# First printing errata

The following pages have been corrected/updated as indicated.

The CPT codes define both *panels* and *individual* tests. For example, the *comprehensive metabolic panel* (CMP) includes an albumin, alkaline phosphatase, ALT, AST, bilirubin, blood urea nitrogen (BUN), calcium, chloride, $CO_2$, creatinine, globulin, glucose, potassium, sodium, and protein.

There are hundreds of individual tests including electrolytes, proteins, liver and renal function tests, enzymes, tumor markers, various serologies, and medication levels.

### 8.2.2 Enzyme-linked immunosorbent assay (Indirect ELISA)*

The ELISA test is performed with any body fluid. The sample containing a specific antibody of interest is placed in a *well* that has been coated with a ligand (binding protein) for that antibody. Antihuman antiglobulin antibody that has been conjugated with an enzyme is then added, which binds to the patient's antibodies adherent to the ligand in the well. A substrate specific for the conjugated enzyme is added, imparting color. The amount of color is then measured proportional to the amount of antibody present in the original patient sample. These process steps are shown in Fig. 8.3.

A typical ELISA plate consists of 96 wells on an $8 \times 12$ matrix, each well being about 1-cm high and 0.7 cm in diameter.

The Abbott Laboratories (Abbott Park, IL) Commander System is an automated, high-throughput immunoassay testing system for the screening of blood for hepatitis, retrovirus, and other analytes. The Commander System can initiate up to 800 tests per hour and consists of a flexible pipetting center, the parallel processing center, and the dynamic incubator.

False positive results may occur, and some analytes such as HIV require retesting by *Western blot*, where ELISA measures antibodies to whole virus, Western blot is an electrophoretic technique that allows analysis of antibodies directed against several viral proteins such as the envelope, core, or reverse transcriptase.

### 8.2.3 Chemiluminescence

Chemiluminescence (CL) is the generation of visible, ultraviolet, and infrared light by the release of energy from a chemical reaction. These reactions can be grouped into three types: (1) *chemiluminescent*, which are chemically induced through synthetic compounds and usually involving a highly oxidized species; (2) *bioluminescent* (BL), which arise from a living organism; and (3) *electrochemiluminescent*, which take place by the use of electrical current. Both CL and BL reactions usually involve the cleavage or fragmentation of the O—O bond of an organic peroxidase compound. These bonds are easily cleaved and liberate a lot of energy.

*Alternatively, in the "sandwich" assay, the sample is added to a well coated with an antibody against an analyte of interest, such as a protein, hormone or drug. A second antianalyte antibody conjugated with an enzyme is then added to the well.

uniform pore sizes, allowing the optimization of membrane parameters for cell immuno-isolation. Bulk and surface micromachining techniques were used to fabricate chambers within single crystalline silicon wafers that would interface with the surrounding biological environment through polycrystalline silicon filter membranes. Membranes were fabricated to present a high density of uniform pores to allow sufficient permeability to nutrients while preventing the passage of immunoglobulins. Advantages included membrane biocompatibility, ease of sterilization, and thermal and chemical stability.

Nanoporous capsules have been developed by Desai et al. (2004) for islet cell replacement. The capsules were fabricated by bulk and surface micromachining to present uniform and well-controlled pore sizes as small as 7 nm. The idea is to provide an immuno-isolating microenvironment, while allowing passage of nutrients and waste materials.

Polyethylene terephthalate membranes may be machined with an excimer laser to produce pores as sieves. Combined with surface UV exposure and chemical etching to increase surface energy for improved nonspecific binding and electro-osmotic flow characteristics, these devices have been successfully used for the isolation of leucocytes for subsequent DNA extraction, and the trapping of silica microspheres for DNA adsorption [Atkin et al., 2004].

### 9.3.4 Dielectrophoresis*

Early research in electric fields demonstrated that unidirectional linear motion of dielectric microparticles was possible by application of high-frequency traveling waves [Fuhr et al., 1991]. Dielectrophoresis is the physical phenomenon whereby dielectric particles, in response to a spatially nonuniform electric field, experience a net force directed toward locations with *increasing* or *decreasing* field intensity according to the physical properties of the particles and medium.

In addition to simple electrode layouts, a series of bar-shaped electrodes can generate a traveling-wave dielectrophoretic force (twDEP), useful for inducing controllable motion in bioparticles. Lee and Fu (2003) review the use of dielectric forces for manipulating cells, proteins, and DNA.

By using the difference of dielectric properties between live and dead cells, Li and Bashir (2002) separated live and heat-treated, fluorescent stained *Listeria innocua cells* with great efficiency on microfabricated devices with interdigitated electrodes.

Dielectrophoresis has also been used in isolation and detection of cancer cells, concentration of cells from dilute suspensions, separation of cells according to specific dielectric properties, and trapping and positioning of individual cells for characterization [Gambari et al., 2003]. Medoro et al. (2003) have shown LOC electronic manipulation and detection of microorganisms based on the use of closed dielectrophoretic cages combined with impedance sensing. A printed

**Magnetophoresis* and *electromagnetophoresis* are analogous techniques whereby particles may be separated based on their physical properties such as density and magnetic susceptibility.

# Second printing errata

The following pages have been updated as indicated.

to achieve 3D structures. Many bioMEMS devices incorporate silicon and use these same techniques.

### 2.1.2.3 Silicon crystals

While a complete discussion of the structure of materials, including intermolecular forces, atomic packing, and bonding is beyond the scope of this book, it is relevant to our discussion of fabrication techniques to review the basic concepts of crystal structures. Mitchell (2004) provides an excellent review of the properties and mechanics of materials, including metals and alloys, ceramics and glasses, composites and polymers.

There are fourteen types of crystal structures in nature (called *space lattices* or *Bravais lattices*) classified into seven *crystal systems* including cubic, orthorhombic, rhombohedral, tetrahedral, monoclinic, triclinic, and hexagonal. The cubic system (Fig. 2.4) for example, is composed of three space lattices or *unit cells*, including the *simple cubic* (SC), *body-centered cubic* (BCC), and *face-centered cubic* (FCC). Aluminum, copper, gold, and platinum all exhibit the FCC lattice.

The cubic structure is not close-packed, and has a large central space, or *interstitial space*. The interstitial space is vacant between atoms that may be occupied by a small impurity atom or alloying element.

Silicon is an element that exists in three forms: *crystalline*, *polycrystalline* (polysilicon), and *amorphous* (glassy). Single crystal silicon wafers may be used as a substrate material for MEMS and bioMEMS devices. Polycrystalline and amorphous silicon are reviewed below for use as thin films (which have thicknesses below 5 μm). Crystalline silicon forms a covalently bonded structure and coordinates itself tetrahedrally. Silicon (and germanium) crystallizes as two interpenetrating FCC lattices.

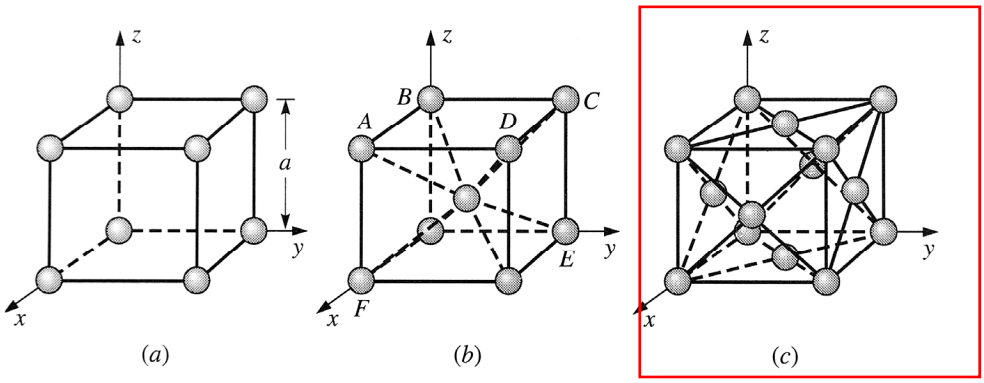



**Figure 2.4** The cubic system is composed of three space lattices or *unit cells*, including (a) the simple cubic, (b) body-centered cubic, and (c) the face-centered cubic. [Reprinted with permission from Sze (1994), copyright John Wiley & Sons.]

## 2.7 Dry-Bulk Surface Micromachining

### 2.7.1 Deep Reactive Ion Etching (DRIE)

Deep reactive ion etching (DRIE) is a method for building high-aspect-ratio micromachined parts, and may be used to make high-aspect micromolds. Plasma sources include *inductively coupled plasma* and *electron-cyclotron resonance*. Etch rate is diffusion limited and decreases with increasing aspect ratio.

Inductively coupled plasma is generated by a helical resonator combined with an electrostatic shield to produce electric field lines that are circumferential in response to the axial RF magnetic field. The power source is driven at 13.56 MHz, producing a high-density, low-pressure, and low-energy plasma.

Electron-cyclotron resonance uses a microwave source, waveguide, magnetic field, and quartz chamber filled with gas at low pressure. The interaction of the microwave and magnetic fields produces intense high-density plasma to which the silicon wafer is exposed.

High-aspect-ratio etching is achieved by the Bosch process. Glow discharge processes have a tendency to create polymeric species by chemical cross-linking. The deposition of this material is typically slower than its removal, and the etching is stopped, or *passivated*, by this layer. The Bosch process takes advantage of this by *alternating* etching and passivation allowing deeply etched trenches (Fig. 2.51). Microscopically, this can be seen as a scalloped

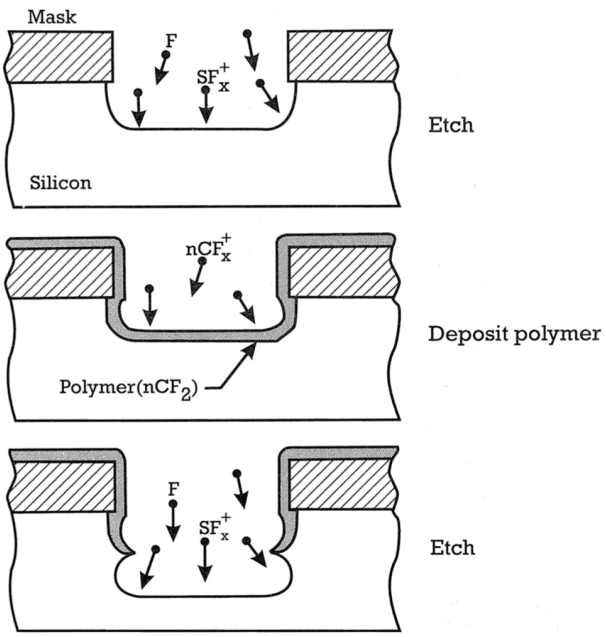



**Figure 2.51** Deep reactive ion etch (DRIE) profile using the Bosch process. The process cycles between $SF_6$ gas etching and $C_4F_8$ polymer deposition. [Reprinted with permission from Maluf (2000), copyright Artech House.]

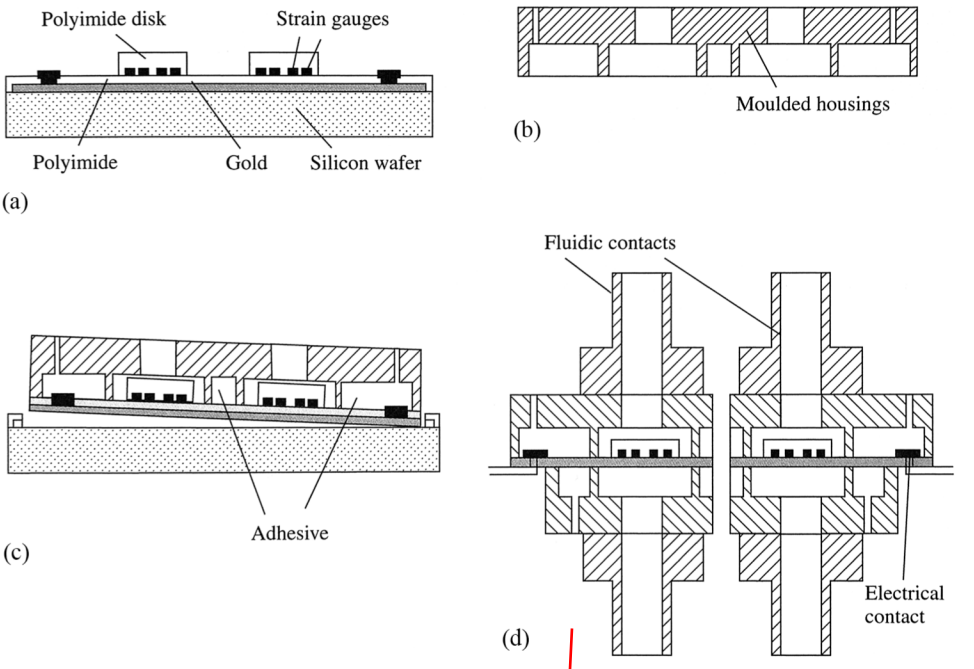
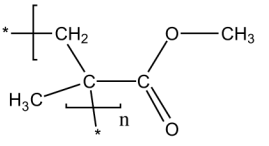



**Figure 3.9** Production of pressure sensors with the AMANDA process: (a) diaphragm is surface micromachined; (b) housings are made by molding; (c) diaphragm is transferred to the housings; and (d) the diced chips with fluidic and electrical contacts. [Reprinted with permission from Schomburg et al. (1998), copyright Elsevier.]

(SU-8) or thick positive photoresist (AZ4620) on silicon is used as a molding template for the casting process to obtain a negative of the desired features in PDMS (allowing high aspect ratios). A technique to fabricate microchannels over a wide range of aspect ratios in PMMA is described. Advantages compared to the conventional methods of fabricating hot embossing tools include rapid processing and a reduction in complexity and cost.




Poly(methyl methacrylate) (PMMA)

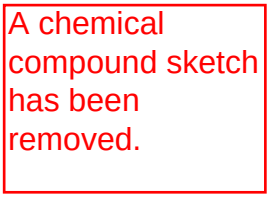
A device for separation of blood from plasma using microchannels manufactured with UV-LIGA and hot embossing has been produced [Blattert et al., 2004].

**Table 3.1** Smart Materials and their Stimulus. [Adapted with permission from Roy and Gupta (2003), copyright Elsevier.]

| Stimulus | Polymer Material |
|---|---|
| pH | Dendrimers* |
| | Poly(L-lysine) ester |
| | Poly(hydroxy-proline) |
| | Lactose-PEG grafted poly(L-lysine) nanoparticle |
| | Poly(L-lysine)-g-poly (histidine) |
| | Poly(n-propyl acrylate) |
| | Poly(ethacrylic acid) (PEA) |
| | Polysilamine (a heterotelechelic oligomer) |
| | Eudragit S-100** |
| | Eudragit L-100** |
| | Chitosan |
| | PMAA-PEG copolymer |
| Calcium | Alginate |
| Magnesium | Chitosan |
| Organic solvent | Eudragit S-100 |
| Temperature | Poly(N-isopropylacrylamide) (PNIPAAm) |
| Magnetic field | PNIPAAm hydrogels with ferromagnetic material |
| Sol-gel transition | Poloxamers (block copolymers of polyethylene glycol (PEG) and polypropylene glycol (PPG)) |
| | Chitosan-glycerol phosphate-water |
| Electric potential | Polythiophen gel |
| IR radiation | Poly(N-vinylcarbazole) composite |
| UV radiation | Polyacrylamide crosslinked with 4-(methyacryloyamino)azobenzene |
| | Polyacrylamide-triphenylmethane leuco derivatives |
| Ultrasound | Dodecyl isocyanate-modified PEG-grafted poly(hydroxyethyl-methacrylate) Poly(HEME) |
| Dual-stimuli stimulus | |
| Calcium and PEG | Carboxymethyl cellulose |
| Calcium and temperature | Eudragit S-100 |
| Calcium and acetonitrile | Eudragit S-100 |
| 32°C and 36°C | Hydrogels of oligoNIPAAm and oligo(N-vinylcaprolactum) |
| pH and temperature | Poly(N-acryloyl-N′-propyl piperazine) |
| Light and temperature | Poly(vinyl alcohol)-graft-poly-acrylamide-triphenylmethane leucocyanide derivative |

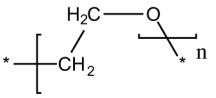
*Dendrimers are large and complex molecules of consistent size and form. They have a regular and highly branched 3D architecture consisting of three components: core, branches, and end groups.

**Eudragit L-100 and Eudragit S-100 (Röhm GmbH & Co., Germany) are ionic copolymers based on methacrylic acid and methyl methacrylate, in ratios of 1:1 and 1:2, respectively.

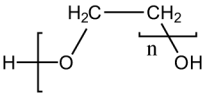


### 3.6.3 Synthetic hydrogels

While chemically synonymous, PEO generally refers to polymers with molecular weight above 20,000 g/mol, and PEG to polymers of lower molecular weight. Poly(ethylene oxide) (PEO) and poly(ethylene glycol) (PEG) are synthetic hydrogel polymers used for tissue engineering. Both are hydrophilic polymers, and can be photo-cross-linked with acrylates or methacrylates.



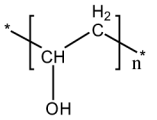

Poly(ethylene oxide) (PEO)




Poly(ethylene glycol) (PEG)

PEO is derived from ethylene oxide and is biocompatible in several ways. It does not promote cell adhesion or protein adsorption, and does not induce thrombosis or activation of the complement system in the body.

Poly(vinyl alcohol) (PVA) is also a synthetic hydrophilic hydrogel polymer and can be cross-linked by repeated freeze-thawing cycles of an aqueous polymer solution, or by chemically cross-linking to form hydrogels [Drury and Mooney, 2003].




Poly(vinyl alcohol)

### 3.6.4 Implementation

Kamijo et al. (1996) describe production of hydrogel microspheres by precipitation polymerization from acrylamide (AAm), methylenebisacrylamide (MBAAm), and methacrylic acid (MAc) in isopropanol. MAc was found to be essential for the preparation of fine spherical particles. The particle size was depended on various polymerization conditions, including the monomer composition, the amount of initiator and the total monomer concentration. The internal structure of microgels was observed by small-angle x-ray scattering (SAXS).

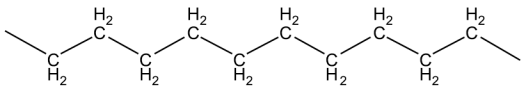
Hydrogels have been studied as a means for controlled drug delivery by Brahim et al. (2002 and 2003), Soppimath et al. (2002), and Ziaie et al. (2004). A thermo-responsive microfluidic actuator was produced by Harmon et al. (2003), an ultrasensitive microcantilever sensor was produced by Hilt et al. (2003), and components for LOC devices were produced by Oosterbroek and van den Berg (2003).

Optically active nanoparticles have been incorporated into hydrogel structures for the purpose of initiating a temperature increase via targeted absorption of near infrared and green light. Sershen et al. (2002) describes a means for optically addressing hydrogels containing one or the other of these nanoparticles, by

into the crystal structure, ferroelectricity, pyroelectric, and piezoelectric properties of polymers.

### 4.1.1 Definitions

*Polymers* are a class of macromolecules that consist of regularly repeating chemical units joined to form a chain molecule. *Monomers* refer to either the repeating chemical unit or the small molecule that polymerizes to give the polymer, though the atomic structures may be different. *Homopolymers* consist of the same type of repeating unit, while *copolymers* consist of two (typically) or more types. Polyethylene for example is a simple homopolymer:



Polyethyelene

The degree of polymerization is the number $N$ of monomers per polymer molecule. *Linear chains* are comprised of atoms or atomic groups linked to two other units through covalent bonds—the *backbone bond.* These are terminated with *end groups.* In polyethylene, single bonds make an angle of 112 deg, and flexibility is achieved due to the low energy required to rotate one part of the molecule with respect to the other. Other polymers may be more rigid because the backbone bonds do not need to be single, but may be collinear.

Nomenclature can sometimes be confusing. Synthetic macromolecules are given the prefix "poly" followed in parenthesis by the monomer, i.e., poly(methyl methacrylate) (PMMS). Here "poly" refers to many polymerized *monomeric units* in contrast to "poly" in organic chemistry referring to two or more *intact substituents.* Simple polymers may be written as one or two words, e.g., polycarbonate (PC) or polyvinyl chloride (PVC).

*Polygroup* names, e.g., polyamides, polyurethanes, and polyesters, refer to classes of polymers, not individual polymers, and are not in parentheses.

Copolymers are identified by the abbreviation "co" between names, such as poly(acrylonitrile-co-butadiene-co-styrene) (ABS).

Systematic names (generic names) or IUPAC names consist of the preferred *constitutional repeating unit* (CRU) in parentheses, prefixed by "poly." Although more exacting in description, the IUPAC names are somewhat cumbersome for use in our discussion of polymers for bioMEMS.

### 4.1.2 Structures

Polymers may be *linear, branched*, or *networked*, resulting in 3D shapes. Combinations of linear chains and/or *cyclic* polymer molecules (two ends that are connected), may result in a number of molecular architectures. These include

including *amidation* and *esterification.* Polycarbonates and polyurethanes for example are produced in this manner.

*Photopolymerization* is based on exposure of a liquid resin to light. Photoinitiated polymerization based on UV curing occurs between 225 and 550 nm. Free radical and cationic curing mechanisms may be used. When the *photoinitiator* is exposed to UV, they break down, leaving components with an unpaired electron, or *free radicals. Propagation* occurs with the addition of monomers and the transfer of the free radical down the propagating chain to continue the process of adding monomers. *Termination* occurs when the chain stops growing. Acrylates are associated with free radical polymerization. Structural polymers and environmentally sensitive hydrogels may be photopolymerized through optically transparent LOC devices for *in-situ* fabrication. Using photolithographic techniques it is possible to pattern structures within microfluidic chips for creation of valves, filters, and other components. Using stereolithography techniques, 3D microfluidic devices can be formed through layer-by-layer photopolymerization, including intricate channel geometries.

## 4.2 Physical Properties

There are a number of properties that may influence the selection of a particular polymer for a bioMEMS application, including mechanical, electrical, and optical properties as discussed here. Further reading is encouraged for review of thermodynamic, kinetic, and heat transport properties. Surface characteristics and the ability to modify them to induce specific functionality will be the topic of later chapters.

### 4.2.1 Mechanical

Polymers are *viscoelastic* and exhibit some of the properties of both *viscous liquids* and *elastic solids.* Mechanical properties are dependent on temperature, as shown in Fig. 4.2. Elevation of the temperature above the glass transition temperature lowers Young's modulus with a change of material from brittle glass to elastic rubber consistency. In the transition, temperature ranges of mixed properties are displayed, including *creep*, or the change in shape under a constant load, and *stress-relaxation*, the lowering of stress required to maintain the strain. Actual polymers may undergo more than one transition, while amorphous and crystalline polymers behave differently.

*Hooke's law* describes the behavior of an *ideal* elastic solid:

$$\sigma = Ee, \tag{4.1}$$

where

$\sigma$ is the tensile stress (force/unit cross section),
$E$ is Young's modulus of the material, and
$e$ is the linear strain ($\Delta$ length/initial length).

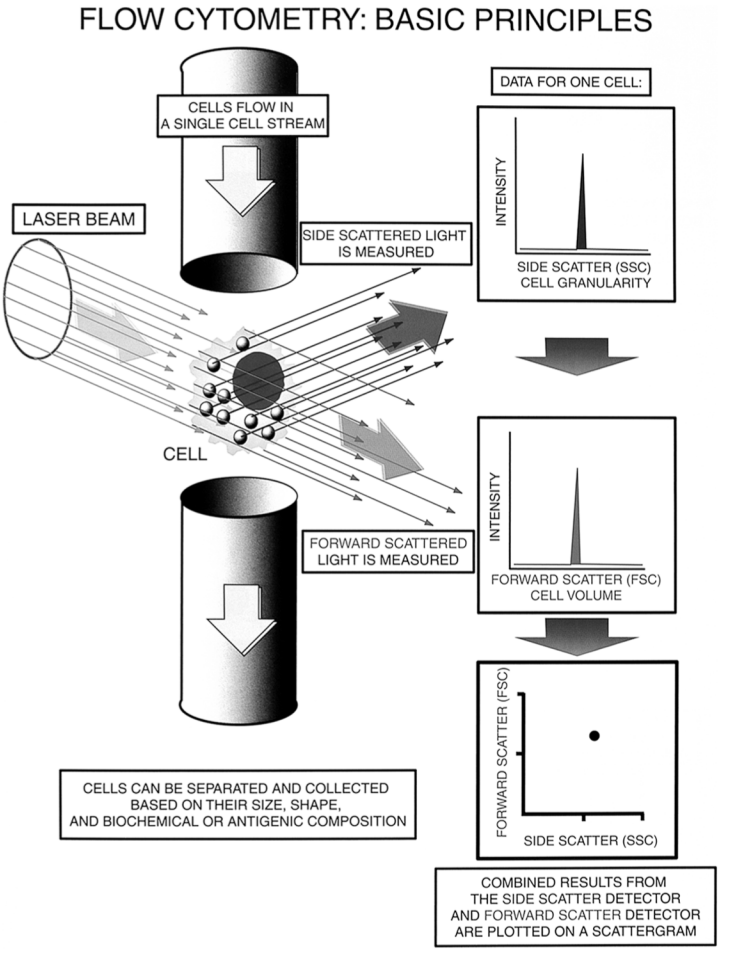



**Figure 8.10** Basic flow cytometry. [Reprinted with permission from Laposata (2002), copyright American Society for Clinical Pathology.]

differentiate between different particle sizes. Higher resolution means more detailed size information.‡

While this technique is suitable for analyzing red blood cells, analyzing white blood cells requires additional *flow cytometry*. The basic principle of flow cytometry is shown in Fig. 8.10. Here, cells flow in a single cell stream past a laser beam (coherent light source) and detector. Light that is forward scattered and side scattered is measured and plotted together as a scattergram. Forward scatter is the result of diffraction and correlates with cell volume. Side scatter (right angle) is the result of refraction and correlates with internal cellular granularity [Laposata, 2002].

‡ www.beckman.com.

magnetic beads and reacted with single-stranded DNA (ssDNA) libraries to select ssDNA that binds to specific protein targets without being removed by washing the beads. The high-affinity ssDNA that remains bound is subsequently amplified by PCR and cycled again for enrichment.

## 10.3 Measurement Systems

### 10.3.1 Confocal laser microscopy

Confocal scanning laser microscopy has significant utility for DNA microarray chips and other LOC devices. Normally, in simple fluorescence microscopy the entire sample is illuminated by the excitation light, causing the entire sample to fluoresce, thereby creating a blurred image. Refer back to Fig. 10.3, where the addition of a pinhole filters out light that is out-of-plane with the desired light. The object lens forms an image at the pinhole surface, and the sample and pinhole planes are known as conjugate planes. The pinhole is *conjugate* to the *focal* point of the lens thus the term *confocal* laser microscopy. As in fluorescence microscopy, light from the laser (lower wavelength) is reflected by the dichroic mirror through the objective lens onto the sample. The fluorescence (higher wavelength) is gathered by the objective lens, passes through the dichroic mirror and is focused onto the pinhole surface. A photomultiplier tube measures the fluorescent energy. Moving mirrors allow the entire sample to be scanned [Weeks, 2004].

Figure 10.6 shows the Berkeley Rotary Confocal Fluorescence Scanner configured for μCAE detection, where laser excitation at 488 nm is reflected by a dichroic beamsplitter through a hollow shaft stepper motor and deflected 1.0-cm off-axis by a rhomb prism mounted on the motor shaft. Laser excitation is focused and fluorescence is collected by the microscope objective, and reflected back through the beamsplitter back to the detector. Fluorescence is spectrally filtered (dichroic beamsplitter and bandpass filter), spatially filtered (pinhole) and four-color processed. Each bandpass filter has 20-nm-wide bands centered at 650, 580, 550 and 520 nm, respectively [Blazej et al., 2003].

A two-mirror microscanner suitable for building a miniaturized confocal laser scanning microscope has been described by Hoffman et al. (1999). The electrostatically driven torsional micromirrors are suitable for fast 2D scanning with high angular precision over large scan angles. The planned initial use is for improved imaging at the tip of an endoscope.

### 10.3.2 Interferometry

Interferometers are measuring instruments that take advantage of the physical phenomena of *interference patterns.* Interference occurs with the superposition of two or more electromagnetic waves. For coherent visible light (wavelengths of 450 to 700 nm) with similar frequency and phase, and traveling in the same direction, this may be observed as bands or *fringes* of light and dark, which

During and after transcription the primary transcript undergoes several modifications before the mature mRNA is released into the cytoplasm for protein translation. Different mature mRNA molecules may result from the primary transcript, resulting in different proteins. From the μTAS developer's perspective, it should be realized that this additional level of encoding exists. The *genetic code* is the *message* carried by mRNA, and is made up of triplets of adjacent nucleotide bases called *codons*.

Once in the cytoplasm, the mature mRNA meets with *ribosomal RNA* (rRNA) and *transfer RNA* (tRNA), which consists of 3-nucleotide sequences, or *anticodon*, that undergo complimentary base pairing with the mRNA codon [Lodish, 2004]. The codon-anticodon interaction aligns the appropriate amino acid (of 20 available) for peptide growth in a sequence determined by the genetic code. Polypeptide synthesis on the ribosome includes initiation, elongation, and termination phases. After synthesis, posttranslational or cotranslational modifications occur for protein folding, targeting, activation, and stability [Tefferi et al., 2002].

*Polymorphism* refers to sequence variation. When the rate of variation at a specific point in the DNA yields a variant sequence that is found in more than 1% of the population, it is referred to as polymorphism. If less than 1% the variation is referred to as a *mutation*. Single nucleotide polymorphism may be detected by microarrays and have the potential to be used in studies of genetic susceptibility to diseases.

## 11.2 Polymerase Chain Reaction (PCR)

The PCR is an *in vitro* method of replicating small DNA sequences into millions of copies over a short period of time. Nanomolar quantities of DNA can be replicated within a few hours. PCR may be used for genetic testing in disease diagnosis, monitoring response to treatment, and tissue typing.

A typical PCR requires (1) two oligonucleotide *primers*, (2) a thermally stable DNA polymerase, (3) supply of free nucleotides, and (4) a small amount of DNA sample that contains the sequence of interest [Tefferi et al., 2002]. The DNA fragment of interest must be known, so that short DNA primer fragments can be synthesized in advance, and are complimentary to the 3′ end of each sample stand. Figure 11.6 shows three cycles of the PCR.

Table 11.1 shows how, with increased number of cycles, the number of actual target replications far exceed the original sample DNA [Carey, 2002].

PCR can lead to incorrect interpretation if one of two different genes amplified with gene-specific primer sets in adjacent regions, preferentially amplifies because of the thermodynamic advantage of one primer set over the other. In addition, two allelic variations of the same gene may amplify differently if the polymorphism affects the secondary structure of the amplified fragment [Shimkets, 2004].

Note that DNA can be amplified by methods other than PCR, such as by *recombinant cloning*. This is accomplished by inserting the target DNA into a bacterium that is capable of extended cell division.

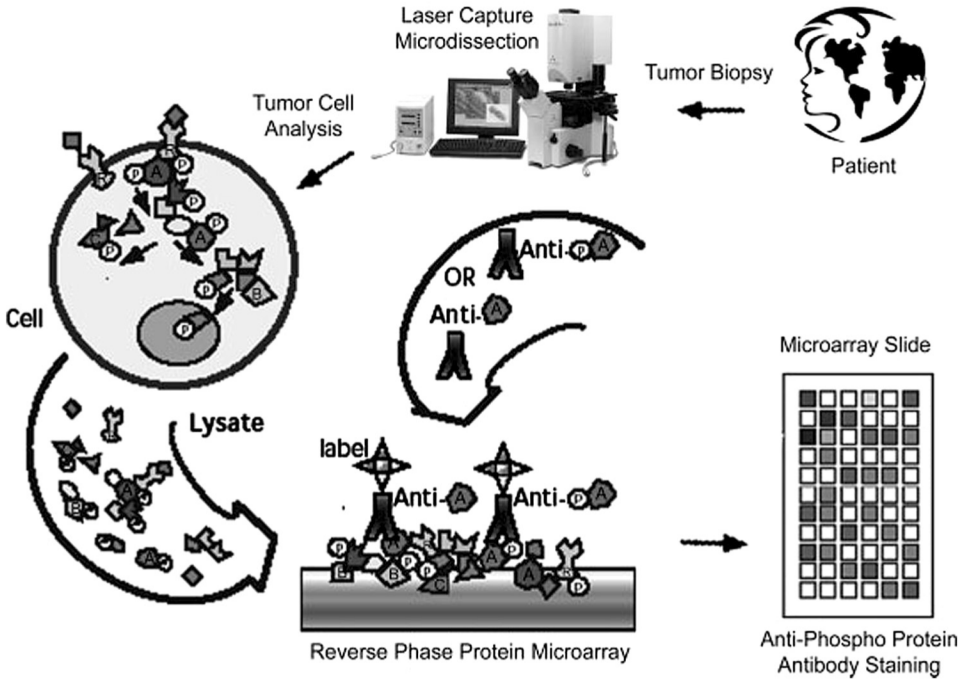



**Figure 12.22** Molecular profiling protocol for patient biopsy samples. [Reprinted with permission from Espina et al. (2003), copyright Wiley VCH.]

#### *12.4.5.3 Oncology*

Reverse phase protein microarrays have been used for molecular profiling protocols for patient biopsy samples [Espina et al., 2003]. Figure 12.22 shows tumor cell analysis from a patient. After tissue microdissection, the isolated cells are lysed and the entire proteome is immobilized on a glass-backed nitrocellulose slide. The immobilized proteins represent total and PTM forms of the signaling proteins. Antibodies directed against the total and phosphorylated forms of the protein are applied, followed by imaging.

It is possible to use reverse-phase protein microarrays for immobilizing an entire proteome representing individual cell populations undergoing disease transition in prostate cancer [Paweletz et al., 2001]. This may prove to be an important tool for following prostate cancer progression and for helping determine when to initiate treatment.

Microarrays spotted with tumor proteins as an alternative to Western blots has been studied [Qiu et al., 2004]. Microarrays provided a high-throughput, high-sensitivity alternative to the use of Western blots for tumor antigen profiling. Microarrays of tumor-derived proteins provide the means for uncovering many tumor antigens that have induced an antibody response in patients with specific cancers.

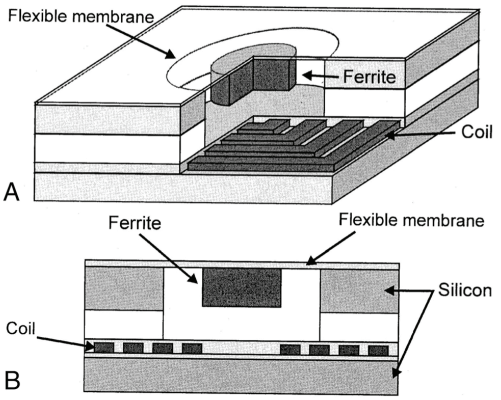



**Figure 14.18** Inductive transensor. (a) 3D representation, and (b) cross section. [Reprinted with permission from Baldi et al. (2002). Copyright IEEE, 2002.]

The design, fabrication, and test of a passive pressure *transensor* have been reported [Baldi et al., 2002]. The sensor uses the self-resonant frequency modulation of an integrated coil to detect pressure variations. A ferrite core is attached to a silicon membrane, and relative motion of the core is detected. Figure 14.18 shows the transensor cut-away view of the coil, and a cross-sectional view. When the membrane is deflected and the core moves toward the coil, inductance is increased, and the self-resonant frequency is reduced. Transduction of pressure changes to inductance changes in this manner has shown good sensitivity.

Other implementations have included a low-power Colpitts microtransmitter using a low-loss silicon platform for biotelemetry application [Ziaie et al., 1997], and an ASIC-based implantable telemetry microsystem for electromyograph (EMG) recording that is powered by inductive coupling with bidirectional data exchange ability [Parramon et al., 1997]. To achieve greater transmission distances it is necessary to consider more sensitive receivers or microstrip circuits. Using a tunnel diode LC circuit, reliable telemetry up to 3 m has been achieved [Suster et al, 2001].

A microstrip patch antenna for communication with medical implants has been described by Soontornpipit et al. (2004). Implantable microstrip antennas pose a challenge because of the *lossy* environment, and inherent antenna efficiency reduction. These devices are sensitive to their environment and dissipate a lot of power in the near-field (discussed below). While drawbacks to communication, these features contribute to their utility as sensors or for generating localized elevations in temperature. The latter is a useful therapeutic tool for cancer therapy and thrombosis ablation. The authors have shown that spiral and serpentine antenna designs were effective radiators for communication in the desired band.

A programmable intraocular CMOS pressure sensor with RF transponder for wireless data transfer and power reception has been described [Stangel et al.,

The interfacial free energy should be 1–3 dyne/cm to have biocompatibility between a polymer and the plasma. Polymer surfaces may be modified by radiation (including ultraviolet), plasma discharge, glow discharge, which are shown to improve material-bone biocompatibility, and chemical treatments such as etching [Wang et al., 2004].

### 15.12.3 Hydrophilicity and hydrophobicity

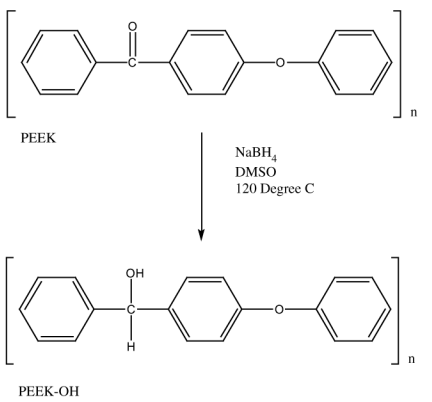
Hydrophobic surfaces adsorb larger amounts of proteins than hydrophilic (low water contact angle) surfaces, suggesting hydrophilic surfaces may be more biocompatible. A balance of hydrophobic and hydrophilic surface characteristics, or *wettability*, may be necessary when both protein and platelet adsorption are taken into account.

Hydrophilic polymers include PEG, PHEMA, PAA, and PVP. *Interpenetrating polymer networks* are a method for immobilizing hydrophilic polymers onto a surface, and may improve the surface properties of polymeric materials for blood-contacting devices.

Catheters coated with hydrophilic polyurethane materials demonstrate less thrombus formation.

### 15.12.4 Functional groups

Altering the chemical structure of a polymer by modification of functional groups may change blood-platelet adhesion and thrombogenesis. For example, cellulose polymers used in hemodialysis may be made more biocompatible by addition of a hydroxyl group. The reduction by sodium borohydride in DMSO of PEEK is shown below:




A number of other surface characteristic are reviewed by Wang including:

(1) Cell membrane constituents such as phosphorylcholine and phospholipid analogs have been incorporated into polymers to improve biocompatibility.

(2) The presence of primary amines in PGA derivatives have a significant toxic effect on red blood cells. Polymers with tertiary amines exhibit lower toxicity.
(3) Hydrogels containing $-OH$, $-C(O)NH$, and $(CH_3)_2N-$ groups induced a spreading of macrophages on polymeric implants, whereas materials containing $-SO_3H$ and $-COOH$ groups inhibited spreading of macrophages.
(4) Higher surface oxygen percentages are associated with low protein adsorption and suppression of cell transformation. Examples include PGA, PEG, and their copolymers.
(5) Targeting ligands onto polymeric surfaces, such as nanoscale clusters of Arg-Gly-Asp (RGD) peptides, may alter cell adhesion.

### 15.12.5 Surface charges in polymers

Neutral polymers and polyanions show less cytotoxicity than polycations.This may be due the fact that anionic surfaces of macromolecules adsorb less protein than cationic surfaces, and most proteins bear a net negative charge. Higher cationic charge density (charge to monomer ratio) and molecular weight polymers cause higher cytotoxicity than those with low-charge density and molecular weight [Wang et al., 2004].

Cationic polymers are known to cause activation of the complement system. These include polybrene, protamine, and poly-L-ornithine. In contrast, polyanions such as dextran sulfate, polyvinyl sulfate, chondroitin sulfate, and poly(inosinic acid) inhibit the classical compliment pathway by inactivating C1 or C2 components below [Loos et al., 1976].

### 15.12.6 Additional characteristics

Low molecular weight polymers have less protein adsorption and platelet adhesion than higher ones.

Conformational changes also influence biocompatibility. The arrangement of cationic charges depends on the 3D structure and flexibility of biomolecules. Molecules that are rigid and globular are less able to attach to cell membranes compared to linear and branched polymers with greater flexibility.

Surface roughness may be more related to inducing thrombosis than other surface properties. Surface features, such as channels may also be used to direct cell growth [Wang et al., 2004].

## 15.13 Biofouling

Biofouling is the process whereby functioning of a bioMEMS device is interfered with by the biological response of the host. This commonly occurs when