Phenolic Based Molecular Glass Resists for Next Generation Lithography

CNF Project # 386-90
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Abstract

The idea of using small molecules instead of polymers for next generation lithography has enabled improved resolution and line edge roughness (LER). Rather than using polymeric materials, we are focusing on a new class of materials known as molecular glasses. These are low molecular weight organic materials that demonstrate high glass transition temperatures despite their modest size. Unlike polymeric resists, these molecules have the added advantages of distinct size and uniformity. We have synthesized a series of molecular resists containing rigid aromatic backbones and phenolic moieties. An increase in glass transition temperature is observed with increasing size and rigidity. Glass transition temperatures (Tgs) between 80-130°C have been observed for resists with molecular weights within the range of 500-900g/mol. These phenolic based resists also show the high sensitivity and sub-50 nm contrast required of candidates for next generation lithography.

Introduction

As the semiconductor industry moves to the 32 nm node and below, obtaining smaller feature sizes with reduced fluctuations on the resist pattern known as line edge roughness (LER) is a main focus [1]. As extreme ultra violet (EUV) lithography gains credibility as the next generation lithographic technology LER, sensitivity and outgassing remain crucial factors. The patterning target for the 32 nm node in 2009 is reported to be LER < 2 nm and sensitivity 2-5 mJ/cm². Hence, novel resist architecture and design strategies need to be introduced to successfully meet these requirements.

A recent advance in resist design has been the introduction a new type of molecular glass (MG) photoresist [2]. These materials combine the beneficial aspects of small molecules along with the favorable aspects of polymers. Like most organic molecules, molecular glasses have a well defined structure and purity. But unlike most small molecules they have a low tendency towards crystallization. These molecules are trapped in a kinetically stable amorphous state. Like polymers, they too demonstrate glass transitions (Tgs) significantly above room temperature.

This report sheds light on the challenges of designing a molecular glass photoresist for EUV lithography. When choosing a robust glass forming core, the molecular architecture is a very important parameter. This defines molecular flexibility as well as the packing ability of various molecular systems. Branched and star shaped molecules are well known glass forming molecules due to their topology. This paper introduces a new family of phenolic based bulky molecular systems with branched architecture. The phenolic component provides rigidity, etch resistance and base solubility due to the presence of the hydroxyl groups that can be modified with a solubility switching functionality.

Experimental Section

The synthesis of polyphenols was performed by the condensation of phenol with a ketone or aldehyde in the presence of hydrochloric and acetic acid [3]. By varying the aromatic core, several compounds were synthesized with increasing mass and phenolic content. The compounds were obtained in relatively moderate yields after column chromatography. These compounds were protected with tert-butoxy carbonyl (t-BOC) to varying degrees (50%-100%) by a standard base catalyzed reaction in the presence of 4-dimethyl amino pyridine (DMAP).

Results and Discussion

Our initial efforts on patterning of MGs were based on commercially available phenolic compounds such as alpha, alpha, alpha'-tris(4-hydroxyphenyl)-1-ethyl-4-isopropylbenzene (CR 1) [4]. Patterns of 70 nm lines were obtained with EUV lithography. When compared with the calix[4]resorcinarene resists that have produced 30 nm resolution, the sub 100°C glass transition was identified as a limiting factor for these phenolic resist to attain sub 50 nm features [5]. Hence the structures (CR2-6) are based on a systematic increase of size and phenolic content around a planar benzene core.
Chemistry

Figure 1: The phenolic MG resist structures.

Table 1: Thermal properties of t-BOC protected phenolic MGs.

<table>
<thead>
<tr>
<th>MG Compound</th>
<th>% of tBOC Protection</th>
<th>Phenolic Function</th>
<th>Mw (g/mol)</th>
<th>Tg (°C)</th>
<th>CO Ratio</th>
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<tr>
<td>CR1-66</td>
<td>66</td>
<td>2</td>
<td>624.8</td>
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<td>2</td>
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<td>4.13</td>
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<tr>
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<td>80</td>
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<tr>
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<tr>
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<tr>
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<td>3.25</td>
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</tbody>
</table>

Lithographic Evaluation

Phenolic MG resists were evaluated through EUV exposure at Albany Sematech RTC and Lawrence Berkeley National Laboratory (LBNL). The contrast curve was obtained for CR 6-50.

The EUV microexposure tool at LBNL is capable of fabricating fine features below 30 nm. For the compounds tested, the films were baked (PEB) at 75, 80, 85 and 90°C for 30s. The best result was obtained using a post-exposure bake of 80°C, developed in 0.26N TMAH solution. Although the PEB temperature was around the Tg of this resist material for CR3-50 sub 50 nm resolution was achieved. The LER was calculated using SuMMIT image analysis software.

References


Figure 2: Contrast curve of CR6-50 obtained at Albany Sematech RTC. PEB = 80°C, 30s, Developed in 0.26N TMAH. Sensitivity = ~ 10 mJcm⁻².

Figure 3: SEM images of EUV exposed resist CR2-50, dose 18.5 mJcm⁻², LER (3σ) 7.3 nm.
New Photoresist Platforms Developable in Super-Critical CO₂

CNF Project # 386-90
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Abstract

For more than a decade, the idea of using supercritical fluids in semiconductor processing has been actively explored by many researchers. Super-critical carbon dioxide (scCO₂) in particular is well-known as an environmentally benign solvent, but it also has many potential performance advantages. With its low critical temperature, zero surface tension, and non-polar inert character, scCO₂ shows great potential for its ability to process sensitive materials with patterned features on a very small length scale.

However, barring excessive fluorination, most materials traditionally used by industry show poor solubility in this solvent. This is where molecular glass resists show their unique nature. Because of their small size, molecular glasses have the potential for scCO₂ solubility while still showing equal performance to polymer photoresists [1]. Also, because of their small, discrete structures, these materials can show lower line-edge roughness compared to traditional polymer resists.

We demonstrate some recent successes in developing photoresist features in the sub-65 nm range with only scCO₂ as the developer solvent [2]. Additionally, we evaluate the effect of molecular structure on photoresist dissolution rate and show the consequences of protecting groups, glass transition, and π-π stacking on dissolution.

Experimental

The setup and use of the scCO₂ dissolution rate apparatus is described in a previous paper [3]. Briefly, a 1 cm by 1 cm piece of a silicon wafer coated with molecular glass film is placed into a 25 ml observation chamber, which is aligned with a laser and fitted with a quartz glass observation window for the laser beams to pass through. At the start of the experiment, CO₂ is quickly introduced into the observation chamber at the specific temperature and pressure. The reflected intensity of the laser on the film (at a measured incident angle of 3° from normal) is continuously logged until complete dissolution, when the reflected intensity from the bare silicon constitutes a steady maximum. For simplicity, the time from when the CO₂ is introduced until the time when the film is completely dissolved is taken to be the dissolution time. Comparison with the original film thickness allows one to calculate the dissolution rate with an estimated ± 3% observational error.

Patterning was performed by including 5 wt% (with respect to molecular glass) of a photoacid generator, triphenylsulfonium perfluoro-1-butanesulfonate, into the molecular glass solution before spin-casting. When exposed to ultraviolet or electron-beam radiation, the photoacid generator generates a proton that subsequently catalyzes the cleavage of tboc groups from the molecular glass. This renders the molecule relatively polar and therefore relatively insoluble in scCO₂. High-resolution patterning was performed with a Leica VB6-HR operating at 100 kV, followed by a post-expose bake at 90°C for 30 seconds to activate the deprotection. Development was performed in the same scCO₂ chamber used for DRM measurements.

Results

In general, the solubility of all molecular glasses should be dependent on their molecular weight. This effect may be seen in their respective dissolutions rates, which are plotted on one master plot in Figure 1. For simplicity, the required pressure at 40°C for each molecular glass to reach a dissolution rate of 400 nm/min is plotted against molecular weight.
In general, for the majority of the data there is an expected linear dependence of dissolution rate on molecular weight. However, there are three outlying points in this case where dissolution is inhibited. Further inspection of the thermal properties indicates this may also be loosely correlated to material glass transition temperature (T_g). This observation suggests that these particular films still exist above their T_g when exposed to scCO_2, unlike the lower T_g materials that are plasticized to a T_g below the scCO_2 temperature. These correlations suggest that in situ T_g is a very important factor in predicting film dissolution rate in scCO_2.

Due to excessive plasticization of these particular molecular glass resist films under scCO_2, using them to form stable, high-fidelity patterns remains a challenge. As a result of their un-crosslinked nature, flow and pattern distortion happens quickly near the T_g. Therefore, only molecular glasses with very high T_g’s can be patterned and developed reliably with scCO_2. Of course, this limitation can be mitigated if the molecular glass is crosslinked upon patterning, as Shiraishi et al. have shown [4]. From the molecular glasses reported in this paper, hexa(hydroxyphenyl)benzene-tboc has been reliably patterned and developed without the assistance of crosslinking. The resulting pattern is shown in Figure 2. Success with this molecular glass is due to the high T_g of the material, which increases upon deprotection and leads to a patterned material that resists plasticization.

References
Architectural Studies in High Resolution, Versatile Resists

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Abstract
Multifunctional atom transfer radical polymerization (ATRP) initiators based on sugars were utilized to grow short tert-butyl methacrylate (tBMA) arms. The kinetics of this system was studied using nuclear magnetic resonance (NMR) and gel permeation chromatography (GPC), and shown to be living. The polymerization was further engineered to obtain samples of controlled degrees of polymerization such that the polymer component only accounted for 55-85% of the total molecular weight of the hybrid molecule. A sucrose-based system was examined using thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC), demonstrating a clear architectural effect on glass transition temperature (T_g). Finally a sample engineered for high T_g but low molecular weight was evaluated using e-beam lithography and scanning electron microscopy (SEM).

Summary of Research
Understanding the role of architecture on photolithographic performance will be crucial in designing new photoresists capable of meeting the requirements of the semiconductor industry for next generation lithography. Block copolymers have been successfully used as additives to enhance resolution [1] and as photoresists themselves to create patterns with sublithographic features [2]. Molecular glass photoresists [3] have also been examined as a viable alternative to conventional polymers [4]. This study lays the groundwork for creating hybrid photoresists containing molecular glass cores and polymeric arms. Hybrid photoresists can be used to study architectural effects on lithographic performance by varying the number of polymer arms (f) and the degree of polymerization of those arms (n). In the limit of n = ∞ the hybrid is a polymer, while in the limit of n = 0 the hybrid is a molecular glass. Polymer and molecular glass photoresists can be viewed, not as separate entities, but rather two ends of an architectural spectrum, as seen in Figure 1. Therefore a systematic study of architecture, its effect on properties and ultimately lithographic performance is possible.

Star poly(tBMA) has been grown from fully converted glucose and sucrose multifunctional ATRP initiators (with f_max = {5,8} respectively) to study polyelectrolytes [5]. In this study, molecules with arms with a degree of polymerization an order of magnitude lower than previously reported were required to observe the hybrid photoresist in the limit as n approaches zero. Kinetics studies were performed in order to obtain samples of the required degrees of polymerization. These were characterized using NMR to determine conversion and GPC to determine molecular weight and polydispersity. Molecular weight versus conversion plots (not shown) were linear—revealing that the systems were living. However the polydispersity was high and polymer arms with n < 10 were unobtainable due to rapid initial conversion. The sucrose system was engineered by modifying the reaction temperature, solvent volume and Cu(I):Cu(II) ratio. This prevented the rapid initial conversion of a monomer resulting in controlled conversion immediately upon initiation as demonstrated in Figure 2. GPC data indicated that the system was still living and samples had a polydispersity index between 1.05 and 1.10.

A series of hybrid resists were synthesized for 1 < n < 10 utilizing the sucrose based initiating system. TGA and DSC were used to characterize the samples effectively mapping the effect of architecture on T_g as the hybrid resist approaches the molecular glass regime as seen in

Figure 1: Schematic of architectural spectrum. From left to right: segmented block copolymer resist, glass-coil block copolymer resist, glass-brush resist, molecular glass resist.
Figure 3. This result is significant as it demonstrates that high molecular weights can be achieved with very short polymer arms.

One of the higher $T_g$ samples was selected for lithographic testing. The photoresist with five weight percent photoacid generator was spin coated onto a primed wafer, exposed to e-beam, developed and viewed with a SEM in Figure 4. Resolutions as low as 70 nm were achieved with 1:3 line spacing before the poor adhesion and insensitivity due to the resist being fully protected with tert-butyl groups became limiting. Further work is required to examine a partially protected resist in order to determine its ultimate resolution.

References


Chemistry

Patterning Organic Materials with Super-Critical CO₂ Soluble Photoresist

CNF Project # 775-99
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Abstract

The fabrication of functional devices from organic materials usually includes at least one patterning step, whether it be organic light-emitting diodes (OLEDs) patterned into pixels for displays, or organic thin-film transistors (OTFTs) which require patterning at the gate, dielectric, electrode and channel material levels. Traditional patterning techniques used on inorganic materials such as metals and silicon do not carry over well to organic materials because of the harsh chemicals used in developing and removing photoresist. In this work, we show that photolithographic patterning of these sensitive materials can be achieved using a specially prepared photoresist which is both developed and removed with super-critical carbon dioxide (scCO₂). Because scCO₂ has little effect on most organic semiconductors, this resist can be seen as a “gentle” alternative to traditional photoresists. Here we demonstrate patterning of both OLED materials and conducting polymers into structures suitable for OTFT electrodes. With further refinements in the process, a robust photolithographic patterning system capable of high resolutions and unlimited layering will be possible with a wide variety of chemically sensitive materials.

Summary of Research

Photolithography is widely used in the semiconductor industry to pattern a wide range of materials. Photoresist is spin-coated from an organic solvent onto a substrate. After exposure, development typically occurs with an alkaline developer and the resist is later removed with more solvent or oxygen plasma ashing. All of these steps (particularly the development and removal steps) are damaging to the materials used in organic electronic devices such as OLEDs and OTFTs. Because of this, photolithography has been eschewed by the organic electronics community, at least for the crucial task of patterning the active organic layer (metal contacts that can be put on first are usually done with photolithography). Yet photolithography is currently the best means of achieving high resolution, high throughput patterns with good registration over an arbitrary number of layers.

Previous attempts by our group to pattern organic materials with photolithography used the chemical vapor deposition (CVD) polymer parylene to make a mechanically peelable stencil mask capable of making features a least as small as one micrometer [1]. This technique has been used to good effect to make polymer contact transistors and also to pattern an ion transporting light emitting material between contacts in order to study ion motion in situ (see the report titled: Direct measurement of the electric field distribution in a light-emitting electrochemical cell). The technique is limited for multi-layer applications because of the parylene etch step involved. It is also problematic to peel parylene from small features without damaging them. This leads us to the present solution, which is to make a photoresist which is itself free from liquid developers and solvents.

Recently, a class of resists that are soluble in supercritical carbon dioxide (scCO₂) has been developed [2]. Both the development and liftoff steps can be accomplished in scCO₂ and the resists are patternable in 248 nm light. The resist used in this work is the random co-polymer P(FDMA-co-MAA). Figure 1 shows the fabrication steps for subtractive and gap filling photolithographic patterning methods.
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patterning of an organic material as well as a second, “gap filling” method. In the subtractive case, resist is first spun on top of the organic layer (the fluorinated solvent used is agreeable to many organics). The resist is patterned in a manner similar to other negative photoresists, except the development step is done in a high pressure reactor with CO$_2$ at 4000 psi and 40°C. The organic layer can then be etched in the unprotected regions and the remaining resist is removed with further scCO$_2$ after exposure to HMDS. The conducting polymer PEDOT:PSS was patterned in this manner, as is shown in Figure 2. Patterning of this type can be used to make polymer electrodes for OTFTs, among other things.

The gap-filling technique was employed to pattern OLED materials. In this case, the PEDOT layer (used for hole injection into the OLED) isn’t etched. Instead, the openings formed in the resist allow the spin coated OLED material to make electrical contact with the PEDOT and underlying ITO layer. Since current can’t flow through the resist, the OLED only lights up in the patterned region. Figure 3 shows the OLED patterned into circles of three different sizes: 1 mm, 100 µm and 10 µm. With more work, this method should be extendable to three colors for display applications. We are also exploring a liftoff technique with the material which would allow for patterning of an organic layer without exposing it to the resist solvent.

References


Dielectric Fluctuations and the Origins of Noncontact Friction

CNF Project # 863-00

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Abstract

Dielectric fluctuations underlie a wide variety of physical phenomena, from ion mobility in electrolyte solutions and decoherence in quantum systems to dynamics in glass-forming materials and conformational changes in proteins. We have shown that dielectric fluctuations also lead to noncontact friction. Using high sensitivity, custom fabricated, single crystal silicon cantilevers, we measured energy losses over poly(methyl methacrylate), poly(vinyl acetate), and polystyrene thin films. A new theoretical analysis, relating noncontact friction to the dielectric response of the film, is consistent with our experimental observations. This work constitutes the first direct, mechanical detection of noncontact friction due to dielectric fluctuations.

Summary

As part of our efforts to bring magnetic resonance imaging to the nanoscale [1], we have investigated the noncontact friction experienced when an ultrathin, highly compliant silicon cantilever is brought near the surface of a polymer film. We find, surprisingly, that the main source of friction experienced by such ultrasensitive cantilevers arises from thermal dielectric fluctuations in underlying polymer film [2, 3].

The cantilever used in this study was similar to cantilevers whose fabrication and characterization we have described previously [4]. We have used such cantilevers to detect nuclear magnetic resonance [1, 5] with record sensitivity, to detect electric spin resonance [6], and to characterize the magnetic properties of individual submicron magnetic particles [7].

The cantilevers used in the noncontact friction study can be seen in Figure 1. The cantilever has dimensions of 250 µm by 5 µm by 340 nm, a force constant of 700 µN, a resonance frequency of 7.385 kHz, and a mechanical quality factor in vacuum of approximately 31,000. The tip region of the cantilever was thinned from 340 nm to < 100 nm using a reactive ion etch. The cantilever tip had a radius of approximately 30 nm and was coated with a thin layer of platinum using a shadow mask technique [8].

We used the cantilever to probe noncontact friction at distances of 3 to 200 nm above thin polymer films, as sketched in Figure 2. The cantilever oscillates parallel to the sample, in contrast to the configuration of conventional atomic force microscopy. The sample is a polymer film of thickness 12 nm to 450 nm, spin-cast onto an epitaxial Au(111) substrate. The tip-sample voltage ($V_{ts}$) was applied to the substrate while the cantilever is grounded. This applied voltage produced a charge on the cantilever tip which interacts with local fluctuating electric fields to produce a time-random force on the cantilever that, in turn, leads to friction.

Figure 1: Ultrathin, highly force compliant cantilevers for detecting dielectric fluctuations in polymer films.
An example of our findings can be seen in Figure 3. Here we plot the friction experienced by the cantilever, as inferred from its ringdown time, as a function of height over a 450 nm thick film made from three different polymers (poly(methyl methacrylate), PMMA; poly(vinyl acetate), PVAc; and polystyrene, PS. It is clear that the friction is dramatically different over the three materials.

Details of the measurement can be found in Reference [2] and a theory for the effect can be found in References [3, 5].
Microfluidic Mixing

CNF Project # 1278-04
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Abstract

Microfluidic systems present advantages and challenges relative to larger systems for performing chemical processes. They facilitate manipulation and analysis of small sample volumes and process parallelization within a small footprint. However, they generally suffer from inefficient mixing and low rates of interfacial mass transfer, due to the laminar flow and the long diffusive mixing times compared to the convective time scale of the flow. We study the effect of passive mixing structures on transport in these systems in the context of inter-stream mixing and mass transport from the fluid to a solid boundary.

Summary

Our research focuses on the understanding and optimization of mass transfer from microfluidic flows. This fundamental process is core to the operation of surface-based sensors, biochips, and electrochemical systems. We exploit a set of obliquely oriented grooves patterned on the walls of the microchannel to generate various classes of three-dimensional flows; this strategy is called the staggered herringbone mixer (SHM) [1]. We are using electrochemistry to characterize rates of mass transfer from these flows to reactive boundaries; we are also developing this system with Prof. Héctor Abreuña’s (Chemistry, Cornell University) to increase power and fuel efficiency in a microfluidic fuel cell [2].

For electrochemical applications, we work on glass substrates for insulation and optical access. The process of forming the groove structures starts with a 400 nm film of amorphous silicon (a-Si) deposited by plasma-enhanced chemical vapor deposition (PECVD) onto a 500 µm thick borosilicate glass wafer. Photoresist is spun and patterned to expose regions of the a-Si that are then etched with an SF$_6$/O$_2$ reactive ion etch to expose the glass substrate. The wafer is submerged in concentrated HF to etch the glass to a depth of 50 µm through the windows in the a-Si. The a-Si is then stripped with another SF$_6$/O$_2$ etch, revealing the grooved mixing structures. Due to the isotropic nature of the HF etch, the grooves are half-cylindrical with smooth walls (see Figure 1). To create a conductive and electrocatalytic surface, the structured glass surface is metalized: an adhesion layer of Ti (8 nm) and a seed layer of Au (150 nm) are deposited by electron beam evaporation. A 5 µm layer of electroplated gold is deposited to increase conductivity and improve the stability and durability of the metal surface during electrochemical operation.

To form an electrochemical cell, a silicone gasket is placed between two electrodes; the gaskets are produced by soft lithography in polydimethylsiloxane (PDMS). A master of the desired structure is photolithographically patterned in SU-8 on a silicon wafer. After silanization, the master is covered with PDMS and a flat glass plate is used to contact the SU-8 and produce a PDMS gasket of the desired thickness (~ 100 µm). Through-holes for the inlets and outlet are sandblasted through the glass electrodes and the system is assembled and pressure-sealed in an acrylic jig. The system can be run as a potential cell (electroactive species flow

Figure 1: SEM micrograph of structured electrode before electroplating.
over the electrodes, potential is applied and the resulting current is measured) or as a fuel cell (fuel flows over one electrode and oxidant over the other, producing a potential difference and current through a load). Experiments are currently being carried out in both systems, to elucidate the nature of transport to boundaries in the SHM flow and to quantify the enhancements in a system based on our collaborators’ microfluidic fuel cell [2]. Preliminary results with sodium ferrocyanide in the potential cell demonstrate increased scaling of current with the Peclet number Pe at high flow rate (Pe = Q/WD, with volumetric flow rate Q, channel width W, and diffusivity D). Current scales roughly as the square root of Pe, rather than the cube root scaling expected from the case of a flat electrode surface [3] (see Figure 2). The fuel cell system shows increased current density and power output, demonstrating the system’s feasibility as a power source for consumer electronics and similar applications.

References

Nanostructure-Tailored Chemiresistor Sensor Arrays

CNF Project # 1345-05
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Abstract

This project focuses on the study of how design parameters influence the performance of sensor arrays constructed from nanostructured thin films and chemiresistor arrays. The chemiresistor sensor array consists of interdigitated microelectrodes fabricated using the CNF. The ability to tune interparticle spatial properties is essential for the design of sensing nanomaterials toward the desired sensitivity and selectivity for the detection of volatile organic compounds. The results have provided important insights into the detailed delineation between the interparticle spacing and the nanostructured sensing properties.

Summary

We have carried work in three closely-related areas of this project. First, we have studied several design parameters influencing the performance of sensor arrays constructed from nanostructured thin films and interdigitated microelectrodes (IMEs) [1]. The nanostructured thin films on the IME devices were prepared from nonanedithiol (NDT) and mercaptoundecanoic acid (MUA)-linked assemblies of 2 nm sized gold nanoparticles. The sensor array data in response to volatile organic compounds were collected and analyzed using fractional factorial experimental design and analysis of variance for understanding effects of the design parameters on the sensitivity.

While the smaller value for the microelectrode space, width, and length generally led to higher response sensitivity, a strong dependence on the nature of the nanostructured thin films was found. The microelectrode space was the most important design parameter for NDT-based thin films. The principal component analysis results for classification performances of the arrays consisting of a set of thin films have demonstrated the possibility of optimizing sensor arrays by appropriate selections of microelectrode parameters and nanostructured sensing films.

Secondly, we have studied the particle size and interparticle spatial effects on the electrical conductivity properties of molecularly mediated thin film assemblies of nanoparticles (Figure 1) [2], which is important for exploring the unique electrical properties in applications such as chemical sensors and biosensors. We investigated such effects for thin film assemblies of gold nanoparticles of highly-monodispersed sizes (2-4 nm) using alkyl dithiols of different chain lengths (0.8-2 nm). The conductivities of the thin films were measured using interdigitated microelectrodes as

Figure 1: An illustration of the molecularly-mediated thin film assembly of nanoparticles between microelectrodes (Cover page in J. Mater. Chem., 17, 457, (2007)).
the platform. Experimental results have shown that the activation energy increases with chain length and decreases with particle size, and the electron tunneling decay term decreases with particle size. The results have revealed that the experimentally determined conductivity and activation energy data for the nanoparticle films quantitatively match the calculations from electrostatic model of granular metals through the electron tunneling mechanism. The strong correlation between the experimental and calculated data was attributed to a combination of the high monodispersity of the nanoparticles and the uniformity and stability of the thin film assemblies. These findings have important implications for the fine-tuning of nanostructured thin films as chemical and biological sensing materials.

Finally, we studied the tuning of the interparticle spatial properties of nanoparticle assemblies for the design of sensing materials toward desired sensitivity and selectivity [3]. Molecularly mediated thin film assemblies of metal nanoparticles with controllable interparticle spatial properties were used as a sensing array. The interparticle spatial properties are controlled by a combination of difunctional alkyl mediators (X-(CH$_2$)$_n$-X) such as alkyl dithiols, dicarboxylate acids, and alkanethiol shells capped on nanoparticles. Alkanethiolate-capped gold and gold-silver alloy nanoparticles (2-3 nm) were studied as model building blocks toward the thin film assemblies, whereas the variation of alkyl chain length manipulates the interparticle spacing. The thin films assembled on an interdigitated microelectrode array platform are characterized for determining their responses to the sorption of volatile organic compounds (VOCs).

The correlation between the response sensitivity and the interparticle spacing properties revealed not only a clear dependence of the sensitivity on alkyl chain length but also the occurrence of a dramatic change of the sensitivity in a region of chain length for the alkyl mediator comparable with that of the capping alkyl chains (Figure 2). This finding reflects a balance between the interparticle chain-chain cohesive interdigitation and the nanostructure-vapor interaction which determines the relative change of the electrical conductivity of the inked nanoparticle thin film in response to vapor sorption. The results have provided important insights into the detailed delineation between the interparticle spacing and the nanostructured sensing properties.

References

Figure 2: The correlation between the response sensitivity and the interparticle spacing properties in response to three different VOCs.
Microfluidic Device for Combinatorial Chemistry

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Abstract

This work presents a microfluidic device that has the unique capability of automating combinatorial processes such as protein refolding and bioconjugate synthesis. Conventionally, these processes are done by hand-pipetting or using robotic systems. The microfluidic approach offers the advantages of automation, cost-effectiveness, compatibility with optical detection, and a million-fold reduction in sample volumes. Successful devices will greatly reduce the cost of realizing biopharmaceuticals.

Introduction

In this work, we develop a microfluidic device designed specifically for protein refolding applications. Protein refolding has been a bottleneck in the production of biopharmaceuticals on a large scale. In order to maximize the production of proteins, bacterial hosts are induced with promoters, resulting in the production of aggregated, over-expressed proteins. The process of refolding, which involves the conversion of these inactive aggregated proteins into their functional native state, is a highly empirical process. Determination of solution conditions to properly refold a protein is a combinatorial process which can be automated using our microfluidic device.

This microfluidic approach also has potential applications in bioconjugate synthesis for gene silencing. Short-interfering RNAs (siRNA) are small nucleotide chains which associate with the corresponding mRNA and suppress the expression of specific disease-causing proteins. Introduction of siRNA into cells needs a delivery vector. The combinatorial process of creating polymeric delivery vectors can be automated using our microfluidic device.

Summary of Research

Lysozyme refolding has been chosen as the model system for evaluating device performance, as its refolding protocols and activity assays have been widely developed [1]. We implement a combinatorial protocol using 16 refolding chaperones. The inactive aggregated lysozyme is solubilized in a strong denaturing medium (8 M guanidinium chloride, 1 mM EDTA, 50 mM Tris HCl and 16 mM dithiothreitol). This solubilized lysozyme along with the denaturants is diluted in a renaturing medium, which consists of the renaturing buffer (50 mM Tris HCl, 1 mM EDTA, 5 mM glutathione, 2 mM dithiothreitol, 0.85 M guanidinium chloride) and a mixture of three artificial chaperones, chosen combinatorially. The 16 chaperones are used in two different concentrations and this results in a total of 4480 combinations.

Reagent aliquoting and mixing is achieved using microfluidic control [2]. The device consists of two layers of PDMS (poly (dimethylsiloxane)) on a glass slide. The schematic of the channel layout is shown in Figure 1. The layout consists of input channels for protein and reagent solutions, an annular mixer and an output channel for...
the refolded protein. High pressure air is passed through control channels to control fluid flow in flow channels. The device is integrated with a control unit which enables automation of the processes (Figure 2).

Results and Discussion

Peristaltic pumps present on each flow channel allow precise control of the amount of fluid through the channel. The flow rate of the fluid in the flow channel depends on the frequency of actuation of the control channels. The volume injection rate as a function of the actuation frequency was calibrated by monitoring the dye-water interface (Figure 3). Dye-water mixing experiments performed at different frequencies resulted in a maximum flow rate of 1.07 nL/s. This corresponds to an actuation frequency of 25 Hz and a mixing time of 45s.

Preliminary experiments with protein solutions were performed on a three-input device (Figure 4). A solution of the solubilized lysozyme in denaturing medium was metered through one input. Solutions of urea (46.88 mg/mL) and guanidinium chloride (55.96 mg/mL), used as the artificial chaperones, were prepared independently in the renaturing buffer and were metered through the other two inputs. All the flow channels connected to the annular mixer were closed with control valves and the peristaltic pump on the annulus was actuated to mix the solutions. A solution of partially refolded lysozyme was obtained from the output channel.

Future work includes thorough calibration of the flow channels to meter precise fluid volumes into the mixer and scaling up of the device to include more chaperone inputs and combinatorial capabilities.

Conclusion

In conclusion, by integrating the control capabilities with the PDMS device, we can facilitate automation of combinatorial protein refolding protocols. The system is compatible with on-chip detection using terahertz spectroscopy [3], which gives the potential for real-time monitoring of kinetic intermediates.

References

Electroactive Nanowells for Concentration, Electrochemical Sensing and Spectrographic Microfluidic Memory

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Abstract
In this work we describe the development of electroactive micro-/nanowells which exploit highly localized electrokinetic effects in order to actively concentrate, confine, store and reject particles in well defined geometries. In this article we present experimental results demonstrating repeatable trapping and repulsion of polystyrene particles in wells ranging in diameter from 100 nm to 20 µm. Immediate applications include active cell trapping and concentration and unlabeled sensing and the development of a spectrographic microfluidic memory.

Summary of Research
The ability to deliver individual or small numbers of particles into confined geometries is of great importance for a number of biological applications (including high throughput pathogen detection, enhanced sensitivity for surface phase binding assays, parallel single cell trapping, interrogation and storage) and non-biological applications (including storage of information, directed or passive self-assembly processes and organic electronics). Within this broader set of devices, microwell arrays have become a popular tool for trapping and storage of particles as they enable discrete immobilization of cells without the need for surface binding chemistry (as the trapping site geometry is designed to prohibit trapped particles from dislodging easily) in a simple platform compatible with fluorescence microscopy.

Devices and Fabrication
Figure 1a shows a schematic of our “electroactive microwells” outlining the basic architecture. The electric field is applied between the upper and lower indium-tin-oxide (ITO) electrodes, and the wells are defined photolithographically in a polyimide (PI) dielectric. As can be seen, particles are driven, sensed and repelled from the well depending on the polarity. Microwells with sizes ranging from 6 to 25 µm were patterned on a 5 µm thick spin-on photoactive polyimide dielectric on top of an 8 Ω/square surface resistivity indium tin oxide (ITO) coated glass slide. An additional ITO electrode was inserted on top of the wells, separated from the polyimide by two 70 µm spacers, serving to enclose the channel structure and to close the electric circuit. Figure 1b is a finite element simulation of the electric field in the well.

Figure 2 shows our initial trapping experiments using a 0.1 mM phosphate buffer solution at pH 7 containing 1.9 µm diameter polystyrene particles. These particles were carboxyl modified, giving them a negative ζ-potential. It is expected that by applying a positive voltage on the bottom electrode, the PS beads will be driven from the bulk flow into the well, and they will be ejected by reversing the polarity. Figure 2 displays time lapse images of particle trapping and rejection in a 20 µm well for the case of a 5V applied DC bias and an imposed pressure driven flow of 30 µm/s (average velocity). During the attraction phase, Figure 2 (a-d), particles were drawn...
from the bulk solution into the well over 30 seconds. Here particles which were either initially positioned or convected into a region approximately three times the diameter of the well would be captured (we refer to this region as the “attraction basin”). However, particles which approached the well in a plane near the surface were observed to be repulsed from it in an upwards and radial direction, implying that additional electrokinetic effects aside from the expected electrophoresis have significant impact on the overall attraction process. When the polarity is reversed, Figures 2 (e-f), particles are repelled out of plane as they approach the well’s edge. Particles ejected from the wells form ring-like patterns, suggesting a strong repulsion force that points radially outward from the well’s center. The size of the ring shown in Figure 2f roughly coincides with the attraction basin, suggesting that particles decelerate due to both the drop in field intensity away from the well and the contribution of viscous drag.

Spectrographic Microfluidic Memory

Current optical storage devices such as DVDs have their read/write capabilities fundamentally restricted by the diffraction limit of light. We are also developing an optofluidic architecture for storing cocktails of colloidal quantum dots in electroactive nanowell structures. One application of these devices is the development of a fluidic memory approach which could enable the generation, reading and erasing of multiple bit information packages on single light diffraction limited data marks by spectral and intensity multiplexing of quantum dot cocktails (Figure 3). Here we focus on the development of the electroactive nanowell trapping architecture. Briefly, we have shown that by applying an electric potential between a top and bottom indium tin oxide (ITO) electrodes, microparticles suspended in solution can be attracted, stored and rejected from a targeted well structure by electrokinetic actuation. Nanowells 100 nm in diameter and 1 µm deep were fabricated by depositing silicon and a small oxide thin film on top of an ITO cover slip, patterning the wells on electron beam resist followed by a series of dry etching steps that leave the ITO substrate exposed in the well sites (Figure 4). When the quantum dots are electrokinetically transported to their sensing sites, they are then excited by a UV-blue light, and their discrete fluorescent signal is captured by a fiber spectrometer. Data erasure can be selectively performed by reversing the polarity of the field and ejecting the quantum dots from the nanowell data marks.
Fabrication of Nanofluidic Filter Device for Surface Enhanced Raman Spectroscopy

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Abstract
We have fabricated a nanofluidic filter device that can reproducibly form nanoparticle-molecule clusters at a specific location for surface enhanced Raman spectroscopy (SERS). This device can provide much higher Raman signals with better reproducibility comparing to convention SERS approach. The device was fabricated on a Pyrex™ 7740 wafer using conventional photolithographic and etching techniques. With a micro-nanochannel pinched structure, SERS-active nanoparticles can be trapped to form the cluster which provides a reliable detection spot for SERS. Adenine was successfully detected with this device and the electromagnetic enhancement factor over conventional SERS technique was calculated to be ~ $10^8$.

Summary of Research
To improve the reproducibility and sensitivity of current surface enhanced Raman spectroscopy (SERS) technique, we report a novel nanofluidic filter device that can trap nanoparticles and molecules at a specific location to form nanoparticles/molecules clusters with reliable and hot spot site. The nanofluidic filter device has a pinched micro-nanochannel structure, which enable trapping nanoparticles and molecules. Nanoparticles with a dimension larger than the depth of nanochannel can be trapped and aggregated into clusters at the entrance of the nanochannel. These nanoparticle clusters have turned out to contain hot spot area that can produce high SERS signals. Figure 1 shows the schematic diagram of side view of nanofluidic filter device and the mechanism of forming nanoparticle clusters at the entrance of the nanochannel.

The nanofluidic filter device was fabricated on a double-size polished Pyrex wafer with conventional photolithography and etching process. A shallow trench of 40 nm was first patterned and dry etched. This nanochannel is critical for entrapment of gold nanoparticles for SERS applications, as shown in Figure 2. As a hard mask for subsequent wet
etching, 10 nm Cr and 50 nm Au layers were sequentially electron-beam evaporated onto the wafer. Then, a deep trench of 6 µm that is directly connected to the reservoirs as well as nanochannels was patterned and wet etched with concentrated hydrofluoric acid (HF 49%) solution. After removing the remaining Cr and Au layers, the inlet and outlet holes were drilled by the sand-blasting. For the final step, the glass wafer was bonded with a cover Pyrex wafer by clinging each other using de-ionized water.

Gold colloids, SERS-active substrates, with a diameter of 60 nm in aqueous solution, were blended with adenine molecules at a volume ratio of 5:1 and dispensed into the device through the reservoir. By the capillary force, the sample solution was pulled into the channel within a couple of seconds. The gold colloids are trapped at the entrance of the nanochannel and aggregated to form clusters. Then, the SERS signals were monitored as the function of time. From the measured Raman intensity, as shown in Figure 3, the electromagnetic enhancement factor of the nanofluidic filter device was calculated to be ~ 10^8.

In conclusion, we successfully demonstrated a nanofluidic device, which provides much higher Raman signal at a designated hot spot with better reproducibility. This approach can potentially be extended to detection of many other bio-molecules of practical importance, which are difficult to detect in a low concentration using the SERS technique.

References
