# PHYSICOCHEMICAL SURFACE MODIFICATION OF MATERIALS USED IN MEDICINE

- The biological response to biomaterials and devices is controlled largely by their surface chemistry and structure

- **The rationale for the surface modification of biomaterials is retaining key physical properties of a biomaterial while modifying only the outermost surface to influence the biointeraction.**

- If such surface modification is properly effected, the mechanical properties and functionality of the device will be unaffected, but the bioresponse related to the tissue–device interface will be improved or modulated.

- Materials can be surface modified by using **biological, mechanical or physicochemical methods**

# ❑ Physicochemical surface modifications

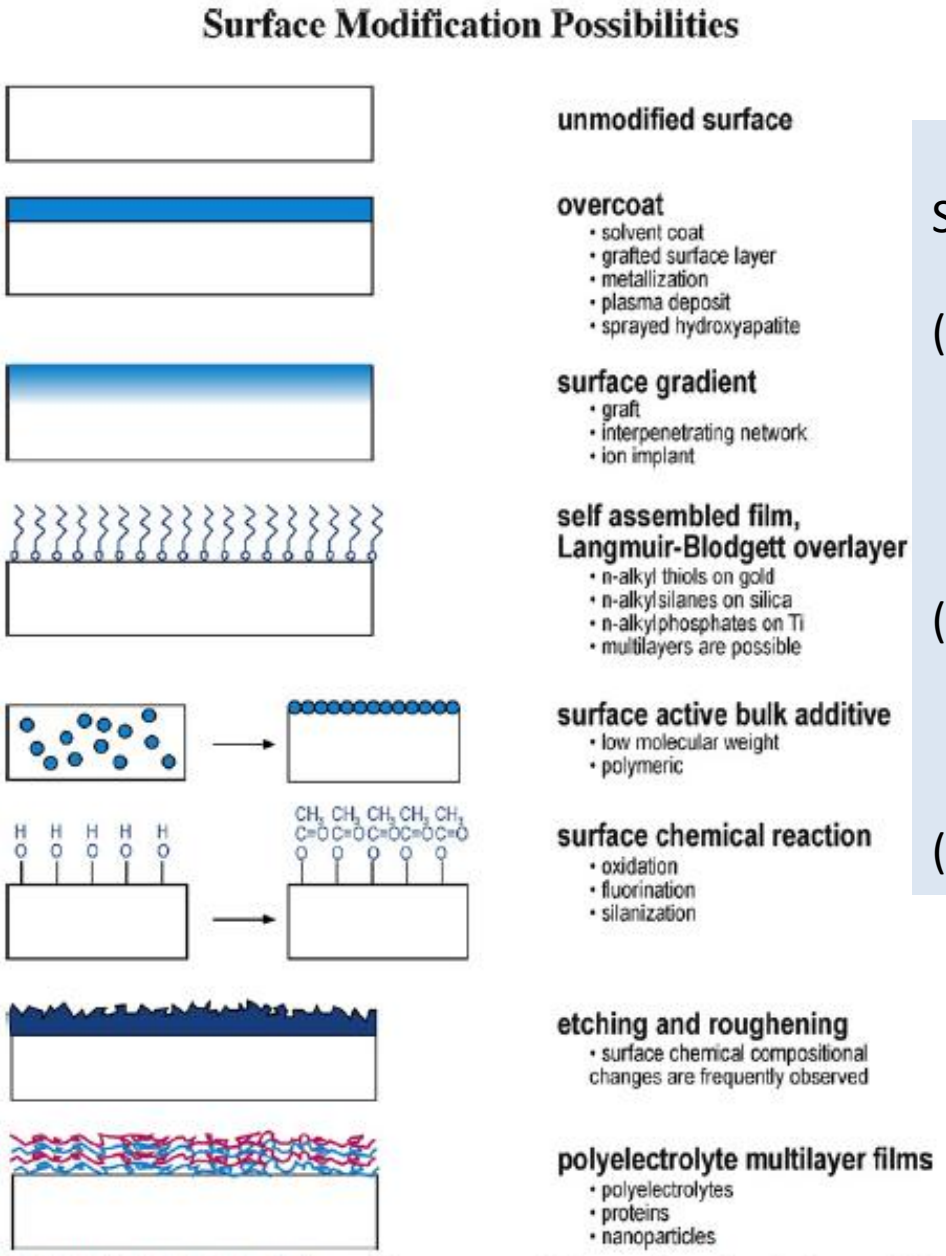



FIGURE I.2.12.1 Schematic representations of methods to modify surfaces.

Surface modifications fall into three categories:

(1) chemically or physically altering the atoms, compounds or molecules in the existing surface (chemical modification, etching, mechanical roughening);

(2) overcoating the existing surface with a material having a different composition (coating, grafting, thin film deposition)

(3) creating surface textures or patterns

# Why do we use surface modification Techniques?

| TABLE I.2.12.1 | Examples of Surface Modified Biomaterials by Physicochemical Methods |
|---|---|
| **To Modify Blood Compatibility** | |
| Octadecyl group attachment to surfaces (albumin affinity) | |
| Silicone-containing block copolymer additive | |
| Plasma fluoropolymer deposition | |
| Plasma siloxane polymer deposition | |
| Grafted poly(ethylene glycol) (PEG) or PEG-containing polymers | |
| Chemically-modified polystyrene for heparin-like activity | |
| **To Modulate Cell Adhesion and Growth** | |
| Oxidized polystyrene surface | |
| Ammonia plasma-treated surface | |
| Plasma-deposited acetone or methanol film | |
| Plasma fluoropolymer deposition (reduce corneal endothelial adhesion and modify blood interactions) | |
| Varying surface modulus | |
| Anti-bacterial treatments? | |
| **To Control Protein Adsorption** | |
| Surface with immobilized poly(ethylene glycol) (reduce adsorption) | |
| Treated ELISA dish surface (increase adsorption) | |
| Affinity chromatography column | |
| Surface cross-linked contact lens (reduce adsorption) | |
| **To Improve Lubricity** | |
| Plasma treatment? | |
| Radiation grafting (hydrogels) | |
| Interpenetrating polymeric networks | |
| **To Improve Wear Resistance and Corrosion Resistance** | |
| Ion implantation | |
| Diamond deposition | |
| Anodization | |
| **To Alter Transport Properties** | |
| Polyelectrolyte grafting | |
| Surface self-assembled film barrier | |
| Plasma-deposited barrier layer | |
| **To Modify Electrical Characteristics** | |
| Polyelectrolyte grafting | |
| Magnetron sputtering of titanium | |
| Surface fluoropolymer insulation | |

# METHODS FOR MODIFYING THE SURFACES OF MATERIALS

## ➢ Chemical Reaction

- Chemical reactions are those performed with reagents that react with atoms or molecules at the surface
- Chemical reactions can be classified as nonspecific and specific.
  - **Nonspecific reactions** leave a distribution of different functional groups at the surface.
  - **Specific chemical surface reactions** change only one functional group into another with a high yield and few side reactions.
- There are hundreds of chemical reactions that can be used to modify the chemistry of a surface.

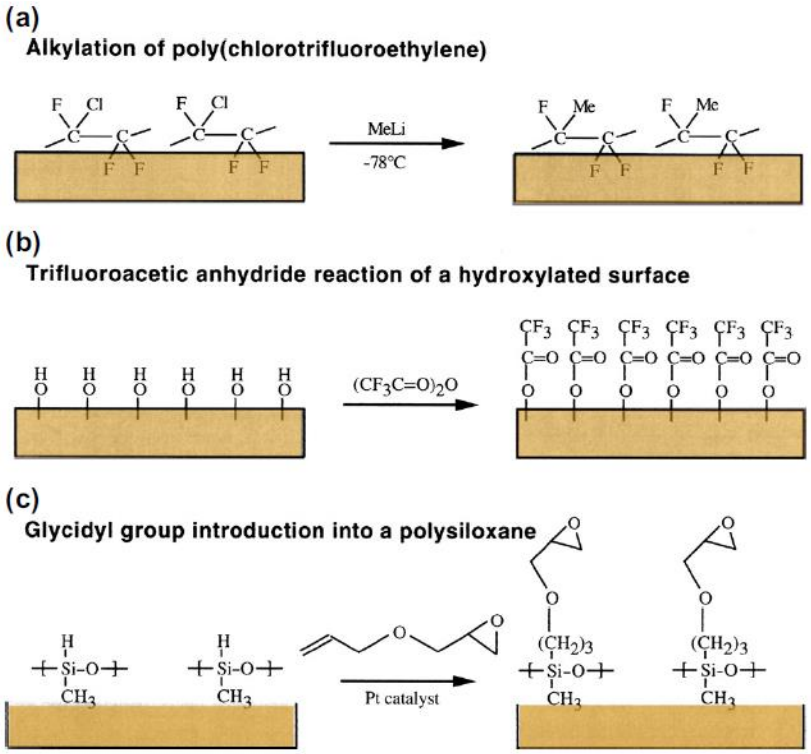



FIGURE I.2.12.2 Some specific chemical reactions to modify surfaces.

## ➢ Surface Grafting

- Surface grafting methods can be divided into two general categories:

1. **Using energetic or highly reactive species to activate chemically inert surface permitting the attachment of desired surface species**

➢ Four types of reactions can be distinguished in this category

i. grafting using ionizing radiation sources (most commonly, a cobalt 60 or cesium 137 gamma radiation source)
ii. grafting using UV radiation (photografting)
iii. grafting using high-energy electron beams
iv. grafting using a reactive, surface-activating species such as ozone

- The radiation or reactive chemical breaks chemical bonds in the material to be grafted, forming free radicals, peroxides or other reactive species.
- These reactive surface groups are then exposed to a monomer.
- The monomer reacts with the free radicals at the surface and propagates as a free radical chain reaction incorporating other monomers into a surface grafted polymer

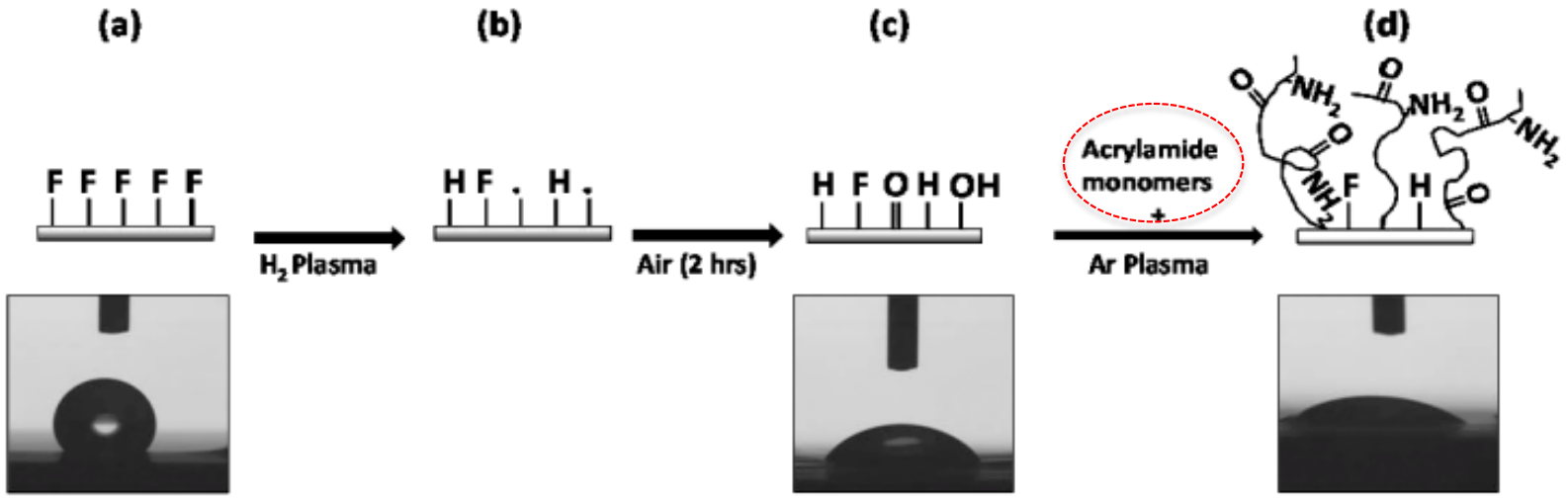



**Figure 4.** The schematic presentation of proposed mechanism for surface modification. Corresponding water contact angle results are presented below each step. (a) Untreated PTFE, (b) PTFE after $H_2$ plasma treatment; free radical formation occurs and some fluorine atoms are replaced by hydrogen, (c) air exposure; oxygen and water vapor in the air react with free radicals and (d) acrylamide grafting by argon plasma; monomers and oligomers are attached to the surface.

**2. Using reactive surface chemical groups to covalently attach the surface modifying species (a polymer, a low molecular weight compound, a drug, a protein, etc.)**

- The earliest biomedical surface modification studies focused on attaching chemically reactable groups (-OH, -COOH, -$NH_2$, etc.) to the surfaces of relatively inert hydrophobic polymers

## ➢ (Radio Frequency Glow Discharge) RFGD Plasma Deposition and Other Plasma Gas Processes

- RFGD plasmas are low-pressure ionized gas environments typically at ambient (or slightly above ambient) temperature.
- Plasmas can be used to modify existing surfaces by ablation or etching reactions or, in a deposition mode, to overcoat surfaces.
- Some biomedical applications of plasma-modified biomaterials

**TABLE I.2.12.3 Biomedical Applications of Glow Discharge Plasma-Induced Surface Modification Processes**

A. Plasma Treatment (Etching)
   1. Clean
   2. Sterilize
   3. Cross-link surface molecules

B. Plasma Treatment (Etching) and Plasma Deposition
   1. Form barrier films
      a. Protective coating
      b. Electrically insulating coating
      c. Reduce absorption of material from the environment
      d. Inhibit release of leachables
      e. Control drug delivery rate
   2. Modify cell and protein reactions
      a. Modulate biointeractions
      b. Promote selective protein adsorption
      c. Enhance cell adhesion
      d. Improve cell growth
      e. Form nonfouling surfaces
      f. Increase lubricity

**Anti-Bacterial Properties?**

   3. Provide reactive sites
      a. For grafting or polymerizing polymers
      b. For immobilizing biomolecules

**Advantages of plasma-deposited films (and to some extent, plasma-treated surfaces) for biomedical applications are:**

1. Because of the convective diffusion of plasma, **complex geometric shapes** can be treated.

2. Plasma-deposited films can **coat almost any clean solid, including polymers, metals, ceramics, and semiconductors.** Other surface grafting or surface modification technologies are highly dependent upon the chemical nature of the substrate.

3. They exhibit **good adhesion to the substrate**.

1. These films are **easily prepared**. Once the apparatus is set up and optimized for a specific deposition, treatment of additional substrates is rapid and simple.

**2. Plasma surface modifications can be characterized by infrared (IR), nuclear magnetic resonance (NMR), electron spectroscopy for chemical analysis (ESCA)**

3. Plasma-treated surfaces a**re sterile when removed from the reactor, offering an additional advantage for cost-efficient production of medical devices**.

## The Nature of the Plasma Environment

- Plasmas are atomically and molecularly dissociated gaseous environments.
- A plasma environment contains positive ions, negative ions, free radicals, electrons, atoms, molecules, and photons (visible and near UV).
- Typical conditions within the plasma include an electron energy of 1–10 eV, a gas temperature of 25–60°C, an electron density of $10^{-9}$ to $10^{-12}/cm^2$, and an operating pressure of 0.025–1.0 torr.

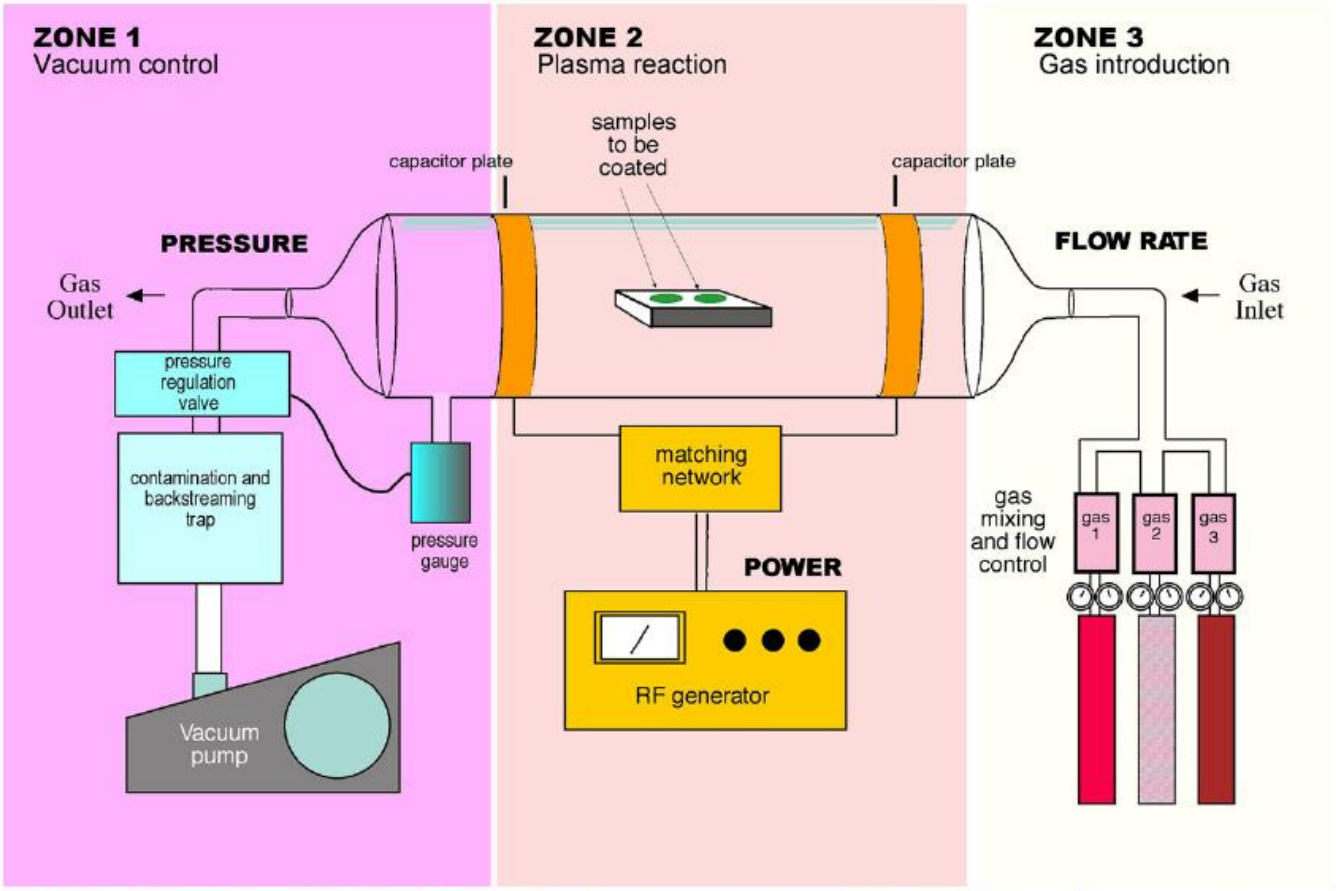
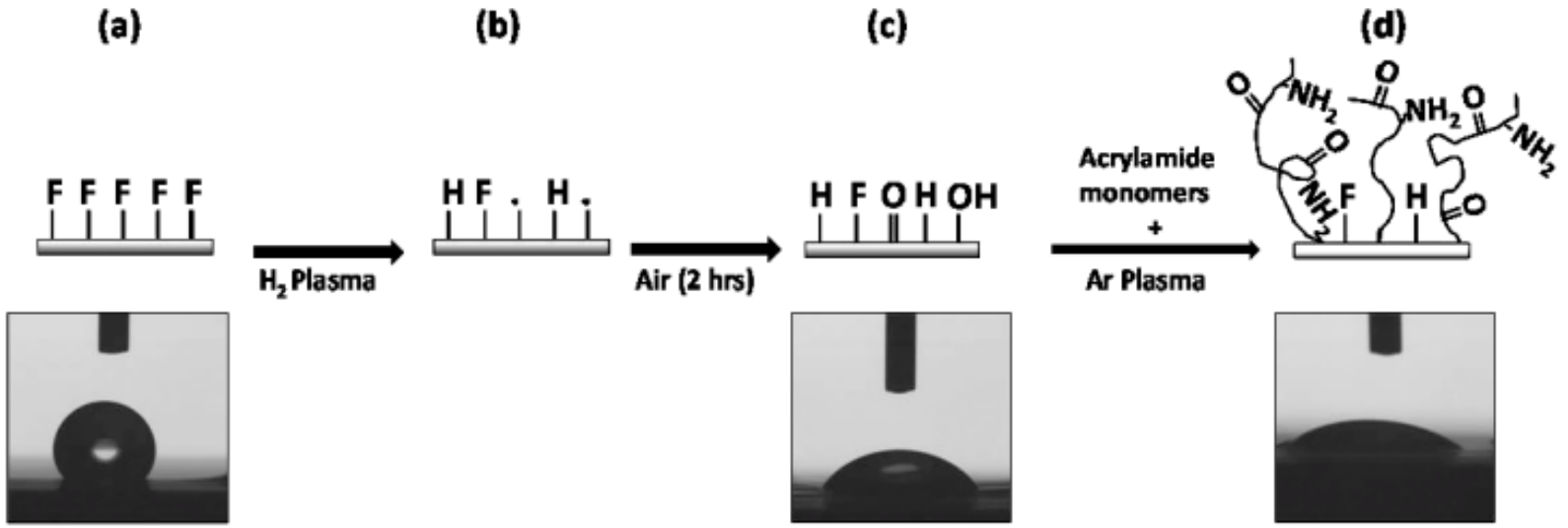



FIGURE I.2.12.3 A capacitively-coupled RF plasma reactor. Redish colors indicate gas storage and mixing. Yellow colors are components that power the reactor. Zone 1: Vacuum system (pressure measurement and control); Zone 2: Plasma generation and sample placement; Zone 3: Gas introduction and flow control.

watch the video

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# ➢ Silanization

- Silane reactions are most often used to modify hydroxylated surfaces. Since glass, silicon, alumina, titania, and quartz surfaces, as well as other metal oxide surfaces, are rich in hydroxyl groups, silanes are particularly useful for modifying these materials.

- A typical silane surface modification:

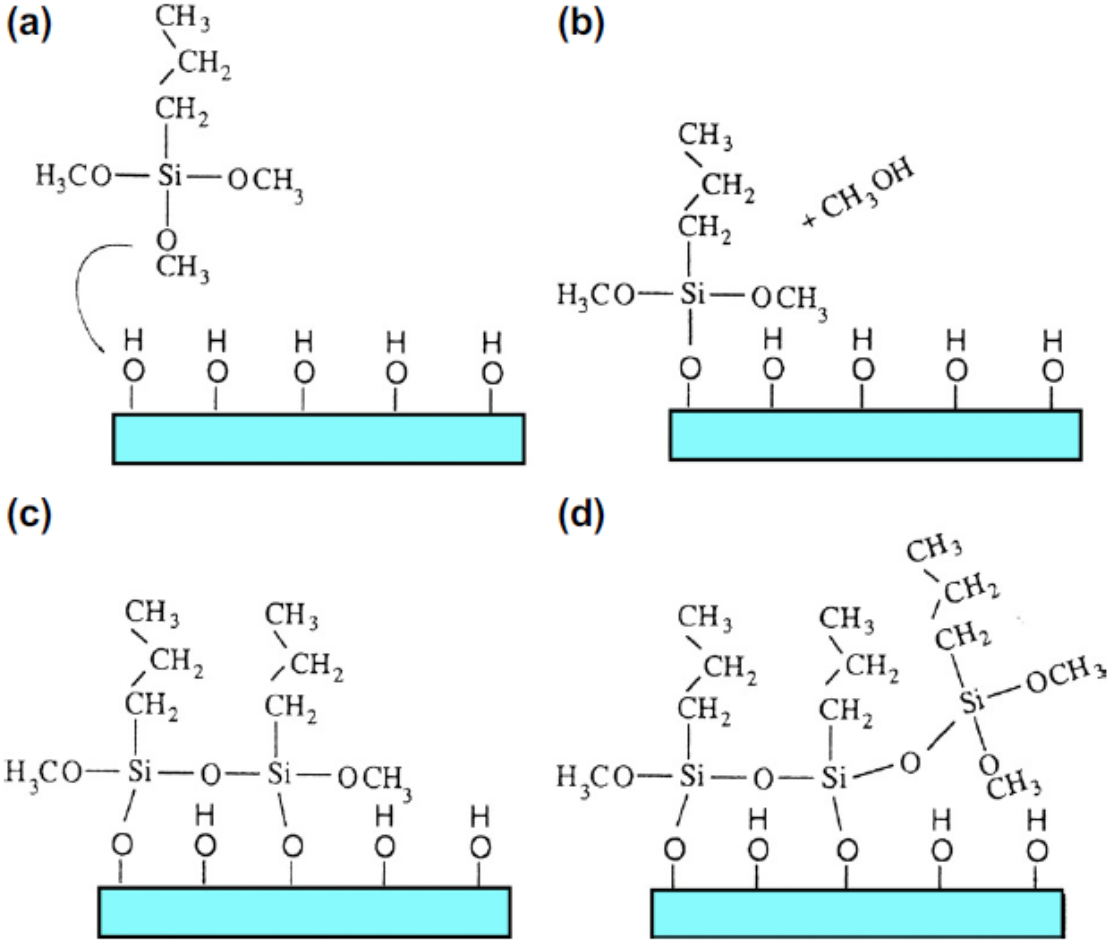
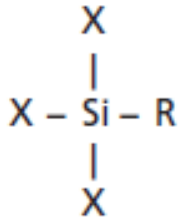
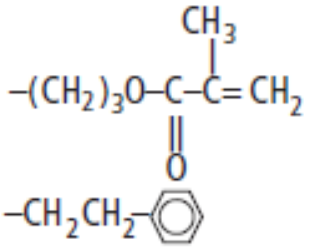



FIGURE I.2.12.4 The chemistry of a typical silane surface modification reaction: (a) a hydroxylated surface is immersed in a solution containing n-propyl trimethoxysilane (nPTMS); (b) one of the methoxy groups of the nPTMS couples with a hydroxyl group releasing methanol; (c) two of the methoxy groups on another molecule of the nPTMS have reacted, one with a hydroxyl group and the other with a methoxy group from the first nPTMS molecule; (d) a third nPTMS molecule has reacted only with a methoxy group. This molecule is tied into the silane film network, but is not directly bound to the surface.

- Numerous silane compounds are commercially available, permitting a broad range of chemical functionalities to be incorporated on surfaces.

**TABLE I.2.12.4 Silanes for Surface Modification of Biomaterials**



| X = Leaving Group | R = Functional Group |
|---|---|
| –Cl | $-(CH_2)_nCH_3$ |
| $-OCH_3$ | $-(CH_2)_3NH_2$ |
| $-OCH_2CH_3$ | $-(CH_2)_2(CF_2)_5CF_3$ |
| |  |

- **The advantages of silane reactions** are their simplicity and stability, attributed to their covalent, cross-linked structure.

## ➢ Ion Beam Implantation

- The ion beam method injects accelerated ions with high energies into the surface zone of a material to alter its properties.

- It is largely used with metals and other inorganics such as ceramics, glasses, and semiconductors.

- Ions formed from most of the atoms in the periodic table can be implanted, but not all provide useful modifications to the surface properties.

- Important potential applications for biomaterial surfaces include modification of

    - hardness (wear)
    - Lubricity
    - Toughness
    - Corrosion
    - Conductivity
    - Bioreactivity

➢ Iridium to improve corrosion resistance
➢ Nitrogen to reduce wear
➢ boron and carbon improve fatigue life
➢ Silver to permit cell attachment

# ➢ Langmuir–Blodgett Deposition

- The Langmuir–Blodgett (LB) deposition method overcoats a surface with one or more highly ordered layers of surfactant molecules.
- Each of the molecules that assemble into this layer contains a polar "head" group and a nonpolar "tail" group. The deposition of an LB film using an LB trough is illustrated schematically

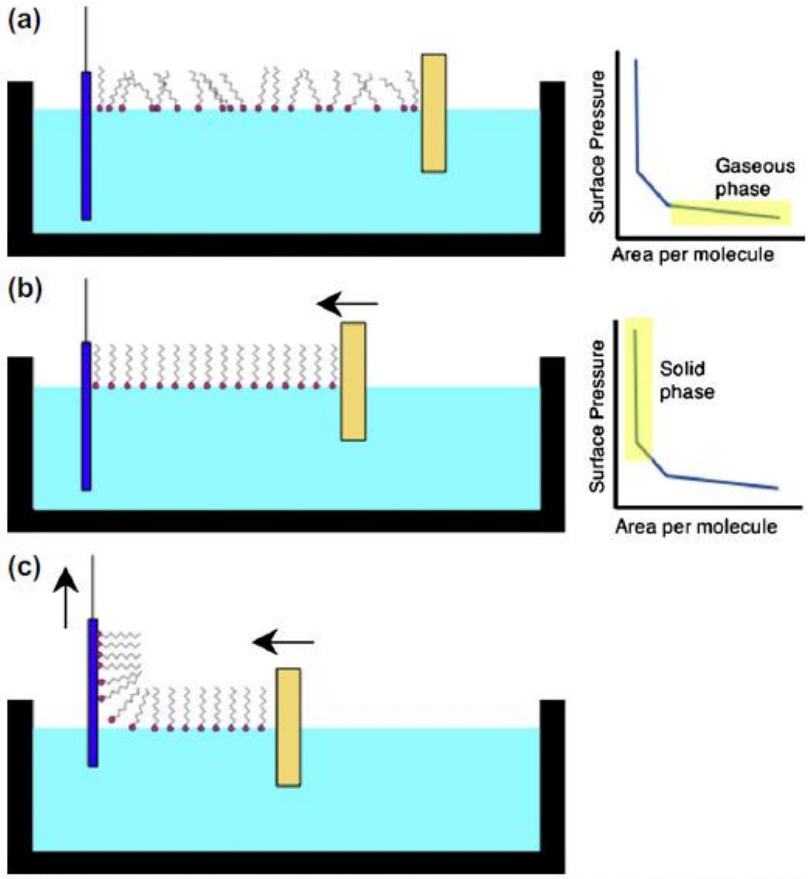



FIGURE I.2.12.6 Deposition of a lipid film onto a glass slide by the Langmuir–Blodgett method: (a) the lipid film is floated on the aqueous layer; (b) the lipid film is compressed by a moveable barrier; (c) the vertical glass slide is withdrawn while pressure is maintained on the floating lipid film with the moveable barrier.

- Some compounds that form organized LB layers

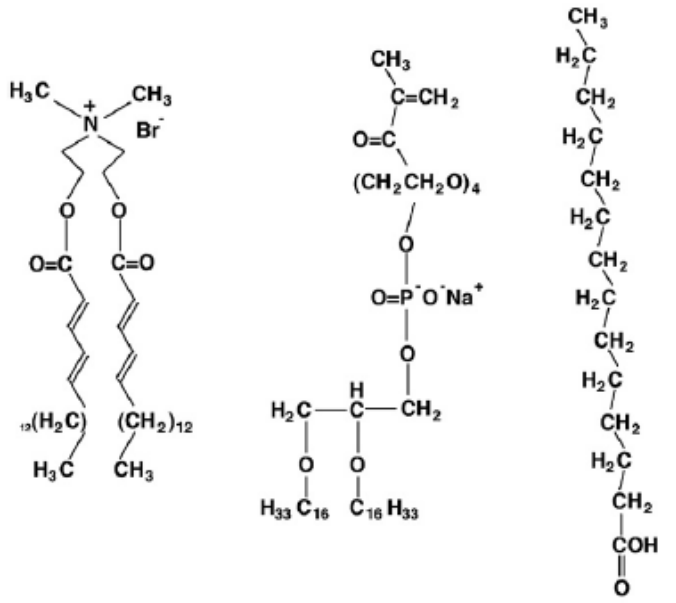



FIGURE I.2.12.7 Three examples of molecules that form organized Langmuir–Blodgett Films.

- **The advantages of films deposited on surfaces by this method are their high degree of order and uniformity, and also their resemblance to the lipid bilayer membranes surrounding living cells.**
- Also, since a wide range of chemical structures can form LB films, there are many options for incorporating new chemistries at surfaces.
- The stability of LB films can be improved by cross-linking or internally polymerizing the molecules after film formation.

# ➢ Layer-by-layer Deposition And Multilayer Polyelectrolyte Deposition

- For Layer-by-layer (L-b-L) deposition surface treatment, a molecule (or polymer or protein) is chosen that adsorbs strong to the substrate (adsorbate 1). Then the substrate is rinsed (retaining adsorbate 1), and dipped in a solution of a molecule that interacts strongly with adsorbate 1 (adsorbate 2).
- After rinsing, the surface layer is again dipped in a solution of adsorbate 1. Absorbate 1, adsorbate 2, and the rinsing step are alternated until the coating has the desired multilayer thickness

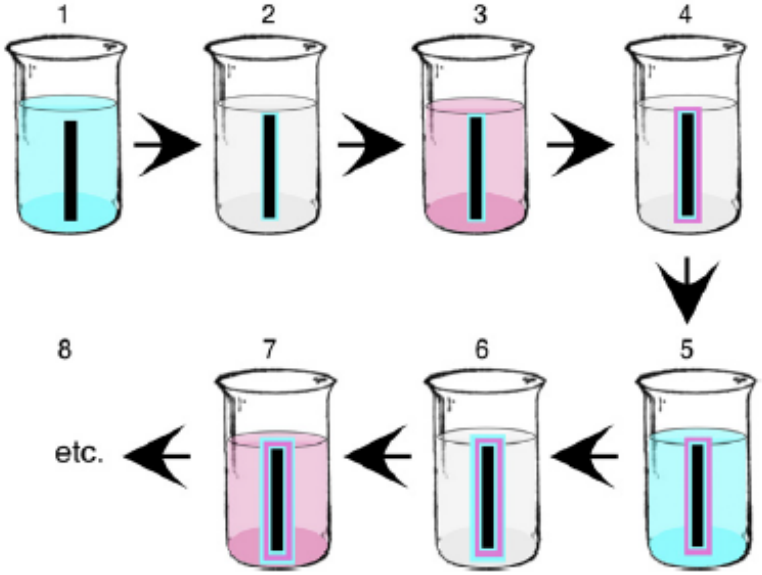



FIGURE I.2.12.9 Layer by layer deposition of a multilayer surface coating. A series of adsorption-rinse steps lead to a multilayer surface deposition: (1) the "blue" compound is adsorbed to the substrate; (2) the adsorbed layer is rinsed in solvent (frequently water) to remove weakly adherent material; (3) the "pink" compound is adsorbed to the blue layer on the substrate; (4) the adsorbed layer is rinsed in solvent to remove weakly adherent material; (5) the "blue" compound is adsorbed to the "pink" adsorbed layer; (6) the adsorbed layer is rinsed in solvent to remove weakly adherent material; (7) the "pink" compound is adsorbed to the blue layer; (8) this process continues to build as many layers as desired.

## ➢ Surface Modifying Additives

- Specifically designed and synthesized surface-active compositions can be added in low concentrations to a material during fabrication, and will spontaneously rise to and dominate the surface.
- These surface modifying additives (SMAs) are well-known for both organic and inorganic systems.

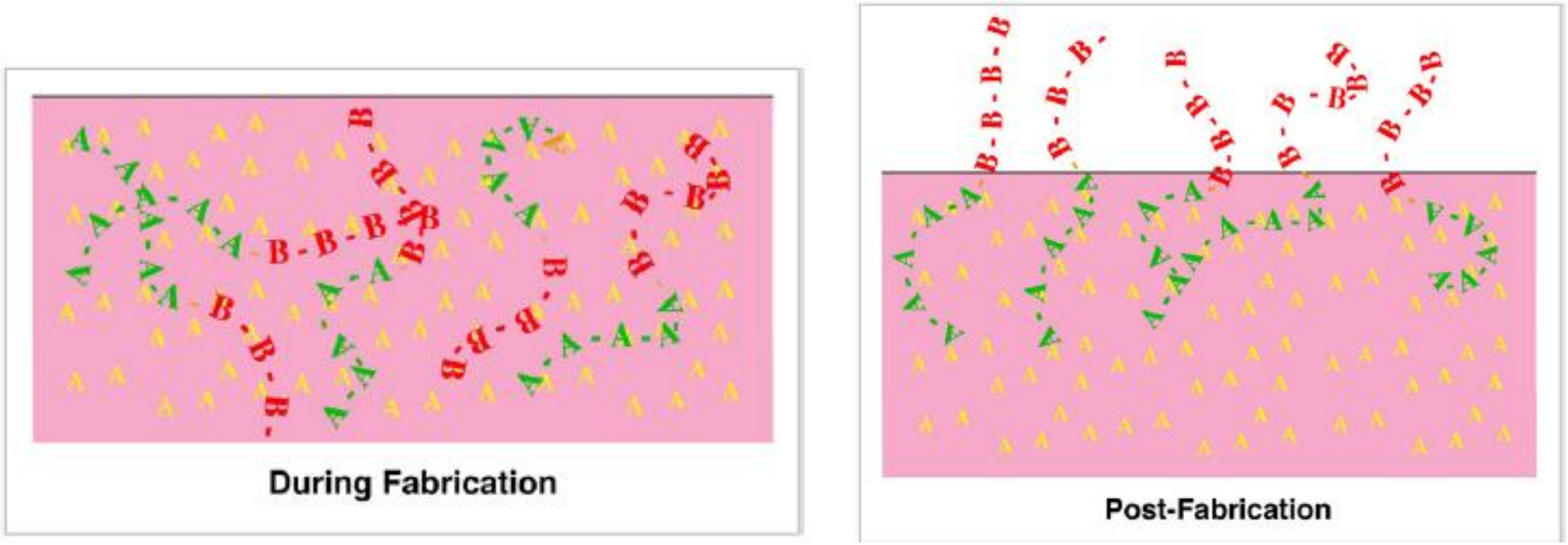



FIGURE I.2.12.10 A block copolymer surface-modifying additive comprised of an "A" block and a "B" block is blended into a support polymer (the bulk) with a composition similar to "A" block. During fabrication, the block copolymer is randomly distributed throughout the support polymer. After curing or annealing, the "A" block anchors the surface-modifying additive into the support, while the low-energy "B" block migrates to the air–polymer interface.

## ➢ Conversion Coatings

- Conversion coatings modify the surface of a metal into a dense oxide-rich layer that imparts corrosion protection, enhanced adhesivity, altered appearance (e.g., color), and sometimes lubricity to the metal.
    - For example, steel is frequently phosphated (treated with phosphoric acid) or chromated (treated with chromic acid).
    - Aluminum is electrochemically anodized in chromic, oxalic or sulfuric acid electrolytes.
- The conversion of metallic surfaces to "oxide-like," electrochemically passive states is a common practice for base metal alloy systems used as biomaterials.
- Standard and recommended techniques have been published (e.g., ASTM F4-86), and are relevant for most musculoskeletal loadbearing surgical implant devices.

## ➢ Laser Methods

- **Lasers can rapidly and specifically induce surface changes (roughness, crystallinity, chemistry) in organic and inorganic materials**

- The advantages of using lasers for such modifications are

  - precise control of the frequency of the light
  - the high energy density
  - the ability to focus and raster the light
  - the possibilities for using both heat and specific excitation to effect change
  - the ability to pulse the source and control reaction time.

- **Laser-induced surface alterations include annealing, etching, deposition, and polymerization.**

- Polymers, metals, ceramics, and even tooth dentin have been effectively surface modified using laser energy.

## ➢ Patterning

- Essentially all of the surface modification methods described can be applied to biomaterial surfaces, either as a uniform surface treatment or as patterns on the surface with length scales of millimeters, microns or even nanometers.

- There are many options to **pattern biomaterial surfaces**. These include

  - ion beam etching
  - electron beam lithography
  - laser methods
  - inkjet printers
  - ...

## ➢ Direct-Write Patterning

- In direct-write patterning techniques, patterns are fabricated by serially scanning a patterning element across a substrate.
- Direct-write patterning is a useful method because patterns of arbitrary feature shape and size can be fabricated on-the-fly, in a process analogous to writing with a pen.
- The drawbacks of direct-write patterning techniques are that they are typically slow, low-throughput, and not particularly suitable for large area patterning, because of the need to serially write the pattern.

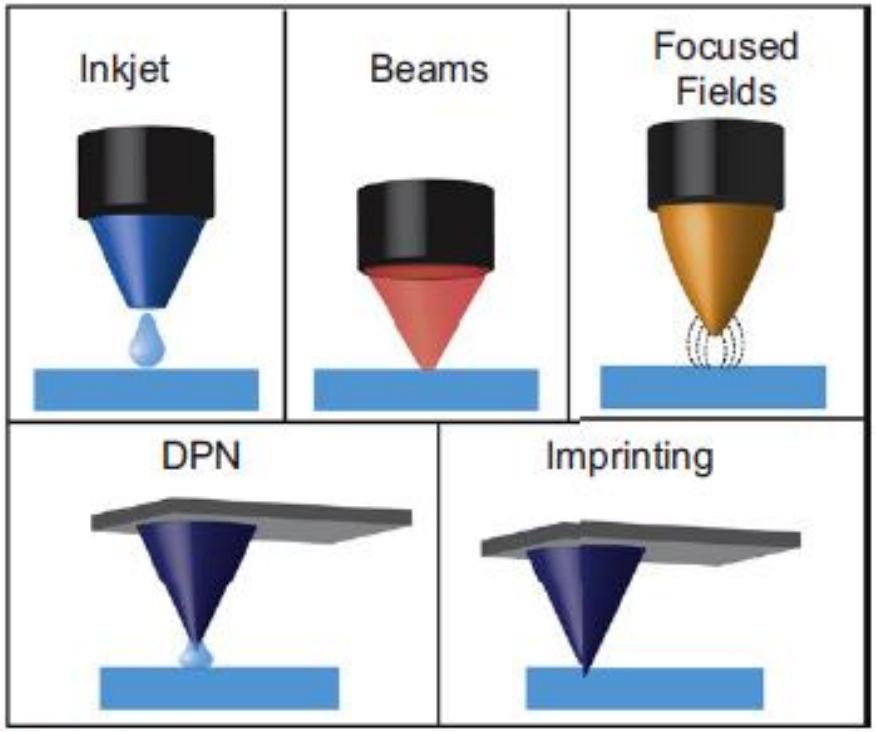



FIGURE I.2.13.3 Types of Direct-Write Patterning. Inkjet, beams, focused fields, dip-pen nanolithography (DPN), and imprinting.

## ➢ Writing with a Stylus.

- Dip-pen nanolithography (DPN), nanoimprinting, and nanoengraving (also called nanoshaving) are typical direct-write methods that **use tips under control of an atomic force microscope (AFM) to write the pattern.**

## ➢ Printing with Inkjets, Quills, and Pins.

- **Inkjet printing** refers to any method where liquid is pumped through a nozzle and onto a substrate in a defined pattern.

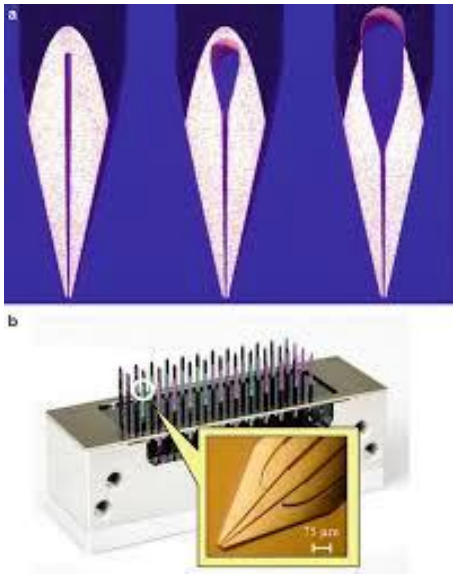
- **Some useful features of inkjet printing are:**

1. patterning is contact-free and can be performed under ambient conditions on a range of solid substrates
2. the method has high positional accuracy
3. multiplexed printing of analytes is easily accomplished by use of multiple nozzles and/or nozzle heads
4. high-throughput patterning over large surface areas can be accomplished by robotic automation.

- “living advertisement” – a colony of bacteria printed in the shape of a university logo – printed.

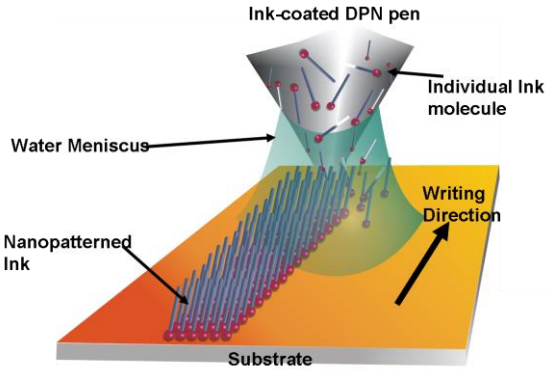

- Pin-based arrayers have also largely been used to fabricate protein arrays, because it is significantly cheaper and less complex to manufacture arrayers with a large number of **pins or quills.**

- Microarrays have also been used as clinical diagnostics to detect specific analytes.




## ➢ Dip-Pen Nanolithography (DPN)

- DPN is the nanoscale equivalent of writing with a quill. In DPN, AFM probes are inked with a solution of molecules and then scanned along a surface to write a pattern of the ink.
- The ink solution forms a small meniscus between the tip of the probe and the surface, which transports biomolecules from the tip to the surface
- DPN has been used to pattern biomolecules including DNA, proteins, functional enzymes, biopolymers, and viruses on many different materials.
- High-throughput DPN can be performed by mounting multiple probes on a single scan head.



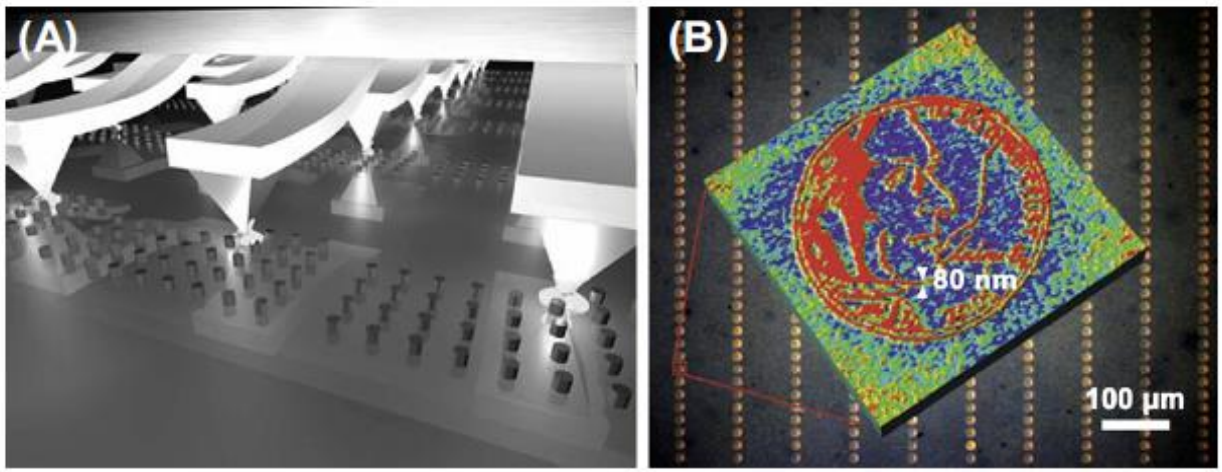




FIGURE I.2.13.5 High-throughput, high-resolution dip-pen nanolithography. For details of figures (A) and (B) please see the text. (Salaita et al., 2006). Adapted with permission from Wiley-Blackwell.

## ➢ Patterning with Masks

- A mask is defined as a template that can spatially modulate a field or radiation that passes through it, or a template that physically masks spatially defined regions of the underlying substrate from exposure to inks or etchants.

- Masking light to create patterns on substrates is the most common form of patterning with masks. Patterning with light and masks is generally called **photolithography.**

- Mask-based patterning can also be performed with radiation (other than light), liquid inks or with chemical or biological etchants.

# ➢ Photolithography with Masks

- In *photolithography*, a mask can be any material that has optically transparent and opaque regions.
- **The critical requirement of a mask-based photolithographic patterning process is that light must pass through spatially defined regions of the mask and lead to the formation of a pattern on a substrate that is located below the mask.**
- In photolithography, patterning is facilitated by a polymer *photoresist* that is coated onto a silicon wafer, activated by light, and developed in a developing solution to create a pattern of the photoresist, which is then subsequently processed to create a pattern in the underlying substrate.

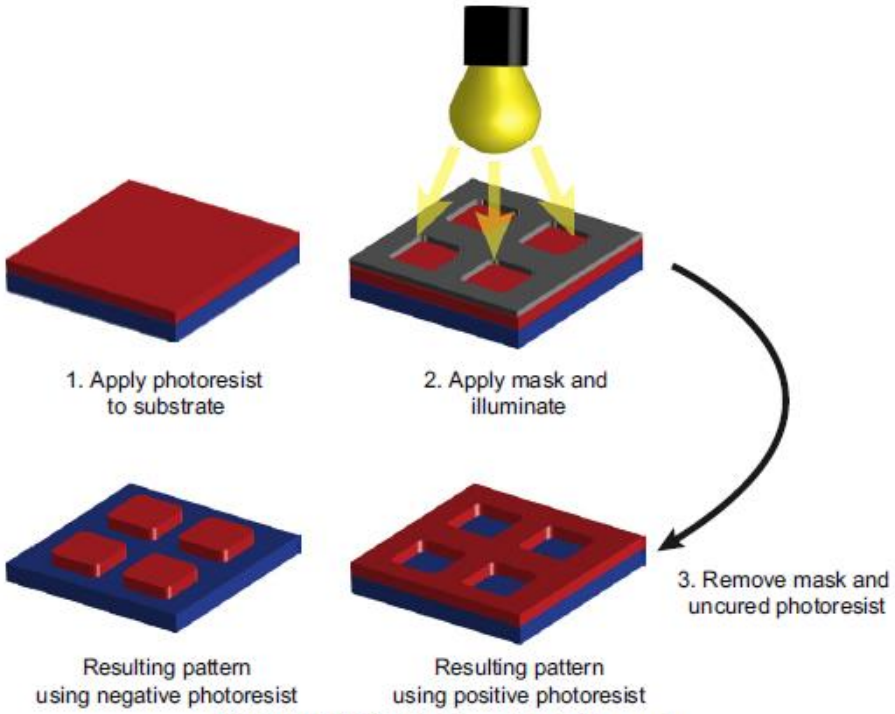
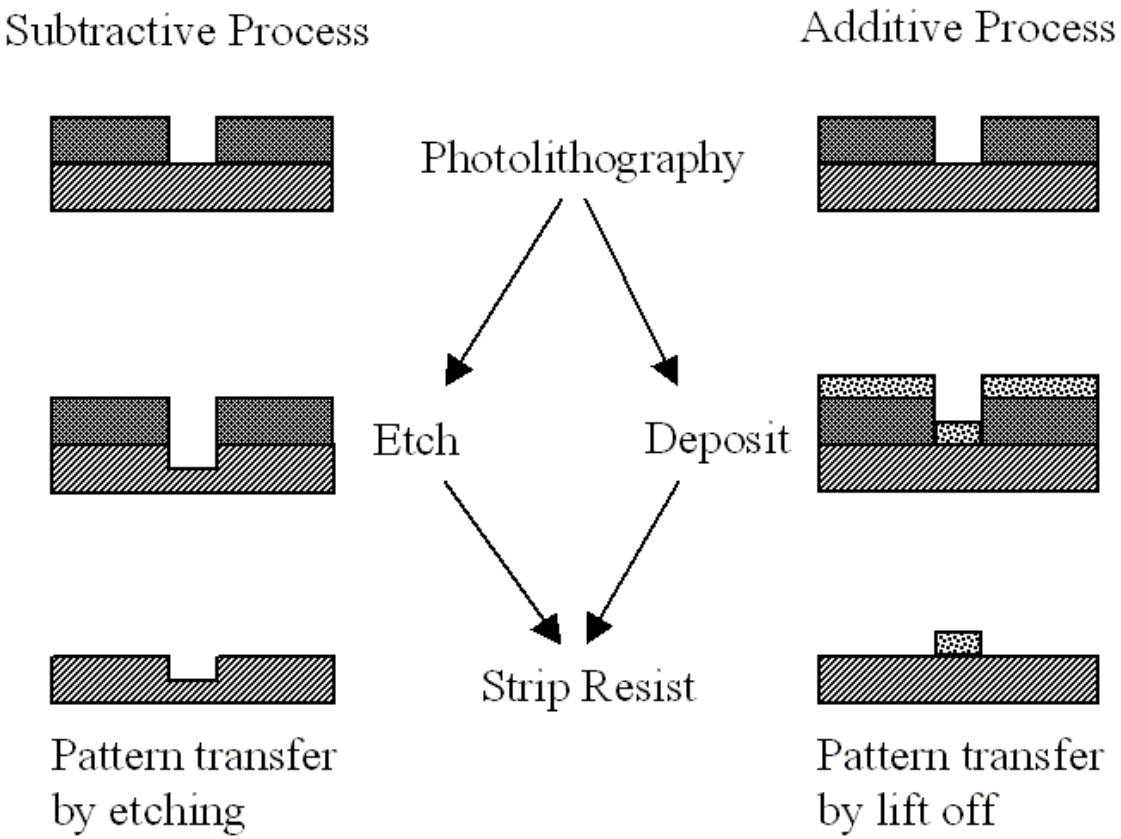



FIGURE I.2.13.8 Mask-Based Photolithography.

- light-based patterning with masks can be accomplished with any material that is light responsive.

# ➢ Deposition/Etching with Masks

- In a deposition process, the mask is applied to a substrate, the combination of which is then exposed to the material to be deposited. Once the mask is removed, areas protected by the mask remain free of the deposited material.
- In an etching process, the mask/substrate is exposed to a form of radiation or an etching chemical, and the areas exposed by the mask are selectively etched.



## ➢ Writing with Beams

- ***direct-write photolithography,*** a beam of focused light is used to pattern a substrate directly. Here, light is usually focused into small spots using conventional light optics, and patterns are formed by photochemical or physical modification of the surface.
    - For example, Holden and Cremer used a laser to pattern enzymes directly within flow channels, a methodology that can be applicable to lab-on-a-chip devices

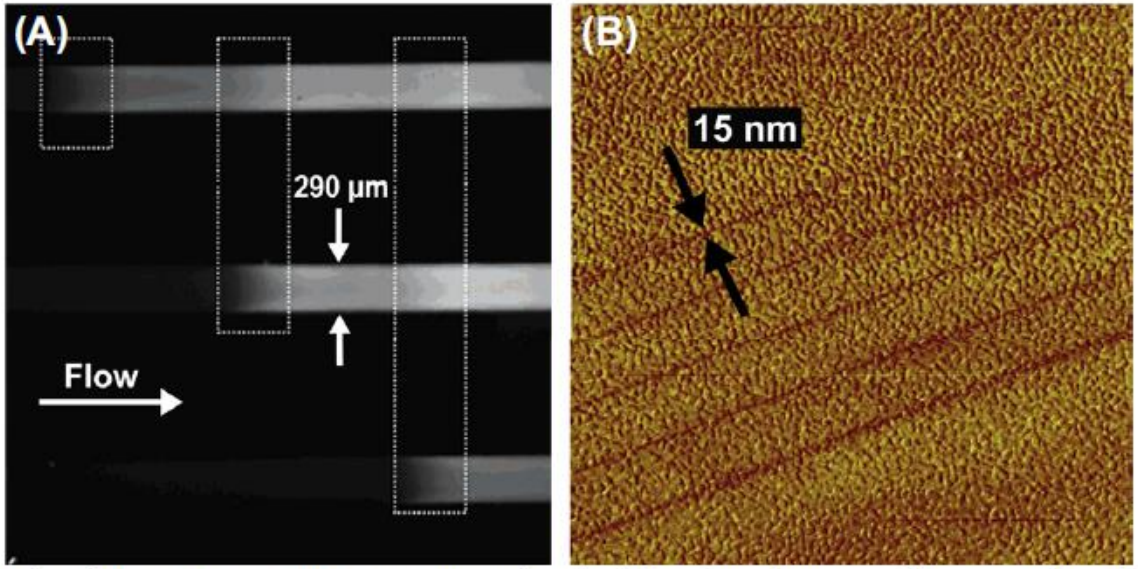
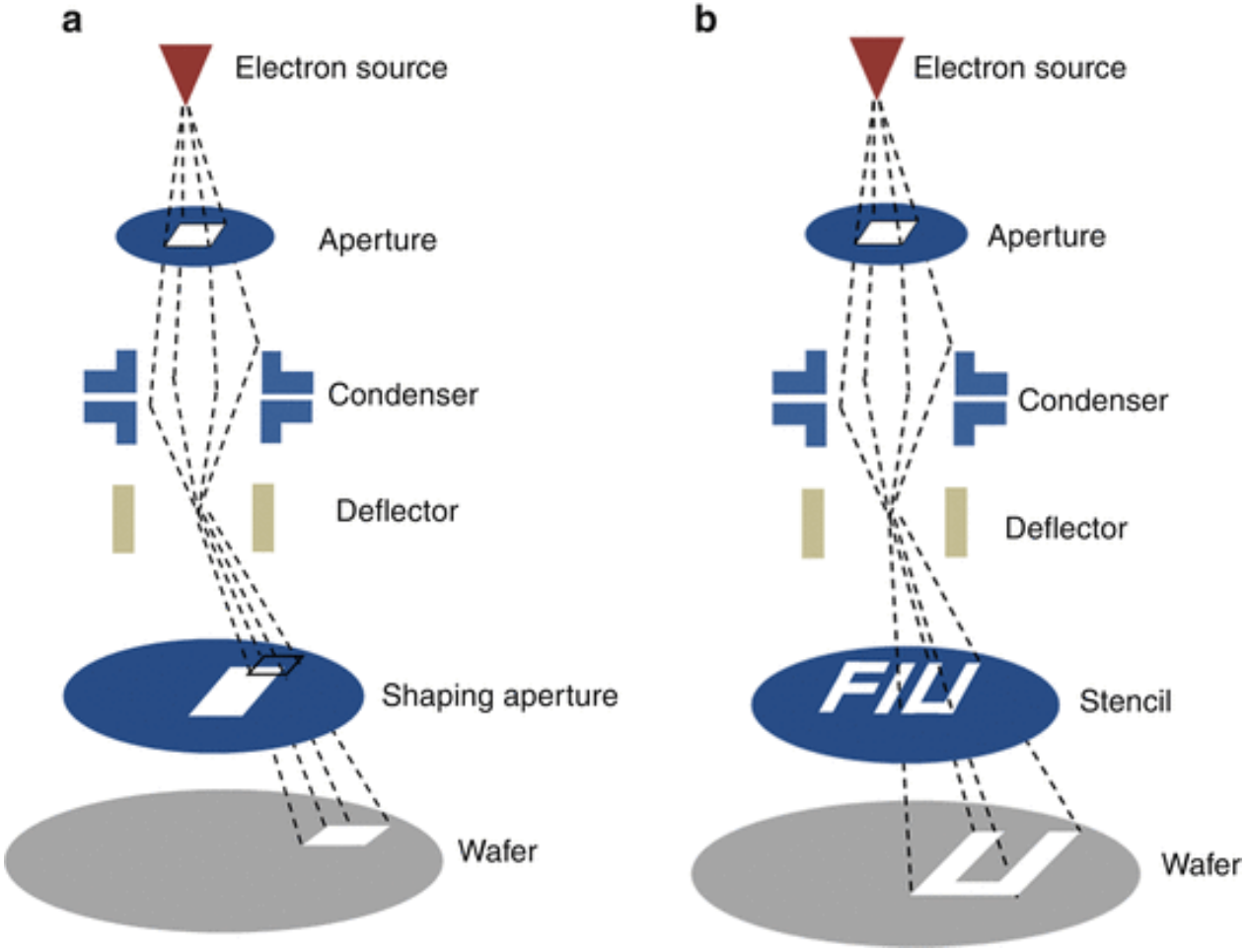



FIGURE I.2.13.6 Examples of Direct-Write Protein Patterning with Light. (A) Patches of enzymes (locations indicated by dashed boxes in the figure) patterned within flow channels produce fluorescent products when exposed to fluorogenic reagents; (B) Sub-diffraction limit features patterned with light using near-field excitation. Here, 15 nm lines were written in a self-assembled monolayer on gold (Ducker et al., 2007b). (A) is adapted with permission from (Holden, M. A., Jung, S. -Y., & Cremer, P. S. (2004). Patterning enzymes inside microfluidic channels via photoattachment chemistry. Anal. Chem., 76(7), 1838–1843). Copyright (2004) American Chemical Society. (B) is adapted with permission from the authors and SPIE.

- **Direct-write *electron beam lithography* (EBL)** , a focused beam of electrons (e-beam) is used as the stylus to write patterns in an e-beam sensitive material. The focused energy from the e-beam can initiate cross-linking or functionalization of surface moieties on the substrate.



- **Focused ion beam (FIB) patterning** makes use of high-mass ions, such as gallium ions, as the energetic particles instead of electrons as in EBL.

- FIB patterning is an inherently destructive process, as the bombardment of a surface with ions causes atomic sputtering of atoms from the surface. For this reason, FIB is typically used as a milling technique to engrave a surface with submicrometer size features.

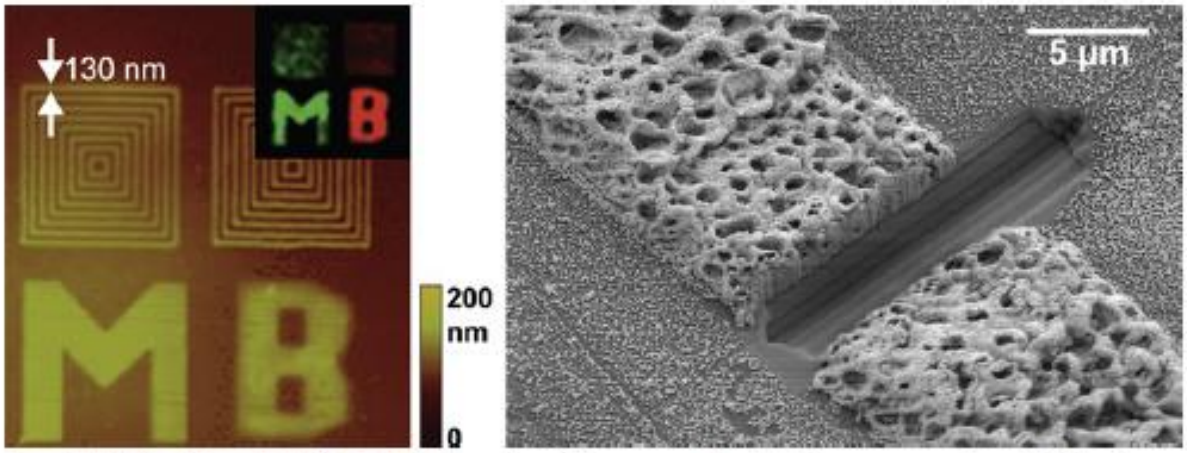



FIGURE I.2.13.7 Examples of EBL (left) and FIB (right) Patterning. Shown on the left is an example of EBL where multi-component protein patterns were formed by electron beam cross-linking and subsequent functionalization of poly(ethylene glycol) molecules. Shown on the right is an example where FIB milling was used to open a conductive circuit by milling a gap in a metallized protein-based wire (scale bar 5 µm). (Left) is adapted with permission from (Christman, K. L., Schopf, E., Broyer, R. M., Li, R. C., Chen, Y., et al. (2009). Positioning multiple proteins at the nanoscale with electron beam cross-linked functional polymers. J. Am. Chem. Soc., 131(2), 521–527.). Copyright (2009) American Chemical Society. (Right) is adapted with permission from (Hill, R. T., Lyon, J., Allen, R., Stevenson, K., & Shear, J. B. (2005). Microfabrication of three-dimensional bioelectronic architectures. J. Am. Chem. Soc., 127(30), 10707–10711). Copyright (2005) American Chemical Society.

# ➢ Patterning with Masters

- A *master* is a template that is used to replicate patterns.
- Rigid masters can be used directly to imprint patterns on substrates.
- the most widespread use of masters for patterning is to create a *mold* which is subsequently used to mold the patterns.
- The most widely used polymer in soft lithography is PDMS

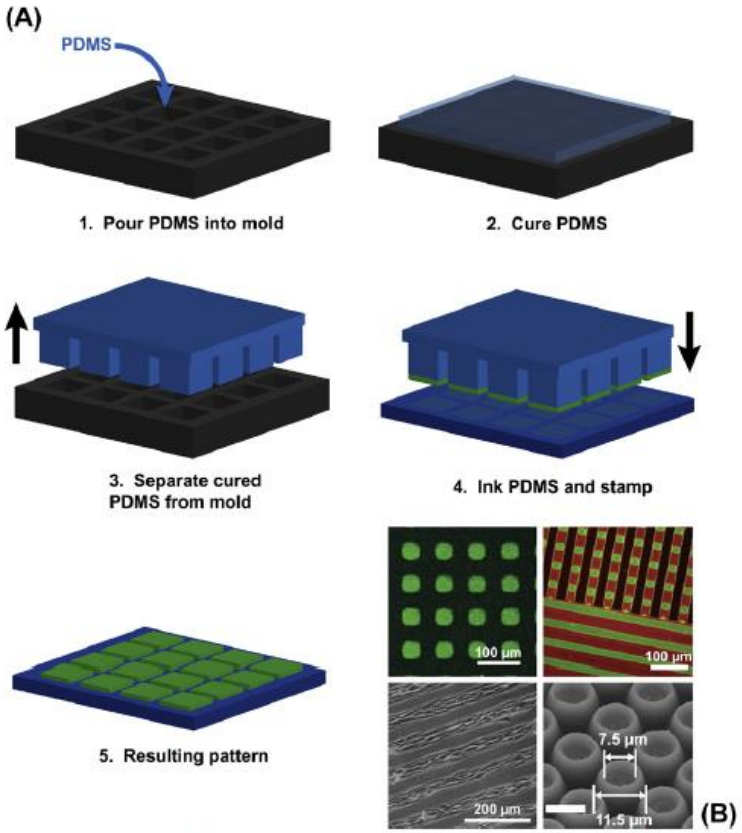
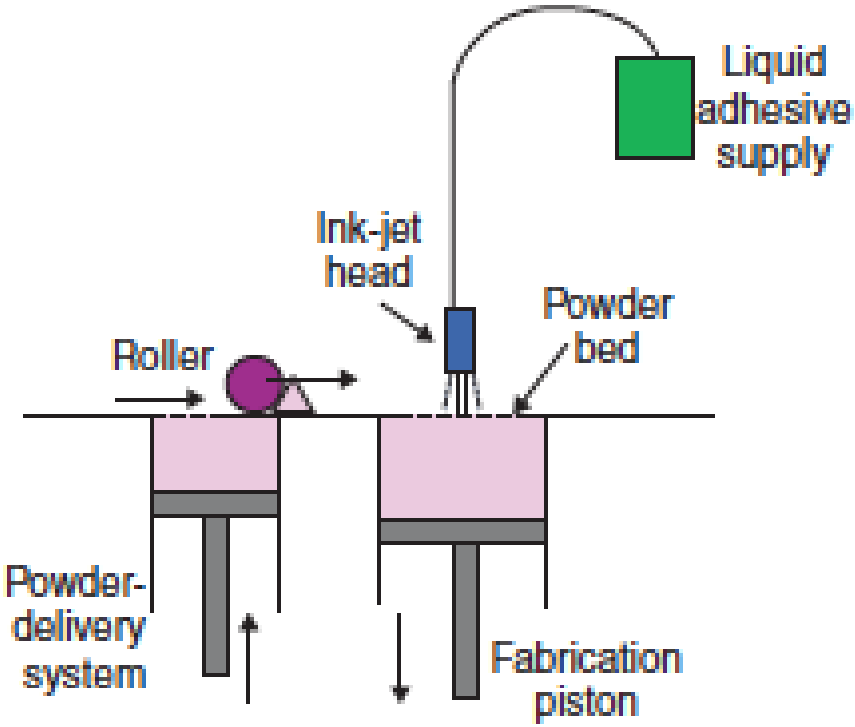



FIGURE I.2.13.11 Microcontact Printing. (A) The typical steps involved in microcontact printing. (B) Clockwise from upper left: checkered pattern of fluorescent protein formed by microcontact printing on a polymer; multicomponent polymer brush patterns formed by microcontact printing; anemone-shaped patterns of stimulus-responsive polymer patterned by microcontact printing (Chen et al., 2009); cell patterning on poly(ethylene terephthalate) by microcontact printing of a protein-resistant comb polymer and backfilling with fibronectin (Hyun et al., 2003). Upper left is adapted with permission from (Ma H., Li, D Sheng, X., Zhao B., & Chilkoti, A. (2006b). Protein-resistant polymer coatings on silicon oxide by surface-initiated atom transfer radical polymerization. Langmuir, 22(8), 3751–3756.). Copyright (2006) American Chemical Society. Upper right is adapted with permission from (Zhou, F., Zheng, Z., Yu, B., Liu, W., & Huck, W. T. S. (2006). Multicomponent polymer brushes. J. Am. Chem. Soc., 128(50), 16253–16258.). Copyright (2006) American Chemical Society. Lower right and left are adapted with permission from Wiley–Blackwell.

## ➢ 3DP

- The 3DP technology is used to create a solid object by inkjet printing a binder into selected areas of sequentually deposited layers of powder.
- Each layer is created by spreading a thin layer of powder over the surface of a powder bed. The powder bed is supported by a piston which descends upon powder spreading and printing of each layer
- Instructions for each layer are derived directly from a CAD representation of the component.
- The individual sliced segments or layers are joined to form the 3D structure.
- The unbound powder supports temporarily unconnected portions of the component as the scaffold is built, but is removed after completion of printing.




3D printing