of specific 3D crystallographic organizations[19,20]. Although crystalline structures resulting from close packing of isotropic spheres may appear to be quite limited in scope, recent research efforts have begun to explore controlled crystallization in the presence a heterogenous mixtures of building blocks of varying sizes, which can provide a rich phase space of resulting structures (**Figure 2C).** This mixture of different particle sizes requires an associated particle ratio to determine crystal phase. This ratio has shown control not only over the crystal phase itself, but over the Wulff construct or aspect ratio of the assembled crystal[21]. Interestingly, that formation of 3D lattices depends also on the number of DNA in NP shells[22], as was investigated for NPs from different types of materials, where different attachment chemistries were employed. It was observed that crystallization can occur only for sufficiently high grafting number for both complementary particles, while intermediate and low grafting numbers would result in amorphous and cluster states.

Additional system parameters are also essential to the crystallization of NP systems, such as salt makeup in the buffer and concentrations of components and additives[23–25]. While base pairing can increase the binding affinity between DNA-coated particles through specific hydrogen bonding, monovalent salts screen the negatively-charged DNA to more easily allow interaction and close-packing. Magnesium, in the case of DNA-based systems, presents not only a higher ionic strength at a given concentration based on its divalent nature, but has the ability to bridge and stabilize electrostatic interaction between DNA strands[26]. The ability to modify salt-screening not only contributes to systems demonstrating different nearest-neighbor spacing within a given crystal phase, but the ability to switch between crystal phases, such as FCC and BCC[23,26,27].

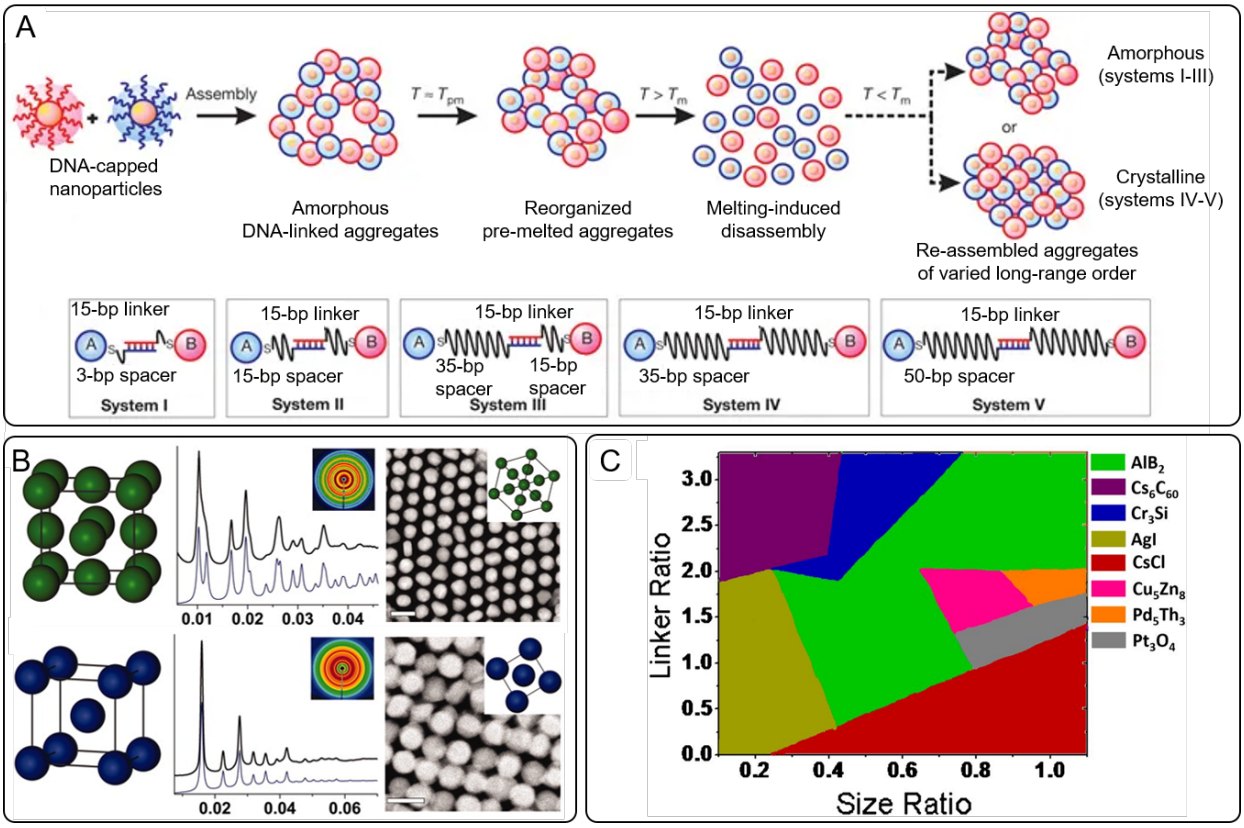


Figure 2: DNA corona design, including strength, softness, and linking ratios, induce significant difference in aggregation and crystal phases. (A) Direct hybridization between DNA-mediated between nanoparticles leads to either crystalline or amorphous states depending on the spacer and binding sequence combinations used in the design[4]. (B) A linker-mediated particle binding system provides different phases depending on linker format and length, with FCC (top) and BCC (bottom) shown with corresponding X-ray scattering and SEM imaging. Scale bars, 50 nm[16]. (C) Phase diagram of binary nanoparticle lattices based on the size ratio of particle hydrodynamic radii (nanoparticle radius plus DNA corona height) and linker ratio (number of grafted ssDNA linkers on nanoparticle)[19].

Anisotropic Nanoparticles and Patchy Interactions

Access to desired crystalline phases beyond that of close-packed systems requires the ability to modulate isotropic interactions, yet such approaches are quite limited in experimental realization. Alternatively, the assembled phase can be controlled through anisotropic interactions. It is possible to prescribe directional binding interactions between components either through nanoparticle shapes or prescription of anisotropic bonds on the surface of an isotropic particle, but the latter remains quite difficult to execute at the nanoscale. It has been predicted that solid polyhedral objects can organize into a variety of structures[28], but those phases might be significantly modified due to the effects of multiple chains[29] and complexity of interactions induced by DNA shells[30*,31*]. It has been demonstrated experimentally that a wide range of shaped nanoparticles can be synthesized in the laboratory, and using the same strategy of grafting DNA sequences to the surfaces can drive their assembly[32]. Increased diversity in the types of 3D organization can be

achieved using binary mixtures of particle shapes[33,34]. Normally, particles of different shapes would phase separate in solution; however, the interactions between complementary DNA shells drives their co-assembly. More complex NP morphologies, such as bipyramidal gold NPs, were used to assemble varying architectures of colloidal analogs for clathrates, an important crystal phase for host-guest chemistries at the nanoscale [35*], **Figure 3A.**

The contribution of DNA shells to effective NP shape can result not only in a diversity of phases with richness determined by particle placement, but also by particle orientations. Recently, the soft shell of nano-cubes has been shown to produce novel packing[36*]. While entropic considerations do come into play between the particle coronas, it is not only interaction between these brushes that accounts for crystal phase differences but the distribution of DNA itself on the particle. DNA of varying lengths display a dramatically different behavior for particle coating, whereby short strands (16 bases) coat the cube's faces and long strands (86 bases) preferentially bind particle edges. This yields a phase space of the assembled unit cell spanning from simple cubic, body center tetragonal, and finally to body-centered cubic, **Figure 3B**. Most importantly, these systems exhibit a breaking of orientational symmetry within their unit cell, a packing that has not been observed before for cube organization. In this so-called "zig-zag" arrangement (Fig. 3B, iii), the softness of the DNA shell reconciles the contradicting requirements of maximizing interaction with particles of complementary shells and minimizing interactions with particles possessing the same shell.

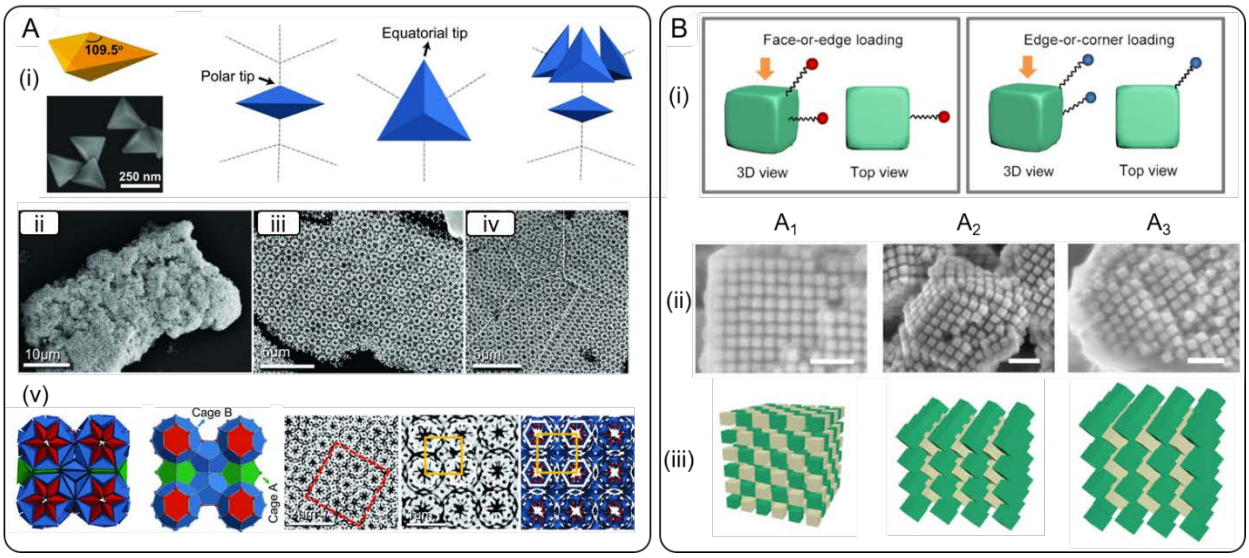


Figure 3: Anisotropic particles and controlled DNA binding can lead to complex, mixed phases. (A) (i) Schematic and SEM image of bipyramidal gold nanoparticle with associated SEM images showing (ii) an overall assembly, (iii) nanostructure clathrate lattice, and (iv) grain boundaries within the clathrate ordering. A schematic (v) demonstrates how the modelled structure translates to imaged patterns within SEM images and computational predictions[35*]. (B) (i) Definition of face-or-edge and edge-or-corner loading of DNA (ii) SEM images showing various structural configurations (SC, BCT, BCC) of crystallized nanoparticle cubes. Scale bars, 200 nm. (iii) 3D models associated with each of the structural configurations[30*].

There is an additional strategy for the prescription of anisotropic bonds—the controlled, anisotropic patterning of a particle's surface. The most common realization of this concept is through the synthesis and interaction of Janus particles, whereby half of the particle is functionalized and the other half left 'bare'. This patchy particle concept has been demonstrated for micron-sized particles[10]; however, it becomes considerably more difficult to achieve this experimentally with nanoscale colloids. Though methodologies have been used to demonstrate functionalization of particles, there are fewer examples of 3D assemblies, with most demonstrating assemblies using microparticles[10] and the assembly of clusters using nanoparticles[37,38]. Advances in nanoparticle patterning with DNA will open up the possibility of realizing high level control over three-dimensional assemblies[39–41].

Simulations using patchy particles are leading the way in demonstrating how specific patterning of isotropic particles can yield a rich array of organizations. In the case of Janus particles, recent work has taken into account both the entropy-dominated translational order for defining primary crystalline structure and enthalpic considerations in rotational order through designated binding in contributing to secondary crystalline order[42]. In moving beyond Janus particles and using more defined patchy topologies possessing binding specificity, Patra et al. has shown that appropriate decoration of tetrahedral patchy regions can guide the assembly of various diamond polymorphs[43**]. Future experimental efforts will integrate specifically patterned patchy particles with ideas only considered computationally until now, leading to the exploration and creation of new and more complex 3D nanoparticle assemblies.

Complex DNA Constructs for Nanoparticle Organization

The specificity of Watson-Crick base pairing has mainly been used in particle crystallization through direct surface functionalization. DNA nanotechnology, however, has advanced to the point where discrete structures consisting entirely of DNA can be designed and synthesized, otherwise known as DNA origami[44–47]. For the first time, precise control over structure topology and binding specificities can be defined at the nanoscale, allowing control over anisotropic, directional binding (**Figure 4A**). These complex constructs synthesized entirely from DNA can now be used as complex linkers for particle organization, where coordination of interactions can be rationally designed. In recent years, this level of control in DNA-based systems has been introduced to nanoparticle systems[46**,47*], and has allowed for the synthesis of three-dimensional systems with a level of flexibility not yet achieved through direct particle packing and crystallization.

The use of DNA constructs is more prevalent in 1D and 2D organizations, owing to attachment being topologically more straightforward than in 3D, where a crystallization pathway is significantly more sensitive to the system details. Recently, high-level control over DNA structure has yielded two manners in which DNA origami has recently been used to direct the assembly of 3D crystal phases[48–51]. The first serves as an analogy to a patchy particle system, whereby particle binding is mediated by a DNA origami[44,52] with a defined valence and topology. As the DNA origami itself sterically fills a volume, only a defined number of origami can actually bind an individual particle through nodal, vertex binding, which in turn is based on both ratio of particle to origami dimensions and the shape of the origami itself[53], **Figure 4B**. The Gang group utilized

this technique to display crystal phases of FCC, SC, BCT, and simple hexagonal using octahedral, cubic, elongated octahedra, and prism origami, respectively[48**]. In taking this concept further, a system consisting of tetrahedron origami was synthesized, whereby a particular origami set possessed the ability to capture a particle internally using specifically designed DNA interactions, **Figure 4C**. In doing so, the first rationally assembled nanoscale diamond particle lattice was realized, with a zinc-blende and wandering zinc-blende lattice also achieved through the use of a smaller node-binding particle[49]. It is important to stress the importance of specific designs of DNA motifs used for linking origami to nanoparticles for the crystallization process[48,49].

The capture of a particle by an origami in a directly-bound 3D dimensional framework, rather than through node-based particle-origami interactions, represents the second manner in which DNA origami can be used to synthesize 3D particle lattices. In this format, a three-dimensional scaffold consisting of all-DNA is synthesized, with particles then attaching to predefinedpoints within the lattice. A DNA scaffold can either be produced by the mixing and annealing of a selected set of ssDNA strands, as Seeman has demonstrated[50], or through a more recent method of annealing previously synthesized DNA origami[51]. Zhang et al. used DNA tensegrity triangles that organize in three-dimensions through base stacking to form a rhombohedral network of particles, **Figure 4D**. This method should prove to be a powerful approach moving forward as the topologies of DNA origami can be specifically engineered towards a modelled crystal phase.

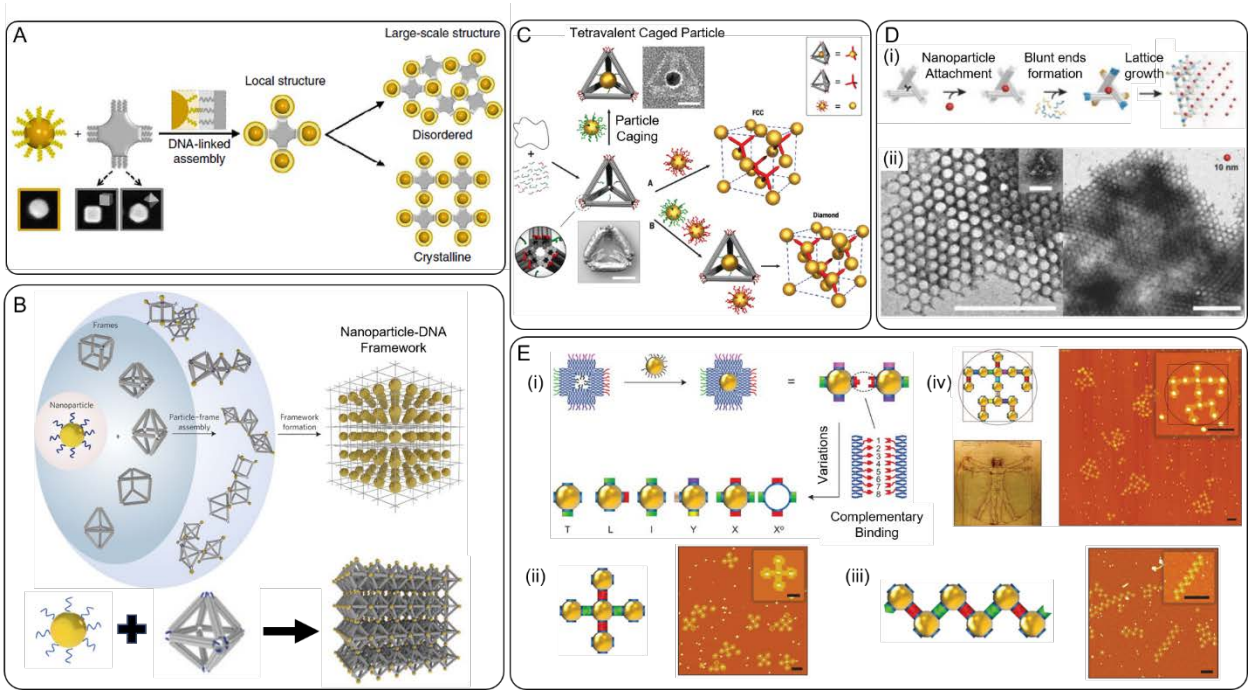


Figure 4: DNA origami can provide prescribed, complex linker topologies to define superlattice organization. (A) Bonding directionality can be introduced to a system of isotropic particles through an anisotropic binding mediator[33]. (B) Specific topologies of particle binding mediators can be designed through DNA origami, forming different classes of 3D lattices[48**]. (C) A DNA origami serving as both a particle binding mediator and a hosting site for an internally bound particle to form a 3D diamond lattice of particles. Scale bars, 20 nm[49*]. (D) DNA origami

organized in a rhombohedral lattice through base-stacking as opposed to base pairing interactions. (i) A schematic of tensegrity triangle organization (ii) TEM images of the resulting lattice. Scale bars, 500 nm, inset, 50 nm[51]. (E) (i) Directional and specific binding associated with a 2D DNA tile, which creates a library of particle interactions that can be used for (ii) clusters of defined size, (iii) zig-zag particle chains, and (iv) arbitrary structure building. Scale bars, 200 nm[52**].

Looking ahead, this research direction can not only more fully realize concepts from patchy particle organization by defining directional interactions through origami structure, but can add prescribed and orthogonal binding specificities to the directionality. For example, a planar origami integrated with nanoparticles was used to create both prescribed patterns and arbitrary mesoscale organizations through prescribed binding 'colors', or specificities, on each of its 4 sides, **Figure 4E**[54**]. By combining directional and 'colored' interactions, different modules were formed through mixing modules at specific stoichiometries. This concept of colored bonds has been theoretically considered in 3D space to achieve assemblies not readily achievable through either isotropic or purely anisotropic binding with a single bond type, such as the aforementioned study of programmable diamond polymorphs[43**].

Dynamic Superlattices

As discussed earlier, DNA is sensitive to a number of solution conditions, particularly salt concentration and the valency of the ion used. Changing additional solution parameters, such as osmotic pressure[55], molecular intercalation of duplex[56], or dielectric constant through the ethanol addition[27], are examples of the ability to modulate interparticle distances and thermal stability of NP lattices. However, in contrast to the many responsive systems with states depending on thermodynamic conditions or solution environment, DNA-NP lattices can be reconfigured in a highly specific way using DNA to trigger transformations.

DNA replacement or exchange reactions represent another path to inducing dynamic changes in lattice reformation using a highly specific molecular stimulus. This permits, for example, changing the lattice constant through incorporation and activation of a DNA actuator linker for a particle superlattice[57,58]. Moreover, since superlattice formation is a balance between entropic and enthalpic conditions, when binding strength between particles in a lattice is modified the resulting enthalpic change can induce a crystal phase transformation. Zhang et al. leveraged this concept to transform a BCC 'mother' phase' into differing 'daughter' phases by the introduction of input ssDNA, **Figure 5A**. This DNA signal induced shell changes that resulted in lattice restructuring by changing the binding interaction between two types of NPs displaying complementary DNA shells[59]. The lattice transformation was monitored through X-ray scattering *in-situ* to study phase transition based on a specific input of DNA signals. This crystal phase switching was also demonstrated by changing the relative sizes of particles, rather than the strength of interaction, **Figure 5B**. In this manner, a binary particle set containing hairpin DNA as a part of the shell design can modulate the lattice parameters of an assembled crystal phase, while additional annealing facilitates transitions between different crystal phases[60].

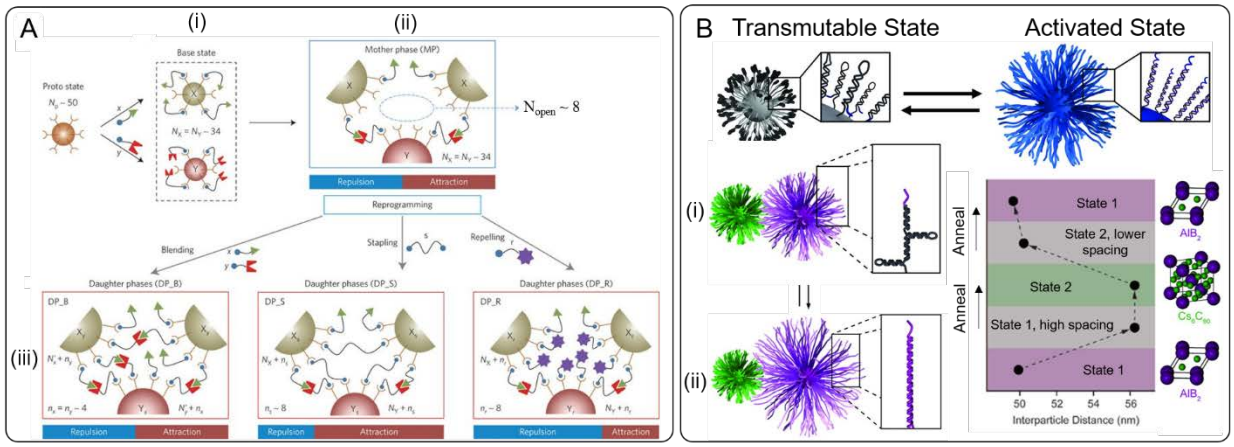


Figure 5: Dynamic superlattices can be synthesized by switching interaction strength between packed particle sets and by actively changing DNA corona heights. (A) A nanoparticle system consisting of (i) two DNA-functionalized sets that can be linked into a (ii) mother phase through introduced ssDNA. Through addition of secondary DNA strands (iii) followed by reannealing, the crystal phase can be transformed based on whether the added strands increase attraction or repulsion between the particle set[59]. (B) A transmutable particle set where one particle's DNA corona can bind in a (i) hairpin state or (ii) extended state based on DNA inputs in solution. The spacing in the hairpin crystalline lattice hairpin (AlB_2) state can be increased upon releasing of the hairpins into the extended state, and a reannealing of the system provides another crystal phase (Cs_6C_{60}); the reverse pathway provides the AlB_2 phase once again[60].

Summary/Outlook

In the last 20 years, DNA-based interactions for the targeted assembly of nanoscale objects, both for colloidal particles and DNA origami, have developed as a powerful approach to design and synthesize organizations with precise nanoscale architectures. The programmable and tunable interactions as prescribed by complementary DNA either grafted to the surface of a nanomaterial of interest, in a variety of shapes and sizes, or directional patches of DNA constructs can be used to access a variety of structural configurations. The merging of concepts such as nanoparticle-based assembly and complex DNA nano-constructs open enormous possibilities for creating designed material systems. Significant efforts have also been pursued to organize multicomponent lattices where the functional components include plasmonic, catalytic, enzymatic, magnetic, and luminescent NPs[22]. Lattices of components with a range of functional properties were developed to investigate synergistic properties[22]. Additional research efforts have been made to enhance the robustness of DNA-based structural materials, both for DNA constructs[61] and crystals[62]. Development of novel approaches for the assembly of 3D DNA scaffolds to organize nanomaterials can serve as significant tool for the assembly of functional materials with nanoscale precision.

Conflict of Interest Statement

The authors declare no conflict of interest.

Acknowledgements

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Annotated References

Papers of particular interest, published within the period covered by the review, have been highlighted as:

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30*. Lu, F. *et al.* Unusual packing of soft-shelled nanocubes. *Sci. Adv.* **5**, (2019).

In this work, it was demonstrated that nanoscale cubes with soft, DNA-grafted shells can be tuned to reveal unexpected packing motifs. This phenomena was attributed to the

interplay between the shape of the anisotropic nanoparticles and the anisotropic grated shell. The anisotropic shell is a result of the grafting of ligands on the particle surface with high curvature. In this case, it was shown that the tuning of anisotropic grafted shells can be used to tune nanoscale packing.

31*. Lin, H. *et al.* Clathrate colloidal crystals. *Science.* **355**, 931–935 (2017).

This work demonstrated the ability to tune the DNA shell of a complex, anisotropic nanoscale colloidal particle, in this case triangular bipyramids, to self-assemble into clathrate architectures. These architectures contain large pores and presented as quite the challenge for collodial assembly. Researchers also used computational means to invesitgate system parameters that led to the assmembly of different clathrate crystal structures and were experimentally identified.

41**. Patra, N. & Tkachenko, A. V. Programmable self-assembly of diamond polymorphs from chromatic patchy particles. *Phys. Rev. E* **98**, 32611 (2018).

The authors presented a method of controlling the polymorphism of the assembled colloidal diamond. Here the idea of "chromatic" or distinguishable bonds was applied to patchy particles. The use of multiple, distinct bonds that were tetravalentally coordinated in dynamic simulations lead to the assembly of both the cubic and the hexagonal diamond lattices. This strategy can be transferred using DNA prescribed bonds to a wide variety of experimental, nanoscale systems.

46**. Tian, Y. *et al.* Lattice engineering through nanoparticle-DNA frameworks. 22 (2016). doi:10.1038/NMAT4571

A variety of crystallographic lattices can be self-assembled through the use complex, three-dimensional linkers and isotropic particles. In this paper, the final 3D assembly of isotropic nanoparticles was dictated by the geometry of the polyhedral DNA origami frames. This rational design strategy can successful be used to self-assemble well-ordered lattices.

47*. Liu, W. *et al.* Diamond family of nanoparticle superlattices. *Science.* **351**, 582–586 (2016).

Researchers were able to experimentally realize two distinct variations of the diamond lattice using nanoscale collodial particles. This strategy ultilized complex DNA origami linkers with tetravalent binding topology. These complex linkers were also designed to host one or several nanomaterials.

52**. Liu, W., Halverson, J., Tian, Y., Tkachenko, A. V. & Gang, O. Self-organized architectures from assorted DNA-framed nanoparticles. *Nat. Chem.* **8**, 867–873 (2016).

This work demonstrated the use of programmed anisotropic and selective bonds embedded onto two-dimensional DNA origami tiles. A diverse set of bonds can be used to generate a library of these tiles to assembly both targeted clusters and periodis arrays. This strategy can also be used to self-assembly complex, non-trivial shapes, an example being a low-resultion version of Leonardo da Vinci's *Vitruvian Man*.