Self-assembly of DNA-coded nanoclusters

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We present a theoretical discussion of a self-assembly scheme which makes it possible to use DNA to uniquely encode the composition and structure of micro- and nanoparticle clusters. These anisotropic DNA-decorated clusters can be further used as building blocks for hierarchical self-assembly of larger structures. We address several important aspects of possible experimental implementation of the proposed scheme: the competition between different types of clusters in a solution, possible jamming in an unwanted configuration, and the degeneracy due to symmetry with respect to particle permutations.

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Over the past decade, a number of proposals have identified potential applications of DNA for self-assembly of micro- and nanostructures [1,2,3,4,5]. Among these proposals, one common theme is finding a way to utilize the high degree of selectivity present in DNA-mediated interactions. An exciting and potentially promising application of these ideas is to use DNA-mediated interactions to programmable self-assemble nanoparticle structures [6,7,8,9]. Generically, these schemes utilize colloidal particles functionalized with specially designed ssDNA (markers), whose sequence defines the particle type. Selective, type-dependent interactions can then be introduced either by making the markers complementary to each other, or by using linker-DNA chains whose ends are complementary to particular maker sequences. Independent of these studies, there are numerous proposals to make sophisticated nano-blocks which can be associated with particle permutation, and potentially may be introduced either by making the markers complementary to each other, or by using linker-DNA chains whose ends are complementary to particular maker sequences. One recent advance in the self-assembly of anisotropic clusters is the work of Manoharan et. al [10]. They devised a scheme to produce stable clusters of n polystyrene microspheres. The clusters were assembled in a colloidal system consisting of evaporating oil droplets suspended in water, with the microspheres attached to the droplet interface. The resulting clusters, unique for each n, are optimal in the sense that they minimize the second moment of the mass distribution $M_2 = \sum_{i=1}^{n} (r_i - r_{cm})^2$.

In this paper, we present a theoretical discussion of a method which essentially merges the two approaches. We propose to utilize DNA to self-assemble colloidal clusters, somewhat similar to those in Ref. [10]. An important new aspect of the scheme is that the clusters are "decorated": each particle in the resulting cluster is distinguished by a unique DNA marker sequence. As a result, the clusters have additional degrees of freedom associated with particle permutation, and potentially may have more selective and sophisticated inter-cluster interactions essential for hierarchic self-assembly. In addition, the formation of such clusters would be an important step towards programmable self-assembly of micro- and nanostructures of an arbitrary shape, as suggested in Ref. [11].

We begin with octopus-like particles functionalized with dsDNA, with each strand terminated by a short ssDNA marker sequence. We assume that each particle is decorated with dsDNA attached to it. We then introduce anchor DNA to the system, ssDNA with sequence $\overline{s}_A\overline{s}_B...\overline{s}_n$, with $\overline{s}_i$ the sequence complementary to the marker sequence $s_i$. The anchor is designed to hybridize with one particle of each type. Consider a cluster of $n$ particles attached to a single anchor.

If we treat the DNA which link the particles to the anchor as Gaussian chains, there is an entropic contribution to the cluster free energy which can be expressed in terms of the particle configuration $\{r_1,...,r_n\}$ as follows. Here $R_g$ is the radius of gyration of the octopus-like DNA arms.

$$F = \frac{3k_BT}{2R_g^2} \sum_{i=1}^{n} (r_i - r_{anchor})^2 \quad (1)$$

This approximation of the DNA arms as Gaussian chains is acceptable provided their length $L$ exceeds the persistence length $l_p \approx 50 \text{ nm}$ and the probability of self-crossing is small [12]. The physical mechanism which determines the final particle configuration in our system is quite different from the capillary forces of Manoharan et al.
et al. However, because the functional form of the free energy is equivalent to the second moment of the mass distribution, the ground state of the cluster should correspond to the same optimal configuration.

Consider a system with \( n \) particle species and an anchor of type \( \overline{s}_A \overline{s}_B \ldots \overline{s}_n \). The clusters we would like to build contain \( n \) distinct particles (each particle in the cluster carries a different DNA marker sequence) attached to a single anchor. Let \( C_n \) denote the molar concentration of the desired one anchor cluster. Because there are many DNA attached to each particle, multiple anchor structures can also form. The question is whether the experiment can be performed in a regime where the desired one anchor structure dominates, avoiding gelation.

We consider the stability of type \( C_n \) with respect to alternative two anchor structures. To do so we determine the concentration \( C_{n+1} \) of \( n+1 \) particle structures which are maximally connected, but do not have a \( 1:1: \ldots :1 \) composition. In particular, these structures contain more than one particle of each type, which could cause problems in our self-assembly scheme\[11\]. There are also \( n \) particle structures \( \tilde{C}_n \) with the correct composition, but which contain two anchors. We would like to avoid the formation of these structures as well, as their presence decreases the overall yield of type \( C_n \). Figure 3 enumerates the various structures for an \( n = 3 \) species system. If the experiment can be performed as hoped, we will find a regime where the ratios \( \frac{C_{n+1}}{C_n} \) and \( \frac{\tilde{C}_n}{C_n} \) are small. To this end, the equilibrium concentrations \( C_n \), \( C_{n+1} \), and \( \tilde{C}_n \) are determined by equilibrating the chemical potential of the clusters with their constituents.

Let \( c_i \) denote the molar concentration of species \( i \), and \( c_a \) the molar anchor concentration. We consider the symmetrical case \( \Delta G_i = \Delta G \) and equal initial particle concentrations \( c_i^{(0)} = c^{(0)} \) for all species \( i \). In this case we have \( c_A = c_B = \ldots = c_n = c \).

\[ C_n = c_a \left( n v_c \exp \left[ \frac{-\Delta G}{k_B T} \right] \right)^n \]  

(2)

The binding free energy of the cluster has a contribution from the hybridization free energy \( \Delta G \) associated with attaching a particle to the anchor, and an entropic contribution from the number of ways to construct the cluster (since each particle has \( N \) hybridizable DNA arms). In addition we must take into account the entropy for the internal degrees of freedom in the structure stemming from the flexibility of the DNA attachments to the anchor. In the Gaussian approximation, neglecting the excluded volume between particles this localization volume \( v = \left( \frac{2\pi}{N} \right)^{\frac{3}{2}} R_g^3 \) can be calculated exactly by integrating over the various particle configurations weighted by the Boltzmann factor: \( v^n = \int d^3r_1 \ldots d^3r_n \exp \left[ -\frac{\Delta E}{k_B T} \right] \).

We now consider the competing two anchor structures \( C_{n+1} \) and \( \tilde{C}_n \). The localization volumes \( v_2 = n^{-2} \frac{3}{2} R_g^3 \) and \( v_3 = n^{-3} \frac{3}{2} R_g^3 \) can be calculated in a similar fashion to \( v \). Since there are many DNA attached to each particle, in what follows we omit factors of \( \frac{N^{-3}}{N} \).

\[ C_{n+1} \approx \frac{v_2^{n+2}}{v^{2n}} \frac{C_n^2}{c_n^{n-1}} \]  

(3)

\[ \tilde{C}_n \approx \frac{v_3^{n+1}}{v^{3n}} \frac{C_n^2}{c_n^{n}} \]  

(4)

The concentration of free anchors \( c_a \) can be determined from the equation for anchor conservation.

\[ c_a^{(0)} = c_a + C_n + 2\tilde{C}_n + 2nC_{n+1} \]  

(5)
We are interested in the low temperature regime where there are no free anchors in solution. We determine the saturation values for the ratios of interest by noting that the Boltzmann factor $\delta \equiv \exp \left[ -\frac{\Delta G}{k_B T} \right] \gg 1$ in this regime.

$$\frac{C_{n+1}}{C_n} \approx n^{-3/2} \left( \frac{R_g}{c^{(o)}_{a}} \right)^{n-2} \frac{c^{(o)}_a}{c^{(o)}} + O \left( \frac{1}{\delta^n} \right)$$  \hspace{1cm} (6)

$$\frac{\tilde{C}_n}{C_n} \approx n^{-3/2} \left( \frac{R_g}{c^{(o)}_{a}} \right)^{n-1} \frac{c^{(o)}_a}{c^{(o)}} + O \left( \frac{1}{\delta^n} \right)$$  \hspace{1cm} (7)

Since $\frac{c^{(o)}_{a+1}}{c^{(o)}_a} < 1$, eq. 6 provides the experimental constraint for suppressing the two anchor structures. Taking the radius of the hard spheres $R \sim R_g$, it can be interpreted as a criterion for choosing the initial anchor concentration $c^{(o)}_a$ for an $n$ species system with $\phi = \frac{4\pi}{3} R_g^3 c^{(o)}$ the particle volume fraction for an individual species.

$$\frac{c^{(o)}_a}{c^{(o)}} \lesssim n \frac{1}{2} (2\phi)^{n-1}$$  \hspace{1cm} (8)

The condition gives the maximum anchor concentration for the two anchor structures to be suppressed. Since $\phi \leq \frac{1}{2}$ the theoretical limits are $\frac{c^{(o)}_a}{c^{(o)}} \lesssim 1, 29, .06$, and .01 for $n = 4, 5, 6$, and 7 respectively. In figure 4 we plot the solution for the concentrations. There is a large temperature regime ($\frac{\Delta G}{k_B T} \lesssim 2$) where the two anchor structures are suppressed in favor of the desired one anchor structures.

The experimental criterion for suppression of the two anchor structures(eq. 8) provides a fairly strict bound on the anchor concentration, and hence the cluster yield for $n \geq 5$. However, the previous discussion considers only the equilibrium concentrations. Below the melting temperature (see Figure 4), the connections are nearly irreversible. In the irreversible regime where the DNA binding is very strong, the probability that a cluster of type $C_n$ becomes attached to a second anchor is $p \sim n \frac{c^{(o)}_a}{c^{(o)}}$. The factor of $n$ counts the possible attachment sites to the cluster. In terms of the fraction of particles in clusters of type $C_n$, the factor of particles $f_2$ in the two anchor structures will be $f_2 \sim \frac{n}{2} f_1 = \frac{n}{2} \left( \frac{c^{(o)}_a}{c^{(o)}} \right)^2$.

Here the factor of $\frac{n}{2}$ is necessary since the initial attachment can be to either of the two anchors. As indicated in Figure 5, provided the anchor concentration is dilute enough, $\frac{c^{(o)}_a}{c^{(o)}} \gtrsim 4$, the formation of the two anchor structures is suppressed.

We now present a brief discussion of the role that jamming plays in preventing the one anchor structures from assuming the minimal second moment configuration. We performed simulations of the assembly of optimal colloidal clusters up to $n = 9$ particles by numerically integrating the particles’ Langevin equations.

$$b^{-1} \frac{d\mathbf{r}_i}{dt} = -\nabla_i H + \eta_i$$  \hspace{1cm} (9)

Here $b$ is the particle mobility, and the thermal noise has been artificially suppressed(i.e. $\eta = 0$). The model Hamiltonian $H$ used in these simulations has been discussed in detail elsewhere. As indicated in Figure 6 the hard sphere system gets trapped in a configuration with a larger $M_2$ than the optimal cluster, whereas the soft-core system is able to fully relax. The jamming behavior is largely determined by the single control parameter $\frac{R_g}{\sigma}$, with $d$ the diameter of the hard sphere. Beyond the critical value $\frac{R_g}{\sigma} \gtrsim .5$ the jamming behavior is either completely eliminated, or greatly reduced in the case of larger clusters.
Building these decorated colloidal clusters is the first major experimental step in a new self-assembly proposal. However, in order to utilize the resulting clusters as building blocks, an additional ordering is necessary. The problem is that the decoration introduces degeneracy in the ground state configuration. This degeneracy was not present in [10] since all the polystyrene spheres were identical. Namely, in the colloidal clusters self-assembled by our method, permuting the particle labels in a cluster does not change the second moment of the mass distribution (see Figure 7). We need a method to select a single "isomer" out of the many present after self-assembly. In the DNA-colloidal system considered here, this isomer selection can be facilitated by "linker" ssDNA. These are short ssDNA with sequence $\overrightarrow{s_A s_B}$ to connect particles $A$ and $B$. We first construct a list of nearest neighbors for the chosen isomer, and introduce linker DNA for each nearest neighbor pair. The octopus-like DNA arms of the given particles will hybridize to the linkers, resulting in a sping-like attraction between the selected particle pairs. Note that the length $L$ of the DNA arms must be on the order of the linear dimension of the original cluster. Otherwise the interparticle links cannot form upon introduction of linker DNA to the system. It should be noted that although this method breaks the permutation degeneracy of a cluster, the right-left degeneracy will still be present.

In conclusion we discussed a method which uses DNA to self-assemble anisotropic colloidal building blocks. We found an experimentally accessible regime where the resulting clusters are minimal second moment configurations. In addition, the clusters are decorated: each particle in the cluster is distinguished by a unique marker DNA sequence. The cluster formation process provides an interesting model system to study a new type of jamming-unjamming transitions in colloids. Constructing decorated colloidal clusters would represent a major step towards realizing the long-term potential of DNA-based self-assembly schemes.

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