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A Programmable DNA Double-Write Material: Synergy of Photolithography and Self-Assembly Nanofabrication

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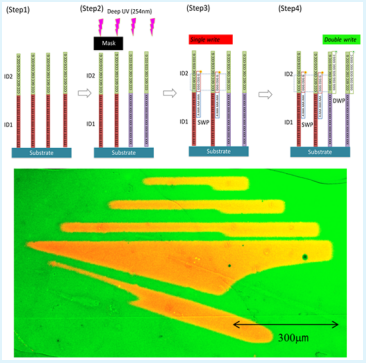
Supporting Information

ABSTRACT: We demonstrate a DNA double-write process that uses UV to pattern a uniquely designed DNA write material, which produces two distinct binding identities for hybridizing two different complementary DNA sequences. The process requires no modification to the DNA by chemical reagents and allows programmed DNA self-assembly and further UV patterning in the UV exposed and nonexposed areas. Multilayered DNA patterning with hybridization of fluorescently labeled complementary DNA sequences, biotin probe/fluorescent streptavidin complexes, and DNA patterns with 500 nm line widths were all demonstrated.



KEYWORDS: *DNA, patterning, photolithography, thymine dimer, displacer effect, self-assembly*

Functional biomaterials based on DNA allow for patterning by a variety of methods,[1,2] as well as self-assembly nanofabrication of DNA derivatized with fluorophores, nanoparticles, and other entities.[3,4] A key advantage for using DNA self-assembly is that oligonucleotide sequences with as few as 16 bases can provide a huge number ($>1 \times 10^9$) of sequence programmed nanoscale structures (1.25 nm × 6 nm). Each of the DNA sequences can be designed with a unique and highly specific binding identity that can form a stable hybrid with its complementary DNA sequence. Self-assembly by hybridization of complementary DNA sequences derivatized with fluorophores, nanoparticles, and other entities is a rapid, simple, and selective process compared to methods that utilize chemical binding agents. Patterning on DNA substrates that produce a single binding identity has been carried out using prepatterned polymer-blocking materials such as poly(methyl methacrylate) (PMMA) and electron beam lithography,[5] and also by destructive micropatterning and rolling-circle amplification methods.[6,7] Other approaches for patterning with DNA and DNA nanoparticles that attempt to merge aspects of top-down and bottom-up techniques include microcontact printing,[8] silk screen patterning,[9] patterning on nanosize prepatterned etched template substrates,[10] and patterning using AFM tips.[11] A DNA patterning photolithography[12,13] process has been developed where UV exposure produces thymine base dimerization preventing hybridization in the exposed areas.[14] This process is single-write in that it only allows subsequent self-assembly by hybridization to occur in the masked areas. Other work has been carried out where UV -sensitive agents such as psoralen have been used to produce cross-linking between two DNA strands.[14−16] More recently, DNA sequences modified with the UV cross-linker cinnamate and UV photocleavage 2-nitobenzyl linker have been used to produce interstrand cross-linking.[17,18] Further efforts have also been carried out on developing wavelength dependence for the photoreversal of a psoralen-DNA cross-linking.[19,20]

Here, we demonstrate a novel DNA double-write material based solely on the design of DNA sequences. The DNA write sequence is designed with discrete placement of thymine bases which are sensitive to UV irradiation,[14,21] while one of the two complementary DNA sequences is designed to produce a displacer probe effect.[22,23] Upon UV patterning of the DNA write sequence, which is immobilized on a support (glass, silicon, etc.), two distinct binding identities are produced to which two different complementary DNA sequences can be hybridized. This allows DNA-based self-assembly as well as further UV patterning to be carried out in both the UV exposed and nonexposed areas. Together these unique sequence design parameters enable the DNA double-write process. The mechanism for blocking hybridization in the DNA write sequence is thymine dimerization induced by deep UV irradiation. Exposure of DNA sequences containing thymine

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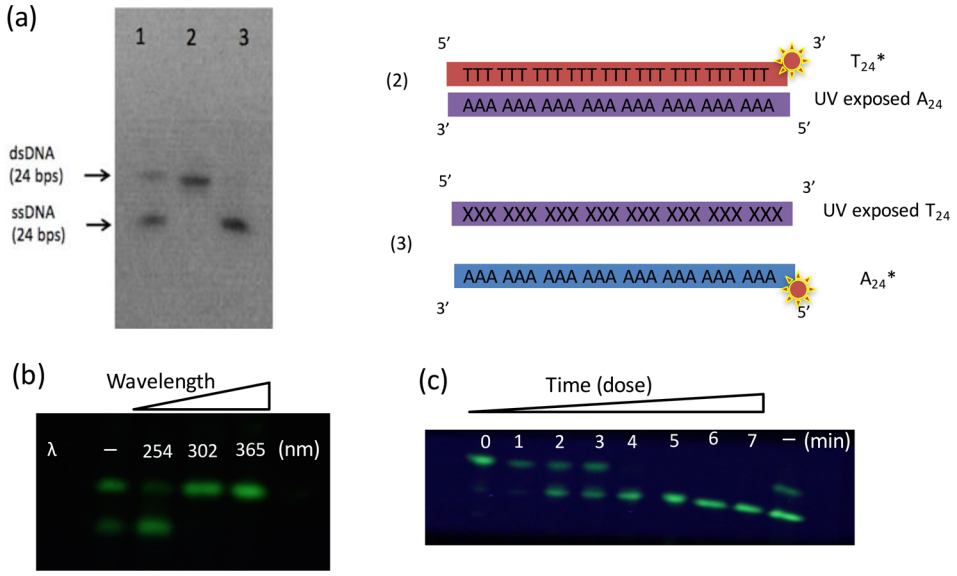

Figure 1. PAGE gels showing thymine dimer formation. (a) ds-DNA T_{24}/A_{24} and ss-DNA T_{24} and A_{24} lane 1, hybridized ds-DNA (T_{24}*lA_{24}) when A_{24} exposed to UV lane 2, dehybridized ss-DNA (T_{24} and A_{24}*) when T_{24} exposed to UV lane 3, (b) dehybridization of ds-DNA at different UV wavelengths, and (c) dehybridization of ds-DNA by UV dose.

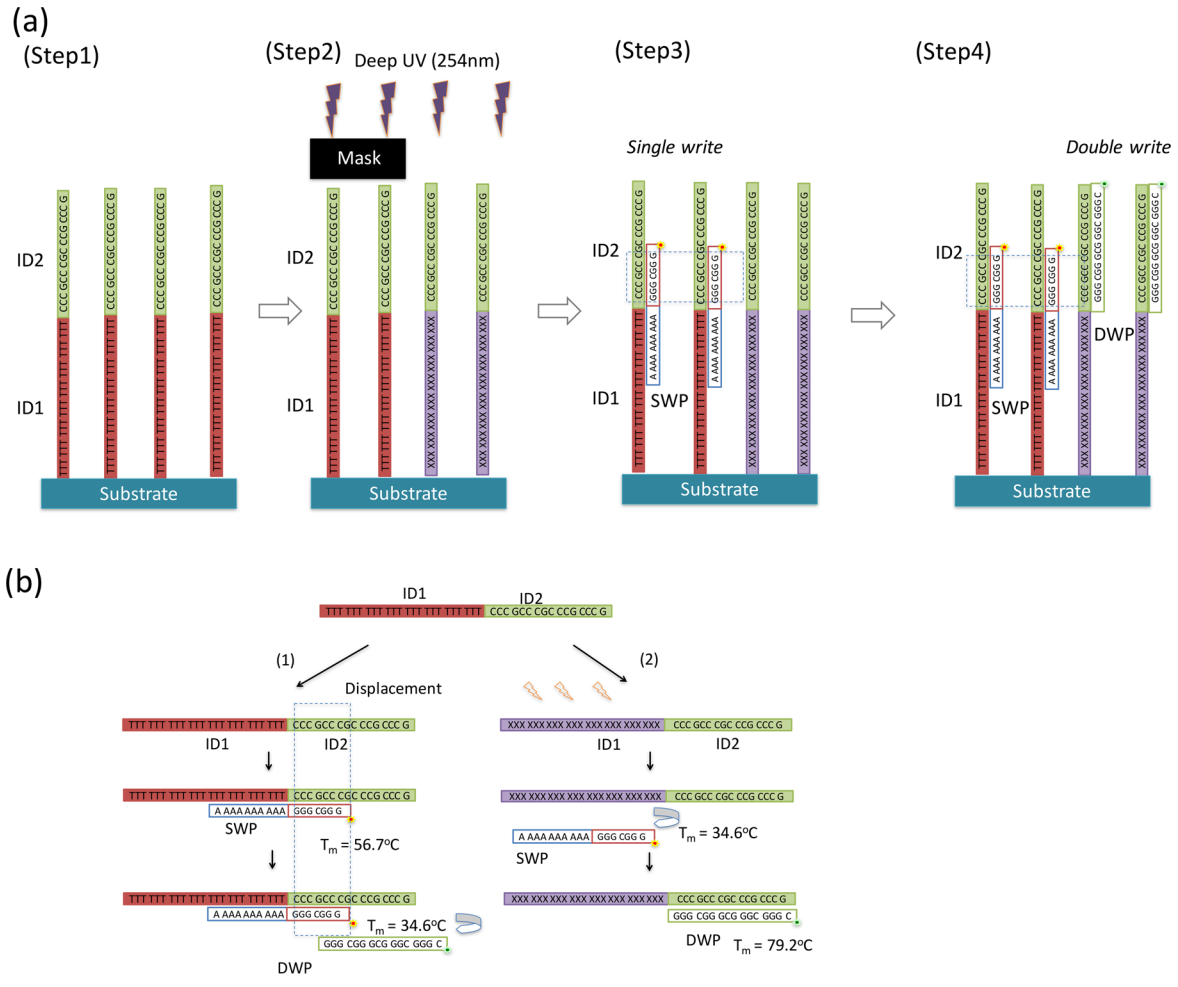

Figure 2. Scheme for the DNA double-write process. (a) Step 1, immobilization of the DNA double-write sequence (FWS:ID1&ID2) onto the glass substrate. Step 2, photomasking and UV exposure. Steps 3 and 4, hybridization of the red fluorescent SWP probe sequence 5′-Alex546-GGG CGG GAA AAA AAA AA-3′ and the green fluorescent DWP probe sequence 5′-Alex488-GGG CGG GCG GGC GGG C-3′. (b) Effect of displacer and thymine dimer formation on probe hybridization and melting temperatures (T_m).

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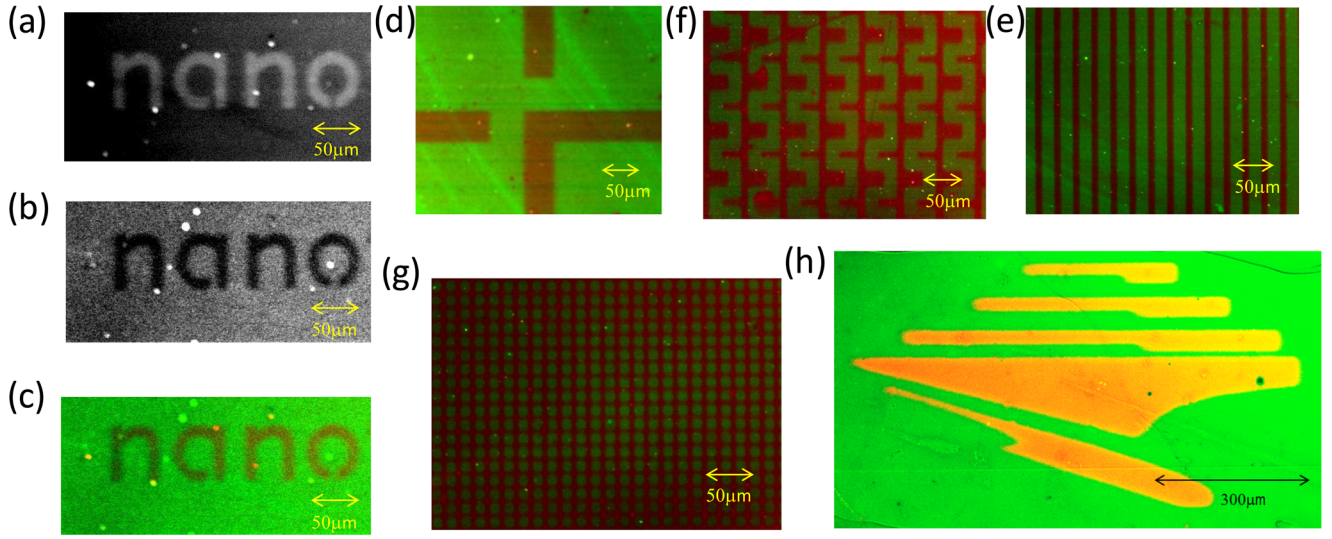

Figure 3. DNA double-write UV pattern images. (a) Black and white image of the single-write with red SWP probe hybridized on the letters. (b) Black and white image of the second write with DWP was hybridized in background. (c) False color image with single-write red SWP probe and second write green DWP probe. (d–h) More double-write images (first write color is red, second write color is green.

bases to short wavelength UV light (~254 nm) causes formation of thymine dimer cyclobutane 6–4 photoproducts.[20,21] The dimerization of the thymine bases prevents hydrogen bonding to the adenine bases in the complementary DNA sequence.

In Figure 1, we show an electrophoretic (PAGE gel) separation demonstrating that a UV exposed A_{24} oligonucleotide can still hybridize to a complementary Cy3-T_{24} oligonucleotide (lane 2), while a fluorescent Cy3-A_{24} oligonucleotide does not hybridize to a UV exposed T_{24} oligonucleotide (lane 3). To optimize the DNA patterning process based on thymine dimer formation, we developed an assay using the T_{24} oligonucleotide hybridization to the Cy3-A_{24} oligonucleotide. Figure 1b shows the results for exposing the T_{24} oligonucleotide to different UV wavelengths (254, 320, and 365 nm) for 5 min. Exposure at 254 nm (5 min) was found to be most effective in preventing the hybridization of the Cy3-A_{24} oligonucleotide to the Cy3-A_{24} oligonucleotide. Next we investigated varying UV exposure times at 3 mW/cm^2 at a 2 cm working distance. Results in Figure 1c show a 2 min exposure was not enough to completely block hybridization, whereas a 5 min exposure appears optimal for preventing hybridization of the complementary Cy3-A_{24} oligonucleotide.

The unique DNA write sequence used in the DNA double-write process is designed to allow two complementary DNA probe sequences with distinguishable identities to bind (hybridize) to the DNA material after UV patterning. The scheme for the DNA double-write process and the DNA sequences are shown in Figure 2a, b. The first step in the overall process is the immobilization of the specially designed first DNA double-write sequence (FWS:ID1&ID2) onto the glass substrate surface (Figure 2a, step 1). The second step in the process is the photomasking and UV exposure, which is carried out for 5 min (Figure 2a, Step 2). The third and fourth steps are hybridization of the red fluorescent SWP probe sequence 5′-Alex546-GGG CGG GAA AAA AAA AA-3′ and the green fluorescent DWP probe sequence 5′-Alex488-GGG CGG GCG GGC GGG C-3′ (Figure 2a, steps 3 and 4). Generally the hybridization steps take about 30 min, including the washings. The first DNA write sequence (FWS:ID1&ID2) 5′-TTT TTT TTT TTT TTT TTT TTT TTT (ID1)-CCC GCC CGC CCG CCC G (ID2)-3′ is designed with two distinct sections, ID1 (red, Figure 2a, b) and ID2 (green, Figure 2a, b). This design allows two different complementary DNA probes to be specifically hybridized to the unexposed regions (red, Figure 2a and 2b(1)) and the UV exposed regions (purple, Figure 2a, b(2)), respectively. The first complementary DNA probe sequence is a red fluorescently labeled single-write probe (SWP) 3′-AAA AAA AAA AGG GCG GG-5′-Alex546, and the second complementary DNA probe sequence is a green fluorescent double-write probe (DWP) 3′-GGG CGG GCG GGC GGG C-5′-Alex488. The design of the UV sensitive thymine base sequence in the ID1 (red) area of the DNA write sequence FWS:ID1&ID2 is of key importance for the double-write process. However, the design of the ID2 (green) sequence, and the design of the SWP and DWP complementary DNA probe sequences are equally important. Special consideration is given to melting temperature (T_m) of the sequences, as well as incorporation of a displacer property into the SWP complementary DNA probe sequence. The displacer property is enabled by designing the SWP probe so it is not only complementary to the ID-1 (red) sequence of the FWS:ID1&ID2, but also has a short segment of sequence (GGGCGGG) that is complementary to a section of the ID-2 (green) sequence (boxed areas in Figure 2a, b). The SWP and DWP hybridization and T_m data in Table S1 show for case 1 with no UV exposure, the hybridization efficiency of SWP probe to the FWS-ID1&ID2 sequences is high (T_m = 56.7 °C). For case 2 with UV exposed, the hybridization efficiency of SWP probe to the FWS-ID1&ID2 sequences is much lower (T_m = 34.6 °C). For case 3 with no UV exposure, the hybridization efficiency of the DWP probe to the FWS-ID1&ID2 sequence with the SWP probe hybridized is now much lower (T_m = 34.6–45 °C). This reduction in T_m for DWP is due to the displacer effect of SWP. For case 4 with UV exposure, the hybridization efficiency of DWP probe to the FWS-ID1&ID2 sequences is high (T_m = 79.2 °C). In this final case, the hybridization of the SWP probe is significantly reduced due to thymine dimerization in write sequence ID1

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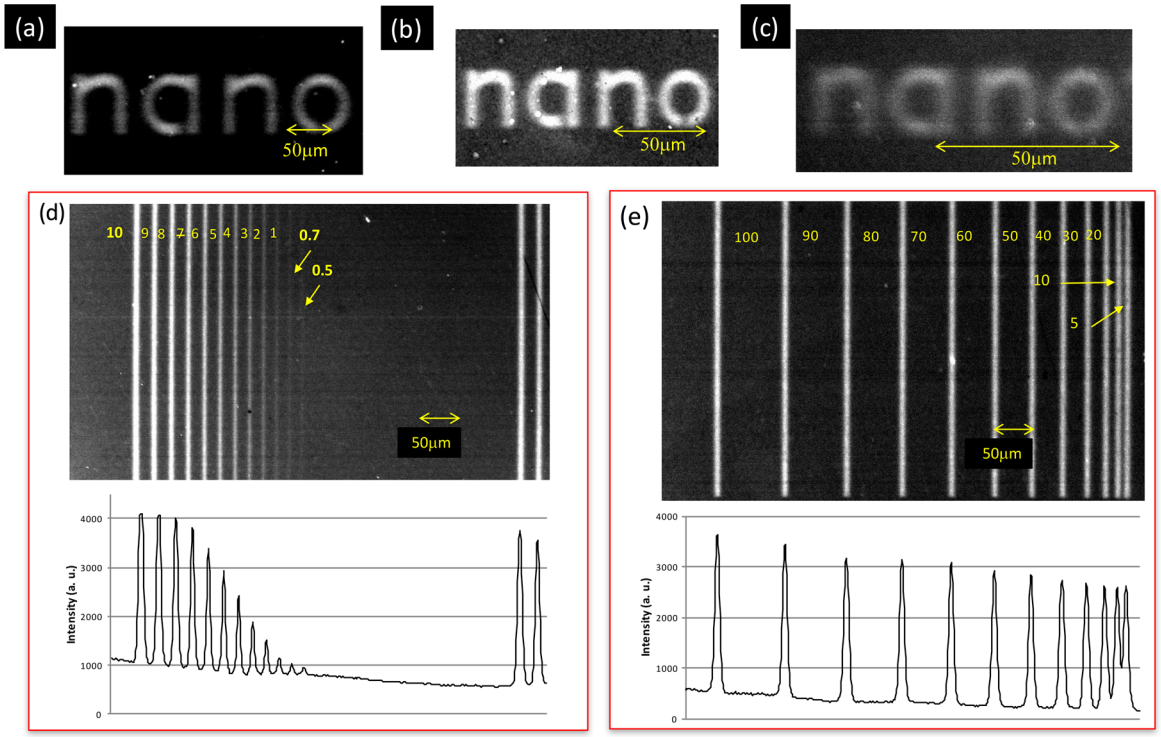

Figure 4. DNA double-write line widths with first level write. (a–c) Images of letters at 10 μm line width, 5 μm line width, and 2 μm line width. (d) Line width resolution from 10 μm to 500 nm. (e) Gap resolution from 100 to 5 μm.

region, and the DWP probe can now hybridize with very high efficiency.

A first set of results for the DNA double-write using the immobilized FWS:ID1&ID2 and the red (SWP) and green (DWP) complementary fluorescent probes are shown in Figure 3. The letters in the patterned feature (nano) are approximately 40 μm in width, resulting from the hybridization of the red probe SWP in the unexposed areas. Figure 3a shows a black and white fluorescent image of the hybridized red SWP (ex 555 nm, em 571 nm) as white letters on a black background. The image in Figure 3b shows the hybridized green DWP (ex 492 nm, em 517 nm) as a white background with darker letters. Figure 3c shows the false color image with the red fluorescent letters (nano) and the green fluorescent background. Finally, Figure 3d–h shows a variety of UV patterned images using the DNA double-write photolithographic process. Some of the spotting and blemishes are due to imperfections and inhomogeneity on the substrate surface. Carrying out the hybridization steps at higher stringency (higher T_m) should improve the hybridization specificity of the SWP and DWP probes to unexposed and UV exposed areas, respectively.

To better demonstrate DNA double-write patterning by deep UV exposure, the next set of experimental results were obtained from the double-write sequence (FWS:ID1&ID2) on the substrate with a thinner DNA layer (1.2–13.6 nm) to improve resolution.[24] In the first step, the DNA write sequence (WS:ID1&ID2) was immobilized on the glass substrate surface. After deep UV light (254 nm) exposure for 5 min through the photomask (with letters blocked), a red fluorescent complementary probe (Alexa546-A_{24}) was hybridized onto the substrate. Figure 3d-h shows three sets of images for the patterned feature, where line widths for the letters are 10 μm (Figure 4a), 5 μm (Figure 4b), and 2 μm (Figure 4c). The line edges of the letters still appear to be very sharp. Figure 4d and 4e provide further results for patterned line images, showing line widths from 10 μm down to 500 nm, with 20 μm spacing gaps (Figure 4d), and patterned spacing gaps from 100 to 5 μm with 10 μm line width (Figure 4e). These results show three times better feature size resolution for the DNA double-write process compared with previous results reported for photo-cross-linking chemistry-based DNA patterning.[24]

In further sets of experiments, we were able to demonstrate a second level DNA write and multilayer patterning with different complementary probes labeled with other fluorophores and fluorescent streptavidin. The second level write was enabled by designing a second DNA write sequence (SWS:ID3&ID4) 3′-CGG GCG GGC GGG CGG G(ID3)-TTT TTT TTT TTT TTT TTT TTT TTT(ID4)-5′ that was able to hybridize to the ID2 section of the FWS:ID1&ID2 sequence originally immobilized on the support (Figure 5a). After a first level UV patterning, the FWS:ID1&ID2 sequence was hybridized with the red fluorescent probe Alexa546-A_{24}, which hybridizes to the unexposed ID1 regions of FWS:ID1&ID2. (A green fluorescent Alexa488-A_{24} was used in the second experiment). The substrate was then hybridized with the SWS:ID3&ID4 sequence, which hybridizes to the ID2 region of FWS:ID1&ID2. A second UV patterning step was then carried out, and a green fluorescent probe Alex488-A_{24} was hybridized to the unexposed ID4 regions of the SWS:ID3&ID4. The results for the hybridization of the red and green fluorescent probes to the first and second DNA layers are shown in Figure 5d. A second experiment was carried out using hybridization of a biotin probe and subsequent labeling with fluorescent streptavidin (Figure 5b). In this case, after the second UV patterning of the substrate, a biotinylated probe (biotin-A_{24}) was hybridized to the unexposed ID3 regions of the SWS:ID3&ID4 sequence. The substrate was then treated with red fluorescent Cy3-Streptavidin which binds to the

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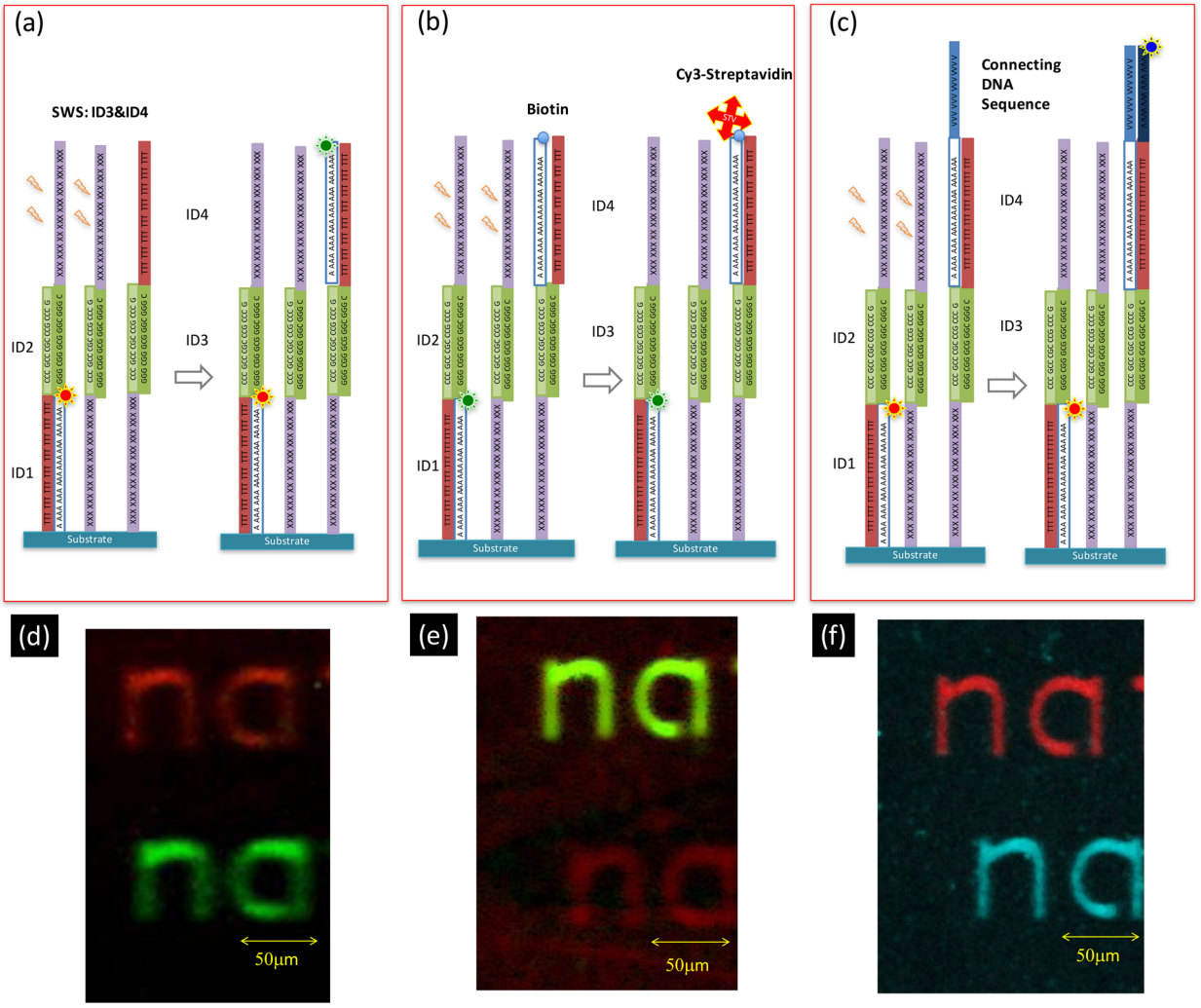

Figure 5. Scheme and results of DNA double-write with second level write. (a–c) Scheme for second level write with write sequences and complementary probes. (d) Confocal images of the DNA double-write with a second level write using complementary red fluorescent probe (upper) and green fluorescent probe (lower). (e) Confocal image of the DNA double-write with a second level write pattern detection by biotin/Cy3-streptavidin (lower). (f) Confocal image of the DNA double-write with a second level write pattern detection of using a connecting DNA probe sequence, with final hybridization of a far red fluorescent probe (lower).

biotin-A_{24} probe. The results for hybridization of the green fluorescent complementary probe to the first DNA layer and the biotin probe/red fluorescent streptavidin to the second DNA layer is shown in Figure 5e. This result is important, as it demonstrates that in addition to self-assembly by hybridization, it is also possible to use biotin–streptavidin ligand binding for further self-assembly. A third experiment was carried out using a connecting probe sequence. In this case, after the second UV patterning of the substrate, the connecting probe 5′-AAA AAA AAA AAA AAA AAA AAA AAA CAG GAC AGA CAG G –3′sequence was hybridized to the unexposed ID3 regions of the SWS:ID3&ID4 sequence (Figure 5c). The far red fluorescent complementary probe 5′-Alex647-CCT GTC TGT CCT G –3′ sequence was then hybridized to the connecting probe sequence. The connecting probe sequence contains a 13 bp target DNA sequence 5′-CAG GAC AGA CAG G-3′ that is complementary to the 5′-CCT GTC TGT CCT G-3′ in the far red probe. The results for hybridization of the red fluorescent complementary probe of the first DNA layer and the connecting probe/far red fluorescent probe of the second DNA layer are shown in Figure 5f. This result is also important in that it demonstrates self-assembly by multiple hybridizations. The three different second level write experiments show the viability of the DNA double-write process, and represent just a few of the many DNA constructs that could be created using DNA write materials.

In this study, we have shown that a DNA double-write material and process could be used to create patterns with 500 nm line width resolution. Ultimately, much higher resolutions and shorter exposure times may be possible by using a sophisticated stepper and a high energy deep UV (192 nm, 254 nm) source. It should also be possible to produce more homogeneous DNA write layers immobilized on smoother, more defect free substrates. A variety of multiple layered DNA hybridization patterns and biotin streptavidin binding reactions were also demonstrated. We have introduced a novel method for UV photolithographic patterning of a unique DNA write material and subsequent self-assembly nanofabrication via hybridization. This approach creates two distinguishable identities after UV exposure, allowing two different complementary probes to be hybridized to the UV exposed and unexposed areas. The key to this new process is in the DNA

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sequence design, which includes the presence of UV sensitive thymidine bases in the write sequences, and the specially designed complementary probe sequences which include a displacer effect for specificity to the UV exposed and unexposed areas. Most importantly, the write sequences and complementary probe designs shown in this study do not preclude encoding a much larger number of unique binding identities into DNA as well as RNA and PNA sequences. The DNA double-write process we have described represents a true synergy of top-down (photolithography) and bottom-up (self-assembly) approaches that will have an impact on DNA nanotechnology. For example, it may be possible to combine our technique with DNA origami[25] and use UV patterning to produce additional conformational changes and interactions within the DNA origami structures.[26] Since our work actually shows selective DNA information changing by UV photolithography, the new materials and process may be used with techniques employed with DNA chemical computing systems;[27] for example, using the displacer effect of ss-DNA with higher melting temperatures[28] with surface connected DNA computing[29] to build an enzyme-free process that allows a translation system for higher sequence specificity.[30] These represent just a few of the potential DNA nanofabrication applications that may be possible using the new DNA double-write materials and process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.6b11361.

PAGE and diagram of dehybridization by UV dose (Figure S1), estimation of melting temperature (Table S1), whole sequences of these experiment (Tables S2 and S3), and experimental detail of DNA (PDF)

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Notes

The authors declare no competing financial interest.

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