Measuring short-range repulsive forces by imaging directed magnetic-particle assembly title

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We present the use of video microscopy of magnetic colloidal particles to measure short range repulsive forces between surfaces. The forces between the particles can be directly measured by monitoring the inter-centroid distances between the particles at various magnetic field strengths. Using a chain consisting of a minimum of 35 micron-sized particles, a distance resolution of ~0.21 nm is achieved. Measurements of the interactions between charged colloids agree well with predicted force interactions calculated using DLVO theory. We also report the first measurements of the force *versus* distance relationship between very short (<75 bases) oligonucleotide-coated surfaces. The interactions between oligonucleotide-coated surfaces agree well with Milner's polymer brush theory for strands greater than 50 bases but deviate for strands less than 35 bases.

Repulsive surface interactions control the dynamics, stability, and phase behavior of a suspension. A number of experimental techniques have been successfully developed to directly measure repulsive surface forces including the atomic force microscope (AFM) colloidal probe,[1,2] optical tweezers (OT),[3–5] and the magnetic chaining technique (MCT).[6,7] The AFM colloidal probe has sub-angstrom distance resolution, but its force measurement is limited to tens of pico-Newtons.[8] Meanwhile, OT and MCT can measure sub-pico-Newton forces the distance resolution is limited to ±3 nm and ±2 nm, respectively.[4–7] Direct measurements of electrostatic interactions between colloidal particles using MCT technique[6] and optical tweezers[9] have been reported. Additionally, the thermal expansion of a magnetic chain was recently used as a simple model of a one-dimensional anharmonic crystal, allowing force *versus* distance relationships between charged colloids to be measured.[10] The interactions between DNA-coated particle surfaces can also be measured using colloidal particles.[5,11] However, these initial studies have not investigated short-range interactions that are of the order of pico-Newtons with angstrom-level distance resolution.

In this Communication, we combine MCT with video microscopy to measure repulsive force *versus* distance relationships between coated colloidal particles with a distance resolution of ~0.21 nm. By measuring the magnetic attractive force between magnetic particles at varying field strength, the repulsive surface forces can be calculated with sub-pico-Newton accuracy.[7] Unlike the Bragg scattering technique used to measure particle spacing in MCT, distance resolution in our technique is achieved by averaging the inter-centroid distances between adjacent particles within a chain under a given magnetic field strength. The validity of this measurement is verified by measuring the repulsive forces between charged colloidal surfaces at various salt concentrations. Our measurements are compared with Derjaguin-Landau-Verwey-Overbeek (DLVO) theory for accuracy. We also demonstrate the feasibility of measuring short-range repulsive forces between colloidal surfaces coated with 15, 35, 50, and 75 base oligonucleotides. Experimental data for the 50 and 75 base oligonucleotide-coated surfaces agrees well with polymer brush theory developed by Milner. Interestingly, the shorter 15 and 35 base oligonucleotide-coated surfaces deviate significantly from theory. This is important in understanding the self- or directed-assembly of DNA-coated colloidal particles.

The particles used in this study are carboxyl-coated paramagnetic polystyrene MyOne beads (Dynal Biotech, Oslo, Norway). The mean particle diameter of the particles is 1.07 ± 0.04 μm, confirmed by dynamic light scattering and scanning electron microscopy (SEM) measurements. The magnetic susceptibility of the particles varies from 1.44 to 0.78 in the field range of 0.1 mT to 50 mT, as provided by the manufacturer. The particles are taken from a stock solution, washed and sonicated in the desired sodium chloride solution (1 mM, 2 mM, or 5 mM), and diluted to a final particle concentration of 80 000 particles/μL. The ζ potentials of the particles are measured to be −48.0 mV, −39.2 mV and −38.7 mV in 1 mM, 2 mM and 5 mM salt solutions, respectively. The particles are injected in a flow cell consisting of two glass coverslips sandwiched together with double-stick tape. The coverslips are washed with sulfuric acid and hydrogen peroxide (7 : 3 v/v) to prevent the particles from sticking to the glass surface. The cell is then sealed with epoxy to prevent evaporation of the solution. The flow cell is placed between a pair of iron-cored Helmholtz coils, used to provide a homogeneous magnetic field within the flow cell, on an inverted optical microscope (Olympus IX71) stage with a 100×/1.4 N.A. oil immersion objective. Chains of paramagnetic colloidal particles are allowed to form under a constant flux density of 10 mT. The magnetic field is then varied and images of the chains are taken using video microscopy with a digital camera (Hamamatsu) at a rate of 5 frames/s for 1 min using Simple PCI software and analyzed using Matlab. Centroid positions of the inner paticles within a chain are calculated *via* image processing[13] and inter-centroid distances between adjacent particles are averaged over inner particle pairs to give the "averaged inter-centroid distance". Note that the inner particles, representing particle 2 to N-1 for a N particle chain, are used to prevent an intensity mismatch between the particles and the background.[12] Fig. 1 shows histograms of the inter-particle spacing generated at various magnetic field strengths by measuring the averaged inter-centroid distance for a chain using 300 frames for each field strength. The standard deviation of a Gaussian fit to the histograms of the centroid distance distribution is ~0.2 nm for forces larger than 4 pN, or a field strength greater than 6 mT, signifying the

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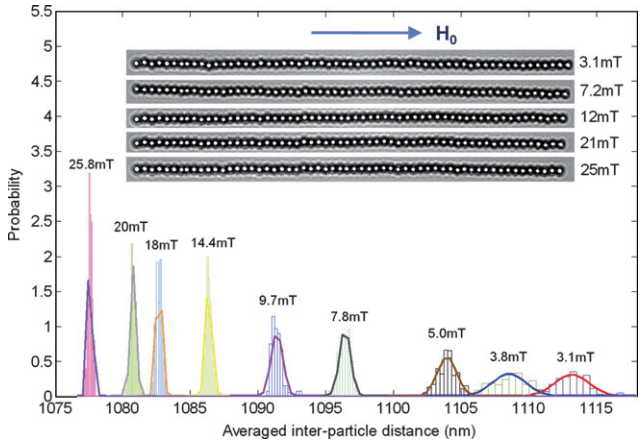

Fig. 1 Probability distributions of particle inter-centroid distances at various magnetic field strengths in 1 mM NaCl solution. Colored lines are Gaussian fits to the distribution data, where the standard deviations provide the error estimates for the inter-centroid distance measurements. Inset: images of a 59-particle chain dispersed in 1 mM NaCl solution taken at magnetic field strengths ranging from 3.1 mT to 25 mT.

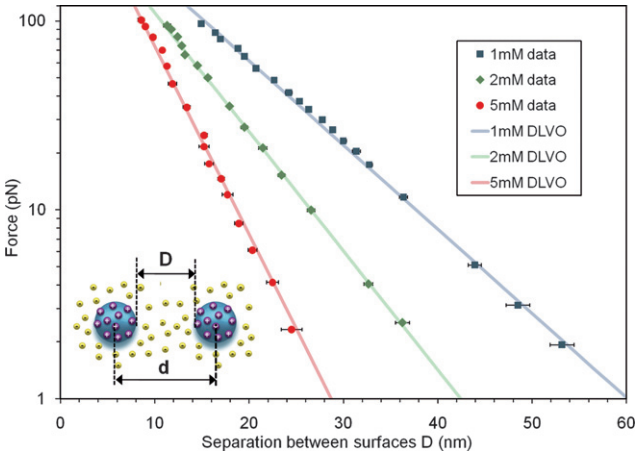

Fig. 2 Experimentally measured force–distance profiles of charged particles at different ionic strengths: 1 mM, 2 mM, and 5 mM. Solid lines in the corresponding colors are obtained from DLVO theory (eqn (2)) using the measured ζ potential of the particles. Separations between surfaces are calculated by using the mean particle diameters (only fitting parameter), found to be 1059 nm (1 mM), 1073.5 nm (2 mM), and 1061 nm (5 mM), from measured inter-centroid distances. The separation error bars are standard deviations of the averaged inter-centroid distances measured using 300 images under each specific magnetic field strength.

distance resolution of our technique. Note that at lower field strengths the inter-particle spacing distribution becomes broader due to an increase in the ratio of thermal energy to magnetic energy.

We quantify the repulsive electrostatic force between the particle surfaces by measuring the magnetic force used to align the particles at a given magnetic field strength. The magnetic force between adjacent particles aligned with the external field is calculated using eqn (1), proposed by Zhang and Widom,[14]

$$F_{\mathrm{mag}} = -\frac{1.202}{2\pi\mu_{\mathrm{o}}} \times \frac{3m^2}{d^4} \tag{1}$$

where μ_0 is the permeability of vacuum, $m = \mu_0 \chi V B_0$ is the magnetic dipole moment of a spherical particle, χ is volumetric magnetic susceptibility, V is the volume of a particle, B_0 is the applied magnetic field strength, and d is the inter-centroid distance between the two particles. Using different salt solutions, the equilibrium inter-centroid distances between particles are measured at different magnetic field strengths and converted into a force *versus* particle surface separation distance relationship using eqn (1), as plotted in Fig. 2. The measured force–distance relations are compared to those obtained using DLVO theory. At equilibrium, the magnetic force balances the electrostatic and van der Waals forces. The van der Waals force is negligible compared to the electrostatic force at surface separations greater than 8 nm.[7,15] The electrostatic force profiles are calculated assuming constant potential boundary conditions, as shown in eqn (2),

$$F_{\mathrm{el}} = 2\pi\varepsilon\phi_{\mathrm{z}}^2 a\kappa \frac{\exp(-\kappa D)}{1+\exp(-\kappa D)} \tag{2}$$

where ε is the dielectric permittivity of the medium, ϕ_z is the ζ potential, κ is the inverse Debye length, and D is the separation between two surfaces. The diameter of the particle surface up to the "slip" plane in the electric double layer, $2a$, cannot be measured *in situ* during the experiments. Therefore, the particle diameter is a fitting parameter found to be 1069 nm, 1073.5 nm and 1061 nm for 1 mM, 2 mM and 5 mM salt solutions, respectively. DLVO theory has shown to accurately describe forces between charged particles at separations greater than 8 nm.[7,8,15,16] The calculated DLVO force profiles, plotted in Fig. 2, show good agreement with the experimental data, indicating that accurate force–distance measurements can be made with our technique.

To prove the capability of our method to capture short-range interactions between colloidal particles with high resolution, we demonstrate the first direct measurement of force–distance profiles between particles grafted with oligonucleotides (15, 35, 50 and 75 bases). Streptavidin-coated particles (Dynal M-270, Dynal Biotech, Oslo, Norway), with a diameter of 3.05 ± 0.1μm and a ζ potential of −50 mV, are used for the following experiments. Oligonucleotides are grafted onto the particle surfaces *via* streptavidn-biotin coupling.[17] Surface grafting densities are measured using a fluorescent-based complementary strand method[18] and found to be 5.0×10^4, 2.8×10^4, 8.0×10^3, and 3.5×10^3 strands μm^{-2} for the 15, 35, 50, and 75-base oligonucleotide grafted particles, respectively. All particles are washed and centrifuged in phosphate buffer solution (pH = 7.4) with ionic strength of 0.12 M. The inter-centriod distances between particles are first measured as the magnetic field strength is increased, representing chain compression, and then as the magnetic field strength is decreased, representing chain expansion. Using eqn (1), the calculated force *versus* distance relationships for the different oligonucleotide-grafted particles are plotted in Fig. 3. No hysteresis is seen in the force *versus* distance data profiles during chain compression and expansion. Also note that the separation distance error bars are much smaller compared to that of the previous experiment due to use of larger particles, which are less susceptible to thermal fluctations.

The theory describing the inter-particle interaction between two spherical particles with end-grafted polymers was first developed by Alexander and de Gennes[19] using scaling arguments and then by Milner using mean field theory.[20] Both theories fit well to experimental data with grafted long chain polymers;[21,22] however, the inter-particle interactions between surfaces grafted with short

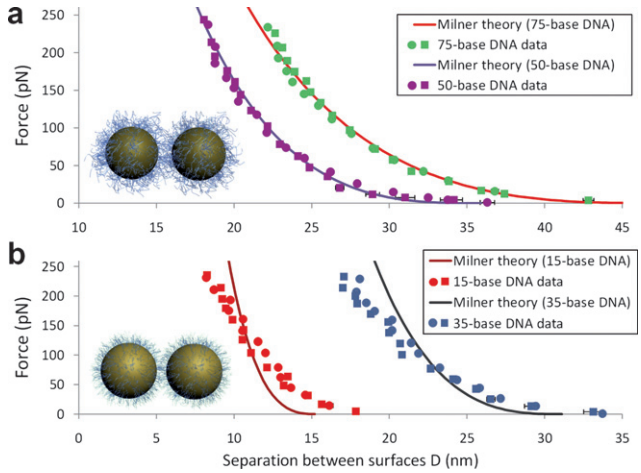

Fig. 3 Experimentally measured force–distance (circles for chain compression and squares for chain expansion) profiles of particles grafted with different oligonucleotide lengths: (a) 50 base and 75 base; and (b) 15 base, and 35 base. Solid lines are calculated from Milner's theory of compressed polymer brushes using the measured oligonucleotide grafting densities. Separations between surfaces are calculated by subtracting mean particle diameters (the only fitting parameter) from measured inter-centroid distances. Separation error bars, given by the standard deviations of averaged inter-centroid distances measured for the 300 images under a specific magnetic field strength, are also plotted.

polymers, such as oligonucleotides with less than 100 bases, have not been confirmed by experiments. Milner's theory predicts a soft repulsive force–distance profile between two planar surfaces with uniformly grafted homopolymers.[20,21] Detailed derivations of the potential-distance law between two flat walls with grafted oligonucleotides is provided elsewhere.[18,20,21] The calculated force *versus* distance relationship, between two spherical particles, shown in Fig. 3, can be derived using the Derjaguin approximation: $F_s(D) = \pi R E_s(D)$, where $F_s(D)$ is the steric repulsive force between two spheres, R is the particle radius and $E_s(D)$ is the steric interaction energy between flat walls grafted with the identical polymer brushes. Experiments for each oligonucleotide-coated particles are repeated six times, both in chain compression and extension, to ensure data reproducibility. Excellent agreement is found between our experimental results and Milner's theory for particles grafted with 50 and 75-base oligonucleotides, as shown in Fig. 3a. However, the experimental force *versus* distance profiles start to deviate from those predicted using Milner's theory for particles grafted with 15 and 35 base oligonucleotides, shown in Fig. 3b. This discrepancy cannot be attributed to oligonucleotide and particle surface charge interactions. To investigate the effect of surface charge, we functionalized streptavidin-coated particles with a much lower surface charge density (ζ potential of -10 mV) (Dynal M-280, Dynal Biotech, Oslo, Norway), with the same 15-base and 35-base oligonucleotides using the same surface grafting densities described previously. Force–distance profiles obtained from these particles overlap with their higher surface-charged particle counterparts (data not shown). This rules out the possibility that the discrepency between the measurments and theory are due to either electrostatic interactions between the particle surfaces or the negatively-charged oligonucleotides. High resolution scanning electron microscopy (Hitachi S-5500 Hi-Res SEM) images indicate that the particles have a surface roughness of ~9 nm. To consider this surface roughness, we have modeled the forces measured between particles with a regular surface pattern and found that the discrepency between our measured forces and those predicted using Milner's theory can be attributed to surface roughness. Additionally, we argue that it is also possible that steric interactions between colloidal particles grafted with very short (<35 bases) oligonucleotides are not well described by Milner's polymer brush theory, which is derived to predict interactions between polymer brushes in the limit of long chains.

This is the first experimental data on force *versus* distance relations between colloidal particles grafted with short oligonucleotides. As increasing interest in the assembly of short oligonucleotide grafted colloids continues to grow, further investigations are necessary to fully understand the force *versus* distance profiles between short oligonucleotide-grafted surfaces.

To quantify the distance resolution of this technique, we measure the maximum standard deviation of the inter-centroid distance between inner particles in linked chain. We record the Brownian motion of a 35-bead chain chemically linked using a 15 base-pair DNA for 30 min during which 11 000 frames are taken (linking procedure provided in ref. 18). The inter-centroid distances between all adjacent inner bead-pairs in a chain are measured and averaged to give the averaged inter-centroid distance, shown in Fig. 4. The change in the averaged inter-centroid distance due to the rigid DNA linkages between particles is insignificant. The standard deviation between adjacent dimers (σ), measured to be 3 ± 1 nm, represents the spatial resolution of a single particle pair technique.[4,16] In the limit of a straight chain, the contour length of the chain has the same standard deviation as that of any dimers within the chain, with no dependence on bead number. When the chain shape roughens, or deviates from a straight line, position errors normal to the chain orientation become less negligible. Thus, the standard deviation of the contour length becomes slightly larger with a weak dependence on the number of beads within the chain. The measured standard

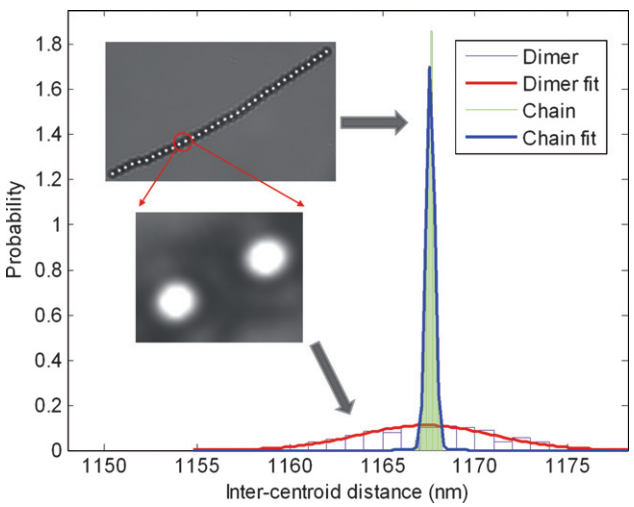

Fig. 4 Probability distributions of inter-centroid distances for chemically linked particles measured using a particle dimer and an entire 35-particle chain. The standard deviation for the dimer distribution measured using a dimer (shown between the 11th and 12th particles) is 3.6 nm. The standard deviation using averaged inter-centroid distances among all particles within the linked chain (35 beads) is 0.21 nm. Solid lines are Gaussian fits to the histograms.

deviation of the contour length of a 33-inner-bead chain is 7.0 nm, slightly larger than the mean standard deviation for dimers, indicating small deviation from a straight line conformation. The standard deviation of averaged inter-centroid distances within the chain is that of the contour length divided by the number of adjacent inner particle dimers (N-3), or 0.21 nm for our 33-inner-bead chain. This standard deviation has two components: the sum of the particle diameters and that of the sum of surface separations. Though the particle diameters may vary individually from each other, the standard deviation of the average diameter is zero since the particles are rigid under the applied forces. Therefore, a 0.21 nm standard deviation of the average inter-centroid distance within the chain represents the measurement error in the average particle surface separation and signifies the distance resolution of our technique.

In this Communication we have demonstrated the feasibility of using video microscopy of directed magnetic particle assembly to measure force *versus* distance relationships between coated surfaces. This technique has a distance resolution of ~0.21 nm when using a 35-bead chain and a sub-picoNewton force resolution. We have shown that it is possible to measure the forces between particles with great precision. This technique also allows us to measure short-range steric interactions between polymer brushes with reasonable accuracy. With ease of manipulation and excellent distance resolution, this technique allows us to measure a variety of short range repulsive force–distance relationship between coated colloidal particles.

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