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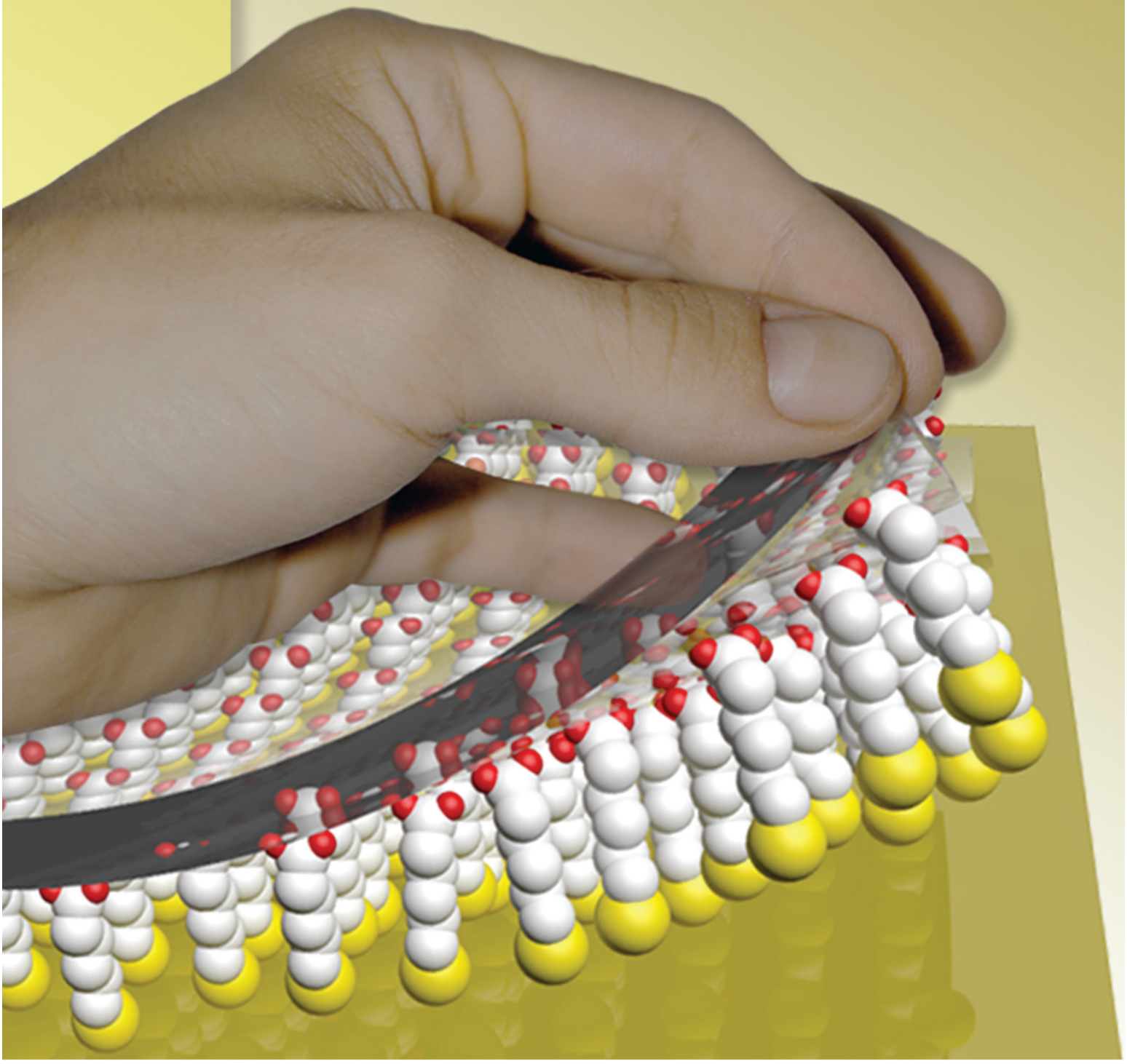

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Double-Sided Opportunities Using Chemical Lift-Off Lithography

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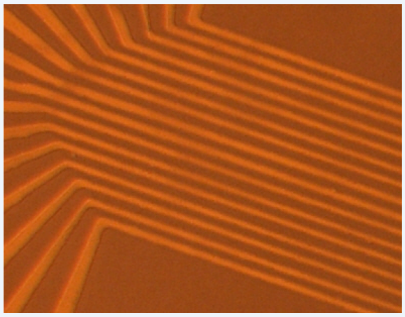
CONSPECTUS: We discuss the origins, motivation, invention, development, applications, and future of chemical lift-off lithography, in which a specified pattern of a self-assembled monolayer is removed, i.e., lifted off, using a reactive, patterned stamp that is brought into contact with the monolayer. For Au substrates, this process produces a supported, patterned monolayer of Au on the stamp in addition to the negative pattern in the original molecular monolayer. Both the patterned molecular monolayer on the original substrate and the patterned supported metal monolayer on the stamp are useful as materials and for further applications in sensing and other areas. Chemical lift-off lithography effectively lowers the barriers to and costs of high-resolution, large-area nanopatterning. On the patterned monolayer side, features in the single-nanometer range can be produced across large (square millimeter or larger) areas. Patterns smaller than the original stamp feature sizes can be produced by controlling the degree of contact between the stamp and the lifted-off monolayer. We note that this process is different than conventional lift-off processes in lithography in that chemical lift-off lithography removes material, whereas conventional lift-off is a positive-tone patterning method. Chemical lift-off lithography is in some ways similar to microtransfer printing. Chemical lift-off lithography has critical advantages in the preparation of biocapture surfaces because the molecules left behind are exploited to space and to orient functional(ized) molecules. On the supported metal monolayer side, a new two-dimensional material has been produced. The useful important chemical properties of Au (vis-à-vis functionalization with thiols) are retained, but the electronic and optical properties of bulk Au or even Au nanoparticles are not. These metal monolayers do not quench excitation and may be useful in optical measurements, particularly in combination with selective binding due to attached molecular recognition elements. In contrast to materials such as graphene that have bonding confined to two dimensions, these metal monolayers can be straightforwardly patterned—by patterning the stamp, the initial monolayer, or the initial substrate. Well-developed thiol−Au and related chemistries can be used on the supported monolayers. As there is little quenching and photoabsorption, spectroscopic imaging methods can be used on these functionalized materials. We anticipate that the properties of the metal monolayers can be tuned by varying the chemical, physical, and electronic connections made by and to the supporting molecular layers. That is, the amount of charge in the layer can be determined by controlling the density of S−Au (or other) connections and the molecular backbone and functionality, which determine the strength with which the chemical contact withdraws charge from the metal. This process should work for other coinage-metal substrates and additional systems where the binding of the outermost layers to the substrate is weaker than the molecule−substrate attachment.



MOTIVATION AND ORIGINS

In early studies of self-assembled monolayers (SAMs) of thiols and related molecules on Au{111},[1−4] the relative strengths of the molecule−substrate S−Au bond and the Au−Au bond were compared by saying that if one could somehow mechanically pull the molecules off the surface, a layer of attached Au atoms would come off as well (this explanation is attributed to Prof. George Whitesides). This description has the advantage of incorporating the subtlety that the adsorption and/or attachment of electronegative species to coinage metals has the effect of reducing the strength of the cohesive energy of the top layer of substrate atoms with the underlying substrate. This effect has been known and used for decades by electrochemists to smooth coinage-metal electrode surfaces since it mobilizes the top layer of substrate atoms;[4] it is also observed in the outward relaxation of the outermost substrate layer in structural measurements and shifts in the Debye−Waller factors for the vibrations of the outermost substrate layer.[3]

With these concepts in mind, we explored the dynamics that lead to phase separation in SAMs[4,5] and discovered that molecular motion takes place predominantly at substrate and

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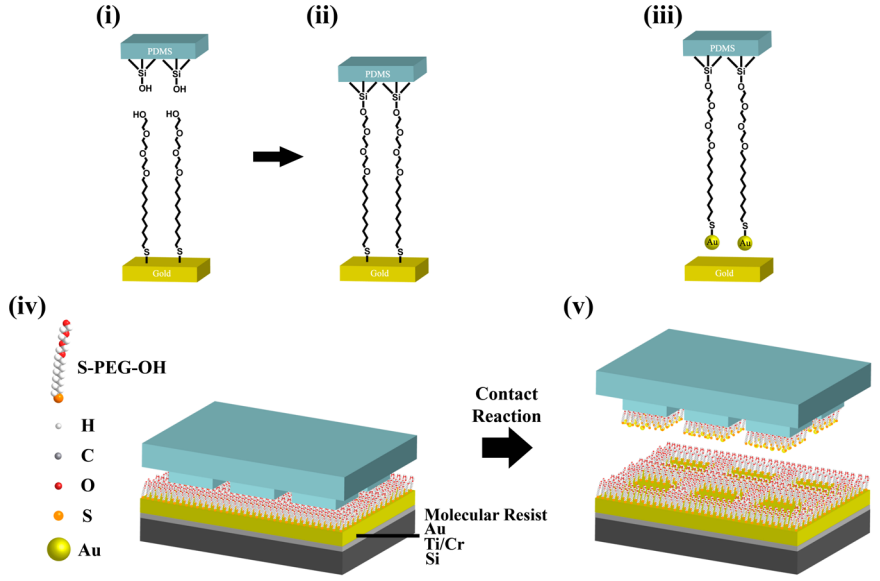

Figure 1. Schematic of chemical lift-off lithography, in which a patterned polymer stamp is activated (oxidized) to be reactive with respect to the exposed chemical functionality of properly terminated self-assembled monolayers (SAMs). When the patterned regions are removed via contact with the monolayer, the molecules of the SAM and attached Au atoms are removed, leaving the SAM subtractively patterned and the stamp additively patterned. Reproduced with permission from ref 34. Copyright 2012 American Association for the Advancement of Science.

monolayer defects and via molecule−substrate atom complexes.[6,7] Key insights were that SAMs on Au{111} never reach equilibrium, but (with sufficient film defects) motion continues in that direction, with domain coalescence, step flow, and other dynamics.[3,4] Conversely, the more complete and perfect the monolayer, the less is the molecular motion within the SAM. Thus, we developed the means to process monolayers to complete the films, such as when SAMs were annealed in the presence of alkanethiol (or other adsorbate) vapor.[8]

As a further step, we isolated single molecules and assemblies by inserting them into defects in SAMs.[9−12] Single, isolated (vs clustered) molecules can be made the most common species of those inserted into SAM matrices by processing the films to make domain boundaries (vs void spaces at substrate step edges and on terraces) the predominant defects on surfaces. Isolated molecules can then be studied using scanning probe microscopy, related spectroscopic imaging methods, or plasmon-enhanced Raman spectroscopy.[8,13−15] Further work enabled the insertion of pairs of proximate molecules by insertion of disulfides, for which the substrate cleaved the disulfide bonds of the inserted molecules.[11] By modification of the processing conditions after codeposition, matrix-isolated lines or clusters of molecules can also be produced.[5,12]

We and others have developed such surfaces for biorecognition. Here, insertion strategies are used to separate tethered small-biomolecule targets from one another stochastically, but with average separations set by the processing conditions that determine the types and defect densities in the SAM matrices.[16−20] In one approach, universal tether molecules were inserted and thereby isolated into prepared (i.e., processed) SAM matrices. These isolated molecules were then reacted with precursors or derivatives of the biomolecular targets to yield bioactive surfaces with SAM matrices that otherwise resist nonspecific binding.[16,17,21] This method has the advantage that the processing and insertion conditions are generalizable. However, a key issue vis-à-vis reactions of molecules already in SAMs is that the reaction exothermicity can mobilize the molecules, annealing and ordering or disordering the films.[22−24] In contrast, reactions of *isolated* molecules do not disrupt the films nor the extant nanostructures.[10,17,23,24]

Whitesides and co-workers developed *microcontact printing* with rubber (polydimethylsiloxane, PDMS) stamps to pattern down to the scale of tens to hundreds of nanometers.[4,25−28] In their seminal work, thiol inks were stamped onto bare Au substrates to create nano- and microscale chemical patterns. This technique led to widespread availability of chemical patterning and was expanded to other inks and substrates and to applications using the patterned inks as resists for nano- and microlithography. However, for "ink" molecules without substantial cohesive energy, the patterns blur as the ink molecules diffuse across the substrate prior to a (typical) backfilling step. It was also difficult to maintain fine registration if multiple patterning steps were required, since the stamps are not rigid. A partial solution to these issues came from precoating the substrates with sacrificial, labile monolayers, such as self-assembled adamantanethiol, with low surface−Au bond density and low intermolecular interaction energies.[29,30] The stamped molecules then displace the labile monolayer where stamp contact is made but do not displace preformed monolayer molecules by diffusion.

Subsequently, we used *insertion* into pre-existing monolayer matrices on surfaces such that relative measurements and multiplexing could be built into single substrates.[10,21,26,31−33] As with displacement printing, the inserted molecules are held in place by the surrounding matrix; diffusion and pattern dissolution are minimized. Beyond typical alkanethiols, we determined that microcontact insertion printing could be used to print hydrophilic ink molecules by tuning the stamp surface energy via controlled oxygen plasma exposure to match the monolayer surface energy.[32] A key consequence was the discovery that oxidized PDMS stamp surfaces lead to reaction with and lift-off of SAM molecules.[34]

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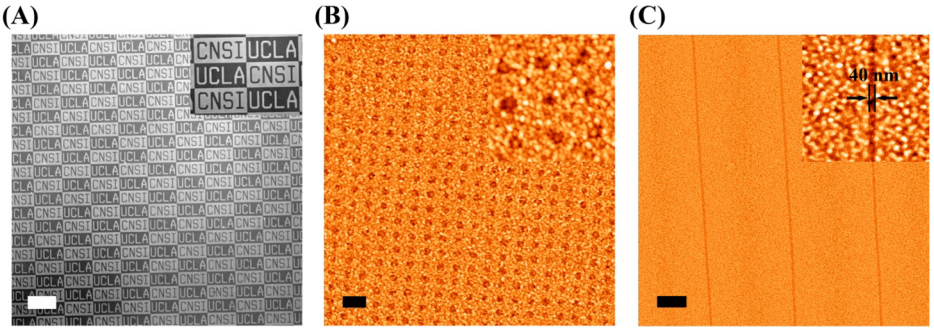

Figure 2. Fluorescence and atomic force microscopy (AFM) images of chemical lift-off lithography used to create micro- and nanoscale features across millimeter areas. (A) Self-assembled tris(ethylene glycol)alkanethiol on Au was subjected to the lift-off process using a polydimethylsiloxane (PDMS) stamp with "UCLA" characters as positive (protruding) features and "CNSI" characters as negative (depressed) features. After the initial patterning step, a new mixed monolayer was deposited into the exposed Au regions ("UCLA" characters and areas surrounding the "CNSI" characters). Bright areas indicate fluorescence associated with fluorescein isothiocyanate-labeled antistreptavidin antibody recognition of streptavidin bound to biotin. The dark areas have minimal fluorescence due to the protein-resistant ethylene glycol-terminated matrix SAM. The sharp fluorescence pattern extends over the entire substrate area (>3 mm^2). The scale bar is 250 μm. (B) Au-coated substrates with SAMs were lifted off using a PDMS stamp with 90 nm diameter holes. After patterning, a SAM of biotin-terminated oligo(ethylene glycol)alkanethiol was deposited and self-assembled into the exposed Au regions (areas surrounding the resulting pillar features). The scale bar is 400 nm. (C) AFM images display biotin−streptavidin recognition separated by narrow line features. The inset shows a line feature made using a stamp with 40 nm channels with 40 ± 2 nm width. The scale bar is 1 μm. Reproduced with permission from ref 34. Copyright 2012 American Association for the Advancement of Science.

CHEMICAL LIFT-OFF LITHOGRAPHY

When plasma-oxidized PDMS stamps are brought into contact with monolayers (or portions of monolayers) terminated with hydroxyl or amine (or other reactive) groups, the activated stamps react with the monolayers, and upon removal of the stamp(s), contacted molecules are *lifted off*. As such, we coined the term "chemical lift-off lithography" for this patterning method (Figure 1).[34] Early measurements showed that Au atoms were indeed lifted off with monolayers, as indicated by the presence of Au on stamp surfaces. The depths of the subtractively patterned monolayer features were the thickness of the SAMs plus 2 Å (±0.5 Å). This additional depth is consistent with a monolayer of Au being removed. Importantly, when stamps are brought into contact with methyl-terminated (, ester-terminated, or other unreactive) monolayers, there is no reaction with the stamp, and Au monolayers are not removed. Notably, the Boxer group at Stanford University had previously used reactive stamps to remove and to pattern supported lipid bilayer membranes and even complex mixtures in membranes.[35,36] Corn used streptavidin-modified PDMS stamp surfaces to lift biotinylated DNA off of gold nanowire arrays to create large-area nanoscale patterns of DNA.[37]

The resolution of patterning by lift-off lithography was initially limited by the feature sizes of the stamps then available (40 nm); however, the observed precision of 2 nm indicated that the ultimate limits would be much finer (Figure 2).[34] Multiple stamping steps produced features with sizes of <20 nm, but registration offsets in stamping steps are difficult to control at these scales (*vide supra*). Soon thereafter, manipulating the polymer stamp produced 20 nm and ultimately even 5 nm features (unpublished). Such strategies are limited in terms of the shapes and pitches that can be produced at these small scales. Nonetheless, just as conventional semiconductor nanolithographic methods use reverse engineering of targeted structures taking into account resolution loss, line-edge roughness, and other aspects of the fabrication process, one could use analogous strategies here.[38]

A key conclusion of the discovery of chemical lift-off lithography was that *both* the subtractively patterned monolayer and the additively patterned supported metal layer lifted off onto the stamp can be used to advantage.

HYBRID LITHOGRAPHIES

As a result of the subtractive patterning process associated with lift-off lithography, lateral diffusion, which reduces resolution and blurs borders, is avoided. Chemical lift-off lithography effectively lowers the requirements and costs of nanopatterning. Higher-resolution patterning is also achievable by manipulating the stamp and controlling the contacted areas between the substrate and the stamp, eliminating the need to perform multiple lift-off steps with precisely controlled stamp registration between steps. With this strategy, feature resolution less than one-tenth the size of the stamp features can be fabricated over large (square centimeter) areas with relative ease compared with conventional nanolithographic techniques.

Recently, we used lift-off lithography in combination with sol−gel processing to print high-quality field-effect transistors (FETs) and biosensor arrays based on chemical functionalization of these FETs (Figure 3).[39] We have also shown that high-quality transistor arrays fabricated via such sol−gel processing can be made into versatile, flexible, conformal biosensor arrays.[40] Changes in surface charge distribution in molecular recognition elements, i.e., aptamers, upon small-molecule neurotransmitter binding were used to gate the devices and to detect subnanomolar dopamine concentrations (Figure 4). Previous transistor-based chemical measurements using aptamers have employed carbon nanotube devices,[41,42] which are not easily fabricated individually or into arrays. Thus, the demonstration of chemically functionalized semiconductor transistors sensitive to charge via biorecognition in devices that can be fabricated simply, reproducibly, and in parallel is an important step toward the multiplexed biomolecular detection needed in many fields.[19,20] We anticipate that this method will be generalizable via the straightforward attachment of molecular recognition elements to transistors in biosensor arrays; others and we are now proceeding to do so.

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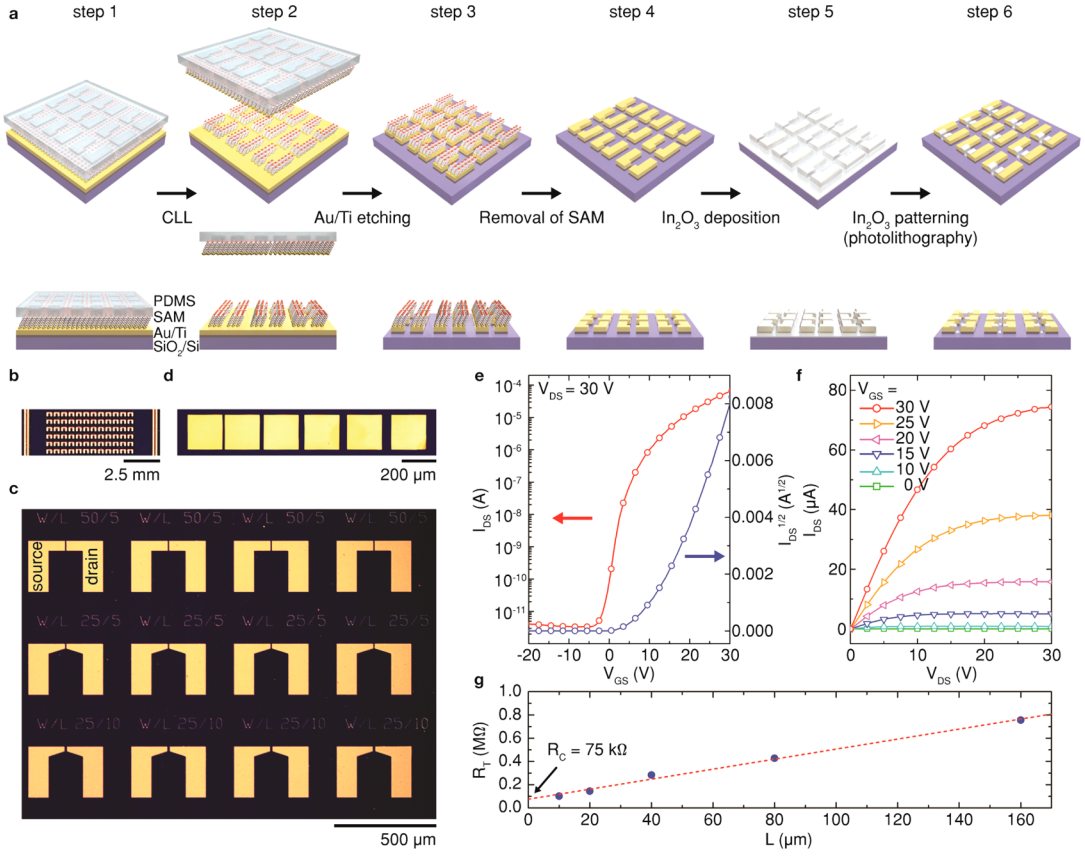

Figure 3. Field-effect transistor (FET) array fabrication using chemical lift-off lithography. (a) Schematic showing the FET fabrication steps. First, PDMS stamps with arrays of device patterns were activated by oxygen plasma and brought into conformal contact with Au surfaces covered with SAMs of hydroxyl-terminated alkanethiols (step 1). The reaction between activated PDMS stamp surfaces and the SAMs resulted in selective removal of molecules in the regions of contact (step 2), leaving patterns that served as masks during the subsequent wet etching of Au and Ti (step 3). After the metals were removed from the unprotected areas, the remaining SAMs were removed using an oxygen plasma (step 4), and ultrathin In_2O_3 layers were deposited via sol–gel processing (step 5). After annealing, In_2O_3 films outside the channel areas were removed by wet etching using photolithographically patterned masks (step 6). (b) Photograph of an FET device array produced by lift-off lithography on a SiO_2 layer on Si. (c, d) Optical microscopy images of the device patterns over large areas showing (c) well-defined source and drain electrodes with channel gaps measuring a few microns and (d) a transmission-line measurement (TLM) pattern with varying channel lengths. (e) Transfer and (f) output characteristics of the ultrathin In_2O_3 FETs showing good device performance with μ_{sat} = 11.5 ± 1.3 $cm^2 V^{-1} s^{-1}$ and $I_{ON}/I_{OFF} \sim 10^7$. (g) The R_C between In_2O_3 and the Au electrodes was ~75 kΩ, using the TLM pattern shown in (d). Reproduced from ref 39. Copyright 2015 American Chemical Society.

THE PATTERNED MONOLAYER

Chemical lift-off lithography has great potential for producing micro- and nanoscale patterns on surfaces, and these patterns can be further modified to control the chemical, physical, and biological properties of the substrates (Figure 5). These capabilities derive predominantly from three key features of the technique: the fabrication of nanoscale patterns over large areas, the definition of border regions with distinct properties, and the extent to which molecules are left on the substrate after lift-off for subsequent use in isolating and orienting molecules added to these regions.[34,43]

The spatially encoded chemical environments of substrates created by lift-off provide a variety of opportunities. For example, selective deposition or passivation is possible when electroplating is combined with lift-off lithography, depending on the backbone and terminal group composition of the SAMs.[10,44,45] Other factors, including stamp contact time, applied potential, *etc.*, all contribute to the ultimate deposition, allowing the resultant properties to be tuned.

Initial applications of chemical lift-off lithography processing were to create biosensor arrays as high-throughput tools for biomolecule sensing, ultimately targeting *in vivo* measurements, and binding-kinetics investigations.[19,20,39] Gold surfaces are commonly used as supporting substrates because of advantages such as robust molecular monolayer immobilization, high conductivity, and air stability.[10] However, nonspecific binding of sensing probes to gold surfaces dramatically decreases the efficiency of microarrays. A number of methods of anchoring surface probes have been demonstrated. For example, Herne and Tarlov[46] developed a two-step procedure of backfilling water-soluble "co-thiols" to reduce nonspecific biomolecular interactions and binding. Insertion methods, described above,[30,43,47] can be used to provide diluted environments for enhanced specific biomolecule recognition. As noted, the matrix can be optimized to minimize nonspecific binding and to separate tethered biomolecular probes at desired distances (stochastically). Recent advances in masked adsorption may ultimately enable more precise isolation and separation.[48]

Although the use of specific SAM molecules can reduce nonspecific biomolecule interactions and improve specific binding efficiency, immobilizing probe molecules into microarrays remains challenging. Backfilled functionalized molecules

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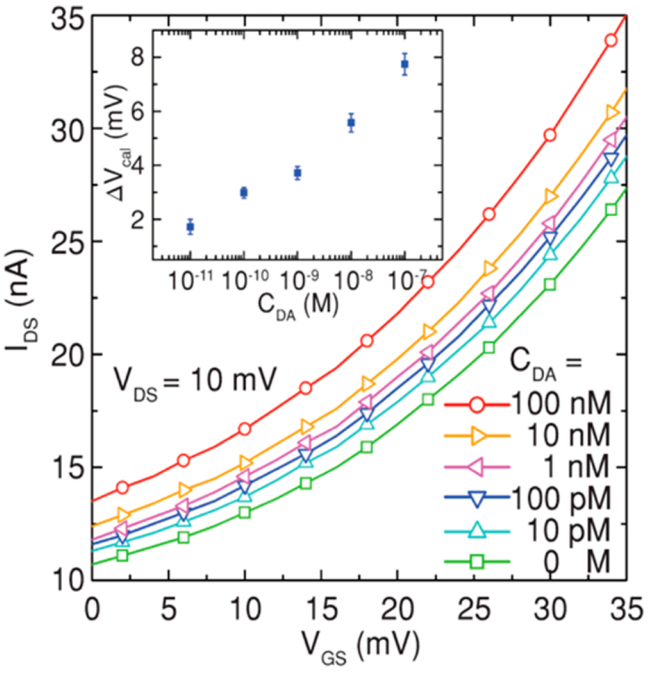

Figure 4. Once In_2O_3 transistor surfaces were functionalized with a DNA aptamer selected for the small-molecule neurotransmitter dopamine, the biosensors were used for subnanomolar dopamine detection. The addition of dopamine to the liquid electrolyte led to increased drain current; the linear working range of the aptamer–In_2O_3 biosensors was found to cover 10^{-11}–10^{-7} M dopamine (inset, ΔV_{cal}: calibrated response). Reproduced from ref 39. Copyright 2015 American Chemical Society.

may not be able to compete with matrix molecules, and microcontact insertion printing requires well-tuned stamp surface conditions.[32] Chemical lift-off lithography is an alternative strategy that readily provides diluted matrix environments for probe insertion. We investigated the use of lift-off lithography to prepare tethered DNA arrays (Figure 6).

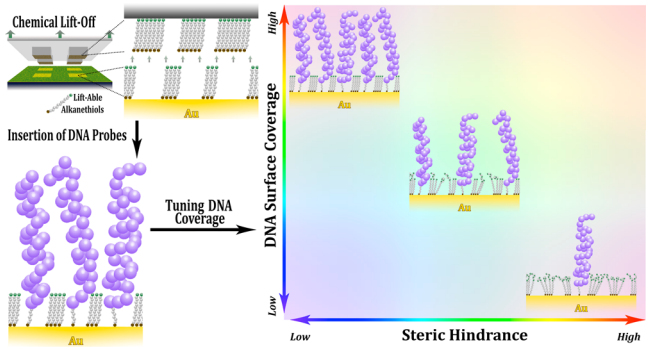

Figure 6. Using chemical lift-off lithography to facilitate insertion of single-stranded DNA probes into monolayer matrices on Au substrates increases the efficiency of subsequent DNA hybridization relative to backfilling and codeposition strategies. The degree of insertion of DNA probe molecules into the stamp-contacted regions depends on the initial matrix composition. The DNA probes are isolated in post-lift-off matrices to improve complementary DNA hybridization. Reproduced from ref 43. Copyright 2015 American Chemical Society.

During the lift-off process, the choice of initial SAM molecule composition can be used to control DNA surface densities and hybridization efficiencies. Compared with conventional methods, while fewer DNA probe molecules are inserted on substrates prepared by lift-off lithography, more complementary

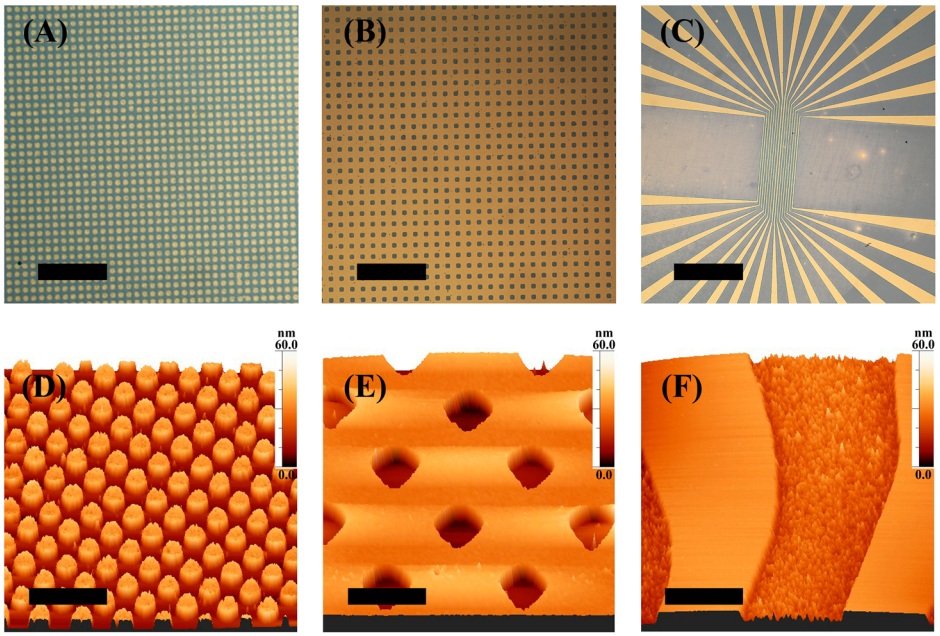

Figure 5. Optical and scanning probe micrographs of Au features patterned by chemical lift-off lithography. Chemical lift-off lithography via activated PDMS stamps was used to produce a variety of patterns in SAMs of hydroxyl-terminated tris(ethylene glycol)undecanethiol on Au. After patterning, the substrates were chemically etched (Fe^{3+}/thiourea) to remove remaining SAM molecules and additional underlying Au in the exposed (lifted-off) regions. The SAM molecular resists in the uncontacted areas remained intact. (A–C) Bright-field microscopy and (D–F) atomic force microscopy, with topographic heights shown, of patterns of (A, D) pillars, (B, E) wells, and (C, F) channels. The scale bars are 18, 130, 1325, 5, 15, and 17.5 μm in (A–F), respectively. Reproduced with permission from ref 34. Copyright 2012 American Association for the Advancement of Science.

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DNA is ultimately hybridized (see Figure 5b in ref 43).[43] We attribute this advantage, in part, to the molecules remaining in the stamp-contacted regions (~30% in refs 34 and 43), which form a dilute matrix to separate tethered DNA, making individual probe strands more accessible for hybridization. Lift-off lithography can provide advantageous, straightforward routes for fabricating biosensors and biosensor arrays. Tethered small-molecule target arrays are also being developed using these methods.[43]

THE SUPPORTED METAL MONOLAYER

Preliminary measurements indicate that the PDMS-stamp-supported Au removed by lift-off lithography retains chemical properties of Au surfaces. For example, we have used thiol−Au chemistry to attach biomolecules and confirmed their presence, where patterned, with fluorophores tied to thiolated molecular recognition elements, such as aptamers and DNA. It should be noted that although we refer to the ultrathin supported metal layer as a "monolayer" on the basis of indirect evidence such as how much Au is removed and our understanding of the effects of electronegative species on coinage-metal surfaces, further characterization is required to determine the structure of the supported metal. Nonetheless, the lifted-off Au is so thin that its electronic and optical properties do not match those of bulk Au or nanoparticles, and thus, we do *not* observe quenching of captured fluorophores (quenching is known to be limited even up to tens of atomic layers, e.g., in 10-nm-thick gold films[49]). Such lifted-off metal monolayers can thus be used as substrates for fluorescence and other optical studies while exploiting the well-developed functionalization chemistries of Au and other surfaces.

We have not yet been able to measure electrical conductivity in these supported metal layers. As with other low-dimensional and ultrathin materials,[50,51] a small amount of optical absorption occurs. We anticipate that both the electronic and optical properties of these supported metal monolayers will be tunable by selection of the attachment(s) and interactions with the supporting organic monolayer (*vide infra*). For example, both thiols and selenols bind Au in SAMs. Molecular backbones can also be used to adjust the electronic structure of the chemical and physical attachment to metal monolayers.[52−55] In two dimensions, metals are known to adopt alternate structural arrangements,[51,56−58] so it will be important to understand the atomic-scale structures formed. Theorists have begun to investigate these questions,[59] and we are working together to elucidate important details of these new materials.

While graphene and other two-dimensional (2D) materials maintain key and extraordinary materials properties because of bonding in 2D or quasi-2D arrangements, the electronic and optical properties of the supported lifted-off Au are not well developed. As new supports are developed, we anticipate using the retained, well-established chemistry of Au to apply these materials as substrates, in combination with molecular recognition elements, for transmission electron microscopy.[60] While Au substrates are typically difficult to use because of poor electron transmission, a single layer of Au atoms would circumvent this difficulty.

Lifted-off metal monolayers can be patterned in three ways (and in combinations). As in any microcontact printing method, stamp contact determines the patterns produced.[27,28] Likewise, the monolayers themselves can be patterned prior to stamp contact using any of a number of techniques.[25,26] Since only reactive terminal SAM functional groups are lifted off, patterned mixtures of reactive and unreactive groups can be placed on surfaces by any chemical patterning method. Finally, the substrate itself can be patterned, as Zheng et al. did with focused ion beams to create nanohole arrays as substrates for enhanced Raman spectroscopy.[14] All of these approaches have been demonstrated and can be used in combination. Thus, whereas graphene and other 2D materials can be difficult to pattern but are relatively straightforward to grow or to exfoliate because of their 2D bonding,[48,51,61−64] supported 2D Au layers produced by lift-off lithography appear to be easily patterned (but may not be as easily removed from their supports).

CONCLUSIONS AND PROSPECTS

Chemical lift-off lithography provides a simple means of chemical patterning across large areas (i.e., square millimeters) at high resolution (down to nanometers). Lift-off lithography can be used in combination with other lithographic processes and chemical patterning methods.[26] Lift-off lithography has critical advantages in the preparation of biocapture surfaces because the molecules left behind are exploited to space and to orient the functional(ized) molecules.[43] Additional substrates, particularly coinage metals with bonding and cohesive energies analogous to those of Au, should also be amenable to chemical lift-off lithography.

Intriguing avenues for exploration include determining the properties and uses of the supported Au monolayers that result from lift-off. These monolayers retain important chemical properties of Au (vis-à-vis functionalization with thiols) but not the electronic and optical properties (of bulk Au or even Au nanoparticles). One result is that excitation quenching is minimized. These supported films may find uses as nearly transparent supports in optical and electron microscopies.

By changing the composition, and thus the chemical and electronic interactions of the supporting molecules, we anticipate that the properties of the supported Au can be shifted and/or tailored.[52−55] Whereas linear mercaptoalkanoic acids and related molecules relax conformationally, cage molecules have rigid backbones and can be functionalized to have multivalent interactions on one or both sides of the cage.[52,65,66] Likewise, the electronic properties of the contacts can be tuned by selecting the molecular contact(s) and cage molecule (e.g., carborane) isomer(s).[52,65,66] Increasing the molecular support rigidity should help to maintain the planarity of the supported Au (and other metal) monolayers. Additional interactions, e.g., hydrogen bonding[5] or cross-links,[67] can be built into the supporting molecular backbones to promote planarity.

Combinations of lift-off lithography, chemical functionalization, and other lithographic processes are poised to make key contributions in nanobiosensing. These applications include the development of general nanoelectronic sensor platforms[39] and ultimately multiplexed biosensor arrays for *in vivo* use and to elucidate the spatiochemical dynamics of the brain, the microbiome, and other complex biological systems.[19,20]

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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