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PERSPECTIVES

Hybrid approaches to nanometer-scale patterning: Exploiting tailored intermolecular interactions

Thomas J. Mullen · Charan Srinivasan · Mitchell J. Shuster · Mark W. Horn · Anne M. Andrews · Paul S. Weiss

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Abstract In this perspective, we explore hybrid approaches to nanometer-scale patterning, where the precision of molecular self-assembly is combined with the sophistication and fidelity of lithography. Two areas—improving existing lithographic techniques through self-assembly and fabricating chemically patterned surfaces—will be discussed in terms of their advantages, limitations, applications, and future outlook. The creation of such chemical patterns enables new capabilities, including the assembly of biospecific surfaces to be recognized by, and to capture analytes from, complex mixtures. Finally, we speculate on the potential impact and upcoming challenges of these hybrid strategies.

T. J. Mullen · M. J. Shuster · P. S. Weiss (✉)
Departments of Chemistry and Physics, The Pennsylvania State University, University Park, PA 16802-6300, USA
e-mail: stm@psu.edu

C. Srinivasan · M. W. Horn
Department of Engineering Science and Mechanics, The Pennsylvania State University, University Park, PA 16802-6300, USA

A. M. Andrews (✉)
Department of Veterinary and Biomedical Science and Huck Institutes of the Life Sciences, The Pennsylvania State University, University Park, PA 16802-6300, USA
e-mail: ama11@psu.edu

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Introduction

Currently, one of the great engineering challenges is to gain the ability to fabricate nanoscale structures at the supramolecular (1–50 nm) length scale with high precision, throughput, and reproducibility. In microelectronics, speed and density have been the driving forces to increase the final resolution of traditional top-down methodologies utilizing deposition, etching, or modification of thin layers on semiconductor substrates. However, the impetus to create features with molecular-scale structures, properties, and interactions has motivated and expanded research into fields outside traditional semiconductor nanofabrication. One approach has been the development of hybrid patterning strategies for a wide range of applications. These utilize self- and directed assembly in conjunction with existing nanofabrication infrastructure (Xia et al. 1999; Lewis et al. 2001a; Smith et al. 2004; Srinivasan et al. 2007).

The initial motivation for the development of micro- and nanoscale patterning came from the fabrication needs of the semiconductor industry. In 1965, when Moore first predicted that the number of components on a silicon wafer would double every year and a half, there were only 30 microscale transistors on a single

microprocessor, and the extrapolated growth was expected for a single decade (Moore 1965). Amazingly, this trend, referred to as "Moore's Law," has been sustained for over 40 years and silicon substrates now contain billions of nanoscale devices (Moore 1995). To attain nanoscale features, the complexity and the cost of nanofabrication facilities have grown tremendously. Figure 1 shows the growth of the cost of a semiconductor fabrication facility over the past 30 years (Thompson and Parthasarathy 2006). If this trend were to continue for the next half century, the cost of a single facility would be greater than the current gross domestic product of the United States (Mannering and Hodge 2007). Over the same time period, the price-per-transistor has decreased seven-fold, enabling cheaper, smaller, and more efficient devices. These two factors underlie many of the advances in the semiconductor industry (Thompson and Parthasarathy 2006). However, this type of scaling will eventually taper off, not only because of fabrication costs, but also due to the physical limitations of the materials and methods currently used to create semiconductor nanoscale features (Lundstrom 2003). In contrast, self-assembly methodologies exploit the inherent chemical and physical properties of molecules to direct and to control their arrangements and locations on surfaces with nanometer or better precision. By engineering molecules with varying structures, intermolecular interaction strengths, and terminal groups, the properties of these chemical films, such as surface reactivity and screening properties, can be tailored (Kumar et al. 1994; Smith et al. 2001; Smith et al. 2004; Dameron et al. 2005a). Despite the ability of self-assembly strategies to control the structures of chemical films, the direct placement and the fabrication of complex multicomponent structures via bottom-up assembly are limited and require further development to become viable alternatives to traditional lithographic techniques (Xia et al. 1999; Mullen et al. 2007b).

In this perspective, we specifically examine and highlight the advantages, limitations, applications, and future outlook of several hybrid patterning technologies where the sophistication and control of lithography are coupled with the molecular precision of self-assembly. A number of comprehensive reviews on hybrid patterning strategies have been published (Xia et al. 1999; Hammond 2004; Gates et al. 2005; Love et al. 2005; Rogers and Nuzzo 2005; Henzie et al. 2006; Saavedra et al. 2008). We first describe how self-assembly can be used to improve the resolution of existing lithographic technologies. Next, we discuss chemically patterned surfaces created by hybrid strategies where the strengths are maximized and the limitations are minimized in terms of ease of use, reproducibility, resolution, and precision. Finally, we explore the potential impact of and future outlook for hybrid strategies.

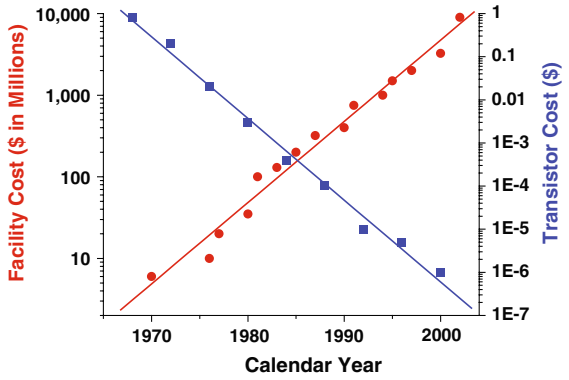

Fig. 1 Traditional semiconductor costs. The cost of a single semiconductor fabrication facility (red circles) and a single transistor (blue squares) over the past 30 years is shown. Graph is *adapted from Thompson and Parthasarathy* 2006

Structures with molecular precision

Initially, we anticipate that hybrid strategies will need to be adapted to transfer the intrinsic molecular precision of self-assembly to established nanofabrication infrastructure and technology. Although the placement and alignment of microscale structures with nanometer-scale precision is difficult using most lithographic techniques, the additional requirement of patterning over large areas (tens of cm^2) for industrial applications makes it extremely challenging using only current top-down strategies (Henzie et al. 2006). For example, photolithography is commonly used to fabricate surface features for integrated circuits in semiconductor manufacturing because of its ability to create reproducible structures with high throughput and relatively low cost (Rai-Choudhury 1997). This parallel methodology fabricates surface structures by patterning a light-sensitive polymer via photon exposure through a mask. The pattern is then developed via wet chemistry methods and etched into the underlying substrate. However, feature sizes resulting from

photolithography are diffraction limited at ~100 nm without resolution enhancement techniques (Brunner 2003). To fabricate smaller features, electron-beam lithography has been utilized. This technology employs high-energy electrons to write a pattern directly into an electron-sensitive polymer, which is then developed, translating the pattern into the underlying substrate. Electron-beam lithography has higher resolution than photolithography, and features down to ~20 nm can now be routinely fabricated. However, because electron-beam lithography is a serial technique, it is expensive and slow compared to photolithography, and thus, is not practical for industrial-scale fabrication applications except in specific highly leveraged circumstances such as photolithographic mask fabrication (Brunner 2003). With hybrid techniques, molecular-scale features can be rapidly created over large areas using conventional top-down lithography to create microscopic features combined with molecular self-assembly to control supramolecular organization (Smith et al. 2004).

One example of this type of hybrid strategy is the molecular-ruler process, where conventional lithography is coupled with selective deposition of multilayers of bifunctional organic molecules and coordinated metal ions. Ultimately, the chemical multilayer film defines the nanometer-scale spacings of the lithographically patterned surface structures (Evans et al. 1991; Hatzor and Weiss 2001; Haes et al. 2004). Figure 2 shows a schematic of the molecular-ruler assembly process. Initially, a lithographically defined gold parent structure is fabricated on an oxidized Si substrate. The molecular ruler, consisting of sequential alternating layers of α,ω-mercaptoalkanoic acid and cupric ions (Cu^{2+}), is then deposited onto the gold parent structure. After the desired thickness of the molecular-ruler stack is achieved via multiple molecular layer deposition steps, a daughter metal is deposited across the entire substrate. The molecular ruler, along with the daughter metal atop the molecular resist, is removed by chemical lift-off, leaving precisely defined spacings (4–100 nm) between the parent and daughter structures. This scheme has the advantage that defects in SAMs (Tiberio et al. 1993; Poirier and Pylant 1996; Jager et al. 1997; Bent 2007) are mitigated through multilayer assembly via the varying stoichiometry possible between the molecules and the ionic ligands (Daniel et al. 2007; Hatzor de Picciotto et al. 2007). This process can also be combined with photolithography (Anderson et al. 2006) or electron-beam lithography (Tanaka et al. 2004) to create patterns at multiple scales. This combination of established patterning methods with a novel chemical processing technique demonstrates the compatibility and robustness of hybrid strategies and holds promise for further miniaturizing electronic devices.

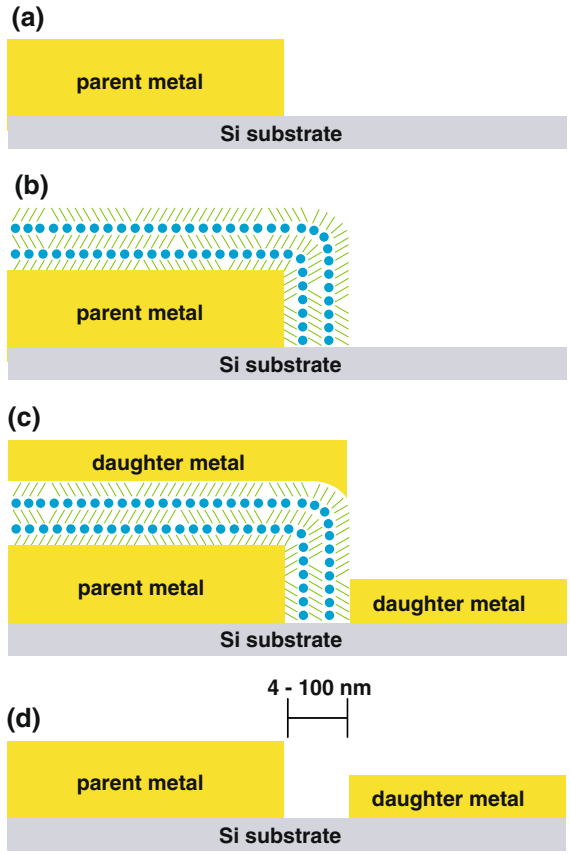

Fig. 2 Molecular-ruler assembly process. (**a**) Initially, a gold parent structure is fabricated by conventional lithography. (**b**) Subsequently, the molecular ruler, consisting of alternating layers of α,ω-mercaptoalkanoic acid (green lines) and cupric ions (Cu^{2+}, blue circles), is deposited onto the gold parent structure until the desired multilayer thickness is achieved. (**c**) Daughter metal is then deposited across the entire substrate. (**d**) The molecular ruler and the daughter metal atop of it are removed with a chemical lift-off process, leaving a precisely defined spacing (1–100 nm) between the parent and daughter structures. Schematic is not to scale

As opposed to exploiting chemical multilayer films to create precise supramolecular spacings, self-assembled block copolymers, consisting of covalently bonded hydrophobic and hydrophilic units, can

enhance the critical dimensions and fidelity of surface features fabricated by lithography (Mansky et al. 1997; Park et al. 1997; Thurn-Albrecht et al. 2000; Hawker and Russell 2005; Stoykovich and Nealey 2006; Black 2007; Stoykovich et al. 2007). Figure 3 depicts the use of block-copolymer-directed assembly to improve the line-edge roughness of a pattern fabricated by conventional lithography. Initially, chemical functionality is patterned on a substrate by conventional lithography, such as electron-beam lithography, and subsequent oxygen plasma treatment. A thin film (<100 nm) of block copolymer is then cast across the patterned substrate and thermally treated such that microphase separation of the block copolymer produces domains that register with the underlying substrate. However, because the block-copolymer assembly is thermodynamically controlled, the defects and irregularities in the underlying chemical pattern are self-corrected in the block-copolymer layer. Finally, the enhanced registration of the block copolymer domains is transferred into the underlying substrate (Stoykovich et al. 2005). This self-healing process is in contrast to current chemically amplified resists, which are based on diffusion-limited processes, where the final patterned features are sensitive to small variations in processing conditions (Tanaka et al. 1998).

Self-assembled monolayers (SAMs) can also spontaneously phase separate into nanoscale domains when two or more molecular species with differing intermolecular interaction strengths are coadsorbed (Stranick et al. 1994; Lewis et al. 2001b; Smith et al. 2001). These interaction strengths can be controlled by selecting the head groups, backbones, and/or tail groups of the deposited molecules (Mullen et al. 2007b). Further, nanoscale domains can be artificially fabricated and manipulated by exploiting the molecular exchange into and displacement of a labile monolayer (Bumm et al. 1999; Dameron et al. 2005a; Mullen et al. 2006). This displacement process has been exploited to improve existing chemical patterning strategies (*vide infra*). Even small multicomponent patches of molecules ($\sim$15 nm) can be made to separate on the nanoscale (Salaita et al. 2005). In many cases, phase separation can be controlled by the selection of the molecules and processing conditions, which determine the dynamics of the structures created (Bumm et al. 1999, Smith et al. 2004). As with block copolymers, separated SAMs enable chemical

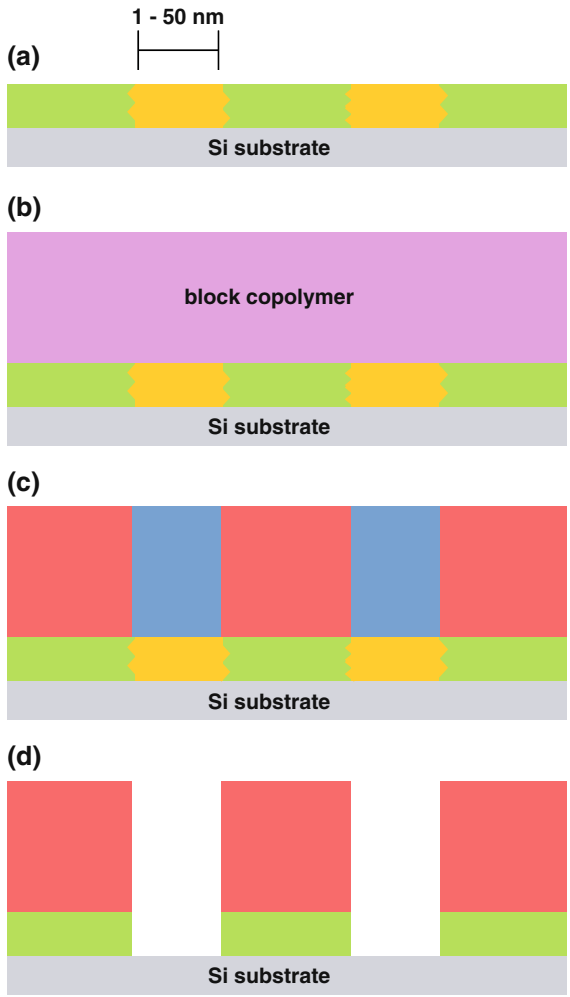

Fig. 3 Block-copolymer-directed assembly. (**a**) A chemical pattern is placed across a substrate via conventional lithography. (**b**) Next, a thin film (<100 nm) of block copolymer is deposited onto the patterned surface and (**c**) thermally annealed such that microphase separation of the block copolymer produces domains that align with the patterned chemical surface. (**d**) The registration and alignment of the block-copolymer domains are translated with molecular-scale precision onto the underlying substrate. Schematic is not to scale

patterns to be created at the few to tens of nanometers scale.

These examples highlight how self-assembly might be used to improve and to enhance existing lithography techniques. An advantage of these hybrid techniques is their ability to interface with and to utilize existing infrastructure. Another advantage is that these techniques are independent of both resolution and the top-down patterning methods employed, allowing them to be adapted to future lithographic technologies.

However, despite the advantages of these hybrid strategies, there are challenges that prevent their immediate translation into industry. First, the majority have only been developed recently and for specialized applications. It is difficult for the semiconductor industry to adopt techniques that have not been demonstrated and optimized for its own specific applications. Additionally, in some instances, the self- and directed assembly strategies employed in hybrid patterning are not yet compatible with the types of materials and processes used in existing semiconductor infrastructure. While efforts have been made to migrate these strategies so that they can be applied directly to technological materials, much remains to be done on this front (Bent 2007).

One of the ultimate goals of combining the intrinsic molecular precision of self-assembly with lithography is to fabricate precise features and to produce structures with higher resolution and lower production costs than structures made using conventional lithographic techniques alone. The molecular-ruler process demonstrates the utility of multilayer chemical films and how they can be used to create precise and proximate nanoscale structures. With self-assembling block copolymers, the domains of the block copolymer enhance the pattern transfer into the underlying substrate. Currently, self-assembled block copolymers are not aimed at improving the resolution of conventional lithography, but rather are intended to improve process control, such as line-edge roughness, and information transfer from the exposure tool to the substrate. In the near term, the continuing research goals for coupling self-assembly to lithography are to develop more diverse approaches to fabricate precise nanoscale structures. By identifying the advantages and limitations of different strategies, the potential for large-scale implementation can be advanced.

Chemically patterned surfaces

Above, we had described how self-assembly can be used to improve existing lithographic techniques. Hybrid strategies are also being employed to create chemically patterned surfaces that make possible a range of new applications. A recent example is the fabrication of biospecific surfaces that recognize and capture specific biomolecules from complex environments. Functionalization of chemically patterned surfaces adds new degrees of utility by enabling surface reactivity to be patterned at the nanometer scale. This has led to nanoscale films being used as biocompatible/bioactive scaffolds, molecular-sized electronic components, selective molecular resists, and other types of surfaces where both patterned structure and molecular interactions are necessary (Chen et al. 1997; Xia and Whitesides 1998a; Smith et al. 2004; Srinivasan et al. 2007). As processes are developed for creating such chemical patterns, metrology tools and methods must be developed in lockstep in order to follow the patterning steps and to optimize the quality of the surfaces obtained. These metrology methods remain in their infancy (Allara and Nuzzo 1985; Porter et al. 1987; Nuzzo et al. 1990; Lopez et al. 1993; Pertsin and Grunze 1994; Lahiri et al. 1999a; Srinivasan et al. 2007; Mrksich 2008).

One technique to fabricate chemically patterned surfaces is lithography-assisted chemical patterning (LACP), where conventional lithography is employed in conjunction with SAMs to create chemical patterns with high fidelity (Anderson et al. 2006; Srinivasan et al. 2007). This is accomplished by exploiting a commercially available lift-off resist that can withstand the self-assembly process without disrupting the underlying SAM. Figure 4a shows an example of the LACP process. Initially, a bilayer resist consisting of an underlying lift-off resist and an overlayer photoresist is cast over a preexisting SAM. This bilayer resist is then patterned via conventional lithography. The photoresist is then removed, leaving behind the underlying lift-off resist; the lift-off resist withstands the solvents used in further self-assembly. Exposed regions can be stripped of the existing monolayer and backfilled with a new monolayer, or molecules can be inserted into the exposed regions of the SAM via solution deposition. The lift-off resist is then removed, leaving the original SAM undisturbed in the underlying regions. Because of the close integration with conventional lithography, LACP is capable of creating 1:1 registered chemical patterns over large areas and enables feature dimensions to be readily scaled down, which is difficult by other chemical patterning strategies.

Soft lithography is another strategy used to fabricate chemically patterned surfaces. This encompasses microcontact printing (μCP) and related techniques. In μCP, an elastomeric stamp coated with molecules is applied to a substrate, and a chemical pattern is formed in the regions where the stamp and substrate are in contact (Kumar and Whitesides 1993; Xia and

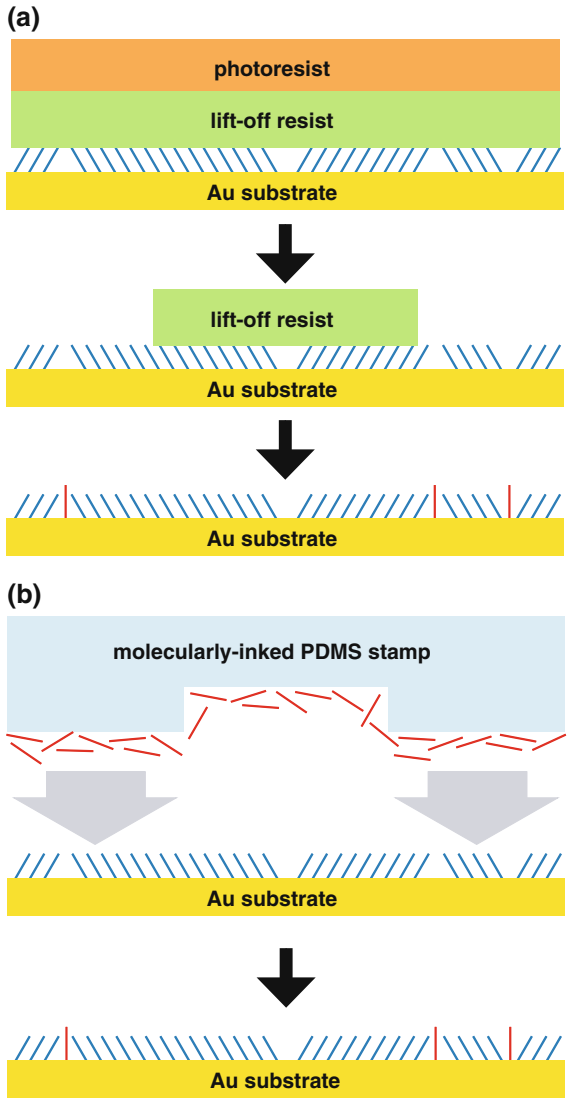

Fig. 4 (**a**) Lithography-assisted chemical patterning. A bilayer resist consisting of lift-off resist and photoresist is deposited across a preexisting SAM and patterned via conventional lithography, leaving behind a chemically robust lift-off layer. Molecules are then inserted into the SAM via solution deposition in regions not protected by the lift-off resist. Finally, the remaining lift-off resist is removed, leaving a patterned SAM. (**b**) Microcontact insertion printing. A patterned elastomeric stamp coated with the molecules to be patterned is brought into contact with a substrate coated with a preexisting monolayer that is *not* easily displaced; the molecules on the stamp *insert* into the defects in the preexisting monolayer where the stamp and substrate are in contact. Schematics are not to scale

Whitesides 1998a; Xia and Whitesides 1998b; Smith et al. 2004). One limitation of μCP is the requirement for patterned molecules to have sufficient intermolecular interaction strengths to prevent lateral diffusion and hence pattern dissolution, both during and after patterning (Delamarche et al. 1998; Dameron et al. 2005b). Microdisplacement printing (μDP) circumvents this limitation by utilizing a preexisting monolayer that is sufficiently labile when exposed to other thiolated molecules via the stamping process but nonetheless prevents lateral diffusion of the patterned molecules (Dameron et al. 2005b, c; Srinivasan et al. 2007). However, in both μCP and μDP, the molecular composition of a patterned film is determined by and restricted to the feature size of the elastomeric stamp. In contrast, the molecular composition of chemically patterned films created by microcontact insertion printing (μCIP) is controlled by other factors such as the density of defects in the initial substrate, the stamping duration, and the concentration of the patterned molecules. Microcontact insertion printing enables dilute and isolated molecules to be patterned within a background SAM matrix, in a way that is not possible by other lithographic strategies (Mullen et al. 2007a; Srinivasan et al. 2007). Diffusion of the inserted molecules is also prevented, as in μDP. Figure 4b depicts the μCIP process. Initially, a patterned molecularly coated elastomeric stamp is brought into contact with a substrate coated with a preexisting monolayer that is *not* easily displaced; the molecules on the stamp then *insert* into the defects in the monolayer only in places where the stamp and substrate are in contact (Bumm et al. 1996; Cygan et al. 1998). Together, these soft-lithographic strategies offer straightforward, versatile, and low-cost methods to fabricate chemical patterns over large areas without the requirement of specialized facilities.

Both LACP and soft lithography can be employed to fabricate functionalized surfaces that exhibit selective molecular recognition. In most cases, fabrication of these surfaces begins with a SAM deposited across a Au substrate engineered to resist non-specific protein adsorption (Prime and Whitesides 1993; Wang et al. 1997; Sigal et al. 1998; Ostuni et al. 2001). In some applications, where proteins or peptides are eventually anchored to SAMs, low percentages of tether molecules are codeposited to form a mixed monolayer. Large biomolecules are then either covalently bound to tethers or specifically oriented by high-affinity linkers (Lahiri et al. 1999a; Lahiri et al. 1999b; Yousaf and Mrksich 1999; Hodneland et al. 2002). In other applications, precursor tether molecules with distinct

terminal functionalities from the preexisitng SAM are inserted into its defect sites (Weck et al. 1999; Mullen et al. 2007b; Shuster et al. 2008). Subsequently, the terminal groups of the tether molecules are functionalized with small-molecule ligands. This type of biospecific surface is currently being developed to separate proteins from biological mixtures (e.g., tissue homogenates, serum, etc.), to elucidate molecular interactions between known proteins and their small-molecule targets, and to identify unknown proteins that bind selectively to small-molecule ligands (Mullen et al. 2007b; Mrksich 2008; Shuster et al. 2008). Further, these surfaces are not limited to functionalization with small biomolecules, but can present other small molecules such as chemical warfare agents and toxic industrial chemicals. In addition to patterning biologically relevant molecules, surfaces bearing tethers with different classes of functional groups can be created, enabling the attachment of many different small molecules, particles, and clusters.

In our recent work, we have utilized this scheme to fabricate chemical films of the neurotransmitter serotonin for creating small-molecule functionalized surfaces. These surfaces have been employed to demonstrate biospecific recognition by serotonin-specific antibodies (Shuster et al. 2008). Figure 5a and b shows inserted tether molecules isolated within a oligo(ethylene glycol)-terminated SAM before and after functionalization of the tether carboxylic acid terminal group with serotonin via EDC/NHS coupling chemistry (Hermanson 1996). Not only were these surfaces shown to discriminate between the capture of proteins specific for serotonin versus those specific for other closely related small molecules, such as dopamine, but they also prevented non-specific recognition of "ubiquitous" proteins such as fibrogen, fibronectin, and bovine serum albumin. The ability to discriminate between large biomolecule binding partners based on their specific non-covalent interactions sets the stage for the creation of multiplexed surfaces, as shown schematically in Figure 5c, where a number of isolated small-molecule probes can be sequentially patterned on the same surface in order to capture multiple types of biomolecules based on their interactions in a competitive environment. It is important to note that in the overlapping patterned regions, the tether molecules (which are functionalized with small-molecule probes) are isolated such that they do not interact with other probe molecules in the surrounding region. This molecular isolation can be controlled and influenced by many factors and has been confirmed by both ensemble and localized analytical techniques (Mullen et al. 2007a; Shuster et al. 2008).

Current traditional lithographic techniques are not capable of producing chemical patterns with this level of precision. Serial techniques have been devised to manipulate and to arrange single atoms as well as to draw molecular patterns on a surface with a scanning probe tip (Eigler and Schweizer 1990; Weiss and Eigler 1992, 1993; Piner et al. 1999; Xu et al. 1999). Although recent work has made creative and inventive efforts to create massive arrays of tips, these techniques require further development and will likely be utilized for specialized applications in analogy to electron-beam lithography (Salaita et al. 2006; Mirkin 2007). A key advantage of LACP, μCIP, and related techniques is the ability to fabricate chemical films of isolated single molecules or bundles of molecules diluted within a background matrix over large areas. The molecular composition of the chemical pattern is influenced by the extent of insertion of the patterned molecules, which can be controlled by tuning the patterning duration, the concentration of the patterned molecules, the quality of the preexisting SAM, and the intermolecular interaction strengths of both the preexisting SAM and the patterned or inserted molecules (Mullen et al. 2007a). This control of molecular composition and isolation is particularly critical for small-molecule functionalized surfaces. If tether molecules linked to small-molecule probes are spaced too closely, non-specific binding increases; whereas if derivatized tethers are spaced too far apart, then the efficiency of capturing large biomolecules is diminished.

It is also important to anticipate the limitations of these hybrid approaches for fabricating patterned small molecules. First, the small-molecule probe must be covalently coupled to the patterned tether molecule via a functional group. This covalent attachment could hinder recognition and capture of larger target analytes. Another limitation of this hybrid strategy is that the patterned molecules are statistically distributed rather than directly placed. This could result in under-utilized areas where no patterned molecules are present or regions where clusters of molecules are inserted. Despite such limitations, insertion self-assembly and μCIP have the potential to be applied to a wide variety of chemical systems and to enable capabilities not previously possible.

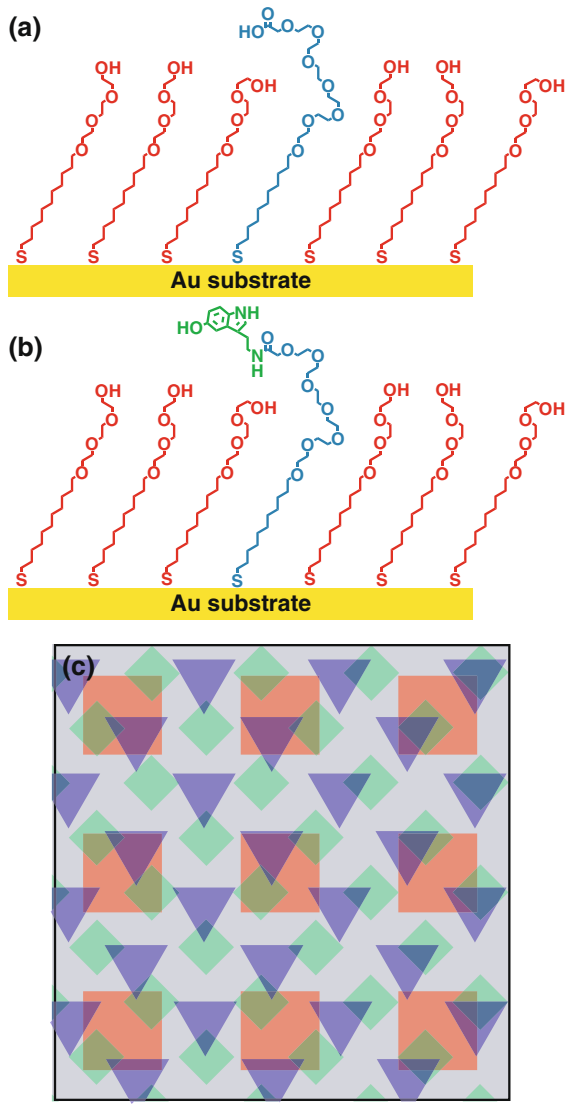

Fig. 5 Patterning Diluted Biospecific Small-Molecule Probe Surfaces. Inserted tether molecules isolated within an oligo(ethylene glycol)-terminated self-assembled monolayer (**a**) before and (**b**) after selective functionalization of carboxylic acid terminal group with serotonin via N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC)/N-hydroxysuccinimide (NHS) coupling chemistry. (**c**) Schematic of a multiplexed surface created by multiple patterning steps where each color/shape represents a different small-molecule ligand

Future prospects and conclusions

When Moore first noted the scaling of semiconductor devices 40 years ago, he could not have imagined the influence and implications it would have on applications outside the semiconductor industry. Incremental improvements continue in the manufacturing processes used in the mature and established semiconductor industry. However, with the hybrid techniques highlighted in this perspective, along with similar strategies, it will become routine to fabricate, to manipulate, and to visualize structures at the 1–50 nm supramolecular scale. For example, hybrid patterning techniques enable access to biological systems with unprecedented molecular precision, allowing for the study and characterization of single and groups of biomolecules in various environments. With this structural and functional resolution of biomolecules, the underlying mechanisms can begin to be understood, enabling structures and devices to be developed and fabricated on the same scales as biological systems. These systems can then be mimicked, engineered, and improved.

The underlying theme for this perspective has been that there is no universal strategy or technique for every application; rather, for each application, there are several possible methods to create patterned surfaces, most of which are just now being developed. It is important to understand the specific requirements and how they relate and can be applied to each technique's advantages and limitations. It is likewise critical to develop the metrology tools and methods to test and to optimize the patterns created. All these hybrid techniques stem from the idea that molecular assembly can be coupled to the fidelity and sophistication of lithography. As our understanding and control of self- and directed assembly increase, the stringency of the underlying lithography will diminish, enabling wider access to and larger utilization for a greater number of applications.

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