Using DNA to program the self-assembly of colloidal nanoparticles and microparticles

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Abstract | DNA is not just the stuff of our genetic code; it is also a means to design self-assembling materials. Grafting DNA onto nano- and microparticles can, in principle, 'program' them with information that tells them exactly how to self-assemble. Although fully programmable assembly has not yet been realized, the groundwork has been laid: with an understanding of how specific interparticle attractions arise from DNA hybridization, we can now make systems that reliably assemble in and out of equilibrium. We discuss these advances, and the design rules that will allow us to control — and ultimately program — the assembly of new materials.

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Compared to what nature builds using self-assembly, the structures that we can make by mixing together synthetic components seem downright primitive. In nature, structural components (proteins), catalysts (RNA and enzymes), responsive containers (clathrin cages) and even entire organisms (viruses) are built using processes that appear — considering that the same structures can be produced *in vitro* in the absence of any external energy input — to be guided by the minimization of free energy[1]. Although there are many beautiful examples of self-assembly in peptides[2,3], polymers[4–7] and colloids[8,9], most synthetic mixtures cannot be targeted towards the wide range of structures and behaviour seen in nature. Indeed, most synthetic self-assembling systems cannot be targeted at all, because the interactions that drive the assembly cannot be precisely engineered and are not understood quantitatively.

There is, however, one exception: DNA. It may seem strange to call DNA a synthetic system. It is, after all, the stuff of our genetic code and its double-helical structure (FIG. 1a) is the key to how it replicates[10]. But the same double helix can be used to assemble structures that have no natural counterparts (see BOX 1). In the field of DNA nanotechnology[11], complex 3D nanostructures are routinely assembled by linking together DNA oligonucleotides with 'sticky ends' (REF. 12) — short, single-stranded domains that hang from double helices. The sequences of these oligonucleotides can be controlled because they are synthesized directly, one nucleotide at a time.

In contrast to genetic DNA, these synthetic DNA sequences generally do not code for proteins. They do carry information, but this information contains the strengths and specificity of the interactions that guide self-assembly. With the aid of thermodynamic models of nucleic-acid hybridization, such interactions can be engineered. The quantitative link between sequence and interactions, combined with the specificity of Watson–Crick base pairing, is why DNA is so widely used in self-assembly.

Synthetic DNA nanostructures now far exceed what nature has built with DNA, at least in terms of their structural complexity (in nature, the primary function of DNA appears to be information storage, not building nanostructures). DNA has been used to build 2D crystals[13], nanotubes[14,15], 3D periodic arrays[16], and a host of other periodic and aperiodic structures made from DNA bricks[17,18] (FIG. 1b) or origami[19–23] (FIG. 1c). DNA can even be used to duplicate the functional complexity of biological and biochemical systems: reaction networks, catalysts, logic switches and circuits have all been demonstrated in systems made entirely of DNA[24,25].

But there are limits to the materials that can be made using DNA. DNA itself does not have remarkable electrical, optical or thermal properties, and although the price of synthetic oligonucleotides has decreased markedly over time, it remains costly to produce large-scale (that is, greater than laboratory-scale) quantities of DNA-based materials[26]. Hence, building materials with DNA requires the integration of other components.

In this Review, we examine how colloidal particles, including both nano- and microparticles, can be integrated with DNA to build materials. The origin of this field lies in two papers[27,28] published in *Nature* in 1996, both of which were inspired by the earlier work

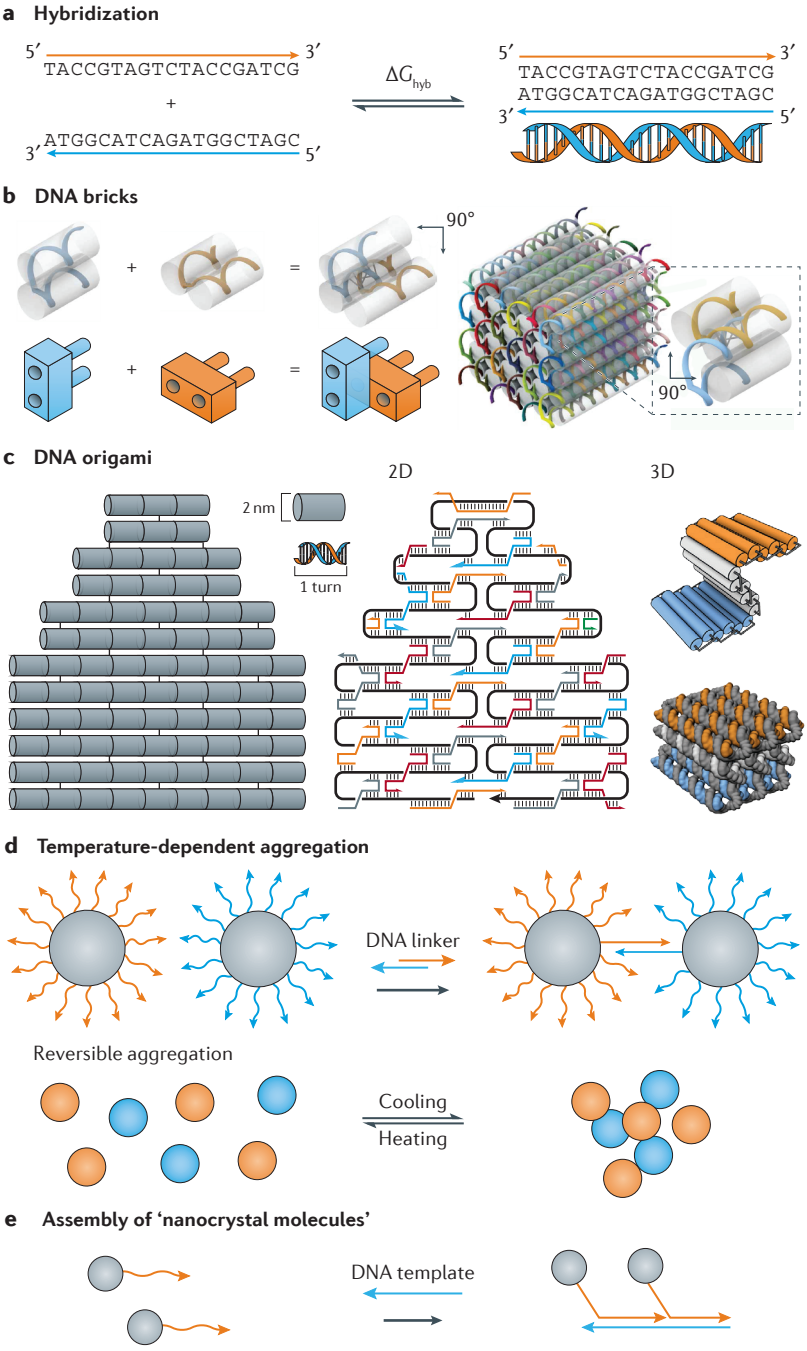


Figure 1 | **Examples of DNA-mediated self-assembly. a** | A single strand of DNA consists of a linear sequence of nucleotides with an associated direction (5′ to 3′). Single strands with complementary sequences can hybridize to form double-stranded DNA, with an associated change in free energy (ΔG_{DNA}) that is accurately predicted from their base sequences and thus can be controlled. The base pairing process occurs in an antiparallel fashion. **b**, **c** | This simple principle has been used to fabricate materials made entirely of DNA with nanometre-scale precision, including a 3D molecular canvas made of single-stranded DNA bricks[17] (**b**) and intricate 2D and 3D structures made by folding a viral genome using single-stranded DNA staples[19,21] (**c**). Hybridization can also direct the assembly of DNA-grafted particles, but in a much cruder fashion. **d** | In 1996, Mirkin *et al.*[27] showed that uniformly grafted particles aggregate in a temperature-dependent way[27]. **e** | Early experiments by Alivisatos *et al.*[28] showed that monofunctional nanoparticles could be assembled together into ‘nanocrystal molecules’. Panel **b** is adapted with permission from REF. 17, American Association of the Advancement of Science. Panel **c** is from REFS 19 and 21, Nature Publishing Group.

of Seeman[11,12] and others at the forefront of the field of DNA nanotechnology: in one paper, Mirkin and co-workers[27] showed that spherical gold nanoparticles (about 13 nm in diameter) with grafted DNA oligonucleotides could be made to aggregate reversibly by varying the temperature, owing to the formation and melting of DNA bridges between particles (FIG. 1d); in the other paper, Alivisatos and co-workers[28] showed that small (1–2 nm) gold clusters, each bearing a single DNA strand, could be assembled into dimers and trimers, which they termed ‘nanocrystal molecules’ (FIG. 1e).

The questions and ideas raised in these papers still echo today. Mirkin and co-workers[27] sought to use DNA to make bulk materials. They realized that interfacing DNA with nanoparticles could produce larger structures at a lower cost than approaches that use DNA alone: the DNA directs the bulk structure, while the particles confer unique electrical, optical or structural properties. Although the community still grapples with the issues of cost and mass production, our control over structure has advanced rapidly. The first structures built with DNA-coated nanoparticles were non-equilibrium gels; now, it is possible to make equilibrium crystals from either nanoparticles or microparticles. This work has been aided by statistical-mechanical models of the interactions between DNA-coated particles. We discuss these models and the experimental advances that have enabled equilibrium self-assembly of bulk materials.

Alivisatos and co-workers[28] sought to control the structure of finite (as opposed to bulk) systems of particles by using multiple DNA sequences. They called these sequences ‘codons’ — harkening back to the biological role of DNA and at the same time pointing the way forward to the use of these sequences in ‘programmable’ self-assembly[29]. ‘Programmable’ here refers to the ability to prescribe an outcome — a structure or dynamical response — of a self-assembly experiment by adding information to the system, such as the sequences of the DNA strands. The connection between information, computation and self-assembly, which is central to DNA nanotechnology[30,31], has recently begun to be explored in DNA-directed assembly of nanoparticles and microparticles. We discuss how concepts from DNA nanotechnology can be integrated with our understanding of DNA-mediated interactions to make fully programmable systems of grafted particles.

Although our Review surveys similar topics to those covered by other recent reviews[32–35], our aims are different. We describe the concepts that link the seemingly disparate fields of DNA nanotechnology, DNA-mediated assembly of nanoparticles and DNA-mediated assembly of microparticles. By comparing and contrasting results across a wide range of length scales, from the molecular scale to nanometre and micrometre scales, we uncover common physical principles. These principles are the basis of design rules that tell us how to assemble — and program the assembly of — new materials.

DNA-mediated interactions

Examining a broad range of length scales necessitates a coarse-grained view of the interactions between the objects that are assembling, whether they are microparticles, nanoparticles or complexes consisting of only DNA strands. In this section, we describe how molecular-level details can be subsumed into effective (or coarse-grained) interactions between components. In subsequent sections, we explore how these interactions govern the assembly of particles both in and out of equilibrium.

DNA-grafted particles can be prepared via several synthetic routes. At the nanoscale, DNA oligonucleotides are often attached to gold nanoparticles through a thiol functional group[27,36]. At the microscale, oligonucleotides can be attached to polymer or silica particles through ligand–receptor binding[37,38], physical grafting[39] or covalent attachment[40,41].

Regardless of the synthetic method, the particles attract one another via the formation of DNA bridges. A bridge forms when a strand grafted to one particle directly hybridizes to a strand grafted to a second particle[37,42], or when the two grafted strands hybridize with a third strand called a linker[43,44] (FIG. 2a). Although the physical model that we describe is agnostic toward the type of bridge, the linker approach offers more flexibility in practice, because the interactions can be tuned without resynthesizing the particles (for example, by adjusting the concentration of linkers).

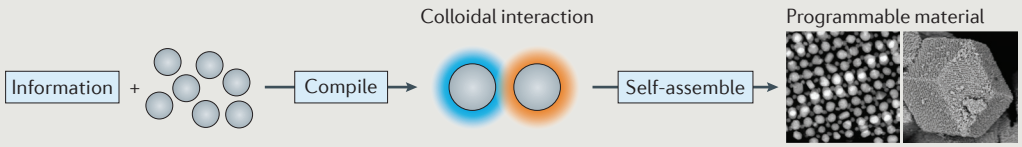
We assume that bridges can form and break on timescales that are much smaller than the characteristic time of particle diffusion. Although terms such as 'sticky end' suggest irreversibility, most DNA-directed assembly techniques require the particles to not behave as if they were coated in glue. When the bridges are transient, they create a specific, effective attraction between the particles. In the following section, we describe the ways in which this effective attraction depends on the DNA sequences and the temperature.

DNA hybridization in solution. A single strand of DNA consists of a linear sequence of four nucleotides: adenine (A), thiamine (T), guanine (G) and cytosine (C). When two strands in solution come together, they can hybridize by base pairing (A binds T; C binds G) to form a duplex with a double-helical structure (FIG. 1a). The sequence contributes to the thermal stability of this duplex through two interactions: base pairing between complementary strands and base stacking between adjacent bases within each strand. Base stacking, not base pairing, is the dominant stabilizing factor in the DNA double helix[45]. As a result, the overall stability of the duplex cannot be determined by simply adding contributions to the free energy from each base pair.

Instead, the effects of neighbouring nucleotides must be considered. The nearest-neighbour model of DNA hybridization predicts the change in free energy as a result of hybridization (ΔG_{DNA}) when two short, complementary oligonucleotides A and A* form a duplex AA*. This model is based on empirical measurements of free energies for many common hybridization motifs[46,47], such as Watson–Crick base pairs, internal mismatches, dangling ends, loops, bulges and hairpins. The equilibrium concentration of AA* as a function of temperature can be predicted analytically from ΔG_{DNA} using a two-state reaction model, $A + A^* \leftrightarrow AA^*$, or more advanced algorithms[48,49], many of which are available as web-based services[50–52]. ΔG_{DNA} increases approximately linearly with increasing temperature because the entropic free-energy penalty of forming a duplex becomes more important than the enthalpic gain[46,47]. Thus, the concentration of AA* decreases with increasing temperature.

Interactions between DNA-grafted particles. Hybridization of grafted strands is the basis of the attraction between DNA-grafted particles. However, the attraction between particles is different from that between two strands. The experimentally observed melting temperature of particles grafted with complementary strands (defined as the temperature at which half of the particles are aggregated) can be lower or higher than the melting temperature of the DNA strands in solution[38]. Furthermore, the melting transition of the particles is steeper (FIG. 2b), owing to the 'multivalency' of the particles (that is, their ability to form more than one DNA bridge at a time). Because the temperature dependence of the effective attraction is critical to controlling self-assembly, several models have been developed to relate

Box 1 | **The meaning of 'programmable' self-assembly**



Self-assembly is a process by which a system of disordered components spontaneously assembles into an ordered pattern or structure without human intervention. In programmable self-assembly, information is added to the system to direct assembly towards a prescribed structure or to yield desired behaviour. In a sense, this information is compiled into a set of local interactions, which then execute the self-assembly of the target structure. The information can take many forms, such as DNA sequences or component shapes, as discussed in the text. The micrographs are adapted with permission from REF. 75, American Association for the Advancement of Science and from REF. 73, Nature Publishing Group.

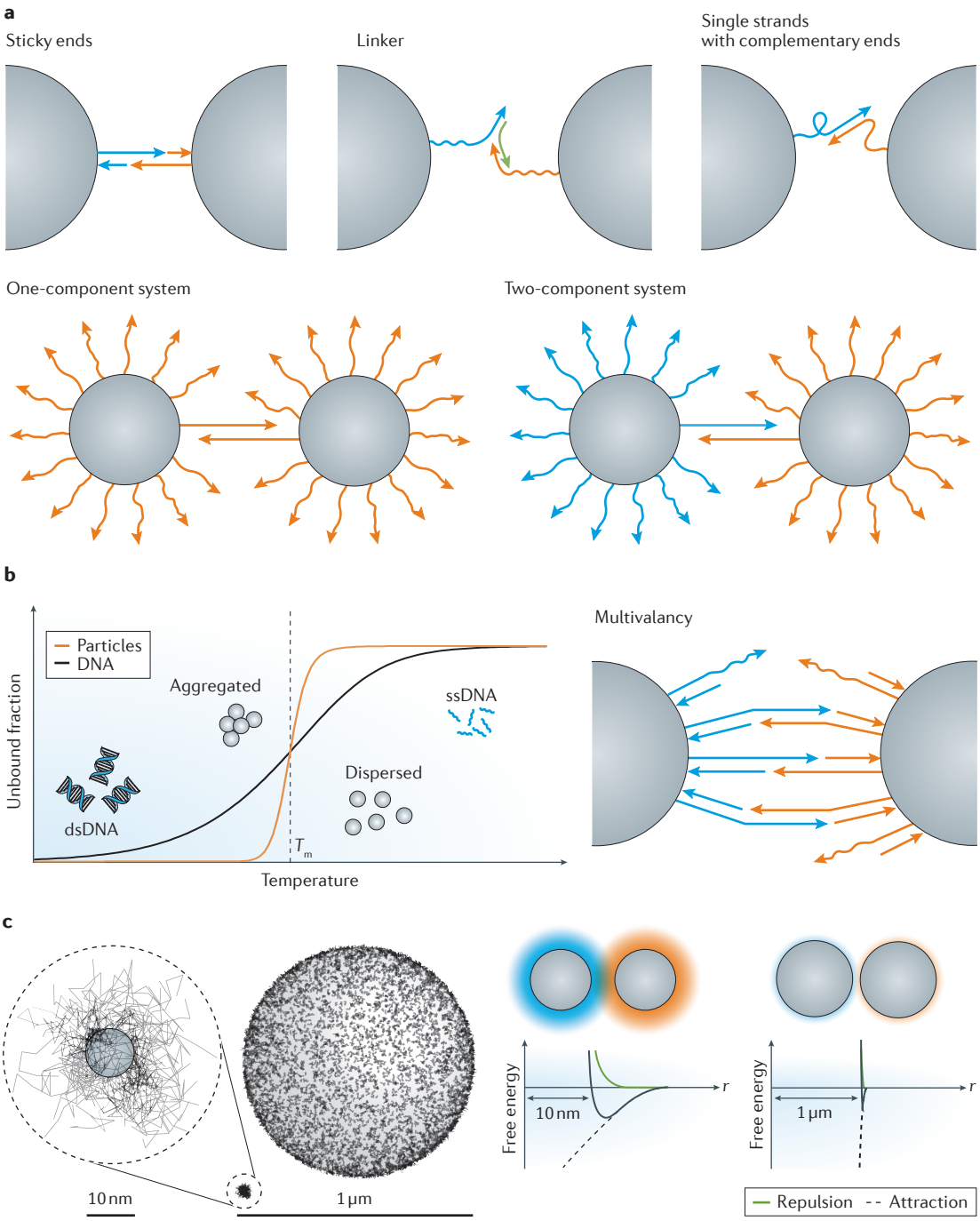


Figure 2 | **DNA hybridization induces an effective interaction potential between DNA-grafted particles.** **a** | DNA-grafted particles experience an effective attraction due to bridge formation, which can be induced by direct hybridization of grafted double-stranded DNA (dsDNA) with dangling 'sticky ends', binding of a partially complementary linker strand from solution or hybridization of grafted single strands with complementary ends. A one-component system consists of particles grafted with the same DNA sequences; a two-component system consists of particles bearing different DNA sequences. **b** | Unlike hybridization of DNA in solution, which is a gradual function of temperature, a suspension of DNA-grafted particles transitions from a dispersed state to an aggregated one over only a few degrees Celsius, owing to multivalency in the interactions. The range of the DNA-induced interaction between particles depends on the length of the grafted strands relative to the particle size. **c** | For DNA-grafted nanoparticles, the length of the DNA is roughly equivalent to the size of the particles (first panel), but for DNA-grafted microparticles it is only about 1% of the particle diameter (second panel). As a result, the interaction free energy between DNA-grafted nanoparticles has a relatively wide potential minimum (third panel), whereas DNA-grafted microparticles interact more like 'sticky spheres' (fourth panel). The black line represents the sum of the attractive and repulsive components of the effective potential. *r*, centre-to-centre distance; ssDNA, single-stranded DNA; T_m, melting temperature.

it to both the density of grafted strands, which controls the multivalency, and the nearest-neighbour predictions of the hybridization free energy, which controls the strength of each DNA bridge.

These models all share a common physical picture: transient formation of bridges pulls the particles together, whereas compression of the grafted DNA molecules pushes them apart. Both effects arise from fluctuations at the molecular scale (FIG. 2c). Therefore, we can think of the particles as interacting through a time-averaged effective potential that, like a Lennard–Jones potential, has a minimum arising from attractive and repulsive components (FIG. 2c). However, because it is averaged over many molecular degrees of freedom, the effective potential is not a true potential energy, but rather a free energy $F(r)$ that depends on the distance between the particles, r, and the temperature, T.

Let us consider a state in which the particles are separated by a distance, r, and are at constant temperature, T. The attractive component of the effective potential is $F_a(r) = -k_B T \ln[Z(r)]$, in which $k_B T$ is the thermal energy and $Z(r)$ is a partition function that accounts for all of the possible combinations of DNA bridges, along with their Boltzmann factors. The reference state is one in which no bridges form. Because there is only one way to form this unbridged state, the probability of observing the system with no bridges is $P_{unbridged}(r) = 1/Z(r)$. Therefore:

$$F_a(r)/(k_B T) = \ln[P_{unbridged}(r)] \quad (1)$$

If we assume that p, the probability of a bridge forming, is spatially uniform and independent of the formation of other bridges, then $P_{unbridged}(r) = (1-p)^N$, in which N is the total number of bridges that can form. As temperature decreases, p increases, because hybridization becomes more thermodynamically favourable at lower temperatures.

This model explains why the melting transition is so steep: because the particles are multivalent, N is typically much greater than 1, and even a small increase in the probability of bridge formation leads to a large decrease in $P_{unbridged}$. In practice, this property means that the attraction between particles varies from negligible to irreversible over a range of only a few degrees Celsius.

Theory versus experiment. The model described above can be made quantitative by accounting for the density of DNA strands. In 2005, Biancaniello and co-workers[43] measured the effective potential between two micrometre-scale particles and modelled their measurements using equation (1), assuming low hybridization yield and large N. To obtain p, they assumed that chemical equilibrium between single strands and duplexes is established locally in space. The effective concentration of grafted DNA strands was then calculated from their surface density, assuming that the strands acted as tethered, freely jointed chains. Although they were able to fit their model to their measurements, the fitted ΔG_{DNA} was much larger than that predicted by the nearest-neighbour model. Also, the predicted temperature dependence, although steep, did not agree quantitatively with the experimental data. In 2011, Rogers and Crocker[53] refined this model to account for the decrease in the concentration of single strands that occurs when some of the strands hybridize. This refined model quantitatively captured the magnitude and temperature dependence of the measured pair potential. The only inputs in the model were the DNA sequence, persistence length, grafting density and ionic strength.

Other approaches to modelling DNA-mediated interactions explicitly consider the configurations of the DNA strands. The first of such models, developed by Licata and Tkachenko[54] and later tested experimentally by Dreyfus *et al.*[38,55], treated the grafted DNA molecules as tethered rigid rods and ignored any correlations arising from competition between neighbouring strands; however, it did account for the effect of the reduced configurational entropy of the DNA strands upon binding on the interaction between the particles. Dreyfus *et al.*[38,55] found that the model was able to reproduce the experimentally observed steep melting transition, although it did not accurately predict the melting temperature. More complete descriptions of the statistical mechanics of binding between grafted molecules, including the correlations arising from the competition for binding, were developed later by Frenkel and collaborators[56–59]. For single-stranded grafted DNA, these models and the previously proposed continuum approach of Rogers and Crocker[53] agree with each other and with experimental results to within the uncertainty of nearest-neighbour estimates of ΔG_{DNA} (REFS 60,61). For other grafted constructs, such as surface-mobile strands[62,63] or double strands with sticky ends[38,55], the configurational entropy penalty might play a more important role. However, the approaches detailed above have not yet been tested against direct measurements of the pair interaction in such systems.

Because all of these coarse-grained models predict the same thermal response and interaction potential, we argue that the interactions between DNA-labelled particles are understood. This understanding allows the phase behaviour[64–67] to be predicted from experimental variables such as sequence, linker design, grafting density and particle size. There are some nuances when the size of the particles becomes comparable to the length of the DNA strands, in which case the interactions are typically not pairwise additive[57,68,69]. This situation arises for small nanoparticles. Because it is difficult to directly measure the interaction potential in such systems, models are usually tested against experimental measurements of the equilibrium phase diagram. With respect to this standard, the predictions of models that coarse-grain the DNA strands to different extents[57,68,70,71] qualitatively agree with experimental results. Quantitative agreement requires further experiments that better constrain the model parameters. Overall, however, the current data validate the concept that transient bridging gives rise to effective interactions.

Equilibrium self-assembly

Understanding the effective interactions provides insight into how to design DNA-grafted systems that can self-assemble in equilibrium. For example, it is evident that temperature control is important: the original

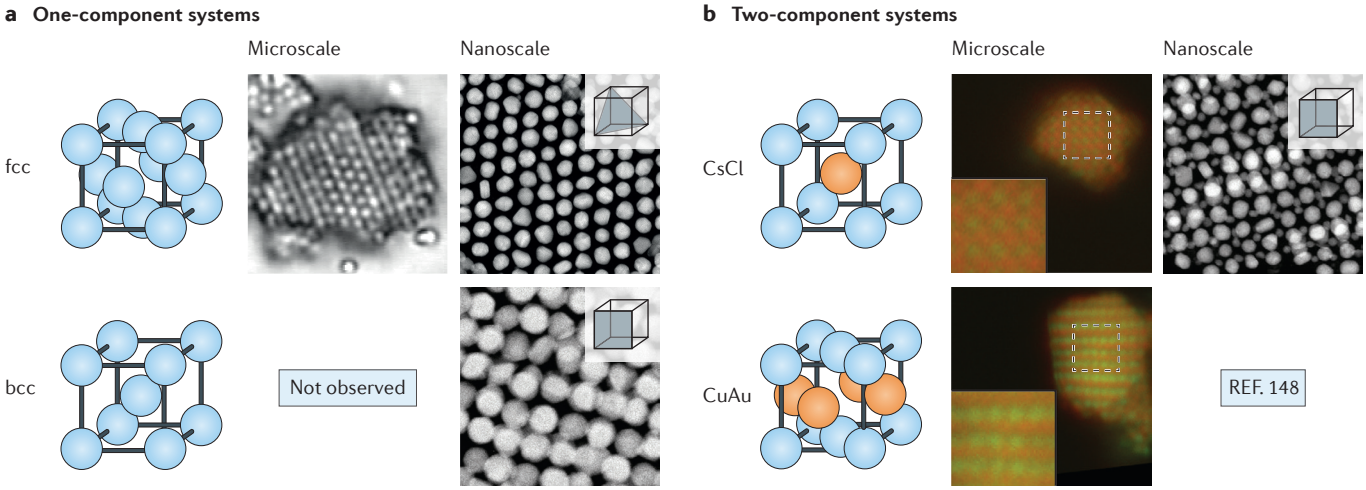


Figure 3 | **Equilibrium phase behaviour of simple systems is similar at the nanoscale and the microscale.** The first successful attempts using DNA to direct the assembly of colloidal crystals resulted in structures with simple ionic and metallic lattices. **a** | The first one-component systems assembled into face-centred cubic (fcc) crystals, both at the microscale[43] and the nanoscale[72,75]. A single-component system of nanoparticles grafted with flexible strands self-assembles into a body-centred cubic (bcc) structure[75,78]. The bcc structure has not been observed in DNA-grafted microparticles, probably because the interaction range is short. **b** | Two-component systems without self-complementary interactions produce structures with a cesium–chloride (CsCl) lattice at the microscale and the nanoscale[42,72]. Increasing the degree of self-complementarity in the two-component systems leads to the formation of crystals with copper–gold (CuAu) symmetry through a diffusionless transformation from CsCl parent crystals[77,148]. Upper middle image in panel **a** is adapted with permission from REF. 43, American Physical Society. Upper right and lower right images in panel **a** are adapted with permission from REF. 75, American Association for the Advancement of Science. Upper middle and lower middle images in panel **b** are from REF. 77, Nature Publishing Group. Upper right image in panel **b** is adapted with permission from REF. 75, American Association for the Advancement of Science

demonstrations of DNA-mediated assembly of particles produced non-equilibrium aggregates because they were conducted at temperatures well below the melting point of the particles, at which the attraction strength between particles is much greater than k_BT. In 2005, Biancaniello *et al.*[43] crystallized DNA-grafted microparticles[43] by incubating the particles for days at a temperature just below the melting point; similar annealing protocols were used in 2008 by Nykypanchuk *et al.*[42] and Park *et al.*[72] to crystallize DNA-grafted nanoparticles. Recently, slow cooling was used[73] to make macroscopic single crystals that contained more than a million DNA-grafted nanoparticles.

Criteria for equilibrium. Temperature is only one of the variables that need to be controlled to achieve equilibrium self-assembly; it is also necessary to minimize non-specific interactions such as van der Waals forces. Typical assembly experiments use salt concentrations of the order of 100 mM to screen the electrostatic repulsion between DNA phosphate backbones, thereby promoting efficient hybridization. However, such high salt concentrations also screen the electrostatic repulsion that stabilizes the particles against aggregation. Consequently, most current experiments involving gold nanoparticles use a protocol[36] that involves gradually increasing the surface density of DNA strands via the stepwise addition of salt and DNA. This protocol ensures that, at any salt concentration, there is a sufficiently high grafting density of DNA strands to sterically stabilize the particles.

High grafting density also ensures that the kinetics of binding are sufficiently fast to achieve equilibrium. As we have discussed, equilibrium self-assembly requires the attractions between particles to be a few k_BT in strength; however, this condition alone is not sufficient to achieve equilibrium. Let us consider particles with a small number of strands that bind strongly (corresponding to low N and large p in equation (1)). The effective attraction will be a few k_BT in strength, but the lifetime of each DNA bond will be large, which hinders rotational diffusion — and, hence, equilibration — of the particles[74]. Equilibration therefore requires particles with a high number of strands that bind weakly. This is why newly developed grafting methods[40,41] aim to achieve high grafting density. In addition, most experimental systems now feature short binding domains (4–6 bases) to ensure that the kinetics of bridge formation and breaking are fast at modest temperatures.

Finally, using a flexible tether between the particle surface and the binding domain of the DNA strand can increase the separation between the particle surfaces, thus reducing the van der Waals attraction. Biancaniello *et al.*[43] found that particles with DNA strands attached to a polymer tether crystallized, whereas those in which the DNA was covalently attached to surface functional groups did not. Moreover, both Nykypanchuk *et al.*[42] and Park *et al.*[72] were able to make crystals only when the sticky ends were separated from the particle surfaces by a long DNA tether.

Crystallization. Most equilibrium experiments on DNA-grafted particles have focused on assembling crystal lattices. Macfarlane and co-workers[75,76] developed a rule — the complementary contact model — to explain which lattice should form in equilibrium. This rule states that the equilibrium lattice is the one that maximizes the contact between spheres that have complementary strands. Here, we summarize the experiments that led to the development of this rule and explain how the results of these experiments — and the rule itself — can be understood in terms of effective interactions.

Despite some minor differences, the equilibrium structures formed by nanoscale and microscale particles look strikingly similar. Nykypanchuk *et al.*[42] and Park *et al.*[72] showed that two 'species' (which we call A and B) of gold nanoparticles, each of which contained strands with domains complementary to those on the other, crystallize into a cesium–chloride (CsCl) lattice[42,72] (FIG. 3). The CsCl structure consists of two interpenetrating simple cubic lattices and is equivalent to a body-centred cubic (bcc) lattice if we do not distinguish the particles. Later, Casey *et al.*[77] showed that the same lattice formed in a two-component system of polymer particles[77] that were 10–100 times larger than the gold nanoparticles of Nykypanchuk *et al.* and Park *et al.*

Interestingly, the CsCl structure is not the only structure that can form. Another possible equilibrium structure is the copper–gold (CuAu) lattice (FIG. 3), in which each particle also has eight neighbours of the opposite type. (The CuAu structure is equivalent to a face-centred cubic (fcc) lattice if we do not distinguish the particles.) Using both theory and experiment, Casey *et al.*[77] incorporated A–A and B–B, as well as A–B attractions into their system, and found that the CuAu lattice was thermodynamically favoured over CsCl for all but the weakest A–A or B–B attraction strengths[77].

The relative stabilities of CuAu and CsCl are related to differences in the number of neighbours of the same type. In CuAu, each particle has four neighbours of the same type in addition to eight neighbours of the opposite type. Thus, if the A–A or B–B interactions are large enough, the complementary contact rule suggests that the CuAu structure should be favoured because it has more interacting pairs of particles.

Many other crystal structures can be obtained in both one- and two-component systems of particles by varying not only the interaction strengths, but also the particle sizes. Using nanoparticles grafted with only a single DNA sequence per species, Macfarlane and co-workers[75,76] assembled eight different crystal structures with symmetries ranging from fcc to Cs_6C_{60}. Many of these symmetries were subsequently observed[40] in colloidal crystals composed of polymer spheres 100 times larger than the nanoparticles used by Macfarlane and co-workers. The crystal structures at both of these scales can be explained by the complementary contact rule.

However, there are exceptions to this rule. The CsCl structure is favoured over the CuAu structure for small but non-zero (~$0.3k_BT$) A–A or B–B attraction strengths[67], even though CuAu would maximize the number of touching spheres. Furthermore, for certain kinds of grafted constructs, bcc symmetry (eight nearest neighbours; see FIG. 3) is favoured over fcc (12 nearest neighbours) in a single-component system of nanoparticles[78].

These exceptions, and the complementary contact rule itself, can be understood in terms of the effective potential. The equilibrium structure of the entire system (particles and DNA included) is that which minimizes the free energy $F = U - TS$, in which U is the total effective potential (that is, the sum of all the time-averaged interactions) and S is the entropy. In most cases, F can be minimized by maximizing the number of attractive pair interactions between particles, thus minimizing U. This is the basis of the complementary contact rule.

Exceptions to the rule must involve cases in which either the interactions are long-ranged or the entropic contribution TS is large. If the potential is long-ranged, then U is no longer proportional to the number of nearest-neighbour pairs. When next-nearest-neighbour interactions are possible, bcc symmetry should be favoured over fcc in an attractive one-component system[79], which perhaps explains the aforementioned observation of such[78]. If the crystal has 'soft' vibrational modes, then TS can dominate the total effective potential, U. Because the configurational entropy of the strands is included in the effective potential (and so contributes to U, not S), the entropy, S, depends only on the collective degrees of freedom of the crystal. Thus, for certain interaction ranges and strengths, the CsCl lattice, which has soft modes, should be favoured over CuAu, which does not.

Contrasting the nanoscale and the microscale. Thus far we have emphasized the similarities between the equilibrium self-assembled structures formed by nanoscale and microscale structures. However, there are differences between the two scales that might be important in future experiments and applications. For example, different particle shapes can be made at different scales. The experiments discussed so far all used spherical particles, but this need not be the case. Gold, the material of choice for DNA-functionalized nanoparticles, can be synthesized in a variety of shapes, including nanorods and polyhedra, by controlling the growth of different crystal planes[80–84]. At the microscale, most materials that can be functionalized with DNA are amorphous polymers or glasses[41]. Several synthetic techniques have been developed to make non-spherical particles from these amorphous materials, including sphere doublets[85], clusters[86,87] and silica-coated polyhedra[88,89], as well as spherical particles with indentations[90,91]. Thus, at both the nanoscale and the microscale, there are many different shapes of particles that can be functionalized with DNA, but the intersection between these two sets of shapes is small.

The material properties and, in particular, the optical properties of the self-assembled structures also differ between the two scales. Metallic nanoparticles have plasmonic resonances in the visible and near-infrared region of the spectrum that can be exploited in optical metamaterials[92–95] or light-harvesting structures[96]. Polymer microparticles have Mie resonances in the

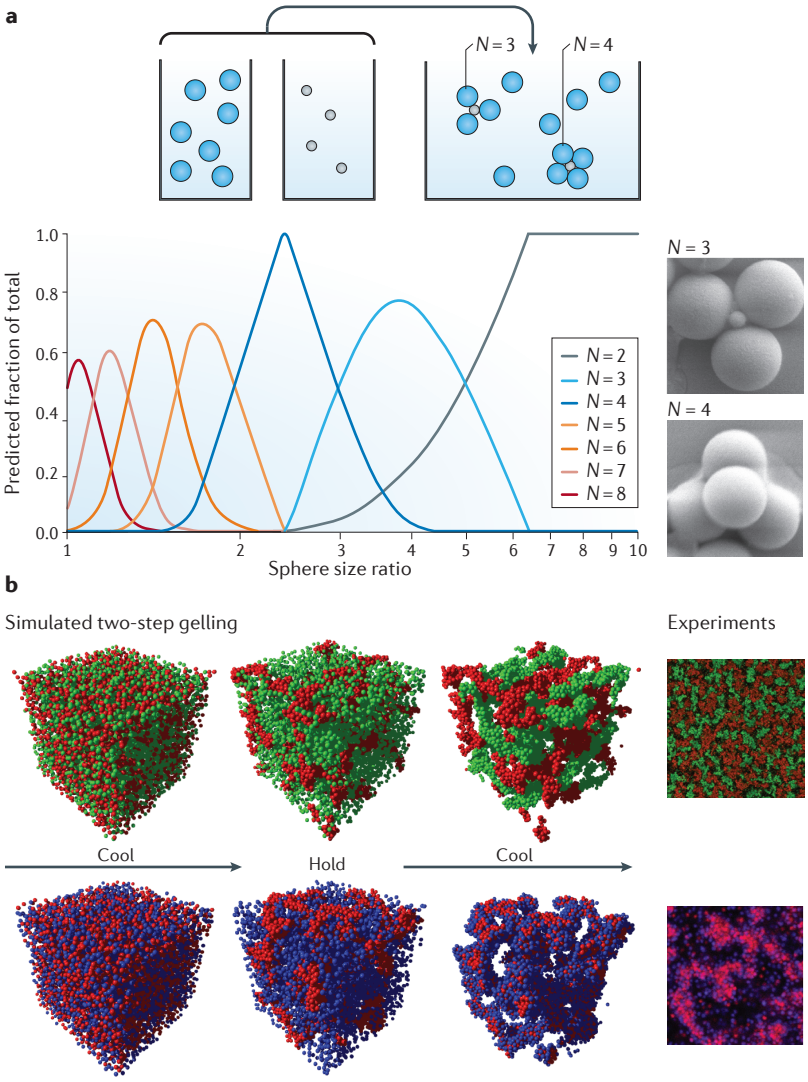


Figure 4 | **Non-equilibrium routes to assembly produce colloidal clusters and bicontinuous gels. a** | Bidisperse mixtures of DNA-grafted particles prepared well below their melting temperature form finite-sized aggregates: the large particles 'park' on the surface of the smaller ones. The number of large particles, *N*, in the resulting clusters (inset shows clusters of size $N = 3$ and $N = 4$) is tuned by changing the size ratio of the two species. At a sphere size ratio of 2.41, 100% of the clusters are predicted to be tetrahedral with $N = 4$. At other size ratios, a mixture of different cluster types is obtained (for example, at a sphere size ratio of 4, approximately 75% of the clusters are predicted to have $N = 3$, 20% to have $N = 2$ and 5% to have $N = 4$). **b** | Colloidal gels with unique topology are prepared from binary mixtures of DNA-grafted colloidal particles using a hierarchical assembly approach. First, a gel composed of one species of DNA-grafted particles with a high melting temperature is assembled; then, the temperature is quenched and a second gel is formed from the second species, which either penetrates the pores of the high-temperature gel (top) or coats its surface (bottom). Schematic and plot in panel **a** are adapted with permission from REF. 102, American Physical Society. Images in panel **a** are adapted with permission from REF. 101, American Chemical Society. Panel **b** is from REF. 105, Nature Publishing Group.

visible spectrum that make them useful for photonic crystals[97] or other strongly scattering materials such as paints and coatings[98,99].

Neither of these differences changes our understanding of how DNA-grafted particles self-assemble; for example, if a particular particle shape could be made at both the nanoscale and the microscale, then, in general, we would expect the equilibrium self-assembled structures to be the same at both scales. However, in certain cases, the range of interaction may lead to differences in phase behaviour. The range of interaction between two nanoparticles coated with 50-base-long grafted DNA strands is comparable to the diameter of the nanoparticles. By contrast, the range of interaction between two microparticles coated with the same strands is only about 1% of their diameter (FIG. 2c). Therefore, a bcc crystal might be stable in a one-component system of nanoparticles, but be metastable in a system of microparticles[79]. The kinetics of phase transitions should also differ between the two scales because the critical nucleus size depends on the interaction range[100]. Consequently, some crystal phases formed at the nanoscale might not form at the microscale (or vice versa) because the structures are either thermodynamically unstable or kinetically inaccessible.

Non-equilibrium self-assembly

As discussed above, achieving equilibrium self-assembly of DNA-grafted particles requires control over the temperature, grafting density and DNA sequences. But if our goal is to assemble particles out of equilibrium, the sensitivity of the interactions to these variables is a useful feature because it allows us to tune the interaction strengths and kinetics of bridging over a wide range; for example, a small change in temperature changes the strength of the effective attraction by tens or even hundreds of k_BT (REF. 55).

DNA-mediated interactions are distinguished from other strong interactions such as van der Waals forces by their specificity. With interactions that are both strong and specific, one can control the structure of non-equilibrium aggregates. For example, binary mixtures of DNA-coated particles with strong and specific interactions can be made into clusters with well-defined morphologies (such as tetrahedra) through random aggregation or 'parking' (REFS 101,102) (FIG. 4a). Because the interactions are too strong to allow the system to relax to equilibrium, growth is halted before the system can assemble into a bulk phase. This approach might be useful for making plasmonic clusters for use in optical metamaterials[92,103,104]. DNA can also be used to assemble gels with a controlled structure (FIG. 4b). The correlations between particles can be engineered[105] by adjusting the temperature schedule (that is, the changes in temperature as a function of time) and relative rates of aggregation between different species of DNA-grafted particles, to yield, for example, bicontinuous gels. This technique could be used in the future to make bulk materials with controllable porosity and tortuosity.

Furthermore, at a fixed interaction strength, the nucleation, growth and annealing of self-assembled structures[66,75,106] can be modulated by controlling the kinetics of bridge formation and rupture[74,75]; for example, the kinetics can be tuned to trap compositional defects in a growing crystal. As shown in experiments[72] and later in simulations[67], slowly cooling a binary system of DNA-grafted nanoparticles results in compositionally

disordered fcc crystals, whereas quenching and annealing the same system leads to the expected CsCl-type crystals. A similar mechanism is thought to explain the observation[75] of hexagonal close-packed (hcp) crystals of DNA-grafted nanoparticles. In this case, decreasing the surface density of the DNA, and thus slowing the kinetics of bridge formation and breakage near the melting temperature, led to hcp crystals instead of the more thermodynamically stable fcc crystals.

Kinetics are also important for selecting the final self-assembled state when there are several possible degenerate states. In particular, hydrodynamic correlations between particles seem to favour specific pathways between crystal structures in systems of DNA-grafted microparticles[107]. This finding was based on an examination of an earlier experimental study[77] in which crystals with the CsCl structure converted to the CuAu structure via a diffusionless transformation, analogous to a martensitic transformation in metals. The hydrodynamic model[107] explains why only the observed CuAu structure forms out of the myriad possible states with randomly stacked hexagonal planes.

Towards programmable self-assembly

The examples of equilibrium and non-equilibrium assembly we have discussed thus far demonstrate simple programmable self-assembly schemes. By 'programmable' we mean that information is added to the system to direct the assembly; for instance, in the case of equilibrium crystals in two-component systems, the information is the DNA sequences grafted to the two different species of particles. By analogy to computer programming, the sequences act as 'source code' that is 'compiled' into a set of interparticle interactions ('machine code') that dictate the structure and function of the assembled material. The assembly is programmable if we understand how the inputs are compiled into interactions. When this is the case — as it is for DNA-grafted particles, owing to the statistical-mechanical models of the effective interactions — the experimenter can determine what changes in input will produce the desired output behaviour.

Our ability to program the self-assembly of colloidal particles using DNA is, however, still at a primitive level. The number of specific interactions between particle species and the complexity of the colloidal crystal structures that are observed in equilibrium do not yet exceed those found in other colloidal systems, such as binary suspensions of oppositely charged colloidal particles[108] or one- and two-component systems of particles interacting through excluded volume[109]. By contrast, in the field of DNA nanotechnology, thousands of different components (unique DNA strands) are used to create complex self-assembled structures. Furthermore, the complexity of these structures can be extended far beyond that of simple periodic arrays[110,111] through algorithmic assembly schemes, in which logic gates are implemented via DNA sequences[112,113].

The next step is to extend the programmability of DNA-grafted particles so that they can self-assemble not just into crystals, but into any prescribed structure. In the following subsections, we explore how DNA nanotechnology can help us reach this goal. First, we show how lessons and design rules learned from DNA nanotechnology can be applied to nano- and microparticles; second, we examine how the programmability of DNA-grafted particles can be extended by directly incorporating constructs from DNA nanotechnology.

Specificity for programming structure. The remarkable feature of DNA-mediated interactions is that the number of distinct species in the system can be as large as the total number of 'building blocks' (which might be either DNA constructs or DNA-grafted particles). Furthermore, the sequences can be designed to control all the possible interactions between the various species (FIG. 5a). With such control, it is possible to program the self-assembly of a target structure by first breaking it down into subunits, then determining how many unique species are needed and finally mixing various species of building blocks that bind only to their neighbours. In this scheme, each building block is encoded with information about where it must go in the final structure.

Surprisingly, this 'maximal specificity' scheme works for assembling complex 3D structures, as has been demonstrated in experiments on DNA bricks[17,18] (FIG. 5a). We say 'surprisingly' because there are many ways in which such a scheme can go awry[114]; for example, in the presence of any weak non-specific interactions, partially formed target structures can aggregate. However, simulations and experiments show that even thousands of distinct DNA bricks can reliably self-assemble into prescribed structures with high yield.

The key to achieving high yield appears to be the annealing protocol, which is generally tuned empirically in experiments. Simulations[114,115] show that, at high temperatures, there is a free-energy barrier to nucleating a precursor to the target structure. As the temperature is lowered, each nucleated precursor slowly grows until it forms the full target structure. Interestingly, in this scheme, the target need not be the thermodynamically stable product at any temperature. Although the precursor to the target must be thermodynamically favoured in the nucleation regime, at lower temperature, the favourable state is probably an aggregate of these partially formed targets. Avoiding aggregation requires an annealing protocol that ensures that growth takes place by the addition of free building blocks; thus, it is crucial to tune the nucleation conditions and the temperature schedule.

Similar schemes might also be applied to DNA-grafted particles. Simulations have shown that maximally specific systems of such particles can be programmed to assemble into target structures with high yield[116]. In particular, specific, finite-sized structures with various degrees of symmetry can be formed with near-perfect yield in the simplest multicomponent colloidal system — isotropic particles of the same size interacting through specific interactions. Moreover, the yield is maximized when the interactions are maximally specific[116]. A later study[117] revealed how different kinds of defect affect the yield and complexity of structures assembled from maximally specific systems. These simulations showed that

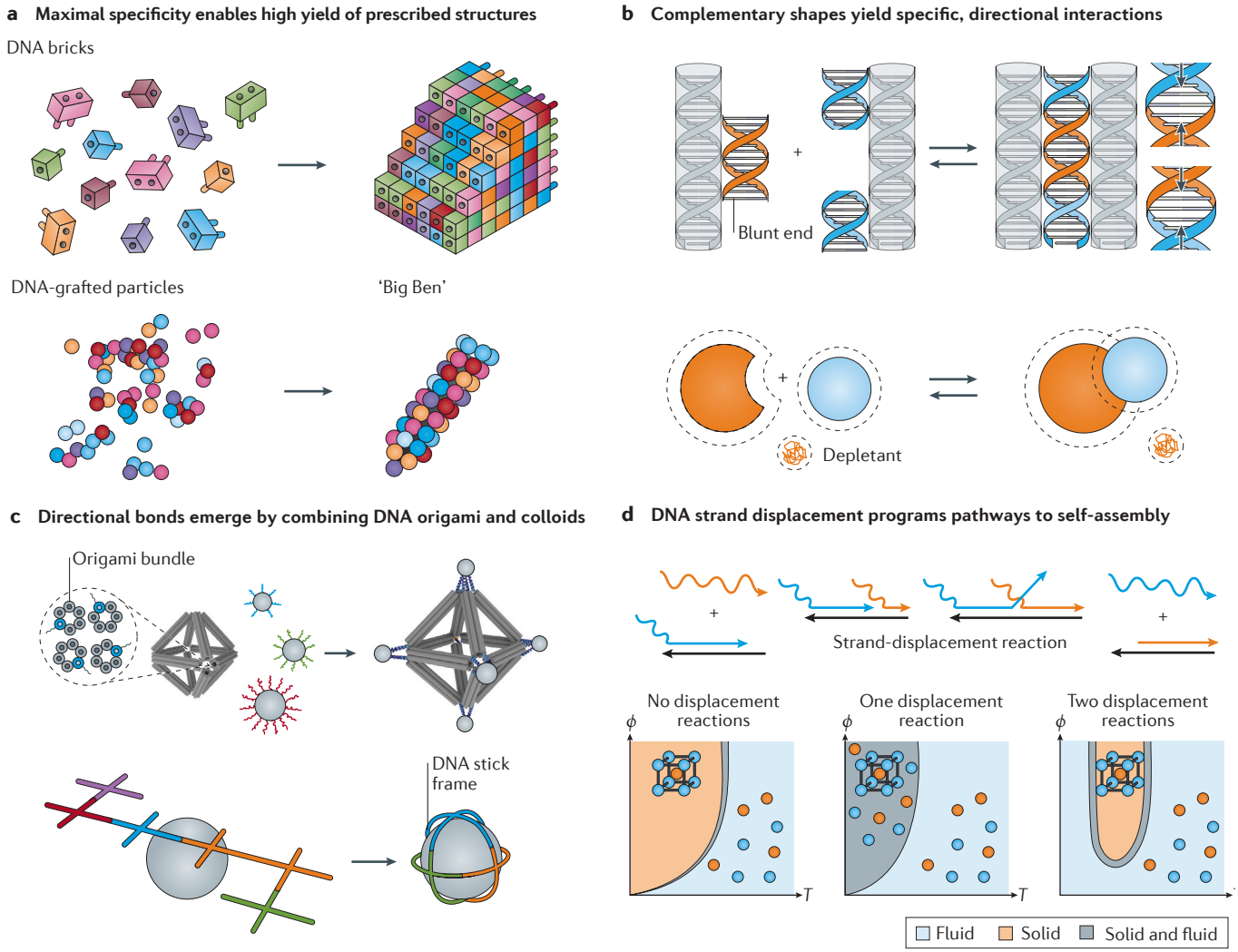


Figure 5 | **Forms of information for programming self-assembly. a** | Specificity. DNA sequences are used to create orthogonal interactions between many species. By controlling these interactions the experimenter constrains the allowed contacts between components and markedly enhances the yield of prescribed structures, as shown in the self-assembly of DNA 'bricks' (top) and in a simulation of the assembly of 'Big Ben' from spherical microparticles (bottom). **b** | Shape complementarity. Components with complementary shapes further constrain the connectivity between species to yield specific, directional interactions, as seen in blunt-end stacking between DNA bundles (top) and lock-and-key interactions between colloidal particles (bottom). **c** | DNA nanostructures. Combining DNA origami with colloidal self-assembly enables the assembly of nanoparticle clusters with prescribed symmetry and handedness as a result of emergent directional interactions (top); wireframe cages could enable similar assembly at the microscale (bottom). **d** | DNA strand displacement. Programmability can be extended to the thermal response of colloidal phases by modulating the thermodynamics of the bridge-formation process using DNA strand displacement. *T*, temperature; *φ*, volume fraction of particles. Panel **a** (top) is adapted with permission from REF. 17, American Association for the Advancement of Science. Panel **a** (bottom) is adapted with permission from REF. 117, National Academy of Sciences. Panel **b** (top) is from REF. 130, Nature Publishing Group. Panel **c** (top) is from REF. 131, Nature Publishing Group. Panel **d** (bottom) is adapted with permission from REF. 133, American Association for the Advancement of Science.

arbitrary structures, including a 69-particle model of Big Ben (FIG. 5a), could be formed with high yield using this scheme[117].

All of these simulations avoid the problem of aggregation of nuclei by starting with a system that can form only one copy of the target structure. Thus, the assembly can take place under equilibrium conditions at constant temperature. Other simulations[118,119] showed that particles with both specific and directional interactions assemble into multiple copies of aperiodic target structures in the bulk. The directional interactions (which we discuss further in the next subsection) can enhance the kinetics because they prevent the formation of unwanted metastable configurations. However, these simulations were not performed in the nucleation regime; instead, they were seeded with an initial suspension of nuclei, the structures of which were subsets of the target.

The programmed assembly of DNA bricks provides some important lessons for programming the assembly of DNA-grafted particles. In previous sections we focused on the conditions for achieving equilibrium assembly or assembly far from equilibrium; however, the successful self-assembly of prescribed, non-periodic structures from DNA bricks demonstrates that it is beneficial to work in between these two extremes, using conditions that shift continuously. Furthermore, experiments and simulations show that maximal specificity is a valid design rule for programming the assembly of complex 3D structures.

In one respect, maximal specificity might be easier to achieve in DNA-grafted particles than in DNA bricks. Because the binding between particles is multivalent, a small change in the hybridization free energy produces a large change in the strength of interaction between two particles. Thus, each particle can be synthesized with many different specific interactions through small changes in sequence. Wu and co-workers[120] argued that microscale particles could be made with more than 40 different orthogonal interactions; however, it remains a challenge to make particles in which all the different interactions have the same temperature dependence.

Programming with directional interactions. Recently, synthetic schemes have been developed to produce particles that, like DNA bricks, have both specific and directional interactions (FIG. 5b). At the microscale, directionality can be enforced by chemically patterning particles with patches of DNA. This approach has been demonstrated by direct synthesis[121] and by selective protection and crosslinking of DNA linkers on otherwise isotropically labelled particles[122]. At the nanoscale, directional interactions can be imprinted using similar methods[123], but can also arise naturally from anisotropy in the particle shape: specific orientations between particles, which typically involve the alignment of crystal facets, can be favoured enthalpically if they permit the formation of additional DNA bridges or entropically if they increase the configurational freedom of the system[124–126].

We have only just begun to explore experimentally the variety of structures that can be assembled from these new kinds of particles. These particles cannot yet mimic DNA bricks; there is still no way to make hundreds or thousands of unique species of particles with specific and directional interactions. However, there are interesting questions that can be addressed with existing systems and with the help of theory and simulation. For example, for a given target structure, what is the smallest degree of specificity and the simplest directional interactions needed for it to assemble in high yield? Resolving such questions would help to establish rules that link the complexity of a structure to the type and amount of information required to program its assembly.

As stated before, there are lessons to be learned from DNA nanotechnology. In several recent studies, the use of blunt-end interactions between double-stranded DNA (dsDNA) has been explored. Although these interactions arise from base stacking rather than base pairing[127], they are highly specific to the shapes of the dsDNA complexes. One geometry involves the end-on linkage of shape-compatible, jagged bundles of double helices[127–129]; another involves the lateral connection between bundles of double helices with shape-compatible 'plugs' and 'holes' (REF. 130). In the second example, each plug is formed by a pair of blunt-end-terminated double helices that decorates the lateral face of a bundle, whereas the corresponding hole is formed by flanking pairs of blunt-end-terminated double helices that decorate the lateral face of the shape-compatible bundle (FIG. 5b). This strategy enables the construction of an interface that spans a large area and yet is maintained by a modest number of weak interactions. In this way, substantial directional control between interaction partners is achieved. At the same time, the interface can be disrupted with a small and programmable energy input.

'Shape complementarity' might be used in addition to sequence complementarity to program self-assembly. Shape-specific interactions were also demonstrated previously in 'lock-and-key' colloidal particles. Such particles contain concave regions that bind to convex regions of other particles in the presence of a depletion force (FIG. 5b). The interactions are specific to the curvature: the lock particles and key particles maximize the depletion interaction when they mate. Experiments on blunt-end dsDNA show that this principle can be extended to create multiple orthogonal interactions that program assembly. Taken together, these results show that it might be possible to make maximally specific DNA-grafted particle systems by using a combination of shape and sequence complementarity. Using both types of specificity might make it easier to synthesize maximally specific DNA-grated colloids than using either type alone.

DNA nanotechnology meets colloidal self-assembly. In the previous subsections, we discussed how to transfer knowledge about programmable assembly from DNA nanotechnology to DNA-grafted particles. Here we examine how combining constructs from DNA nanotechnology with colloidal particles enables assembly schemes that are not easily realizable with either system alone. For example, DNA origami can behave as a core around which spherical nanoparticle satellites, each isotropically coated with DNA strands[94,95,131], organize (FIG. 5c). Self-assembled DNA octahedra with 30-nm edge lengths and unique DNA strands displayed on each vertex have been used to programmably capture gold nanoparticles[131]. Because each satellite can be made to display its own unique sequence, these core–satellite assemblages are the closest analogues to DNA bricks at the particle scale. It is therefore possible that they could be used to assemble open lattices or finite structures with prescribed symmetry and handedness.

Such schemes have yet to be extended to microparticles. DNA wireframe cages that can wrap around such particles would be floppy and lack structural integrity unless the edges were thick, making them challenging to assemble. However, an interesting synergy might emerge from the combination of DNA origami and

microparticles: a DNA cage wrapped around a microparticle provides specific binding sites to the particle, while the particle could give structure to the cage. One strategy to achieve this assembly would be to decorate a DNA stick frame with short, single-stranded handles that link reversibly to complementary strands decorating the colloidal sphere (FIG. 5c). In a second step, the terminal branches could be linked by connecting strands. The sphere could help by restricting the fluctuations of the stick frame to its 2D surface.

This concept provides an example of how DNA nanotechnology and colloidal particles might be integrated to yield behaviour — in this case, a combination of rigidity and directionality — that is not easily achieved at either the molecular or colloidal scale individually. A related strategy is to use structural DNA nanotechnology to fabricate cavities that are small enough to exclude crowding agents (for example, polyethylene glycols above a certain size). Such cavities could therefore be driven to join with shape-compatible plugs by depletion forces induced by the crowding agents. We anticipate that plugs and sockets could be implemented on colloidal particles to endow them with lock-and-key interactions.

Programmability need not be limited to the structural domain. Simulations have shown that competitive binding in a mixture of particles with directional interactions can program the thermal response of gels[132]. A similar scheme was later implemented[133] in experiments using isotropic, DNA-mediated interactions. These experiments used strand displacement[25,134] — a tool borrowed from dynamic DNA nanotechnology — to make systems in which soluble single strands can interfere with bridge formation. Controlling the thermodynamics of the strand-displacement reactions allows the phase diagram to be programmed in various ways — for example, to include low-temperature fluid phases that crystallize upon heating[133] (FIG. 5d). The ability to control the thermal response could prove useful for programming new pathways in self-assembly, which could enable the synthesis of materials that cannot be formed through a single, equilibrium phase transition.

Future work might focus on 'active' or dynamic nanosystems that self-organize through energy-dissipating processes (for example, by consuming molecular 'fuel'). Such systems have been designed at both the colloidal[135–137] and DNA[25,138] scale, but few have been realized that combine both scales. The combination of DNA nanotechnology and colloidal particles could be used to produce materials that correct errors during assembly[139,140], move in preprogrammed ways[141,142] or self-replicate[143–145].

Conclusions and perspective

After nearly 20 years of research, the field of DNA-directed colloidal assembly has developed a firm footing in terms of chemistry, physics and engineering: synthesis methods have been refined, models of interactions and collective behaviour have been validated and design rules for equilibrium and non-equilibrium structures have been discovered. These design rules are based on our understanding of how the effective interactions between particles emerge from the transient formation of DNA bridges; for example, to achieve equilibrium assembly, we must use short binding sequences and high grafting densities to ensure that the kinetics of particle rearrangement are fast.

New design rules adopted from DNA nanotechnology point the way towards programmable self-assembly of DNA-grafted particles. One such rule is maximal specificity. The most straightforward approach to making maximally specific DNA-grafted colloids will probably involve both sequence and shape complementarity. Another rule, which applies to maximally specific systems, is to control the nucleation of target structures and prevent aggregation of partially formed targets by cooling, such that growth of the programmed structures takes place by the addition of single particles.

The field of DNA-directed colloidal assembly is now moving towards integrating other constructs from both structural and dynamic DNA nanotechnology, which should enable more applications than are possible on either the DNA or colloidal scale individually. One potential area of synergy is the design of new functional materials. Although there are many ways to assemble colloids, directing their assembly with DNA allows us to decouple the interactions between particles from their composition and to tune the distance between particles independently of their size. These advantages are important for synthesizing materials with unique photonic and plasmonic properties. There are, of course, constraints with respect to the mass production of such materials: processing must be done in aqueous media and a large amount of DNA will be required. However, many chemical processes are already moving to 'greener' solvents such as water[146], and enzymatic amplification techniques may make mass production of oligonucleotides with specific sequences cost effective[147].

All of this is to say that the field is poised to grow further. Not only are there enormous possibilities and challenges for applications, but there are also new scientific territories to explore: non-equilibrium assembly, active systems and the fundamental limits on what can be made using self-assembly. The foundations have been laid; now the fun begins.

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Competing interests statement
The authors declare no competing interests.