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Soft lithography

Soft lithography refers to a suite of techniques for replicating patterns of organic molecules or other materials (for example, ceramics or metals) on both planar (flat) and nonplanar (curved) substrates. It is applicable to structures ranging in size from tens of nanometers to centimeters. For most applications, soft lithography uses mechanical processes to transfer organic material by physical contact between a topographically patterned stamp or mold and a substrate. The mechanisms for pattern transfer (molding, embossing, and printing) are more similar to methods used for bulk manufacturing (for example, plastic parts and newspapers) than they are to those used commonly in fabricating microelectronic devices (for example, photolithography or electron-beam lithography, where beams of light or beams of electrons write patterns in polymeric materials). The term "soft" originally came from physics usage where organic materials are known as soft matter. Soft lithography initially referred to the rubbery, organic stamps used to transfer patterns. It now generally refers to both the system used for pattern transfer and to the organic or organometallic materials patterned, regardless of whether a rubber stamp or a hard stamp (usually fabricated of quartz or glass) is used, and has applications in electronics, optics, and biology.

Master versus replica. Most fabrication processes are divided into two steps: the fabrication of a master, and the replication of that master. To fabricate a master for use in soft lithography, a high-precision technique such as photolithography is used to form a three-dimensional pattern in a photosensitive polymer supported on a rigid substrate (**Fig. 1**). Then a liquid precursor for an elastomeric polymer, such as polydimethylsiloxane, is poured onto the topographically patterned master and cured to form a rubbery (elastomeric) solid. The polymer forms a negative replica of the original pattern with high fidelity. The topographically patterned, polymeric block acts as a stamp or mold for depositing or transferring the pattern from the master into organic structures supported on another substrate. Polydimethylsiloxane (which is a common material, often found in bathtub caulking and rubber toys) is used for the stamp or mold element in soft lithography because it is inexpensive, commercially available, nontoxic, elastomeric, and optically transparent. Relief features on the stamp define the shape, size, and distance of separation between the printed or molded regions. The flexibility of the polydimethylsiloxane stamp allows molecular-level or conformal contact between the stamp and the surface. This feature is important for preparing uniform and reproducible patterns of molecules on rigid substrates.

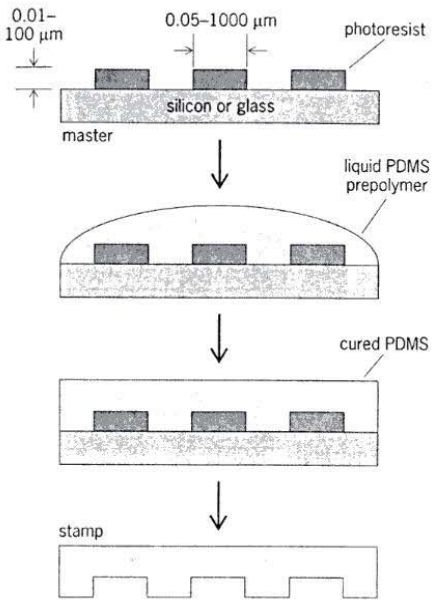

Fig. 1. Scheme of the replication of a topographically patterned substrate. The liquid precursor for polydimethylsiloxane (PMDS) is cast on the master and thermally cured. The solid, rubbery stamp is removed from the substrate; the molded surface is patterned with the inverse topography of the substrate.

Techniques. The two most common mechanisms for transferring patterns by soft-lithographic techniques are molding and printing (**Fig. 2**). A polydimethylsiloxane mold, pressed into contact with a liquid prepolymer, produces replicas with features that are inverted from the mold. Variations of this method, using rigid stamps, are used in the production of compact discs and holograms. Alternatively, a low-viscosity precursor to a polymer can fill the mold by capillary action. The molded precursor is cured by exposure to heat or to ultraviolet light or by evaporation of a solvent. The elastic properties and low surface energy of the polydimethylsiloxane make it easy to release the mold from the cured polymer. These procedures enable the replication of three-dimensional topologies in polymers, ceramics, glassy carbon, colloids, and salts in a single step.

Another soft-lithographic technique, microcontact printing, is analogous to a rubber stamp printing on paper; that is, a chemical "ink" is transferred upon contact between the stamp and a surface. The ink often is composed of organic molecules that spontaneously organize into an ordered array only one molecule thick on the surface. These self-assembled

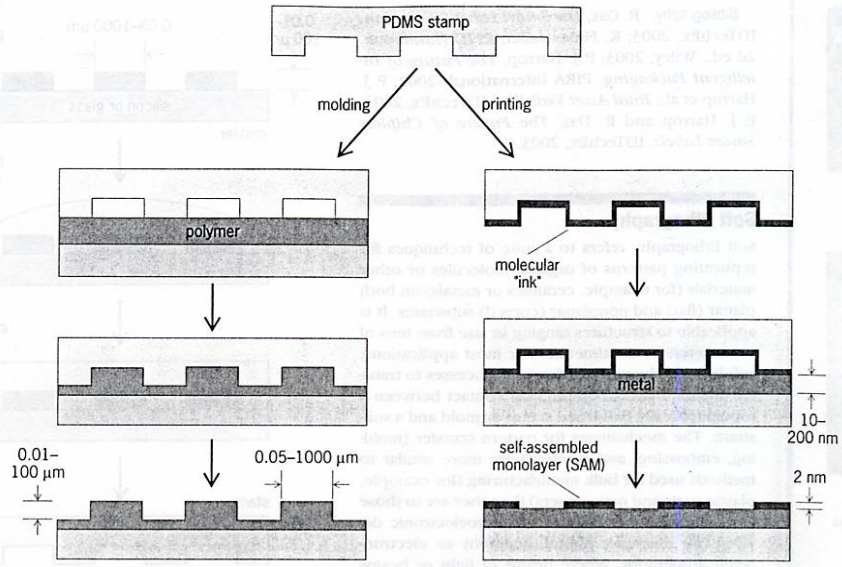

Fig. 2. Two methods common in soft lithography using a polydimethylsiloxane (PMDS) stamp.

monolayers present specific chemical functionalities on the surface that can modify its physical properties, for example, wettability or adhesion. Alkanethiols [$CH_3(CH_2)_nSH$] are used commonly to form self-assembled monolayers on coinage metals such as gold, silver, palladium, and copper. The sulfur in the thiol moiety binds to the surface of the metal, and the hydrocarbon chains arrange and form an ordered, hydrophobic surface.

Uses and applications. Soft lithography is particularly useful in rapidly prototyping micro- and nanostructures for applications in electronics, optics, and biology. The appropriate choice of soft-lithographic techniques can reduce the duration of the design cycle from an initial idea to a working prototype in less than 24 h. This feature is attractive at both the research and production levels.

Surface patterning and biology. The capability to control the macro- and microscopic properties of surfaces is useful (especially in biology) whenever nonspecific adsorption of proteins to surfaces is a significant problem. Soft lithography can generate patterns of biomolecules on a surface that direct proteins, cells, or other biologically relevant molecules to interact, spread, or avoid specific locations on a surface. This ability has enabled the development of applications such as cell-based assays for the study of cancer cells and their response to small molecules (**Fig. 3***a*).

Micro/nanofabrication. Soft-lithographic techniques can pattern metallic and polymeric features over large areas in a single fabrication process for use in electronic and optical devices. The stamps are used as masks in a photolithographic technique, called phase-shifting lithography, which transfers the pattern of the edges of the features defined in the stamp to the photoresist material because the intensity of the light at the edges of the features is lower than that passing through the other regions of the stamp. Bandpass filters and polarizers are examples of optical elements fabricated by this technique. Microelectronic devices such as transistors and sensors (for H_2) are easily fabricated by techniques such as microcontact printing (Fig. 3*b*).

Microfluidics. Polymer-based microfluidic devices have two significant advantages over those produced in glass by etching: (1) the materials and the processes used to fabricate the polymer-based devices are inexpensive, and (2) the polymer-based channels are mechanically stable. The polydimethylsiloxane-based, two-dimensional channels can be sealed to rigid or flexible substrates and used to form complicated, three-dimensional fluidic networks. These channels are useful for biological assays (solution gradients and serial dilutors), for optical devices (waveguides), and for particle alignment (nanowires and colloidal crystals) [Fig. 3*c*]. *See* MICROFLUIDICS; MINIATURIZED ANALYSIS SYSTEMS.

Advantages and disadvantages. Four areas of science and technology where soft lithography offers significant advantages over other lithographic methods are (1) the fabrication of microstructures on curved surfaces, (2) the fabrication of nanostructures, (3) the development of microsystems for cell biology, and (4) the fabrication of micro- (and

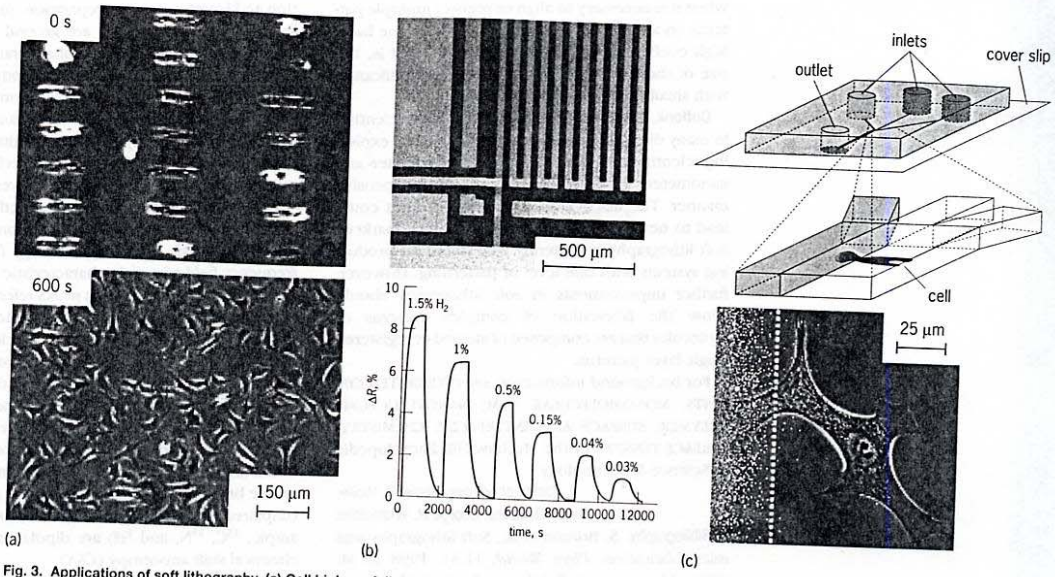

Fig. 3. Applications of soft lithography. (a) Cell biology. Adhesion sites for bovine capillary endothelial cells patterned by microcontact printing localize the cells to specific regions and geometries on a surface. The optical micrographs show an initial configuration of confined cells and an image of the system 10 min after a mild electrochemical pulse was applied to release the barriers on the surface that prevented the cells from spreading. This type of assay is useful for studying the spreading behavior of normal and cancerous cells. (b) Microfabrication. A palladium-based microsensor fabricated by microcontact printing and selective etching responds electrically to the presence of hydrogen (H_2) gas. The image is a scanning electron micrograph that shows one section of the palladium sensor. The graph shows the change in resistance of the sensor as a function of the H_2 concentration. (c) Microfluidics. Microfluidic channels can address different parts of a single cell by controlling the flow inside the channels. The scheme shows a channel that is placed over a cell. There are three inlets to the channel. Fluid streams introduced in each inlet do not mix by turbulence because the dimensions of the channel are small (<100-μm diameter). This physical phenomenon (known as laminar flow) allows the delivery of reagents to specific parts of a cell. In this case, the optical micrograph shows the mitochondria on the left side of the cell that have been stained with a fluorescent dye.

perhaps nano-) structures over large areas at low cost. Photolithography uses rigid, planar materials (for example, silicon wafers) as substrates and physical masks in microfabrication. The rigid masks cannot conform to curved substrates (for example, optical lenses), and optical systems require highly specialized lenses to project patterns in focus onto curved surfaces. Soft-lithographic methods, however, can generate microstructures on nonplanar surfaces (for example, fiber optics) because the rubber stamps easily conform to the surface.

Soft lithography also can fabricate simple arrays of nanostructures over large areas. State-of-the-art systems for photolithography can produce features down to 25 nm in the laboratory and features of 70–100 nm in mass production. Diffraction of the light used in photolithography (~150–200-nm wavelengths) physically limits the minimum resolution of photolithographic processes but, in principle, only the size of the molecules in the replica (~1 nm) limits the resolution of soft-lithographic techniques based on molding. Another limitation of photolithography is that the tools are expensive (~$10 million). This cost may not deter microelectronics manufacturers, but it can be prohibitive to researchers in areas of biology, chemistry, physics, and materials science who wish to study systems with critical dimensions below 100 micrometers (and especially below 100 nm). The initial cost of defining a master with nanostructures for soft lithography is offset by the ease and low cost of producing polydimethylsiloxane replicas for further experiments to fabricate nanostructures.

Soft lithography also is useful for developing microtools to study living cells, as many biologists and chemists interested in studying cell behaviors are not familiar with, or do not have access to, the tools used in microelectronic manufacturing. Techniques for rapidly prototyping microstructures use transparency masks generated on high-resolution printers to define the patterns in a photoresist, and do not require special facilities such as cleanrooms. It is, therefore, straightforward to design and implement systems for studying cells on surfaces using polydimethylsiloxane molds.

The disadvantages of soft lithography using polydimethylsiloxane replicas are (1) the softness of polydimethylsiloxane can cause distortions in printed or molded structures; (2) polydimethylsiloxane is not stable to many organic solvents or at high temperatures; (3) polydimethylsiloxane is not a good choice

when it is necessary to align or register multiple patterns on a substrate; (4) polydimethylsiloxane has a high coefficient of thermal expansion, that is, the size of the features in the mold varies significantly with small changes in temperature.

Outlook. Soft lithography allows research scientists in many disciplines to develop new tools for exploring scientific problems that require micrometer- and nanometer-scale structures in a simple, inexpensive manner. The discoveries from these studies could lead to new technologies for commercial markets. Soft lithography is currently well suited for producing systems with one level of patterning. However, further improvements in soft lithography should allow the fabrication of complex patterns of molecules that are composed of aligned or registered single-layer patterns.

For background information *see* INTEGRATED CIRCUITS; MONOMOLECULAR FILM; NANOSTRUCTURE; POLYMER; SURFACE AND INTERFACIAL CHEMISTRY; SURFACE TENSION in the McGraw-Hill Encyclopedia of Science & Technology.

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Solid-state NMR spectroscopy

The processing and formulation (dosage form) of a drug may affect important pharmaceutical properties, such as form purity (whether the drug contains polymorphic or amorphous content, which might make it less therapeutically active), dissolution characteristics, chemical and physical stability, and bioavailability. Although it currently is not widely used for the characterization of pharmaceutical formulations, solid-state nuclear magnetic resonance (NMR) spectroscopy is a powerful technique that is useful for studying pharmaceutical materials. Because the spectrum for each polymorphic/amorphous form is often unique, the NMR method makes it possible to identify the state of the drug as well as the inactive ingredients used in drugs (excipients). Peaks from excipients are usually in a different region (chemical shift or frequency) of the NMR spectrum than are the peaks from drugs.

Solid-state NMR spectroscopy is also relatively insensitive to particle size and surface effects, eliminating some of the problems often associated with x-ray diffraction techniques, such as the preferred orientation and lengthy sample preparation. In many cases, samples for x-ray analysis are ground up, thereby increasing the possibility for phase transformations due to mechanical strain imposed on the crystal. With NMR spectroscopy, an intact formulated tablet can be analyzed directly. A further advantage of solid-state NMR spectroscopy is that quantitation of mixtures of polymorphic forms can be performed without the need to prepare standard curves.

Solid-state analysis. Nuclear magnetic resonance is a phenomenon exhibited when atomic nuclei in a static magnetic field absorb energy from a radio-frequency field of certain characteristic frequencies. The NMR spectrum contains peaks referred to as resonances. The intensity of the resonance is directly proportional to the number of nuclei that produce the signal. Nuclear magnetic resonance spectroscopy is routinely performed on solutions because rapid molecular motion results in a spectrum with narrow lines (high resolution). In the solid state, however, the absence of molecular motion leads to broad lines (low resolution). The two main sources of line broadening for nuclei that have nuclear spin (unpaired protons or neutrons) values of 1/2 (for example, ^{13}C, ^{15}N, and ^{1}H) are dipolar coupling and chemical shift anisotropy (CSA).

Dipolar coupling and decoupling. Because nuclei have magnetic moments, one nucleus can affect the magnetic field of a neighboring nucleus if they are close together. Such interactions between two (or more) spin-1/2 nuclei are known as dipolar couplings. The magnitude of the dipolar coupling has a $1/r^3$ dependence and is proportional to the magnetogyric ratios of the coupled nuclei. Either homonuclear (for example, between two ^{13}C nuclei) or heteronuclear (for example, between ^{1}H and ^{13}C nuclei) coupling is possible. The low natural abundance of ^{13}C (1.1%) makes the probability of two ^{13}C nuclei being in proximity very small, so in the case of solid-state ^{13}C NMR spectroscopy, only heteronuclear dipolar interactions between ^{1}H and ^{13}C are significant. High-power ^{1}H decoupling is used to eliminate or reduce ^{1}H and ^{13}C dipolar interactions. During the acquisition of the resonance signal, called the free induction decay, a continuous, high-power, radio-frequency pulse at the ^{1}H Larmor (angular) frequency is applied to the sample. The ^{1}H spins can be thought of as rapidly flipping, so the ^{13}C nucleus sees only the average dipolar interaction (which is zero).

Chemical shift anisotropy and magic-angle spinning. The other main broadening factor in solid-state NMR spectra is chemical shift anisotropy; that is, the chemical shift of a nucleus is highly dependent upon the orientation of the molecule with respect to the static magnetic field. When a polycrystalline sample is placed in the magnetic field, each crystallite has a different orientation in the static magnetic field. This results in a range of chemical shifts observed in the spectrum, which is typically called a powder pattern. Powder patterns can be ~200 parts per million (ppm) broad for a single sp^2 hybridized carbon (carbonyl, aromatic, and so on). When multiple carbon