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Nature uses replication to amplify the information necessary for the intricate structures vital for life. Despite some successes with pure nucleotide structures, constructing synthetic microscale systems capable of replication remains largely out of reach. Here, a functioning strategy is shown for the replication of microscale particle assemblies using DNA-coated colloids. By positioning DNA-functionalized colloids using capillary forces and embedding them into a polymer layer, programmable sequences of patchy particles are created that act as a primer and offer precise binding of complementary particles from suspension. The strings of complementary colloids are cross-linked, released from the primer, and purified via flow cytometric sorting to achieve a purity of up to 81% of the replicated sequences. The replication of strings of up to five colloids and non-linear shapes is demonstrated with particles of different sizes and materials. Furthermore, a pathway for exponential self-replication is outlined, including preliminary data that shows the transfer of patches and binding of a second-generation of assemblies from suspension.

1. Introduction

Self-replication, a pivotal attribute of life, empowers organisms to proliferate and rapidly adapt through Darwinian evolution. The endeavor to construct artificial self-replicating systems, in addition to seeking to unravel profound questions regarding the origins of life, offers the option to explore novel engineering paradigms, where large numbers of complex entities grow from a single initial structure. However, achieving this feat is far from being straightforward. With significant effort, only a few "man-made" examples of replicating systems based on simple peptides,[1] small molecules,[2,3] and DNA-origamis,[4–6] have been developed.

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Nucleic acids, in particular, purposely perform a crucial role in natural self-replication through the transmission, storage, and variation of genetic information via complementary base pair binding. In the last decade, researchers have thus explored leveraging the unique properties of DNA to fashion self-replicating nanostructures, building upon the foundational concept of natural DNA self-replication but incorporating the use of DNA origami rafts.[5,6] The original development of these systems started with replicating DNA origami sequences from solid substrates,[7] evolving from there into true exponential replication.[4] The use of templates is also common in the solid-state synthesis of peptides[8] or for sequence-controlled polymers,[9–11] and it involves selective binding of building blocks, such as base pairs, monomers, or particles, to a primer in the correct orientation. Finally, these bound units are linked to produce a complementary copy, which is then separated from the template, allowing the process to be repeated over multiple iteration cycles.[12–14]

Despite the progress achieved for pure-nucleotide nanostructures, translating the template-based replication concept to other nanoscale and microscale systems, such as colloidal particles made of diverse materials, remains a significant hurdle. However, if overcome, this step could enable the scalable production of the complex building blocks required for sophisticated microarchitectures.[15] The distinctive properties of DNA, including its selective binding, sharp binding/unbinding transitions, and the tunability of binding energy through nucleotide sequence design, indeed position it as a valuable ligand for precisely controlling colloidal assembly.[16–24] The concept of DNA-based replication of colloidal structures, in fact, emerged shortly after the initial demonstrations of colloidal assembly using DNA ligands.[16,25] Early efforts by groups led by David Pine and Paul Chaikin laid the groundwork for replication with DNA-coated colloids, pre-dating the development of self-replicating DNA origami rafts. However, unsolved challenges remain to date.[25] Namely, the main obstacles concern controlling the binding orientation of inherently spherical monomers[12] and creating well-defined, programmable colloid sequences that serve as initial replication templates. In the originally proposed scheme, the colloidal templates were generated by the directed assembly of DNA-coated colloids under external magnetic fields, generating linear sequences with random order and polydisperse length.

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Recent advancements in capillary assembly techniques now facilitate the patterning of well-defined multi-component particle sequences and clusters in large numbers, presenting a new opportunity for developing alternative schemes for template-based colloidal replication.[26,27] Inspired by the trajectory followed to achieve self-replicating DNA origamis, in this work, we present a strategy to replicate colloidal clusters from well-defined templates on a solid substrate, aiming for significant numbers and yields as a first step to inspire future developments.

In this work, we design and demonstrate a successful colloidal replication method based on the six following key steps (more details in the Experimental Section):

1) *Fabrication of the primer sequences*: The starting point for the replication experiments are colloids coated with complementary DNA strands that can spontaneously bind. We use existing procedures to functionalize 2.7 µm SiO_2 colloids with streptavidin[28] or use commercial streptavidin-coated magnetic colloids and then add biotinylated double-stranded DNA (dsDNA) with a six-base pair sticky end on those colloids.[25] The DNA coating is determined to be around $1.3-0.5 \ 10^6$ strands per particle with a melting temperature of 36.5 ± 1.2 °C (see Section S2, Supporting Information for details). Each DNA sequence has a fluorescent label, which results in the following color-coded complementary pairs; orange and green for A and A', and red and blue for B and B', respectively. We use sequential capillarity-assisted particle assembly (sCAPA)[27] to create large numbers (>10'000) of well-defined colloidal sequences of A and B DNA-coated SiO_2 colloids on a template. sCAPA uses capillary forces to deposit colloidal particles from a moving and evaporating droplet into microcavities, i.e., traps embossed on an elastomeric (polydimethylsiloxane, i.e., PDMS) template. By controlling the deposition conditions,[26] individual particles are added one by one to the traps after each droplet passage and fixed in place by Van der Waals forces. Single sCAPA depositions have a yield of up to 99 %, and the flexibility of the method enables the "writing" of specific sequences of differently functionalized particles one colloid at a time (**Figure 1**.1).

2) *Introducing patchiness for directional binding*: Directional binding is essential for correctly pairing the monomer colloids to the template and requires endowing the deposited primer sequence with surface patches.[12,29] We achieve this by transferring the sCAPA-assembled colloidal sequences to a polymer layer. Upon melting the polymer, the particles sink into a controlled depth, leaving exposed only a small patch with DNA available for binding (Figure 1.2).

3) *Selective binding of complementary colloidal "monomers"*: In the binding step, we add the A' and B' magnetic colloids as monomers to attach to the primer sequences of patches (Figure 1.3). The binding is performed in a microfluidic device that flows the monomers over the primers with good control over the binding rate and enables the removal of excess monomers.

4) *Cross-linking of replicated sequences*: In order to release the copied sequences from the template without them breaking apart, the former must be cross-linked with bonds substantially stronger than the DNA bonds connecting them to the primer sequence. Previous studies have already established

that such cross-linking needs to be induced by interactions orthogonal to the DNA bonds, e.g., by light activation or adding cross-linking agents.[12–14] We use electrostatic bridging with a cationic polyelectrolyte (polyDADMAC), following a pre-alignment step with a magnetic field, to achieve high-yield cross-linking (Figure 1.4).

5) *Release from the template*: We apply mechanical vibration to release the cross-linked sequences as an effective alternative to melting the DNA bond,[25] (Figure 1.5).

6) *Purification*: Finally, after release, the replicated colloidal sequences are purified using fluorescence-assisted cell-sorting (FACS) (Figure 1.6).[30]

2. Results and Discussion

After introducing the workflow, we now present and discuss the experimental results. The sCAPA of DNA-coated colloids presents additional challenges relative to unfunctionalized particles. Due to the presence of a DNA brush on the particle surface, the adhesion between the PDMS and the particle after deposition is lower than with standard microspheres, which leads to some particles being removed from the traps during subsequent deposition steps. To overcome this issue, we heat the template to above 130 °C for a few seconds between depositions to fix the colloids in the sCAPA traps. We optimized the sCAPA conditions and trap design to consistently achieve an 80 % yield for a three-particle deposition, with an average yield of 93% per deposition (see Section S3.1, Supporting Information for details).

A trap depth of 1 µm implies that the complementary monomer particles have access to 63% of the deposited particles' surface for binding. This leads to a lack of directionality and the possibility of multiple bindings onto a single template particle. In order to decrease the available binding area, we embed the template particles into a spin-coated layer of polymer (polystyrene (PS) or polymethylmethacrylate (PMMA)). Upon heating the polymer above its melting temperature, the particles sink into the polymer to a depth determined by the contact angle between the polymer melt and the particle's surface, allowing the patch area to be adjusted based on the wetting of the polymer on the colloid (**Figure 2**a,b).[31] The insets of Figure 2b show that the number of binding particles is reduced by reducing the patch area, and, for PS, we achieve a minimum patch area of 9 %.

Nonetheless, we observed that the complementary colloids were rarely perfectly aligned with the template and that a broad distribution of binding angles was present.[32] Smaller patches restrict the range of binding angles, which avoids highly misaligned particles inhibiting access to the third colloid during sequence assembly (as shown in Figure 2c). For the replication experiments, we thus used the smallest patch sizes obtained by sinking the colloidal sequences in PS layers at a temperature of 140 °C to ensure the directional binding of single particles over a large area (Figure 2e).

We efficiently bind the complementary particles (**Figure 3**a) by flowing them over the template with a simple microfluidic chip (design and fabrication detailed in Extended Methods Section S1.3, Supporting Information). The controlled flow moves a monomer suspension, sedimented over the template, allowing easy binding (Movie S1, Supporting Information). The binding process takes approximately 15–20 min and yields 66%
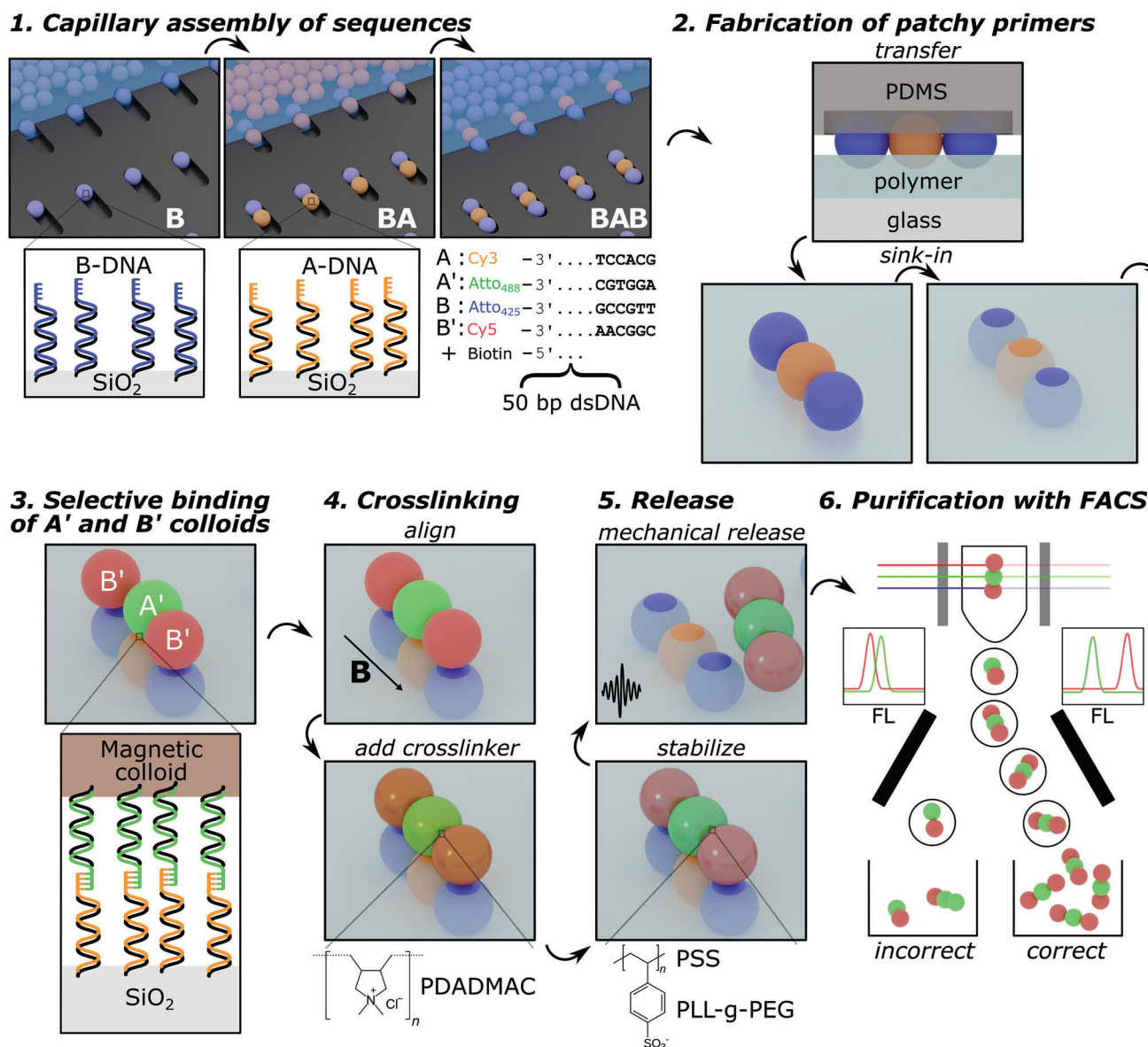
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Figure 1. Schematic overview of the process flow to replicate colloidal assemblies. The arrows follow the flow of the full process. 1) sCAPA of DNA-coated colloids to make BAB colloidal assemblies in three deposition steps. With schematic of the colloid's surface coated by dsDNA with sticky ends and fluorescent labels 2) Transfer and embedding of the colloidal assembly into a polymer layer to generate surface patches. 3) Binding of complementary colloids to the primer assemblies to obtain the B'A'B' sequence. 4) The alignment of the colloids with a magnetic field and the longitudinal cross-linking of the complementary sequence with a cationic poly-electrolyte (pDADMAC). 5) The addition of PSS and PLL-g-PEG stabilizes the cross-linked sequences, and mechanical vibration releases the complementary sequence from the template. 6) Sorting of the colloidal sequences using FACS.

binding of the correct sequences (Figure 3a,b. Further details in Section S3.1, Supporting Information).

However, as mentioned above, the distribution of binding angles implies that monomers are often not in close contact after binding. In these sub-optimal conditions, cross-linking is still possible with complementary SiO$_2$ colloids. Nonetheless, under these circumstances, the random spacing between colloids often results in inefficient cross-linking, with only 11% of the deposited sequences remaining intact after release (further details provided in Section S3.2, Supporting Information). However, this yield can be significantly improved by using su-

perparamagnetic colloids of the same size, such as Dynabeads M-270. After binding, a homogeneous magnetic field parallel to the direction of the sequences is applied with a pair of Helmholtz coils to pull the bound colloids together due to dipolar interactions (Figure 3a.2; and Movie S2, Supporting Information).[33] The particles are cross-linked with the field on, improving the yield of cross-linked sequences up to 92%. Note that all free monomers must be removed before the magnetic field is applied, as these unbound monomers may attach randomly to the end of the sequences under the magnetic field.
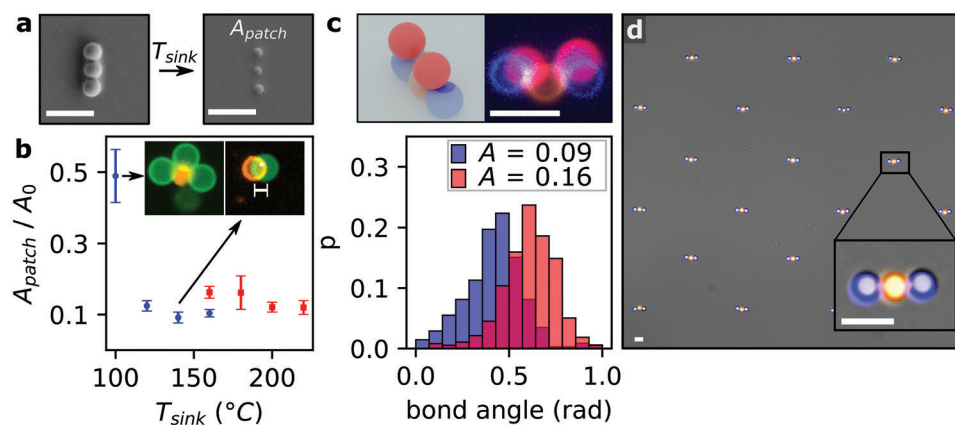
Figure 2. Formation and characterization of the patchy colloidal sequences. a) SEM micrographs of the particles on top (left) and sunken into the polystyrene (PS) (right). b) Patch surface area A_{patch} normalized by the colloid's total surface area A_0 as a function of sink-in temperature measured with atomic force microscopy (AFM) for PS (blue) and PMMA (red) films. The error bars correspond to the standard deviation of nine different colloids for each data point. The inset shows fluorescent composite micrographs of the complementary colloids binding to particles for two different patch sizes. c) The bottom graph shows the distribution of binding angles for normalized patch areas A of 0.09 (made with PS, blue) and 0.16 (made with PMMA, red), referring to the schematics and composite fluorescent micrograph of two B' colloids (red) on a BAB (blue-orange-blue) template blocking the center A' colloid from binding, as shown on top. The histograms are constructed by measuring 359 colloids for blue and 381 for red, respectively. d) Composite bright-field and fluorescence micrographs of a large area of BAB colloidal sequences made with sCAPA. Scale bars are 5 μm.

Even though different cross-liking approaches have been proposed in the literature,[20,25] we found that the most effective way to connect the complementary sequences was physically bridging the anionic colloids with a cationic polyelectrolyte (polyDADMAC) (more details on the cross-linking can be found in Section S4, Supporting Information) added to the bound monomers in the microfluidic chip. While polyDADMAC is a very effective cross-linker, it negatively affects the colloidal stability of the harvested sequences, which were further stabilized by the sequential addition of polystyrene sulfonate (PSS), poly(L-lysine)-g-poly(ethylene glycol) (PLL-g-PEG), and then PSS again (see Experimental Section for details). Although multiple functionalization steps are required, this approach gives highly reproducible results and robust structures.

The next step in the process involves releasing the complementary cross-linked sequences from the template. Despite the melting temperature of the DNA bonds being 38 °C, only a few colloids (≈ 15%) are released when heated to 70 °C (as detailed in Section S5.1, Supporting Information). We were instead able to release ≈ 95 % of the copied sequences from the template by mechanical vibration, as simply applied by an electric toothbrush (Oral-B, vibrating at 106 Hz with an amplitude of 0.7 mm, see Section S5.2, Supporting Information for further details). Moreover, 93% of the bound sequences were intact after release (Figure 3a,b). The released structures are stable for several days and withstand being pipetted, vortexed, and sorted by FACS, as presented later. We hypothesize that the polyDADMAC is too big to reach the primer colloids, and thus, the primer and monomers are not linked.

Making multiple copies of one template is essential for any replication system. The template sequences can be re-used for multiple replications (see Section S3.3, Supporting Information for details). However, the binding yield decreases by 60 % over three replication cycles, most likely due to the polyelectrolyte

blocking of the primer sequence over multiple exposures, and more work is needed to address this issue.

With the current replication method, we reach, at best, a final purity of around 50% of the correct sequences. In order to improve the purity of the final product, we utilize flow cytometry-based sorting (FACS). This technique is well-established for sorting in biology but has been rarely used for colloidal particles.[30] FACS is particularly effective in sorting the replicated colloidal sequences since they consist of discrete fluorescent particles that can be easily identified and sorted based on their composition. However, while FACS can sort different populations of particles, it cannot distinguish the order of the colloids within each cluster, i.e., isomers. The results of the FACS of replicated B'A'B' sequences are reported in **Figure 4a,b**. After extraction from the microfluidic device, the purity of the sample slightly decreased to 35 % due to monomer colloids and random clusters that were stuck in the tubing (see Section S3.3, Supporting Information for details).

The FACS sorted multiple populations, including the target population of two B' and one A' colloids, as well as the one A', one B', and two A', one B' fractions (Figure 4a), leading to a sample purity to 81 % of the target B'A'B' sequence with a sorting time of around 15 min (Figure 4b). The final yield is not 100 % due to the presence of the isomers and sequences broken during sorting, but it offers a great improvement (See Section S6, Supporting Information for details).

With the foundation set, we aimed to expand our colloidal replication approach by exploring a wider range of colloidal structures, which can easily be obtained by sCAPA. We first increased the length of linear sequences from three to four (Figure 4d) and five particles (Figure 4e). While it is theoretically feasible to replicate longer sequences; constructing these sequences one deposition at a time with sCAPA proves time-consuming, and the yield can dwindle with extended sequence lengths, owing to the multistep nature of the process, e.g., even with a 95% success rate for
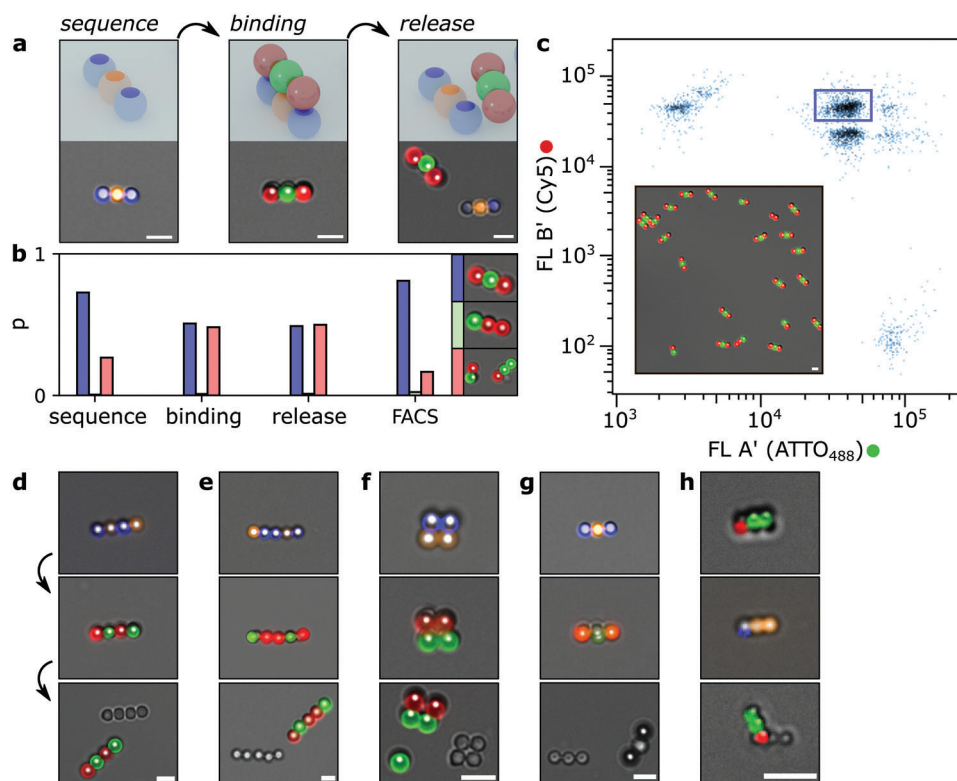
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Figure 3. Experimental replication of colloidal sequences a) Left) BAB (blue-orange-blue) sequences embedded in PS. Middle) Binding of A' (green) and B' (red) colloids on top and cross-linking of the complementary sequence. Right) Release of the complementary sequence. Top: schematic. Bottom: corresponding composite bright-field and fluorescence micrographs. b) Distribution of colloidal clusters after sink-in, binding, release, and FACS. The populations are divided into the target sequence (blue), sequences that are composed of the same colloids but in the wrong order/shape, i.e., isomers (green) and other sequences (red). Total cluster counts are: sequence 3341, binding 3167, release 3063, and FACS 403. c) FACS scatter plot showing the Cy5 (B') and ATTO488 (A') fluorescence intensity of the colloidal clusters obtained from replicating a BAB sequence. The blue rectangle indicates the target gate. The inset shows a composite bright-field and fluorescence micrograph. d–h) Replication of different colloidal structures. Top: composite bright-field and fluorescence micrographs of the template structure. Center: bound complementary sequences. Bottom: released complementary sequences next to the template. d) four-particle BABA sequence, e) five-particle BABBA sequence, f) BBAA square structure, g) multi-material BAB sequence with magnetic colloids (B) and SiO$_2$ (A) colloids, (the final panel is bright-field only to show the material contrast better.) h) BAA sequence with 1.3 µm colloids. Scale bars are 5 µm.

each deposition step, over a five-particle sequence, one gets 77% of the correct sequences at best.

In addition to linear chains, we replicated colloidal squares of two A and two B colloids (Figure 4f). We can moreover use different materials of the A' and B' particles, e.g., SiO$_2$ and magnetic colloids (Figure 4g), and we have also demonstrated our method with smaller 1.3 µm particles, using SiO$_2$ colloids as the primers and magnetic colloids (Dynabeads MyOne T1) as the monomers (Figure 4h). Even if the process is successful, there are some limitations worth noting. The yield of longer replicated structures is lower compared to three-particle clusters (see Sections S3.4 to S3.6, Supporting Information for details). Apart from requiring additional optimization work, longer sequences posed a higher risk of monomers blocking each other, resulting in decreased binding yield. In addition, cross-linking the squares and the bi-material structures proved to be difficult due to the limitations of the magnetic field bringing colloids together. Replication of smaller 1.3 µm colloidal sequences presented several difficulties, including a lower propensity to come into contact with the primer due to a lower buoyant weight, decreased effectiveness of cross-

linking due to the lower amount of magnetic material, and difficulties in releasing the sequences from the primer. These challenges provide areas of improvement for future colloidal replication methods, and we are optimistic that these obstacles can be overcome in future work.

3. Conclusion and Outlook

In summary, this study introduces and validates an innovative method for the microscale replication of programmable primer sequences into complementary copies with significant yield and purity. Beyond its efficacy, we extend the versatility of our approach by demonstrating its applicability across arbitrary sequences involving up to five particles of varying sizes and materials, surpassing existing synthetic replicating systems in terms of complexity, flexibility, and programmability. By successfully addressing significant experimental challenges, we believe that this approach represents a substantial step forward in the realm of replicating colloidal systems. Our methods' intricacies
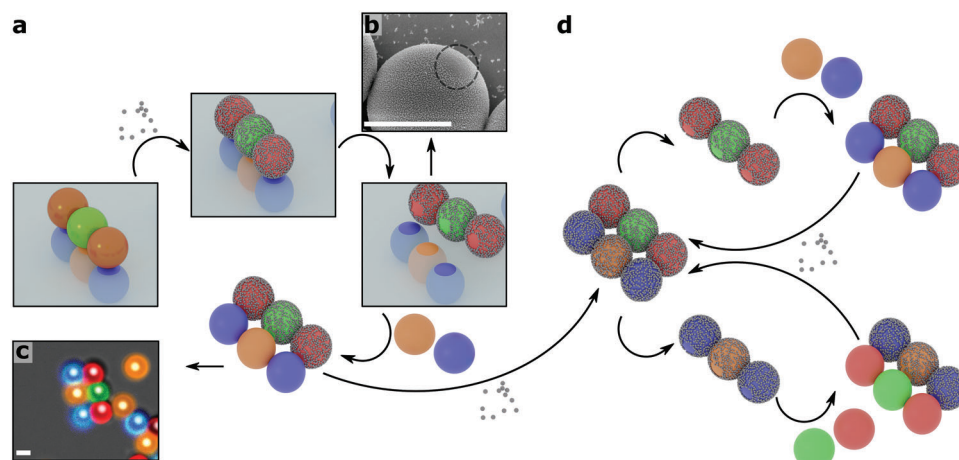
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Figure 4. Outlook: patch transfer and exponential replication in suspension. a) Schematic of the preliminary experiments for transferring surface patches: step 1) cross-linked colloids on the primer; step 2) addition of SiO$_2$ nanoparticles to block access to the DNA; step 3) releasing the first-generation replica to expose the non-blocked patches; step 4) adding the complementary A and B colloids to obtain the second replica. b) SEM micrograph of the empty patch on the surface of a 2.7 µm SiO$_2$ colloid after exposure to 8 nm SiO$_2$ nanoparticles. c) Composite bright-field and fluorescence micrographs of A (orange) and B (blue) colloids that selectively bind to a B'A'B' (red-green-red) patchy copy sequence. d) Schematic of an envisaged future pathway for exponential replication cycles. After the substrate-based replication and patch transfer, more nanoparticles are added to cross-link and generate patches on the bound sequence. The sequences are split into B'A'B' and BAB sequences, and complementary colloids are added. Subsequently, the free DNA is blocked, and colloids are cross-linked, ending up at the initial configuration. From there, the cycle can be repeated, doubling the number of colloidal sequences in each cycle. Scale bars are 2 µm.

underscore the hard challenges associated with template-based replication using particles.

While the current methodology, implemented on a solid substrate, facilitates linear growth in each replication cycle, the ultimate objective would be to achieve exponential replication, as demonstrated by other replicating systems.[4–6] The next critical developmental step involves transitioning from a substrate-based system to a suspension while maintaining well-oriented patches that support directional binding. A promising avenue for imparting surface patches to next-generation sequences involves blocking access to DNA on colloid's surfaces with nanoparticles while still bound to the primer, creating patches of available DNA with the correct size and orientation (Figure 4a). Preliminary experiments involving adding negatively-charged SiO$_2$ nanoparticles after the polyDADMAC treatment demonstrate the successful creation of small patches on the first replicas (Figure 4b; Section S7.1, Supporting Information provides additional details) and, upon addition of complementary A and B colloids, selective and directional binding in suspension (Figure 4c), albeit with a currently low yield (refer to Section S7.2, Supporting Information for details). These results showcase the feasibility of transferring surface patches and binding a second-generation primer sequence in suspension.

Envisaging future exponential processes, a similar strategy involves generating patchy colloidal sequences from surface patterns, as demonstrated in this work. In each replication cycle, free DNA is blocked during the binding/cross-linking phase, with blocking agents ideally doubling as cross-linkers (Figure 4d). The primary challenge lies in precisely controlling the moment of binding between blockers and colloids to prevent premature blocking or nonspecific cross-linking, which is not feasible with the current methods. Functionalizing the colloids with additional DNA[25,34] or finely tuned electrostatic interactions[35] could fa-

cilitate this control. The proposed approach significantly benefits from separating monomer colloids and colloidal sequences before blocking, achievable through FACS or precise microfluidic filters/sorters.[36–38] Microfluidic platforms could also facilitate the automated and controlled addition and removal of chemical components during replication cycles.

In conclusion, while this work represents an initial foray into this exploration and the current methods for replication are in their early stages and thus somewhat cumbersome, the presented preliminary data suggest the potential for achieving exponential self-replication in the near future. Self-replicating microstructures could revolutionize fabrication for various applications, such as colloid-based micromachines[39–43] or building blocks for self-assembled materials.[15,20,44] Moreover, self-replication could provide a platform for optimizing structures in an evolution-like manner through random mutations and selection.[6] Even if the dream of exponential replication proves elusive, our current methods, with minor refinements, hold considerable utility. They could in fact not only facilitate the automated (linear) production of colloidal assemblies but also serve as a novel microfluidic platform of precisely positioned DNA patches, enabling the capture and study of diverse microorganisms.

4. Experimental Section

DNA was grafted onto the colloids with streptavidin using protocols adapted from literature.[25,28] Following functionalization, the DNA-coated colloids were stored in a phosphate buffer (10 mM phosphate, 50 mM NaCl, 0.5 % Pluronic F-127, pH 7.4) at 0.5 % w/w. These colloids were assembled with sCAPA as described in literature[27] in a PDMS template using 0.015 % w/w colloids in an optimized sCAPA buffer (10 mM phosphate, 50 mM NaCl pH 7.4, 2 mM SDS, 0.02 % v/v Triton X-45). Between deposition steps, the PDMS template was heated to 130 °C for

45 s to improve adhesion. A layer of PS was spin-coated on a 0.17 mm glass coverslip using 40 % w/w PS 40 kDA in PGMEA at 4000 rpm for 30 s (approximate thickness 5 µm). After baking and annealing the PS film, the colloids were transferred to the PS on a hotplate at 110 °C for 20 s, and then the colloids were sunken in at 140 °C for 15 s (PMMA process described in the Extended methods). The polymer film loaded with the primer particle sequences became the bottom of a microfluidic cell comprising a 0.12 mm-thick double-sided sticky spacer (SecureSeal, Grace-bio) and a PDMS roof that was bonded at 120 °C for 1 min. The different liquids were pulled into the microfluidic cell using a syringe pump, starting with 3 µl of the complementary DNA-coated colloid suspension. Then, these colloids were bound to the primer colloids at 7 µl s^{-1} (velocity of 9.3 $\pm$ 0.7 µm s^{-1}) in 10 mM phosphate, 250 mM NaCl, 0.5 % Pluronic F-127 pH 7.4. Following the binding, a magnetic field was applied, and the samples were cross-linked with 0.1 w/w % PDADMAC, followed by sequential additions of 0.1 w/w % PSS and 0.1 w/w % PLL-g-PEG with washings in between. Finally, the complementary colloidal clusters were released by mechanical vibration using the tip of an electric toothbrush (Oral-B). The yields of the different steps were characterized using fluorescence microscopy (Nikon, Eclipse Ti-2), and FACS (BD-FACSAriaIII) was used to purify the samples. Extended Methods can be found in the Supporting Information.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

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