

**BMED3201 INTRODUCTION TO BIOMATERIALS**  
**SYLLABUS**

Date: February 26, 2021

Semester : 2021 Spring  
Course : BME302.01, Introduction to Biomaterials  
Level of Course : Undergraduate  
Year of Study : 3  
Type of Course : BME  
Language of Instruction : English

**Instructor** : Assist. Prof. Dr. Sakip ONDER

**Instructor's office hours** : ---

**Instructor's office no/phone no/e-mail address** : Room No. LMF 421, (0216) 5287019, [sakip.onder@isikun.edu.tr](mailto:sakip.onder@isikun.edu.tr)

**Class hours** : BMED3201 / FFF 123

**Prerequisite** :

**Corequisite** :

**Course description**

The Nature of Matter and Materials, Classes of Materials Used in Medicine: Polymers, Metals, Ceramics, Glasses, Glass-Ceramics, composites, hydrogels, Non-fouling surfaces, Physicochemical surface modification and surface patterning, Cell-tissue and biomaterial interaction, Host Reaction to Biomaterials, Biological testing of biomaterials, Applications of biomaterials.

**Recommended Textbook (s)** :

- 1- Buddy D. Ratner, Allan S. Hoffman, Frederick J. Schoen and Jack E. Lemons, Biomaterials Science (Third Edition) An Introduction to Materials in Medicine, Elsevier Inc. (2013)

**Tentative Schedule**

Weeks	Topics
1	Introduction to Biomaterials
2	The Nature of Matter and Materials
3	Surface Characterization Techniques
4	Classes of Materials Used in Medicine: Polymers
5	Classes of Materials Used in Medicine: Metals
6	Classes of Materials Used in Medicine: Ceramics, Glasses, Glass-Ceramics
7	Midterm I
8	Classes of Materials Used in Medicine: composites, hydrogels and non-fouling surfaces
9	Physicochemical surface modification and surface patterning
10	Cell-tissue and biomaterial interaction
11	Host Reaction to Biomaterials
12	Biological testing of biomaterials
13	Applications of biomaterials (student presentations)
14	Applications of biomaterials (student presentations)

**Grading Policy:**

Final course grades will be computed according to the following:

Midterm I	20%
Student presentations	40%
Final	40%

**Important Dates:**

- Last date to add/drop from BMED 3201 : March 1, 2021

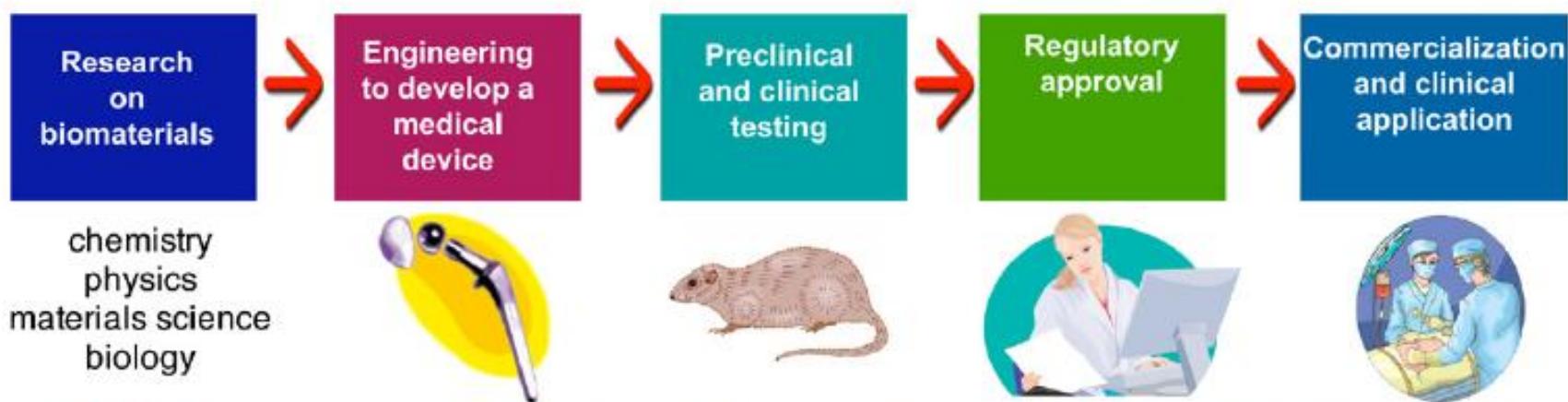
The Black-board will be the main source of information for the course. Homework and announcements will be posted. It is the student's responsibility to download and print the necessary documents needed in the course.

|

# INTRODUCTION

# BIOMATERIALS AND BIOMATERIALS SCIENCE

- Biomaterials science addresses both therapeutics and diagnostics. It encompasses basic sciences (biology, chemistry, physics), and engineering and medicine.



**FIGURE 1** The path from the basic science of biomaterials, to a medical device, to clinical application.

## KEY DEFINITIONS

Biomaterial :

*A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems.*

**Williams, 1987**

Biomaterials science :

the study (from the physical and/or biological perspective) of materials with the biological environment.

Biocompatibility :

*“Biocompatibility” is the ability of a material to perform with an appropriate host response in a specific application.*

**Williams, 1987**

**Examples of appropriate host responses :** resistance to blood clotting, resistance to bacterial colonization, and normal, uncomplicated healing.

**Examples of specific applications:** a hemodialysis membrane, a urinary catheter or a hip joint replacement prosthesis.

- a few applications for synthetic and natural materials in the body.

TABLE 1 Key Applications of Synthetic Materials and Modified Natural Materials In Medicine*		
Application	Biomaterials Used	Number/Year – World (or World Market in US\$)
<b>Skeletal system</b>		
Joint replacements (hip, knee, shoulder)	Titanium, stainless steel, polyethylene	2,500,000
Bone fixation plates and screws	Metals, poly(lactic acid) (PLA)	1,500,000
Spine disks and fusion hardware		800,000
Bone cement	Poly(methyl methacrylate)	(\$600M)
Bone defect repair	Calcium phosphates	–
Artificial tendon or ligament	Polyester fibers	–
Dental Implant-tooth fixation	Titanium	(\$4B)
<b>Cardiovascular system</b>		
Blood vessel prosthesis	Dacron, expanded Teflon	200,000
Heart valve	Dacron, carbon, metal, treated natural tissue	400,000
Pacemaker	Titanium, polyurethane	600,000
Implantable defibrillator	Titanium, polyurethane	300,000
Stent	Stainless steel, other metals, PLA	1,500,000
Catheter	Teflon, silicone, polyurethane	1B (\$20B)
<b>Organs</b>		
Heart assist device	Polyurethane, titanium, stainless steel	4000
Hemodialysis	Polysulfone, silicone	1,800,000 patients (\$70B)
Blood oxygenator	silicone	1,000,000
Skin substitute	Collagen, cadaver skin, nylon, silicone	(\$1B)
<b>Ophthalmologic</b>		
Contact lens	Acrylate/methacrylate/silicone polymers	150,000,000
Intraocular lens	Acrylate/methacrylate polymers	7,000,000
Corneal bandage lens	hydrogel	–
Glaucoma drain	Silicone, polypropylene	(\$200M)
<b>Other</b>		
Cochlear prosthesis	Platinum, platinum-iridium, silicone	250,000 total users
Breast implant	Silicone	700,000
Hernia mesh	Silicone, polypropylene, Teflon	200,000 (\$4B)
Sutures	PLA, polydioxanone, polypropylene, stainless steel	(\$2B)
Blood bags	Poly(vinyl chloride)	–
Ear tubes (Tympanostomy)	Silicone, Teflon	1,500,000
Intrauterine device (IUD)	Silicone, copper	1,000,000

\*Data compiled from many sources – these numbers should be considered rough estimates that are changing with growing markets and new technologies.

Where only US numbers are available, world usage is estimated at approximately 2.5x of US usage.

NOTE: M = millions, B = billions.

- It includes many classes of materials such as metals, ceramics, polymers, glasses, carbons, and composite materials.
- Such materials are used as molded or machined parts, coatings, fibers, films, membranes, foams, fabrics, and nanoparticles.

- the size of the commercial market for biomaterials and medical devices, is impressive .

TABLE 2   The Biomaterials and Healthcare Market: Facts and Figures (Per Year)	
Total US healthcare expenditures (1990)	\$714 billion
Total US healthcare expenditures (2009)	\$2.5 trillion
Total US health research and development expenditure (2009)	\$139 billion
Number of medical device companies in the US	12,000
Jobs in the US medical device industry (2008)	425,000
Sales by US medical device industry (2008)	\$136 billion
World medical device market forecast for 2013*	\$286 billion

\*Source: Medical Market Fact Book 2008.

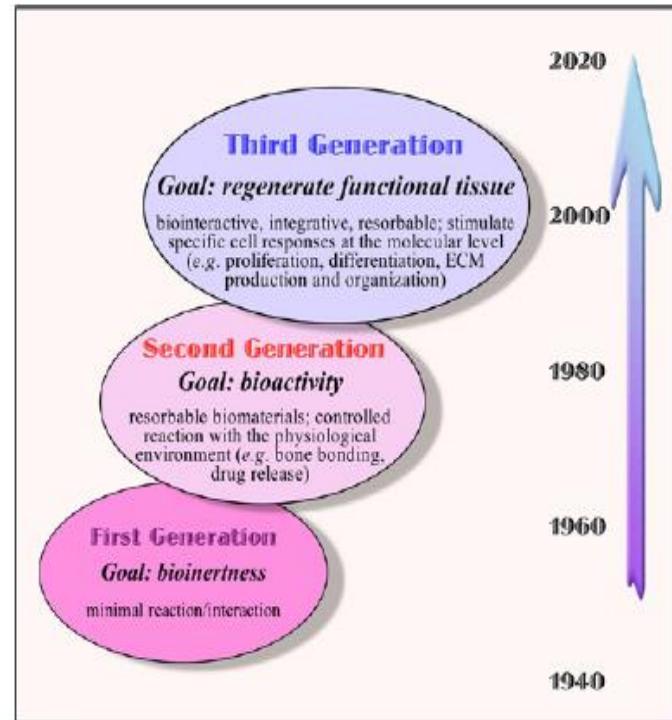
# THE EVOLUTION OF THE BIOMATERIALS FIELD

① first generation biomaterials was to achieve a suitable combination of functional properties to adequately match those of the replaced tissue without deleterious response by the host.

- they were *bioinert* (i.e., they elicited minimal response from the host tissues), and therefore they were considered *biocompatible*

② Second generation biomaterials evolved from those early biomaterials, and were intended to elicit a controlled reaction with the tissues into which they were implanted in order to induce a desired therapeutic effect.

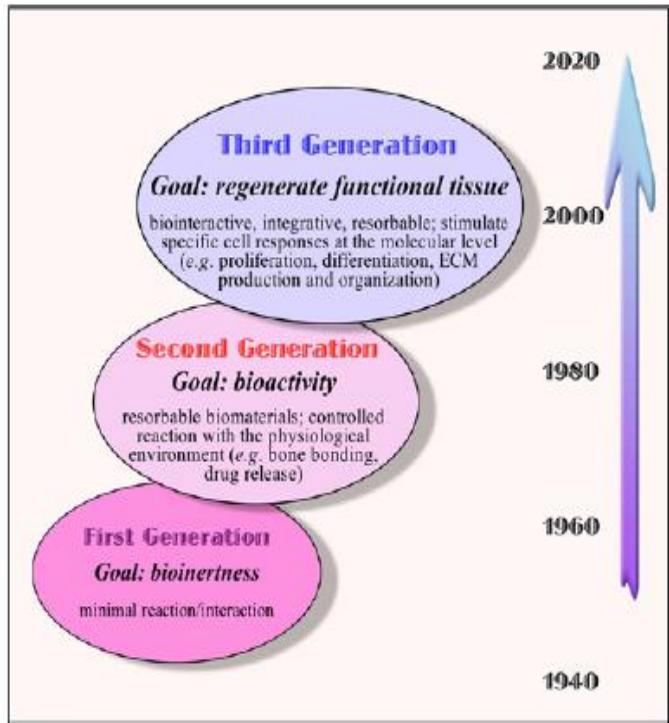
- delivery of drugs, active proteins, and other macromolecules localized to the site where the drug is needed.
- controlled drug delivery is now capable of targeting a wide range of drugs to tumors, to diseased blood vessels, to the pulmonary alveoli, etc.



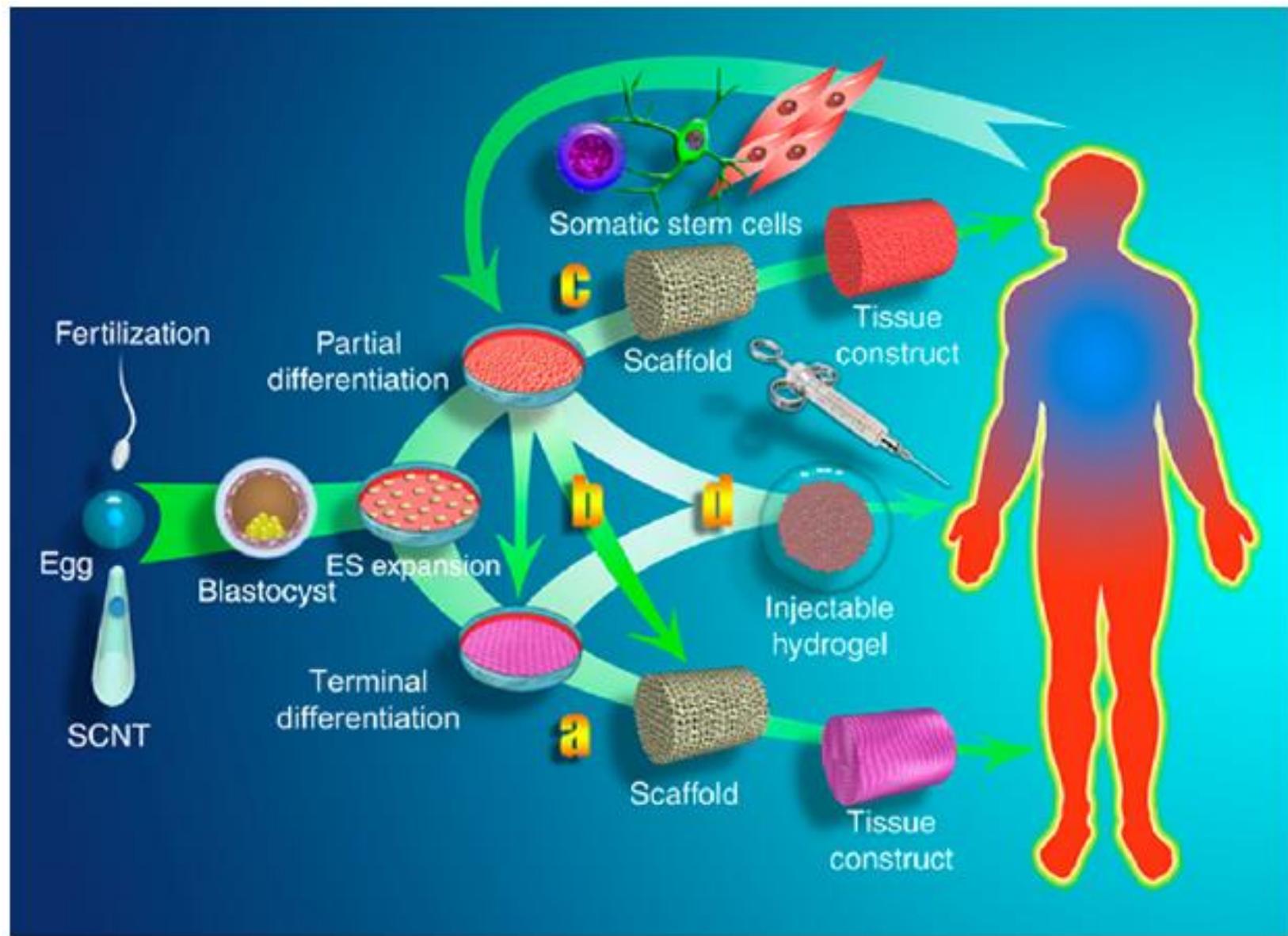
**FIGURE 2** Evolution of biomaterials science and technology.  
(Based upon Rabkin, E. & Schoen, F. J. (2002). Cardiovascular tissue engineering. *Cardiovasc Pathol*, 11: 305.)

③ The third generation of biomaterials has the goal of supporting and stimulating the regeneration of functional tissue.

- it seems that true replacement with living tissue will be possible.
- Tissue engineering uses living cells (or attract endogenous cells) to aid tissue formation or regeneration.
- Tissue engineering has led to the replacement in humans of damaged bladders, trachea, skin, corneal epithelium, and cartilage.



**FIGURE 2** Evolution of biomaterials science and technology.  
(Based upon Rabkin, E. & Schoen, F. J. (2002). Cardiovascular tissue engineering. *Cardiovasc Pathol*, 11: 305.)

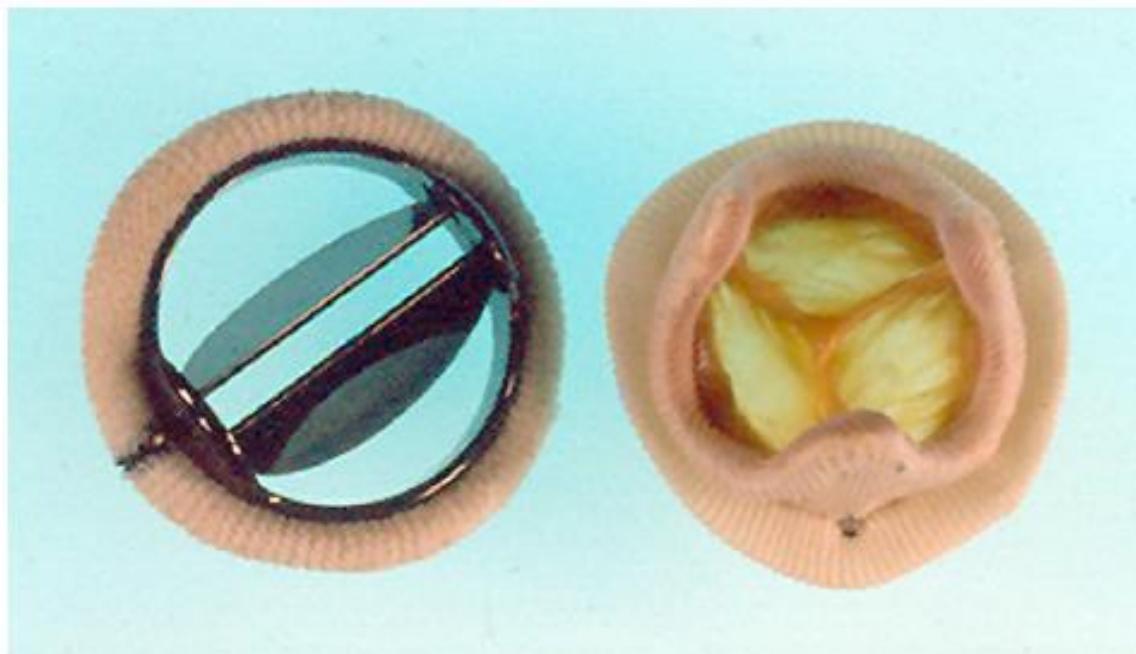


**FIGURE 3** The tissue engineering paradigm – various cell types are seeded on porous scaffolds, possibly proliferated in a bioreactor, and finally implanted in various tissue sites to restore or regenerate damaged or missing tissue. (nature.com.)

## EXAMPLES OF TODAY'S BIOMATERIALS APPLICATIONS

### ➤ Heart Valve Prostheses

- Diseases and degeneration of the heart valves often make surgical repair or replacement necessary.
- Approximately 250,000 replacement valves are implanted each year worldwide, because of acquired damage to the natural valve and congenital heart anomalies.
- There are many types of heart valve prostheses, and they are fabricated from carbons, metals, elastomers, plastics and animal or human tissues chemically pretreated to reduce their immunologic reactivity, and to enhance durability.



**FIGURE 4** Prosthetic heart valves. Left: A bileaflet tilting disk mechanical heart valve. (St. Jude Medical Inc., St. Paul, MN.) Right: A bioprosthetic (xenograft) tissue heart valve (Hancock® valve, Medtronic Inc., MN.)

## ➤ Total Hip Replacement Prostheses

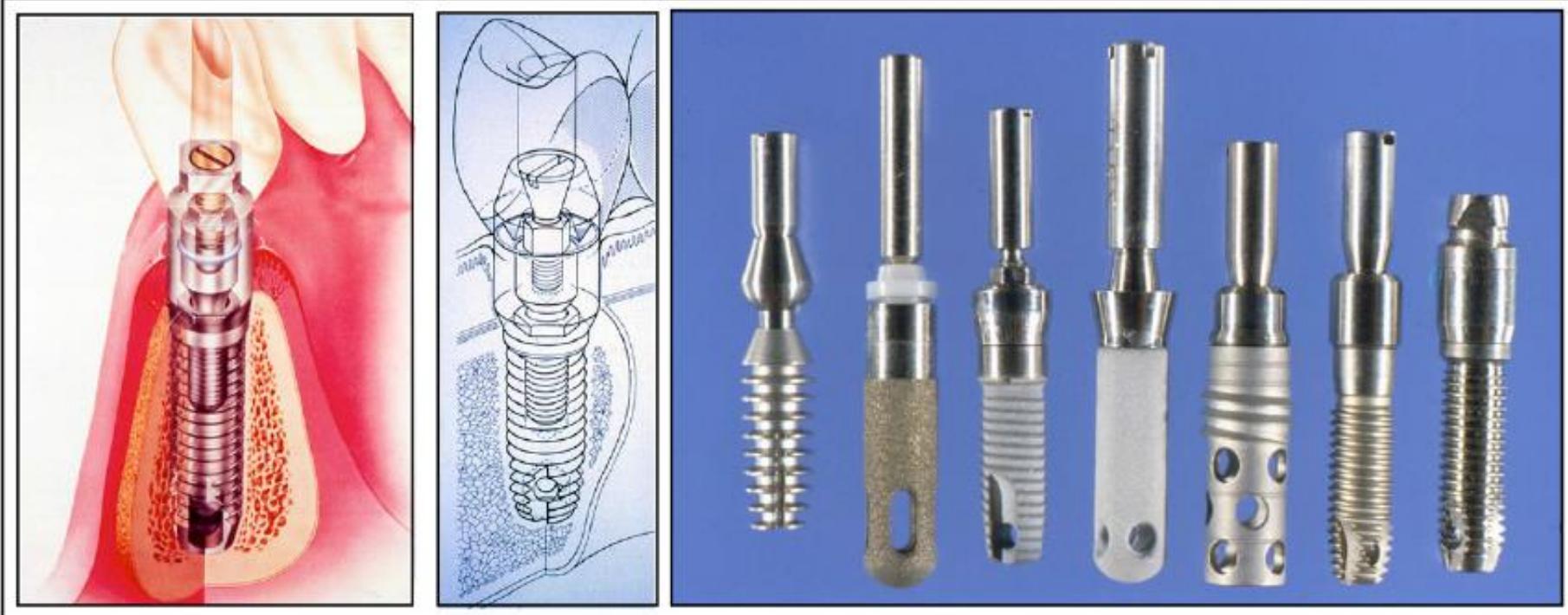
- The human hip joint is subjected to high levels of mechanical stress.
- after 50 or more years of cyclic mechanical stress or because of degenerative or rheumatoid disease, the natural joint wears out, leading to loss of mobility.
- Hip joint prostheses are fabricated from a variety of materials, including titanium, stainless steel, special high-strength alloys, ceramics, composites, and ultrahigh molecular weight polyethylene (UHMWPE).
- Replacement hip joints are implanted in more than 200,000 humans each year in the United States alone.
- After 10–15 years, many of these implants fail by loosening, which usually necessitates another operation (a revision procedure).



**FIGURE 5** A hip prosthesis. Microplasty® titanium alloy femoral stem, Biolox® alumina-zirconia ceramic femoral head, ultra-high molecular weight polyethylene acetabular cup infused with vitamin E antioxidant. (Image courtesy of Biomet, Inc.)

## ➤ Dental Implants

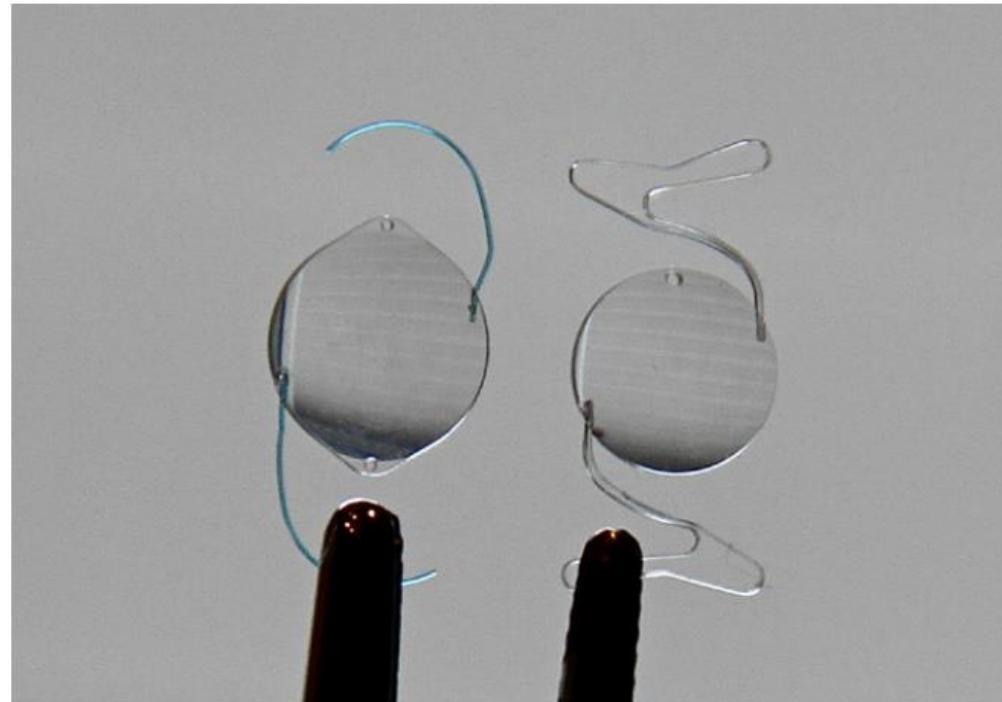
- The development of root form designs of titanium implants revolutionized dental implantology.
- These devices form an implanted artificial tooth anchor upon which a crown is affixed, and are implanted in 2,000,000 people each year in the US alone, according to the American Dental Association.
- the tooth is connected to the jaw by the periodontal ligament, and is not directly attached to the jawbone.
- Titanium based implants are commonly used in dental applications because of their excellent osteointegrasyon properties with the bone of the jaw.



**FIGURE 6** Schematic images of early dental root form implants and a photograph of several designs used in clinical practice.

## ➤ Intraocular Lenses

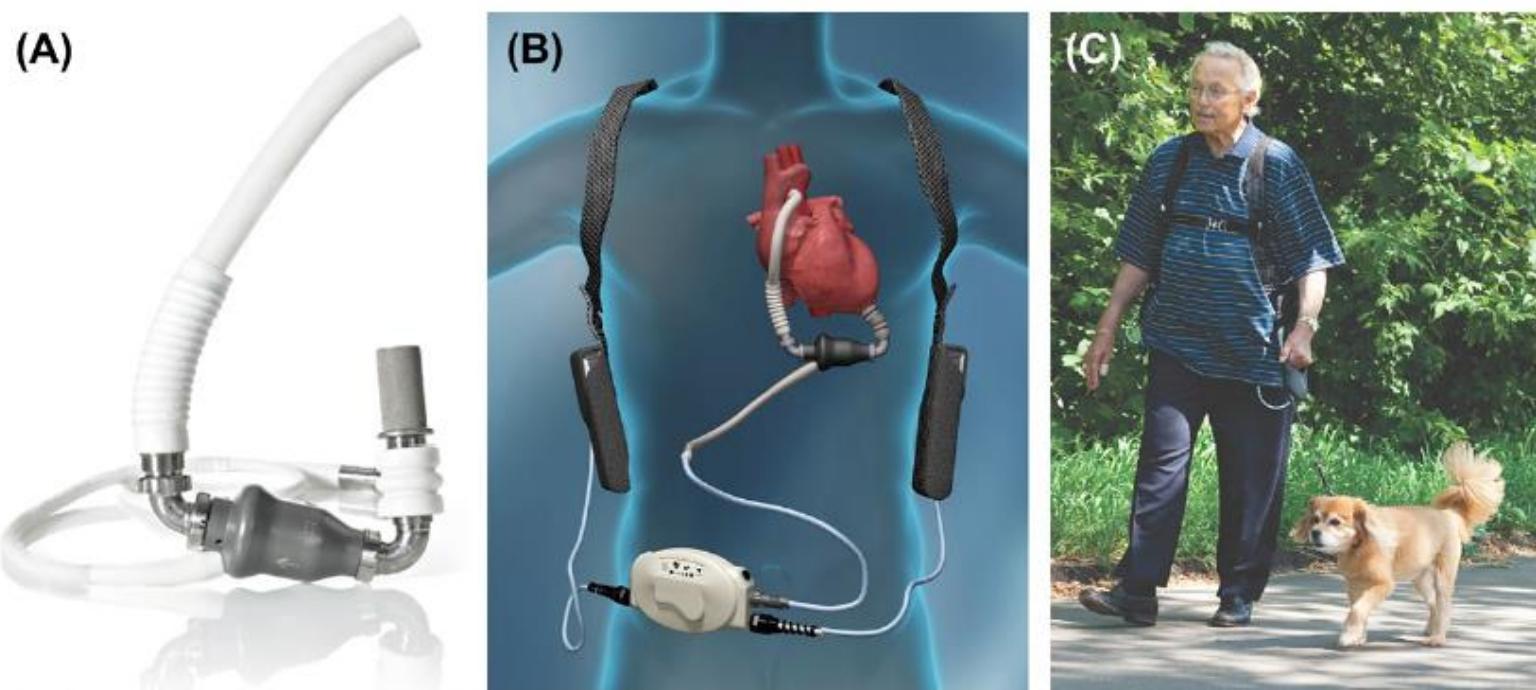
- Implants to replace lenses in the eye that have clouded due to cataracts are called intraocular lenses (IOLs).
- They have been fabricated from a variety of transparent materials including poly(methyl methacrylate), silicone elastomer, soft acrylic polymers, and hydrogels.
- By the age of 75, more than 50% of the population suffers from cataracts
- More than three million implantations in the US alone each year, and more than double that number worldwide.



**FIGURE 7** Two styles of multipiece intraocular lenses.

## ➤ Left Ventricular Assist Devices

- Nearly 5,000,000 Americans are living with seriously failing hearts (congestive heart failure), and 300,000 individuals will die each year from this disease.
- According to the American Heart Association, 50,000–100,000 of these individuals might benefit from cardiac transplantation or mechanical assist.
- LVADs are used to maintain a patient with a failing heart while the patient awaits the availability of a transplant heart.
- LVAD recipients can have considerable mobility and freedom while cardiac support is provided by the device. Patients have lived on LVAD support for more than four years



**FIGURE 8** Left ventricular assist device (LVAD). (A) Continuous flow pump with associated inflow/outflow grafts and electrical drive line (Heartmate II® device). (B) Schematic of LVAD implanted as a left ventricular assist device with associated external power source. (C) Patient (human) implanted with this LVAD device illustrating freedom of activity. (Reprinted with the permission of Thoratec Corporation, Pleasantville, CA.)

# CHARACTERISTICS OF BIOMATERIALS SCIENCE

## ➤ Multidisciplinary

- biomaterials science brings together teams of researchers from diverse academic and industrial backgrounds, who must clearly communicate and integrate complex concepts and data

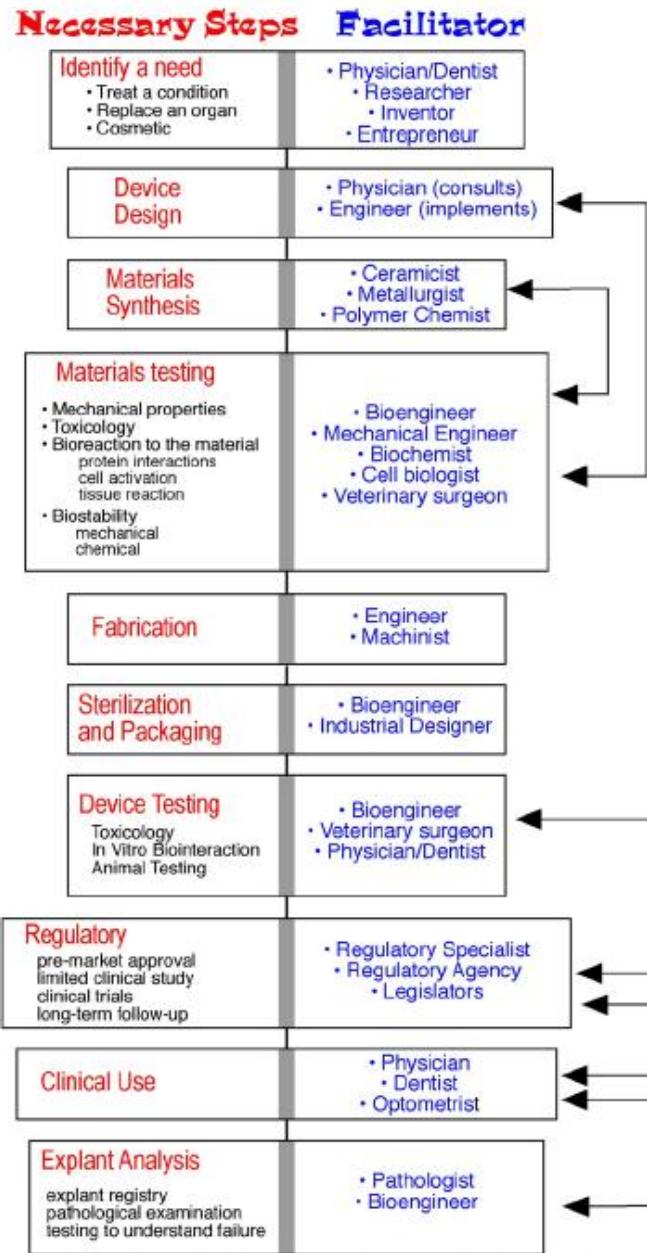


FIGURE 9 The path from an identified need to a clinical product, and some of the disciplines that facilitate this development process.

## ➤ Diverse Materials are Used

- The biomaterials scientist use different types of in medical applications including polymers, metals, ceramics, glasses, composites.
- There is a tendency to group biomaterials and researchers into the “hard tissue replacement”, typically represented by those involved in orthopedic and dental materials, and the “soft tissue replacement”, frequently associated with cardiovascular implants and general plastic surgery materials.
- Hard tissue biomaterials researchers are thought to focus on metals and ceramics, while soft tissue biomaterials researchers are considered polymer experts.
- In practice, this division is artificial: a heart valve may be fabricated from polymers, metals, and carbons. A hip joint will also be composed of metals and polymers (and sometimes ceramics), and will be interfaced to the body via a polymeric bone cement.

## ➤ Magnitude of the Field & Company

- The magnitude of the medical device field expresses both the magnitude of the need and a sizeable commercial market
- The process of biomaterial/medical device innovation is driven by clinical need: a patient or a physician defines a need and then initiates an invention.
- However, someone must test and manufacture the device, and shepherd it through the complex, expensive regulatory process. This “someone” is a company, and a company exists (by law) to return value to its shareholders.

## ➤ Success and Failure

- All manufactured devices have a failure rate.
- all humans are different, with differing ethnicities, ages, genetics, gender, body chemistries, living environments, and degrees of physical activity.
- physicians implant or use these devices with varying degrees of skill.
- The other side to the medical device success story is that there are problems, compromises, complications, and unintended consequences that often occur with medical devices.

- Central issues for the biomaterials scientist, manufacturer, patient, physician are:
  - ① Is the design competent and optimal?
  - ② who should be responsible when devices perform “with an inappropriate host response”?
  - ③ what are the cost:risk or cost:benefit ratios for the implant or therapy?

## SUBJECTS INTEGRAL TO BIOMATERIALS SCIENCE

### ➤ **Toxicology.**

- A biomaterial should not be toxic, unless it is specifically engineered for such requirements (e.g., a “smart” drug delivery system that targets cancer cells with a toxic drug and destroys them).

### ➤ **Biocompatibility.**

- biocompatibility is defined in terms of performance or success at a specific task.

### ➤ **Inflammation and Healing.**

- Specialized biological mechanisms are triggered when a material or device interfaces with the body. Injury to tissue will stimulate the well-defined inflammatory reaction sequence that ultimately leads to healing.
- Healing can be normal (physiological) or abnormal (pathological). Where a foreign body (e.g., an implant) is present in the wound site (the surgical incision), the reaction sequence is referred to as the “foreign-body reaction”

## ➤ Functional Tissue Structure and Pathobiology.

- Biomaterials-based medical devices are implanted into almost all tissues and organs.
- Tissues and organs vary widely in cell composition, morphological organization, vascularization, and innervation.
- Implantation of a biomaterial into bone, liver, or heart will have special physiological consequences.
- Therefore,
  - key principles governing the structure of normal (and abnormal) cells, tissues, and organs are important to biomaterials researchers,
  - techniques by which the structure and function of normal and abnormal tissue are studied must be mastered,
  - fundamental mechanisms leading to abnormal cell, tissue, and organ structures (i.e., diseases and other pathologies) are critical considerations to biomaterials researchers .

## ➤ Dependence on Specific Anatomical Sites of Implantation.

- Consideration of the anatomical site of an implant is essential.
- An intraocular lens may be implanted into the lens capsule or the anterior chamber of the eye.
- A hip joint may be implanted in bone across an articulating joint space.
- A prosthetic heart valve will be sutured into cardiac muscle, and will contact both soft tissue and blood.
- A catheter may be placed in an artery, a vein or the urinary tract.
- Each of these sites challenges the biomedical device designer with special requirements for anatomy, physiology, geometry, size, mechanical properties, and bioresponses.

## ➤ Mechanical Requirements and Physical Performance Requirements

- Each biomaterial and device has mechanical and performance requirements originating from the need to perform a physiological function.
  - A hip prosthesis must be strong and rigid
  - A bone plate may fulfill its function in six months or longer
  - The dialysis membrane has a specified permeability,
  - the acetabular cup of the hip joint must have high lubricity
  - the intraocular lens has transparency and refraction requirements

## ➤ Industrial Involvement

- A significant basic research effort is now under way, primarily at universities, to understand how biomaterials function and how to optimize them.
- At the same time, companies are producing implants for use in humans and, appropriate to the mission of a company, earning profits on the sale of medical devices.
- A risk–benefit analysis must be considered in developing new devices and improving existing devices.

## ➤ Ethics

- A wide range of ethical considerations impact biomaterials science. Some key ethical questions in biomaterials science are summarized

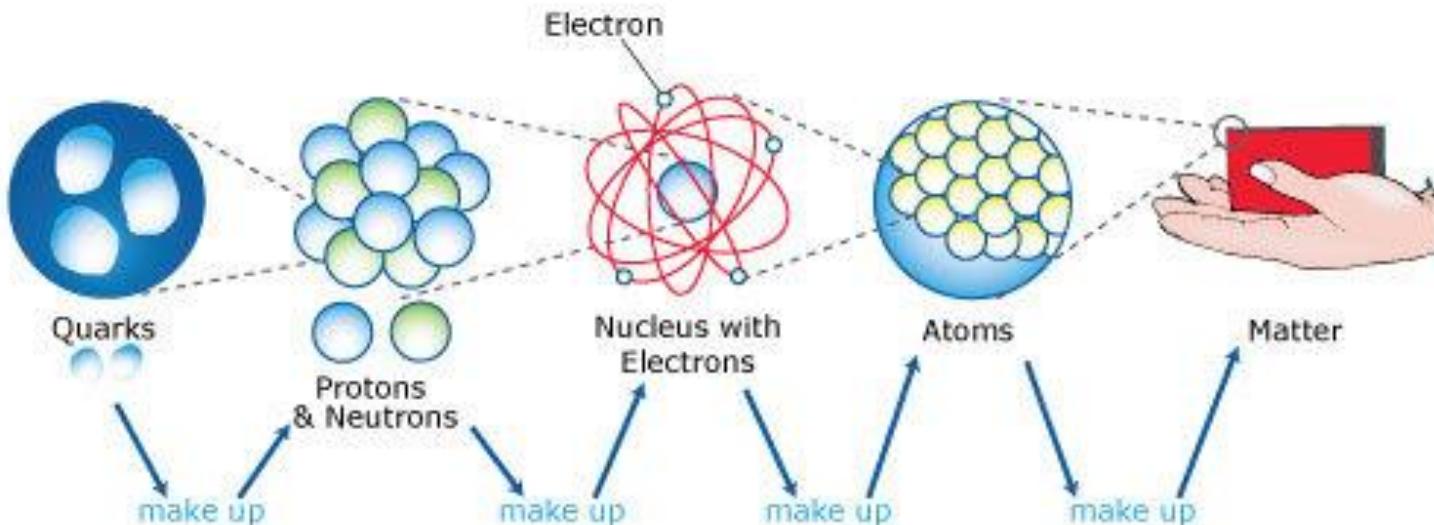
TABLE 3 Ethical Concerns Relevant to Biomaterials Science	
<b>Animals</b>	Is the animal model relevant to human physiology? Specifically, is the experiment well-designed and outcome sufficiently important so that the data obtained will justify the suffering and sacrifice of the life of a living creature?
<b>Human Subjects</b>	How should human subject research be conducted to minimize negative outcomes to the patient and offer a reasonable risk-to-benefit ratio? How can we best ensure informed consent?
<b>Industrial Involvement</b>	Companies fund much biomaterials research and also own proprietary biomaterials. How can the needs of the patient be best balanced with the financial goals of a company? Consider that someone must manufacture devices – these would not be available if a company did not choose to manufacture them.
<b>Researchers</b>	Since researchers often stand to benefit financially from a successful biomedical device, and sometimes even have devices named after them, how can investigator bias be minimized in biomaterials research?
<b>Patients</b>	For life-sustaining devices, what is the trade-off between sustaining life and the quality of life with the device for the patient? Should the patient be permitted to "pull the plug" if the quality of life is not satisfactory?
<b>Regulatory Agencies</b>	With so many unanswered questions about the basic science of biomaterials, do government regulatory agencies have sufficient information to define adequate tests for materials and devices and to properly regulate biomaterials?

## ➤ Regulation.

- To prevent inadequately tested devices and materials from coming on the market, and to screen out those clearly unqualified to produce biomaterials, the United States government has evolved a complex regulatory system administered by the US Food and Drug Administration (FDA).
- The International Standards Organization (ISO) has introduced international standards for the world community.

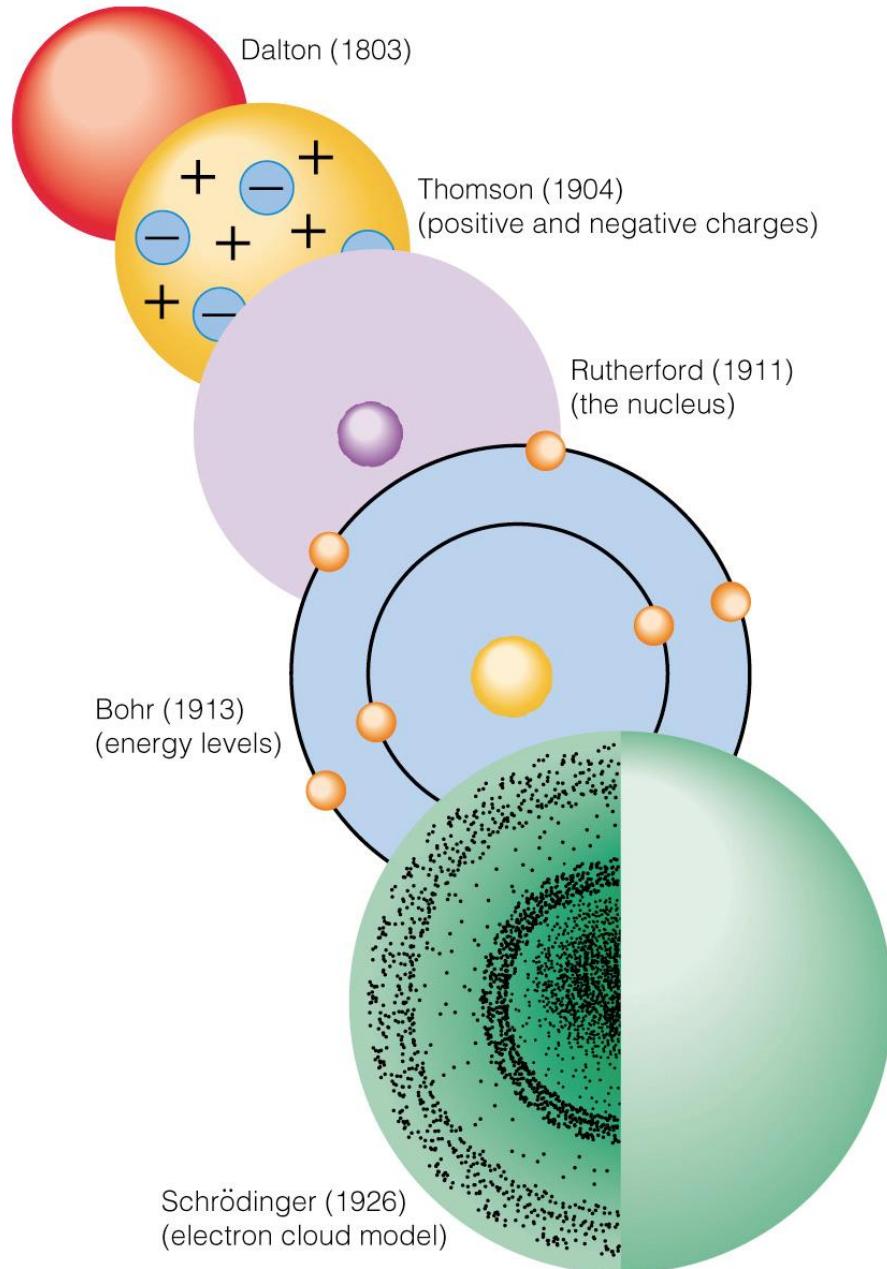
# **THE NATURE OF MATTER AND MATERIALS**

# Structure of matter flow diagram



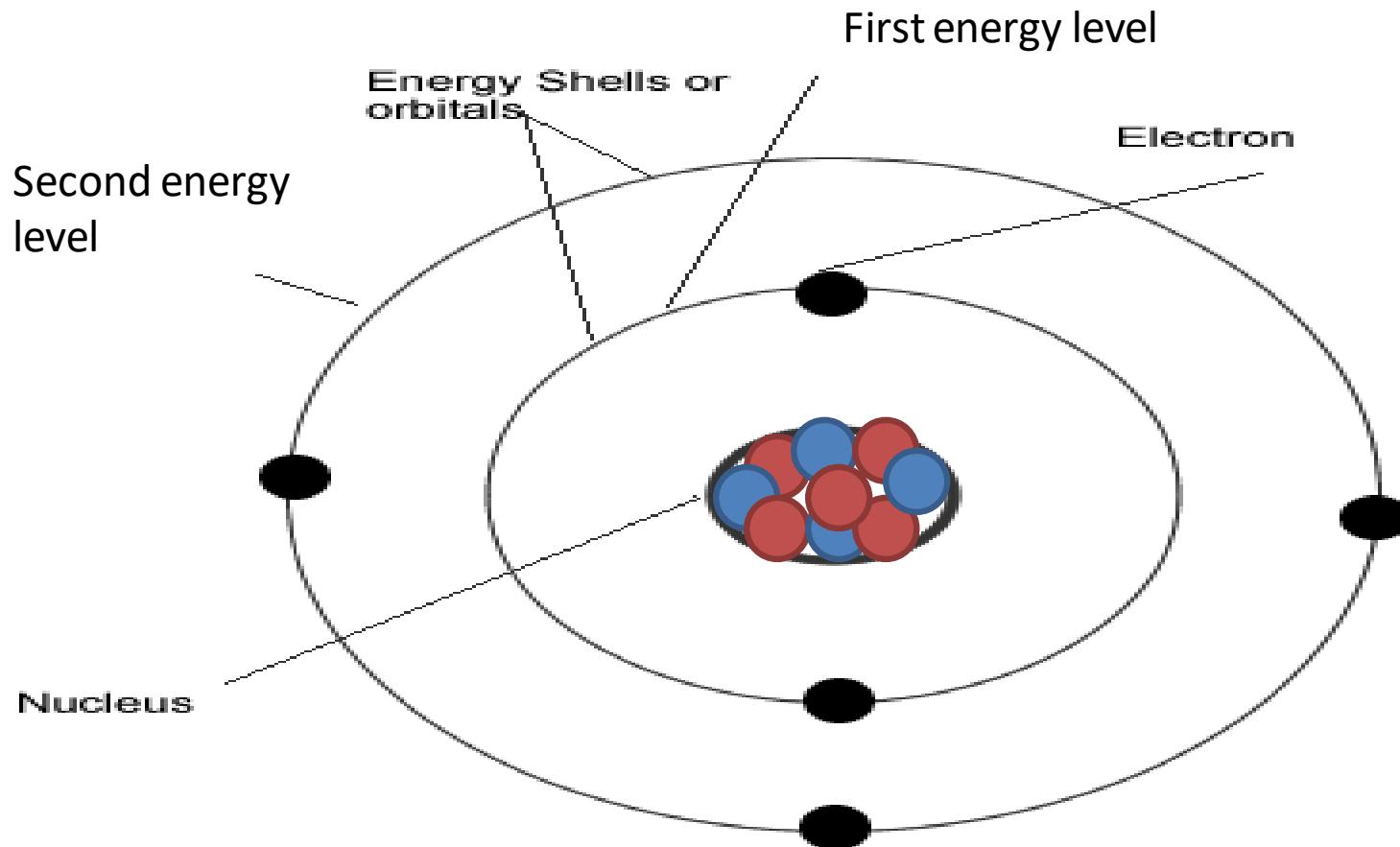
<https://www.sciencelearn.org.nz/images/2151-structure-of-matter-flow-diagram>

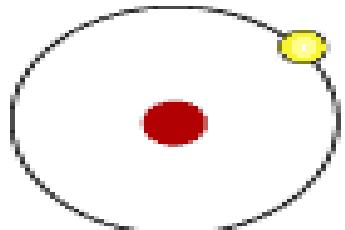
# 5 Models of the Atom



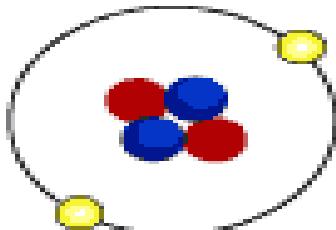
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|-------------|---------------------------------------------------------------------------------------------------------------------------------|
| <b>1803</b> | Dalton proposes the indivisible unit of an element is the atom.                                                                 |
| <b>1904</b> | Thomson discovers electrons, believed to reside within a sphere of uniform positive charge (the plum pudding model).            |
| <b>1911</b> | Rutherford demonstrates the existence of a positively charged nucleus that contains nearly all the mass of an atom.             |
| <b>1913</b> | Bohr proposes fixed circular orbits around the nucleus for electrons.                                                           |
| <b>1926</b> | In the current model of the atom, electrons occupy regions of space (orbitals) around the nucleus determined by their energies. |

- Bohr Atom Model is known as the "planetary model" of the atom that is used as a symbol for atomic energy levels.
- The neutrons and protons are in the nucleus, and the electrons orbit the nucleus much like planets orbiting the Sun.

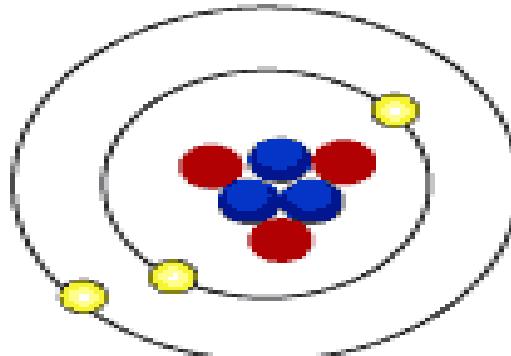




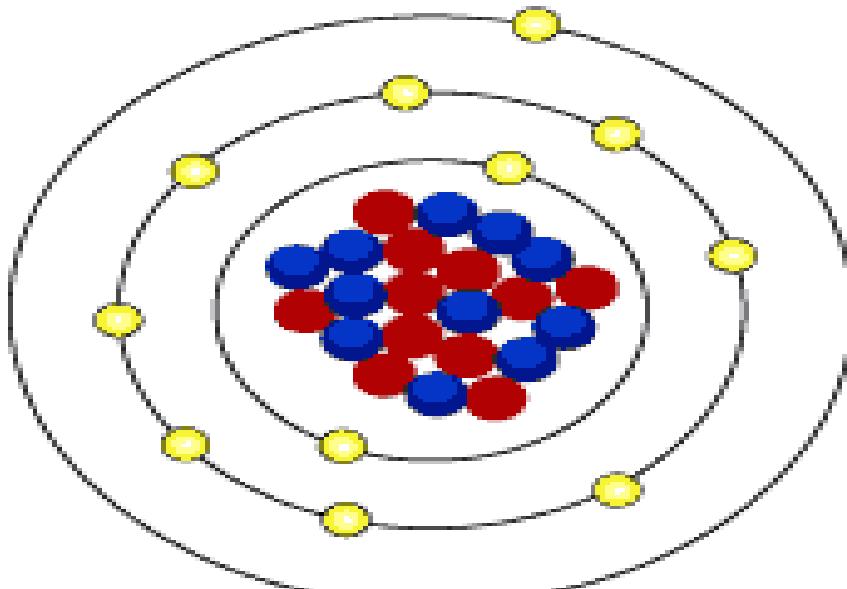
**Hydrogen-1**



**Helium-4**



**Lithium-6**



**Sodium-22**

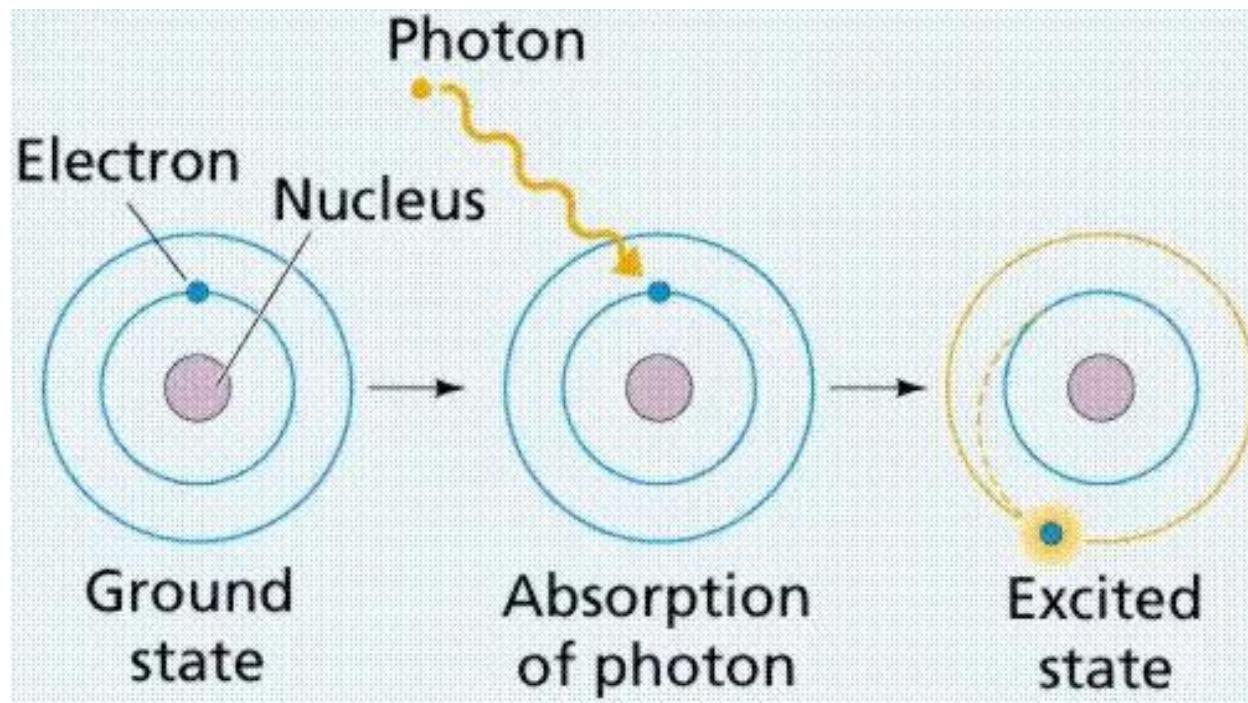
**Neutron**

**Proton**

**Electron**

- **Principles of the Bohr Model**

1. Electrons assume only certain orbits around the nucleus. These orbits are stable.
2. Each orbit has an energy associated with it. For example the orbit closest to the nucleus has an energy  $E_1$ , the next closest  $E_2$  and so on.
3. Light is emitted when an electron jumps from a higher orbit to a lower orbit and absorbed when it jumps from a lower to higher orbit.



**What holds atoms and molecules together to make a strong nylon fiber or a cell membrane or a hard, brittle hydroxyapatite ceramic, or a sheet of gold, or a drop of water?**

Isaac Newton was pondering this issue: “There are agents in nature able to make the particles of bodies stick together by very strong attractions” (18th century).

- The key to understanding matter is to understand attractive and interactive forces between atoms.
- For example;
  - Argon is a gas at room temperature due to the very weak interaction of an argon atom with another argon atom (weak attraction) → **so at room temperature** thermal fluctuations that randomly propel the atoms exceed attractive forces that might result in the coalescence to a solid material.
    - When it is cooled to extremely low temperatures, Ar gas transforms into liquid form.
  - A titanium atom strongly interacts with another titanium atom. Extremely high temperatures are required to vaporize titanium and liberate those atoms from each other.

## ➤ Four attractive forces in universe:

□ **Gravitational force:** Gravity holds us to the surface of the planet Earth.

- For example; but the gravitational potential energy of two argon atoms is only about  $10^{-52}$  J, 30 orders of magnitude weaker than is observed for intermolecular forces.

□ **Weak and strong nuclear force:** The weak nuclear force and the strong nuclear force are only significant over  $10^{-4}$  nm – but molecular dimensions are  $5 \times 10^{-1}$  nm. So these forces do not explain what holds atoms together.

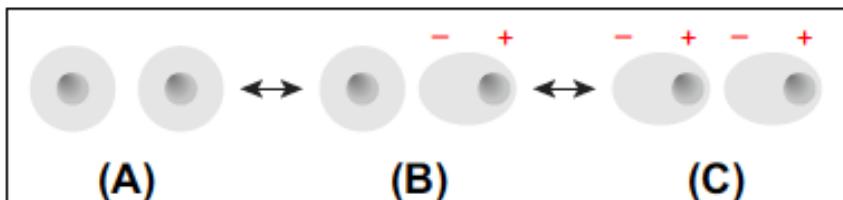
- The force that binds together protons and neutrons inside the nucleus is called the **Nuclear Force**.
- It does not depend on charge
- It is very short range
- It is much stronger than the electric force

□ **Electromagnetic force:** Electromagnetic forces rely on the principle of positive charge attracts negative charge.

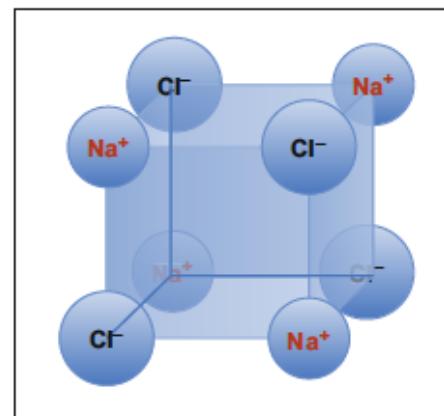
- Electromagnetic forces have appropriate magnitudes and distance dependencies to justify why atoms interact.
- Interactions can be weak, leading to liquids, or stronger, leading to solids.
- The types of interactions usually observed between atoms (all explained by electrostatics) are summarized in Table I.1.2.1.

**TABLE I.1.2.1** Forces that Hold Atoms Together

Interatomic Force	Explanation	Relative Strength	Examples
Van der Waals interactions	Transient fluctuations in the spatial localization of electron clouds surrounding atoms lead to transient positive and negative charges, and consequent interactive forces in molecules would seem to have no permanent polarity	Weak	Argon at cryogenic temperatures. Polyethylene (the forces that hold the chains together to make a solid)
Ionic	Atoms with a permanent positive (+) charge attract atoms with a permanent negative (-) charge	Very strong	NaCl CaCl <sub>2</sub>
Hydrogen (H) bonding	The interaction of a covalently bound hydrogen with an electronegative atom, such as oxygen or fluorine	Medium	Water ice Nylon (the forces that hold the chains together to make a strong, high-melting point solid)
Metallic	The attractive force between a "sea" of positively charged atoms and delocalized electrons	Medium-strong	Gold Titanium metal
Covalent	A sharing of electrons between two atoms	Strong	The carbon–carbon bond Cross-links in a polyacrylamide hydrogel



**FIGURE I.1.2.1** (A) Consider the electron clouds (charge density in space) of two atoms or molecules, both without permanent dipole moments. (B) Electron clouds are continuously in motion and can shift to one side of the atom or molecule; therefore, at any moment, the atoms or molecules can create a "fluctuating instantaneous dipole." (C) The "fluctuating instantaneous dipole" in one molecule electrostatically induces such an "instantaneous dipole" in the next molecule.



**FIGURE I.1.2.2** The unit cell of a sodium chloride crystal illustrating the plus-minus electrostatic interactions.

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Metallic	The attractive force between a "sea" of positively charged atoms and delocalized electrons	Medium-strong	Gold Titanium metal
Covalent	A sharing of electrons between two atoms	Strong	The carbon–carbon bond Cross-links in a polyacrylamide hydrogel

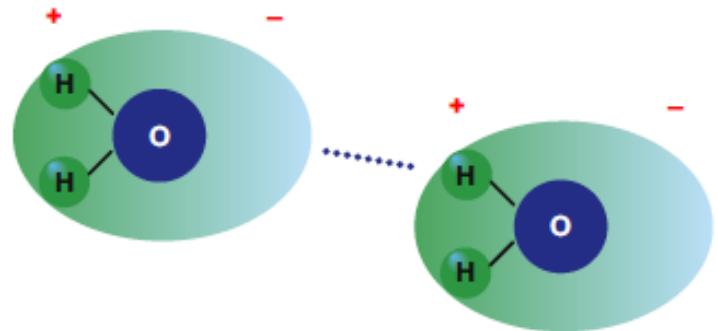


FIGURE I.1.2.3 A hydrogen bond between two water molecules.

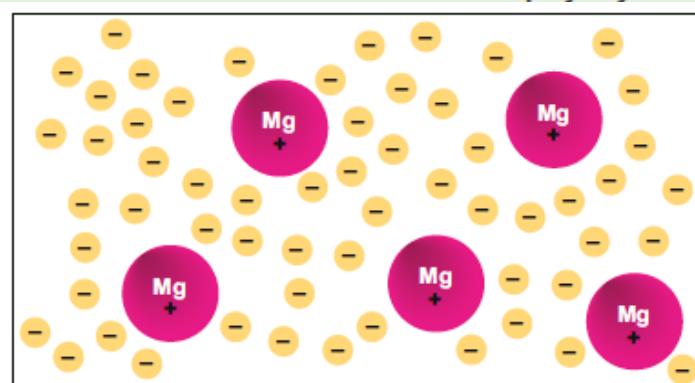
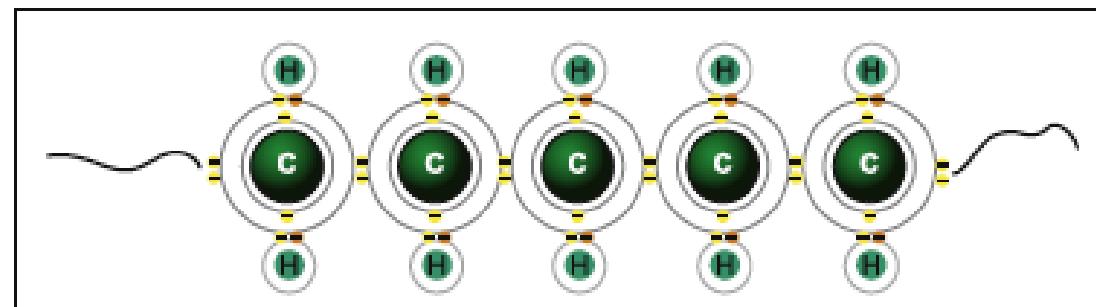


FIGURE I.1.2.4 Metallic bonding in magnesium. The 12 electrons from each Mg atom are shared among positively charged nuclear cores (the single + charge on each magnesium atom in the figure is simply intended to indicate there is some degree of positive charge on each magnesium nuclear core).

TABLE I.1.2.1 Forces that Hold Atoms Together

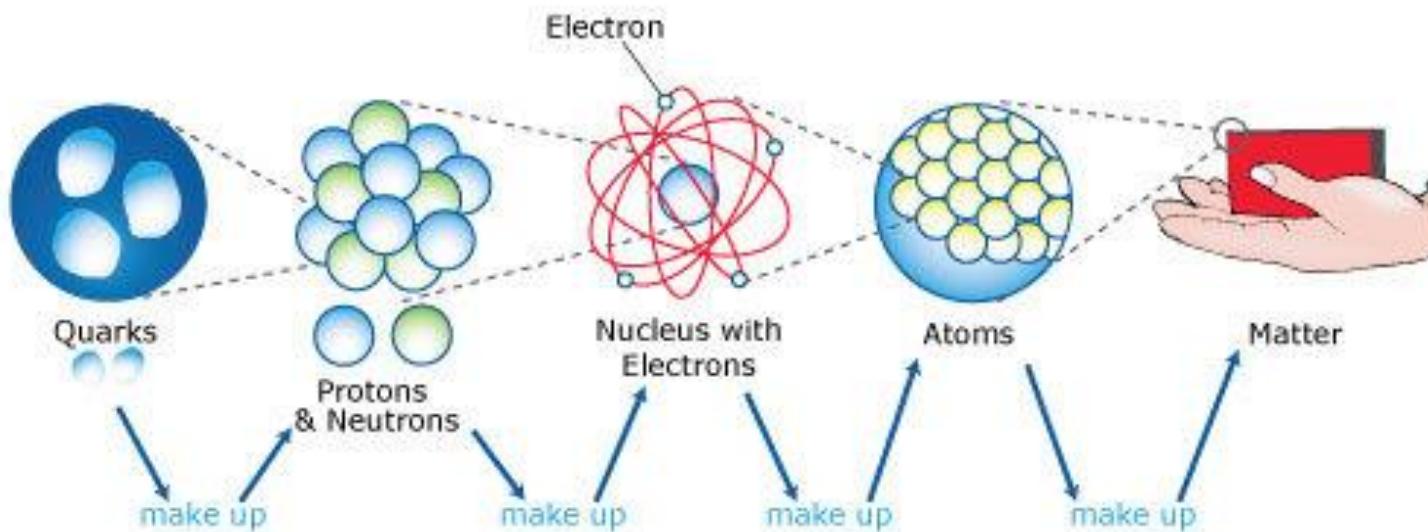
Interatomic Force	Explanation	Relative Strength	Examples
Van der Waals interactions	Transient fluctuations in the spatial localization of electron clouds surrounding atoms lead to transient positive and negative charges, and consequent interactive forces in molecules would seem to have no permanent polarity	Weak	Argon at cryogenic temperatures. Polyethylene (the forces that hold the chains together to make a solid)
Ionic	Atoms with a permanent positive (+) charge attract atoms with a permanent negative (-) charge	Very strong	NaCl CaCl <sub>2</sub>
Hydrogen (H) bonding	The interaction of a covalently bound hydrogen with an electronegative atom, such as oxygen or fluorine	Medium	Water ice Nylon (the forces that hold the chains together to make a strong, high-melting point solid)
Metallic	The attractive force between a "sea" of positively charged atoms and delocalized electrons	Medium-strong	Gold Titanium metal
Covalent	A sharing of electrons between two atoms	Strong	The carbon–carbon bond Cross-links in a polyacrylamide hydrogel



**FIGURE I.1.2.5** Covalent bonding along a section of polyethylene chain. Carbons share pairs of electrons with each other, and each hydrogen shares an electron pair with carbon.

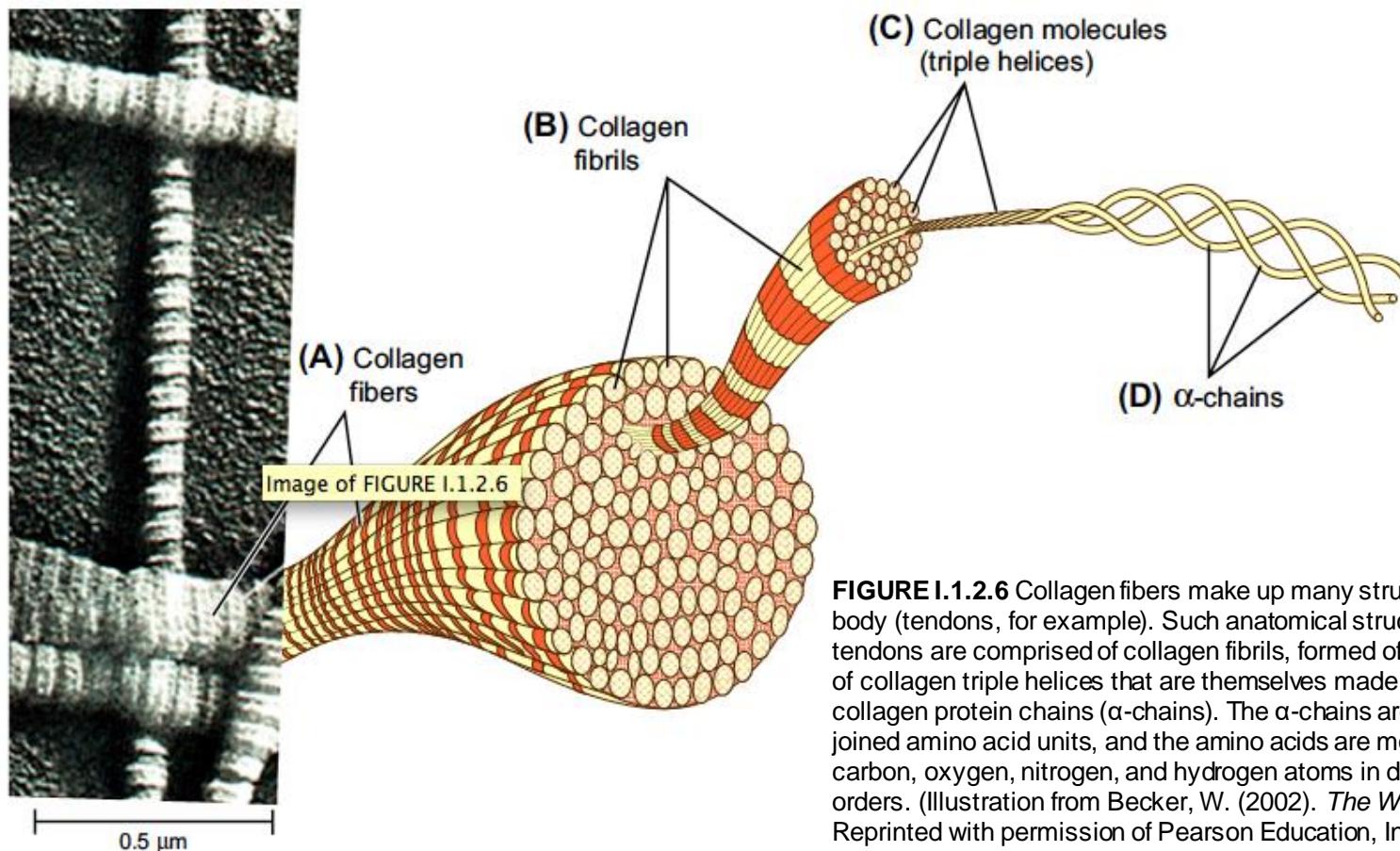
## ➤ Hierarchical structures of material:

- The smallest size scale in materials is atoms (about 0.2 nm, in diameter)
- Atoms combine to form molecules (1 - 100 nm).
- Molecules may assemble or order to form supramolecular structures with dimensions up to 1000 nm or more.
- Supramolecular structures may organize in bundles, fibers or larger assemblies with dimensions reaching into the range visible to the human eye.



## Ex: Collagen Fibers

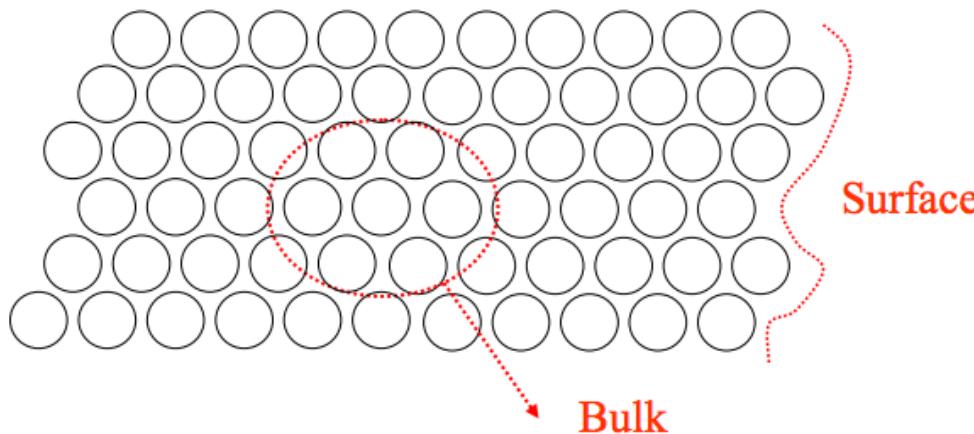
- Collagen fibers make up many structures in the body, for example: tendons
- Tendons are comprised of collagen fibrils, formed of aligned bundles of collagen triple helices that are themselves made up of single collagen protein chains ( $\alpha$ - chains)
- $\alpha$  - chains are constructed of joined amino acid units
- The amino acids are made molecules of carbon, oxygen, nitrogen and hydrogen atoms in defined ratios and orders.



**FIGURE I.1.2.6** Collagen fibers make up many structures in the body (tendons, for example). Such anatomical structures as tendons are comprised of collagen fibrils, formed of aligned bundles of collagen triple helices that are themselves made up of single collagen protein chains ( $\alpha$ -chains). The  $\alpha$ -chains are constructed of joined amino acid units, and the amino acids are molecules of carbon, oxygen, nitrogen, and hydrogen atoms in defined ratios and orders. (Illustration from Becker, W. (2002). *The World of the Cell*. Reprinted with permission of Pearson Education, Inc.)

# BULK PROPERTIES OF MATERIALS

## Bulk Versus Surface



- The success or failure of many biomaterials depends on the physical and chemical characteristics of their **surface**.
- Surface properties dictate interactions between a material and its environment, and thus indicate whether a permanently implanted material will be tolerated or rejected
- In cases where the implanted material is required to degrade at a controlled rate then the bulk material must be capable of sustaining those properties continuously as it becomes the new surface.
  - when the implant is a temporary support, such as a dissolving suture or a scaffolding for cells that regenerate tissue

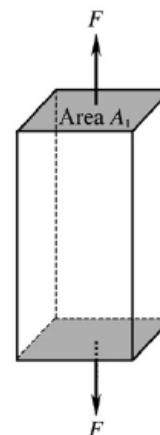
- Biomaterials are also required to exhibit certain **bulk** characteristics, especially including those attributes (mechanical properties) that relate to the ability to carry loads dependably without undue deflection or premature failure.
- The bulk properties of a material depend on
  - what types of atoms and molecules it contains (composition),
  - how those atoms and molecules are arranged (microstructure).
- Bulk properties that are depend on the composition of materials being characterized, and not on the microstructure are referred to as *intrinsic properties*. e.g. the stiffness of a metal, density, heat capacity.
- Bulk properties that are depend on attributes such as the average grain (crystal) size, as well as the number and distribution of defects in the crystal structure are referred as *extrinsic property*. e.g. yield strength.

## NOMINAL (ENGINEERING) STRESS, ELONGATION and NOMINAL (ENGINEERING) STRAIN

- When a load (force) is applied to an object, the possible consequences include translation, rotation, and deformation of the object.
- Let a force  $F$  be applied normal to a pair of opposite faces (in this case the top and bottom faces) of the sample, which initially each have area  $A_1$ .
- The actual shape of the sample is not important for the analysis , however the cross-section perpendicular to the applied force should be uniform.
- The ratio:

$$\sigma_n = \frac{F}{A_1}$$

defines the *nominal stress (engineering stress)* being applied to the sample.



Tensile (normal) stress

**FIGURE I.1.3.1** Examples of a tensile (normal) stress, a shear stress, and a mixed stress with both normal and shear components, illustrating the relationship between load direction and surface orientation in each case. For the example of shear stress, the originally rectangular front face of the sample distorts to a parallelogram as shown, and the corresponding shear strain is defined as  $\tan \theta$ .

- The stress is tensile if it is a “pull,” elongating the sample, and it is compressive if it is a “push,” shortening the sample.

- Quantification of the effect of loads (and their related stresses) by considering the resultant length change per unit length is commonly known as *strain*.
- If the initial length of the sample is  $l_1$ , and the applied stress causes a change to length  $l_2$ , then the *nominal (or engineering) strain* is given by:

$$\epsilon_n = \frac{l_2 - l_1}{l_1} = \frac{\Delta l}{l_1} = \lambda_{1 \rightarrow 2} - 1$$

where  $\lambda$  denotes the extension ratio, i.e., the ratio of final length to initial length.

## TRUE STRESS AND TRUE STRAIN

- A more realistic sense of stress imposed on a material during a stress–strain test is obtained if the applied force is scaled with reference to the actual cross-sectional area of the sample, because the actual value of the area (cross-section) to which the load is applied will change as the sample deforms in response to the load
- In that case, we refer to the sample being subjected to a *true stress* defined by:

$$\sigma_t = \frac{F}{A}$$

- because A changes continuously during the course of a stress–strain test, it can be difficult to measure in practice, so nominal stress is so often used instead of true stress.
- Length change of the sample is measured in very small increments  $dl$ , with each increment being scaled relative to the length  $l$  of the sample immediately prior to that increment. Thus, a small increment in *true strain* is defined as:

$$d\epsilon_t = \frac{dl}{l}$$

## SHEAR STRESS AND SHEAR STRAIN

- Consider the effect of applying the force  $F$  parallel to a pair of opposite faces (in this case the top and bottom faces), which initially each have area  $A_1$ . For this configuration of applied load, the ratio:

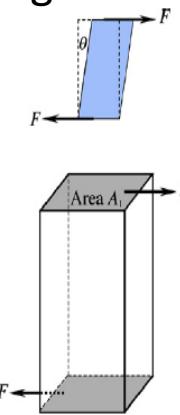
$$\tau = \frac{F}{A_1}$$

defines the *shear stress* being applied to the sample.

- Seen from the front of the sample, the outline becomes distorted from a rectangle to a more general parallelogram. This shape change can be used to describe the *shear strain*  $\gamma$  caused by the *shear stress*:

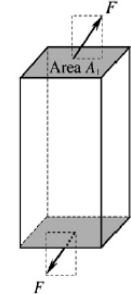
$$\gamma = \tan \theta$$

- If a force is applied obliquely (neither perpendicular nor parallel) to a pair of opposite faces of the sample, the ensuing stress can be resolved into normal and shear components, as can the resulting strain.



Shear stress

FIGURE I.1.3.1 Examples of a tensile (normal) stress, a shear stress, and a mixed stress with both normal and shear components, illustrating the relationship between load direction and surface orientation in each case. For the example of shear stress, the originally rectangular front face of the sample distorts to a parallelogram as shown, and the corresponding shear strain is defined as  $\tan \theta$ .



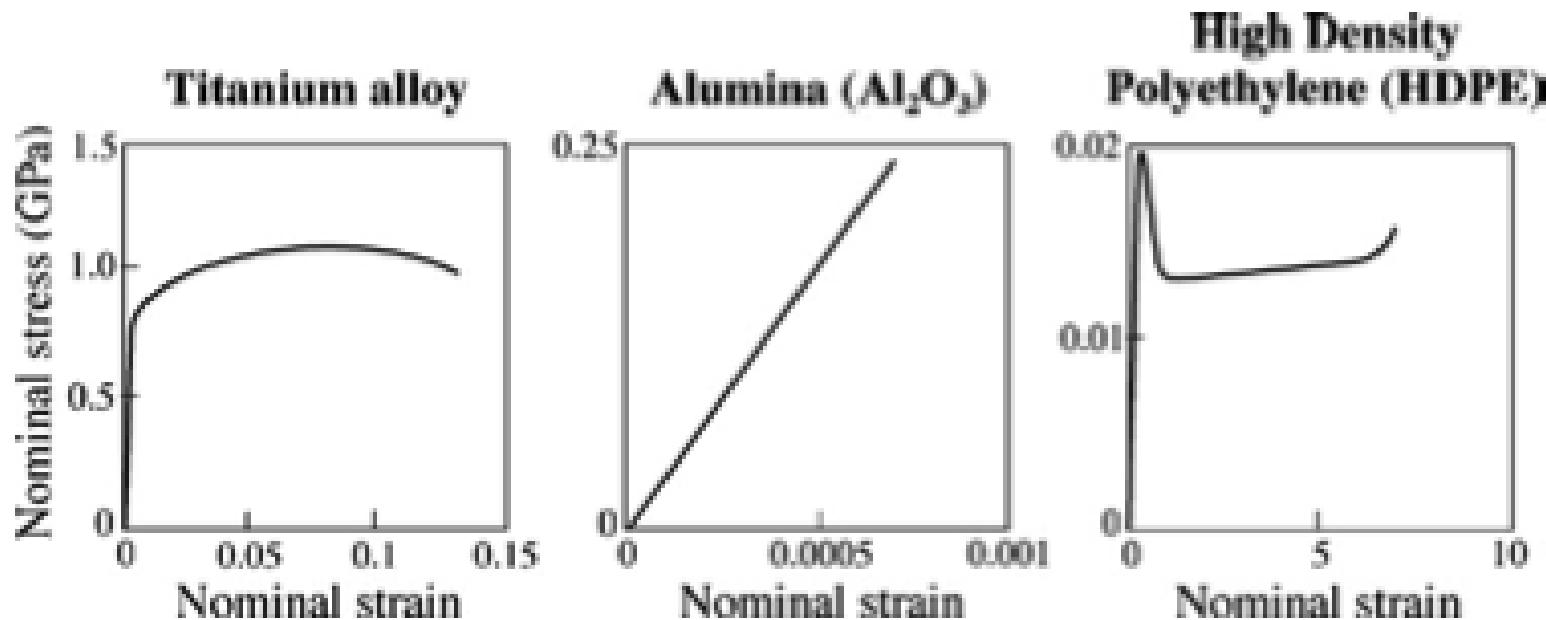
Stress with normal and shear components

FIGURE I.1.3.1 Examples of a tensile (normal) stress, a shear stress, and a mixed stress with both normal and shear components, illustrating the relationship between load direction and surface orientation in each case. For the example of shear stress, the originally rectangular front face of the sample distorts to a parallelogram as shown, and the corresponding shear strain is defined as  $\tan \theta$ .

- The relationship between stress and resultant strain is commonly summarized in a stress–strain plot, where by convention the stress is plotted vertically and the strain is plotted horizontally, with data being collected while the sample is deformed at a constant strain rate.

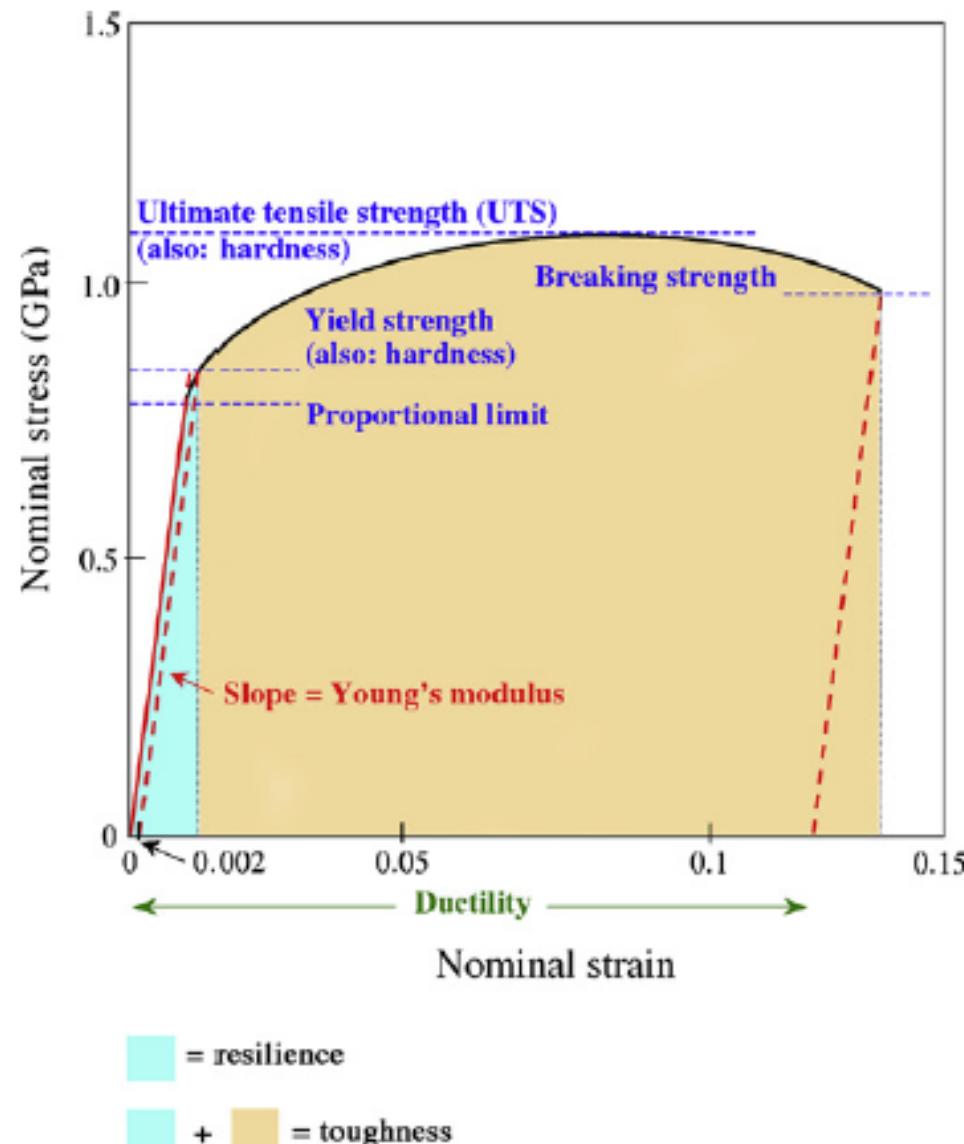
## BULK MECHANICAL PROPERTIES DETERMINED FROM STRESS–STRAIN PLOTS

- Simple stress–strain plots can be used to define and quantify several mechanical properties of a material.



**FIGURE I.1.3.2** Representative nominal stress versus nominal strain plots for three different classes of implantable material: ductile metal (titanium alloy; 6 wt% Al, 4 wt% V); ceramic (alumina); and crystalline polymer (high density polyethylene).

## # Schematic nominal stress versus nominal strain plot for a ductile metal (Titanium) #



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

# Elastic Deformation

## ➤ Elastic Constants

- The relationship between stress and strain is initially linear as the stress is increased from zero.
- In the case of bulk material, the constant of proportionality between tensile (or compressive) stress and strain is known as the *Young's modulus*, E:

$$\sigma = E \epsilon$$

- The equivalent constant of proportionality in the case of a shear stress being applied is known as the *shear modulus*, G:

$$\tau = G \gamma$$

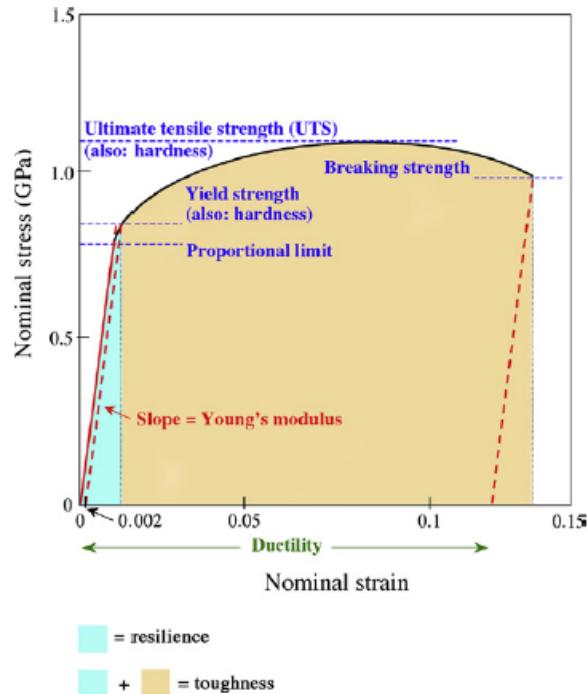
- Similarly, we can define a *bulk modulus*, K, as the constant of proportionality relating pressure to the volume change caused by that pressure:

$$P = -K \frac{V_2 - V_1}{V_1} = -K \frac{\Delta V}{V_1}$$

where a pressure P causes a reduction in volume from an initial volume  $V_1$  to a final volume  $V_2$ .

In all three cases, the definitions of the different types of elastic modulus assume that:

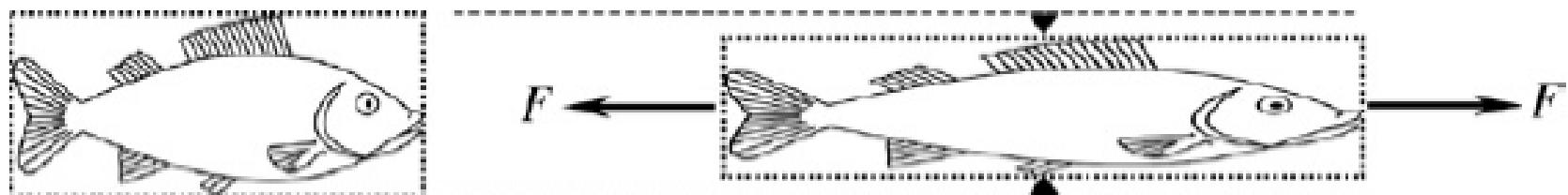
- the cause of deformation (tensile stress, shear stress or pressure) is sufficiently small and the response (tensile strain, shear strain or volume change) is *proportional* to the cause.
- It also ensures that the response is *reversible*; when the stress or pressure is removed, **the material returns to its original dimensions**.



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

- Another constant that is commonly encountered in the context of the elastic deformation of materials is *Poisson's ratio,  $\nu$* .
- when we pull on a piece of material, it usually becomes thinner as well as longer. Poisson's ratio is defined as:

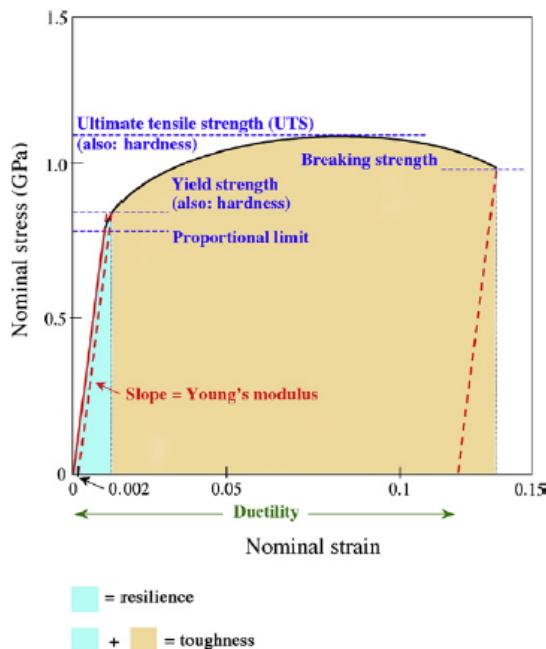
$$\nu = -\frac{\epsilon_{transverse}}{\epsilon_{longitudinal}}$$



**FIGURE I.1.3.4** Longitudinal elastic strain (in this case elongation) parallel to the direction of the applied load is accompanied by a transverse elastic strain (in this case contraction) perpendicular to the direction of the applied load. The negative of the ratio of transverse elastic strain to longitudinal elastic strain defines Poisson's ratio.

# Plastic Deformation

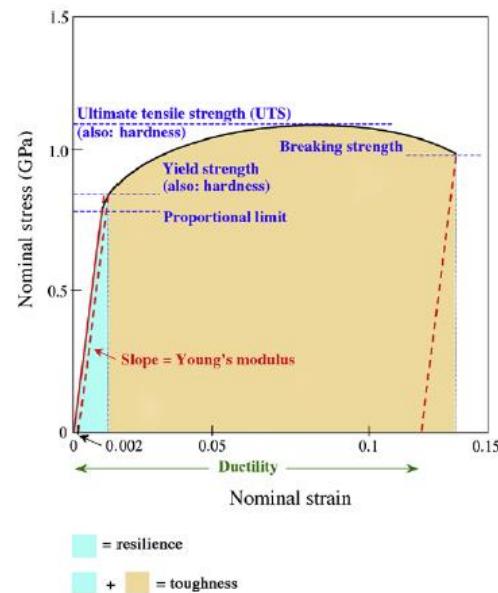
- As the stress on a material increases, a point may be reached where the response is no longer linear.
- There is a permanent (irreversible) deformation and deformation that is not recovered on removing the stress. Irreversible deformation is known as *plastic deformation*.
- It occurs commonly in metals and polymers, and rarely in ceramics.



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

## ➤ Yield Strength and Ductility.

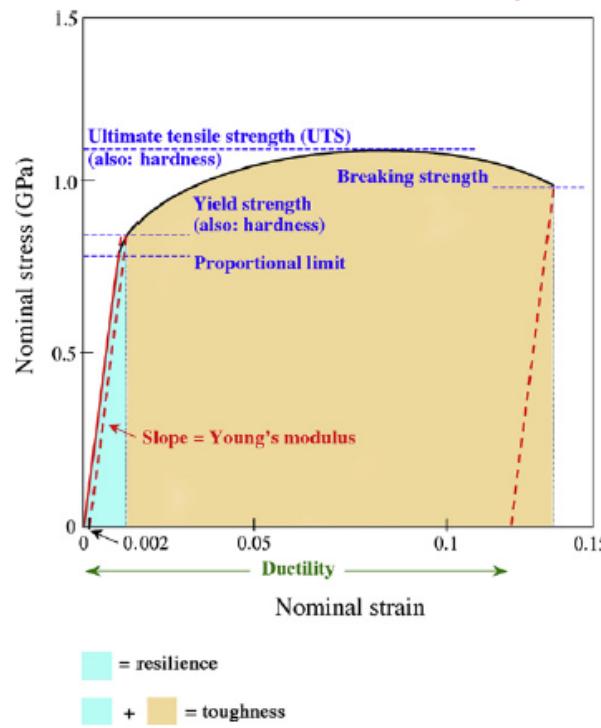
- The amount of plastic deformation associated with a given stress is found by drawing a line from the point of interest on the stress–strain curve, parallel to the initial linear segment of the curve, and marking the point where this constructed line intersects the horizontal (strain) axis.
- The horizontal distance from the origin to the point of intersection is a measure of the plastic strain. The value of plastic strain required to break the material defines the **ductility**
- The stress at which departure from a linear stress–strain relationship occurs is known as the **proportional limit**
- It is not always easy to ascertain the proportional limit accurately, and so a more practical determination of the condition for plastic deformation is provided by the **yield strength**, which is the stress at which *noticeable* plastic strain occurs.



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

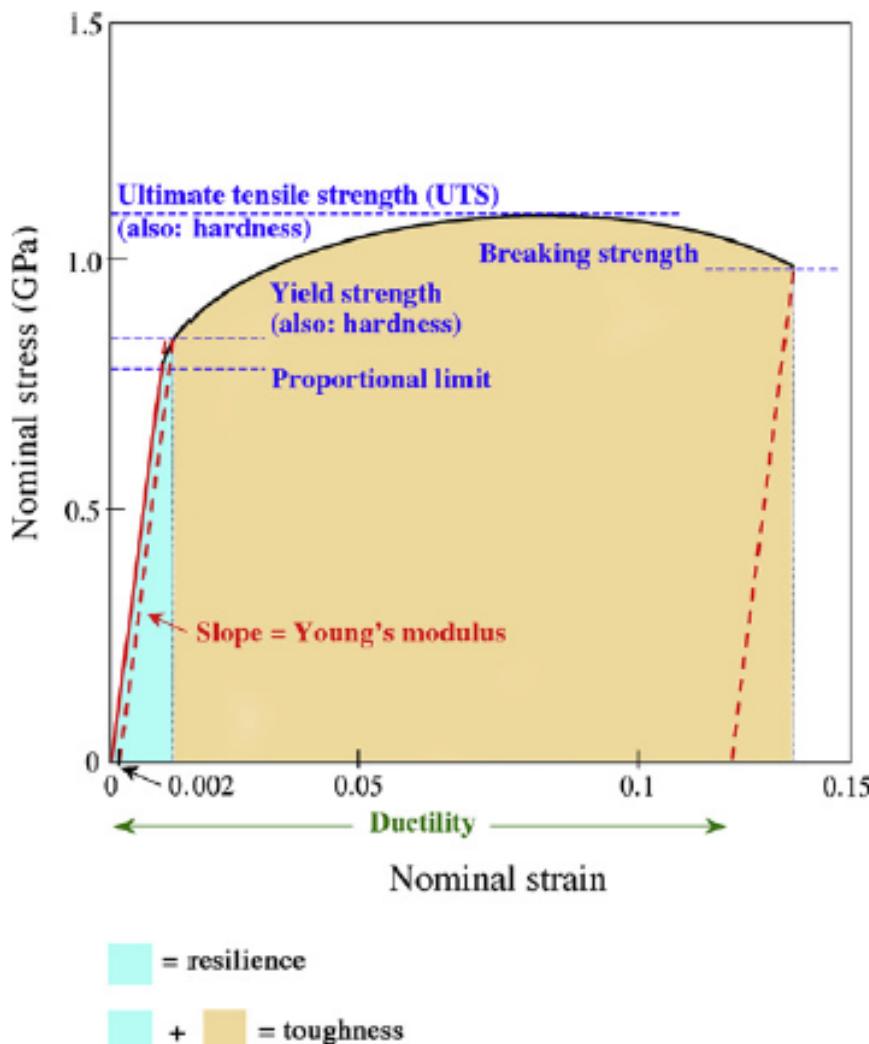
## ➤ Strength and Failure.

- For materials in which permanent deformation (and the attendant shape change) is acceptable, failure may be deemed to occur when a noticeable “neck” (constriction) develops in the material.
- The effect of the neck is to concentrate the load on a smaller area; therefore, the load that can be supported by the sample is decreased.
- On a nominal stress versus nominal strain plot, the stress required for additional deformation decreases.
- Therefore, the onset of necking corresponds to a maximum in the nominal stress versus nominal strain plot, defining the ***ultimate tensile strength (UTS)*** or simply the ***tensile strength*** of the material.



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

- On both nominal stress versus nominal strain and true stress versus true strain plots, a ***breaking strength*** can be defined at the point where the material actually breaks.



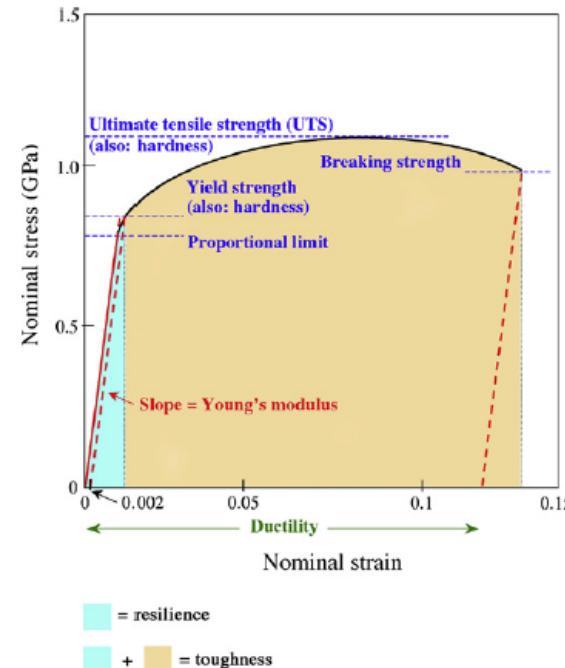
**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

## ➤ Hardness

- hardness provides a measure of how successfully a material resists plastic deformation, which in turn is characterized by both yield strength and tensile strength.
- It is therefore possible to empirically develop calibration charts that can be used to convert hardness measurements into both yield strength and tensile strength values

## ➤ Resilience

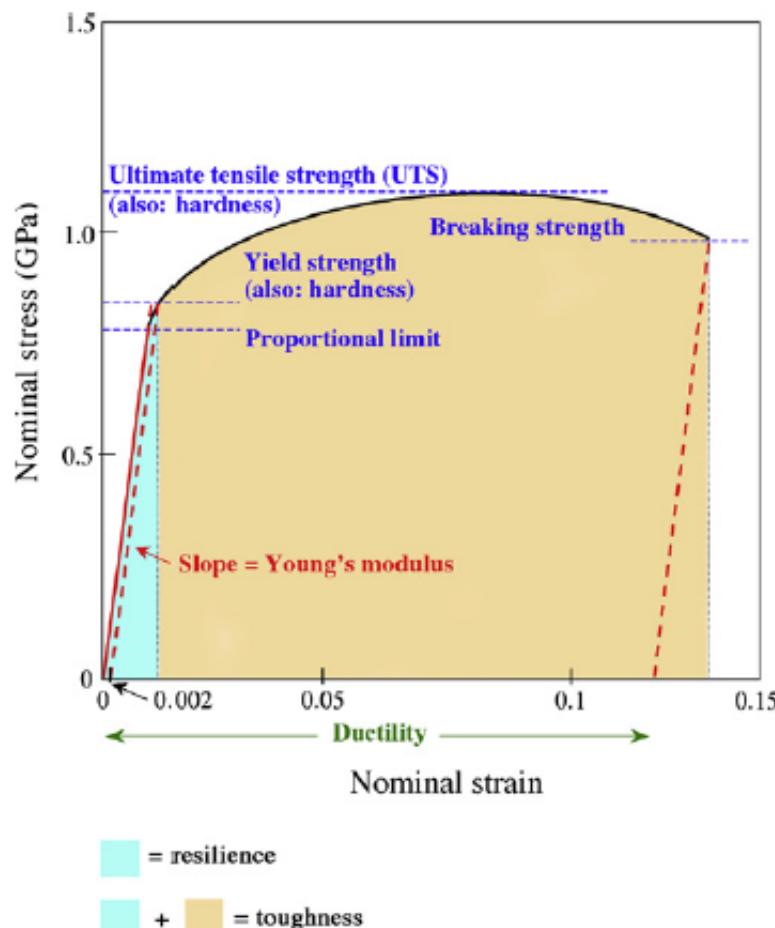
- *Resilience* is a measure of the *elastic energy* that can be stored in a unit volume of stressed material.
- It corresponds to the area underneath a stress versus strain plot, extending from zero strain up to the strain at which the sample yields



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

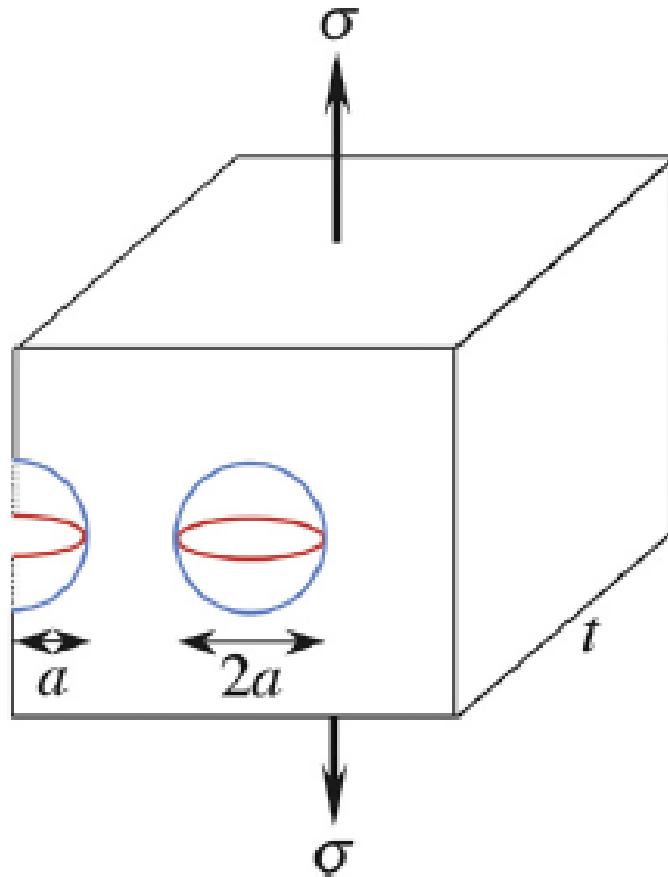
## ➤ Toughness and Fracture Toughness

- **Toughness** is a measure of the energy required to deform a unit volume of material to its breaking point. Therefore, the definition is similar to that used for resilience, except that we now take into account the entire area under the stress versus strain plot, extending from zero strain up to the strain at which the sample breaks.



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

- **Fracture toughness** is a measure of how successfully a material resists the propagation of cracks.



**FIGURE I.1.3.8** Sample geometry used in defining the fracture toughness of a material. Examples of both a surface crack and an internal crack are shown. The cracks are assumed to be cylindrical (blue circles) for ease of mathematical description; a flattened profile (red ellipses) would be more realistic.

## OTHER BULK PROPERTIES

- The bulk properties of a material are not limited to performance in mechanical tests. Other types of bulk properties that may have to be taken into account during the selection of a biomaterial include:
  - ✓ thermal properties
  - ✓ optical properties
  - ✓ electrical properties
  - ✓ magnetic properties

### **Thermal Properties**

- Thermal conductivity becomes a significant consideration if an implanted material contributes to an unnatural flow of heat through the surrounding tissue.
  - ✧ For example, metal rods selected for their combination of stiffness, strength, fracture toughness, and biocompatibility can promote heat loss and cause the patient to feel colder than normal.

## Optical Properties

- In the context of biomaterials, the most significant bulk optical properties are color, refractive index, and transparency; all three are important in the selection of materials for intraocular lenses or fluids.
  - The color of a transparent material is controlled by composition, and therefore demands a high degree of quality control to avoid impurities that could adversely affect color
  - the effectiveness of a material as a lens is directly related to its refractive index
  - *Transparency* is a qualitative term that describes the ability of a material to transmit light without attenuating (absorbing or scattering) it

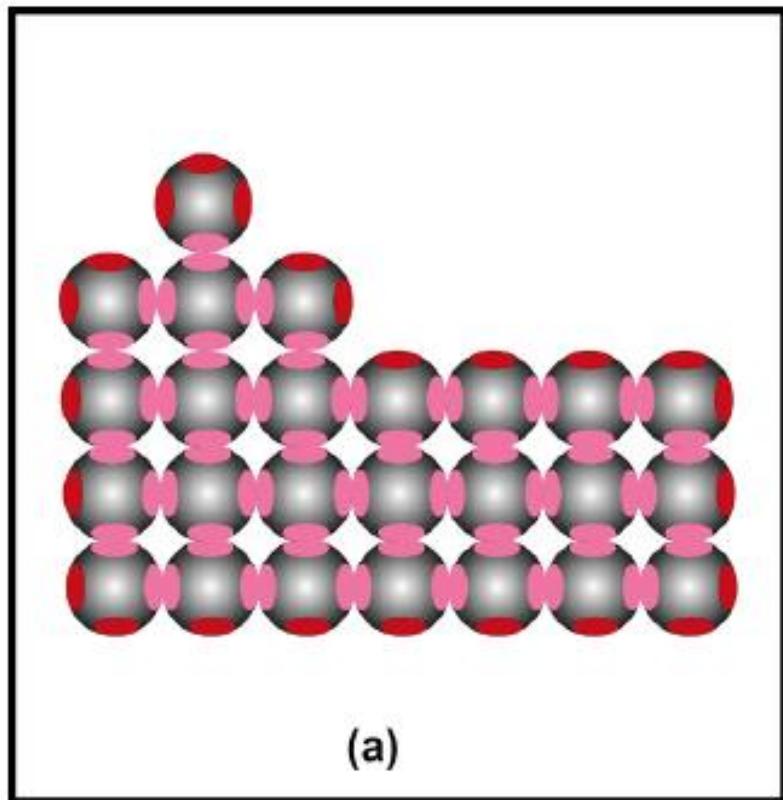
# SURFACE PROPERTIES AND SURFACE CHARACTERIZATION OF BIOMATERIALS

- Biomaterials “show” to the world (and the biological environment) only surfaces. Atoms and molecules make up the outermost surface of a biomaterial (the interface between the material and the world).
- The success or failure of many biomaterials depends on the physical and chemical characteristics of their surface.
- Surface properties dictate interactions between a material and its environment, and thus indicate whether a permanently implanted material will be tolerated or rejected

Atoms and molecules that reside at the surface of a biomaterial have special reactivity and direct biological response.

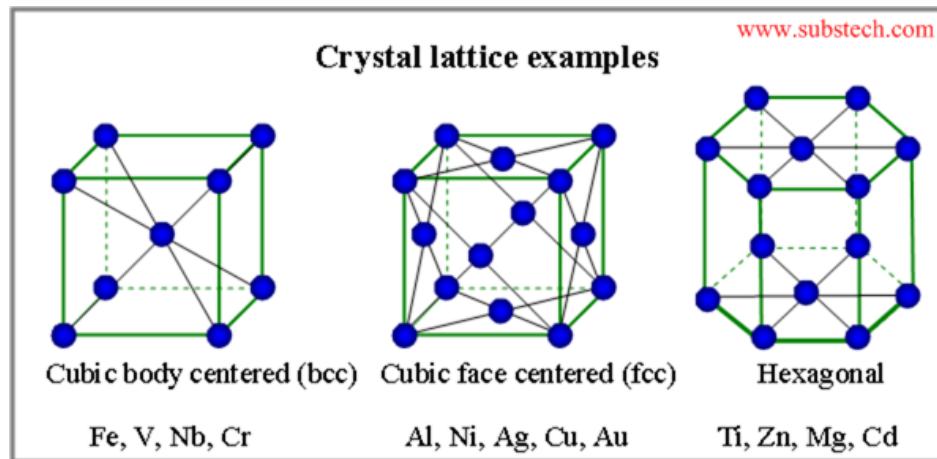
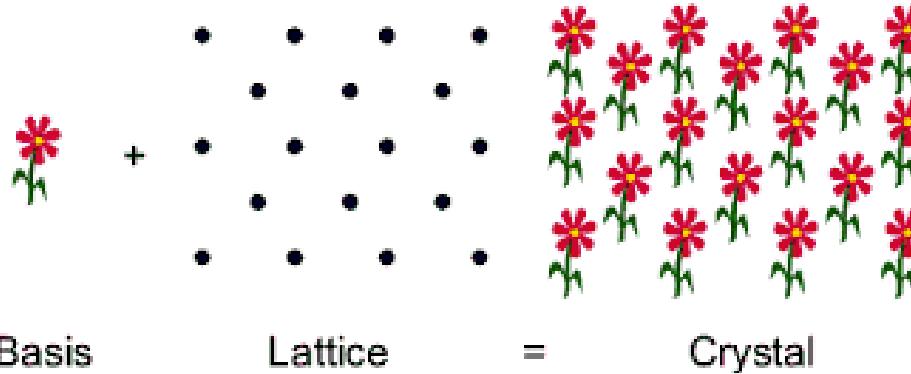
## General Surface Considerations

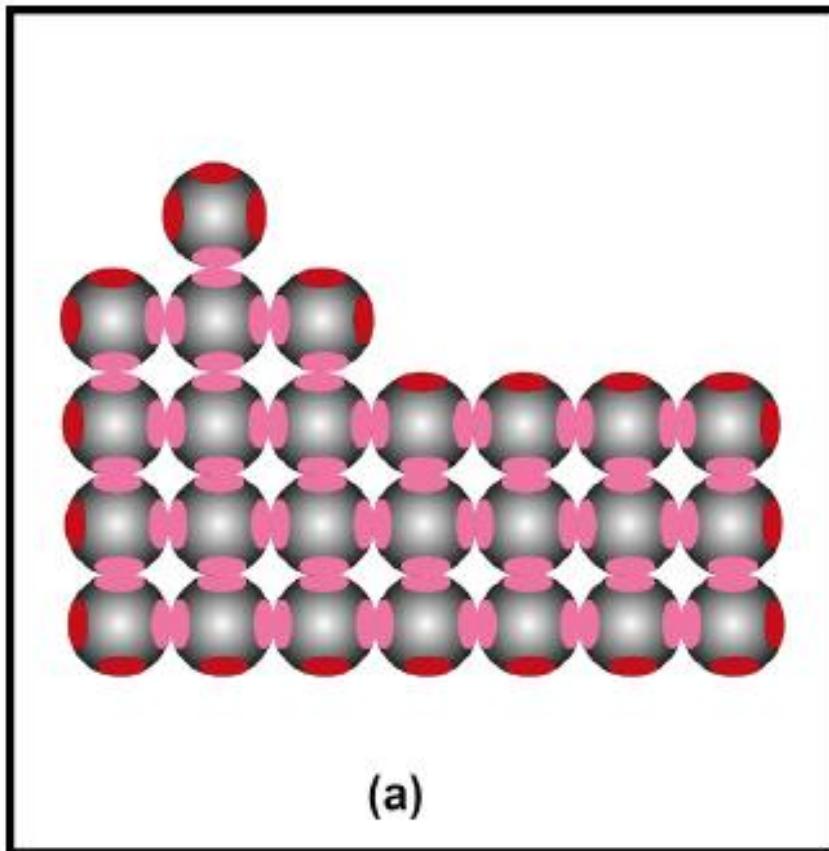
- A two-dimensional representation of a crystal lattice suggesting bonding orbitals (red or pink ovals).



# Crystal structure = lattice + basis

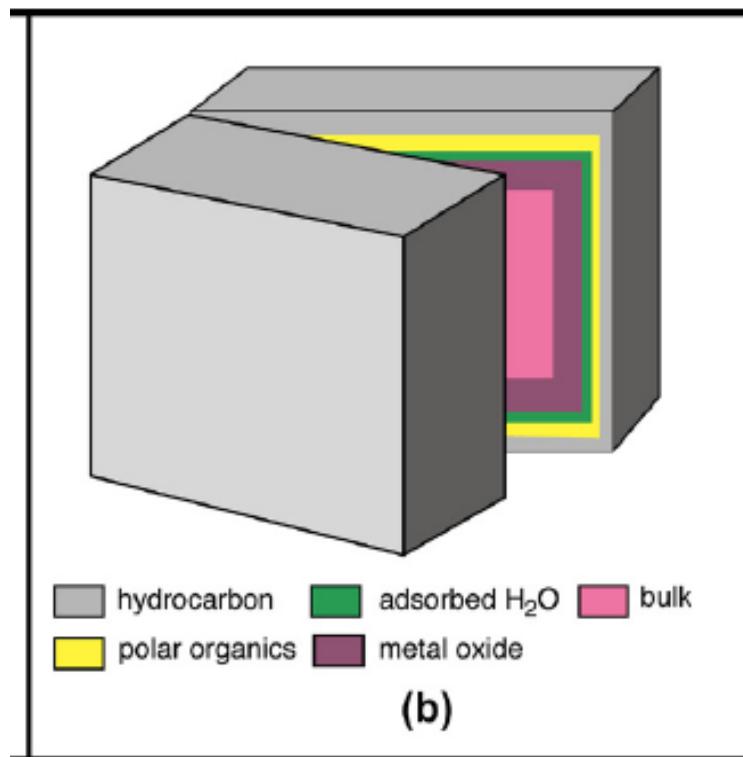
- A lattice is a set of regular and periodic geometrical points in space
- A basis is a collection of atoms or molecules at a lattice point
- A crystal is a collection of atoms or molecules arranged at all the lattice points.



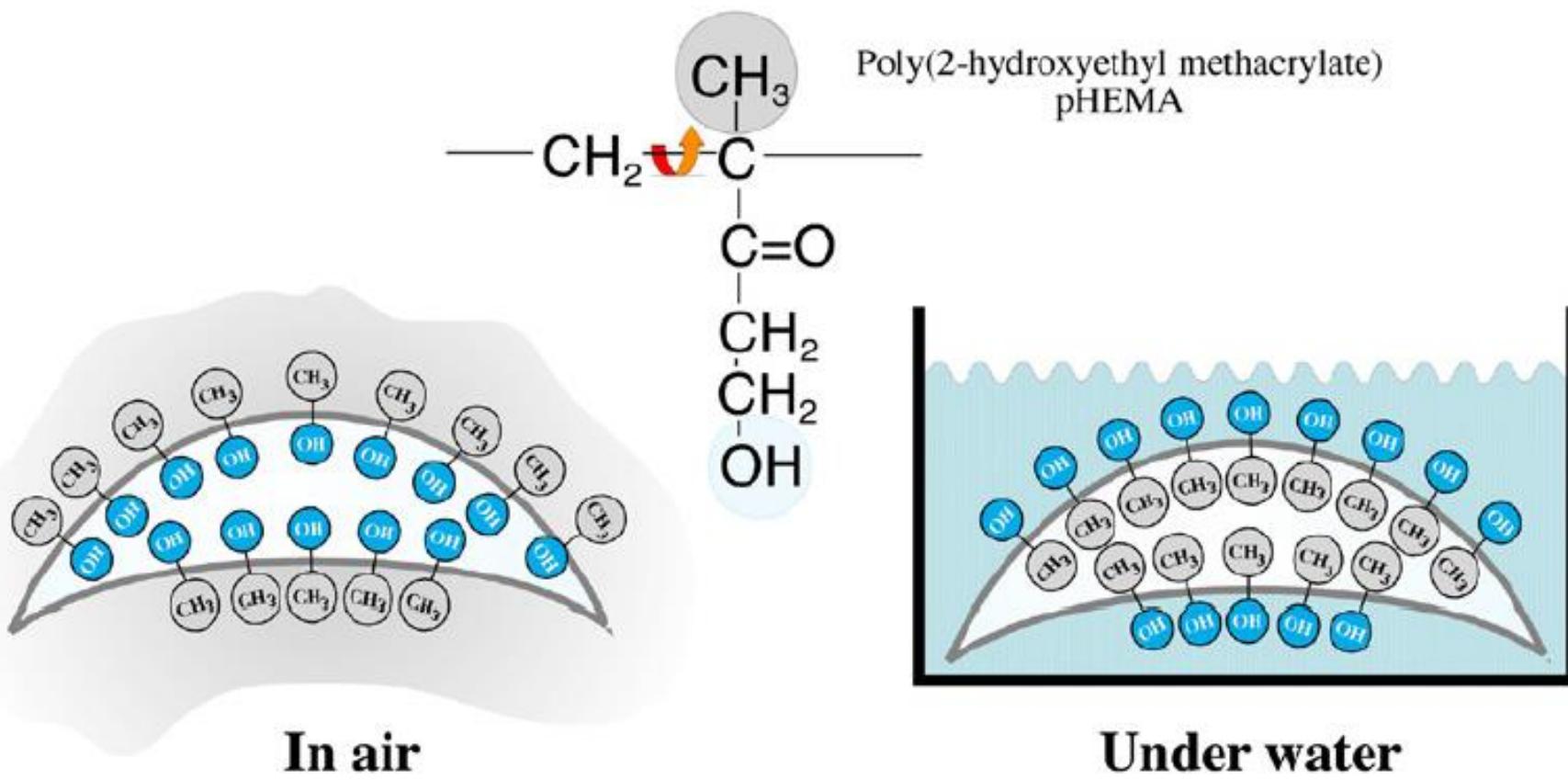


- For atoms in the center (bulk) of the crystal (pink ovals), all binding sites have associations with those of other atoms (sharing electrons).
- At planar exterior surfaces, one of the bonding sites is unfulfilled (red oval).
- At corners, two bonding sites are unfulfilled.
- The single atom on top of the crystal (an adatom) has three unfulfilled valencies.

- If we cleave a “real-world” material (a block of metal from an orthopedic device, for example), we should find
  - hydrocarbon on the outermost layer (perhaps 3 nm, surface energy  $\sim$ 22 ergs/cm $^2$ ),
  - polar organic molecules (>1 nm, surface energy  $\sim$ 45 ergs/cm $^2$ )
  - adsorbed water (<1 nm, surface energy  $\sim$ 72 ergs/cm $^2$ )
  - metal oxide (approximately 5 nm, surface energy  $\sim$ 200 ergs/cm $^2$ )
  - the uniform bulk interior (surface energy  $\sim$ 1000 ergs/cm $^2$ ).



- The movement of atoms and molecules near the surface in response to the outside environment is often highly significant.
- In response to a hydrophobic environment (e.g., air), more hydrophobic (lower energy) components may migrate to the surface of a material – a process that reduces interfacial energy



**FIGURE I.1.5.2** Many materials can undergo a reversal of surface structure when transferred from air into a water environment. In this schematic illustration, a hydroxylated polymer (for example a pHEMA contact lens) exhibits a surface rich in methyl groups (from the polymer chain backbone) in air, and a surface rich in hydroxyl groups under water. This has been observed experimentally, see Ratner et al. (1978). *J Appl Polym Sci*, 22, 643; Chen et al. (1999). *J Am Chem Soc*, 121(2); 446.

## **Five Points About Surfaces**

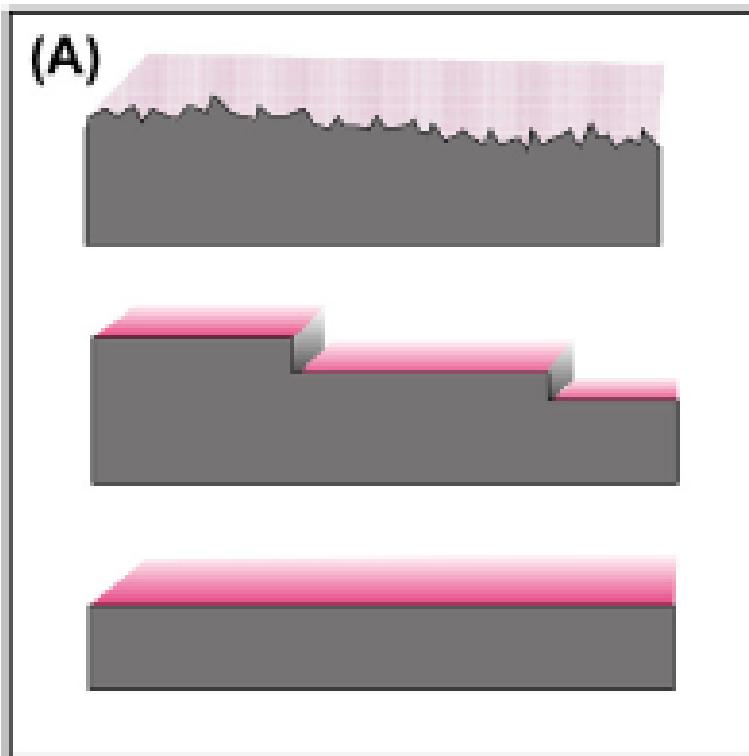
1. Surfaces have unique reactivity
2. The surface is inevitably different from the bulk
3. The mass of material that makes up the surface zone is very small
4. Surfaces readily contaminate
5. Surface molecules can exhibit considerable mobility.

### **Definition**

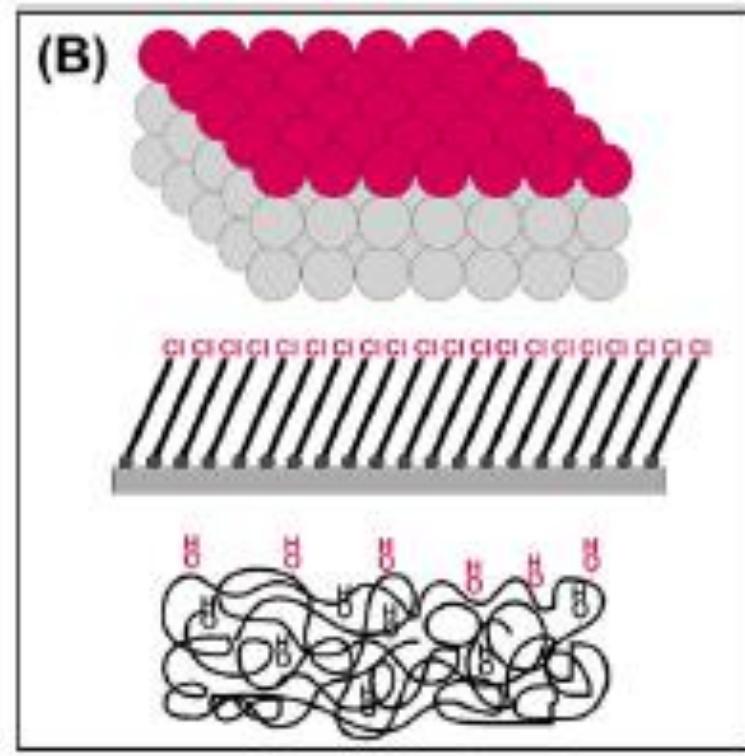
- When we say “surface,” a question that immediately comes to mind is: “how deep into the material does it extend?”
- **the surface is the zone where the structure and composition differs from the average (bulk) composition and structure.**

## What Surface Properties are we Interested in?

- A surface is fully described by many parameters

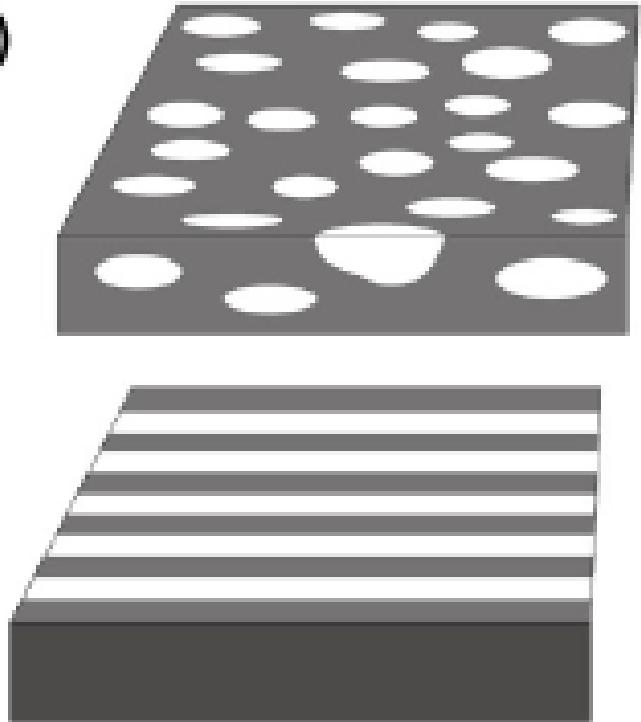


(A) Surfaces can be rough, stepped or smooth.



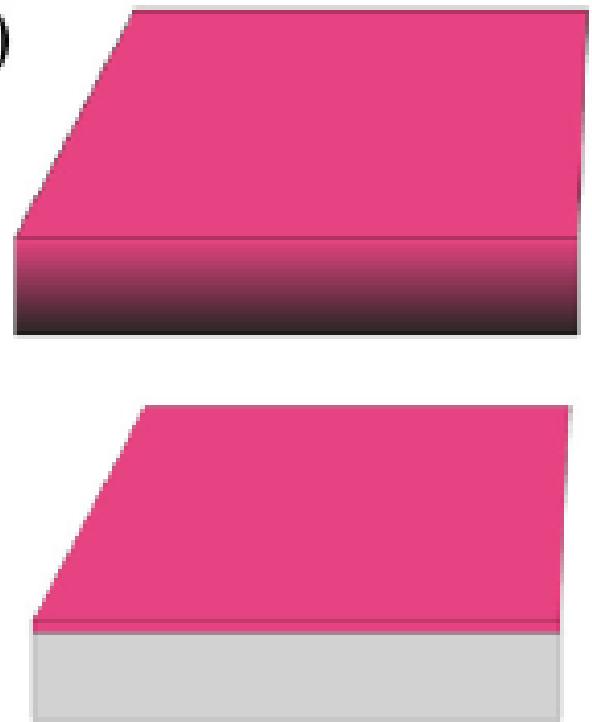
(B) Surfaces can be comprised of different chemistries

(C)



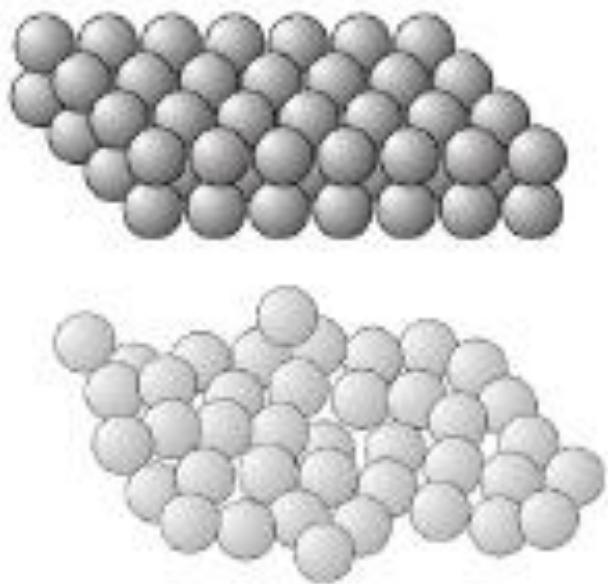
(C) Surfaces may be structurally or compositionally inhomogeneous in the plane of the surface such as phase-separated domains or micro-contact printed lanes.

(D)

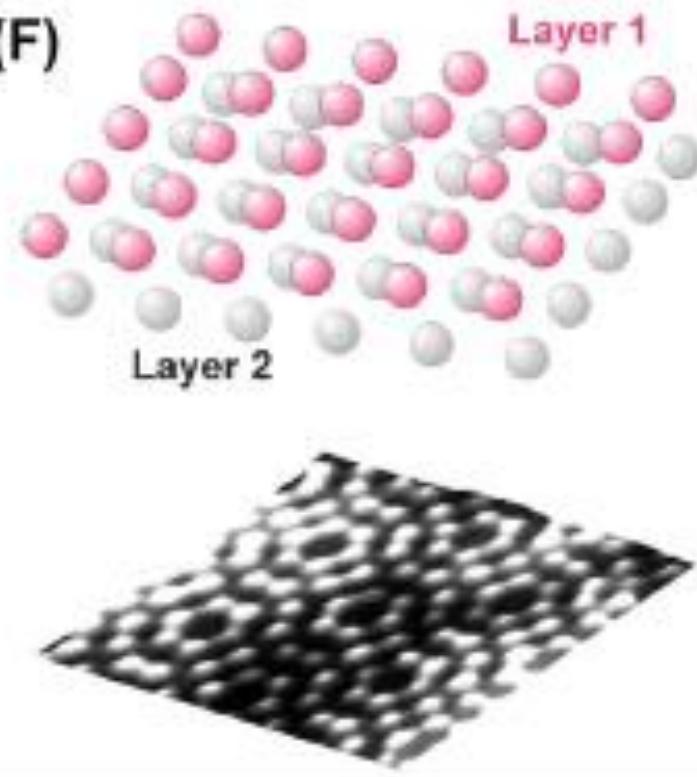


(D) Surfaces may be inhomogeneous with depth into the specimen or simply overlaid with a thin film.

(E)



(F)



(E) Surfaces may be highly crystalline or disordered.

(F) Crystalline surfaces are found with many organizations such as a silicon (100) unreconstructed surface or a silicon (111) (7 × 7) reconstructed surface.

- The more of these parameters we measure, the more we can piece together a complete description of the surface.
- A complete characterization requires a series of techniques to examine the many facets that contribute to the surface properties.
- Unfortunately, we cannot yet specify which parameters are most important for understanding specific biological responses to surfaces.
- Studies have been published on the importance of
  - roughness
  - patterns
  - wettability
  - surface mobility
  - chemical composition
  - electrical charge
  - crystallinity
  - modulus
  - Heterogeneity

on biological reaction.

- We cannot be certain which surface factors are predominant in each situation so variable or variables must be independently measured and correlated.
- For this purpose; we use surface analysis techniques

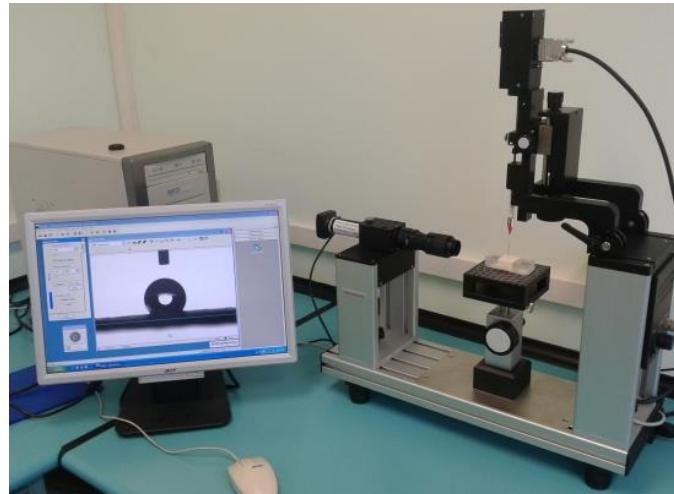
# SURFACE ANALYSIS TECHNIQUES: PRINCIPLES AND METHODS

TABLE I.1.5.1

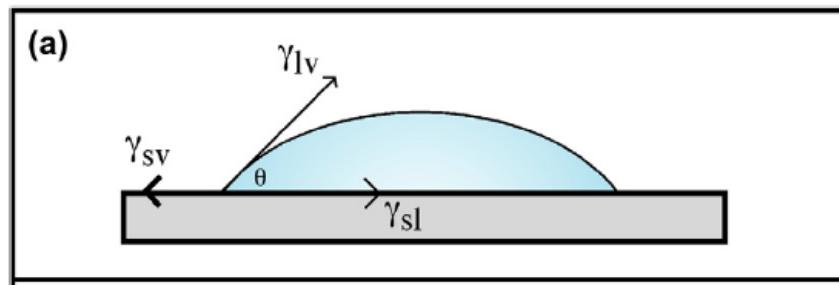
Common Methods to Characterize Biomaterial Surfaces

Method	Principle	Depth Analyzed	Spatial Resolution	Analytical Sensitivity	Cost
Contact Angles	Liquid wetting of surfaces is used to estimate the energy of surfaces	3–20 Å	1 mm	Low or high depending on the chemistry	\$
ESCA (XPS)	X-rays induce the emission of electrons of characteristic energy	10–250 Å	10–150 µm	0.1 atom %	\$\$\$
Auger Electron Spectroscopy*	A focused electron beam stimulates the emission of Auger electrons	50–100 Å	100 Å	0.1 atom %	\$\$\$
SIMS	Ion bombardment sputters secondary ions from the surface	10 Å–1 µm**	100 Å	Very high	\$\$\$
FTIR-ATR	IR radiation is adsorbed and excites molecular vibrations	1–5 µm	10 µm	1 mole %	\$\$
STM	Measurement of the quantum tunneling current between a metal tip and a conductive surface	5 Å	1 Å	single atoms	\$\$
SEM	Secondary electron emission induced by a focused electron beam is spatially imaged	5 Å	40 Å typically	High, but not quantitative	\$\$

## ➤ Contact Angle Method



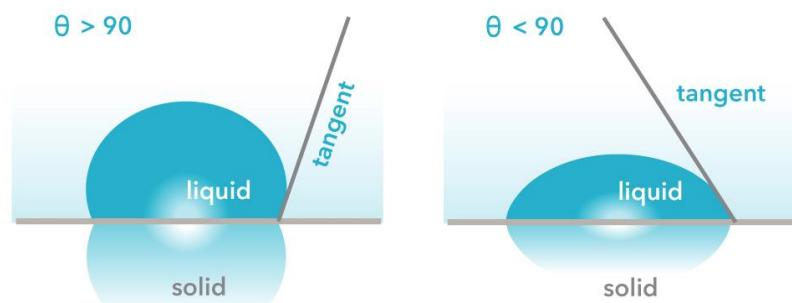
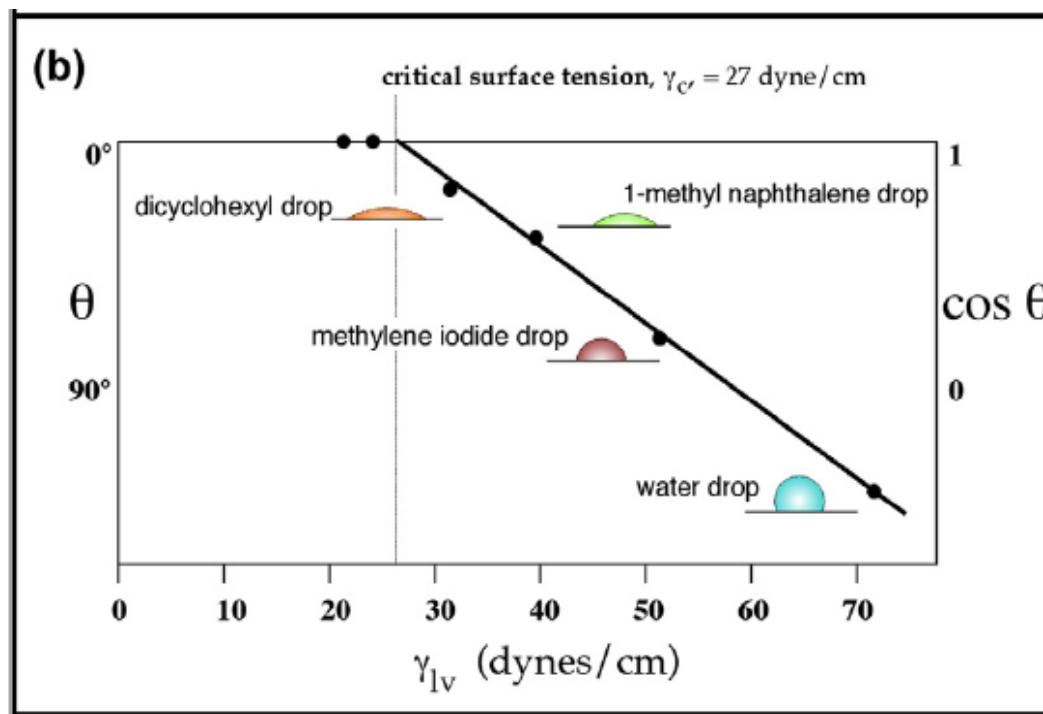
- A drop of liquid sitting on a solid surface represents a simple, but potentially powerful, method to probe surface properties.
- The phenomenon of the contact angle can be explained as a balance between the force with which the molecules of the drop liquid are being attracted to each other ( a cohesive force) and the attraction of the liquid molecules for the surface (an adhesive force).
- An equilibrium is established between surface tension forces contracting a liquid drop to a spherical shape and forces interacting the drop with the surface.

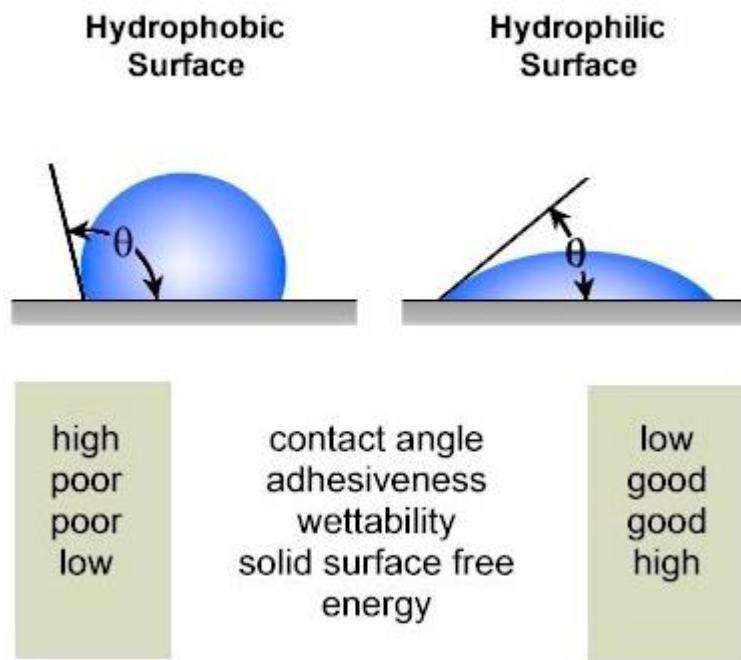


$$\gamma_{sv} = \gamma_{sl} + \gamma_{lv} \cos\theta$$

The force balance between the liquid–vapor surface tension ( $\gamma_{lv}$ ) of a liquid drop and the interfacial tension between a solid and the drop ( $\gamma_{sl}$ ), manifested through the contact angle ( $\theta$ ) of the drop can be used to quantitatively characterize the surface–vapor interfacial tension ( $\gamma_{sv}$ ).

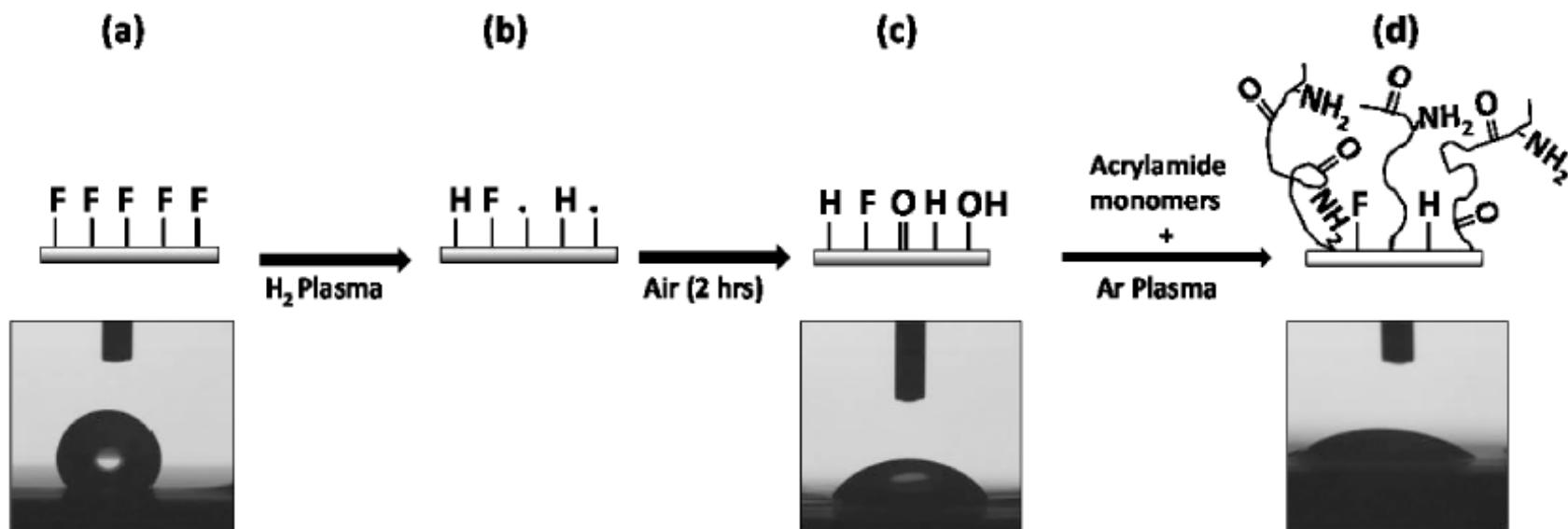
- The Zisman method permits a critical surface tension value, an approximation to the solid surface tension, to be measured.
- Drops of liquids of different surface tensions are placed on the solid, and the contact angles of the drops are measured.





*S. Onder et al. / Journal of Biomaterials Science 22 (2011) 1443–1457*

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- Some critical surface tensions for common materials

**TABLE I.1.5.2**

**Critical Surface Tension Values  
for Common Polymeric Materials  
Calculated from Contact Angle  
Measurements**

Material	Critical Surface Tension (dynes/cm)
Polytetrafluoroethylene	19
Poly(dimethyl siloxane)	24
Poly(vinylidene fluoride)	25
Poly(vinyl fluoride)	28
Polyethylene	31
Polystyrene	33
Poly(2-hydroxyethyl methacrylate)	37
Poly(vinyl alcohol)	37
Poly(methyl methacrylate)	39
Poly(vinyl chloride)	39
Polycaproamide (nylon 6)	42
Poly(ethylene oxide)-diol	43
Poly(ethylene terephthalate)	43
Polyacrylonitrile	50

Contact angles directly measure surface wettability, and indirectly probe surface energy, roughness, heterogeneity, contamination, and molecular mobility.

- Contact angle measurements provide a “first line” characterization of materials and can be performed in any laboratory.
- Contact angle measurements provide unique insight into how the surface will interact with the external world. However, in performing such measurements, a number of concerns must be addressed to obtain meaningful data

**TABLE I.1.5.3**

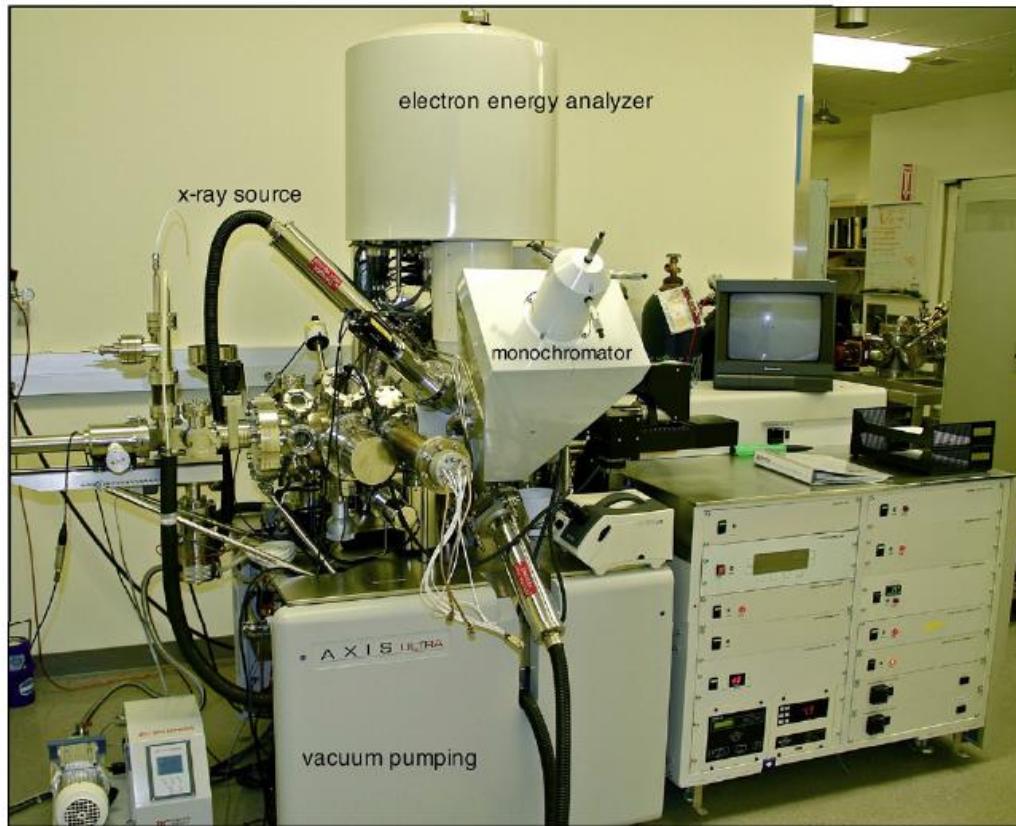
**Concerns in Contact Angle Measurement**

- The measurement is operator dependent (for manual, goniometer instruments)
- Surface roughness influences the results
- Surface heterogeneity influences the results
- The liquids used are easily contaminated (typically reducing their  $\gamma_{lv}$ )
- Liquid evaporation and temperature changes can impact measurement
- The liquids used can reorient the surface structure
- The liquids used can absorb into the surface, leading to swelling
- The liquids used can dissolve the surface
- Few sample geometries are appropriate for contact angle measurement
- Information on surface structure must be inferred from the data obtained

## ➤ Electron Spectroscopy for Chemical Analysis

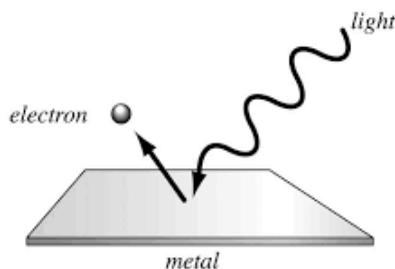
- Electron spectroscopy for chemical analysis (ESCA) provides a comprehensive qualitative and quantitative overview of a surface
- In contrast to the contact angle technique, ESCA requires complex, expensive apparatus and demands considerable training to perform the measurements

(a)



**FIGURE I.1.5.6 (a)** Photograph of a contemporary ESCA instrument (photo by Kratos Analytical Corp.).

- The ESCA method (also called X-ray photoelectron spectroscopy, XPS) is based upon the photoelectric effect, properly described by Einstein in 1905.



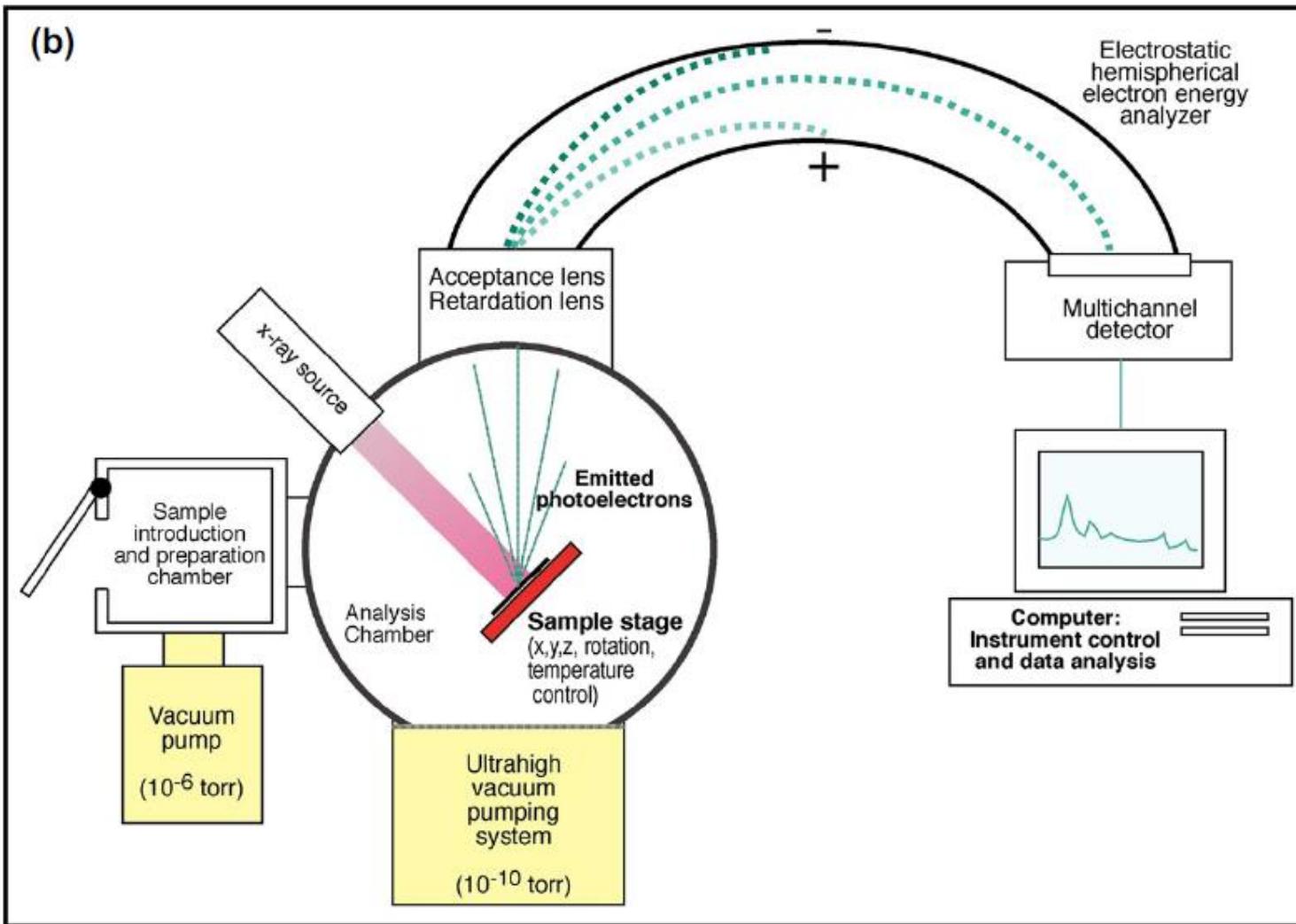
- X-rays are focused upon a specimen. The interaction of the X-rays with the atoms in the specimen causes the emission of core level (inner shell) electrons.
- The energy of these electrons is measured and their values provide information about the nature and environment of the atom or atoms from which they came.
- The basic energy balance describing this process is given by the relationship:

$$BE = h\nu - KE$$

where

- BE is the energy binding the electron to an atom (the value desired)
- KE is the kinetic energy of the emitted electron (the value measured in the ESCA spectrometer)
- $h\nu$  is the energy of the X-rays, a known value.

(b)



(b) Schematic diagram of a monochromatized ESCA instrument.

- types of information about the nature of a surface that can be obtained by using ESCA

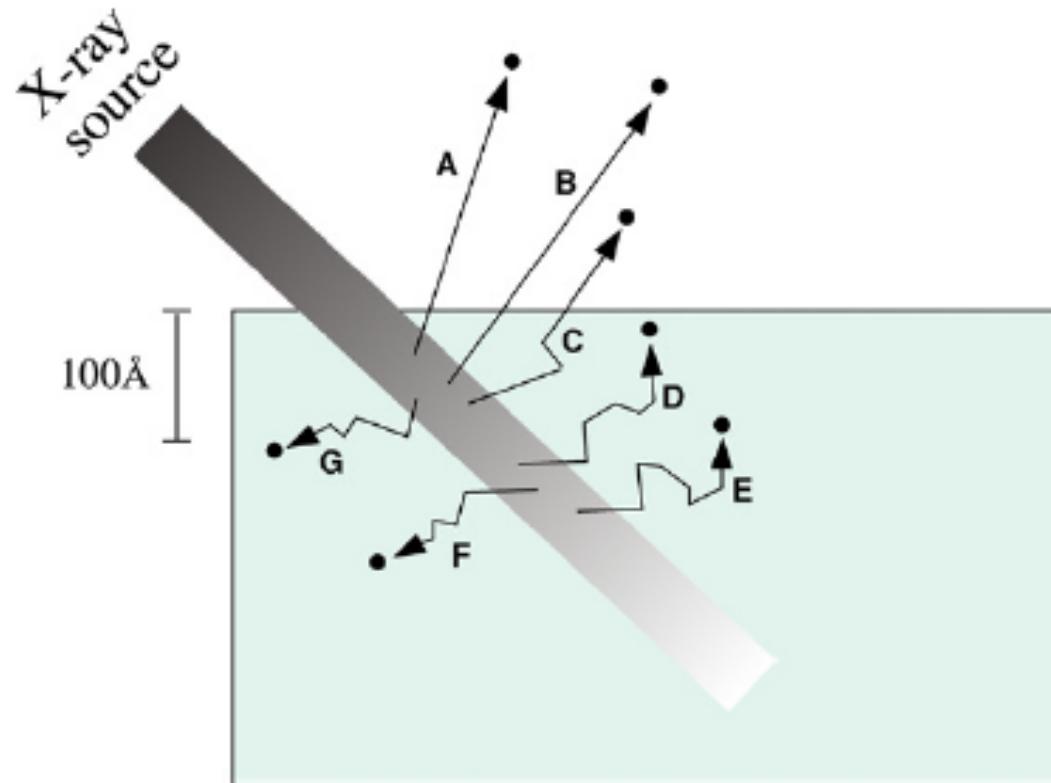
**TABLE I.1.5.4** **Information Derived From an ESCA Experiment**

**In the outermost 100 Å of a surface, ESCA can provide:**

- Identification of all elements (except H and He) present at concentrations >0.1 atomic %
- Semiquantitative determination of the approximate elemental surface composition ( $\pm 10\%$ )
- Information about the molecular environment (oxidation state, bonding atoms, etc.)
- Information about aromatic or unsaturated structures from shake-up  $\pi^* \leftarrow \pi$  transitions
- Identification of organic groups using derivatization reactions
- Nondestructive elemental depth profiles 100 Å into the sample and surface heterogeneity assessment using angular-dependent ESCA studies and photoelectrons with differing escape depths
- Destructive elemental depth profiles several thousand angstroms into the sample using argon etching (for inorganics)
- Lateral variations in surface composition (spatial resolution 8–150  $\mu\text{m}$ , depending upon the instrument)
- “Fingerprinting” of materials using valence band spectra and identification of bonding orbitals
- Studies on hydrated (frozen) surfaces

ESCA analyzes to approximately 10 nm and gives information on elements present, their concentrations and their bonding environments.

- surface sensitivity of ESCA



**FIGURE I.1.5.7** ESCA is a surface-sensitive method. Although the X-ray beam can penetrate deeply into a specimen, electrons emitted deep in the specimen (D, E, F, G) will lose their energy in inelastic collisions and never emerge from the surface. Only those electrons emitted near the surface that lose no energy (A, B) will contribute to the ESCA signal used analytically. Electrons that lose some energy, but still have sufficient energy to emerge from the surface (C) contribute to the background signal.

- ESCA has many advantages, and a few disadvantages, for studying biomaterials

➤ The advantages include

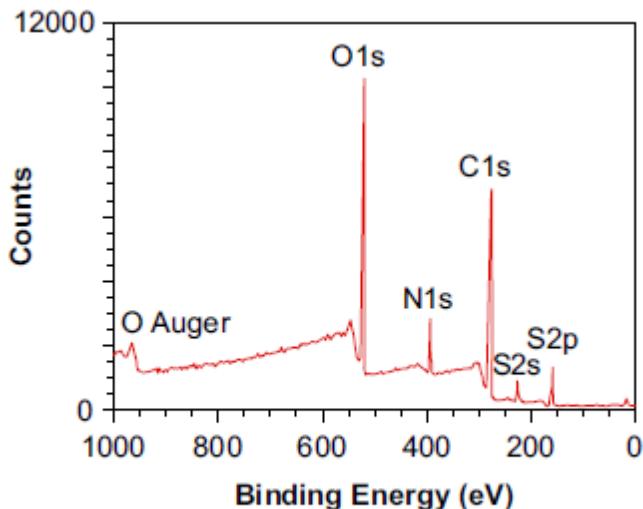
- high information content ,
- surface localization of the measurement (outermost 8–10 nm),
- speed of analysis,
- the ability to analyze most samples with no special specimen preparation.
  - This is particularly important since biomedical devices (or parts of devices) can often be inserted, as fabricated and sterilized, directly in the analysis chamber for study.

➤ The disadvantages include

- the need for vacuum compatibility (i.e., no outgassing of volatile components)
- the vacuum environment and its impact on the specimen (particularly for hydrated specimens)
- the possibility of sample damage by X-rays if long analysis times are used
- the need for experienced operators
- the cost associated with this complex instrumentation

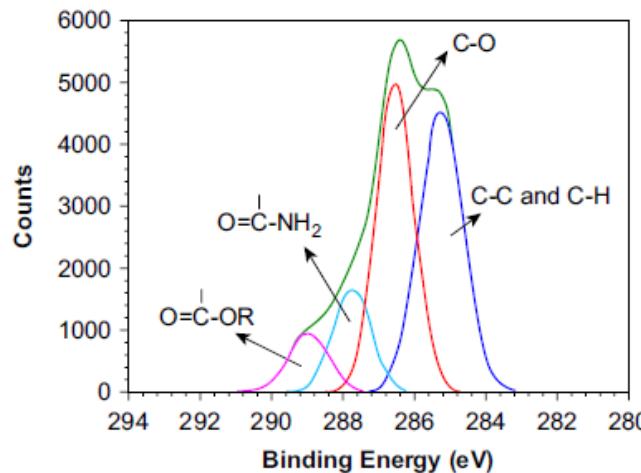
- The use of ESCA ; a brief example.

First, a wide scan is made in which the energies of all emitted electrons over a 1000 eV range are detected



**FIGURE I.1.5.8** ESCA wide scan of a surface-modified poly(methyl methacrylate) ophthalmologic device.

Then, narrow scans are made in which each of the elements detected in the wide scan is examined in higher resolution



**FIGURE I.1.5.9** The carbon 1s narrow scan ESCA spectrum of a surface-modified poly(methyl methacrylate) ophthalmologic device. Narrow scan spectra can be generated for each element seen in low energy resolution mode in Figure I.1.5.8.

- From the wide scan, we learn that the specimen contains carbon, oxygen, nitrogen, and sulfur. The presence of sulfur and nitrogen is unexpected for PMMA. We can calculate atomic percentage composition from the wide scan spectral data. The sample surface contains 58.2% carbon, 27.7% oxygen, 9.5% nitrogen, and 4.5% sulfur.
- The narrow scan for the carbon region (C1s spectrum) suggests four classes of compounds: hydrocarbons; carbons singly bonded to oxygen (the predominant species); carbons in amide-like molecular environments; and carbons in carboxylic acid or ester environments

## Secondary Ion Mass Spectrometry

- SIMS produces a mass spectrum of the outermost 1–2 nm of a surface.
- Like ESCA, it requires complex instrumentation and an ultrahigh vacuum chamber for the analysis. However, it provides unique information that is complementary to ESCA, and greatly aids in understanding surface composition.
- Some of the analytical capabilities of SIMS are

TABLE I.1.5.5

Analytical Capabilities of SIMS

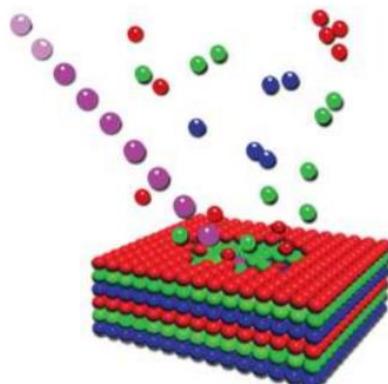
	Static SIMS	Dynamic SIMS
Identify hydrogen and deuterium	✓	✓
Identify other elements (often must be inferred from the data)	✓	✓
Suggest molecular structures (inferred from the data)	✓	—
Observe extremely high mass fragments (proteins, polymers)	✓	—
Detection of extremely low concentrations	✓	✓
Depth profile to 1 $\mu\text{m}$ into the sample	*	✓
Observe the outermost 1–2 atomic layers	✓	—
High spatial resolution (features as small as approximately 400 $\text{\AA}$ )	✓	✓
Semiquantitative analysis (for limited sets of specimens)	✓	—
Useful for polymers	✓	—
Useful for inorganics (metals, ceramics, etc.)	✓	✓
Useful for powders, films, fibers, etc.	✓	✓

\*Cluster ion sources allow depth profiling with static-SIMS-like information content.

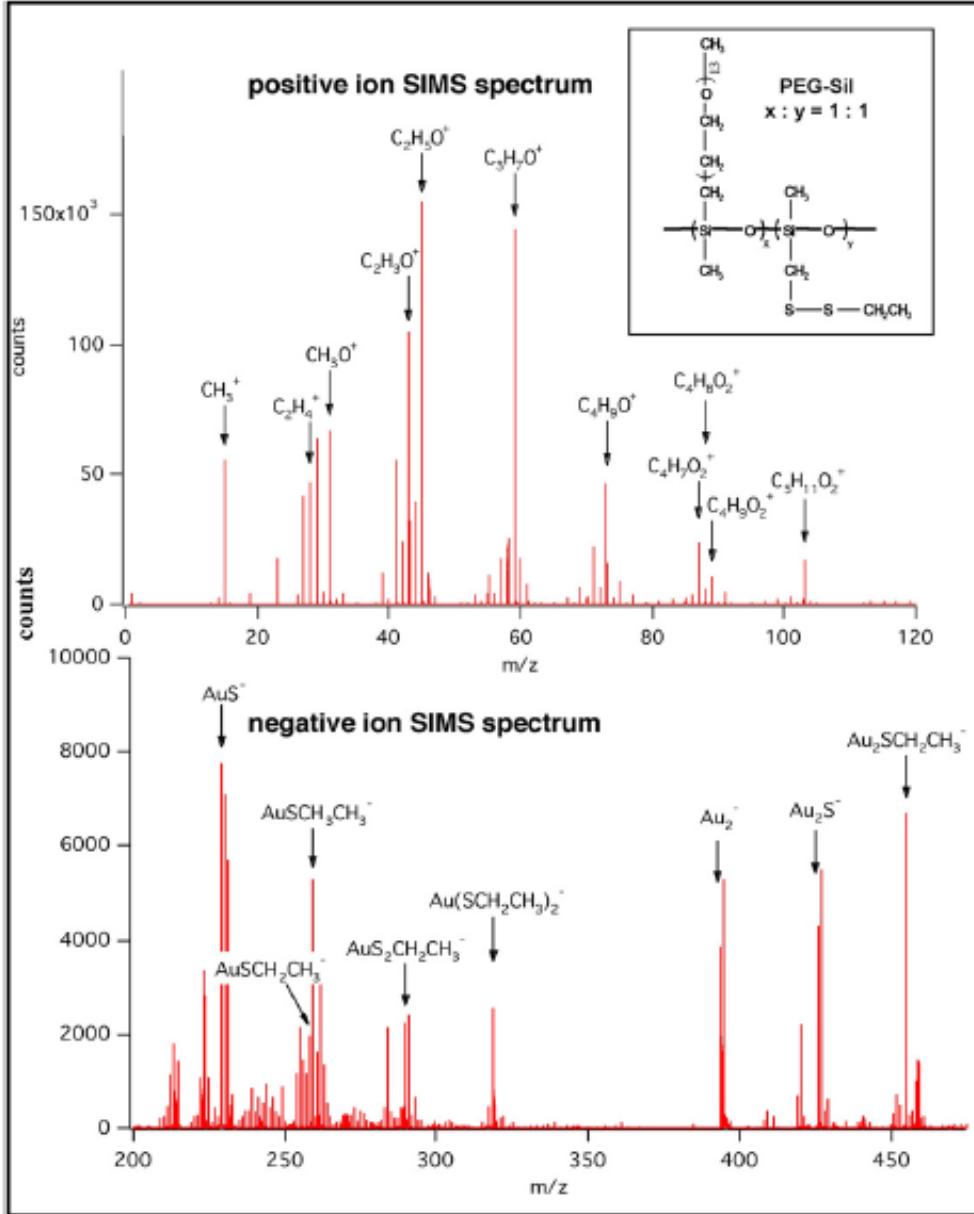
- In SIMS analysis, a surface is bombarded with a beam of accelerated ions. The collision of these ions with the atoms and molecules in the surface zone can transfer enough energy that they sputter\* from the surface into the vacuum phase.
- In SIMS, positive ions (cesium, gallium, bismuth, C<sub>60</sub>-buckyballs, and cluster ions are commonly used) that are accelerated at the surface to be analyzed with energies of 5000–20,000 eV. The particles ejected from the surface are positive and negative ions (secondary ions), radicals, excited states, and neutrals. Only the secondary ions are measured in SIMS.
- In ESCA, the energy of emitted particles (electrons) is measured. SIMS measures the mass of emitted ions (more rigorously, the ratio of mass to charge, m/z) using a time-of-flight (TOF) mass analyzer, magnetic sector analyzer or, in older instruments, a quadrupole mass analyzer.

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\* Sputtering is a term used to describe the mechanism in which atoms are ejected from the surface of a material when that surface is bombarded by sufficiently energetic particles.



- There are two modes for SIMS analysis, **dynamic and static**.
- Dynamic SIMS uses high ion doses over a given analysis time. Depending on the primary ion used, for example, cesium or gallium, and its energy, the high-flux ion beam can destroy organic samples and relevant organic fragments, and predominantly atomic fragments (e.g., C-, CH-, O-, OH-, Na<sup>+</sup>, etc.) will be detected.
- Static SIMS, in contrast, induces minimal surface destruction. The ion dose is adjusted so that during the period of the analysis less than 10% of one monolayer of surface atoms is sputtered.



Static SIMS provides qualitative information on the atomic and molecular composition in the outermost 1–2 nm of surface with high analytical sensitivity and excellent x,y spatial resolution.

**FIGURE I.1.5.10** Static positive and negative ion SIMS spectra of a poly(ethylene glycol)-poly(dimethyl siloxane) copolymer containing disulfide side groups on a gold surface. The primary peaks are identified. The low mass region of the negative ion spectrum offers little insight into the polymer structure, but the high mass region is rich in information. In this case, the low mass positive spectrum is rich in information. Further details on this class of polymers can be found in *Macromolecules*, 27, 3053 (1994). (Figure supplied by D. Castner.)

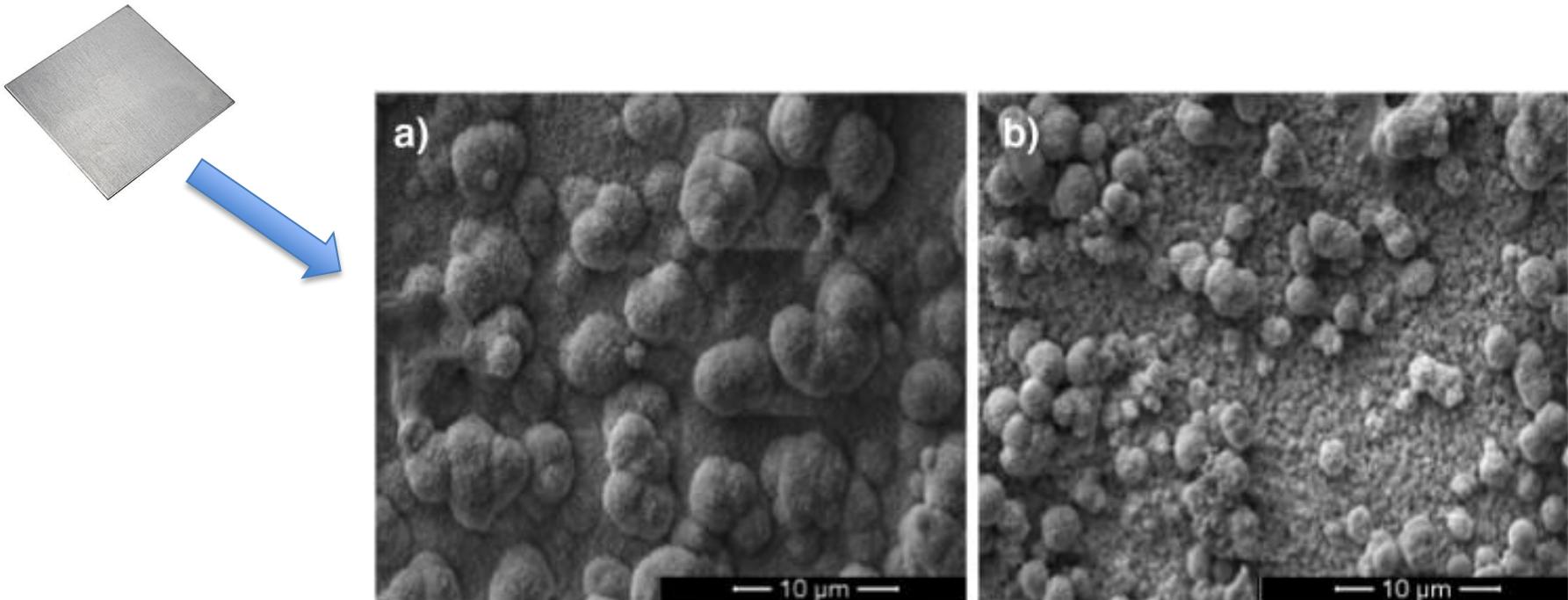
## ➤ Scanning Electron Microscopy



- Scanning electron microscopy (SEM) images of surfaces have great resolution and depth of field, with a three-dimensional quality.
- SEM functions by focusing and rastering a relatively high-energy electron beam (typically, 5–100 keV) on a specimen that is under vacuum.
- Low-energy secondary electrons (1–20 eV) are emitted from each spot where the focused electron beam makes an impact.
- The intensity of the secondary electron emission is a function of the atomic composition of the sample and the geometry of the features under observation.
- The image of the surface is spatially reconstructed on a phosphor screen (or CCD detector) from the intensity of the secondary electron emission at each point.

- Nonconductive materials observed in the SEM are typically coated with a thin, to minimize negative charge accumulation from the electron beam.
- This metal layer is always thick enough ( $>200 \text{ \AA}$ ) so that the electrons emitted from the sample beneath cannot penetrate.
- Therefore, in SEM analysis of nonconductors, the surface of the metal coating is being monitored.
- If the metal coat is truly conformal, a good representation of the surface geometry will be conveyed. However, the specimen surface chemistry no longer influences secondary electron emission.

SEM provides a high resolution image of the surface. On insulating materials, metallic coating is required and the image is actually of the coating surface, not the underlying material.



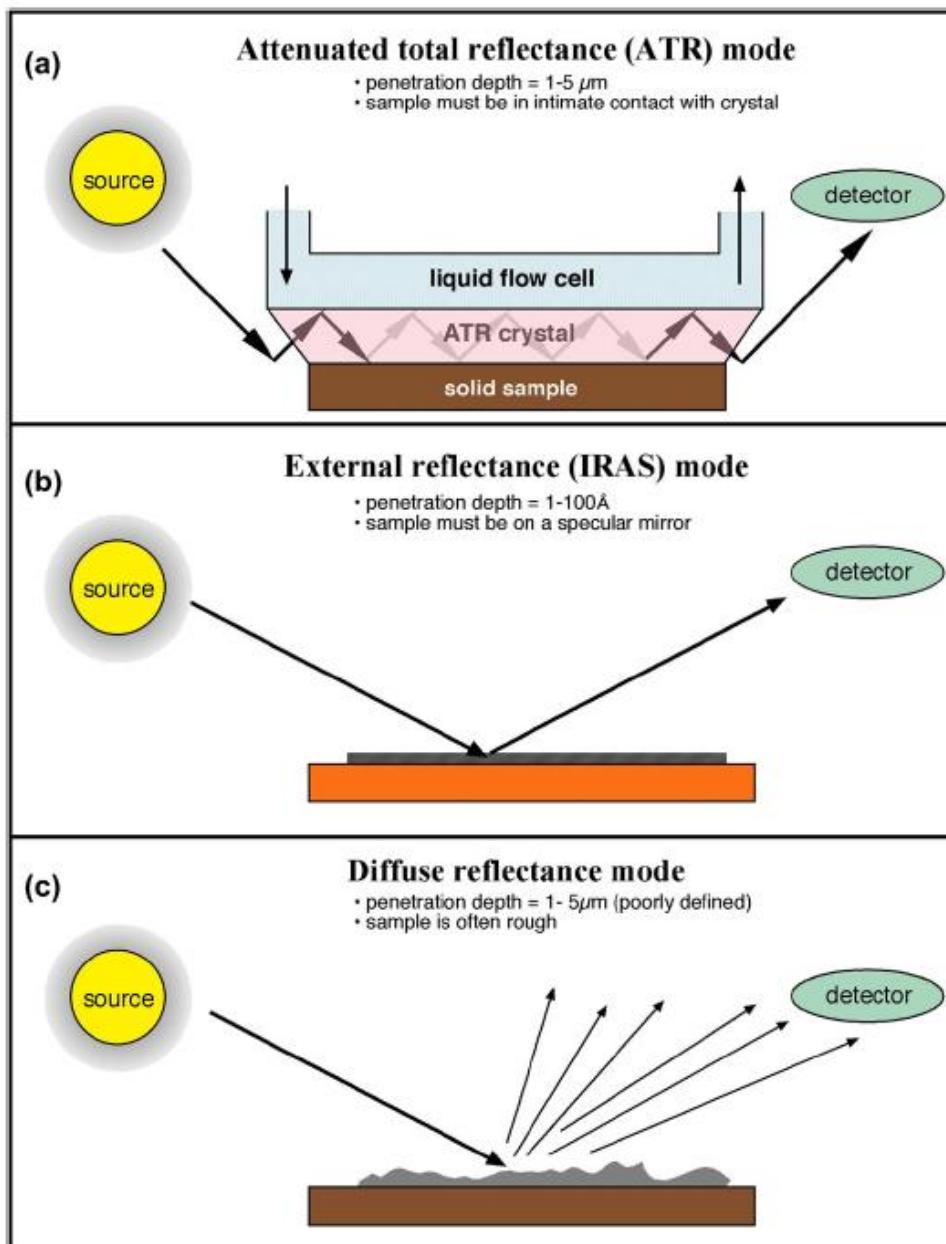
SEM micrographs of (a)  $(\text{Ti},\text{Mg})\text{N}$  and (b) TiN coatings after 5X SBF tests.

- SEM is an important corroborative method to use in conjunction with other surface analysis methods.
  - Surface roughness and texture can have a profound influence on data from ESCA, SIMS, and contact angle determinations.
  - SEM provides important information in the interpretation of data from these methods.

## ➤ Infrared Spectroscopy

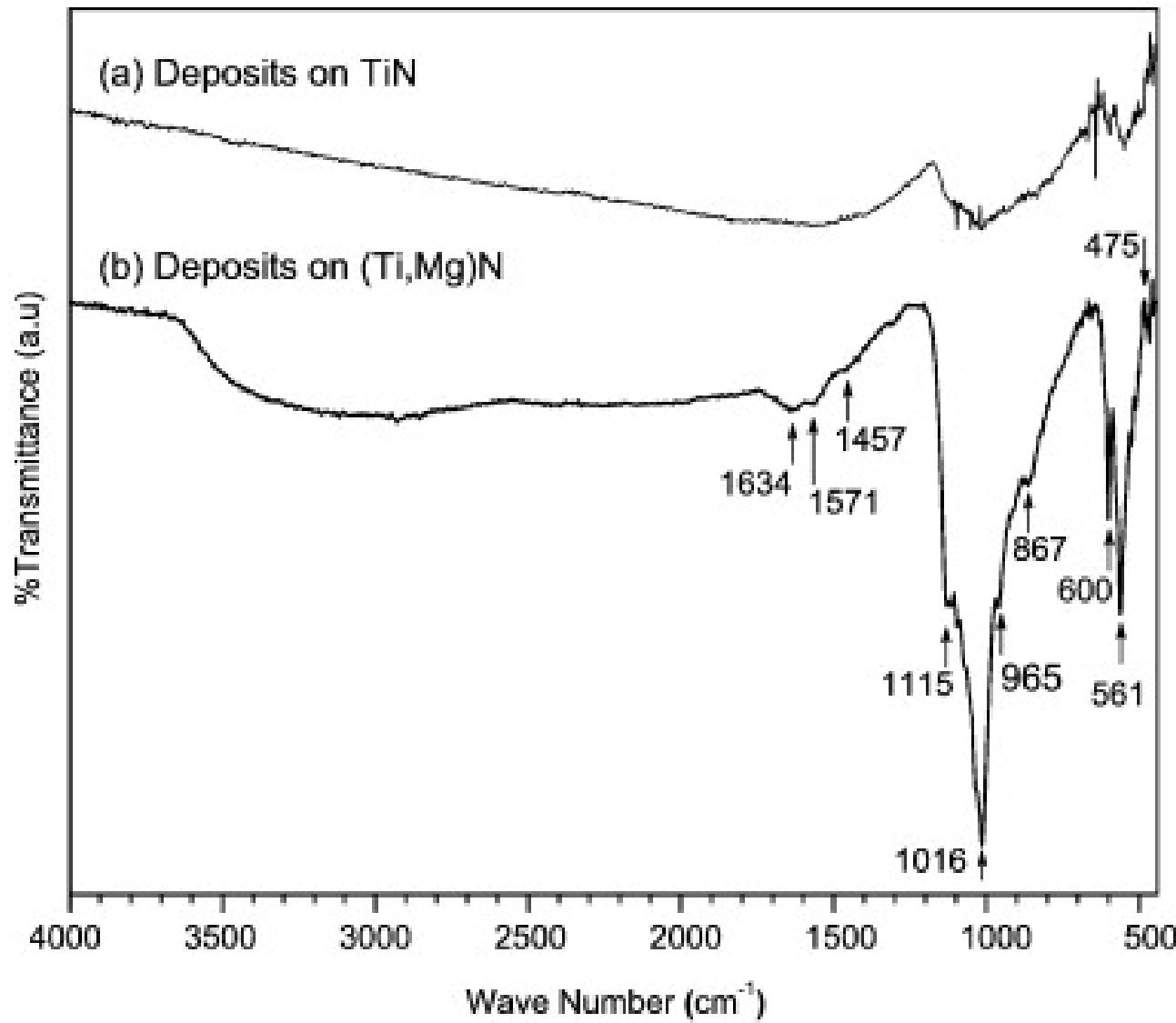
- Infrared spectroscopy provides information on the bond vibrations of molecular species.
- It is a widely used analytical method that can reveal information on specific chemistries and the orientation of structures.
- Fourier transform infrared (FTIR) spectrometry offers outstanding signal-to-noise ratio (S/N) and spectral accuracy.
- Surface FTIR methods couple the infrared radiation to the sample surface to increase the intensity of the surface signal and reduce the bulk signal

- Some of these sampling modes, and their characteristics



ATR-IR permits detailed molecular analysis of the outermost 1-5 microns of a sample.

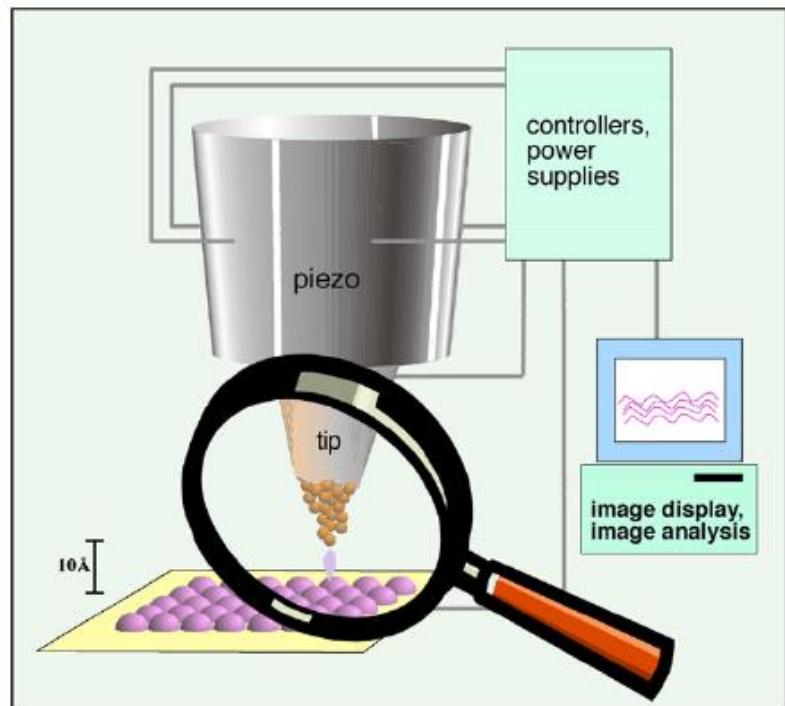
**FIGURE I.1.5.12** Three surface-sensitive infrared sampling modes. (a) Attenuated total reflectance infrared (ATR-IR); (b) infrared reflection absorption spectroscopy (IRAS); (c) diffuse reflectance infrared spectroscopy.



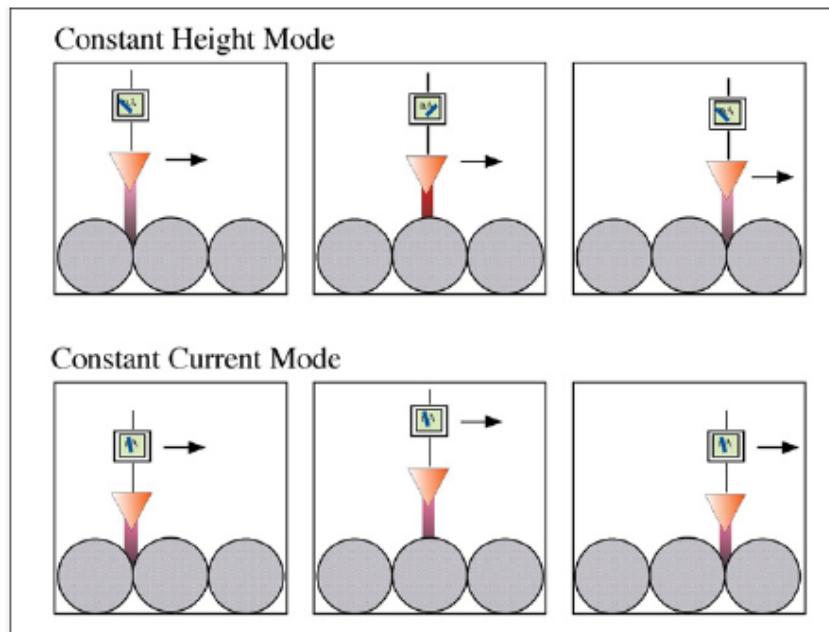
FTIR spectra of (a) TiN and (b) (Ti,Mg)N coatings after Mg-free 5X SBF tests.

## ➤ Scanning Tunneling Microscopy (STM)

- The STM capitalizes on quantum tunneling to generate an atom-scale, electron density image of a surface.
- A metal tip terminating in a single atom is brought within 5–10 Å of an electrically conducting surface. At these distances, the electron cloud of the atom at the “tip of the tip” will significantly overlap the electron cloud of an atom on the surface.
- If a potential is applied between the tip and the surface, an electron tunneling current will be established



**FIGURE I.1.5.13** Schematic diagram illustrating the principle of the scanning tunneling microscope – a tip terminating in a single atom permits localized quantum tunneling current from surface features (or atoms) to tip. This tunneling current can be spatially reconstructed to form an image.

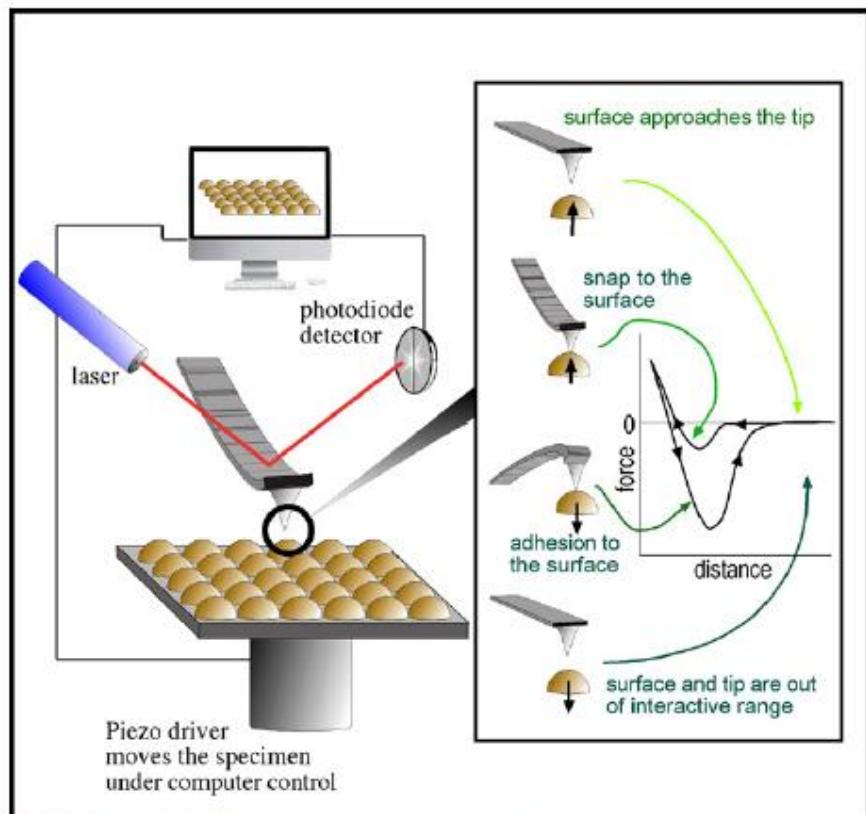


**FIGURE I.1.5.14** Scanning tunneling microscopy can be performed in two modes. In constant height mode, the tip is scanned a constant distance from the surface (typically 5–10 Å) and the change in tunneling current is recorded. In constant current mode, the tip height is adjusted so that the tunneling current is always constant, and the tip distance from the surface is recorded as a function of distance traveled in the plane of the surface.

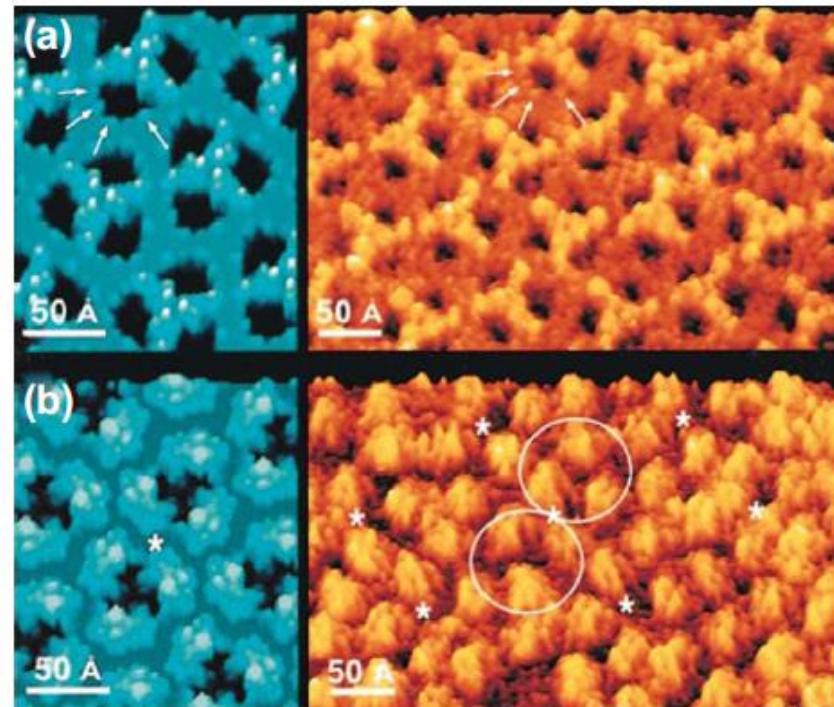
## ➤ Atomic Force Microscopy (AFM)

- The AFM uses a similar mechanism.
- Instead of recording tunneling current, the deflection of a tip mounted on a flexible cantilever arm due to van der Waals forces and electrostatic repulsion/attraction between an atom at the tip and an atom on the surface is measured.

AFM allows imaging of surfaces at sub-nanometer resolutions, and also provides detail on surface mechanics and molecular interactions.



**FIGURE I.1.5.15** Schematic diagram illustrating the principle of the atomic force microscope.



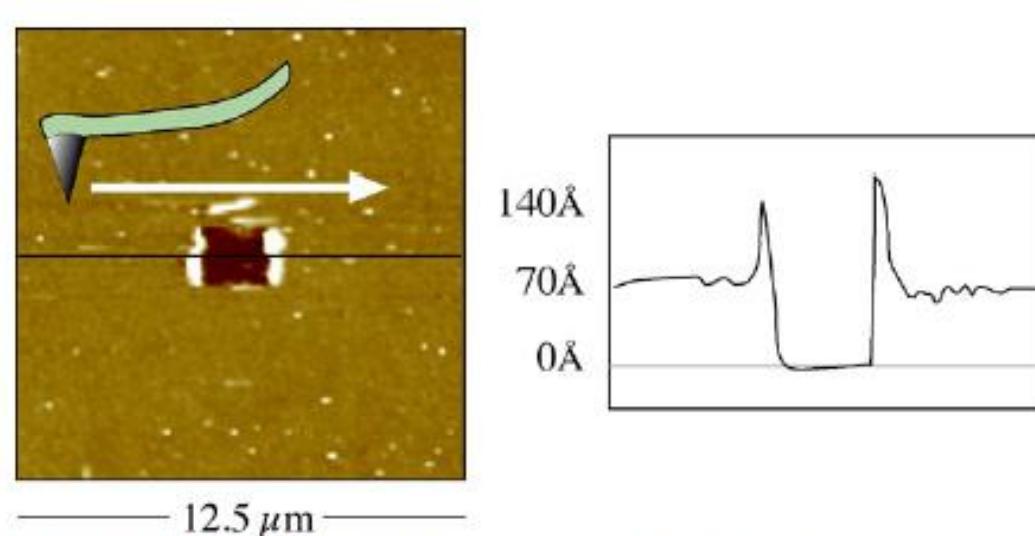
**FIGURE I.1.5.16** An AFM image of porin proteins from the outer membrane of *E. coli* imaged with nanoscale resolution. Comparison of high-resolution AFM images of OmpF crystals (in brown-yellow) and the atomic model rendered at 3 Å (in blue). (From Müller, D. J. & Engel, A. (1999). Journal of Molecular Biology, 285, 1347, used with permission of the authors and the publisher.)

- The potential of the AFM to explore surface problems has been greatly expanded by ingenious variants of the technique. In fact, the term “atomic force microscopy” has been generalized to “scanning probe microscopy” (SPM).

**TABLE I.1.5.6 | Scanning Probe Microscopy (SPM) Modes**

Name	Acronym	Use
Contact mode	CM-AFM	Topographic imaging of harder specimens
Tapping (intermittent force) mode	IF-AFM	Imaging softer specimens
Non-contact mode	NCM-AFM	Imaging soft structures
Force modulation (allows slope of force-distance curve to be measured)	FM-AFM	Enhances image contrast based on surface mechanics
Scanning surface potential microscopy (Kelvin probe microscopy)	SSPM, KPM	Measures the spatial distribution of surface potential
Magnetic force microscopy	MFM	Maps the surface magnetic forces
Scanning thermal microscopy	SThM	Maps the thermal conductivity characteristics of a surface
Recognition force microscopy	RFM	Uses a biomolecule on a tip to probe for regions of specific biorecognition on a surface
Chemical force microscopy	CFM	A tip derivatized with a given chemistry is scanned on a surface to spatially measure differences of interaction strength
Lateral force microscopy	LFM	Maps frictional force on a surface
Electrochemical force microscopy	EFM	The tip is scanned under water and the electrochemical potential between tip and surface is spatially measured
Nearfield scanning optical microscopy	NSOM	A sharp optical fiber is scanned over a surface allowing optical microscopy or spectroscopy at 100 nm resolution
Electrostatic force microscopy	EFM	Surface electrostatic potential are mapped
Scanning capacitance microscopy	SCM	Surface capacitance is mapped
Conductive atomic force microscopy	CAFM	Surface conductivity is mapped with an AFM instrument
Nanolithographic AFM	NAFM	An AFM tip etches, oxidizes or reacts a space permitting pattern fabrication at 10 nm or better resolution
Dip-pen nanolithography	DPN	An AFM tip, inked with a thiol or other molecule, writes on a surface at the nanometer scale

- Since the AFM measures force, it can be used with both conductive and nonconductive specimens.
- Force must be applied to bend a cantilever, so AFM is subject to artifacts caused by damage to fragile structures on the surface
- Both AFM and STM can function well for specimens under water, in air or under vacuum
- For exploring biomolecules or mobile organic surfaces, the “pushing around” of structures by the tip is a significant concern.
- This surface artifact can be capitalized upon to write and fabricate surface structures at the nanometer scale



**FIGURE I.1.5.17** An AFM tip, using relatively high force, was used to scratch a rectangular feature into a thin ( $70 \text{ \AA}$ ) plasma-deposited film. The AFM also characterized the feature created.

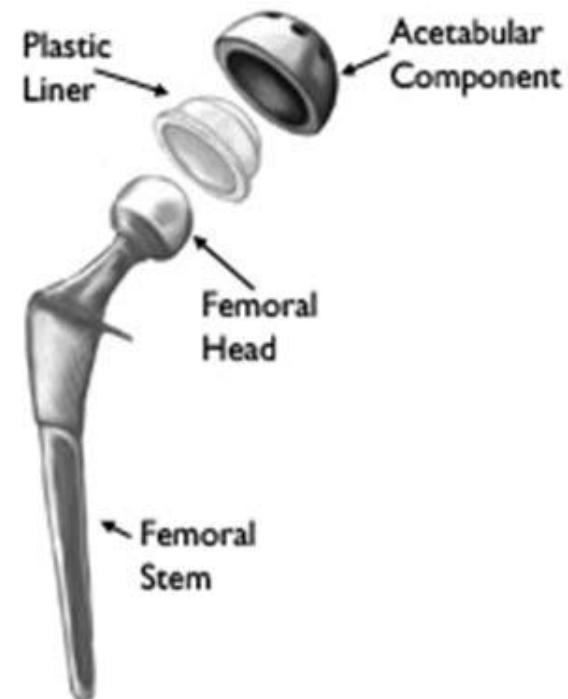
# Classes of Materials Used in Medicine:

**Polymers**

# THE POLYMER MOLECULE

- Polymer materials possess an array of unique properties which make them useful in a wide variety of biomaterial applications such as;

## ✓ Orthopedics



## ✓ Dental



- Denture bases and teeth
- Soft liners
- Cementing materials

- ✓ hard and soft tissue replacements
- ✓ cardiovascular devices.



Heart valve

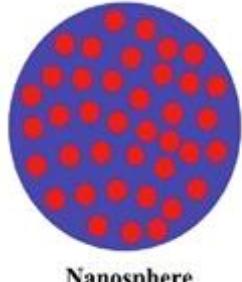


Artificial skin



blood vessel

- ✓ Drug release systems



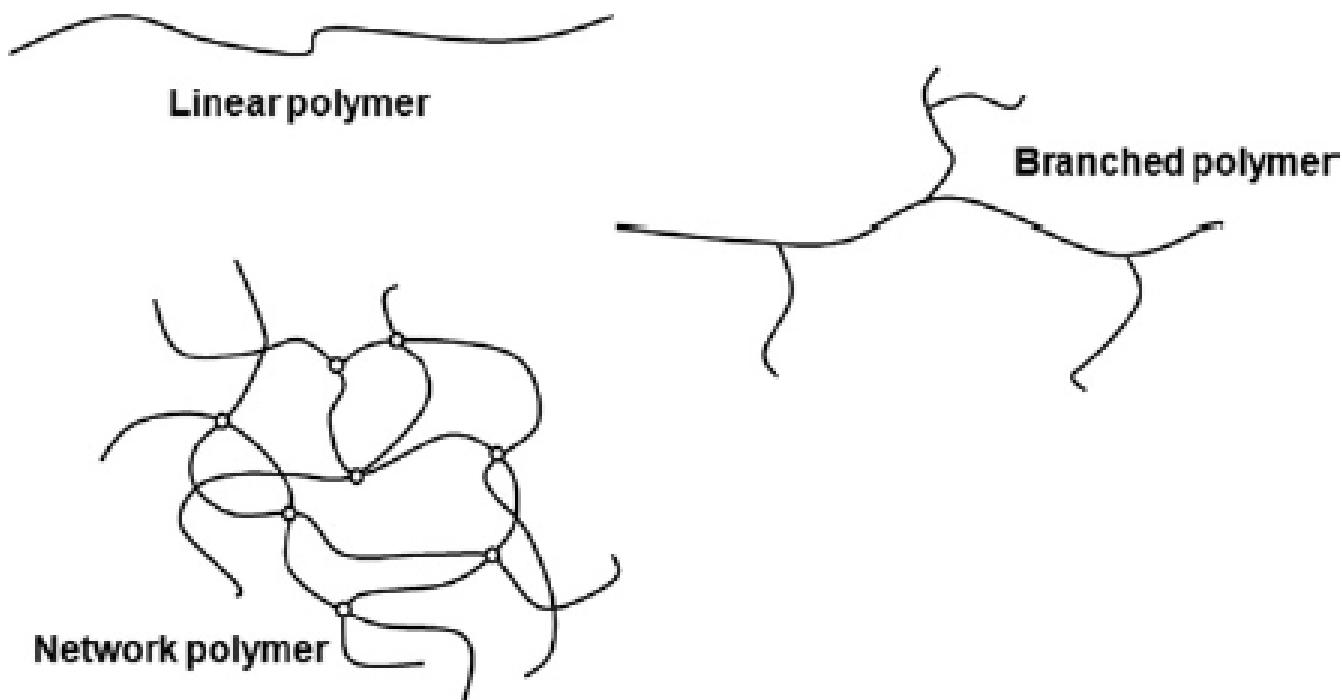
= Entrapped Drug



✓ Scaffolds

## Molecular Structure of Single Polymer Molecules

- A single polymer molecule could have a molecular weight of 200,000 Da compared to a water molecule, which has a molecular weight of 18 Da.
- Polymer molecules are organized into different architectures.

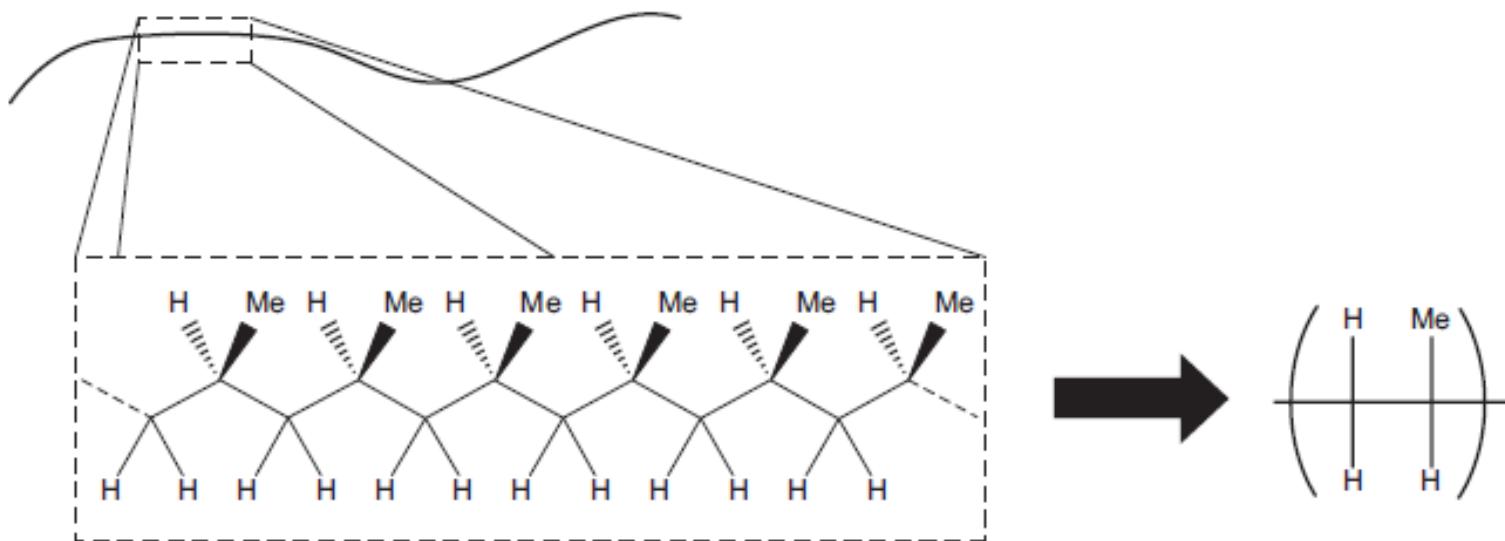


**FIGURE 1.2.2.1** Some of the molecular structures available for polymer molecules. In the schematic of the network, polymer open circles indicate cross-link sites.

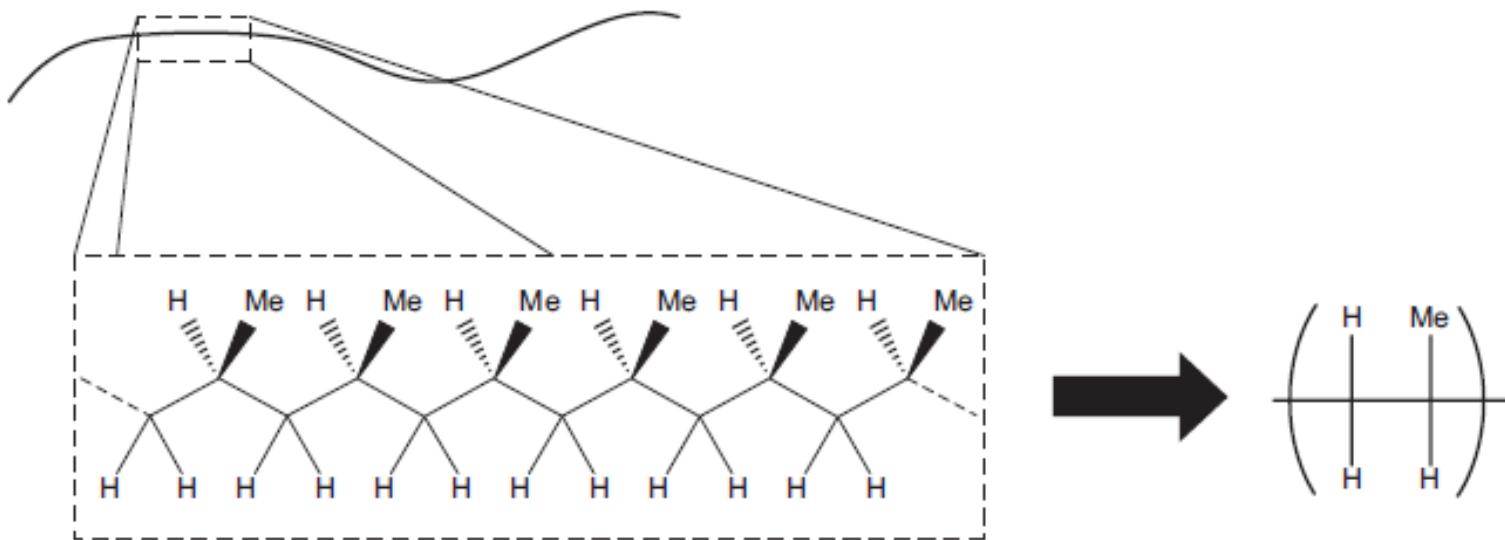
- When **linear chains** of two different composition polymers (e.g., A and B) are linked together, the resultant polymer is called an A–B block copolymer. If another chain is added to the second chain, it may be called an A–B–C triblock copolymer, or more simply, an A–B–C block copolymer .
- **Branched structures** are also possible where a central polymer backbone has smaller side chains extending from it.
- If you took a linear polymer molecule and covalently bond it to the backbone of another linear chain and repeat this act many times, you would eventually link all of the polymer chains together into one very large ***network polymer***.
- This is also possible by using “cross-linker” molecules to react with terminal reactive groups on linear polymer chains, eventually yielding a network polymer.

## Chemical Structure of Single Polymer Molecules

- If you were able to see the individual atoms making up a polymer molecule, you would notice the same basic structure repeats over and over again.

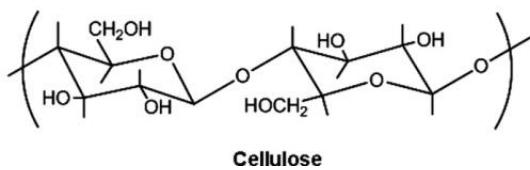
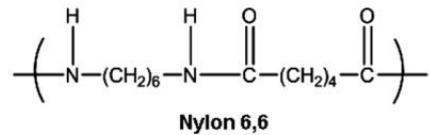
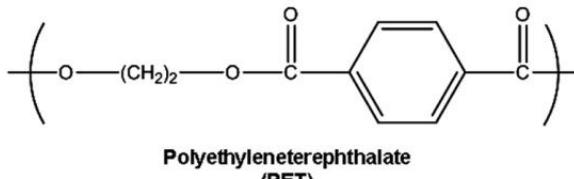
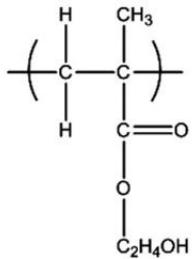
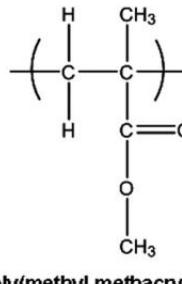
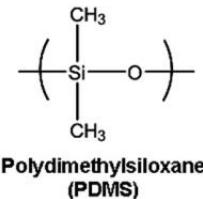
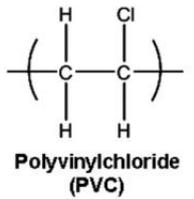
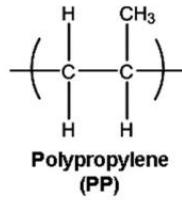
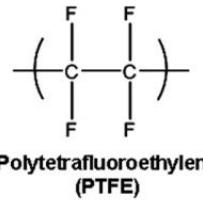
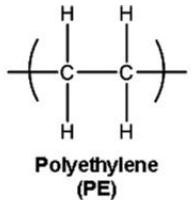


schematic of a linear polypropylene molecule.



- The polymer backbone is a series of carbon–carbon single bonds, while the hydrogen atoms and methyl group are ***pendant groups***.
- The polymer chain is composed of many  $\text{--CH}_2\text{--CHMe--}$  groups covalently linked end-to-end. This structure is called the ***repeat unit*** of a polymer molecule.

- Repeat unit of common polymer biomaterials.



The repeat unit can be controlled through polymer synthesis and plays a large role in the macroscopic behavior of the polymer

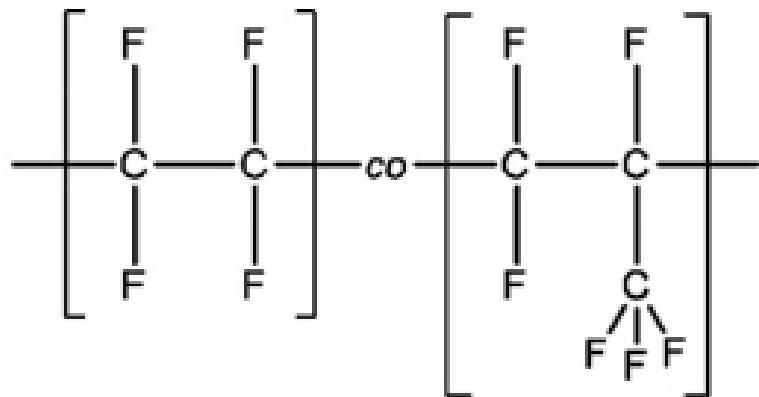
## Copolymers

- Copolymers contain more than one chemically distinct repeat unit polymer which contains repeat units “A” and “B.”
- There are many different ways the repeat units could be organized such as:
  - Random
  - Alternating
  - Block
  - Graft

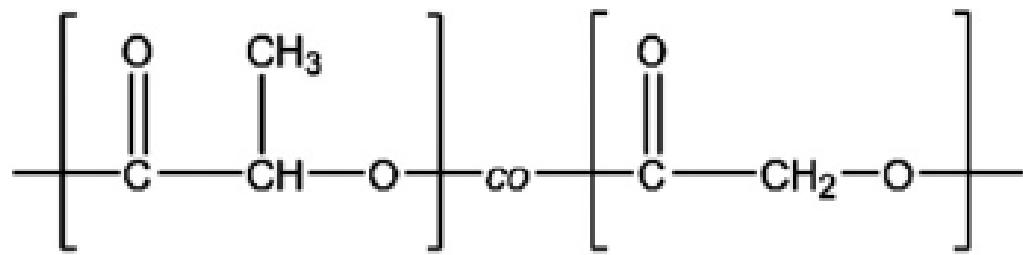


**FIGURE 1.2.2.4** Some of the molecular structures available for copolymers.

**the arrangement of repeat units affects the physical behavior of the biomaterial.**



Poly(tetrafluoroethylene-co-hexafluoropropylene) random copolymer

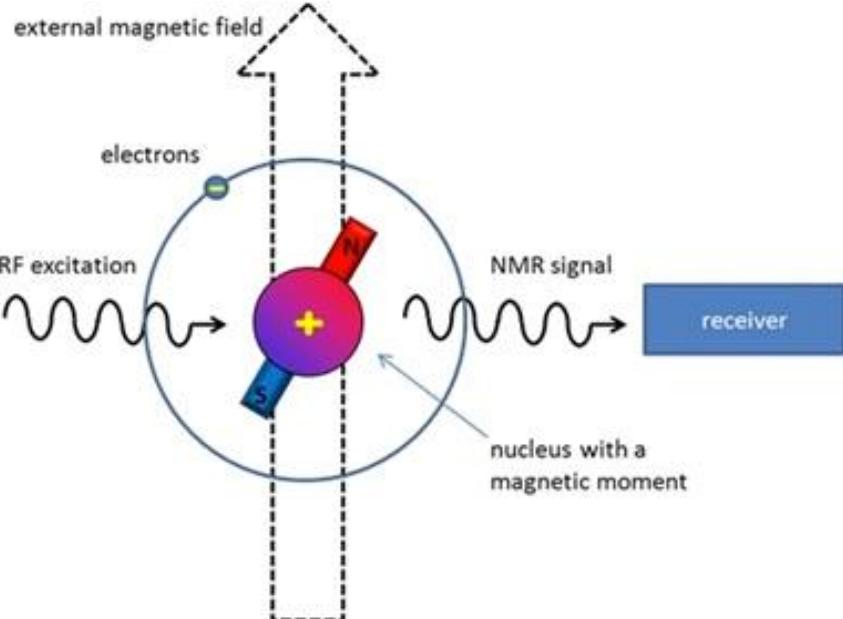


Poly(lactide-co-glycolide) random copolymer

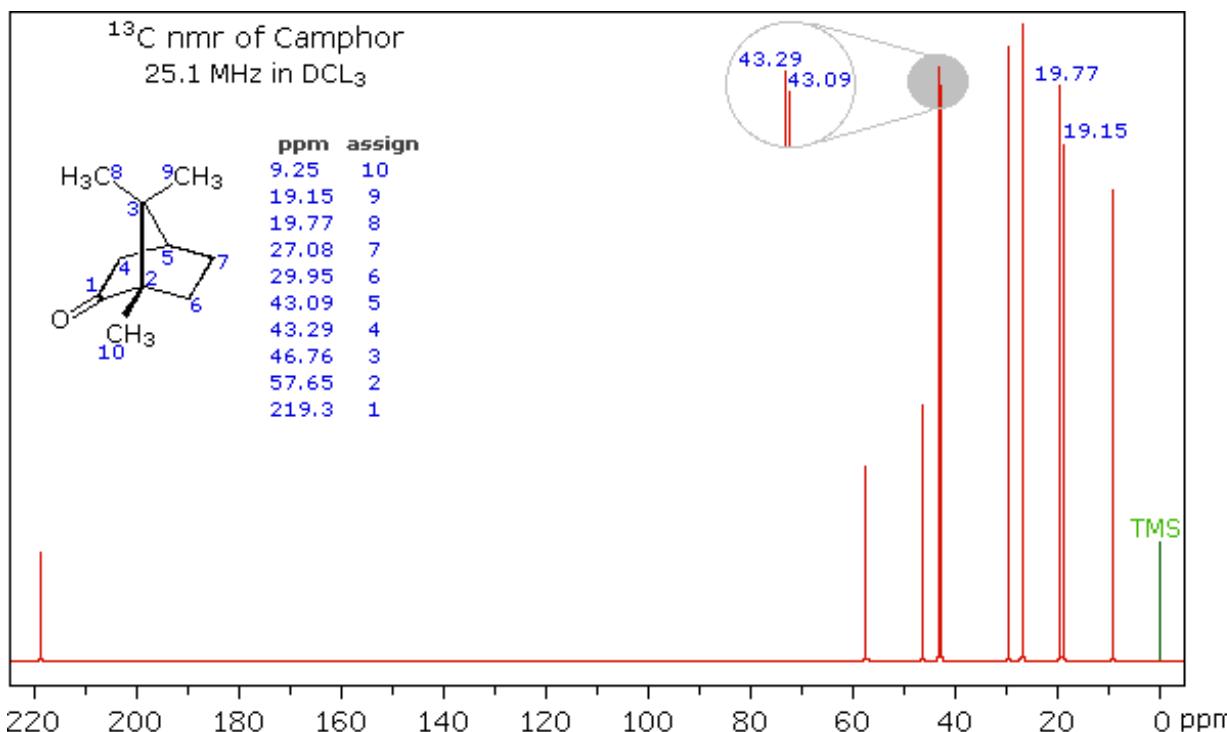
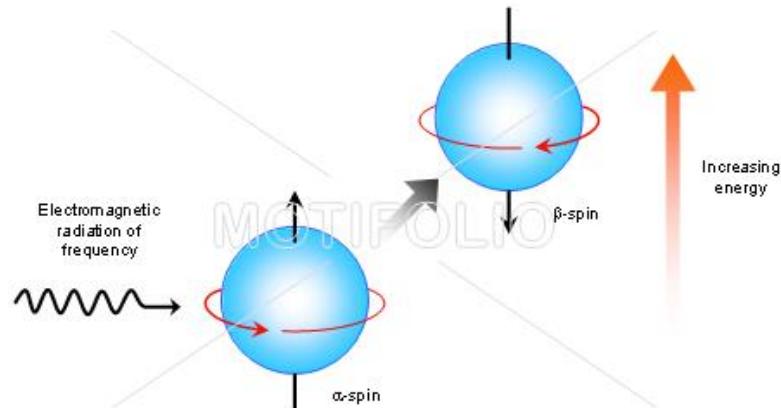
**FIGURE I.2.2.5** Repeat unit of two common copolymer biomaterials.

## Determination of Chemical Composition

- A researcher will often need to verify the chemical structure of polymers or determine the composition of copolymer systems.
- Common techniques a scientist would use are **nuclear magnetic resonance spectroscopy (NMR)**, **infrared spectroscopy (IR)**, and **X-ray photoelectron spectroscopy (XPS)** .
- NMR is an analytical technique which exploits the magnetic moments associated with nuclei containing an odd number of protons (most commonly the  $^1\text{H}$  and  $^{13}\text{C}$  isotopes). These protons are excited to a higher energy state through a burst of radiofrequency radiation. Then the nuclei relax to a lower energy state which is measured as an electric signal.
- Due to shielding, protons attached to different structural units will display chemical shifts, meaning their peaks in the NMR spectrum will be at different frequencies.
- Through analysis of the peak placement and intensity, the chemical structure of molecules can be determined .



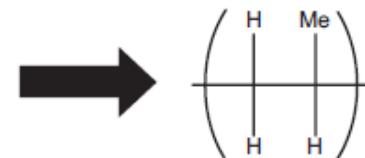
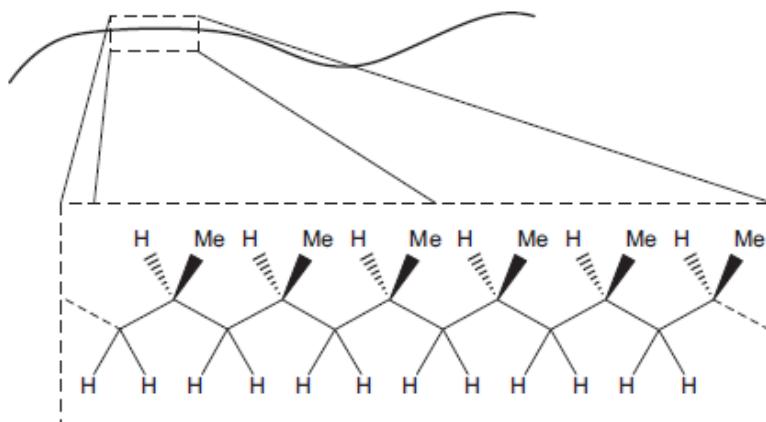
The basis of NMR spectroscopy



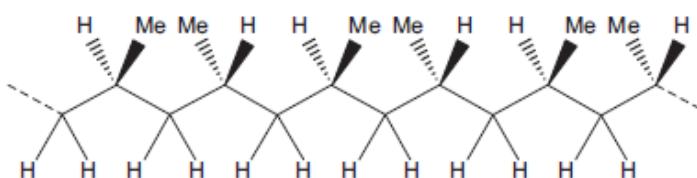
- **Infrared spectroscopy (IR)**; the sample of interest is irradiated with infrared radiation and the sample adsorbs certain wavelengths, resulting in specific molecular motion (such as C–H stretching).
- **X-ray photoelectron spectroscopy (XPS)** – also known as electron spectroscopy for chemical analysis (ESCA) – is a common technique.
- A sample is bombarded with X-rays which results in the ejection of inner shell electrons from the atoms displayed on the material surface.
- The kinetic energies of the ejected electrons are measured and interpreted into information about the chemical composition of the surface

## ☐ Tacticity

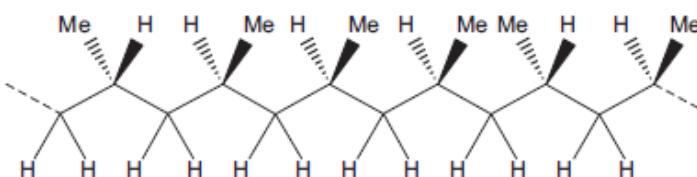
- Tacticity describes the stereochemistry of the repeat units in polymer chains.



Isotactic PP



Syndiotactic PP



Atactic PP

- sometimes the methyl groups are all on one side of the backbone, sometimes they alternate from side to side, and sometimes they are randomly distributed.

FIGURE I.2.2.2 Polypropylene repeat unit and different tactic isomers. In the schematic Me indicates a methyl group.

## Molecular Weight

- During polymerization, polymer chains are built up from low molecular weight monomers. The number of monomer repeat units in each polymer chain is called the ***degree of polymerization***.
- Degree of polymerization may change for each polymer chain.
- For instance, in the polymerization of polyethylene, one polymer chain may add 3000 monomers, a second may add 4500 monomers, and a third may only add 1500. Therefore, most polymer systems have a ***distribution of molecular weights***.

## CONNECTING PHYSICAL BEHAVIOR WITH CHEMICAL CHARACTERISTICS

- Key characteristics of polymer molecules are:
  - molecular architecture
  - chemical composition
  - Tacticity
  - molecular weight.

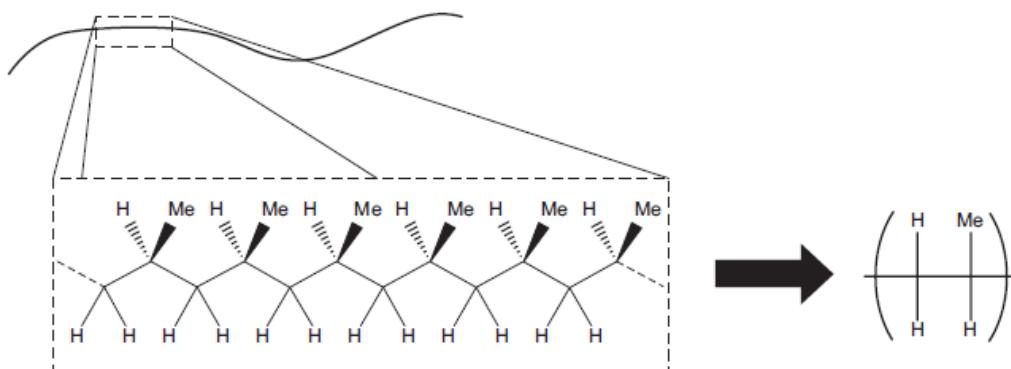
**How these molecular characteristics are related with to macroscopic properties?**

**How these characteristics can be manipulated to create a polymer system with the desired behavior?**

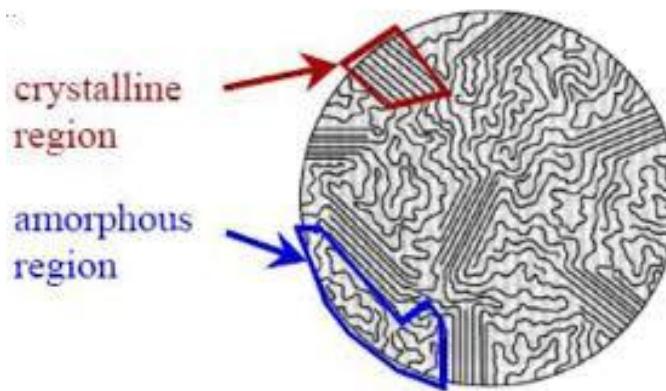
## **Physical States of Linear Polymers.**

- When designing a biomaterial, physical behavior is a key feature.
  - if you were creating a cement for use in loadbearing bones (tibia or femur) you would have to ensure the material is both strong enough to act as a cement, but not so brittle that it would fail due to low fracture toughness .
- The four most fundamental molecular characteristics of polymer chains which determine the physical behavior of a polymer are
  - ① **chain stiffness**
  - ② **chain composition**
  - ③ **chain architecture**
  - ④ **molecular weight.**
- Physical states of linear polymers are:
  - Rubbery State
  - Glassy State
  - Semi crystalline State

- Polypropylene molecules extended into planar zigzags shown in the figure but this type of extended structure is rarely seen in nature



- More often, polymer molecules are found as unorganized and three-dimensional structures called the ***random coil***.
- In an ***amorphous structure***, each random coil is highly interpenetrated with its neighbors.



- Polymers in the **rubbery state or the glassy state** have this amorphous molecular arrangement.
- Under certain conditions, some polymers will arrange themselves into highly organized crystalline domains resulting in a **semi-crystalline material**.

## ➤ The Rubbery State.

- Rubbery polymers are amorphous
- Macroscopically these materials are soft, flexible, and extensible

## ➤ The Glassy State

- As the polymer system is cooled, main chain bonds in a polymer chain gets stiffer and stiffer. Eventually, at a low enough temperature, random coils become frozen in space. This is called the **glassy state**.
- The temperature where single bond rotation ceases is called the glass transition temperature ( $T_g$ ).
- A material below its  $T_g$  is called a glass because it is hard, stiff, and brittle.
- Molecules in the glassy state can no longer rearrange themselves under applied stress, so deformation results.
- The opposite occurs when an amorphous polymer is heated: the amorphous region goes from hard and glassy, to rubbery, and if the material is not cross-linked, it will eventually flow as a viscous fluid and can be processed into shapes.

# Glass Transition Temperature ( $T_g$ )

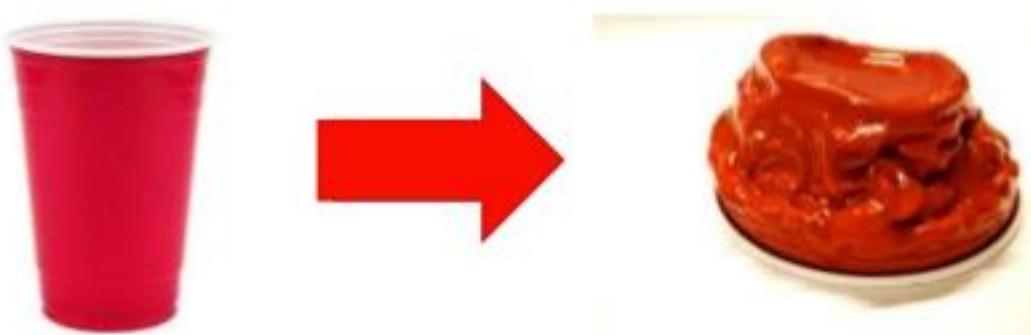


Figure 6 – Visual representation of polymers' actions at  $T_g$ .

## ➤ The Semi-Crystalline State.

- All polymer systems form glasses at sufficiently low temperatures. However, as a melt is cooled, certain polymers have the ability to pack into a regular lattice, leading to the formation of stable **crystalline** domains.
- If only a portion of the long polymer chains crystallize (some segments will not be able to pack into the crystallites), this state is called **semi-crystalline**.
- The temperature above which such crystalline regions will melt is called the crystalline melting point ( $T_m$ ).
- Crystallites act to **stiffen and reinforce the bulk material**, and extend the stiffness and strength properties of a material well above the glass transition temperature

## The Physical Behavior of Linear and Amorphous Polymers

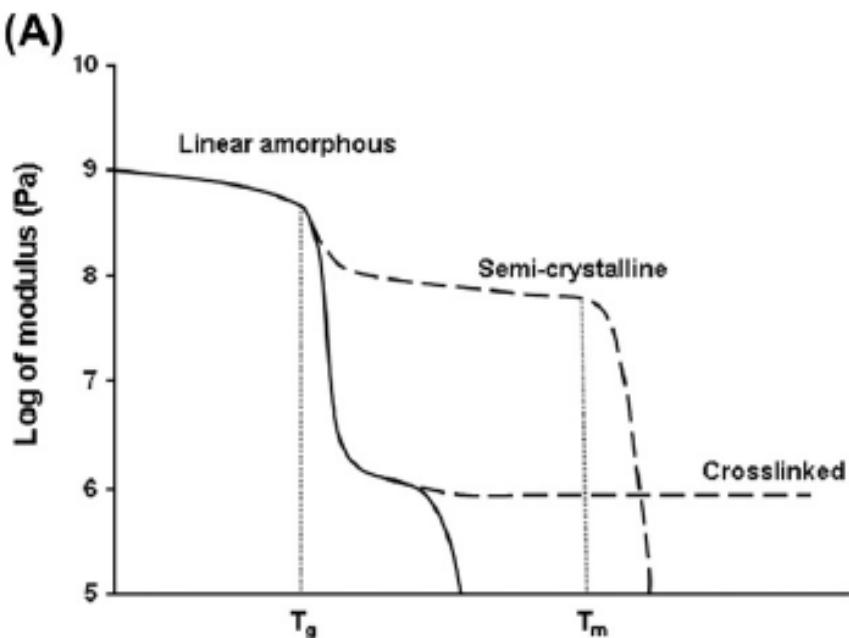
- Unlike metals which are held together by metallic bonds and atomic crystals which are held together by covalent bonds, polymer materials are held together by secondary interactions such as Van der Waals, and hydrogen bonding. For this reason, **polymers are often mechanically weaker than other classes of materials**; however, they can display physical behavior more similar to native tissue.
- When **rubbery materials (amorphous)** are strained, the polymer molecules are able to deform and extend resulting in a material which is macroscopically soft and weak, yet highly extensible. However, as the T<sub>g</sub> of the material approaches and exceeds the environmental conditions, the material becomes a glass and is much stronger yet stiffer.



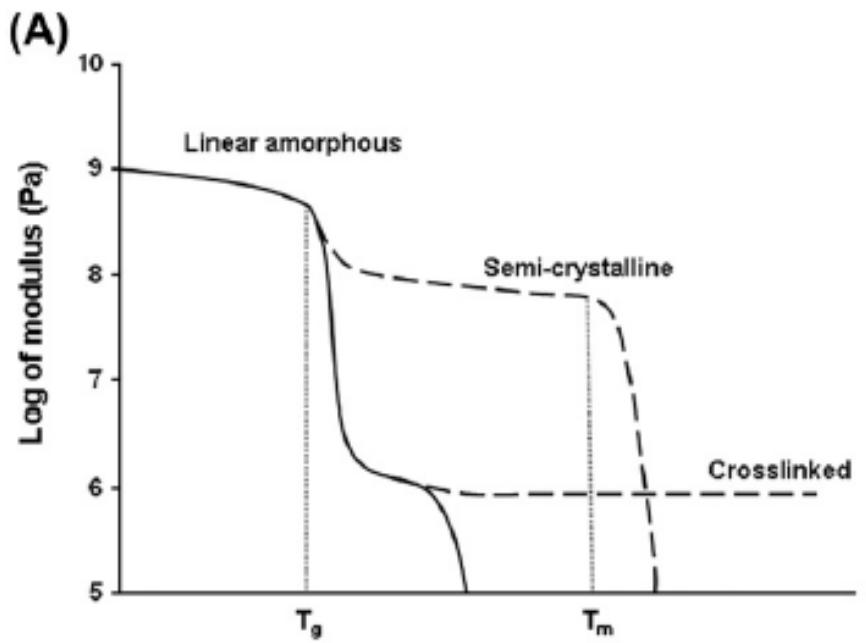
## The Physical Behavior of Other Physical States

- Cross-linking, crystallinity, and copolymerization greatly affect the physical behavior of polymer systems, and controlling these parameters gives a polymer scientist ways of specifying the physical behavior of a polymer system.

- Below the  $T_g$ , the material is a glass and has a high modulus.
- However, at the glass transition temperature we see a dramatic drop in modulus due to the increased mobility within the polymer structure.
- At temperatures just higher than the  $T_g$ , we see a plateau on the curve where modulus declines more slowly with temperature. This is called the rubbery plateau, and in this region the polymer is still solid-like but soft, flexible, and extensible.
- Eventually, as the temperature is increased more, we see the modulus curve take another drop corresponding to the material beginning to flow.
- Notice that amorphous materials do not have a melting temperature. Melting refers to the loss of crystallinity, and since these materials are non-crystalline they never truly melt.

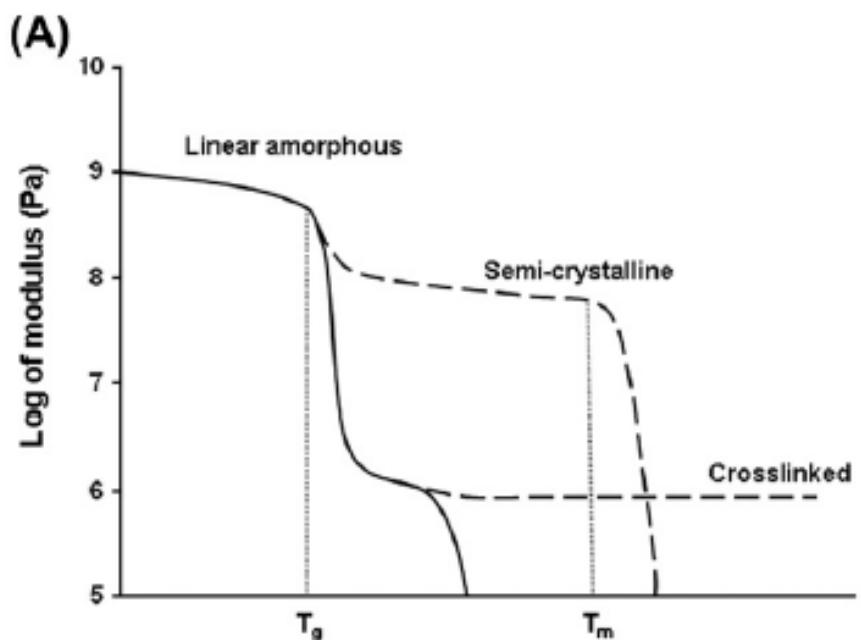


standard modulus–temperature behavior of a linear and amorphous polymer system (solid line).



modulus–temperature behavior of a semi-crystalline material

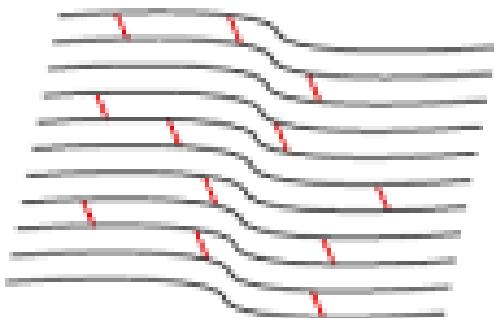
- a small drop in the modulus at the glass transition temperature, due to the amorphous regions of the polymer. Since crystallites are unaffected by the  $T_g$ , the magnitude of this drop is greatly affected by the amount of crystallinity in the system.
- After the  $T_g$  we see that the modulus holds steady until the melting point, illustrating that crystallinity is a way to increase the window of temperatures in which a polymer can be employed.
- At  $T_m$  the crystallites melt and the polymer begins to flow.



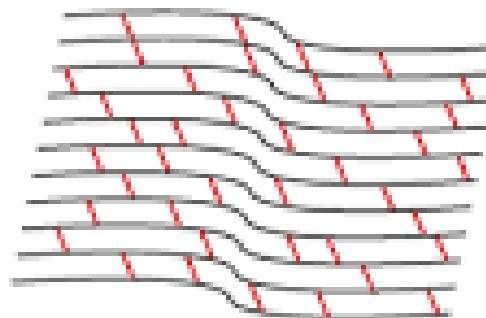
modulus– temperature behavior of a cross-linked polymer.

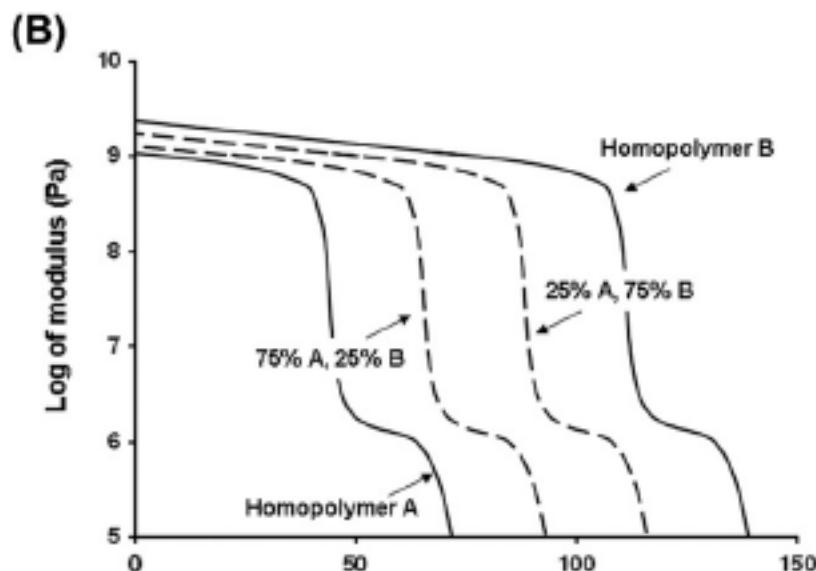
- at the glass transition temperature a decrease in modulus, however, above the  $T_g$  the modulus is relatively independent of temperature because the cross-links act to tether the polymer chains in place.
- In fact, the cross-linked polymer will not experience a large decrease in modulus until the temperature is high enough to begin thermally degrading the bonds holding the structure together.

Less Cross-linking (weaker)



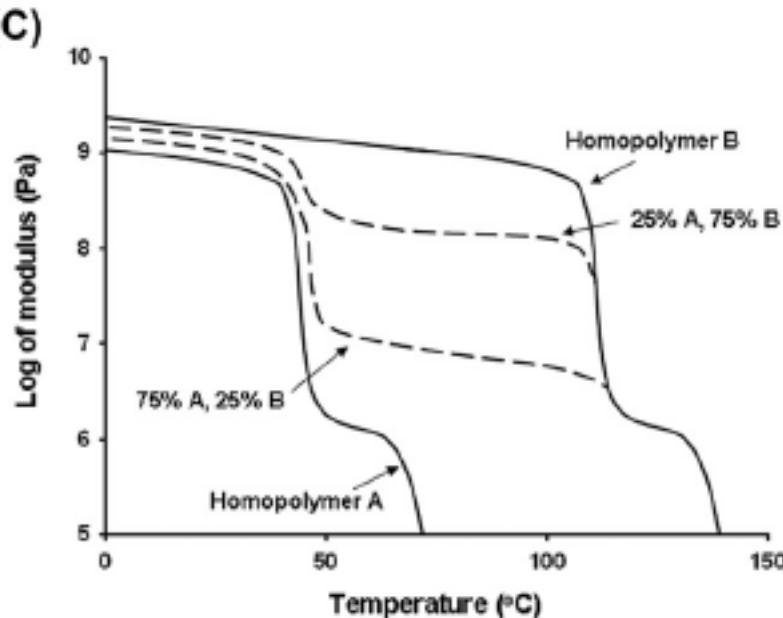
More Cross-linking (stronger)





modulus–temperature curves for a random copolymer system

- the shape of the curve is maintained, but shifted laterally.

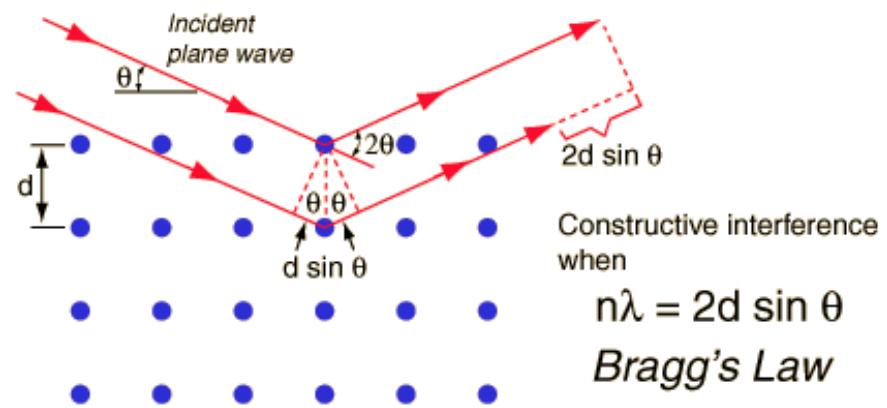
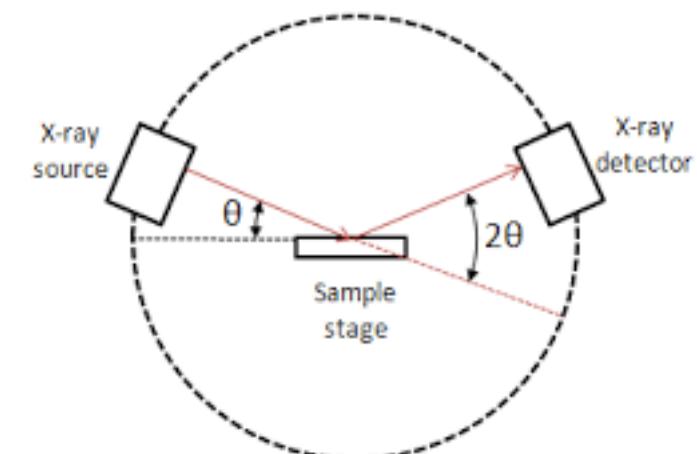
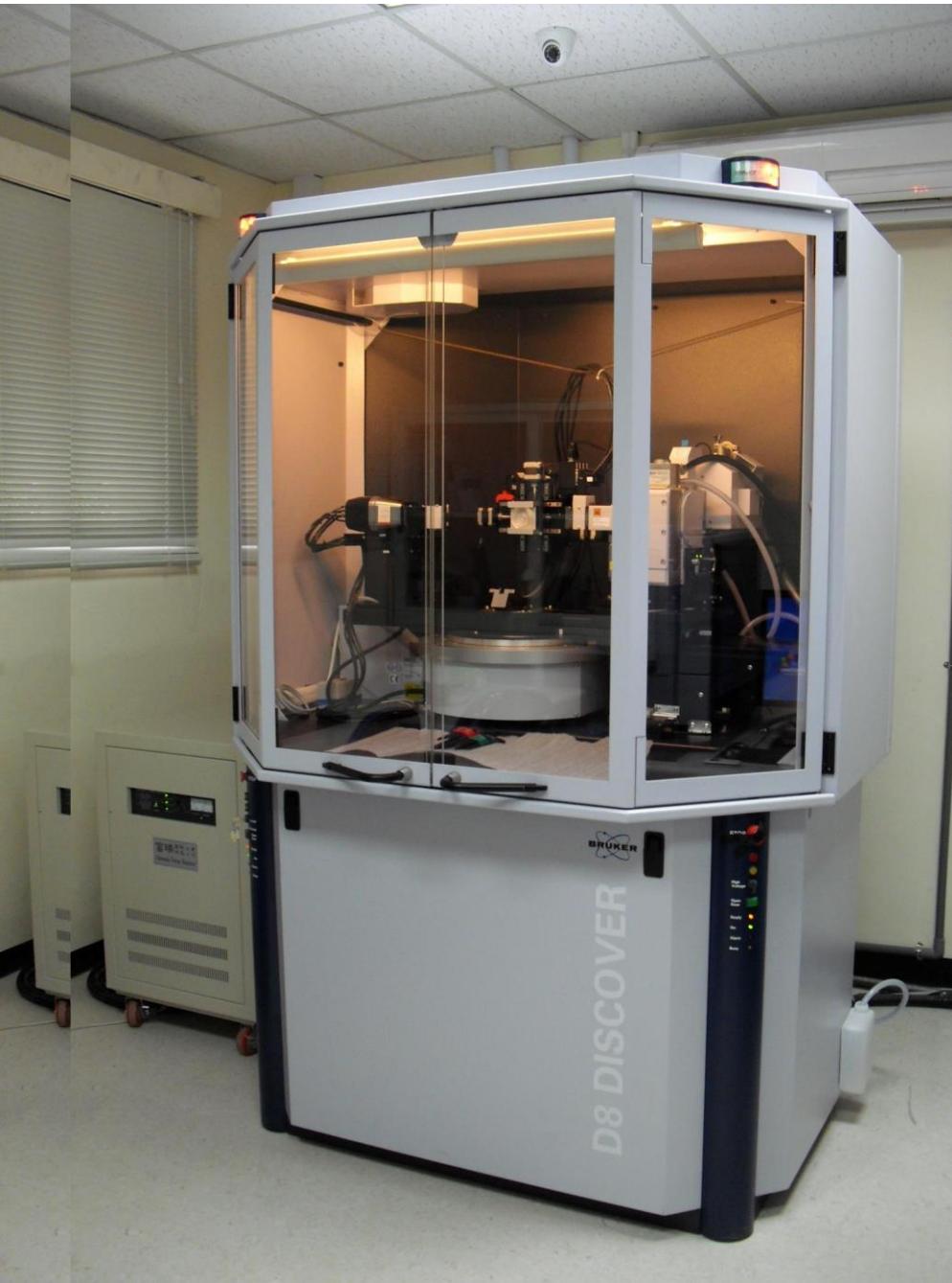


modulus–temperature curves for block copolymers

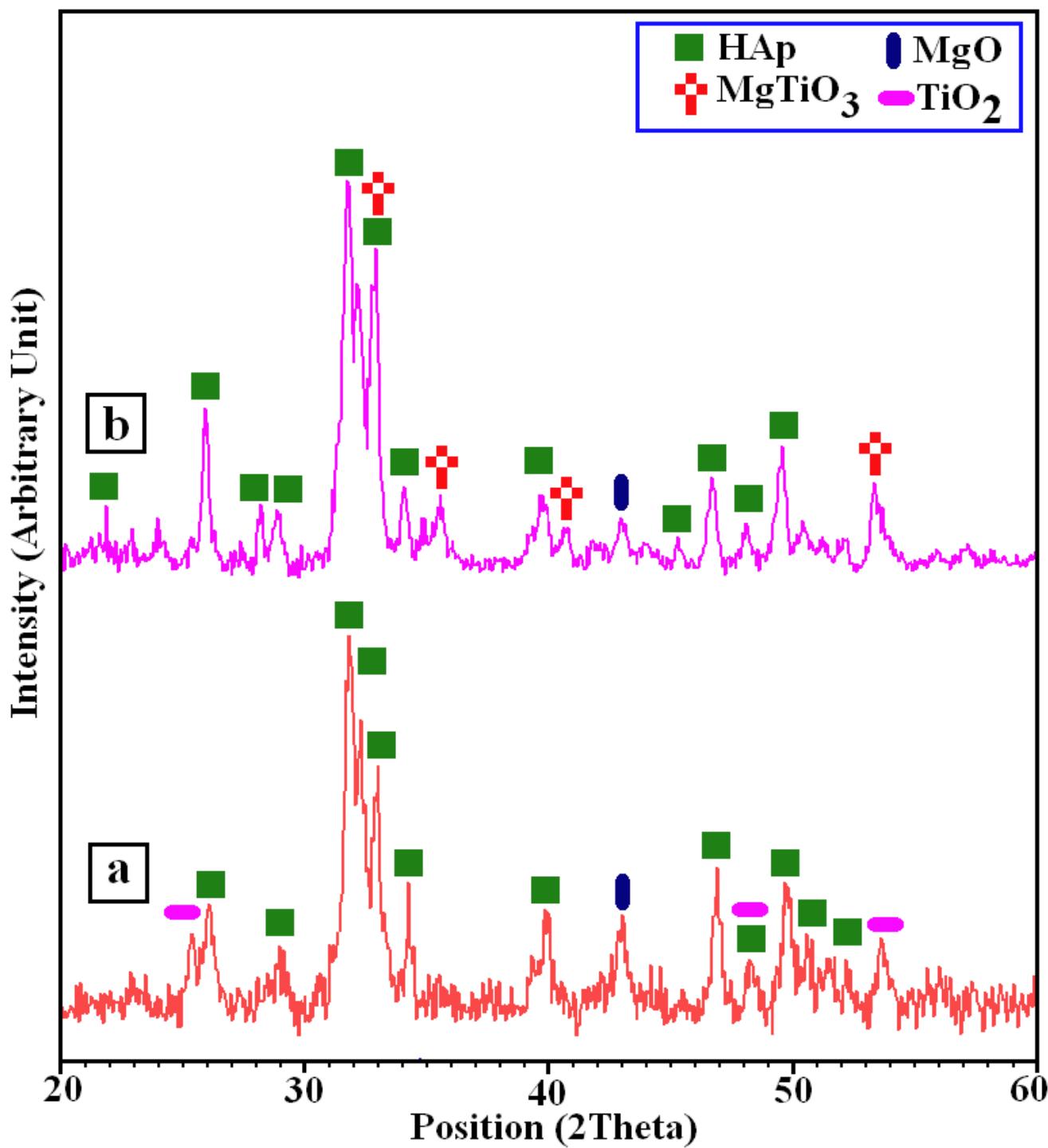
- distinct transition of both materials used to generate the copolymer

## Characterizing a Polymer's Physical State and Behavior

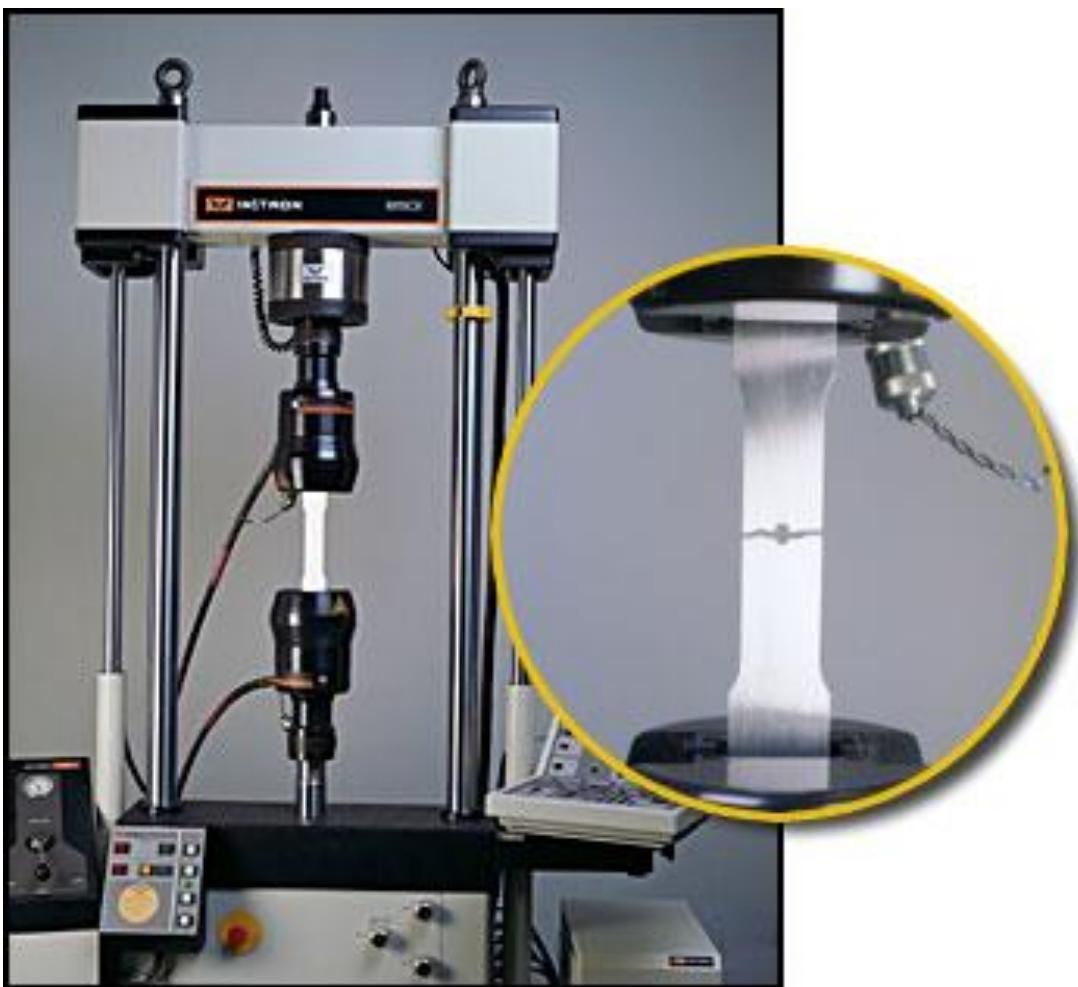
- **Crystallinity** plays a large role in determining polymer behavior.
- The *degree of crystallinity* – a measurement of how much of the polymer is incorporated into crystalline regions – can be studied with techniques such as measurement of density, **X-ray diffraction (XRD)**, and **infrared spectroscopy**.
- In **XRD experiments** a polymer sample is bombarded with X-ray radiation and the intensity of the scattered X-rays is measured as a function of scattering angle.
- A fully amorphous material would produce a very broad peak, covering all scattering angles. However, crystalline materials will produce sharp peaks at specific angles.
- The placement of these peaks corresponds to a particular crystalline structure.



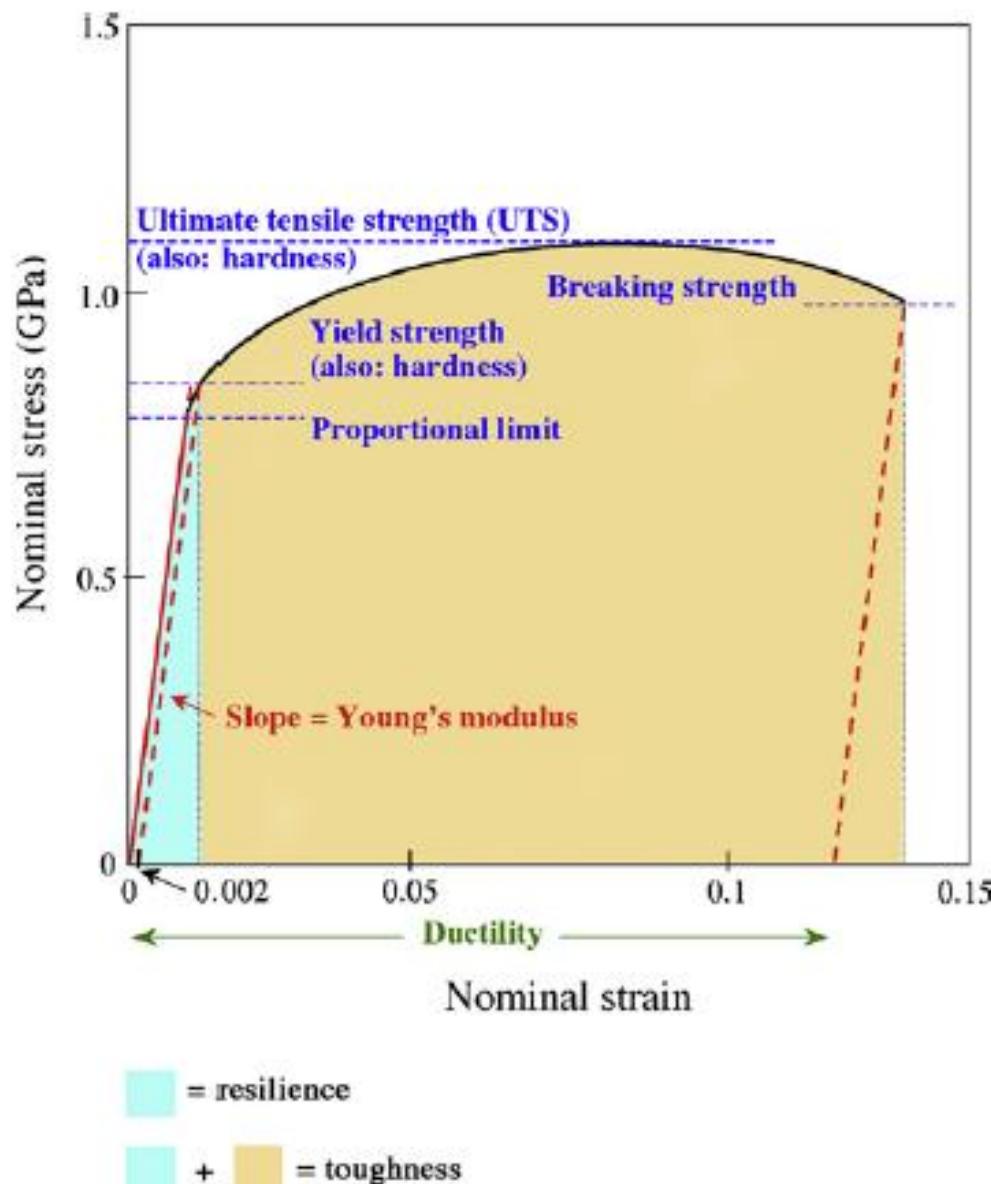
Video # 1



- **Stress-strain analysis** provides information about the mechanical behavior of a polymeric biomaterial. In this test a polymer sample of known dimensions is deformed at a given rate, and the force needed to cause the deformation is recorded.



Video # 2



**FIGURE I.1.3.3** Schematic nominal stress versus nominal strain plot for a ductile metal, emphasizing the features that relate to specific mechanical properties.

- From this analysis several key material properties can be determined:
  - modulus (a measurement of material stiffness)
  - tensile strength (the stress at failure)
  - percent elongation (the amount of deformation at failure).

## The room temperature mechanical properties of several polymeric biomaterials

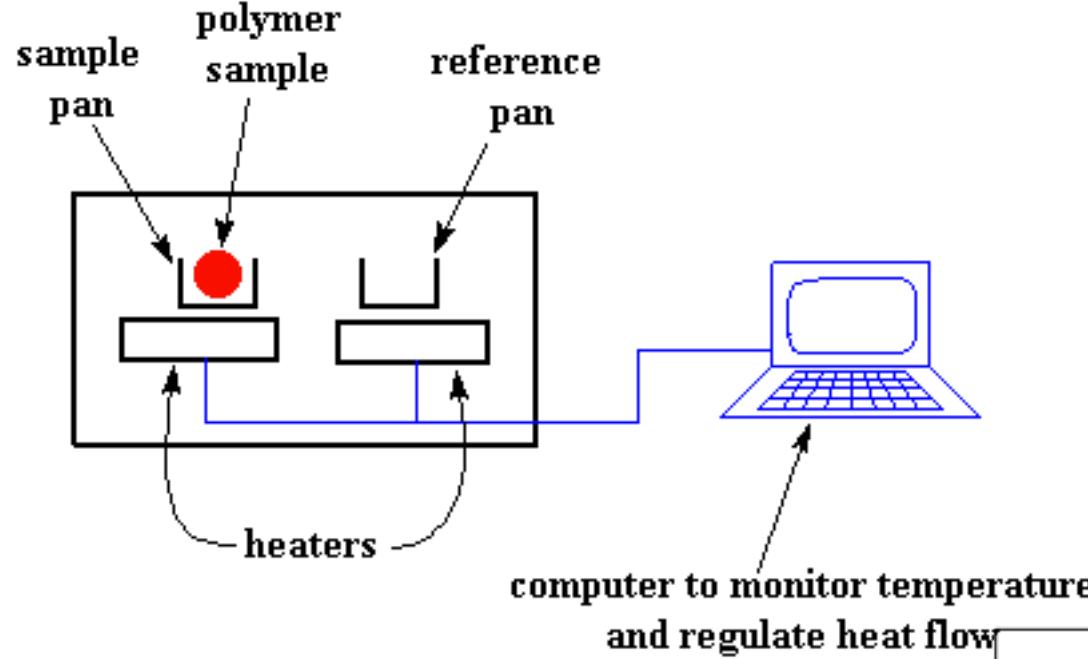
**TABLE I.2.2.1 Physical Properties and Equilibrium Water Absorption of Common Polymeric Biomaterials**

Material	Tensile Modulus (GPa)	Tensile Strength (MPa)	Elongation at Break (%)	Water Absorption (%)
Polyethylene (PE)	0.8–2.2	30–40	130–500	0.001–0.02
Poly(methyl methacrylate) (PMMA)	3–4.8	38–80	2.5–6	0.1–0.4
Polytetrafluoroethylene (PTFE)	1–2	15–40	250–550	0.1–0.5
Polylactide (PLA)	3.4	53	4.1	<0.5
Poly(hydroxyethyl methacrylate) <sup>†</sup> (PHEMA)	0.29	0.15	71	40
Polypropylene (PP)	1.6–2.5	21–40	100–300	0.01–0.035
Poly(ethylene terephthalate) (PET)	3–4.9	42–80	50–500	0.06–0.3

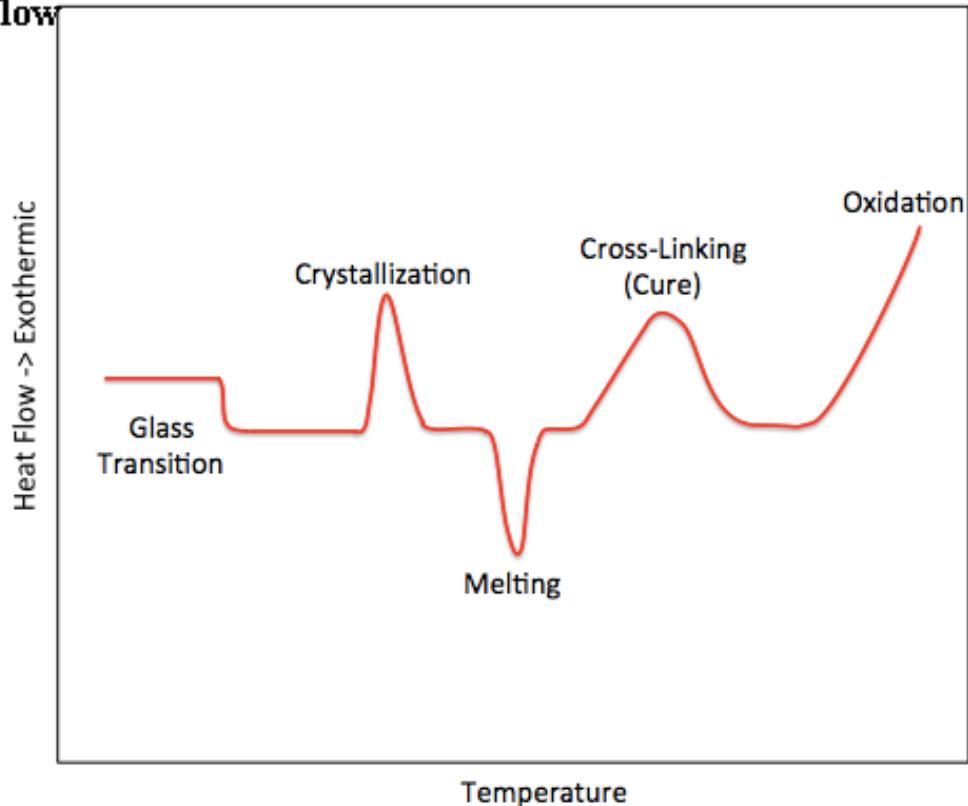
<sup>†</sup>Tensile properties were measured after the polymer was equilibrated with water.

## Measuring the Transition Temperatures Between States

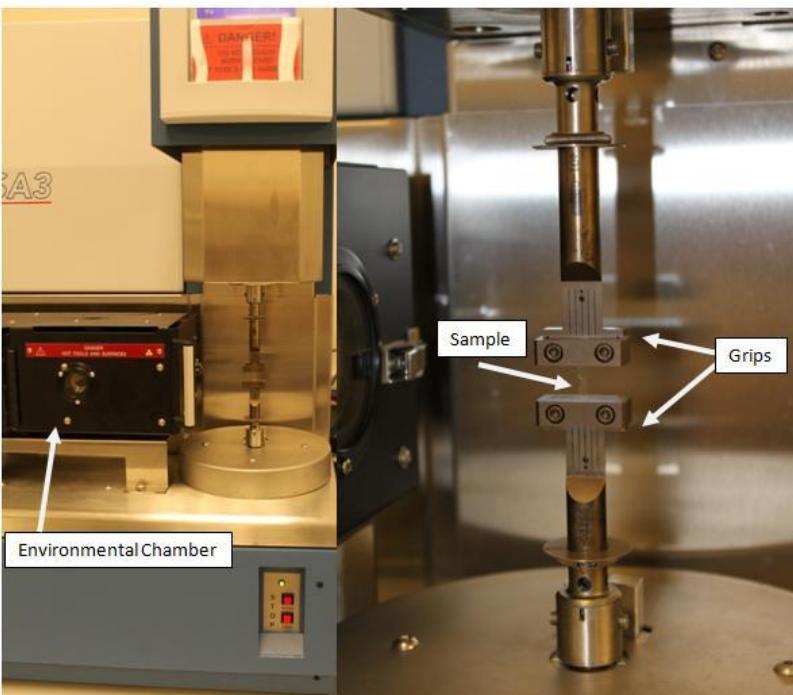
- Measuring transition temperatures ( $T_g$  and  $T_m$ ) is important to understanding how a material will behave in a certain application.
- Two common methods for determining the transition temperatures in polymer systems are **differential scanning calorimetry (DSC)** and **dynamic mechanical analysis (DMA)**
- In DSC experiments a polymer sample is heated at a constant temperature rate (generally 10–20°C/min) and the amount of heat supplied to the sample to obtain the temperature increase is recorded.
- The output from this experiment is a plot of supplied heat versus temperature.



Video # 3



- When performing a **dynamic mechanical analysis (DMA) experiment**, one measures the modulus (stiffness) of the material over a temperature range.
- The glass transition temperature of the material is physically observed as the softening point of the material.
- In a DMA study the modulus drops by approximately three orders of magnitude at the T<sub>g</sub>.
- At the T<sub>m</sub> another drop is observed, associated with the softening due to melting of the polymer crystalline units and the onset of flow behavior.



## Interactions with Water

- Biomaterials are often employed in highly hydrated environments, so their interaction with water is an important design characteristic
- Relatively non-polar and electrically neutral polymers such as polyethylene or poly(methylmethacrylate) are very hydrophobic and absorb <1 wt% water. However, as polarity is incorporated into the polymer, it will imbibe more water due to polar (and coulombic) interactions.
- One can tailor the interaction of a polymer with water in several ways, such as by controlling the ratio of hydrophobic and hydrophilic monomers in a copolymer.
- Crystalline regions in polymers usually resist infiltration of water molecules.
- If a polymer is processed in a way to control the degree of crystallization, the swelling character of the polymer can thereby be controlled.
- Cross-linked hydrophilic polymers generate hydrogels that can imbibe upwards of 200 wt% water.

### Measuring the Hydrophilicity of Polymer Materials?

- The surface hydrophilicity is probed through either static or dynamic contact angle experiments

## Degradation Characteristics

- Depending on the application, one may desire a polymer material that is either **biodegradable or biostable**.
  - For instance, a polymer that will be used for a tissue engineered scaffold needs to be biodegradable, and to “disappear” as functioning tissue is regenerated by cells. However, some biomaterials, such as dental implants, vascular grafts, and intraocular lenses need to be biostable so that they retain their function for the lifetime of the patient.
- The main type of polymer degradation reaction occurring in the body is **hydrolysis**
  - the reaction of the polymer backbone bonds with water, which results in the hydrolysis of those bonds and loss of the polymer’s mechanical properties.
- The ultimate stability of polymers in the body depends on **two key factors**: water absorption and the susceptibility of main chain bonds to hydrolysis.
  - The **carbon–carbon single bond** is very stable and those materials with main chain C–C bonds, such as polyethylene, polypropylene or PMMA, do not lose their properties due to degradation of the backbone.
  - the presence of other bonds in the polymer backbone (**heterochain polymers**) can lead to hydrolytic breakdown, and the rate of this hydrolysis is greatly affected by the polymer’s molecular structure.

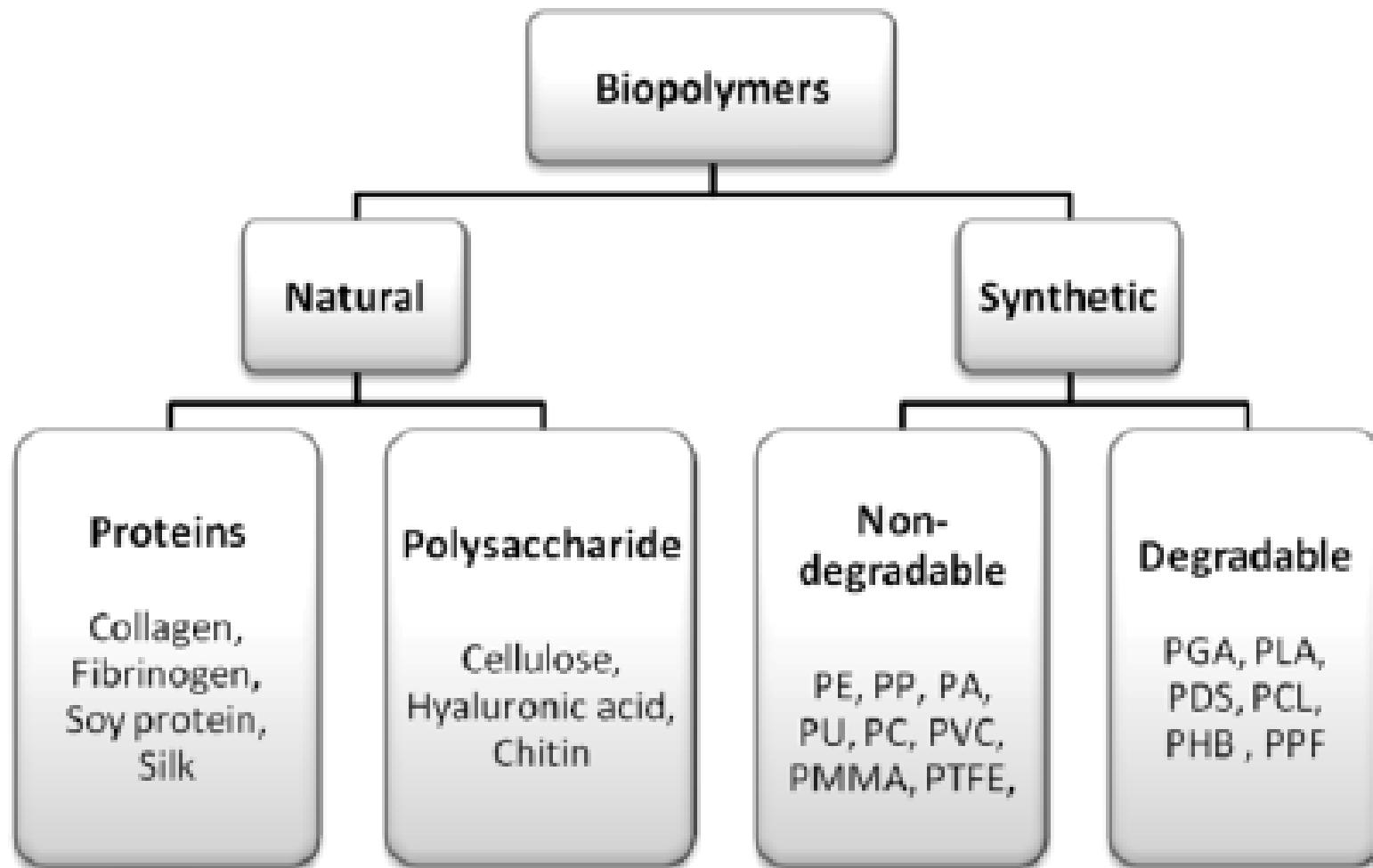
# Chemical Characteristics Of Several Polymeric Biomaterials, and Their Clinical Applications.

**TABLE I.2.2.4**

**Common Polymeric Biomaterials with Their Applications and the Properties That Make Them Useful in the Medical Field**

Material	Characteristics	Uses
Poly(methyl methacrylate) (PMMA)	Hydrophobic polymer which is hard, rigid, and biostable. The amorphous material is clear allowing light transmittance	Bone cement Intraocular lenses Hard contact lenses
Polyacrylamide (PA)	Cross-linking produces a hydrogel with molecular-sized pores and allows the gel to be used as a separation medium	Separation gel used in electrophoresis
Poly(acrylic acid) (PAA)	The liquid monomer can be cured with a photo-initiator. If inorganic salts are added, ionic cross-linking can occur. The material is glassy and rigid, and has the potential to bond to enamel	Glass ionomer cement used in dental restoration
Polyethylene (high density) (PE)	Low density PE cannot withstand sterilization temperatures; however, high density PE has good toughness and wear resistance	Tubing for drains and catheters Prosthetic joints
Poly(vinyl chloride) (PVC)	PVC is plasticized to make flexible materials. This material is used for short-term applications since plasticizers can be leached resulting in embrittlement of the material	Tubing Blood storage bags
Polypropylene (PP)	Isotactic PP is semi-crystalline, has high rigidity and tensile strength, and good biostability	Non-degradable sutures Hernia repair
Polydimethylsiloxane (PDMS)	Due to its silicone backbone, this material has a very low $T_g$ making it extremely flexible and providing it with good fatigue resistance at physiological conditions	Finger joints Heart valves Breast implants Ear, chin, and nose reconstruction
Poly(ethylene terephthalate) (PET)	The aromatic rings in the backbone generate a polymer with a high melting point ( $T_m = 267^\circ\text{C}$ ). It is semi-crystalline and possesses excellent tensile strength	Vascular grafts Fixation of implants Hernia repair Ligament reconstruction
Cellulose acetate (CA)	Unique transport properties make it excellent for use in the separation of complex biological mixtures	Dialysis membranes Osmotic drug delivery devices

# Classification of biopolymers



# NATURAL POLYMERS VERSUS SYNTHETIC POLYMERS

Natural polymers are polymer compounds that can be found naturally in our environment

Occur naturally

Produced from biological processes

Most polymers are easily degraded by biological processes

Synthetic polymers are polymer compounds that are produced artificially by humans

Do not occur naturally

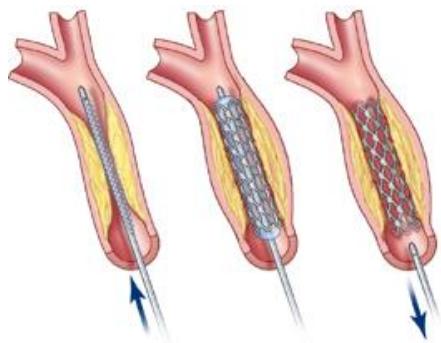
Produced from chemical processes

Most polymers are hard to degrade naturally by biological processes

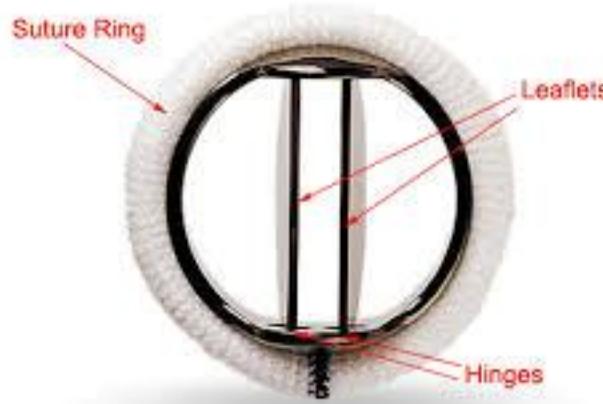
# Classes of Materials Used in Medicine:

**Metals**

- Large segments of the medical device industry rely on implants with one or more metallic parts



Stents



heart valves



artificial hip joints



dental implants



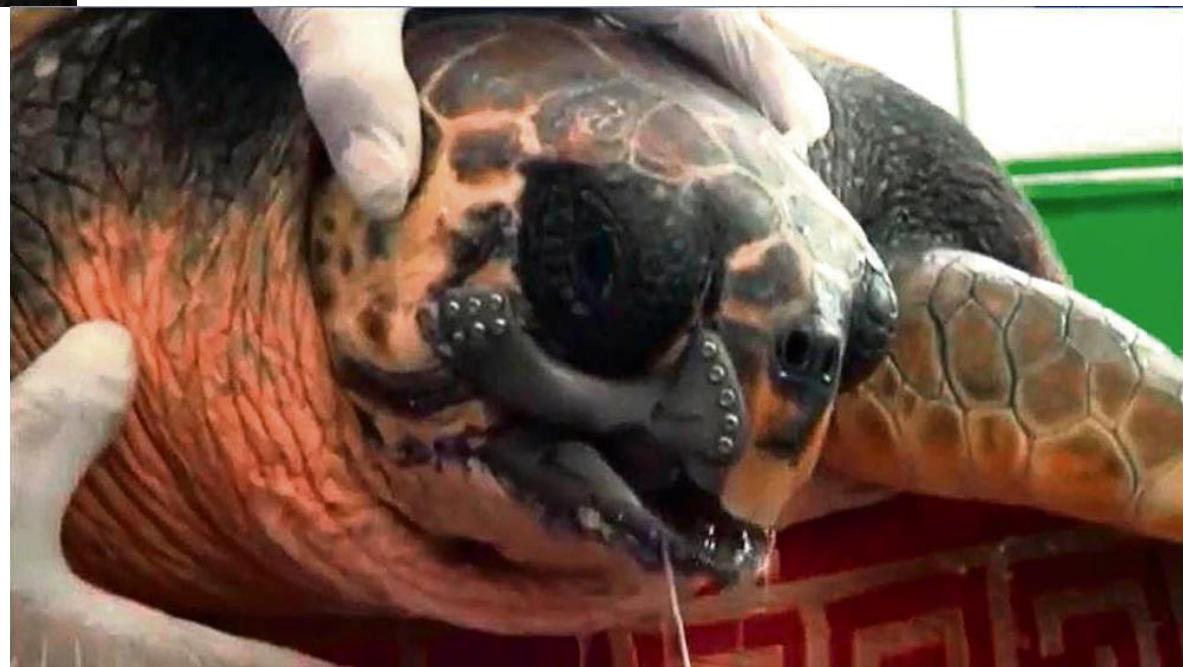
Screws

Plate

# Injured sea turtle gets 3D printed jaw/ <http://www.bbc.com/news/technology-32780674>



Akut-3



Video- Akut-3

## Reconstruction with a patient-specific titanium implant after a wide anterior chest wall resection

Akif Turna,<sup>a</sup> Kuthan Kavaklı,<sup>b,\*</sup> Ersin Sapmaz,<sup>b</sup> Hakan Arslan,<sup>c</sup> Hasan Caylak,<sup>b</sup> Hasan Suat Gökçe,<sup>d</sup> and Ahmet Demirkaya<sup>a</sup>

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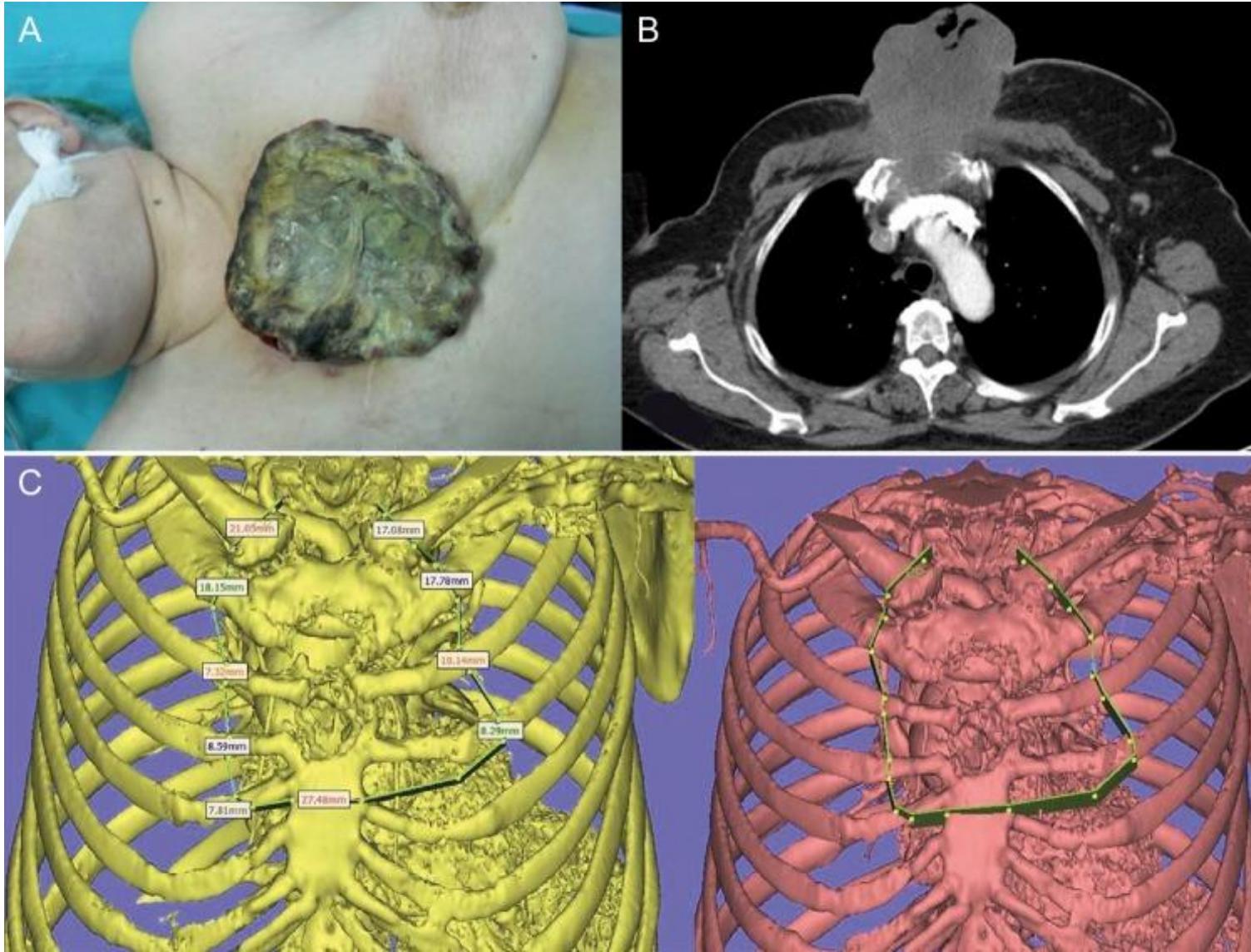
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### Abstract

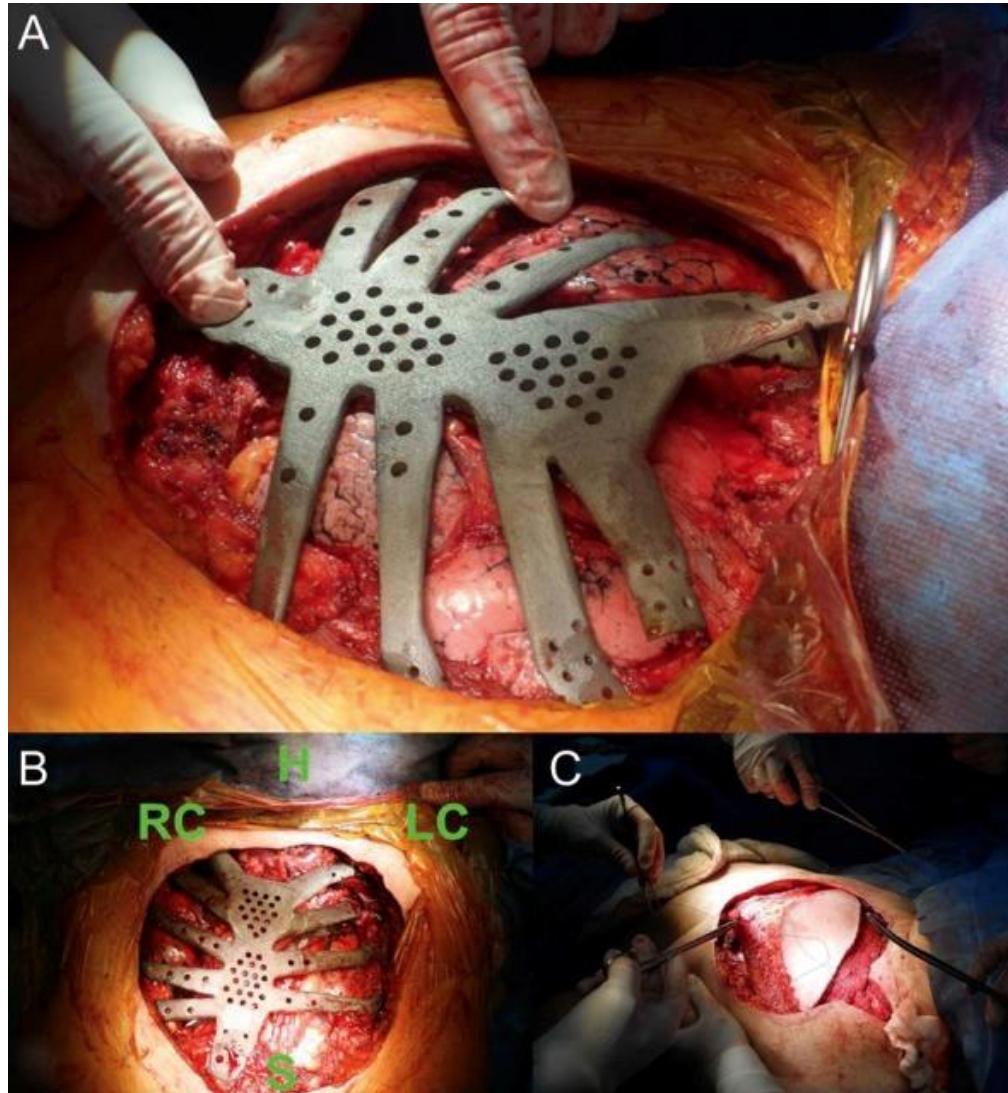
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The reconstruction of full-thickness chest wall defects is a challenging problem for thoracic surgeons, particularly after a wide resection of the chest wall that includes the sternum. The location and the size of the defect play a major role when selecting the method of reconstruction, while acceptable cosmetic and functional results remain the primary goal. Improvements in preoperative imaging techniques and reconstruction materials have an important role when planning and performing a wide chest wall resection with a low morbidity rate. In this report, we describe the reconstruction of a wide anterior chest wall defect with a patient-specific custom-made titanium implant. An infected mammary tumour recurrence in a 62-year old female, located at the anterior chest wall including the sternum, was resected, followed by a large custom-made titanium implant. Latissimus dorsi flap and split-thickness graft were also used for covering the implant successfully. A titanium custom-made chest wall implant could be a viable alternative for patients who had large chest wall tumours.

**Keywords:** Chest wall resection, Reconstruction, Implant, Thoracic surgery



Preoperative view of the chest wall tumour. The mass involves the skin and anterior chest wall including manubrium sterni (A). The preoperative computed tomographic scan of the patient reveals no invasion to the vascular structures of the mediastinum. It also shows that most parts of the anterior chest wall bone structures were invaded by the mass (B). The resection plan was marked on the 3D reconstruction of the computed tomography scan (C).



The patient specific titanium implant is compatible with the bony structures of the chest wall of patient. The angle between the clavica and first rib can be seen clearly (A). The orientation view of the operative field. H: head of the patient, RC: right clavica, LC: left clavica, S: one-third distal part of the sternum ( B). The soft tissue coverage of titanium implant with latissimus dorsi musculocutaneous-rotated flap (C).

- Any of metallic devices must support high mechanical load and resistance of material against breakage is essential.

### A comparison of general material properties

	Ceramics	Metals	Polymers
Hardness	Very High	High	Very Low
Elastic Modules	Very High	High	Low
Ductility	Low	High	High
Thermal Expansion	Low	High	High
Corrosion Resistance	High	Low	Low
Resistance to Wear	High	Low	Low
Density	Low	High	Very Low
Electrical Conductivity	High/Low	High	Low
Heat Conductivity	High/Low	High	Low

- Metals have a highly significant place in the biomaterials market.

TABLE 1   Key Applications of Synthetic Materials and Modified Natural Materials In Medicine*		
Application	Biomaterials Used	Number/Year – World (or World Market in US\$)
<b>Skeletal system</b>		
Joint replacements (hip, knee, shoulder)	Titanium, stainless steel, polyethylene	2,500,000
Bone fixation plates and screws	Metals, poly(lactic acid) (PLA)	1,500,000
Spine disks and fusion hardware		800,000
Bone cement	Poly(methyl methacrylate)	(\$600M)
Bone defect repair	Calcium phosphates	–
Artificial tendon or ligament	Polyester fibers	–
Dental implant-tooth fixation	Titanium	(\$4B)
<b>Cardiovascular system</b>		
Blood vessel prostheses	Dacron, expanded Teflon	200,000
Heart valve	Dacron, carbon, metal, treated natural tissue	400,000
Pacemaker	Titanium, polyurethane	600,000
Implantable defibrillator	Titanium, polyurethane	300,000
Stent	Stainless steel, other metals, PLA	1,500,000
Catheter	Teflon, silicone, polyurethane	1B (\$20B)
<b>Organs</b>		
Heart assist device	Polyurethane, titanium, stainless steel	4000
Hemodialysis	Polysulfone, silicone	1,800,000 patients (\$70B)
Blood oxygenator	silicone	1,000,000
Skin substitute	Collagen, cadaver skin, nylon, silicone	(\$1B)
<b>Ophthalmologic</b>		
Contact lens	Acrylate/methacrylate/silicone polymers	150,000,000
Intraocular lens	Acrylate/methacrylate polymers	7,000,000
Corneal bandage lens	hydrogel	–
Glaucoma drain	Silicone, polypropylene	(\$200M)
<b>Other</b>		
Cochlear prosthesis	Platinum, platinum-Iridium, silicone	250,000 total users
Breast implant	Silicone	700,000
Hernia mesh	Silicone, polypropylene, Teflon	200,000 (\$4B)
Sutures	PLA, polydioxanone, polypropylene, stainless steel	(\$2B)
Blood bags	Poly(vinyl chloride)	–
Ear tubes (Tympanostomy)	Silicone, Teflon	1,500,000
Intrauterine device (IUD)	Silicone, copper	1,000,000

\*Data compiled from many sources – these numbers should be considered rough estimates that are changing with growing markets and new technologies.

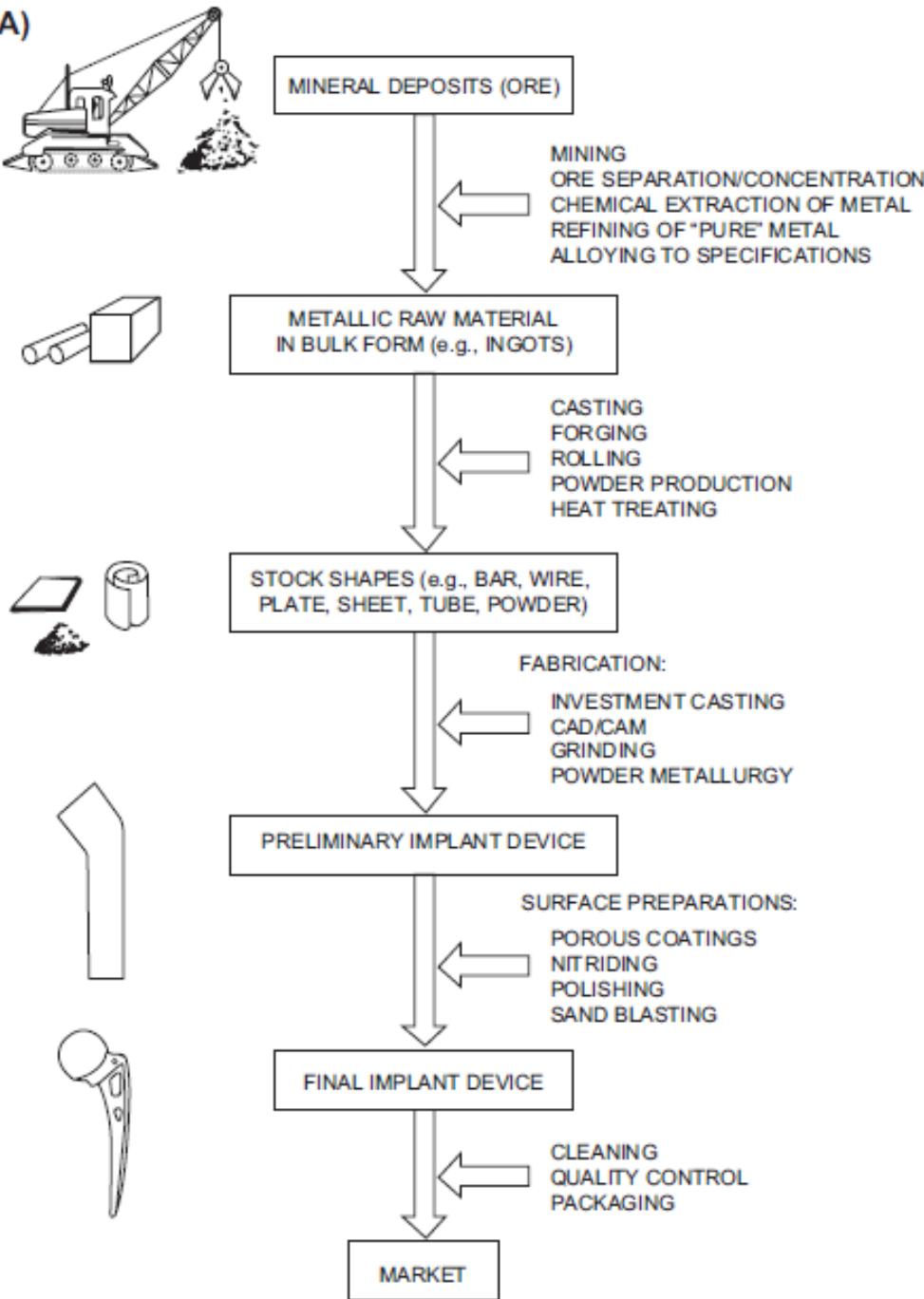
Where only US numbers are available, world usage is estimated at approximately 2.5x of US usage.

NOTE: M = millions, B = billions.

## STEPS IN THE FABRICATION OF METALLIC BIOMATERIALS

- Understanding the structure and properties of metallic implant materials requires an appreciation of the metallurgical significance of the material's processing history.
- Typically, any metallic medical device will differ in exactly how it is manufactured.

(A)



## ① Metal-Containing Ore to Raw Metal Product

- With the exception of noble metals such as gold (which do not represent a major fraction of implant metals), **metals exist in the Earth's crust in mineral form**, wherein the metal is chemically combined with other elements.
- These mineral deposits, or “ore,” must be located, mined, separated, and **enriched** for **further processing into pure metal or various alloys**.
- In the case of **multicomponent metallic implant alloys** (i.e., made up of more than one element), the raw metal product will usually have to be **further processed** both chemically and physically.
- Processing steps** can include remelting, addition of specific alloying elements, and controlled solidification from the melt, in order to produce an alloy that meets certain chemical and metallurgical specifications

FIGURE I.2.3.1 (A) Generic processing history of a typical metallic implant device, in this case a hip implant.

- For example, to make ASTM (American Society for Testing and Materials) F138 316L stainless steel, iron is alloyed with specific amounts of carbon, silicon, nickel, and chromium; and to make ASTM F75 or F90 alloy, cobalt is alloyed with specific amounts of chromium, molybdenum, carbon, nickel, and other elements.
- Table I.2.3.1 lists ASTM designations and typical properties of common metallic alloys for surgical implants.

**TABLE I.2.3.1 | Typical Mechanical Properties of Implant Metals<sup>a</sup>**

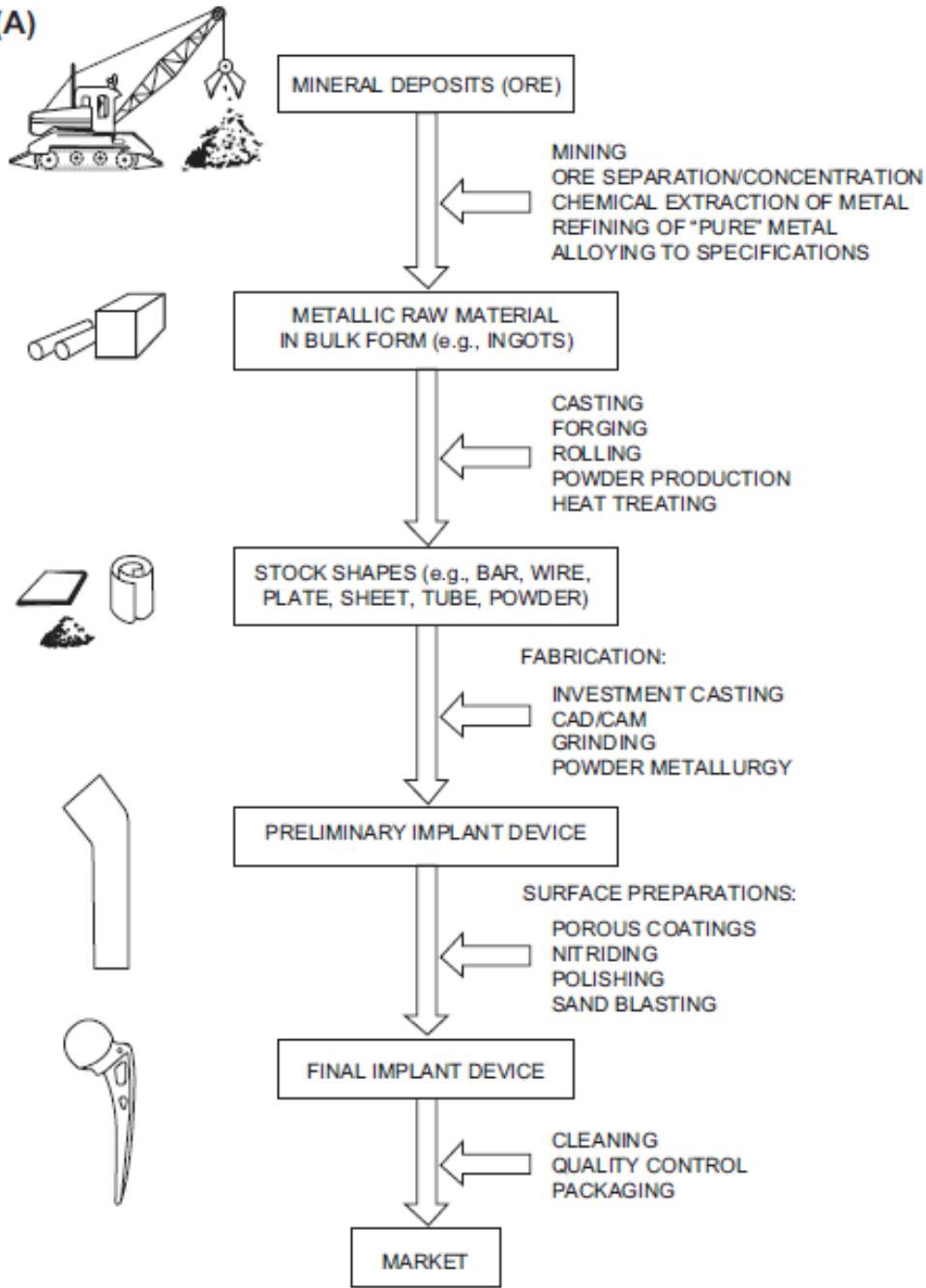
Material	ASTM Designation	Condition	Young's Modulus (GPa)	Yield Strength (MPa)	Tensile Strength (MPa)	Fatigue Endurance Limit Strength (at 10 <sup>7</sup> cycles, R = -1 <sup>c</sup> ) (MPa)
Stainless steel	F745 F55, F56, F138, F139	Annealed	190	221	483	221–280
		Annealed	190	331	586	241–276
		30% Cold-worked	190	792	930	310–448
		Cold forged	190	1213	1351	820
Co–Cr alloys	F75	As-cast/annealed	210	448–517	655–889	207–310
		P/M HIP <sup>b</sup>	253	841	1277	725–950
	F799	Hot forged	210	896–1200	1399–1586	600–896
		Annealed	210	448–648	951–1220	Not available
	F90	44% Cold-worked	210	1606	1896	586
		Hot forged	232	965–1000	1206	500
		Cold-worked, aged	232	1500	1795	689–793 (axial tension R = 0.05, 30 Hz)
Ti alloys	F67	30% Cold-worked Grade 4	110	485	760	300
		Forged annealed	116	896	965	620
	F136	Forged, heat treated	116	1034	1103	620–689

<sup>a</sup> Data collected from references noted at the end of this chapter, especially Table 1 in Davidson and Georgette (1986).

<sup>b</sup> P/M HIP: Powder metallurgy product, hot-isostatically pressed.

<sup>c</sup> R is defined as  $\sigma_{\min}/\sigma_{\max}$ .

(A)



## ② Raw Metal Product to Stock Metal Shapes

- A metal supplier will typically **further process** the bulk raw metal product (metal or alloy) **into stock bulk shapes**, such as bars, wire, sheet, rods, plates, tubes or powders.
- These **stock shapes** may then **be sold to implant manufacturers**, who typically want a stock shape that is closer to the final implant shape
  - e.g., a maker of screw-shaped dental implants would often buy rod stock of the appropriate metal as feedstock for screw-manufacturing machines.
- A metal supplier might transform the raw metal product into stock shapes by a variety of processes, including
  - remelting
  - continuous casting
  - hot rolling
  - Forging
  - cold drawing, etc.

FIGURE I.2.3.1 (A) Generic processing history of a typical metallic implant device, in this case a hip implant.

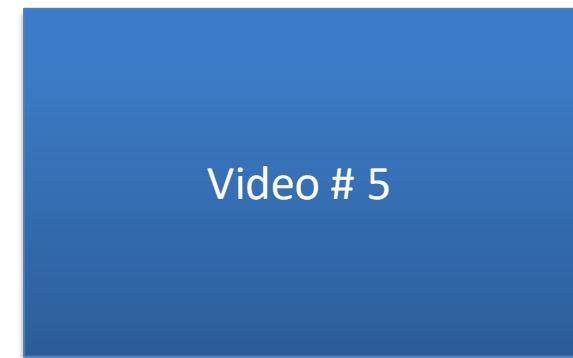
### ③ Stock Metal Shapes to Preliminary and Final Metal Devices

- An implant manufacturer will buy stock material and then fabricate preliminary and final forms of the device.
  - Final geometry of the implant depends on a number of factors such as the forming and machining properties of the metal, and the costs of alternative fabrication methods.
  - Typical fabrication methods include
    - investment casting
    - conventional and computer-based machining (CAD/CAM)
    - Forging
    - powder metallurgical processes
- and a range of grinding and polishing steps.

- A variety of fabrication methods are required because not all implant alloys can be feasibly or economically fabricated into a final form in the same way.
  - For example, cobalt-based alloys are extremely difficult to machine into the complicated shapes of some implants by conventional machining methods. Therefore, many cobalt-based alloys are frequently shaped into implant forms by investment casting (e.g., Figure I.2.3.1B) or by powder metallurgy.



**FIGURE I.2.3.1** (B) Image of one step during the investment casting (“lost wax”) process of manufacturing hip stems; a rack of hip stems can be seen attached to a system of sprues through which molten metal can flow. At this point, ceramic investment material composes the mold into which the molten metal will flow and solidify during casting, thereby replicating the intended shape of a hip stem.



- On the other hand, titanium is relatively difficult to cast, and is therefore often machined.

## MICROSTRUCTURES AND PROPERTIES OF IMPLANT METALS

- The most common metallic biomaterials are;

- ✓ stainless steels
- ✓ Co-Based alloys
- ✓ Ti-based alloys.

so discussion on microstructure-mechanical property relation on these metallic biomaterials may be meaningful.

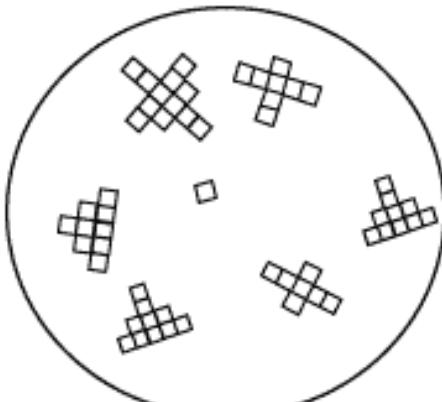
➤ **316L Stainless Steel.**

- In this alloy, two common strengthening methods are **cold-working** and **controlling grain size**.
- In cold-working, the idea is to introduce more and more plastic deformation such that additional plastic flow becomes even more difficult.
  - With 316L stainless (ASTM F138), typically it is used in a 30% cold-worked state, because this cold-worked metal has a markedly increased yield, ultimate tensile, and fatigue strength relative to the annealed state.

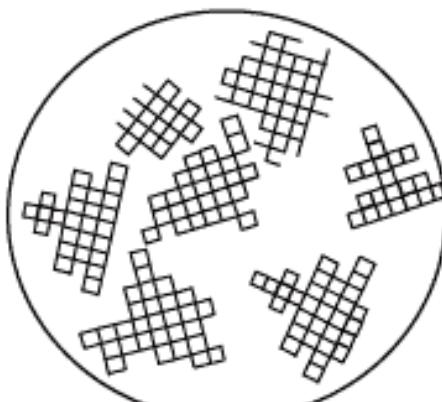
Video # 6

- In decreasing grain size, the idea is to have more grain boundaries to interfere with the flow of dislocations on slip systems within each grain.

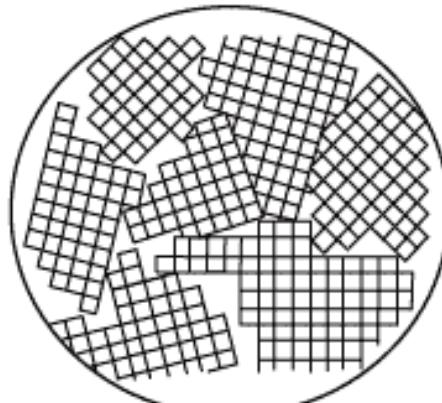
- Polycrystalline or multicrystalline materials, or polycrystals are solids that are composed of many crystallites of varying size and orientation. Crystallites are also referred to as **grains**.
  - They are small or even microscopic crystals and form during the **cooling** of many materials.
  - Their orientation can be random with no preferred direction, called random texture, or directed, possibly due to growth and processing conditions.
  - The areas where crystallite grains meet are known as **grain boundaries**.



(a)



(b)



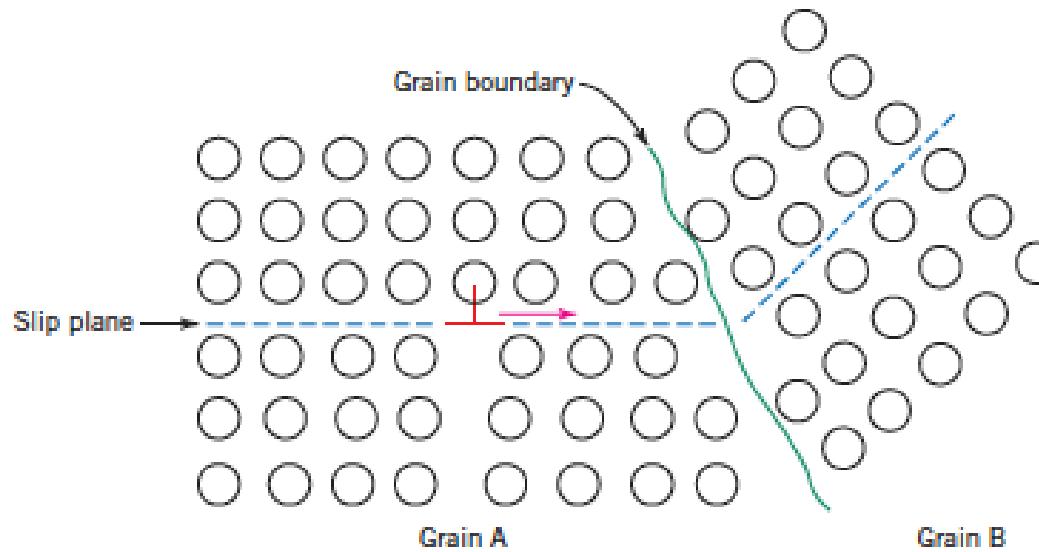
(c)



(d)

- a) Nucleation of crystals
- b) crystal growth
- c) irregular grains form as crystals grow together
- d) grain boundaries as seen in a microscope.

- **Dislocations** are defects or disturbed regions in the crystal lattice.



- The grain boundary acts as a barrier to dislocation motion for two reasons:
  1. The two grains are of different orientations, a dislocation passing into next grain must change its direction of motion → becomes more difficult as the misorientation increases.
  2. The atomic disorder within a grain boundary region results in a discontinuity of slip planes from one grain into the other.

- A key determinant of grain size is manufacturing history including details on
  - solidification conditions
  - cold-working
  - annealing cycles
  - recrystallization.

**TABLE I.2.3.1 Typical Mechanical Properties of Implant Metals<sup>a</sup>**

Material	ASTM Designation	Condition	Young's Modulus (GPa)	Yield Strength (MPa)	Tensile Strength (MPa)	Fatigue Endurance Limit Strength (at 10 <sup>7</sup> cycles, R = -1 <sup>c</sup> ) (MPa)
Stainless steel	F745	Annealed	190	221	483	221–280
		Annealed	190	331	586	241–276
	F55, F56, F138, F139	30% Cold-worked	190	792	930	310–448
		Cold forged	190	1213	1351	820
Co-Cr alloys	F75	As-cast/annealed	210	448–517	655–889	207–310
		P/M HIP <sup>b</sup>	253	841	1277	725–950
	F799	Hot forged	210	896–1200	1399–1586	600–896
		Annealed	210	448–648	951–1220	Not available
	F90	44% Cold-worked	210	1606	1896	586
		Hot forged	232	965–1000	1206	500
		Cold-worked, aged	232	1500	1795	689–793 (axial tension R = 0.05, 30 Hz)
Ti alloys	F67	30% Cold-worked Grade 4	110	485	760	300
		Forged annealed	116	896	965	620
	F136	Forged, heat treated	116	1034	1103	620–689

<sup>a</sup> Data collected from references noted at the end of this chapter, especially Table 1 in Davidson and Georgette (1986).

<sup>b</sup> P/M HIP: Powder metallurgy product, hot-isostatically pressed.

<sup>c</sup> R is defined as  $\sigma_{\min}/\sigma_{\max}$ .

## ➤ Cobalt-Based Alloys.

- Cobalt-based alloys include (ASTM F75 and F90), forged Co-Cr-Mo alloy (ASTM F799), and multiphase (MP) alloy MP35N (ASTM F562).

TABLE I.2.3.1 | Typical Mechanical Properties of Implant Metals<sup>a</sup>

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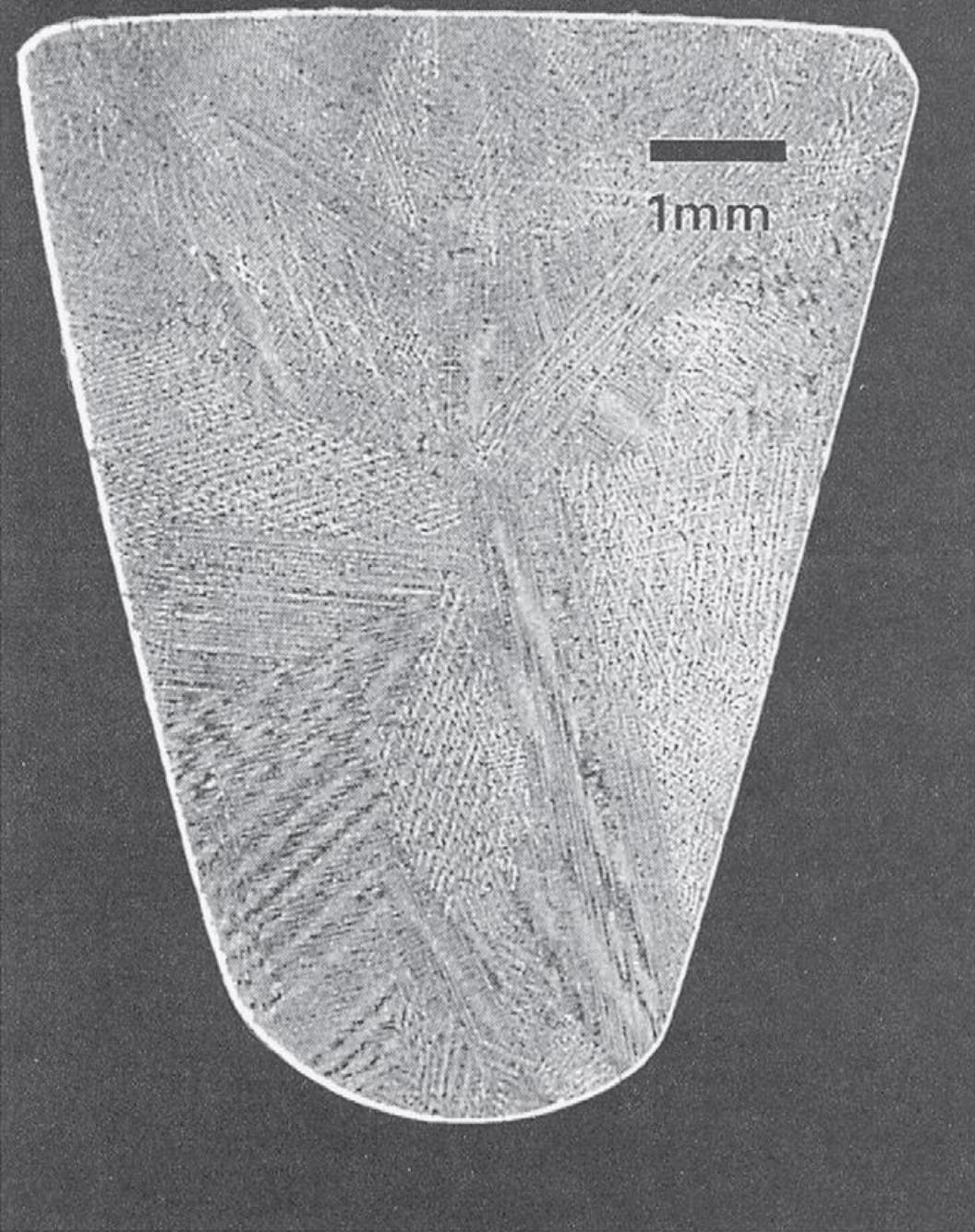
<sup>a</sup> Data collected from references noted at the end of this chapter, especially Table 1 in Davidson and Georgette (1986).

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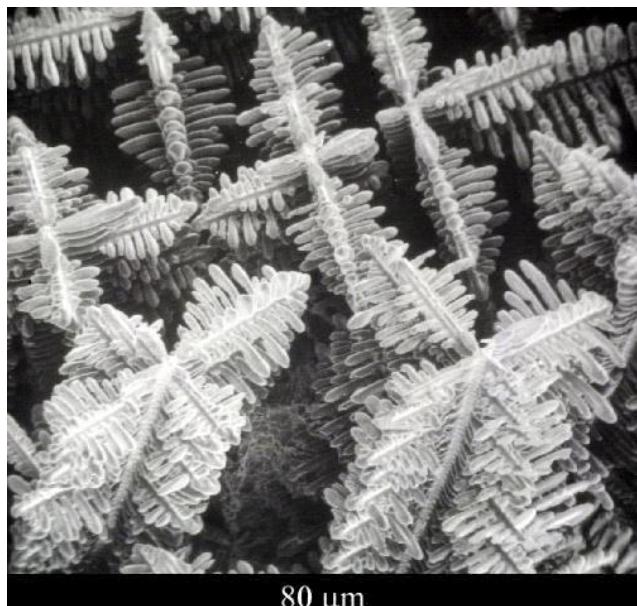
- The F75 and F799 alloys are virtually identical in composition, each being about 58–70% Co and 26–30% Cr, with the key difference in their processing history.
- F90 and F562, have slightly less Co and Cr, but more Ni (F562) or more tungsten (F90).

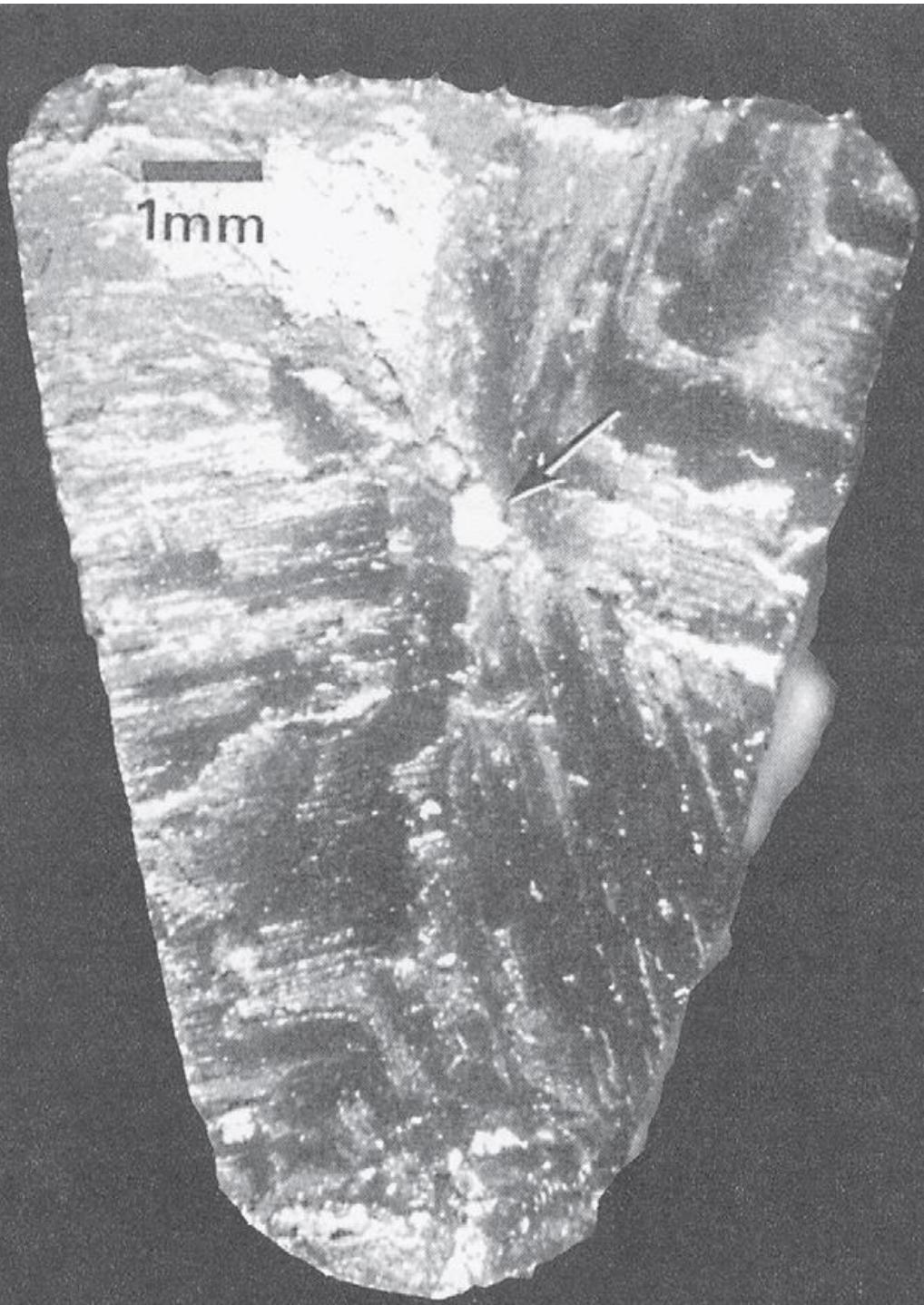
- F75 alloy has been frequently used in both the aerospace and biomedical implant industries because of its high corrosion resistance in chloride environments, which is related to its bulk composition and surface oxide (nominally  $\text{Cr}_2\text{O}_3$ ).
- When F75 is cast into shape by investment casting
  - the alloy is first melted at 1350–1450°C
  - then poured or pressurized into ceramic molds of the desired shape
    - ✓ femoral stems for artificial hips
    - ✓ oral implants
    - ✓ dental partial bridgework
- Depending on the exact details of the casting process, **at least three microstructural features** can come into play as strong determinants of implant properties.
  - “cored” microstructures that develop due to non-equilibrium cooling
  - relatively large grain sizes. This is generally undesirable because it decreases the yield strength
  - Inclusions may arise because of casting defects



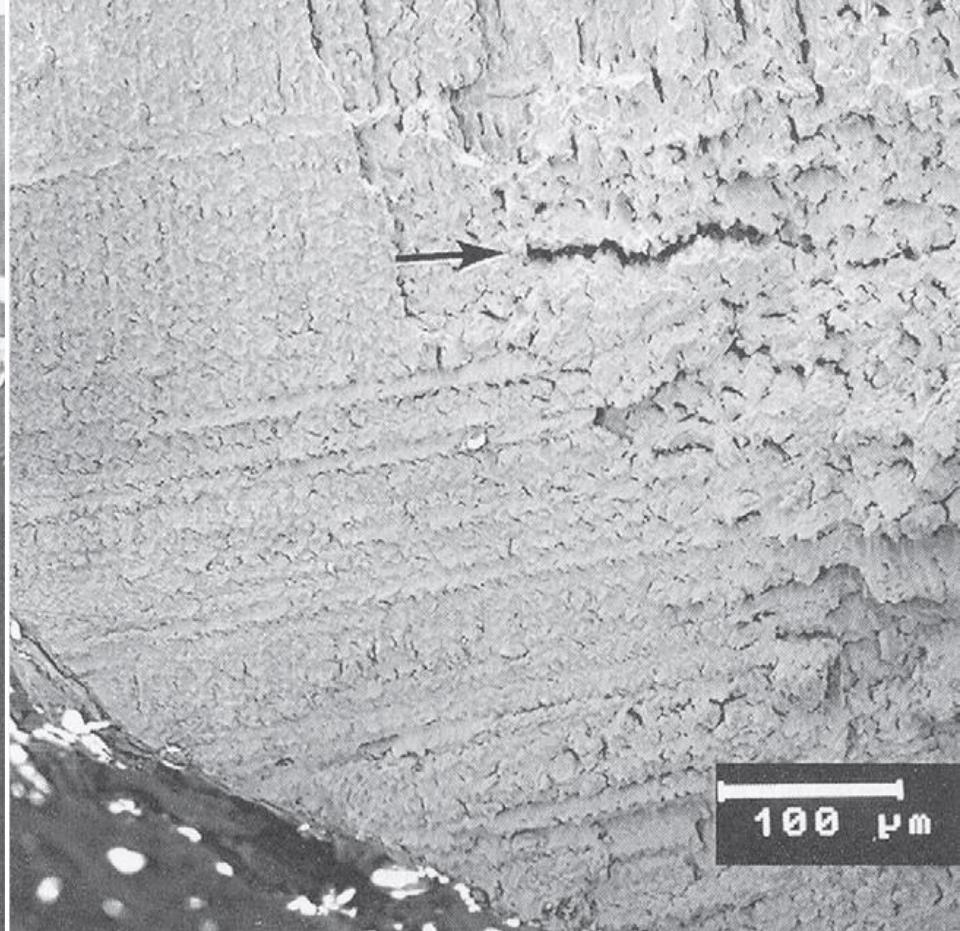
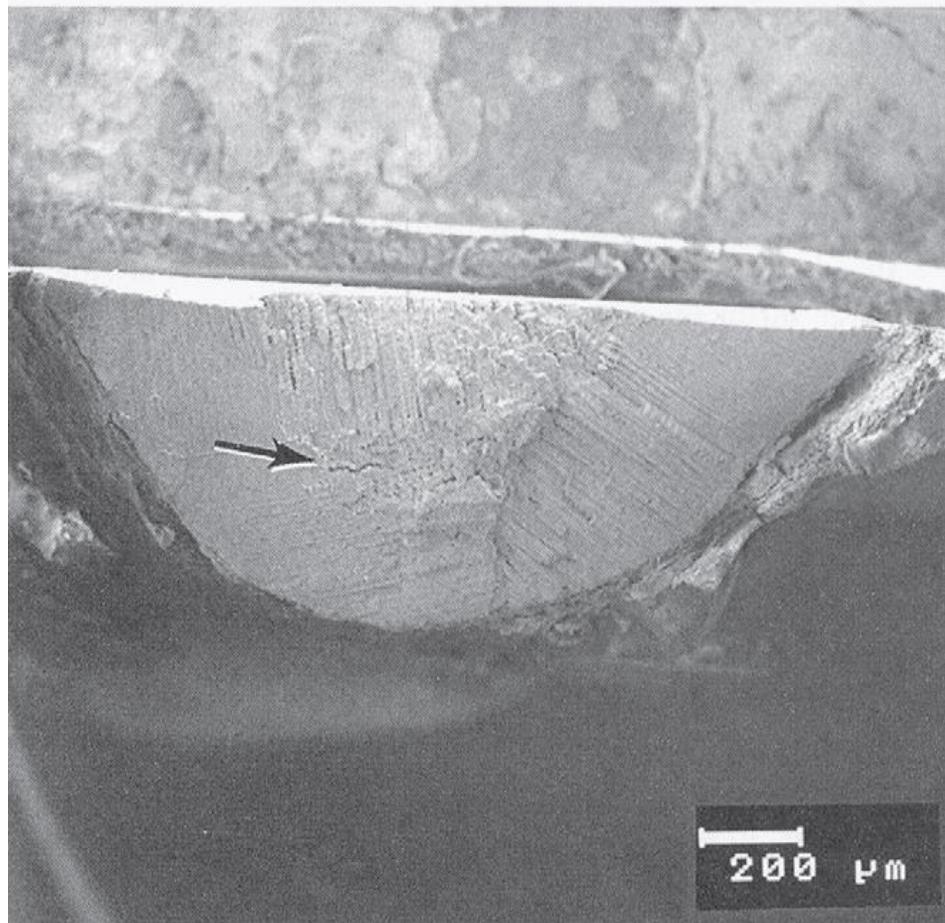
- Macrophoto of a metallographically polished and etched cross-section of a cast Co-Cr-Mo ASTM F75 femoral hip stem, showing dendritic structure and large grain size.

3D structure of dendrites in a cobalt-samarium-copper alloy





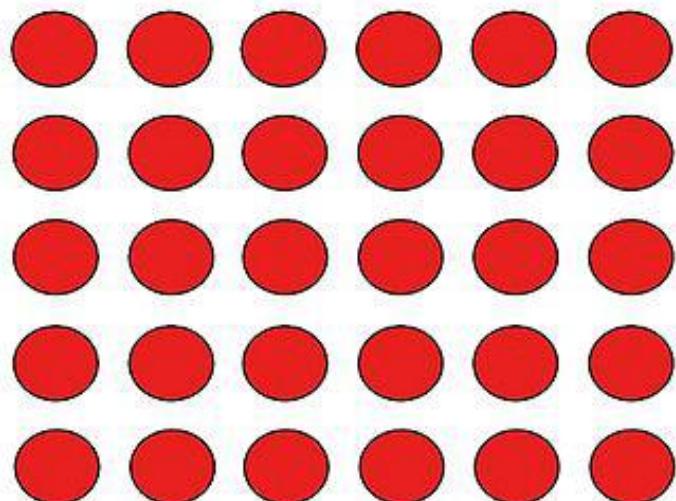
- Macrophoto of the fracture surface of the same femoral hip stem
- Arrow indicates large inclusion within the central region of the cross section
- Fracture of this hip stem occurred *in vivo*



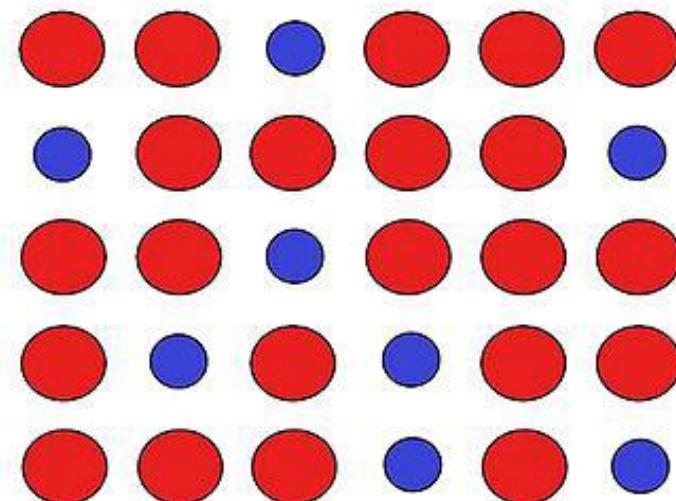
Scanning electron micrographs of the fracture surface from a cast F75 subperiosteal dental implant. Note the large grain size, dendritic microstructure, and interdendritic microporosity

## ➤ Titanium-Based Alloys.

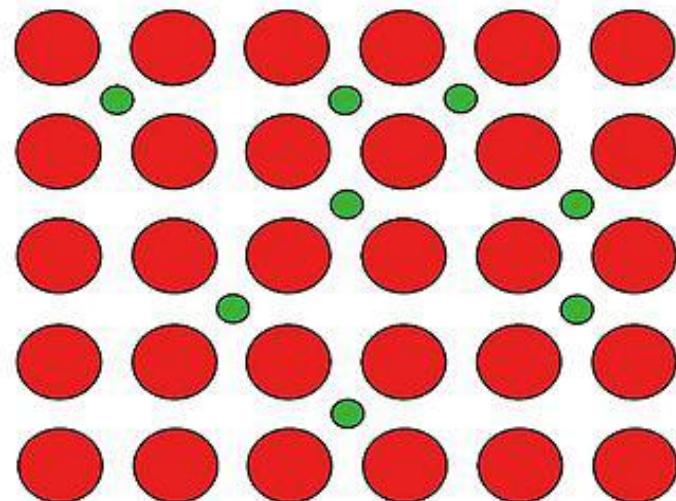
- Commercially pure (CP) titanium and Ti-6Al-4V alloy are the two most common titanium-based implant biomaterials (there are four grades of CP Ti ).
- The oxygen content of CP Ti, as well as the content of other interstitial elements (e.g., C and N), affect its yield, tensile, and fatigue strengths significantly.
- For CP titanium implants typical microstructures are made up of single-phase alpha titanium, in which there is typically mild (30%) cold-work and grain diameters in the range of 10–150 microns, depending on manufacturing.
- Beyond cold-work, interstitial elements (O, C, N) in both CP titanium and the Ti-6Al-4V alloy strengthen the metal with nitrogen having approximately twice the hardening effect (per atom) of either carbon or oxygen.
- The tensile strength increases with oxygen content.
- Fatigue limit of unalloyed CP Ti is typically increased by interstitial content, in particular the oxygen content.



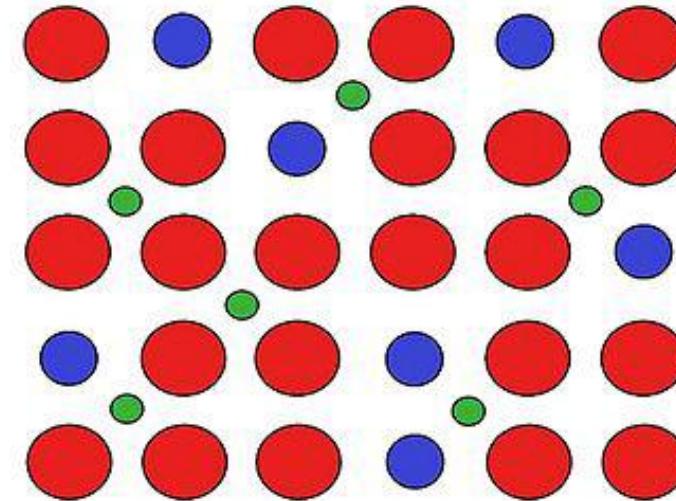
Pure metal



Substitutional alloy

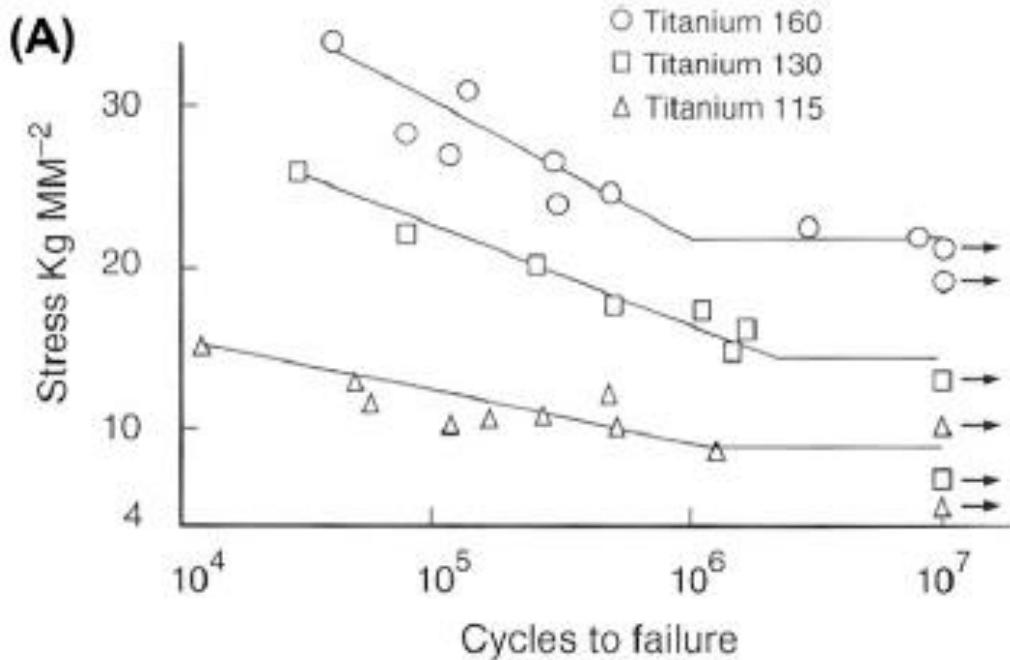


Interstitial alloy



Substitutional/interstitial alloy

- Fatigue study on vacuum-annealed CP Ti having a **grain size in the range 200–300 microns** in tension-compression at 100 cycles/sec.

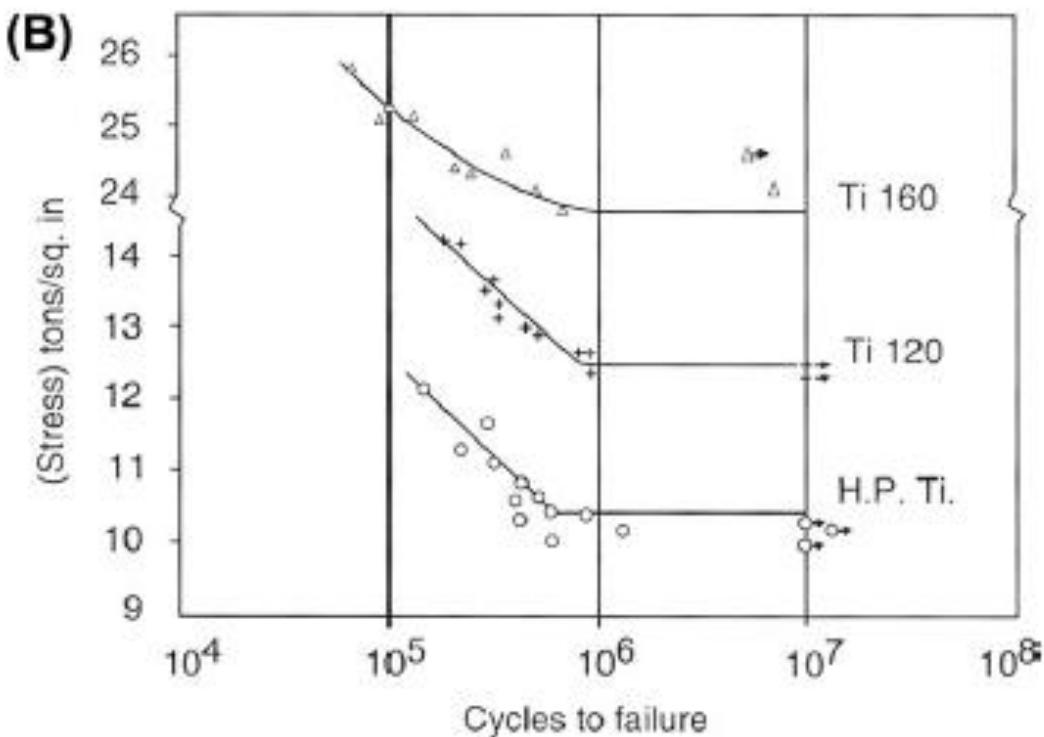


The  $10^7$  cycle endurance limit, or fatigue limit

substrate	oxygen content (wt%)	Endurance(fatigue) limit (Mpa)
Ti 115	0.085 (grade 1)	88.3
Ti 130	0.125 (grade 1)	142
Ti 160	0.270 (grade 3)	216

**FIGURE I.2.3.3 (A)** S–N curves (stress amplitude–number of cycles to failure) at room temperature for CP Ti with varying oxygen content, from Beevers and Robinson (1969).

- Fatigue study on CP Ti (tension-compression, 160 cycles/sec) having a grain size in the range **26–32 micrometers**.



the fatigue limit again increased with increasing oxygen content.

(B) S-N curves at room temperature for CP Ti with varying oxygen content, from Turner and Roberts (1968a).

Video # 9

- It seems clear that interstitial content affects the yield, tensile and fatigue strengths in CP Ti

TABLE I.2.3.1 | Typical Mechanical Properties of Implant Metals<sup>a</sup>

Material	ASTM Designation	Condition	Young's Modulus (GPa)	Yield Strength (MPa)	Tensile Strength (MPa)	Fatigue Endurance Limit Strength (at 10 <sup>7</sup> cycles, R = -1 <sup>c</sup> ) (MPa)
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		P/M HIP <sup>b</sup>	253	841	1277	725–950
	F799	Hot forged	210	896–1200	1399–1586	600–896
		Annealed	210	448–648	951–1220	Not available
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<sup>a</sup> Data collected from references noted at the end of this chapter, especially Table 1 in Davidson and Georgette (1986).<sup>b</sup> P/M HIP: Powder metallurgy product, hot-isostatically pressed.<sup>c</sup> R is defined as  $\sigma_{\min}/\sigma_{\max}$ .

# TITANIUM

- Titanium and its alloys have attracted much attention in the medical implants field as
  - they have unique mechanical properties
  - their superior corrosion resistance when compared to other metals and alloys
  - they do not initiate an allergenic response and have the probably the best tolerance among metallic biomaterials in the body.
- Currently only three alloy systems have extensive use in the industry,
  - commercially pure titanium (cpTi)
  - Ti-6Al-4V
  - Ti-6A1-7Nb.

## Corrosion Resistance

- With the exception of noble metals such as gold or platinum, the common implantable metals and alloys rely on the formation of **protective oxide films** to control corrosion of the material to acceptable levels. These oxides are commonly referred to as **passive films**.
- They are very thin (typically less than 100 microns), dense, and adhere strongly to the underlying substrate.
- They limit transport of metallic ions to the implant surface.
- This is attributed to the spontaneous formation of a few nm thick titanium dioxide film that protects the metal from further oxidation. This behavior depends on alloy composition and corrosive medium
- Ti-13Nb-13Zr confirmed the potential of Ti, Nb, and Zr to develop highly protective passive layers, resulting in a better corrosion resistance compared to Ti-6Al-4V

## Biocompatibility and Surface Modification

- The biocompatibility of a metallic alloy has to be understood in terms of both the biocompatibility of the alloy itself, which is closely associated with its corrosion resistance, and the biocompatibility of its by-products as a result of corrosion.
- It is generally accepted that Ti and its alloys are relatively “bioinert,” and exhibit acceptable *in vitro* and *in vivo* responses for the desired application.
- When implanted in bone, tissue forms new bonds at the bone implant material (osteointegration), however there maybe a thin fibrous layer separating the metallic implant and the bone leading to fail of the implant.
- In order to improve osteointegration, bioactivity, biocompatibility, and corrosion resistance, several surface treatments based on chemical and physical modifications have been developed.

## Mechanical Properties

- Ti and its alloys are very attractive for use in different biomedical devices, particularly orthopedics, due to their elastic modulus which is closer to that of bone in comparison to other alloys.
- The mechanical properties of cpTi and some Ti-based alloys

**TABLE A.1 Titanium Alloys Developed for Orthopedic Applications and Their Mechanical Properties  
(Adapted from Long and Rack, 1998)**

Alloy	Microstructure	Elastic Modulus E (GPa)	Yield Strength YS (MPa)	Ultimate Strength UTS (MPa)
cpTi	α	105	692	785
Ti-6Al-4V	α/β	110	850–900	960–970
Ti-6Al-7Nb	α/β	105	921	1024
Ti-5Al-2.5Fe	Metastable β	110	914	1033
Ti-15Mo-5Zr-3Al	Metastable β	82	771	812
Ti-Zr	Cast α'/β	N/A	N/A	900
Ti-13Nb-13Zr	α'/β	79	900	1030
Ti-15Mo-3Nb-0.30	Metastable β + silicides	82	1020	1020
Ti-35Nb-5Ta-7Zr	Metastable β	55	530	590
Ti-35Nb-5Ta-7Zr-0.40	Metastable β	66	976	1010
Stainless steel 316L	–	205–210	170–750	465–950
Co–Cr–Mo	–	220–230	275–1585	600–1785
Bone	–	10–40		90–140

- Much effort is currently being carried out to develop new alloys with low elastic modulus that mimic that of bone tissue.
- Among the alloys under investigation, the Ti–Nb–Ta– Zr system known as Gum metal (Ti-29Nb-13Ta-4.6Zr) is gaining attention in the field because of its super elastic properties.
  - Young's modulus of 40 Gpa
  - elastic strain of 2.5%
- Ti-35Nb-7Zr-5Ta is an alloy that has shown
  - enhanced osseointegration
  - improved ductility
  - adequate mechanical strength
  - optimal hot and cold workability
  - low elastic modulus (55 Gpa)

# STAINLESS STEELS

- There are a large number of stainless steels available commercially but only a few of these alloys are used as biomaterials for implantable devices.
- The performance of these alloys depends on their chemical composition and processing history. While 316L is the most common stainless steel, alloys with enhanced corrosion resistance and mechanical properties are available.
- chemical composition ranges specified for several common implantable stainless steels

TABLE B.1 Compositions of Common Implantable Stainless Steels (Weight Percent)

Alloy	Cr	Ni	Mn	Mo	C	N	Nb	V	Si	Cu	P	S
316L ASTM F138, ISO 5832-1	17–19	13–15	<2 max	2.25–3	<0.030	<0.10	–	–	<0.75	<0.5	<0.025	<0.010
22-13-5 ASTM F1314	20.5–23.5	11.5–13.5	4–6	2–3	<0.030	0.2–0.4	0.1–0.3	0.1–0.3	<0.75	<0.5	<0.025	<0.010
Rex 734, Ortron 90 ASTM F1586 ISO 5832-9	19.5–22	9–11	2–4.25	2–3	<0.08	0.25–0.5	0.25–0.8	–	<0.75	<0.25	<0.25	<0.010
BioDur® 108 ASTM F 2229	19–23	<0.050	21–24	0.5–1.5	<0.08	0.85–1.10	–	–	<0.75	<0.25	<0.03	<0.010

- Chromium is present in these alloys, primarily to form a protective  $\text{Cr}_2\text{O}_3$  surface layer (passive film) that is crucial to their corrosion resistance.
- Nitrogen additions increase mechanical strength and corrosion resistance.
- Molybdenum additions have a beneficial impact on the pitting corrosion resistance of stainless steels.
- Carbon is controlled to be at low levels to prevent the formation of chromium carbides (the “L” in 316L designates low carbon).
  - Formation of these carbides can result in a phenomenon known as sensitization.
  - If enough carbon is available, chromium carbides can form along grain boundaries, leaving the adjacent areas with depleted chromium levels which are prone to attack by corrosion.

## Corrosion Behavior

- The alloys that contain substantial amounts of chromium cobalt base alloys form a  $\text{Cr}_2\text{O}_3$  layer while alloys rich in titanium form a  $\text{TiO}_2$  layer.
- In general terms, the austenitic stainless steels are not considered to be quite as corrosion resistant as either cobalt-chromium alloys or titanium alloys
- Another factor which influences the corrosion of stainless steels is the presence of foreign particles, known as **inclusions**.
  - These are typically oxide particles such as alumina or silicates which are formed during the initial melting of the alloy and become trapped within the material during subsequent processing.
- Since these inclusions have different corrosion behavior than the alloy, they can act as corrosion initiation sites if they are found at the surface of a component.

## Mechanical Properties

- The mechanical properties of metals and alloys depend on their **chemical composition** and **processing history**.
- **Chemical composition** influences strength by a process known as solid solution strengthening.
  - In stainless steels the metallic alloying elements (**Cr, Ni, etc.**) replace iron atoms at random locations within the crystal structure.
  - Since the **various atoms are not the same size**, additions of alloying elements lead to distortion of the crystal lattice.
  - This distortion makes deformation of the material more difficult (dislocation movements), thus increasing strength (and generally decreasing ductility).

- Another strengthening mechanism available for these materials involves work hardening (also known as “**cold-working**”).
- As the amount of cold-work increases, strength parameters (yield strength and ultimate strength) increase, while the ductility decreases.
- This behavior gives designers the ability to specify a wide range of mechanical properties by proper selection of the alloy composition, processing temperature, and the amount of cold-work.

- Table B.2 lists approximate tensile and fatigue strength properties for some implantable stainless steels produced under different conditions.

**TABLE B.2 | Approximate Mechanical Properties of Stainless Steels**

Alloy	Material Condition	Ultimate Tensile Strength (MPa)	Yield Strength (MPa)	%Elongation	$10^7$ Cycle Endurance Limit (MPa)	Reference
316L	Annealed	550	240	55	180	Shetty & Ottersberg, 1995
316L	30% Cold-worked	896	827	20	380	Shetty & Ottersberg, 1995
316L	60% Cold-worked	1240	1000	12	450	Shetty & Ottersberg, 1995
Rex 734	Hot forged	1140–1230	1050–1179	15–19	585	Windler & Steger, 2003
22-13-5	Annealed	965	760	35	380	Shetty & Ottersberg, 1995
22-13-5	30% Cold-worked	1240	1170	15	530	Shetty & Ottersberg, 1995
22-13-5	60% Cold-worked	1585	1480	9	670	Shetty & Ottersberg, 1995
BioDur®108	Annealed	827–930	517–605	30–50	380	ASTM F 2229 and Technical Data Sheet BioDur®108
BioDur®108	35% Cold-worked	1580	1350	15		Technical Data Sheet BioDur®108
BioDur®108	65% Cold-worked	2000	1790	5		Technical Data Sheet BioDur®108

- A high level of fatigue strength is necessary for many stainless steel medical devices

Classes of Materials Used in Medicine:  
**Ceramics, Glasses, Glass-ceramics**

## INTRODUCTION

- Ceramics, glasses, and glass-ceramics include a broad range of inorganic/nonmetallic compositions.
- In the medical industry, these materials have been essential for
  - Eyeglasses
  - Diagnostic instruments
  - chemical ware
  - Thermometers
  - Tissue culture flasks
  - Fiber optics for endoscopy
- Insoluble porous glasses have been used as carriers for
  - Enzymes
  - Antibodies
  - Antigens

offering the advantages of resistance to microbial attack, pH changes, solvent conditions, temperature

- Insoluble glasses have also been developed as a microinjectable delivery system for radioactive isotopes for *in situ* treatment of tumors.
  - The glass microspheres go to the site of the tumor by way of the blood supply, and the radiation kills the cancer cells with very little damage to the other tissues, saving thousands of patients.
- Ceramics are also widely used in dentistry as restorative materials, such as in
  - gold–porcelain crowns
  - glass-filled ionomer cements
  - dentures
- Glass-ceramics are also widely used for dental restorations including
  - Inlays
  - Onlays
  - crowns
  - multi-unit bridges



- The main difference among inlays, onlays and overlays (crown) is in the size of damage and the area of the tooth being treated.
  - **Inlays cover** the central part of the tooth and are positioned within the hard tissues of the tooth. They do not cover the cusps or the pointed parts of the tooth.
  - **Onlays cover** a larger area. Besides replacing the internal part of the damaged tooth, they also cover one of the cusps. So, they are positioned inside the deep tissues of the tooth as well as cover part of the biting surface of the tooth.



## TYPES OF BIOCERAMICS: TISSUE ATTACHMENT

- It is essential to recognize that **no one material is suitable for all biomaterial applications.**
- As a class of biomaterials, ceramics, glasses, and glass-ceramics are generally used to repair or replace skeletal hard connective tissues.
- Their success depends upon:
  1. achieving a stable attachment to connective tissue when used as bulk implants
  2. stimulating repair and regeneration of bone when used as particulates for bone grafting.
- **The mechanism of tissue attachment is directly related to the type of tissue response at the implant-tissue interface.**
- There are **four types of tissue response** and **four different means of attaching prostheses to the skeletal system.**

**TABLE I.2.4.1****Types of Implant-Tissue Response**

If the material is toxic, the surrounding tissue dies.

If the material is nontoxic and biologically inactive (nearly inert), a fibrous tissue of variable thickness forms.

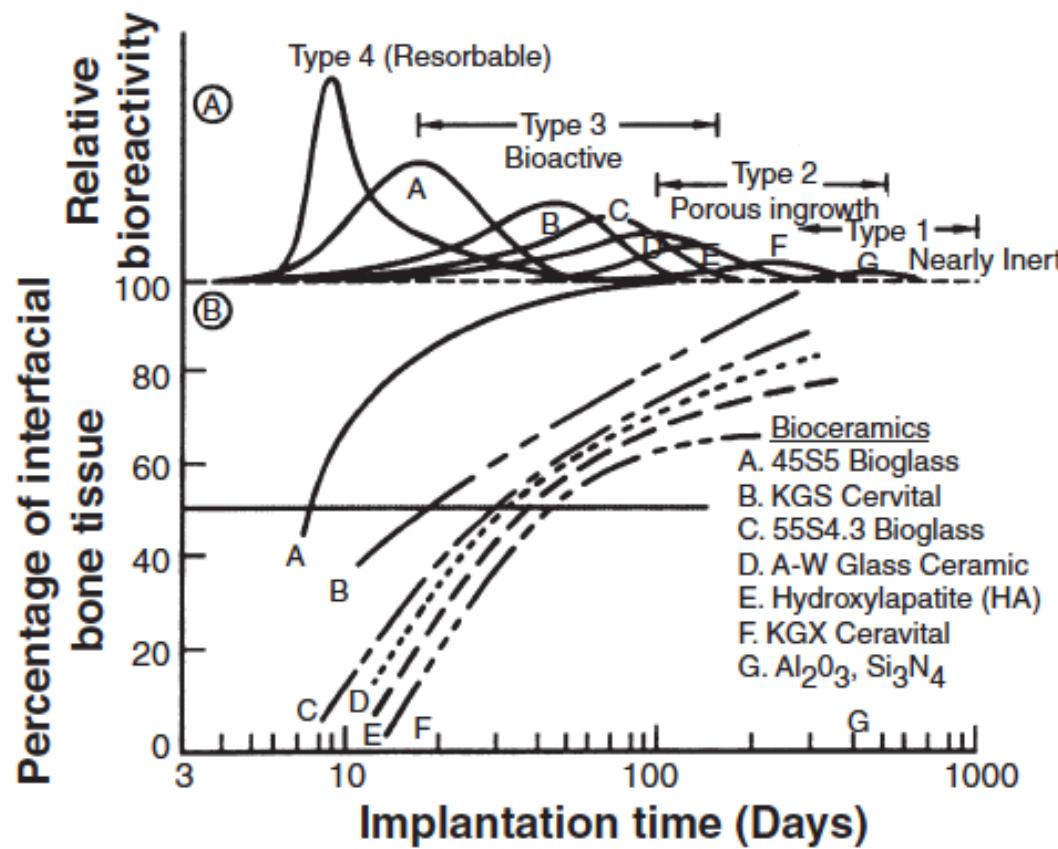
If the material is nontoxic and biologically active (bioactive), an interfacial bond forms.

If the material is nontoxic and dissolves, the surrounding tissue replaces it.

**TABLE I.2.4.2****Types of Bioceramic Tissue Attachment and Their Classification**

1. Dense, nonporous, nearly inert ceramics attach by bone growth into surface irregularities by cementing the device into the tissues or by press-fitting into a defect (termed "morphological fixation").	$\text{Al}_2\text{O}_3$ (single crystal and polycrystalline)
2. For porous inert implants, bone ingrowth occurs that mechanically attaches the bone to the material (termed "biological fixation").	$\text{Al}_2\text{O}_3$ (polycrystalline) Hydroxyapatite-coated porous metals
3. Dense, nonporous surface-reactive ceramics, glasses, and glass-ceramics attach directly by chemical bonding with the bone (termed "bioactive fixation").	Bioactive glasses Bioactive glass-ceramics Hydroxyapatite
4. Dense, nonporous (or porous) resorbable ceramics are designed to be slowly replaced by bone.	Calcium sulfate (Plaster of Paris) Tricalcium phosphate Calcium–phosphate salts

# A comparison of the relative chemical activity of the different types of bioceramics, glasses, and glass-ceramics

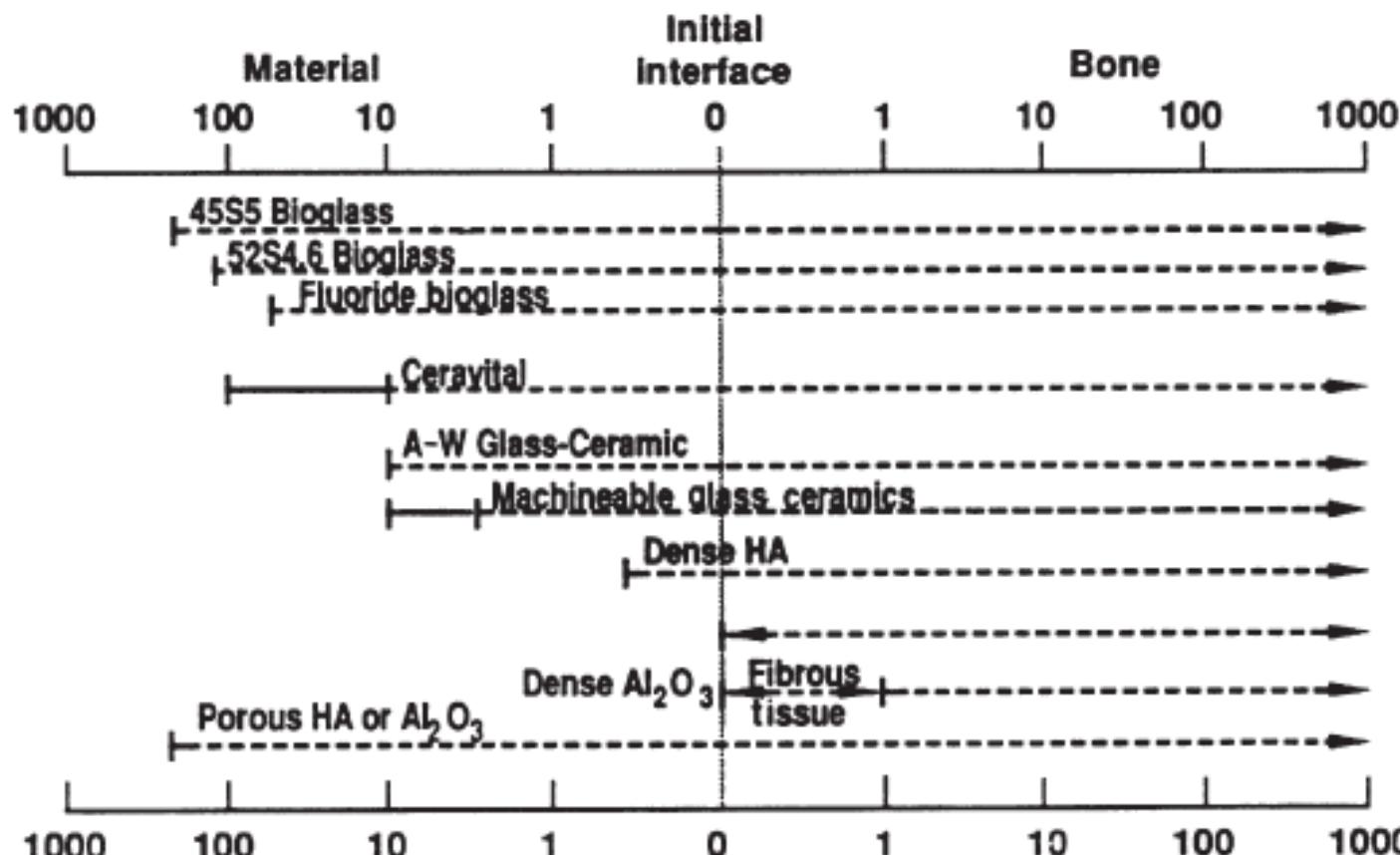


**FIGURE I.2.4.1** Bioactivity spectra for various bioceramic implants:  
(A) Relative rate of bioreactivity; (B) Time-dependence of formation of bone bonding at an implant interface.

- The relative reactivity that is shown in Figure I.2.4.1A correlates very closely with the rate of formation of an interfacial bond of ceramic, glass or glass-ceramic implants with bone (Figure I.2.4.1B).

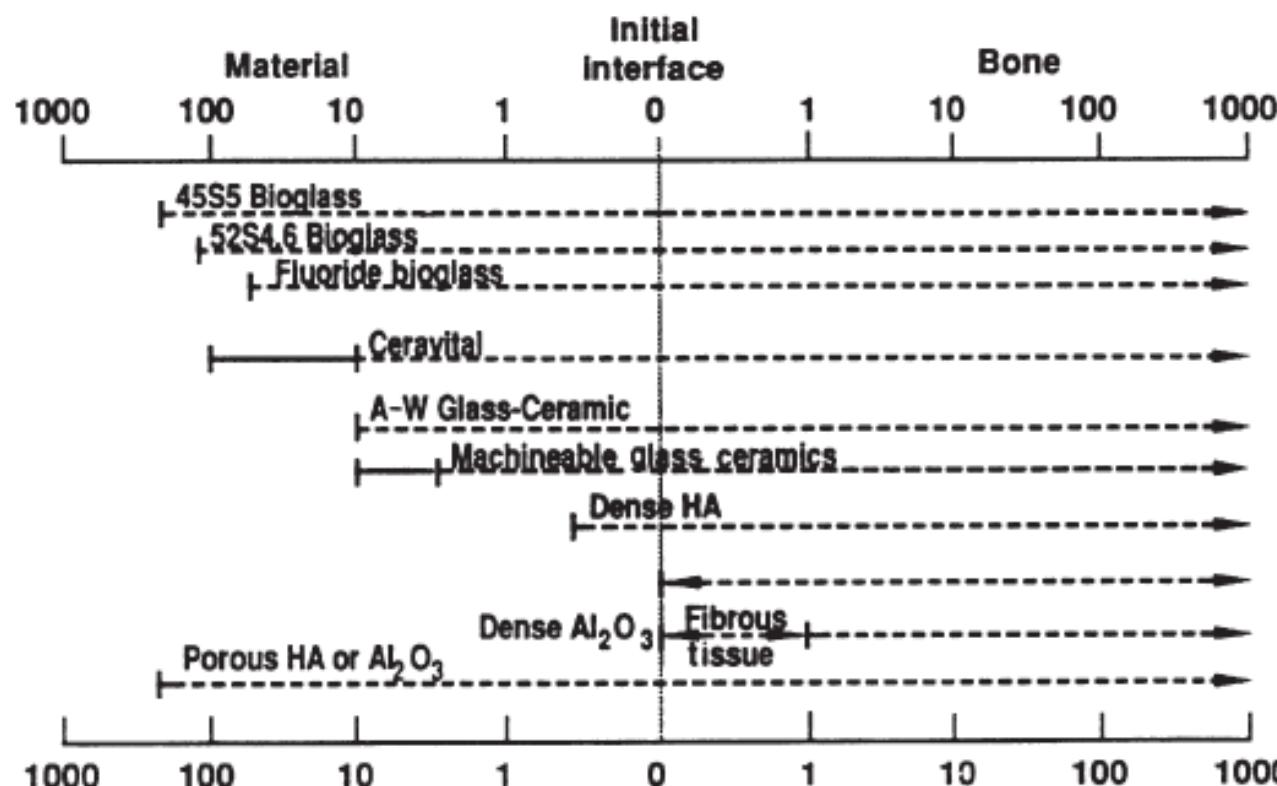
- The relative level of reactivity of an implant influences the thickness of the interfacial zone or layer between the material and tissue
- **Analyses of implant material failures often show failure originating at the biomaterial–tissue interface.**
  - When biomaterials are nearly inert and the interface is not chemically or biologically bonded, there is relative movement and progressive development of a fibrous capsule in soft and hard tissues.
  - The presence of movement at the biomaterial–tissue interface eventually leads to deterioration in function of the implant or the tissue at the interface, or both.
  - Wear particles can accelerate the deterioration of the tissue–implant interface.

- The thickness of the non-adherent capsule varies, depending upon both material (Figure I.2.4.2) and extent of relative motion.



**FIGURE I.2.4.2** Comparison of interfacial thickness ( $\mu\text{m}$ ) of reaction layer of bioactive implants of fibrous tissue of inactive bioceramics in bone.

- The fibrous tissue at the interface of **dense Al<sub>2</sub>O<sub>3</sub> (alumina)** implants is very thin. Consequently, if alumina devices are implanted with a very tight mechanical fit and are loaded primarily in compression, they are very successful.
- In contrast, **if a type 1 nearly inert implant is loaded so that interfacial movement can occur**, the fibrous capsule can become several hundred micrometers thick, and the implant can loosen very quickly.



**FIGURE I.2.4.2** Comparison of interfacial thickness ( $\mu\text{m}$ ) of reaction layer of bioactive implants of fibrous tissue of inactive bioceramics in bone.

- The mechanism behind the use of nearly inert microporous materials (type 2) is the ingrowth of tissue into pores on the surface or throughout the implant.
  - The increased interfacial area between the implant and the tissues results in an increased resistance to movement of the device in the tissue. The interface is established by the living tissue in the pores.
  - This method of attachment is often termed “**biological fixation**.” It is capable of withstanding more complex stress states than type 1 implants with “**morphological fixation**.”
  - The **limitation with type 2 porous implants** is that for the tissue to remain viable and healthy, it is necessary for the **pores to be greater than 50 to 150 μm**
  - The large interfacial area required for porosity is due to the need to provide a blood supply to the ingrown connective tissue (**vascular tissue does not appear in pore sizes less than 100 μm**)

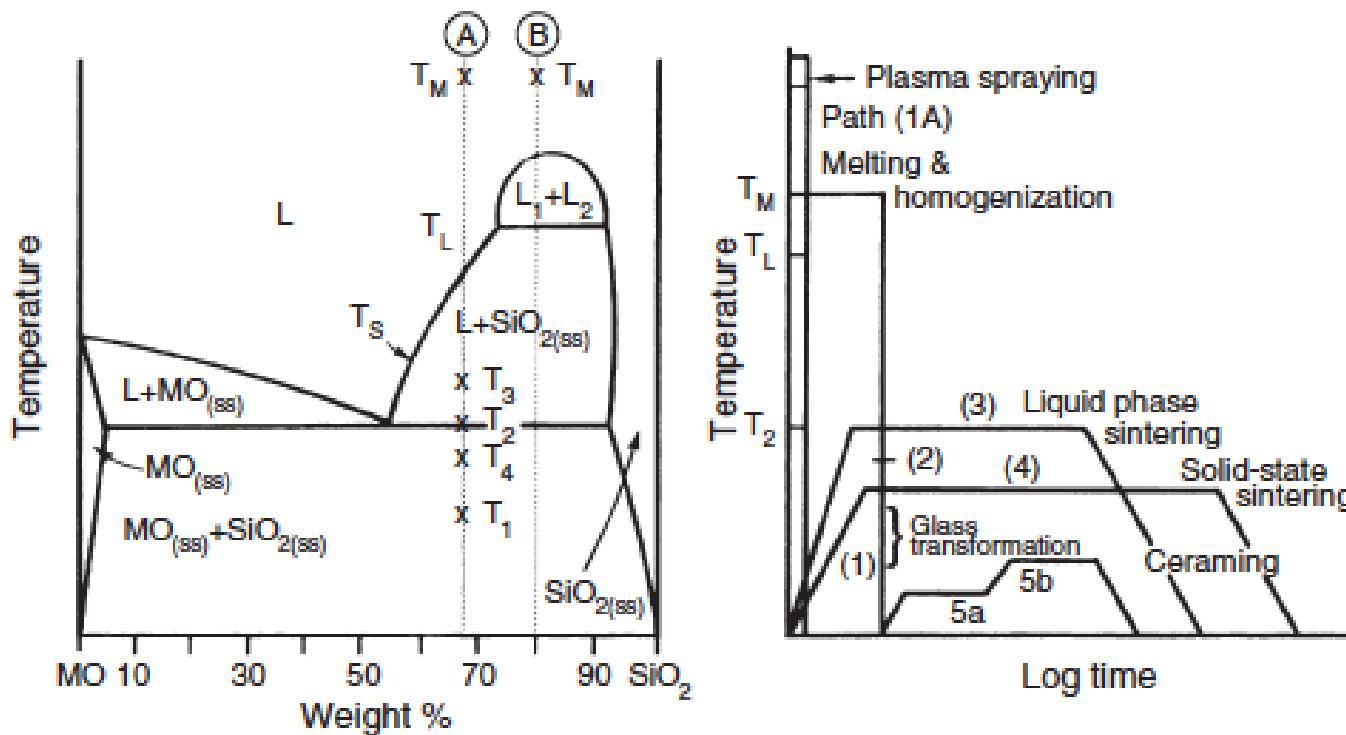
- When the material is a **porous metal**, the large increase in surface area can provide a focus for **corrosion of the implant and loss of metal ions** into the tissues.
  - This can be mediated by using a bioactive ceramic material such as hydroxyapatite (HA) as a coating on the metal.
- The **fraction of large porosity in any material also degrades the strength** of the material proportional to the volume fraction of porosity.
  - This approach works best when materials are used as **coatings or as unloaded space fillers in tissues** to **solve** interfacial stability

- **Resorbable biomaterials (type 4 )** are designed to degrade gradually over a period of time, and to be replaced by the natural host tissue.
- Complications in the development of resorbable bioceramics are:
  1. **maintenance of strength and the stability of the interface** during the degradation period and replacement by the natural host tissue
  2. **matching resorption rates** to the repair rates of body tissues (e.g., some materials dissolve too rapidly and some too slowly).
  3. Because large quantities of material may be replaced, it is also essential that a **resorbable biomaterial consist only of metabolically acceptable substances.**
    - Successful examples of resorbable polymers include poly(lactic acid) and poly(glycolic acid) used for sutures, which are metabolized to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and therefore are able to function for an appropriate time and then dissolve and disappear.
    - Porous or particulate calcium phosphate ceramic materials such as tricalcium phosphate (TCP) have proved successful for resorbable hard tissue replacements when low loads are applied to the material.

- Bioactive materials are intermediate between resorbable and bioinert (type 3).
  - A bioactive material is one that elicits a specific biological response at the interface of the material, resulting in the formation of a bond between the tissues and the material.
  - They include bioactive glasses such as 45S5 Bioglass; bioactive glass-ceramics such as A-W glass-ceramic; dense HA and bioactive composites such as HA-polyethylene.
- All of these materials (type1,2,3,4) form an interfacial bond with adjacent tissue. However, the time dependence of bonding, the strength of bond, the mechanism of bonding, and the thickness of the bonding zone differ for the various materials.

## CHARACTERISTICS AND PROCESSING OF BIOCERAMICS

- The characteristics and properties of the materials differ greatly, depending upon the **processing method used**.
- The primary methods of processing ceramics, glasses, and glass-ceramics are summarized in Figure:

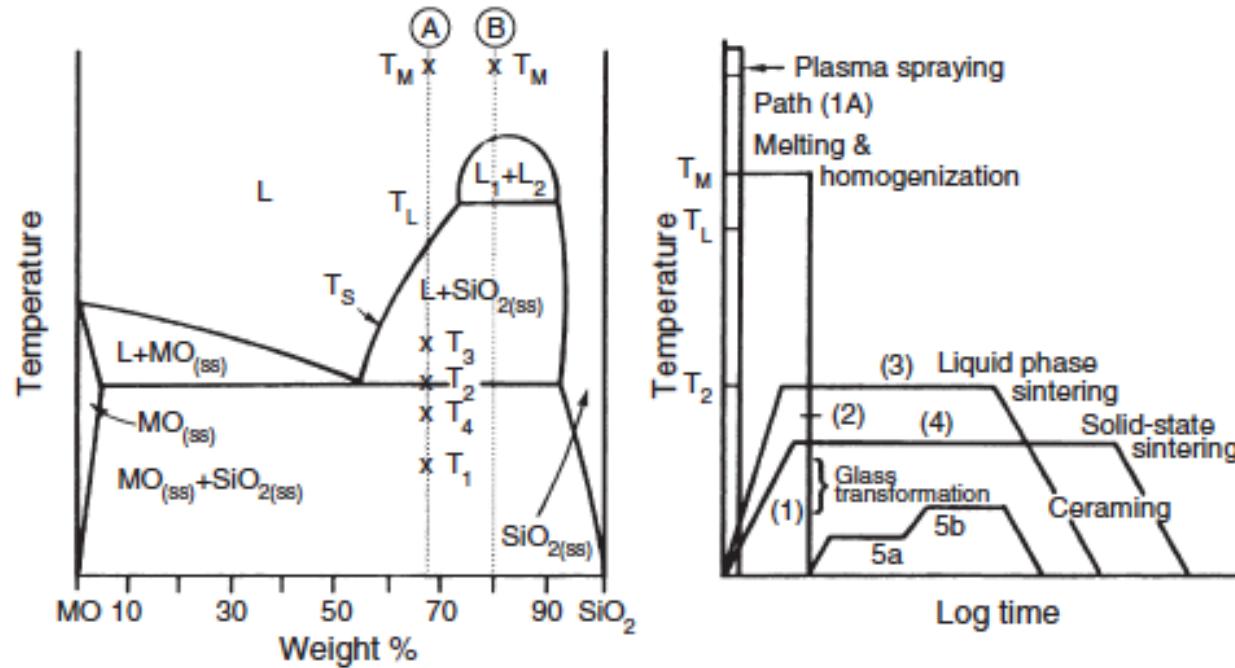


**FIGURE I.2.4.3** Relation of thermal processing schedules of various bioceramics to equilibrium phase diagram.

- These methods yield five categories of microstructures:

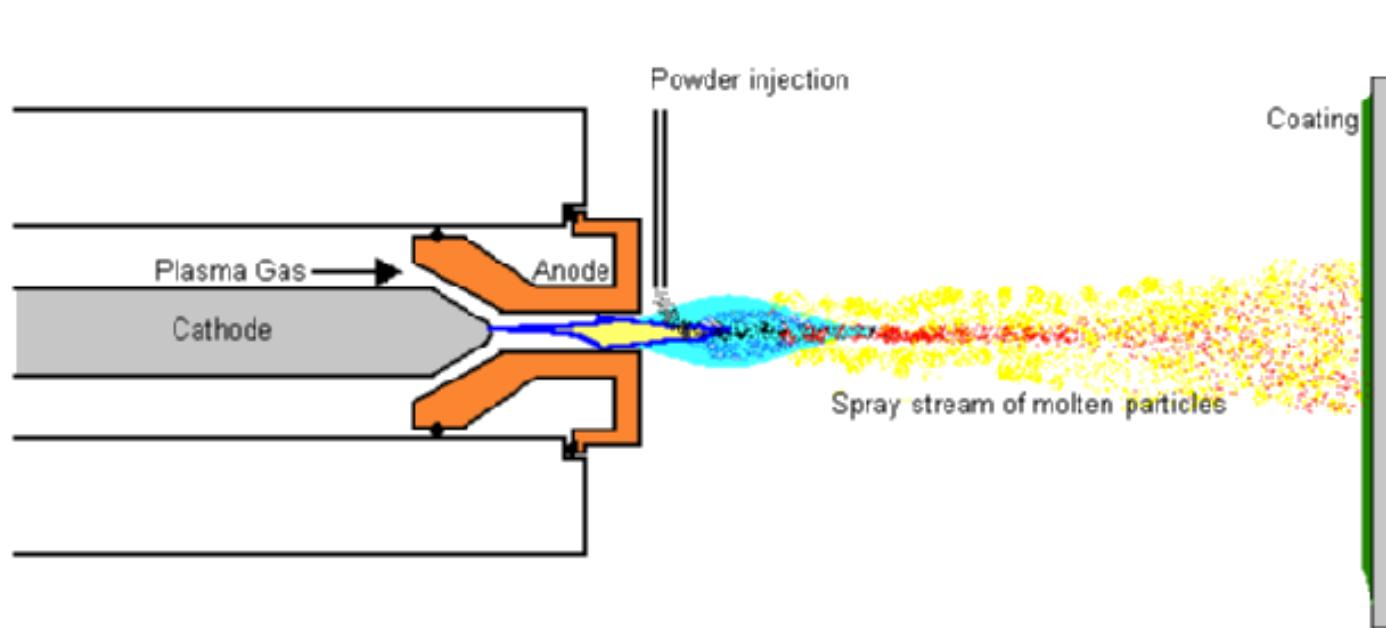
  1. Glass
  2. Cast or plasma-sprayed polycrystalline ceramic
  3. Liquid-phase sintered (vitrified) ceramic;
  4. Solid-state sintered ceramic;
  5. Polycrystalline glass-ceramic.

- **Differences in the microstructures** of the five categories are primarily a result of the **different thermal processing steps** required to produce them.

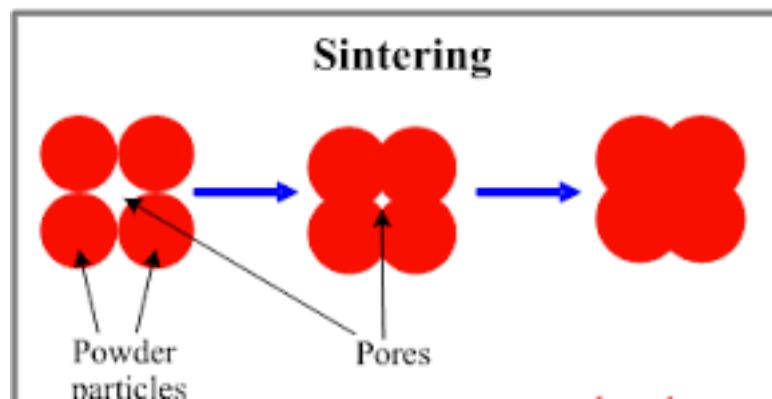


**FIGURE I.2.4.3** Relation of thermal processing schedules of various bioceramics to equilibrium phase diagram.

- Basically the **spraying** of molten or heat softened material onto a surface to provide a coating.
- Material in the form of powder is injected into a very high temperature plasma flame, where it is rapidly heated and accelerated to a high velocity.



- **Sintering** is the process of compacting and forming a solid mass of material by heat or pressure without melting it to the point of liquefaction



videos

## Nearly Inert Crystalline Ceramics

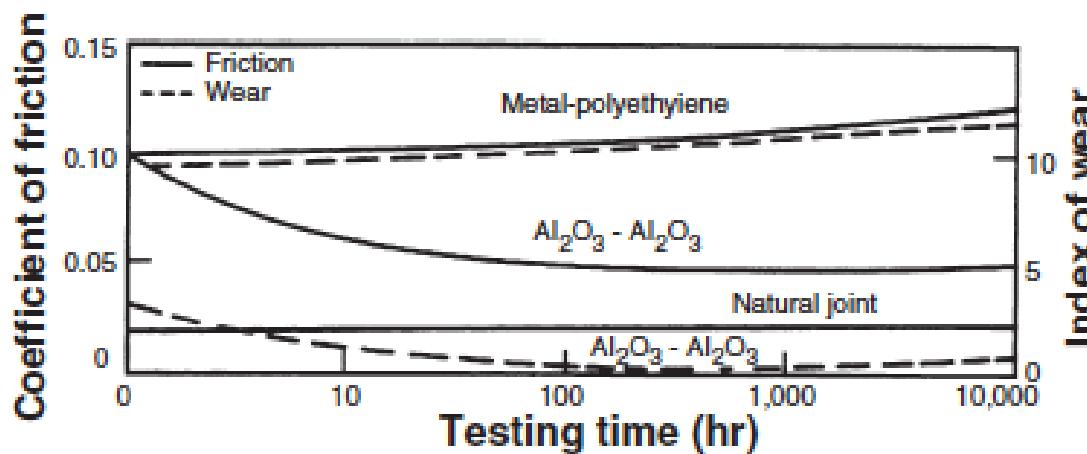
- High-density, high-purity (>99.5%) **alumina ( $\text{Al}_2\text{O}_3$ )** is used in the articulating surfaces of total joint prostheses because of its **excellent corrosion resistance**, good biocompatibility, **high wear resistance**, and high strength
- $\text{Al}_2\text{O}_3$  ceramics with an average grain size of <4  $\mu\text{m}$  and >99.7% purity exhibit good flexural strength and excellent compressive strength.
- Physical properties are summarized in Table I.2.4.4, along with the International Standards Organization (ISO) requirements for alumina implants.

TABLE I.2.4.4   Physical Characteristics of $\text{Al}_2\text{O}_3$ Bloceramics		
	High Alumina Ceramics	ISO Standard 6474
Alumina content (% by weight)	>99.8	$\geq 99.50$
Density (g/cm <sup>3</sup> )	>3.93	$\geq 3.90$
Average grain size ( $\mu\text{m}$ )	3–6	<7
R <sub>a</sub> ( $\mu\text{m}$ ) <sup>a</sup>	0.02	
Hardness(Vickers hardness number, VHN)	2300	>2000
Compressive strength (MPa)	4500	
Bending strength (MPa) (after testing in Ringer's solution)	550	400
Young's modulus (GPa)	380	
Fracture toughness ( $K_{\text{I}}\text{C}$ ) (MPa <sup>1/2</sup> )	5–6	
Slow crack growth	10–52	

- super tribiologic properties (friction and wear)

<sup>a</sup>Surface roughness value.

- The long-term coefficient of friction of an alumina–alumina joint decreases with time and approaches the values of a normal joint.



**FIGURE I.2.4.4** Time dependence of coefficient of friction and wear of alumina–alumina versus metal–polyethylene hip joint (*in vitro* testing).

- This leads to wear on alumina-articulating surfaces being nearly 10 times lower than metal–polyethylene surfaces, and **eliminates formation of polyethylene wear particles** that are associated with loosening of total joint prostheses.
- Low wear rates have led to widespread use in Europe of alumina **noncemented cups press-fitted into the acetabulum of the hip**. The cups are stabilized by the growth of bone into grooves
- Long-term results in general are good, especially for younger patients.**



- Christel et al. (1988) **caution** that stress shielding, owing to the high elastic modulus of alumina, may be responsible for **cancellous bone atrophy and loosening of the acetabular cup in old patients** with senile osteoporosis or rheumatoid arthritis.
  - Consequently, it is essential that the age of the patient, nature of the disease of the joint, and biomechanics of the repair be considered carefully before any prosthesis is used, including alumina ceramics.

- **zirconia** was also used in a similar way to alumina for articulating applications in hip and knee replacement
  - However a series of **implant failures around the year 2000**, resulted in the **withdrawal of zirconia** for these applications.
  - Today, there is **significant interest in the use of zirconia toughened alumina implants** due to the potential to **enhance strength and toughness properties** over those of alumina.
  - Zirconia is **used widely for dental applications** due to aesthetic and mechanical benefits the material offers.
- Other clinical applications of alumina prostheses include knee prostheses; bone screws; alveolar ridge and maxillofacial reconstruction; ossicular bone substitutes; keratoprostheses (corneal replacements); segmental bone replacements; and blade, screw, and post-dental implants.

## Porous Ceramics

- The potential advantage offered by a porous ceramic implant is its **inertness combined with the mechanical stability** of the highly-convoluted interface that develops when bone grows into the pores of the ceramic.
- The mechanical requirements of prostheses, however, severely **restrict the use** of low-strength porous ceramics to **nonloadbearing** applications.
- when loadbearing is not a primary requirement, porous ceramics can provide a functional implant.
- When **pore sizes** exceed 100 µm, bone will grow within the interconnecting pore channels near the surface and maintain **its vascularity** and long-term viability. In this manner, the implant serves as a structural bridge or scaffold for bone formation.
- **Commercially available porous products** originate from two sources: hydroxyapatite converted from coral or animal bone.
- **Porous materials are weaker** than the equivalent bulk form in proportion to the percentage of porosity, so that as the porosity increases, the **strength** of the material decreases rapidly

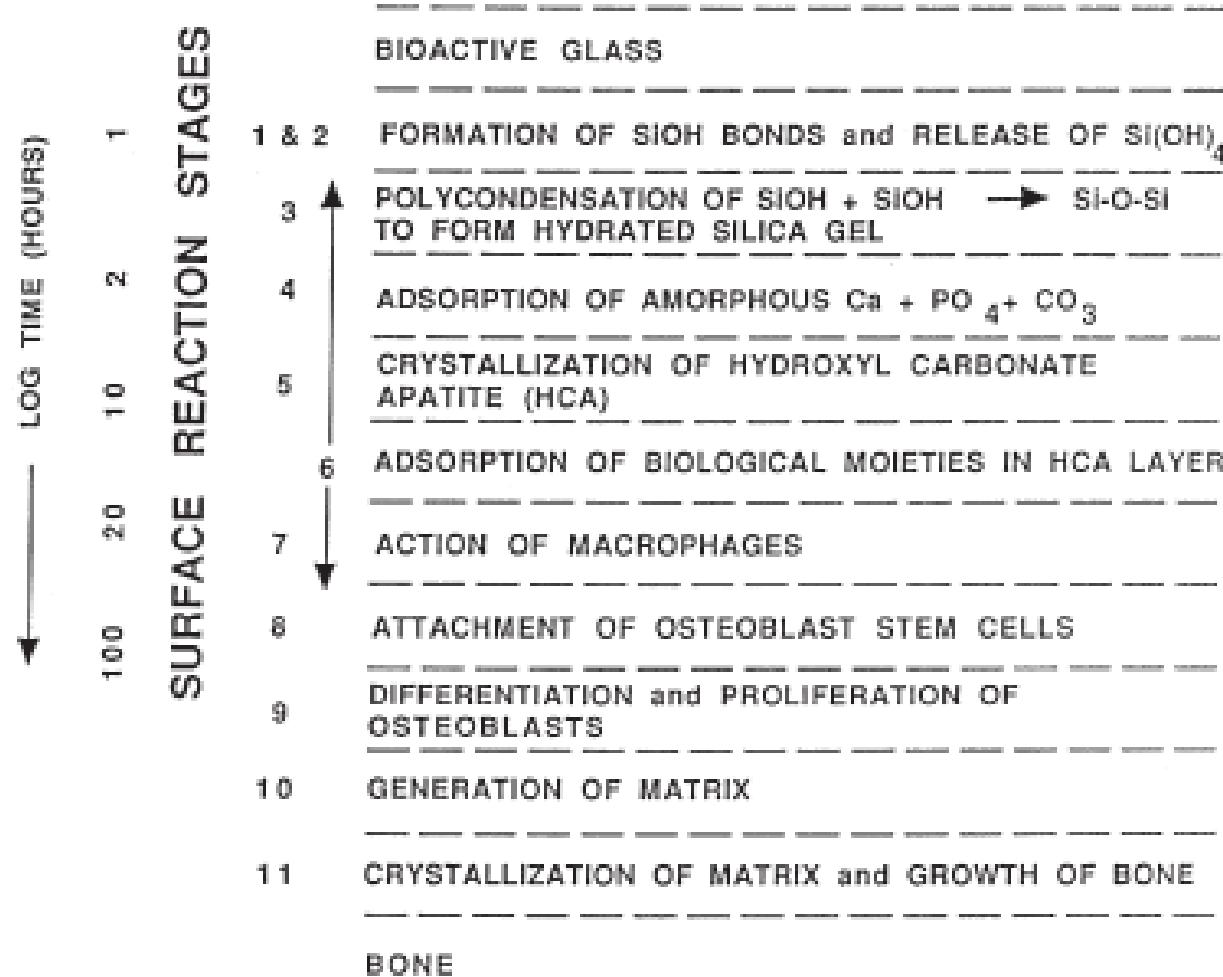
## Bioactive Glasses and Glass-ceramics

- Certain compositions of glasses, ceramics, glass-ceramics, and composites have been shown to bond to bone. These materials have become known as bioactive ceramics.
- Some specialized compositions of bioactive glasses will bond to soft tissues as well as bone
- The surface forms a **biologically-active carbonated HA** layer (HCA) that provides the bonding interface with tissues.
- Bonding to bone was **first demonstrated** for a compositional range of bioactive glasses that contained SiO<sub>2</sub>, Na<sub>2</sub>O, CaO, and P<sub>2</sub>O<sub>5</sub> in specific proportions

TABLE I.2.4.5 | Composition of Bioactive Glasses and Glass-Ceramics (In Weight Percent)

	45S5 Bloglass	45S5F Bloglass	45S5.4F Bloglass	40S5B5 Bloglass	52S4.6 Bloglass	55S4.3 Bloglass	KGC Ceravital	KGS Ceravital	KGy213 Ceravital	A-W GC	MB GC
SiO <sub>2</sub>	45	45	45	40	52	55	46.2	46	38	34.2	19–52
P <sub>2</sub> O <sub>5</sub>	6	6	6	6	6	6				16.3	4–24
CaO	24.5	12.25	14.7	24.5	21	19.5	20.2	33	31	44.9	9–3
Ca(PO <sub>4</sub> ) <sub>2</sub>							25.5	16	13.5		
CaF <sub>2</sub>		12.25	9.8							0.5	
MgO							2.9			4.6	5–15
MgF <sub>2</sub>											
Na <sub>2</sub> O	24.5	24.5	24.5	24.5	21	19.5	4.8	5	4		3–5
K <sub>2</sub> O							0.4				3–5
Al <sub>2</sub> O <sub>3</sub>									7		12–33
B <sub>2</sub> O <sub>3</sub>					5						
Ta <sub>2</sub> O <sub>5</sub> /TiO <sub>2</sub>									6.5		
Structure	Glass	Glass	Glass	Glass	Glass		Glass-ceramic	Glass-ceramic		Glass-ceramic	Glass-ceramic
Reference	Hench et al. (1982)	Gross et al. (1988)	Gross et al. (1988)		Nakamura et al. (1985)	Höeland and Vogel (1993)					

- Surface reaction steps of silica glass in aqueous or physiological solutions



**FIGURE I.2.4.6** Types of silicate glass interfaces with aqueous or physiological solutions.

## ➤ Bioactivity Reaction Stages

- There is a sequence of 11 reaction stages that occur at the surface of a Class A bioactive glass, as summarized in Figure I.2.4.6
- Controlled rates of dissolution of the glass provide the critical concentration of the biologically active ions to the cells via the interfacial solution.
- The families of genes that are upregulated and/or activated are shown in Table I.2.4.7

**TABLE I.2.4.7**

**Families of Genes In Human Osteoblasts Activated or Up-Regulated by Ionic Dissolution Products of Bioactive Glasses**

- |                                                     |
|-----------------------------------------------------|
| (1) Transcription Factors and Cell Cycle Regulators |
| (2) DNA Synthesis, Repair and Recombination         |
| (3) Apoptosis Regulators                            |
| (4) Growth Factors and Cytokines                    |
| (5) Cell Surface Antigens and Receptors             |
| (6) Signal Transduction Molecules                   |
| (7) Extracellular Matrix Compounds                  |

## lists the clinical applications of 45S5 bioactive glass.

<b>TABLE I.2.4.6</b>	<b>Typical Clinical Applications of Bioactive Ceramics, Glasses and Glass Ceramics (highlighting 45S5 and Hydroxyapatite as Examples)</b>
<b>Orthopedics</b>	
Trauma:	
Long bone fracture (acute and/or comminuted); alone and with internal fixation	
Femoral non-union repair	
Tibial plateau fracture	
Arthroplasty	
Filler around implants (acetabular reconstruction)	
Impaction grafting	
General	
Filling of bone after cyst/tumor removal	
Spine Fusion	
Interbody fusion (cervical, thoracolumbar, lumbar)	
Posterolateral fusion	
Adolescent idiopathic scoliosis	
<b>Cranial-Facial</b>	
Cranioplasty	
Facial reconstruction	
General oral/dental defects	
Extraction sites	
Ridge Augmentation	
Sinus elevation	
Cystectomies	
Osteotomies	
Periodontal Repair	
<b>Dental- Maxillofacial- ENT</b>	
Toothpaste and treatments for dentinal hypersensitivity and inhibition of gingivitis	
Pulp capping	
Sinus obliteration	
Repair of orbital floor fracture	
Endosseous ridge maintenance implants	
Middle ear ossicular replacements (Douek MED)	

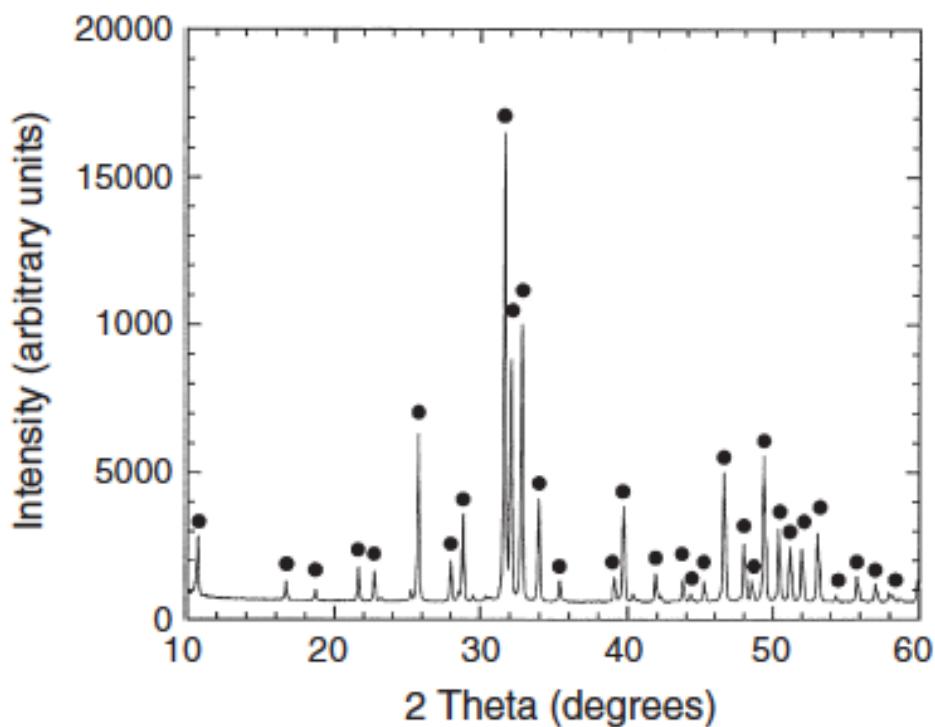
## CALCIUM PHOSPHATE CERAMICS

- Bone typically consists by weight of 25% water, 15% organic materials, and 60% mineral phases.
- The mineral phase consists primarily of calcium and phosphate ions, with traces of magnesium, carbonate, hydroxyl, chloride, fluoride, and citrate ions.
- Hence, calcium phosphates occur naturally in the body, but they also occur within nature as mineral rocks, and certain compounds can be synthesized in the laboratory.
- Table I.2.4.8 summarizes the mineral name, chemical name, and composition of various phases of calcium phosphates.

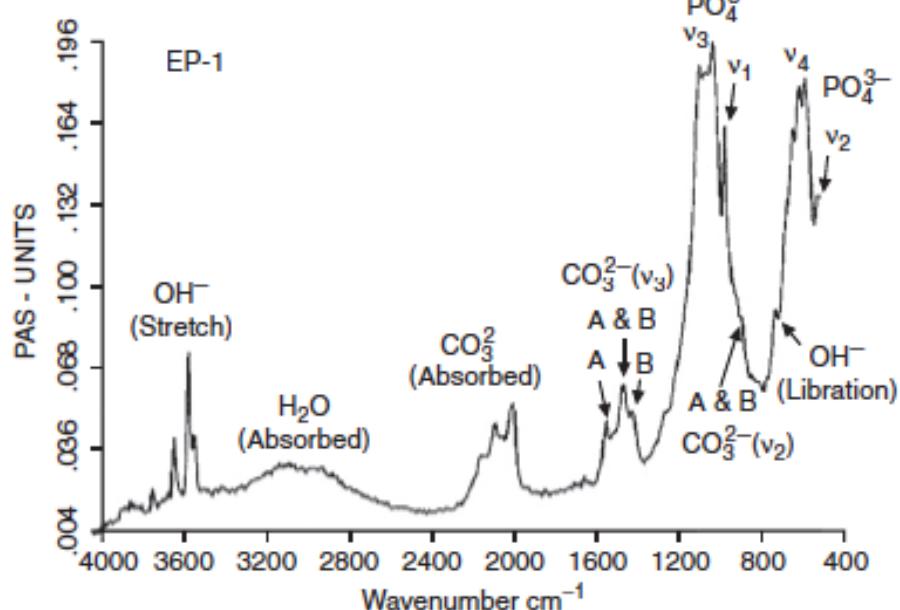
TABLE I.2.4.8 | Calcium Phosphates

Ca:P	Mineral Name	Formula	Chemical Name
1.0	Monetite	$\text{CaHPO}_4$	Dicalcium phosphate (DCP)
1.0	Brushite	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	Dihydrate (DCPD) Dicalcium phosphate
1.33	—	$\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$	Octocalcium phosphate (OCP)
1.43	Whitlockite	$\text{Ca}_{10}(\text{HPO}_4)(\text{PO}_4)_6$	
1.5	—	$\text{Ca}_3(\text{PO}_4)_2$	Tricalcium phosphate (TCP)
1.67	Hydroxyapatite	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	
2.0		$\text{Ca}_4\text{P}_2\text{O}_9$	Tetracalcium phosphate

- interest has intensified in the use of calcium phosphates as biomaterials, but only certain compounds are useful for implantation in the body, since both their solubility and speed of hydrolysis increase with a decreasing calcium-to-phosphorus ratio.
  - Driessens (1983) stated that those compounds with a Ca/P ratio of less than 1:1 are not suitable for biological implantation.
- A wide variety of methods have been investigated to produce synthetic hydroxyapatite.
  - The most commercially popular routes are based on aqueous precipitation or conversion from other calcium compounds.
  - The stoichiometry of HA is highly significant where thermal processing of the material is required.
  - Slight imbalances in the stoichiometric ratio of calcium and phosphorus in HA (from the standard molar ratio of 1.67) can lead to the appearance of either  $\alpha$ - or  $\beta$ -tricalcium phosphate
  - X-ray diffraction and infrared spectroscopy should be used to reveal the phase purity of hydroxyapatite.(the standard molar ratio of calcium and phosphorus in HA: 1.67)



**FIGURE I.2.4.9** X-ray diffraction of hydroxyapatite.



**FIGURE I.2.4.10** Typical FT-IR spectrum for a bone mineral-derived hydroxyapatite.

- Typical data for one commercial hydroxyapatite powder are:

**TABLE I.2.4.9**

**Trace Elements In a Commercial Hydroxyapatite**

Trace Element	PPM
Al	600
Cu	1
Fe	1000
Ge	100
Mg	2000
Mn	300
Na	3000
Pb	4
Si	500
Tl	30

- Other ions which may be incorporated into the HA structure, either intentionally or unintentionally, include
  - carbonate ions (substituting for hydroxyl or phosphate groups)
  - fluoride ions (substituting for hydroxyl groups)
  - silicon or silicate ions (substituting for phosphorus or phosphate groups)
  - magnesium ions substituting for calcium

## CALCIUM PHOSPHATE COATINGS

- The clinical application of calcium phosphate ceramics is largely **limited to bone grafting** applications or to **non-major loadbearing** parts of the skeleton.
- This is because of relatively poor mechanical strength and toughness, and inferior mechanical properties, and it was partly for this reason that interest was directed toward the use of calcium phosphate coatings on metallic implant substrates.
- Many techniques are available for the deposition of hydroxyapatite coatings, including
  - Electrophoresis
  - sol-gel routes
  - electrochemical routes
  - biomimetic routes
  - sputter techniques

but

- the most popular commercial routes are those based on plasma spraying. Plasma sprayed coatings have been found to be highly successful, and are now widely used in hip joint replacement.

## RESORBABLE CALCIUM PHOSPHATES

- Resorption or biodegradation of calcium phosphate ceramics is caused by three factors:
  1. Physiochemical dissolution, which depends on the solubility product of the material and local pH of its environment.
  2. Physical disintegration into small particles as a result of preferential chemical attack of grain boundaries.
  3. Biological factors, such as phagocytosis, which causes a decrease in local pH concentrations.

- All calcium phosphate ceramics biodegrade to varying degrees; the rate of biodegradation increases as:
  1. Surface area increases (powders > porous solid > dense solid)
  2. Crystallinity decreases
  3. Crystal perfection decreases
  4. Crystal and grain size decrease
  5. There are ionic substitutions of  $\text{CO}_3^{2-}$ ,  $\text{Mg}^{2+}$ , and  $\text{Sr}^{2+}$  in HA.

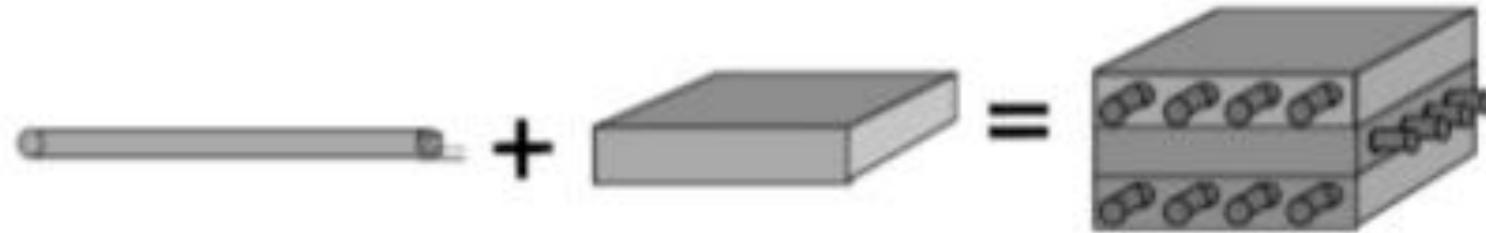
## CALCIUM PHOSPHATE BONE CEMENTS

- These materials offer the potential for *in situ* molding and injectability.
- There are a variety of different combinations of calcium compounds (e.g.,  $\alpha$ -tricalcium phosphate and dicalcium phosphate) which are used in the formulation of these bone cements
- In the development and production of the bone cements a number of factors need to be considered, including
  - the processing parameters (such as solid and liquid component composition, particle size, and liquid-to-powder ratio)
  - setting properties
  - cohesion time
  - the injectability of the paste
- These will in turn significantly influence the microstructure and porosity, and hence mechanical behavior of the cement.

# Classes of Materials Used in Medicine

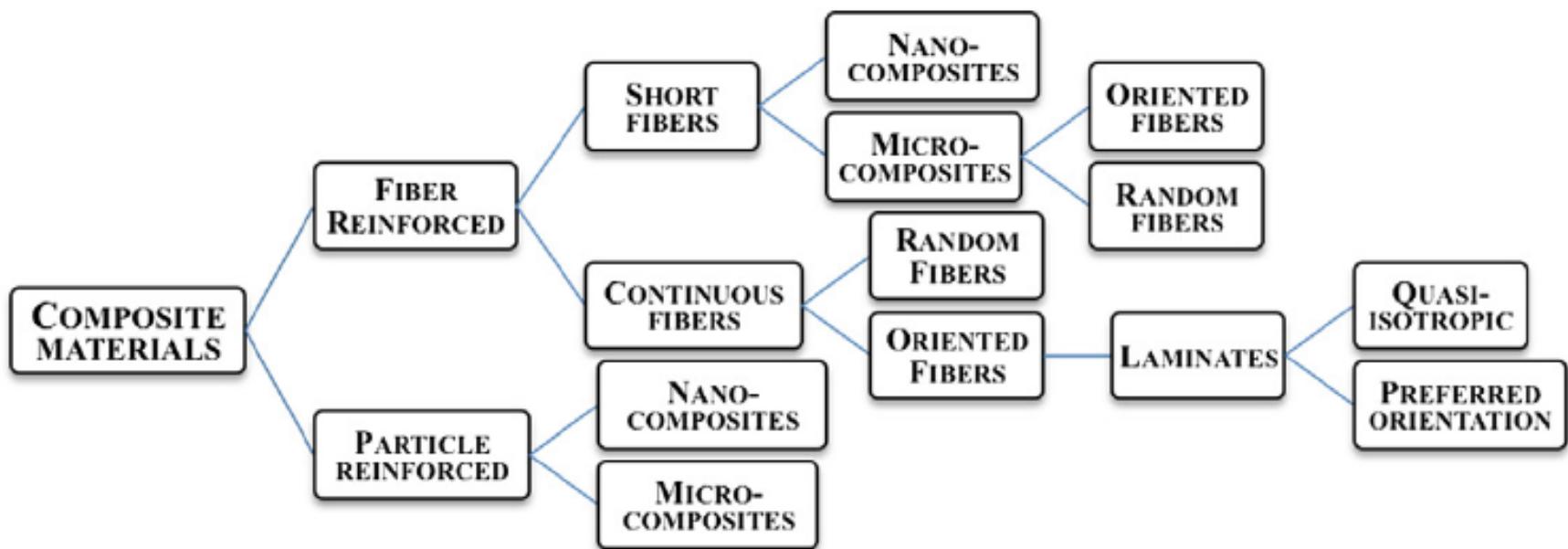
**Composites, Pyrolytic Carbon, Hydrogels**

- The word **composite** means “consisting of two or more distinct parts.”
- At the atomic level, materials such as metal alloys and polymeric materials could be called composite materials in that **they consist of different and distinct atomic groupings.**
- At the microstructural level (about 1 to 10 microns), **constituents may be observed distinctly in the optical microscope.**
- In engineering, a composite material usually **refers to a material consisting of constituents in the nano- to micro- to macrosize range, each having a distinct interface separating them.** Such composites usually consist of one or more discontinuous phases embedded within a continuous phase
- The discontinuous phase is usually harder and stronger than the continuous phase, and is called the **reinforcement** or **reinforcing material**, whereas the continuous phase is termed the **matrix.**



- For example:
- In some cases, tough fillers, e.g., rubber particles, are combined with brittle matrices in order to produce higher toughness materials with better impact strength.
- In other cases, the “reinforcement” could be aimed at achieving specific functional properties, such as bioactivity in the case of biomedical composites.
- Many body tissues are composites, such as extracellular matrix (ECM), tendons, ligaments, skin, bone, and so on, with an additional complexity due to their hierarchical structure.

- Most composite materials are **fabricated to provide desired mechanical properties** such as strength, stiffness, toughness, and fatigue resistance.
- The strengthening mechanism of composites **strongly depends upon the geometry of the reinforcement.**
- **classification of composites** are made on the basis of the geometry of a representative unit of reinforcement more than on the type of matrix, e.g., composites with long fibers, short fibers or particles



**FIGURE I.2.9.1** Classification of composite materials.

## REINFORCING SYSTEMS

- The main reinforcing materials that have been used in biomedical composites are **carbon fibers, polymer fibers, ceramic particles, glass fibers & particles**. Depending upon the application, the reinforcements have either been inert or absorbable.

### ➤ Carbon Fiber

- Carbon fiber is a lightweight, flexible, high strength, and high tensile modulus material .
- Due to their **low density and high mechanical properties** (they can be much stiffer and stronger than steel!) these fibers are used in composites in a variety of applications that demand light weight and high mechanical properties.
- **carbon fibers display unique properties** for the fabrication of loadbearing medical devices.
- Most successful applications are **for prosthetics where carbon fiber composites exhibit unique properties in term of lightness, stiffness, and strength.**

## ➤ Polymer Fibers

- **Polymer fibers are not comparable to carbon fibers in strength or stiffness when used to reinforce other polymers.**
- For biomedical applications, biocompatibility, high strength and fatigue resistance are compulsory, while **stiffness is a design parameter to be adapted to the specific conditions.**
- Thanks to **their absorbability**, not to their mechanical superiority, certain absorbable fibers have been employed in medical applications such as
  - *aramid*
  - polyethylene
  - Dacron™
  - Poly(lactic acid) (PLA)
  - poly(glycolic acid) (PGA)
  - Copolymers (poly(lactic-co-glycolic acid) PLGA) , Polycaprolactone (PCL)

## ➤ Ceramics

- A number of different ceramic materials have been used to reinforce biomedical composites.
- Since **most biocompatible ceramics are relatively weak and brittle** materials compared to metals, **the preferred form for this reinforcement has usually been particulate**.
- These reinforcements have included various calcium phosphates, aluminum- and zinc-based phosphates, glass and glass–ceramics, and bone mineral.
- **Tricalcium phosphates and hydroxyapatite are commonly referred as bioceramics**, i.e., bioactive ceramics. The definition refers to their ability to elicit a specific biological response that results in the formation of a bond between the tissues and material
- **The calcium phosphate ceramic systems have been the most intensely studied ceramic systems**. Of particular interest are the calcium phosphates having calcium to phosphorous ratios of 1.5–1.67.
- Hydroxyapatite (HA) ceramic and tricalcium phosphates are used in orthopedics and dentistry, **alone or in combination with other substances or also as coating of metal implants**.

## ➤ Glasses

- Glass fibers are used to reinforce plastic matrices to form structural composites and molding compounds.
- Commercial glass fiber plastic composite materials have favorable characteristics such as
  - high strength-to-weight ratio
  - good dimensional stability
  - **good resistance to heat, cold, moisture, and corrosion**
  - good electrical insulation properties
  - ease of fabrication
  - relatively low cost.
- For example
  - Glass fibers have also been used to **increase the mechanical properties of acrylic resins for applications in dentistry.**

## ➤ Nanoparticles and Nanofibers: “Nanofillers”

- Polymers filled with nanoparticles or nanofibers have been proposed for several applications in medicine.
  - **nano-reinforcements** that have been investigated for biomedical use includes silica nanoparticles, carbon nanotubes etc.
- some examples of nanocomposites:
- **nanocomposites for blood contacting applications –**
    - the use of poly(carbonate)- urethane-POSS nanocomposites for blood contacting applications.
    - These materials were found to be thrombo-resistant, biostable, and more compliant than PTFE vascular grafts *in vitro*.
  - **Carbon nanotubes**
    - Their exceptionally **high mechanical properties have stimulated numerous researchers to study their application for composites, also for biomedical applications.**
    - For instance, carbon nanotubes have been used to produce electrospun silk fibroin nanocomposites for potential tissue engineering applications

# MATRIX SYSTEMS

- Ceramic matrix or metal matrix composites have important technological applications, but their use is mostly in **non-biomedical applications** (e.g., cutting tools, power generation equipment, process industries, aerospace), with **just a few examples** for biomedical applications (e.g., calcium phosphate bone cements).
- Most biomedical composites have polymeric matrices that can be bioabsorbable or not.

## Some Examples of Biomedical Composite Systems

TABLE I.2.9.1   Some Examples of Biomedical Composite Systems		
Applications	Matrix/Reinforcement*	Reference
External fixator Bone fracture fixation plates, pins, screws	Epoxy resin/CF Epoxy resins/CF	Baidya et al., 2001; Migliaresi et al., 2004 Ali et al., 1990; Veerabagu et al., 2003; Pemberton et al., 1994
	PMMA/CF PSU/CF PP/CF PE/CF PBT/CF PEEK/CF PEEK/GF	Woo et al., 1974 Claes et al., 1997 Christel et al., 1980 Rushton and Rae, 1984 Gillett et al., 1986 Fujihara et al., 2001 Lin et al., 1997
	PLLA/HA PLLA/PLLA fibers PGA/PGA fibers	Furukawa et al., 2000 a,b Tormala, 1992; Rokkanen et al., 2000 Tormala, 1992; Rokkanen et al., 2000
Spine surgery	PU/Bioglass PSU/Bioglass PEEK/CF Hydrogels/PET fibers PLA/PLA fibers/CP	Claes et al., 1999 Marcolongo et al., 1998 Ciappetti et al., 1997 Ambrosio et al., 1996 Hutunnen et al., 2006
Bone cement	PMMA/HA particles PMMA/Glass beads Calcium phosphate/arramid fibers, CF, GF, PLGA fibers PMMA/UHMWPE fibers	Morita et al., 1998 Shinzato et al., 2000 Xu et al., 2000
Dental cements and other dental applications	Bis-GMA/inorganic particles PMMA/KF	Yang et al., 1997 Moszner and Salz, 2001 Pourdeyhimi et al., 1986; Vallittu, 1996
Acetabular cups Hip prostheses stem	PEEK/CF PEI/CF-GF PEEK/CF CF/PA12	Wang et al., 1998 De Santis et al., 2000 Akay and Aslan, 1996; Kwarteng, 1990 Campbell et al., 2008
Bone replacement, substitute Bone filling, regeneration	PE/HA particles Poly(propylene fumarate)/TCP PEG-PBT/HA PLGA/HA fibers P(DLLA-CL)/HA particles Starch/HA particles	Bonfield, 1988; Bonfield et al., 1998 Yaszemski et al., 1996 Qing et al., 1997 Thomson et al., 1998 Ural et al., 2000 Reis and Cunha, 2000; Leonor et al., 2003
Tendons and ligaments	Hydrogels/PET Polyolefins/UHMWPE fibers	Kolarik et al., 1981; Iannace et al., 1995
Vascular grafts Prosthetic limbs	PELA/Polyurethane fibers Epoxy resins/CF, GF, KF	Kazanci et al., 2002 Gershon et al., 1990; Gershon et al., 1992 Dawson, 2000

\*See Glossary of Terms.

## ABSORBABLE MATRIX COMPOSITES

- Absorbable matrix composites have been used in situations where absorption of the matrix is desired.
- Matrix absorption may be desired to expose surfaces to tissue or to release admixed materials such as antibiotics or growth factors (drug release)
- However, the most common reasons for the use of this class of matrices for composites has been to accomplish time-varying mechanical properties and ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns.
- This type of composite would contain an absorbable matrix as well as absorbable reinforcing fillers. A typical clinical example is fracture fixation

### ➤ Fracture Fixation

- Rigid internal fixation of fractures has conventionally been accomplished with metallic plates, screws, and rods.
- During the early stages of fracture healing, rigid internal fixation maintains alignment and promotes primary osseous union by stabilization and compression.
- Unfortunately, as healing progresses, or after healing is complete, rigid fixation may cause bone to undergo stress protection atrophy. This can result in significant loss of bone mass and osteoporosis.

- Additionally, there may be a basic mechanical incompatibility between the metal implants and bone.
  - The elastic modulus of cortical bone ranges from 17 to 24 GPa, depending upon the age and location of the specimen, while the commonly used alloys have moduli ranging from 110 GPa (titanium alloys) to 210 GPa (316L steel). **This large difference in stiffness** can result in disproportionate load sharing, which can lead to relative motion between the implant and bone upon loading, as well as to **high stress concentrations at bone–implant junctions**.
- Another potential problem is that the metal alloys currently used for plates corrode to some degree.
  - Metal ions are released and they have been reported to cause adverse local tissue reactions, which in turn raises questions of adverse effects on bone mineralization, as well as adverse systemic responses such as local tumor formation.
  - Consequently, it is usually recommended that a second operation be performed to remove the metal hardware after healing

- **The advantages of absorbable devices are thus two-fold.**

- First, the devices degrade mechanically with time, reducing stress protection and the accompanying osteoporosis.
- Second, there is no need for secondary surgical procedures to remove absorbable devices. The state of stress at the fracture site gradually returns to normal, allowing normal bone remodeling.
  - **Absorbable fracture fixation devices have been produced from poly(L-lactic acid) polymer (PLLA), PGA polymer, and polydioxanone.**
  - **The degradation product of PLLA is mainly lactic acid**, which is nontoxic, biocompatible, easily absorbed into and eliminated from the body.
  - Lactic acid enters the lactic acid cycle of metabolites within cells. Ultimately it is metabolized to carbon dioxide and water.

## NON-ABSORBABLE MATRIX COMPOSITES

- Non-absorbable matrix composites are generally used to provide specific mechanical properties unattainable with homogeneous materials.
- Because the matrices and fillers are non-absorbable, they are used for “lifelong” implants such as orthopedic appliances and total joint replacements.

## ➤ Total Joint Replacement

- the **most studied** and potentially the most valuable use of **non-absorbable composites** has been **in total joint replacement**.
- **Bone resorption** in the femur leading to aseptic loosening with the implantation of metallic femoral hip replacement components
- It has long been recognized that bone adapts to functional stress by remodeling to re-establish a stable mechanical environment.
- When applied to the phenomenon of **bone loss around implants**, one can postulate that the **relative stiffness of the metallic component is depriving bone of its accustomed load**.
- Clinical and experimental results have shown the significant role that implant elastic characteristics play in allowing the femur to attain a physiologically acceptable stress state.

- **Composite materials technology offers the ability to alter the elastic characteristics of an implant and provide a better mechanical match with the host bone, potentially leading to a more favorable bone remodeling response.**
- **Using different polymer matrices reinforced with carbon fiber, a large range of mechanical properties is possible**
  - Poly(ether-ether-ketone) (PEEK) matrix has been one of the most studied matrices for bone interfacing prostheses.
  - An *in vitro* study of Scotchford et al. (2003) showed a **similar osteoblast attachment and proliferation on a PEEK/carbon fiber stem component as referred to Ti6Al4V stems.**



## Tissue Engineering Scaffolds

- Composites have been widely proposed as tissue engineering (TE) scaffolds. The **aim** of the addition of fillers to a biodegradable polymer matrix is **not only to reinforce the matrix, but also to impart to the scaffold specific bioactive properties, such as drug delivery.**
- The role of the scaffold is to **provide a support** to the newly forming tissue through a favorable interaction with cells, but also **fulfilling specific requirements of the implant site**
- Sometimes, polymeric particles have been added to polymeric matrices to promote sustained **release of specific molecules.**
- For instance, **gelatin microparticles** have been added to injectable cross-linked oligo(ethylene glycol fumarate) matrices to **release drugs or growth factors** for regenerating tissue in an **osteochondral defect**

**Pyrolytic Carbon**

- Carbon materials are ubiquitous and of great interest because the majority of substances that make up living organisms are carbon compounds.
- Although many engineering materials and biomaterials are based on carbon or contain carbon in some form, elemental carbon itself is also an important and very successful biomaterial.

## ELEMENTAL CARBON

- Elemental carbon is found in nature as two crystalline allotrophic forms: graphite and diamond.
- Recently a third crystalline form of elemental carbon, the fullerene structure, has been discovered.
- The crystalline polymorphs of elemental carbon are shown :

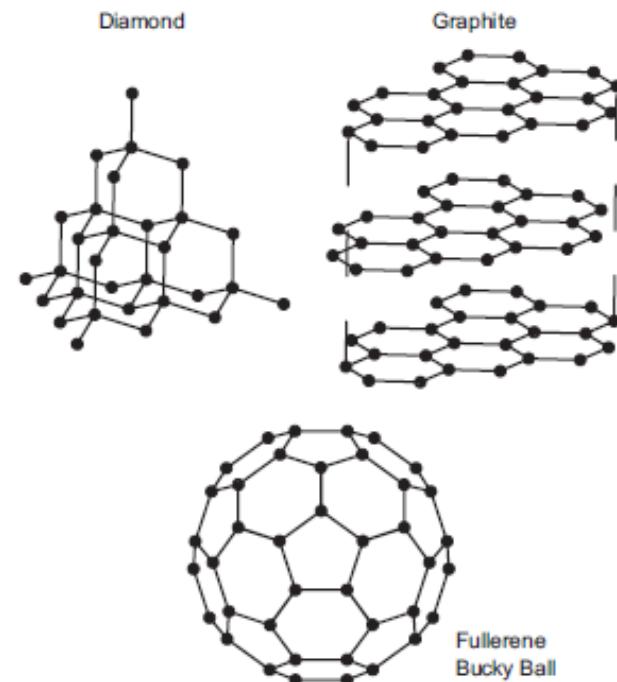
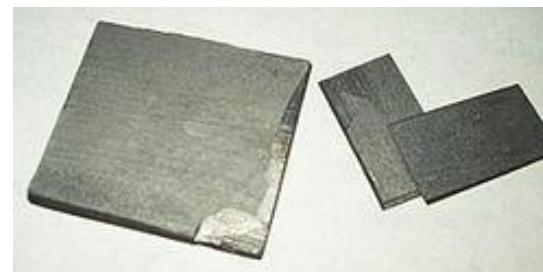


FIGURE I.2.8.1 Allotropic crystalline forms of carbon: diamond, graphite, and fullerene.

- The properties of the elemental carbon crystalline forms vary widely according to their structure.
- **Diamond** is one of the hardest materials known.
- **Graphite** is a soft material and has low hardness and a lubricating property
- **Fullerenes** have yet to be produced in bulk, but their properties on a microscale are entirely different from those of their crystalline counterparts.

## PYROLYTIC CARBON (PyC)



- The biomaterial known as **pyrolytic carbon is not found in nature**; it is manmade
  - It is a material **similar to graphite**, but with some covalent bonding between its graphene sheets as a result of **imperfections in its production**.
- Pyrolytic carbon components have been **used in more than 25 different prosthetic heart valve designs** since the late 1960s, and have accumulated a clinical experience in the order of 16 million patient-years.
- Among the materials available for mechanical heart valve prostheses, pyrolytic carbon has the **best combination of blood compatibility, physical and mechanical properties, and durability**.

## CLINICAL APPLICATIONS

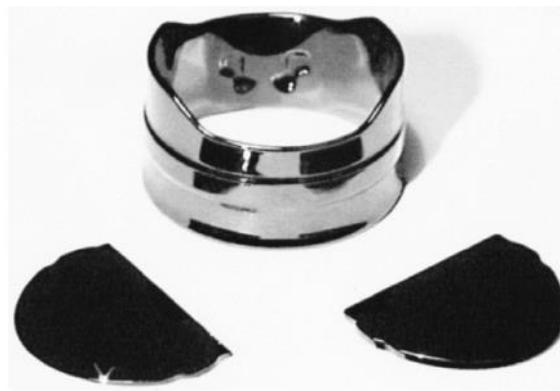
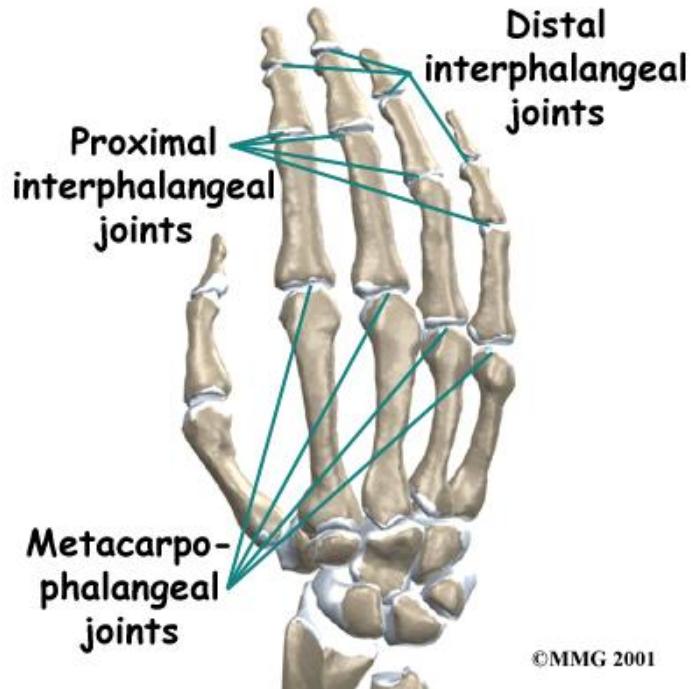


FIGURE I.2.8.9 Components for On-X bileaflet heart valve.

- Widespread clinical use of pyrolytic carbon components for **heart valve replacement** began in October of 1968.
  - However, patients with mechanical valve prostheses require chronic anticoagulation therapy because of the risk of valve-related hemostatic complications.
- PyC has also been used as a **loadbearing material for small orthopedic joint replacement implants**
  - Successful applications for upper limb total joint prostheses include the metacarpophalangeal (MCP) joint and the proximal interphalangeal (PIP) joint



- Pure PyC is a nearly ideal material for orthopedic application with demonstrated advantages over traditional materials such as polymers, ceramics, and metals which include:
  - ✓ Elimination of wear-related failures
  - ✓ Absence of osteolytic adverse tissue reactions
  - ✓ Excellent fatigue resistance
  - ✓ Non-cemented fixation via bone apposition
  - ✓ Minimization of stress shielding effects and bone resorption
  - ✓ Excellent compatibility with joint cartilage and bone tissues.

# Hydrogels

- Hydrogels have received significant attention because of their high water contents and related potential for many biomedical applications.
- **Hydrogels are polymeric structures held together as water-swollen gels by:**
  - (1) primary covalent cross-links
  - (2) ionic forces
  - (3) hydrogen bonds
  - (4) affinity or “bio-recognition” interactions
  - (5) hydrophobic interactions
  - (6) polymer crystallites
  - (7) physical entanglements of individual polymer chains
  - (8) a combination of two or more of the above interactions.
- Many natural polymers such as collagen, gelatin, fibrin, hyaluronic acid, heparin, alginates, pectins, chitosan, and others can be used to form hydrogels, and some of these gels have been used in biomedical application

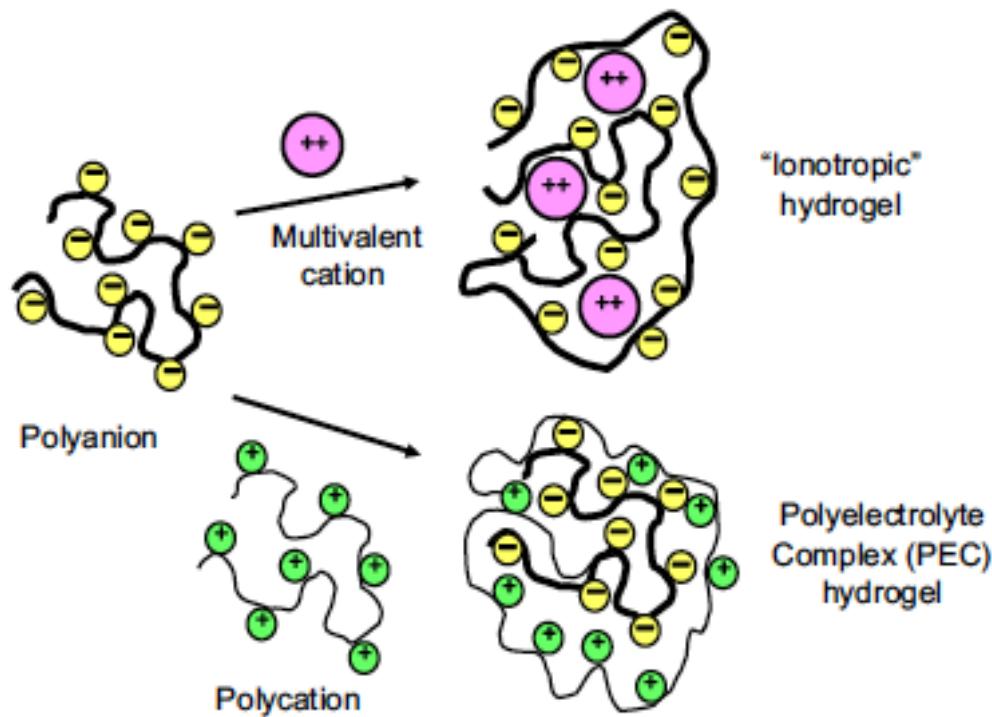
# CLASSIFICATION AND BASIC STRUCTURES OF HYDROGELS

- Depending on their **method of preparation, ionic charge, or physical structure features, hydrogels may be classified in several categories.**
- Based on the method of preparation, they may be:
  1. *homopolymer hydrogels*
  2. *copolymer hydrogels*
  3. *multi-polymer hydrogels*
  4. *interpenetrating network (IPN) hydrogels.*
- ***Homopolymer hydrogels*** are cross-linked networks of one type of hydrophilic monomer unit, whereas ***copolymer hydrogels*** are produced by cross-linking of chains composed of two comonomer units, at least one of which must be hydrophilic to render them water swellable.
- ***Multi-polymer hydrogels*** are produced from three or more comonomers reacting together
- ***interpenetrating network (IPN) hydrogels*** are produced with polymerizing one monomer within a different cross-linked hydrogel network. The monomer polymerizes to form a polymer or a second cross-linked network that is intermeshed with the first network.

➤ *Ionic hydrogels*, with ionic charges on the backbone polymers, may be classified as:

1. *neutral hydrogels* (uncharged)
2. *anionic hydrogels* (having negative charges only)
3. *cationic hydrogels* (having positive charges only)
4. *ampholytic hydrogels* (having both positive and negative charges).

## *Ionic hydrogels*

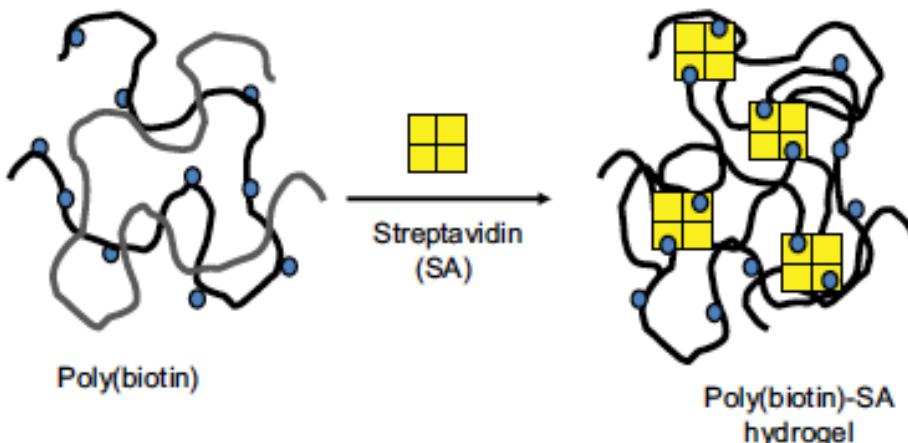


**FIGURE I.2.5.5** Formation of ionic hydrogels. (Hoffman, 2002.)

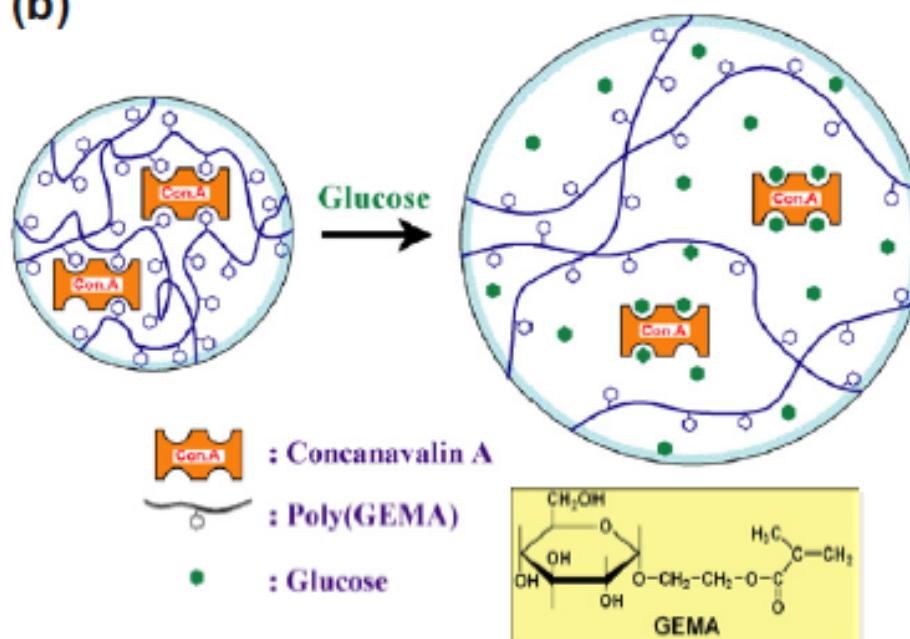
- Based on physico-chemical structural features of the network, hydrogels may also be classified as:
    1. *amorphous hydrogels* (having covalent cross-links)
    2. *semi-crystalline hydrogels* (may or may not have covalent cross-links).
  - **amorphous hydrogels**, the macromolecular chains are arranged randomly.
  - **Semi-crystalline hydrogels** are characterized by self-assembled regions of ordered macromolecular chains (crystallites).
- 
- Another type of classification of hydrogels includes the “complexation hydrogels”, which are held together by specific types of secondary forces.
    - These include **hydrogen bonds**, **hydrophobic group associations**, and **affinity “complexes”** (i.e , biotin/streptavidin, antibody/antigen)

## Affinity hydrogels

(a)



(b)



**FIGURE I.2.5.6** (a) Formation of an affinity hydrogel between polybiotin and streptavidin. (Morris et al., 1993.) (b) Glucose-responsive hydrogel swells when free glucose competes with polymeric glucose groups in a ConA-cross-linked GEMA hydrogel. (Miyata et al., 1996.)

## SWELLING BEHAVIOR OF HYDROGELS

- The physical behavior of biomedical hydrogels is dependent on their dynamic swelling and equilibrium in water and in aqueous solutions.
- Knowledge of the swelling characteristics of a polymer is of utmost importance in biomedical and pharmaceutical applications since **the equilibrium degree of swelling influences:**
  1. the solute diffusion coefficient through hydrogels
  2. the surface properties and surface molecule mobility
  3. the optical properties, especially in relation to contact lens applications
  4. the mechanical properties.

## BIOMEDICAL HYDROGELS

**Acrylic Hydrogels**

**Poly(vinyl alcohol) (PVA) Hydrogels**

**Poly(ethylene glycol) (PEG) Hydrogels**

...

# “SMART” OR “INTELLIGENT,” STIMULI-RESPONSIVE HYDROGELS AND THEIR APPLICATIONS

## ➤ pH-Sensitive Hydrogels

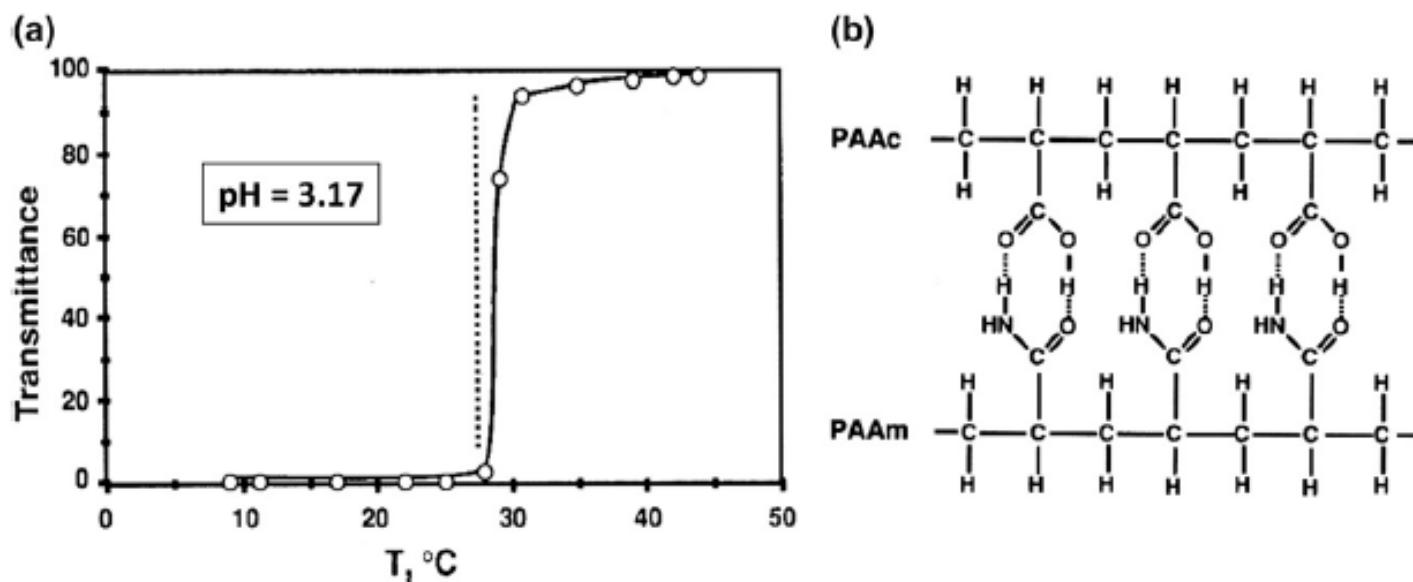
- These hydrogels are swollen ionic networks containing either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize and develop fixed charges on the gel, leading to rapid swelling.
- These gels typically contain ionizable pendant groups such as carboxylic acids or amine groups
- The most commonly studied ionic polymers include poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA), and poly(dimethylaminoethyl methacrylate) (PDMAEMA).

## ➤ pH-Responsive Complexation Hydrogels

- Complexing hydrogels is a class of hydrogels that exhibit responsive behavior.
- complexing hydrogels exhibit drastic changes in their mesh size in response to small changes of pH, which could be useful for drug delivery in varying pH environments in the body, such as in the GI tract, mouth, and on the skin.

## ➤ Temperature-Sensitive Hydrogels

- Temperature-sensitive polymers typically exhibit a lower critical solution temperature (LCST).
- Above this temperature, the polymers may lose their hydrophobically-bound water, and phase separate, causing the gel to collapse.
- Below the LCST, the cross-linked gel re-swells to significantly higher degrees because of the increased hydrophobic bonding with water.



**FIGURE 1.2.5.7** Temperature dependence of light transmission for two H-bonded polymers, PAAc (Polyacrylic acid) and PAAm (Polyacrylamide) at pH 3.17; (a) shows the temperature dependence of light transmission and (b) shows the hypothetical H-bonded structure that would exist at low pH and at temperatures below 30°C, where the COOH groups are protonated and the polymer chains are complexed. The H-bonding is disrupted as temperature rises above 30°C. Data are for an aqueous solution at pH 3.17 (adjusted by HCl). Polymer concentration (wt. %): PAAc, 0.5%; PAAm, 0.5%. (Katono et al., (1991).

## ➤ Affinity Hydrogels

- Some hydrogels may exhibit environmental sensitivity due to the formation of complexes between chains that hold them together as a gel
- Sometimes this complexation is due to affinity recognition interactions, such as
  - between streptavidin, with four binding sites for biotin, and a polymer with multiple pendant biotins **or**
  - Concanavalin A with four binding sites for glucose and a polymer with multiple pendant glucose, **or**
  - an antibody with two binding sites for its antigens

# BIOMEDICAL APPLICATIONS OF HYDROGELS

## ➤ Contact Lenses

- One of the earliest biomedical applications of hydrogels was the use of PHEMA hydrogels in contact lenses
- Hydrogels are particularly useful as contact lenses because of their relatively good mechanical stability and favorable refractive index

## ➤ Blood-Contacting Hydrogels

- Nonionic hydrogels have been prepared from poly(vinyl alcohol), polyacrylamides, PNVP, PHEMA, and poly(ethylene oxide).
- Heparinized polymer hydrogels and heparin-based hydrogels also show promise as materials for blood-contacting applications.

## ➤ Drug Delivery from Hydrogels

- Applications of hydrogels in controlled drug delivery systems (DDS) have become very popular in recent years
- They include equilibrium-swollen hydrogels, i.e., matrices that have a drug incorporated in them and are swollen to equilibrium, releasing the drug.

## ➤ Targeted Drug Delivery from Hydrogels

- Promising new methods for the delivery of chemotherapeutic agents using hydrogels have been recently reported.

## ➤ **Tissue Engineering Scaffolds from Hydrogels**

- It is driven by the same attractive properties that drive the use of hydrogels for drug delivery applications: high water content gels that may be synthesized with degradable backbone polymers, with an added advantage of being able to attach cell adhesion ligands to the network polymer chains.
- There are a number of natural polymer-based hydrogel scaffolds that have been studied (e.g., collagen, gelatin, alginates, hyaluronic acid, chitosan).
- hydrogels they may stimulate stem cell differentiation; that is, when stem cells are deposited on some hydrogel surfaces, depending on the composition and/or mechanical stiffness of the surface, differentiation of the stem cells into certain phenotypes may occur

## ➤ **Miscellaneous Biomedical Applications of Hydrogels**

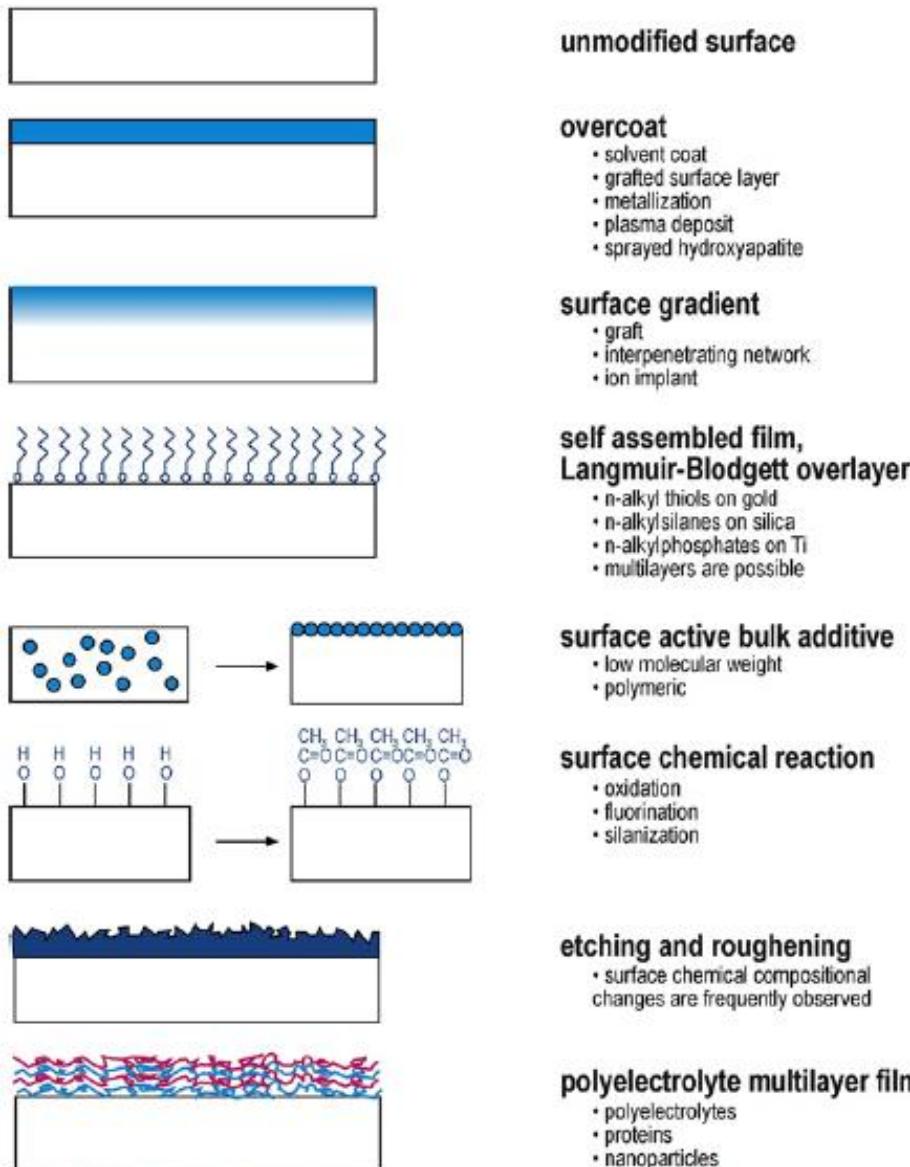
- Other potential applications of hydrogels include artificial tendon materials, wound-healing bioadhesives, artificial kidney membranes, articular cartilage, artificial skin, maxillofacial and sexual organ reconstruction materials.

# **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

## Surface Modification Possibilities



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

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

# 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.

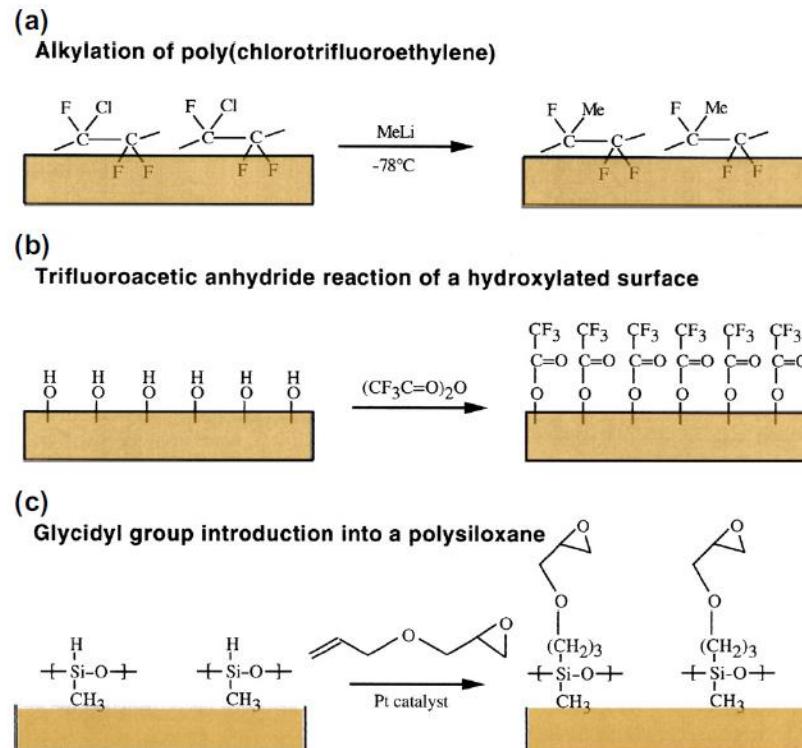
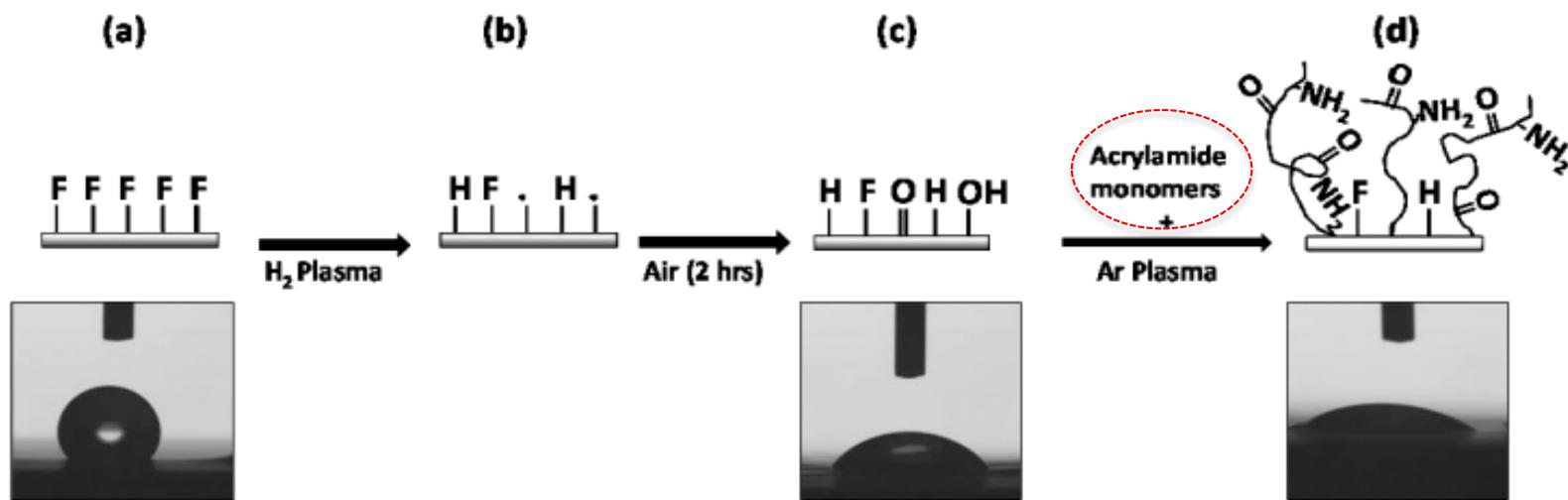


FIGURE I.2.12.2 Some specific chemical reactions to modify surfaces.

## ➤ **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**

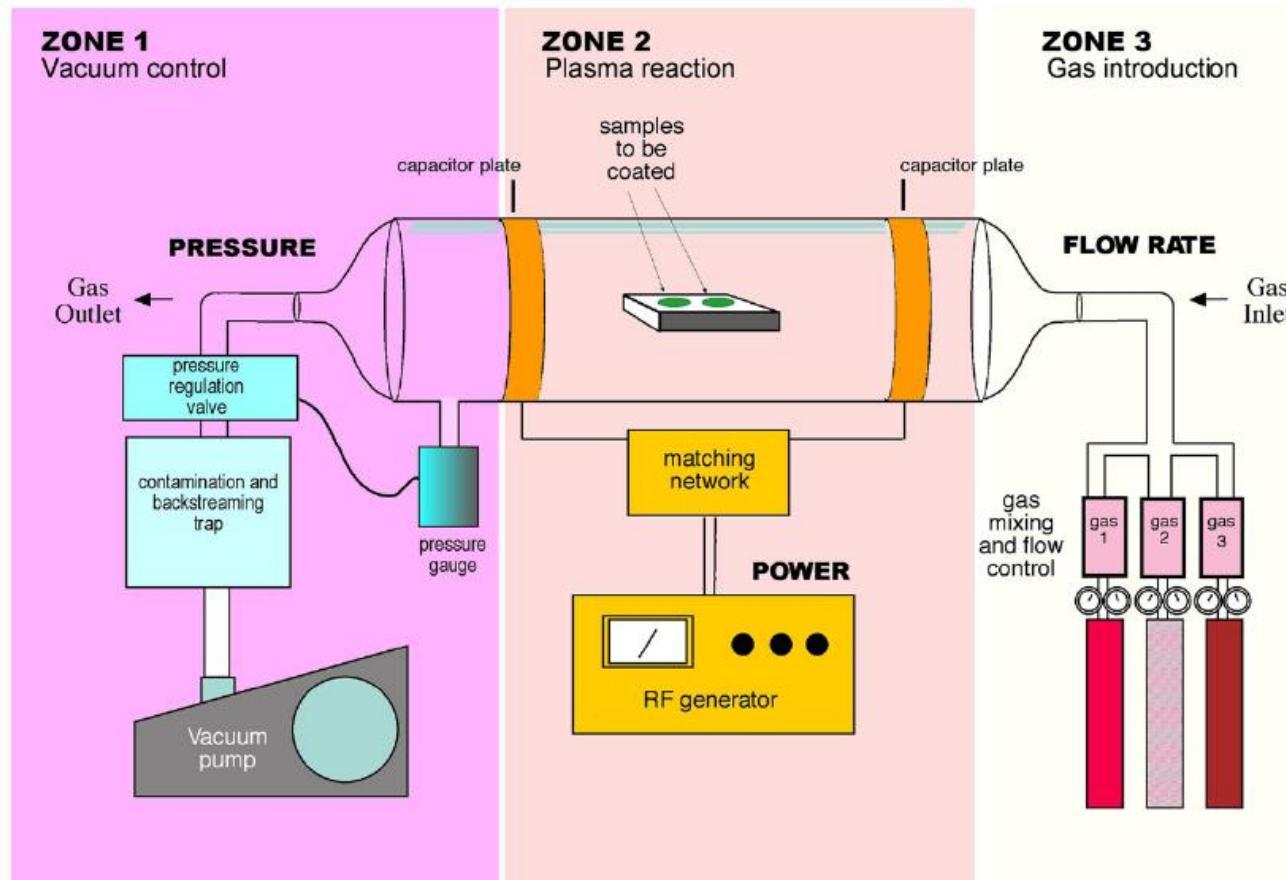
- |                                                       |
|-------------------------------------------------------|
| A. Plasma Treatment (Etching)                         |
| 1. Clean                                              |
| 2. Sterilize                                          |
| 3. Cross-link 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 are **sterile when removed from the reactor, offering an additional advantage for cost-efficient production of medical devices**.

## The Nature of the Plasma Environment

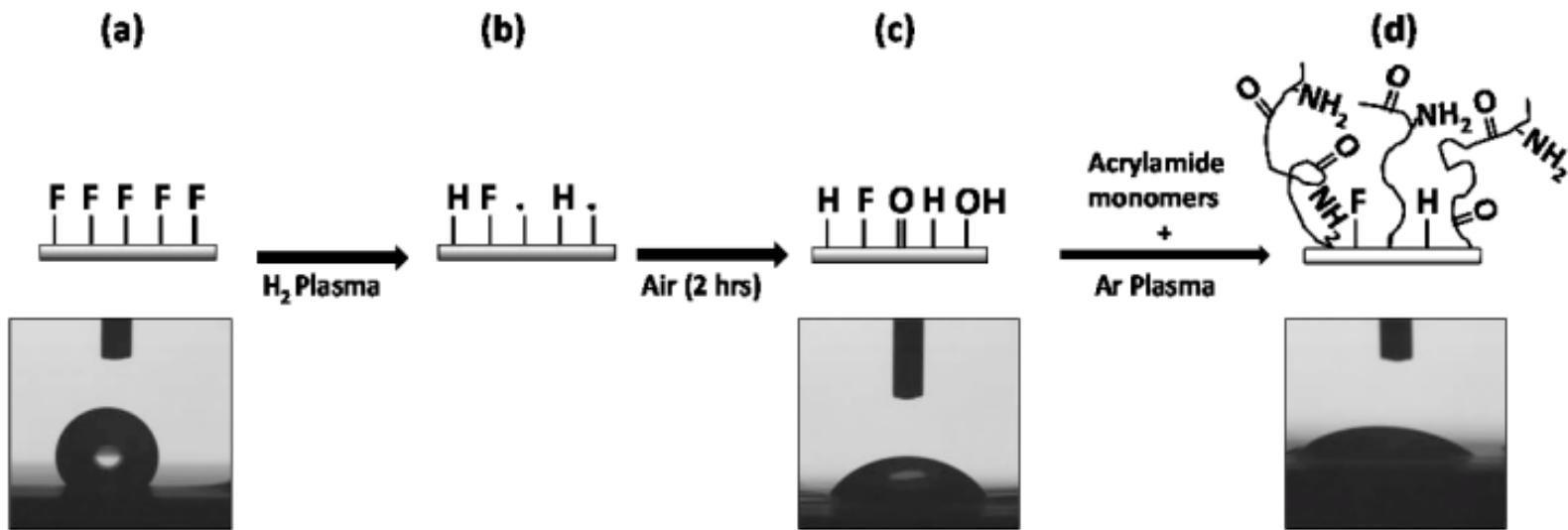
- Plasmas are atomically and molecularly dissociated gaseous environments.
- A plasma environment contains positive ions, negative ions, free radicals, electrons, atoms, molecules, and photons (visible and near UV).
- Typical conditions within the plasma include an electron energy of 1–10 eV, a gas temperature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



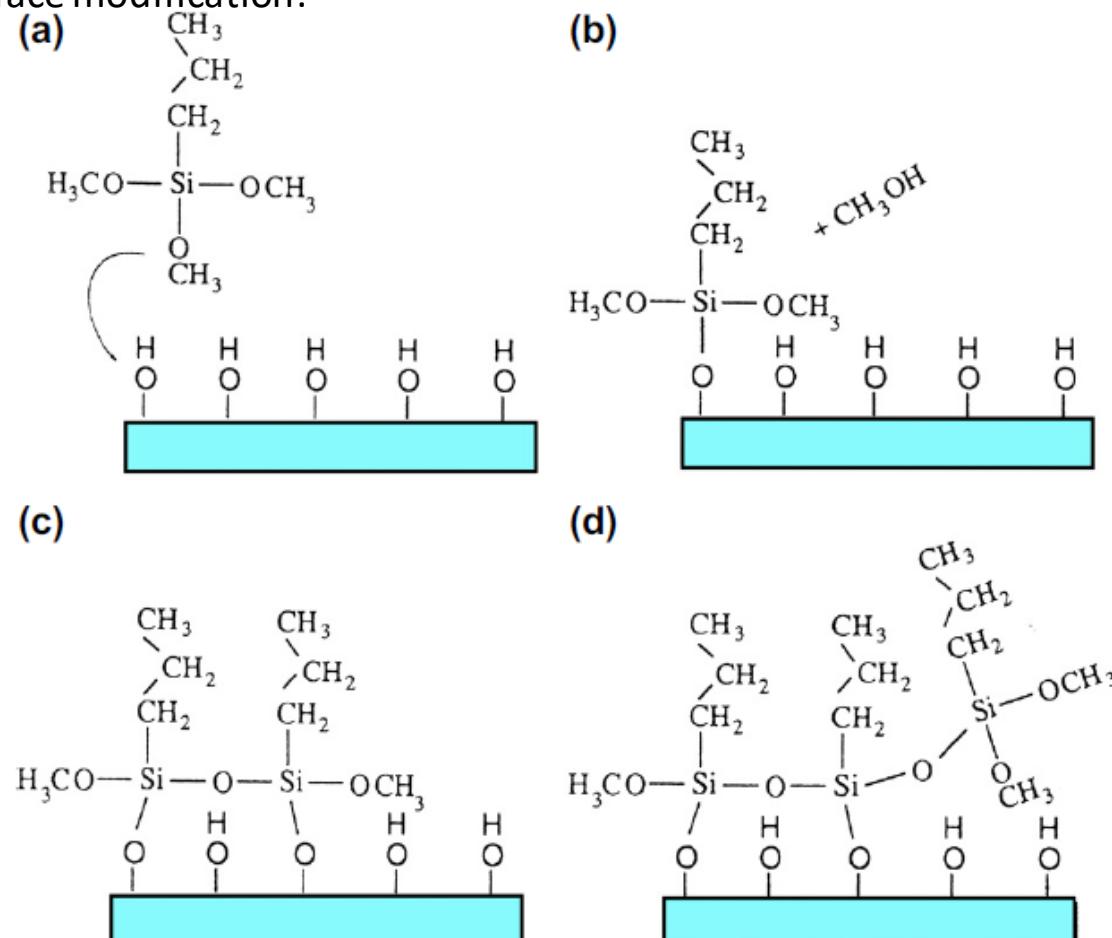
watch the  
video



**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.

## ➤ 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:

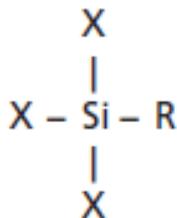


**FIGURE I.2.12.4** The chemistry of a typical silane surface modification reaction: (a) a hydroxylated surface is immersed in a solution containing n-propyl trimethoxysilane (nPTMS); (b) one of the methoxy groups of the nPTMS couples with a hydroxyl group releasing methanol; (c) two of the methoxy groups 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**

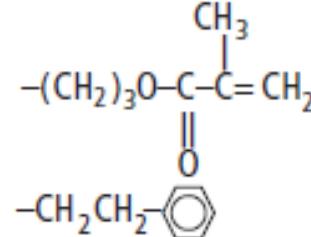


X = Leaving Group

–Cl  
–OCH<sub>3</sub>  
–OCH<sub>2</sub>CH<sub>3</sub>

R = Functional Group

–(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>  
–(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>  
–(CH<sub>2</sub>)<sub>2</sub>(CF<sub>2</sub>)<sub>5</sub>CF<sub>3</sub>



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

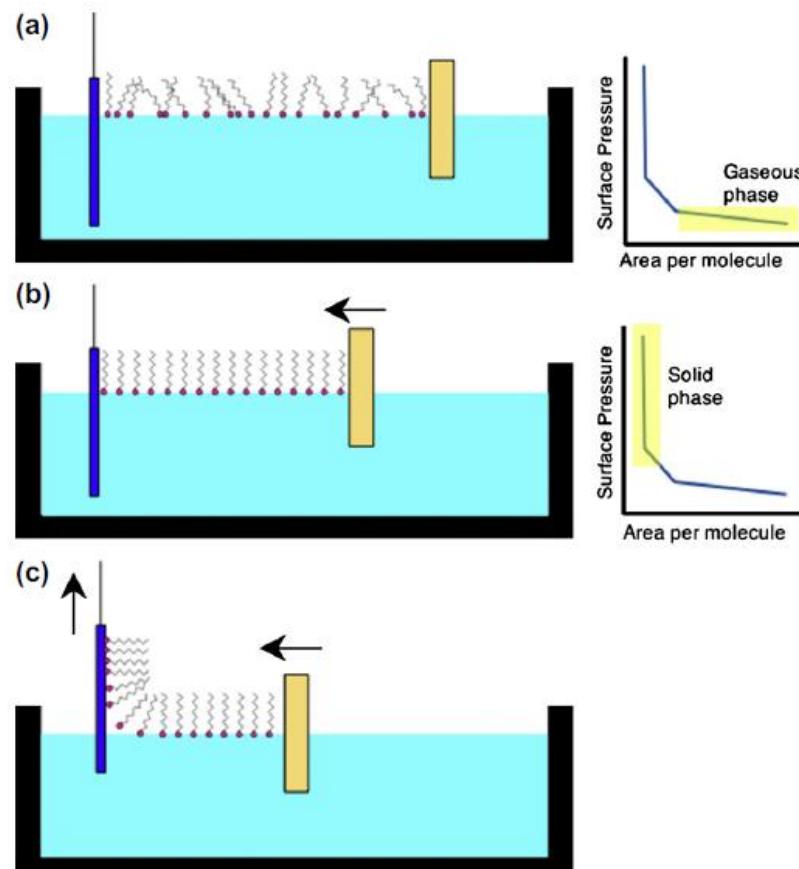
## ➤ Ion Beam Implantation

- 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

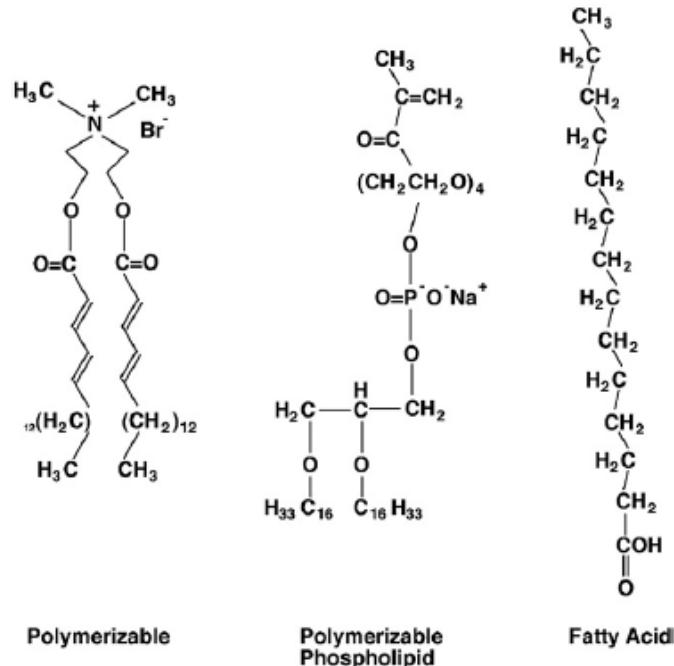
## ➤ Langmuir–Blodgett Deposition

- 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

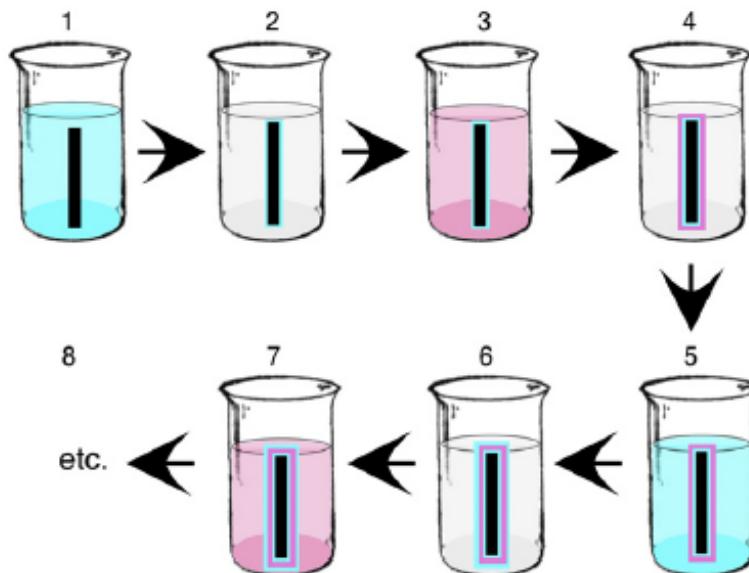


**FIGURE 1.2.12.7** Three examples of molecules that form organized Langmuir-Blodgett Films.

- 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

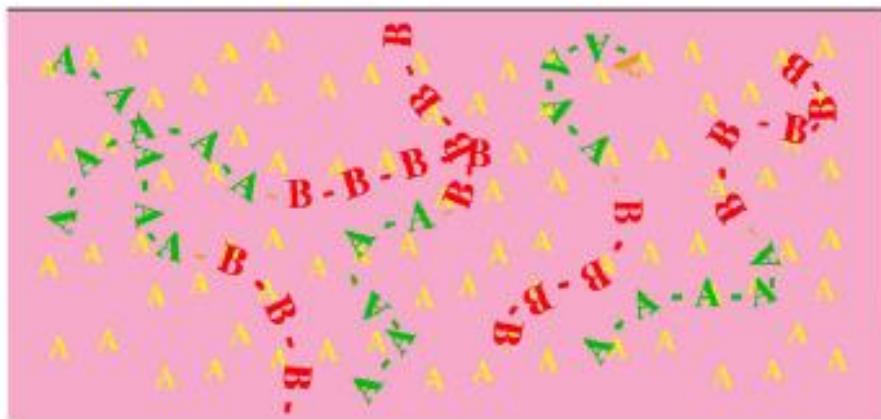
- For Layer-by-layer (L-b-L) deposition surface treatment, a molecule (or polymer or protein) is chosen that adsorbs strong to the substrate (adsorbate 1). Then the substrate is rinsed (retaining adsorbate 1), and dipped in a solution of a molecule that interacts strongly with adsorbate 1 (adsorbate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



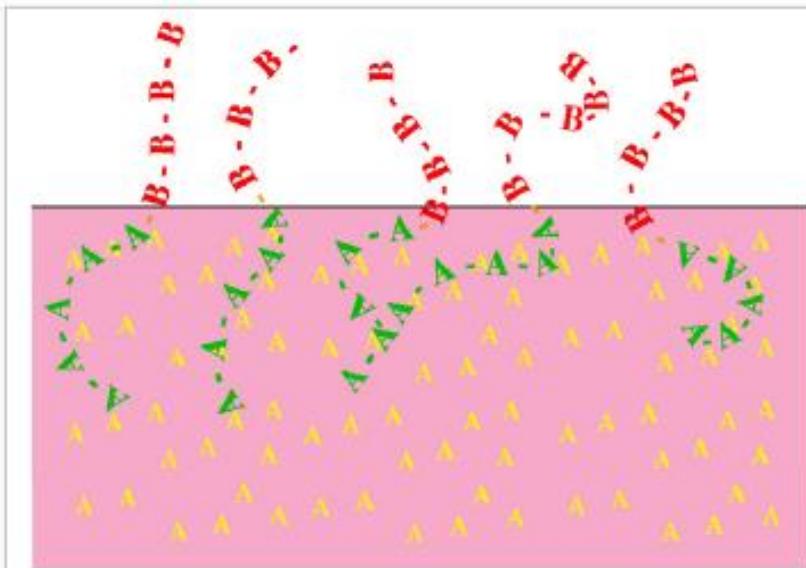
**FIGURE I.2.12.9** Layer by layer deposition of a multilayer surface coating. A series of adsorption-rinse steps lead to a multilayer surface deposition: (1) the “blue” compound is adsorbed to the substrate; (2) the adsorbed layer is rinsed in solvent (frequently water) to remove weakly adherent material; (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.



**During Fabrication**



**Post-Fabrication**

**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.

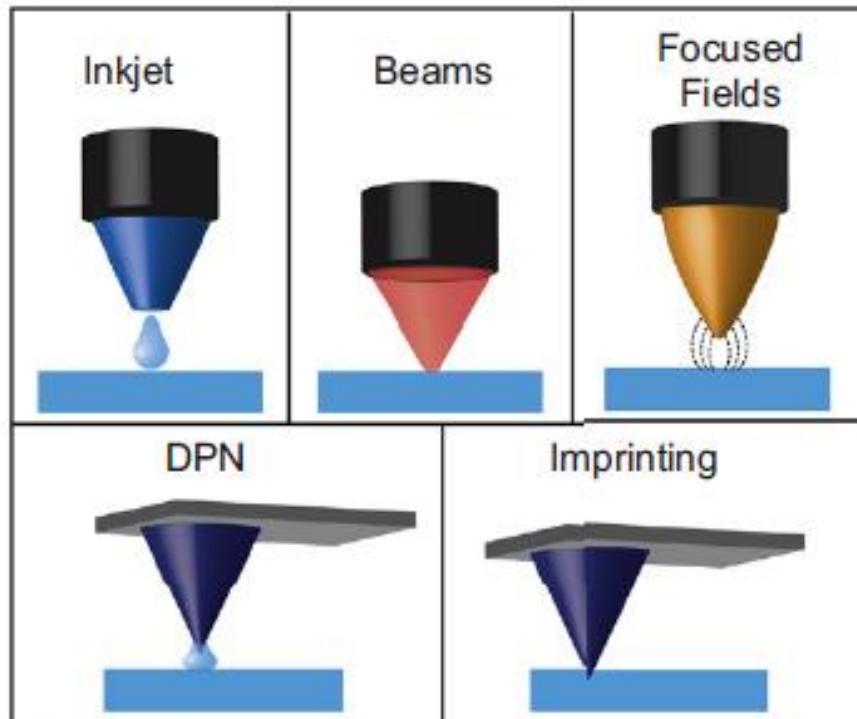
## ➤ Patterning

- 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
  - ...

## PATTERNING TECHNIQUES

### ➤ 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.

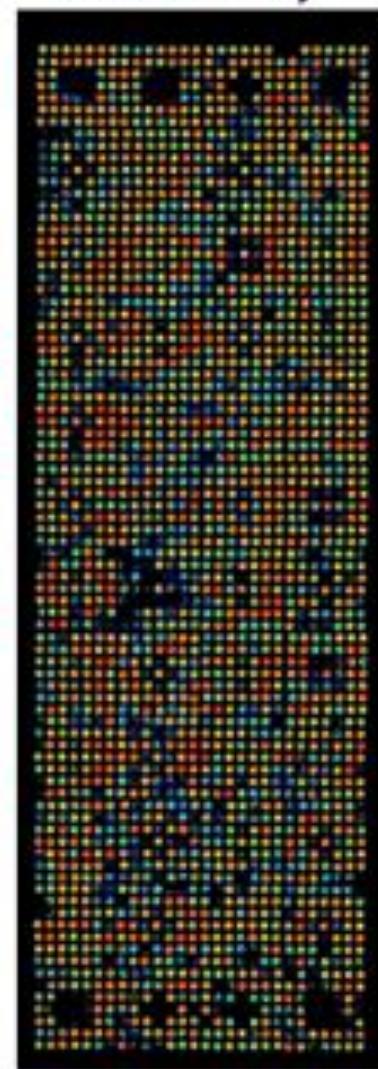
## ➤ Printing with Inkjets, Quills, and Pins.

- **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.

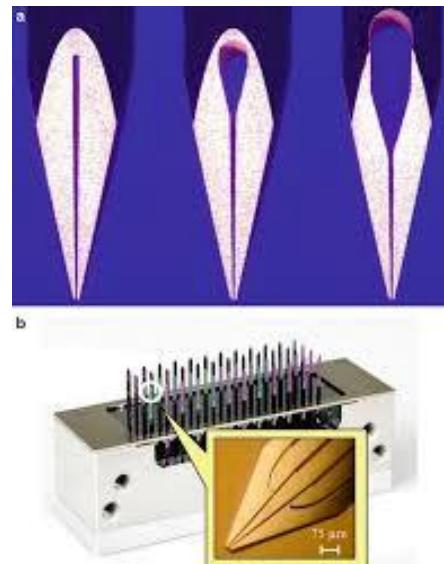
- “living advertisement” – a colony of bacteria printed in the shape of a university logo – printed.



Protein Array

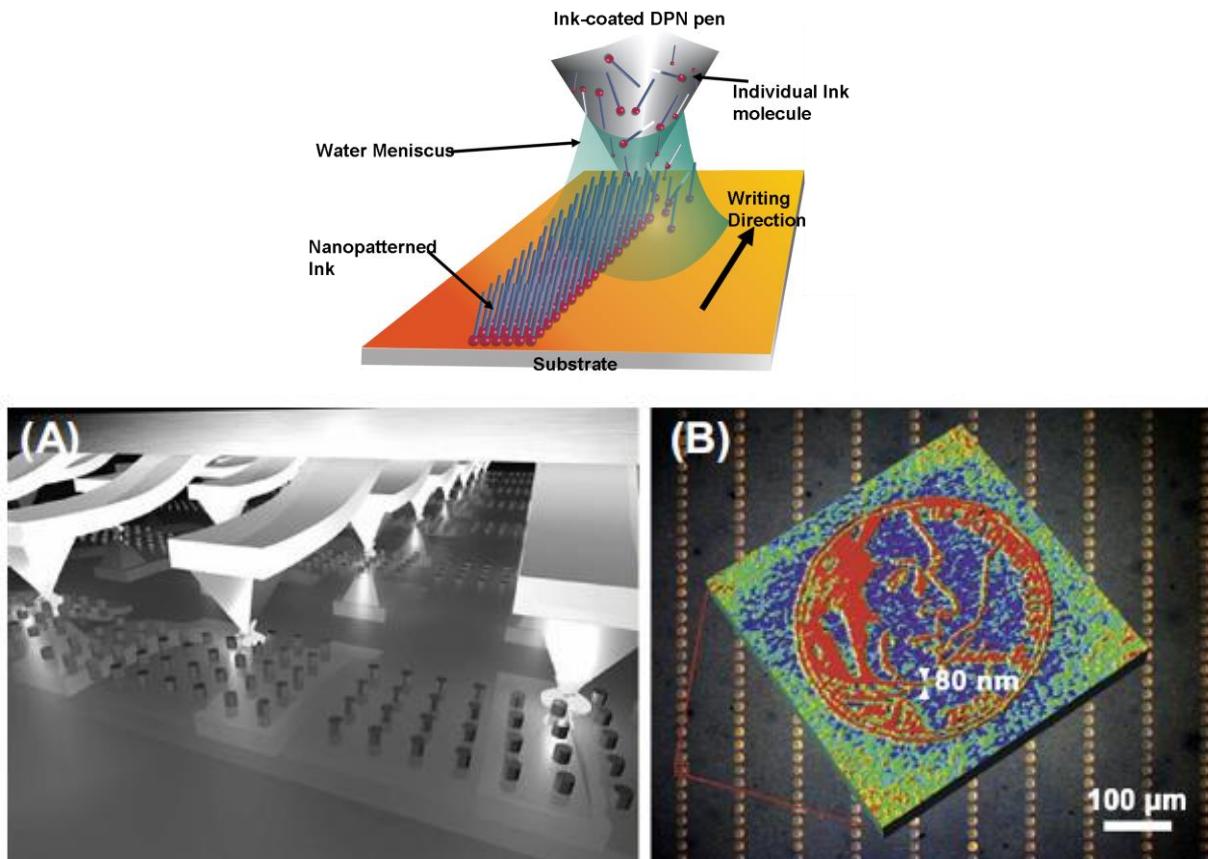


- Pin-based arrayers have also largely been used to fabricate protein arrays, because it is significantly cheaper and less complex to manufacture arrayers with a large number of **pins or quills**.
- Microarrays have also been used as clinical diagnostics to detect specific analytes.



## ➤ 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.

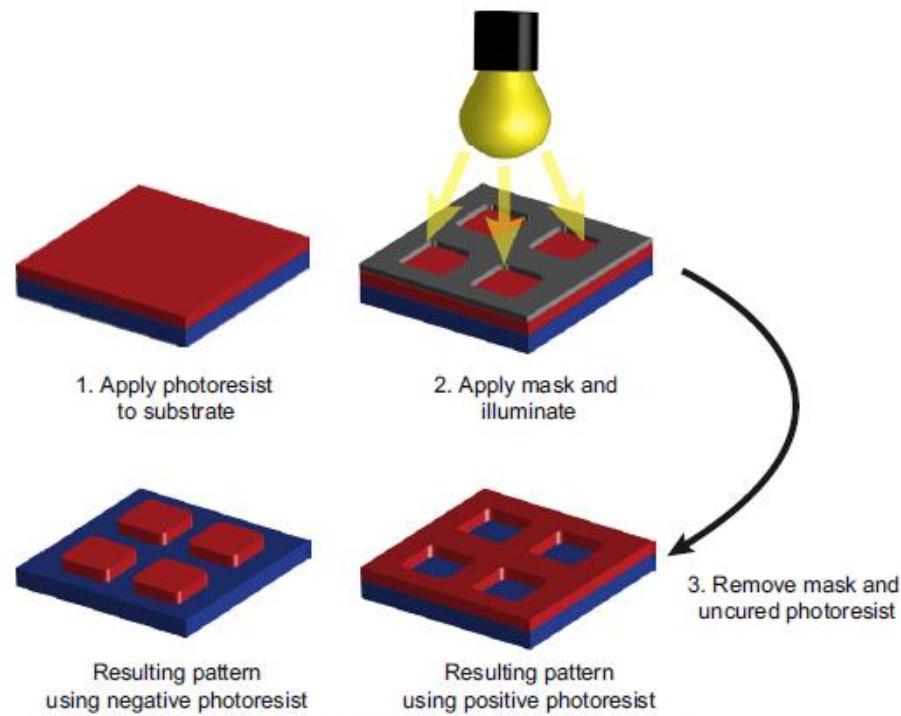


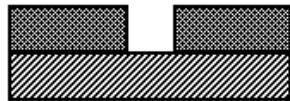
FIGURE I.2.13.8 Mask-Based Photolithography.

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

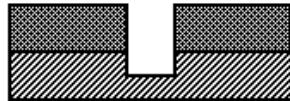
## ➤ Deposition/Etching with Masks

- 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.

Subtractive Process



Photolithography

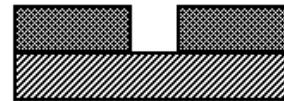


Etch

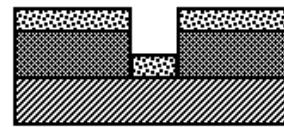


Pattern transfer  
by etching

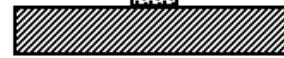
Additive Process



Deposit



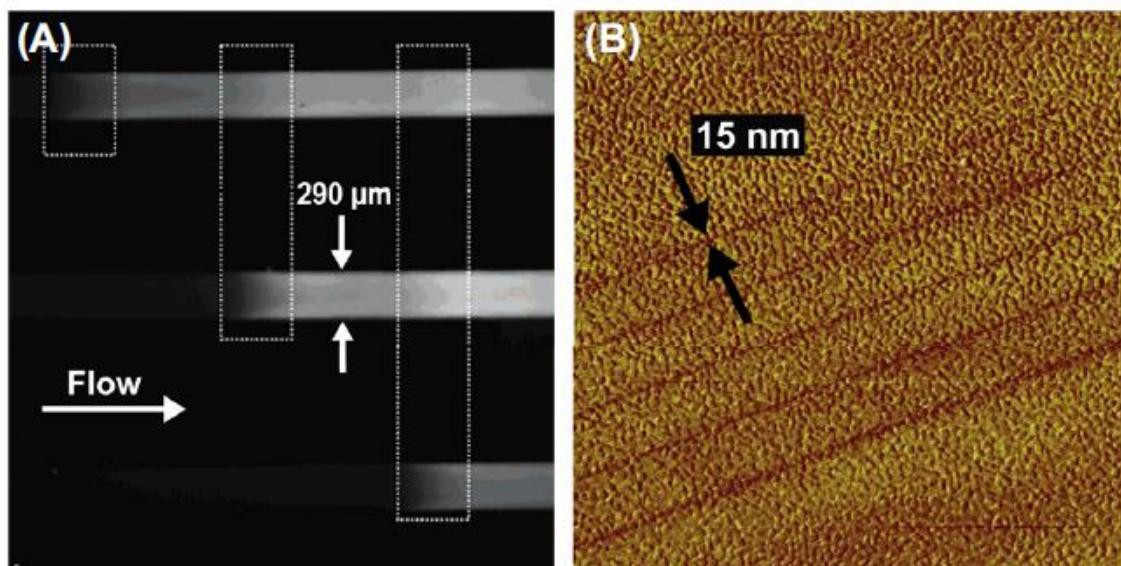
Strip Resist



Pattern transfer  
by lift off

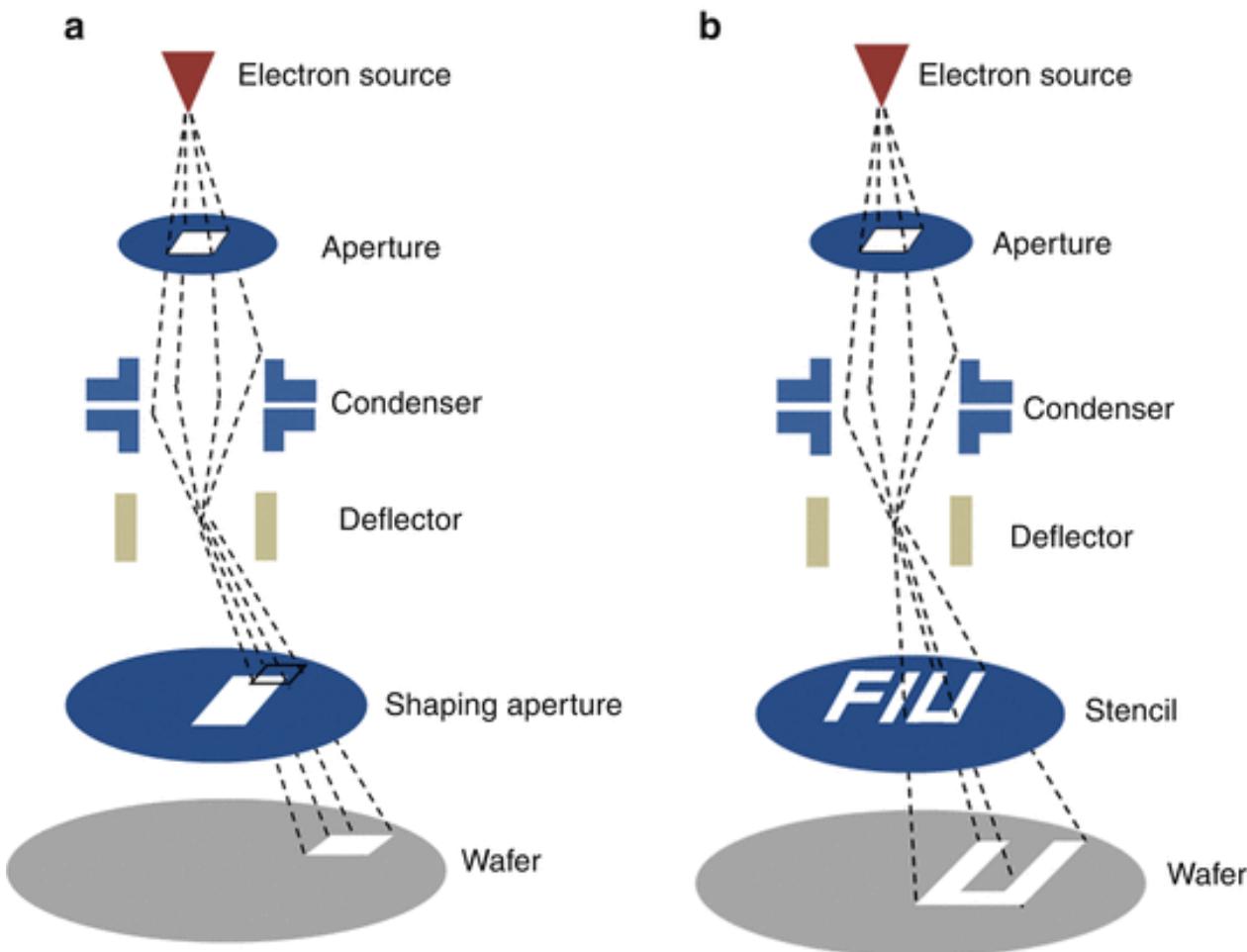
## ➤ Writing with Beams

- ***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

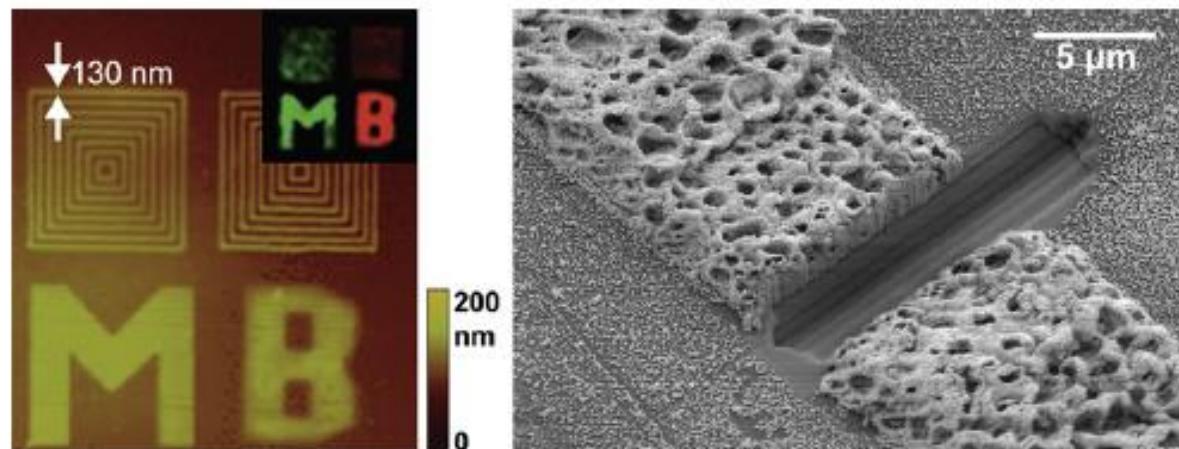


**FIGURE 1.2.13.6** Examples of Direct-Write Protein Patterning with Light. (A) Patches of enzymes (locations indicated by dashed boxes in the figure) patterned within flow channels produce fluorescent products when exposed to fluorogenic reagents; (B) Sub-diffraction limit features patterned with light 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.



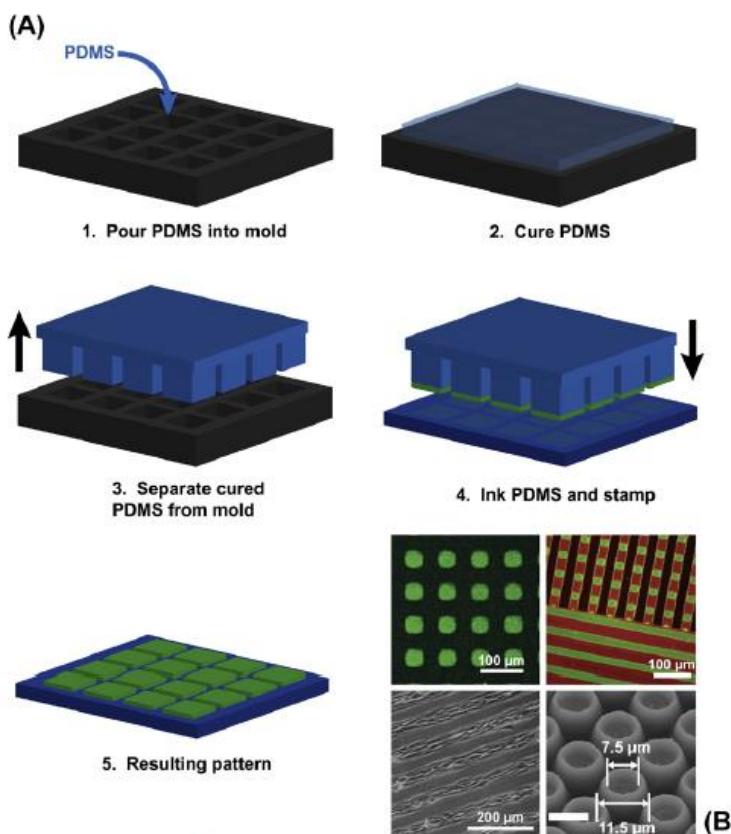
- **Focused ion beam (FIB) patterning** makes use of high-mass ions, such as gallium ions, as the energetic particles instead of electrons as in EBL.
- FIB patterning is an inherently destructive process, as the bombardment of a surface with ions causes atomic sputtering of atoms from the surface. For this reason, FIB is typically used as a milling technique to engrave a surface with submicrometer size features.



**FIGURE 1.2.13.7** 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  $\mu\text{m}$ ). (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

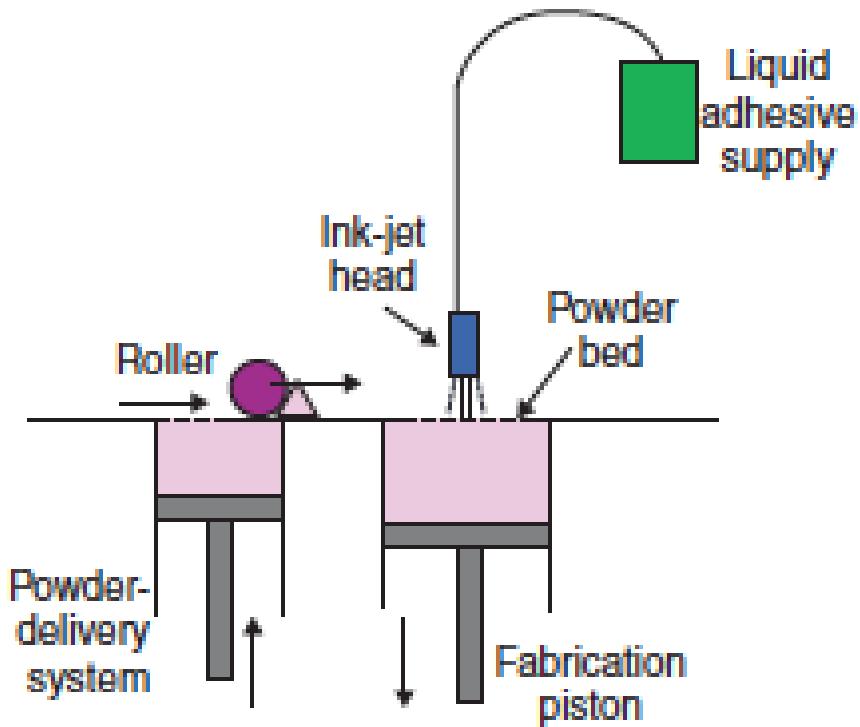
- A *master* is a template that is used to replicate patterns.
- Rigid masters can be used directly to imprint patterns on substrates.
- the most widespread use of masters for patterning is to create a *mold* which is subsequently used to mold the patterns.
- The most widely used polymer in soft lithography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



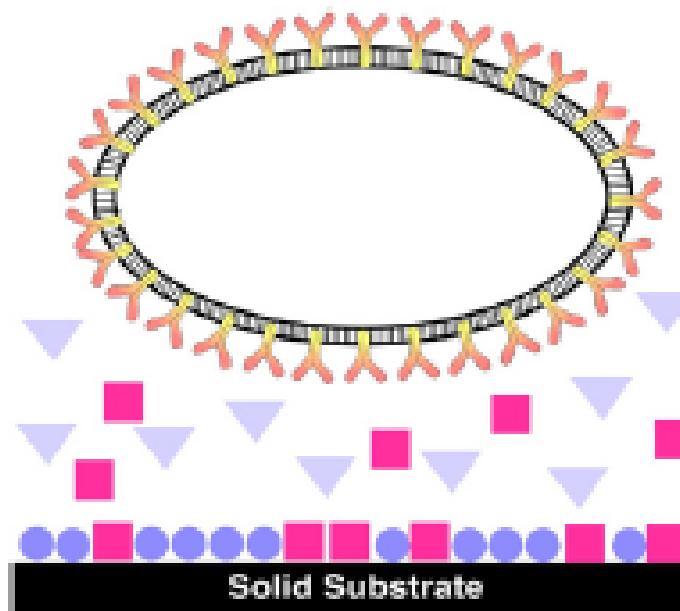
3D printing

# Some Background Concepts

# ADSORBED PROTEINS ON BIOMATERIALS

- The replacement of injured or diseased tissues with devices made from **materials that are not of biologic origin** is the central approach in current biomaterials science and clinical practice due to the fact that **these materials are not attacked by the immune system**, unlike donor tissues or organs.
- This fundamental difference arises from the presence of immunologically recognizable biologic motifs on donor tissue, and their absence on synthetic materials.
- Nonetheless, there are other types of biological responses to implanted biomaterials that often impair their usefulness, including the **clotting of blood and the foreign-body reaction**. Clearly, the body does recognize and respond to biomaterials.
- The basis for these reactions is the adsorption of adhesion proteins to the surface of the biomaterials that are recognized by the integrin receptors present on most cells.

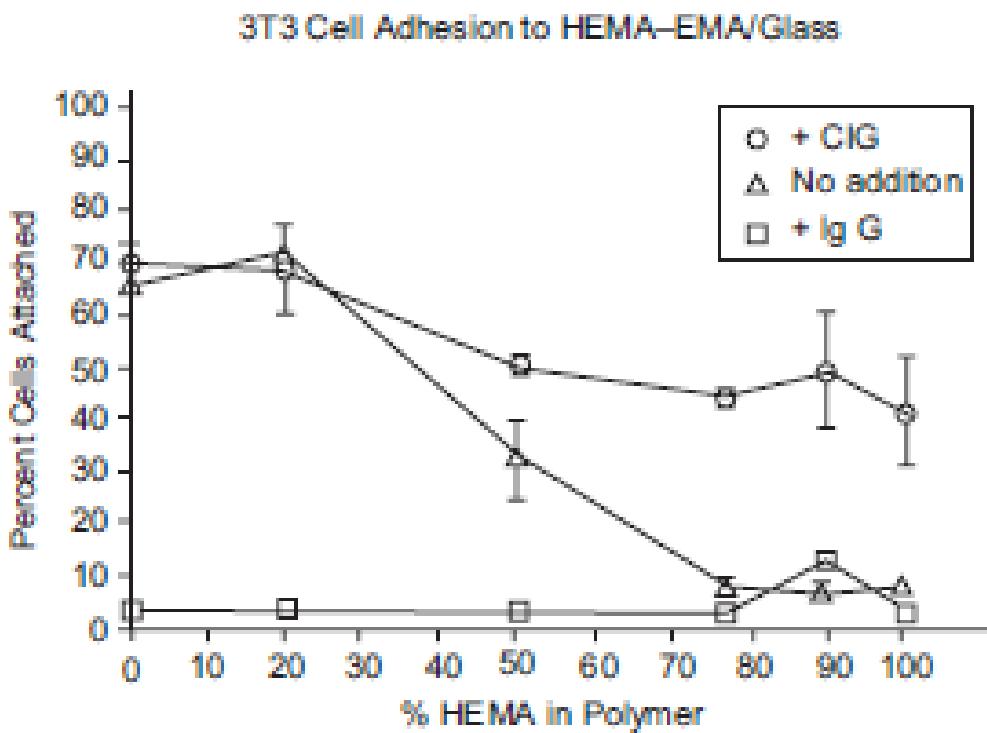
- The adsorption of adhesion proteins to the biomaterial converts it into a biologically recognizable material.



**FIGURE II.1.2.1** Cell interactions with foreign surfaces are mediated by integrin receptors with adsorbed adhesion proteins that sometimes change their biological activity when they adsorb. The cell is shown as a circular space with a bilayer membrane in which the adhesion receptor protein molecules (the slingshot-shaped objects) are partly embedded. The proteins in the extracellular fluid are represented by circles, squares, and triangles. The receptor proteins recognize and cause the cell to adhere to only the surface bound form of one protein, the one represented by a solid blue circle. The bulk phase of this same adhesion protein is represented by a blue triangle, indicating that the solution and solid phase forms of this same protein have a different biological activity. The figure is schematic and not to scale.

## EXAMPLES OF THE EFFECTS OF ADHESION PROTEINS ON CELLULAR INTERACTIONS WITH MATERIALS

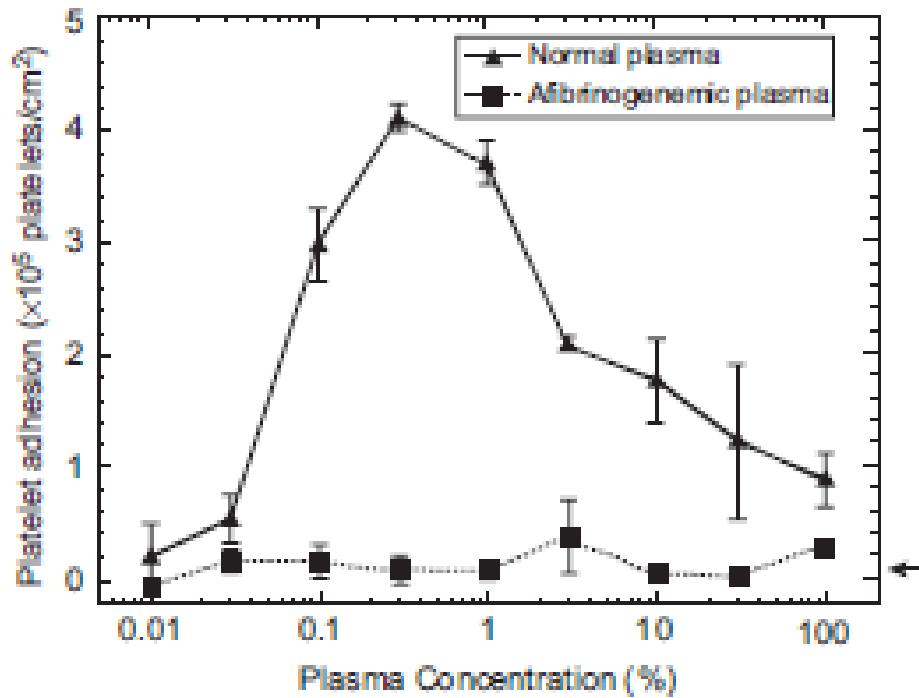
### ➤ The Effects of Preadsorption with Purified Adhesion Proteins



**FIGURE II.1.2.2** 3T3 cell adhesion to HEMA-EMA copolymers varying from hydrophilic (HEMA-rich) to hydrophobic (EMA-rich): effect of no adsorbed protein, preadsorption with fibronectin (designated CIG in the figure) or preadsorption with immunoglobulin G (IgG). The data is from the author's laboratory.

- An example of the effect of fibronectin adsorption is shown in Figure II.1.2.2, which also contrasts it with the effects of the non-adhesive protein immunoglobulin G.
- As shown in the figure, the adhesion of the fibroblast-like 3T3 cells to a series of polymers and copolymers of 2-hydroxyethyl methacrylate (HEMA) and ethyl methacrylate (EMA) not previously adsorbed with protein (and without proteins in the cell suspension) varies, being much less on the hydrophilic polyHEMA-rich surfaces than on the hydrophobic polyEMA-rich surfaces.
- These data are an example of direct or non-specific cell adhesion in which the cells adhere directly to the surfaces, rather than to adsorbed proteins.

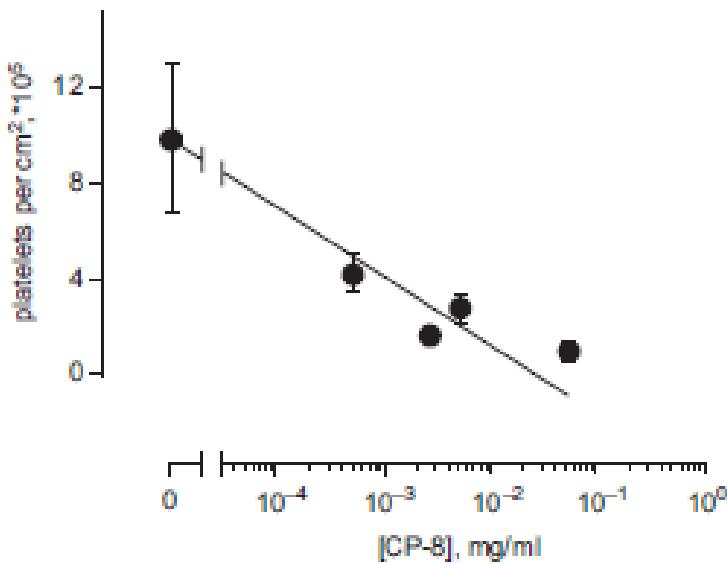
## ➤ Depletion Studies



- Platelet adhesion to surfaces preadsorbed with plasma deficient in fibrinogen is much less than to the same surface preadsorbed with normal plasma

**FIGURE II.1.2.3** Platelet adhesion to Immulon I® preadsorbed with normal plasma (triangles) or afibrinogenemic plasma (squares). The solid line represents the platelet adhesion to Immulon I® preadsorbed with a series of dilutions of normal plasma, whereas the dotted line represents the platelet adhesion to Immulon I® preadsorbed with a series of dilutions of afibrinogenemic plasma. The arrow at the lower right corner indicates platelet adhesion to Immulon I® preadsorbed with 2% BSA only (BSA is bovine serum albumin). (Source: Figure 4 in Tsai and Horbett, 1999. Copyright permission received.)

## ➤ Inhibition of Receptor Activity with Antibodies

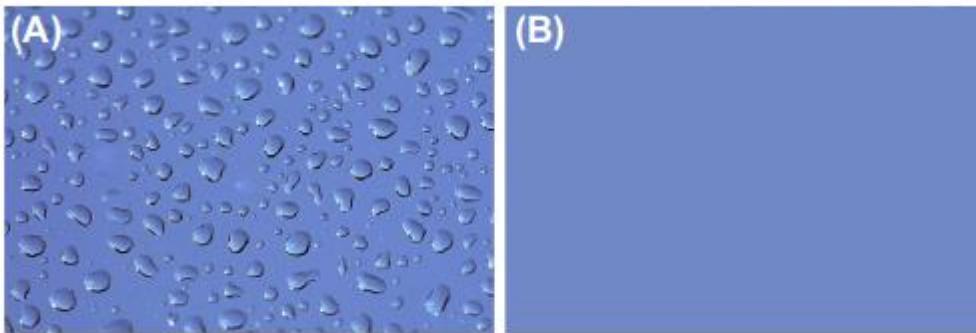


**FIGURE II.1.2.4** Effect of anti-IIb/IIIa antibody on platelet adhesion to Biomer preadsorbed with plasma. Adhesion of platelets incubated in monoclonal antibody CP-8 (monovalent Fab' fragment directed against the glycoprotein (GP) IIb/IIIa complex) to Biomer. Substrates were contacted with 1.0% plasma for 2 hours, then with washed, antibody-treated platelets for 2 hours. (From: Chinn J.A., Horbett T.A., Ratner B.D. (1991). Baboon Fibrinogen Adsorption and Platelet Adhesion to Polymeric Materials. *Thromb Haemost*, 65, 608-17.)

- Platelet receptor-mediated interactions appear to be the primary mechanism of platelet interaction *in vivo* with certain vascular grafts, because platelet deposition is largely inhibited by antibodies to the **glycoprotein IIb/ IIIa receptor, the major integrin on the surface of platelets.**
- *In vitro* platelet adhesion to surfaces preadsorbed with blood plasma is also inhibited by **anti-glycoprotein IIb/IIIa** in a dose-dependent manner

## THE ADSORPTION BEHAVIOR OF PROTEINS AT SOLID–LIQUID INTERFACES

- an experiment that is performed to demonstrate the adsorption of proteins to surfaces

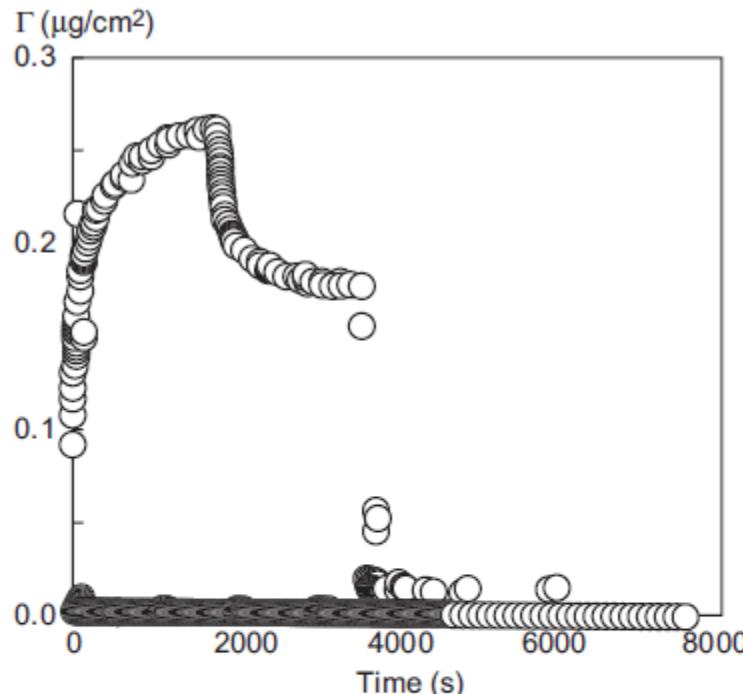


**FIGURE II.1.2.5** The conversion of non-wettable polystyrene surface (A) into one completely wettable by water (B) is due to the adsorption of proteins (simulated images based on actual observations).

- in **part (A)**, water droplets sprayed on the surface of an unused polystyrene cell culture dish are easily visible because **they bead up**. If a cell were placed on a polystyrene dish instead of the water droplet, it would also encounter a very non-wettable surface.
- in **Part (B)** , figure illustrates the results of spraying water droplets on the surface of a polystyrene dish that had first been exposed to a protein solution for a short time, and then rinsed extensively with water.
  - As illustrated, no water droplets can be seen on this surface, reflecting the fact that in this case the added drop of water completely spread out over the surface of the preadsorbed dish. **This happens because the water in part (B) was not able to interact with the polystyrene surface, because the surface had become coated with a layer of the hydrophilic protein adsorbate.**
  - Similarly, **cells that come into contact** with surfaces adsorbed with proteins do not directly “see” the substrate, but instead they interact with the intervening protein adsorbate.

## ➤ Rapid Adsorption Kinetics and Irreversibility

- The time course of adsorption of lysozyme on silica measured with a high speed, automated ellipsometer capable of very rapid measurements



**FIGURE II.1.2.6** The adsorption kinetics of lysozyme to a silica surface as studied with ellipsometry. The adsorbed amount versus time for adsorption of lysozyme to silica followed by buffer rinsing after 1800 seconds, addition of surfactant (sodium dodecyl sulfate) after 3600 seconds, and a final rinse with buffer after 5400 seconds (open circles). Adsorption from a mixture of the protein and surfactant for 1800 seconds followed by rinsing is also included (closed circles). The experiments were carried out at 25°C in 0.01 M phosphate buffer, 0.15 M NaCl, pH 7. (Reprinted with permission from: Arnebrandt and Wahlgren, 1995. Copyright © 1995 American Chemical Society.)

- At the earliest measurement time, less than a second into the study, the adsorption has reached almost half of the steady-state value.
- At 2000 seconds, the protein solution was replaced with a buffer, resulting in some removal of loosely bound protein, but the adsorption stabilizes and would have remained at this value for much longer than shown, due to the tight, irreversible binding.
- At 4000 seconds, a solution of the detergent sodium dodecyl sulfate (SDS) was infused, leading to complete removal of the protein.
- Thus, this experiment illustrates the rapid adsorption of proteins. It also illustrates that most of the adsorbed protein is irreversibly bound, as indicated by the fact that washing the surface with buffer does not remove the protein. The adsorbed protein is only removed when a strong surfactant (SDS in this example) is used. All these features are characteristic of protein adsorption to solid surfaces.

## ➤ The Monolayer Model

- The existence of a close packed monolayer of adsorbed protein is suggested by studies with single protein solutions, in which a saturation effect can often be observed in the adsorption isotherm

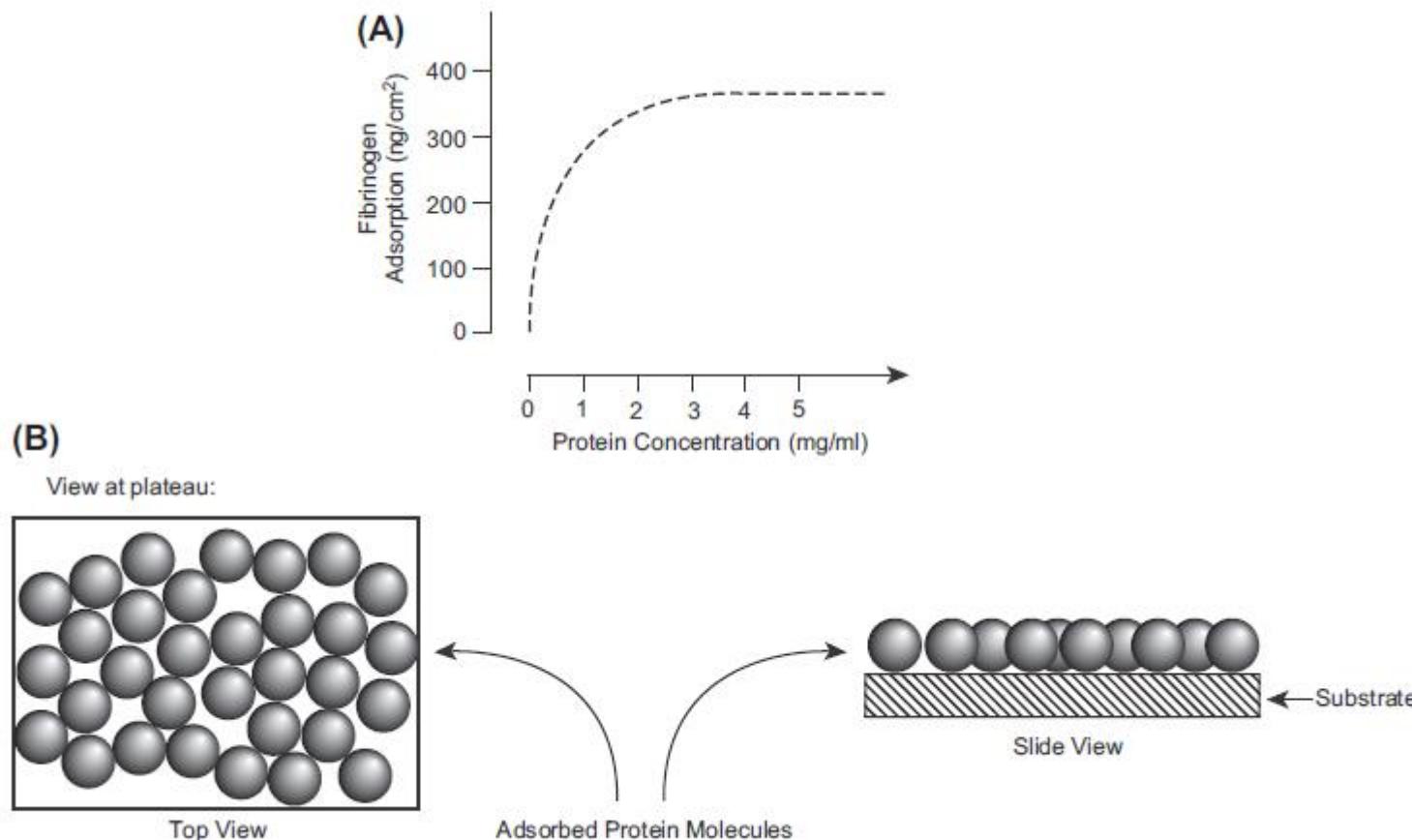
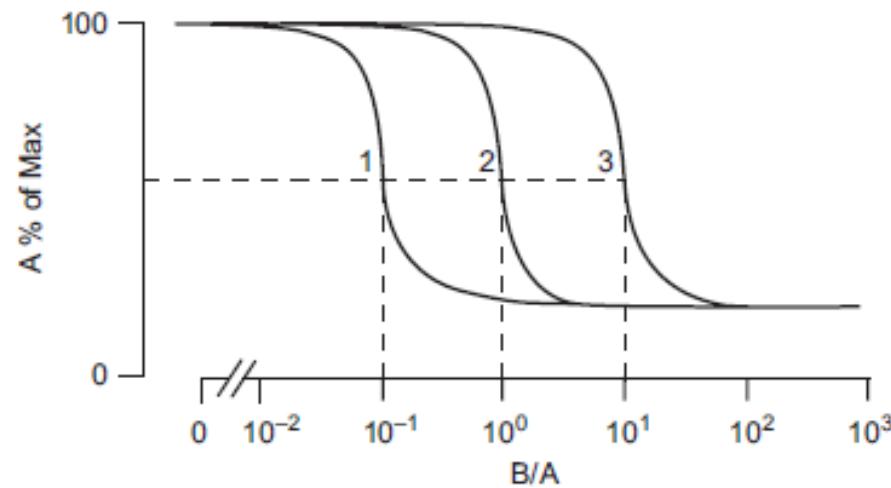


FIGURE II.1.2.8 Adsorption isotherms (A) and the monolayer concept (B).

- Adsorption to surfaces exposed to different concentrations of protein until steady-state adsorption is achieved (2 hours or more) increases steeply at low bulk phase concentrations, but typically reaches a plateau or saturation value at higher bulk concentrations. This behavior is called a Langmuir isotherm.

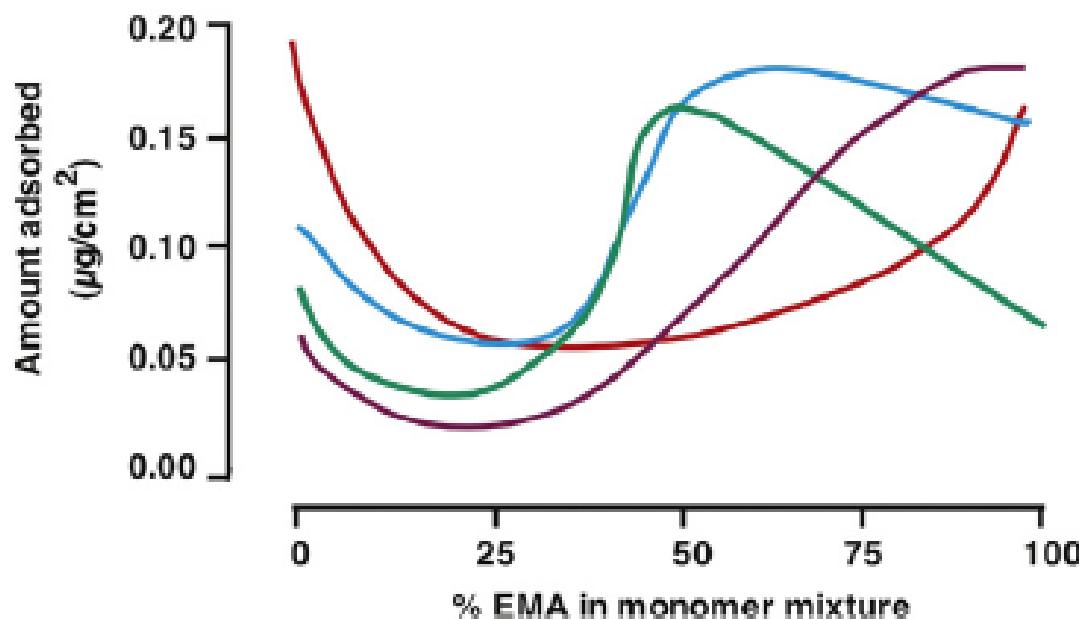
## ➤ Competitive Adsorption of Proteins to Surfaces from Protein Mixtures

- The competitive phenomena underlying differential enrichment from multi-protein mixtures are most clearly illustrated in binary mixtures of proteins
- The curves in Figure represent the typical outcome of **binary mixture studies for three different conditions**.
- when a radiolabeled protein such as fibrinogen ("A" in the figure) is mixed with various amounts of an unlabeled protein such as albumin ("B" in the figure), the adsorption of fibrinogen ("A") always declines when sufficiently high amounts of albumin ("B") are present.
- However, the amount of competing protein needed to inhibit the adsorption of the labeled protein is different in each curve. **This is meant to illustrate that, for a given pair of competing proteins, the competition curves will be different if the surfaces they are competing for are different.**



**FIGURE II.1.2.9** Competitive adsorption of two proteins from a mixture. (From: Horbett, 1993.)

- An experimental example of surface chemistry-dependent selective adsorption of proteins from a complex protein mixture

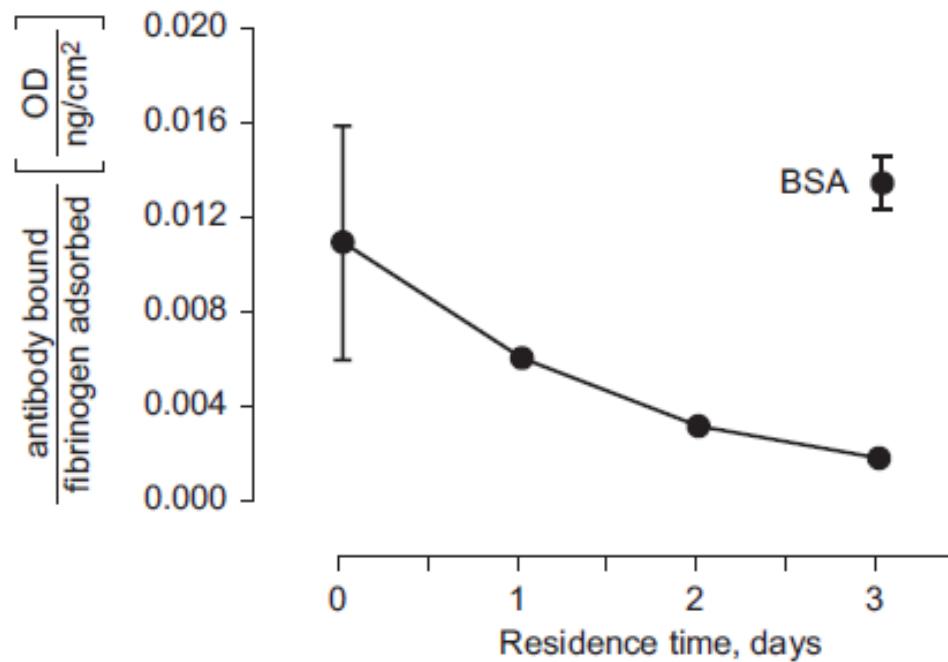


**FIGURE II.1.2.10** Differential affinity of proteins to a series of polymers: adsorption of Fg (green line); IgG (purple line); Alb (red line); and Hb (blue line) from plasma to hydroxyethyl methacrylate – ethyl methacrylate copolymers. (Redrawn version of a figure from: Horbett, 1981.)

## MOLECULAR SPREADING EVENTS: CONFORMATIONAL AND BIOLOGICAL CHANGES IN ADSORBED PROTEINS

- Proteins that adsorb to solid surfaces can undergo conformational changes, because of the relatively low structural stability of proteins and the tendency to unfold to allow further bond formation with the surface.
  - Conformational changes can be detected with many types of physicochemical methods, and also by measuring changes in the biological activity of the adsorbed proteins.
- **Physicochemical Studies of Conformational Changes :** Comparison of the adsorptive behavior of different proteins to their molecular properties indicates that **less stable proteins are more adsorptive**.
- **Changes in Biological Properties of Adsorbed Proteins:** While physicochemical studies sometimes suggest complete denaturation of adsorbed proteins, **most probes for biological activity suggest the changes are more limited**. Thus, enzymes retain at least some of their activity in the adsorbed state, especially when the surfaces are more fully loaded with enzyme.

- Fibrinogen undergoes a time-dependent transition after its adsorption to a surface that results in reduced platelet and antibody binding to the adsorbed fibrinogen



**FIGURE II.1.2.12** Transitions in adsorbed fibrinogen. The effect of three-day residence in buffer or buffered albumin solution upon anti-fibrinogen binding to fibrinogen adsorbed from dilute plasma to Biomer polyurethane is shown. BSA: bovine serum albumin. (From: Fig. 3A in Chinn et al., 1992.)

## CELLS AND SURFACES *IN VITRO*

- **Tissue culture is a general term for the harvest of cells, tissues or organs, and their subsequent growth or maintenance in an artificial environment.**
- Mammalian cells cultured *in vitro* have the same basic requirements as cells growing within an organism.
- *In vitro*, blood is replaced by the culture media, which bathes the cells and provides an energy source (glucose), essential nutrients (salts and amino acids), proteins and hormones (from added serum), and a buffer (to maintain pH balance).
- During culture, the byproducts of cellular metabolism are released into the media as its constituents are depleted.
- Since the culture media is not continually circulated and purified, it must be changed regularly to maintain optimal conditions for cell function.
- These culture conditions are also favorable for the growth of **unwanted organisms such as fungi and bacteria**. Since there is no immune system to control infection *in vitro*, anti-fungal and anti-bacterial agents can be added to the media on a prophylactic basis.
- To further reduce the likelihood of contamination by microorganisms, **cells are manipulated under a laminar flow hood using strict aseptic (sterile) techniques**. Laminar hoods control and direct filtered air to facilitate a sterile working environment by reducing the contact of air-borne bacteria and particulates with the culture dish and hood surfaces.

- Cells in media are contained in culture dishes or flasks and incubated in a temperature-controlled (37°C) and humidified (95%) chamber.
- The exchange of gas at the media surface acts like the lungs to maintain the gas balance necessary for metabolism. CO<sub>2</sub> is usually added to the incubator at a low concentration (5%). The CO<sub>2</sub> interacts with the bicarbonate buffer in the media to help maintain a pH of 7.0–7.4.
- Buffering counteracts pH changes in the media as it accumulates waste from cellular activity. Phenol red is commonly added as an indicator to monitor pH, and a change in the color of the media is often a sign of poor culture conditions.
- Since the culture dishes are not sealed they are prone to evaporation.
- To reduce evaporation, and prevent a subsequent change in media concentration, a water dish (with an anti-fungal/anti-bacterial agent) is usually placed in the bottom of the incubator to maintain a high level of ambient humidity.

- Cells for *in vitro* work may be obtained from tissue (primary culture) or from cell lines.

## ➤ Primary Culture

- Cells for primary culture are obtained by surgical dissection of living tissues. Cells can be obtained by passing media through the marrow cavities of the long bones, by collecting cells or by enzymatic digestion of tissue that contains cells. Enzymatic digestion of small pieces of tissue immersed in collagenase at 37°C breaks down the surrounding ECM and releases entrapped cells.

## ➤ Cell Lines

- Cell lines refer to cells that can be passaged many times without loss of their phenotype. Physiologically, these cells can divide repeatedly, without shortening of their telomeres
- Cell lines differ from other cells in that they have escaped the Hayflick limit and are *immortalized* (Hayflick, 1985). Examples of a handful of commonly used cell lines, from a large number of existing cell lines, are presented in

**TABLE II.1.3.1 Examples of Some Commonly Used Cell Lines**

Cell Line	Organism	Tissue of Origin	Further Cell Information
3T3	Mouse	Embryonic fibroblast	Fibroblasts
AML-12	Mouse	Liver	Liver cells
HeLa	Human	Cervical cancer	Epithelium (first cell line reported)
HUVEC	Human	Umbilical cord vein	Endothelium (stem cells)
MC3T3-E1	Mouse	Calvarial fibroblast	Differentiate to osteoblast

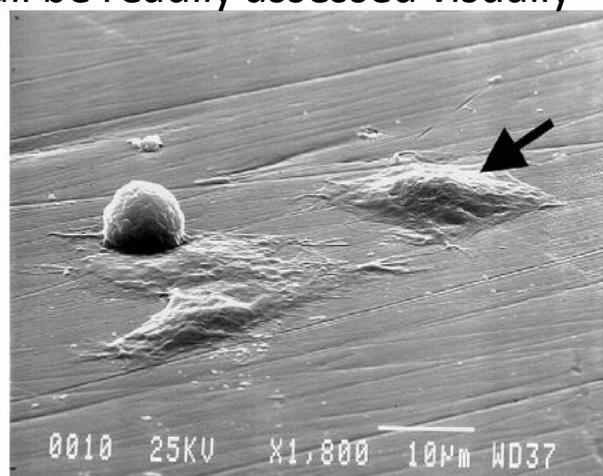
- Cell lines can be obtained from nonprofit organizations such as the American Type Culture Collection (ATCC), the European Collection of Cell Cultures (ECACC), and the Coriell Institute for Medical Research (CIMR).

## UNDERSTANDING CELL–SUBSTRATE INTERACTIONS

- Surface chemistry, topography, and elastic modulus (stiffness) of the substrate are all means to control and guide cell activity, and ultimately modulate tissue formation.
- Since most cells interact with a substrate (e.g., within the ECM) it is often desirable to control the interaction of cells with substrates *in vitro*.
- **Modulation of the culture surface by fabrication of “engineered surfaces” comprised of micro- and nanosized chemical and topographical patterns or coatings have been used to investigate cell behavior such as adhesion, morphology, migration, proliferation, cell–cell communication, gene expression, production of ECM, differentiation, and responsiveness to extracellular signaling.**

### ➤ Surfaces for Cell Culture

- Cell attachment is often characterized by a change in cell morphology.
- Adherent cells possess a “flattened” appearance, often with an irregular cell shape and the extension of cellular processes.
- Regular observation of cells *in vitro* is essential for successful culture as cell density, state, and contamination can all be readily assessed visually



**FIGURE II.1.3.1** Scanning electron microscopy image of MC3T3-E1 cells at various stages of adherence on polished titanium substrate demonstrating changes in cell morphology during attachment. Attached cells have a flattened morphology and form intimate contact with the substrate. Detached cells are round. SEM 1800X.

## ➤ **Process of Cell Attachment *In Vitro***

- **Cell attachment is the initial step in a cascade of cell– biomaterial interactions,** and is important to cellular processes such as cell guidance, proliferation, and differentiation.
- *In vitro*, when hydrophilic surfaces like tissue culture polystyrene (TCP) are exposed to culture media containing serum, they are rapidly coated by a thin (~20 nm) layer comprised mainly of proteins that adsorb to the culture surface in a monolayer.
- The process of cell attachment to TCP (and many other materials) is indirect, since **cells do not bind directly to TCP but instead bind to the adsorbed protein monolayer.**
- **Cells make contact with, and anchor to, the adsorbed proteins at discrete peptide regions referred to as focal contacts.**
- **Cells possess heterodimeric transmembrane proteins composed of  $\alpha$  and  $\beta$  subunits called *integrins*.**
- Integrins are receptors that recognize and bind to specific anchoring proteins present on the conditioned TCP surface.

- Integrins recognize and bind to specific ligands such as fibronectin, vitronectin, collagen, and laminin.
- A common peptide receptor for integrin is the RGD (arginine–glycine– aspartic acid) sequence. For the majority of cells cultured *in vitro*, fibronectin and vitronectin are important for cell attachment to TCP.

**TABLE II.1.3.2 Specific Peptide Sequences on Cell Anchoring Proteins**

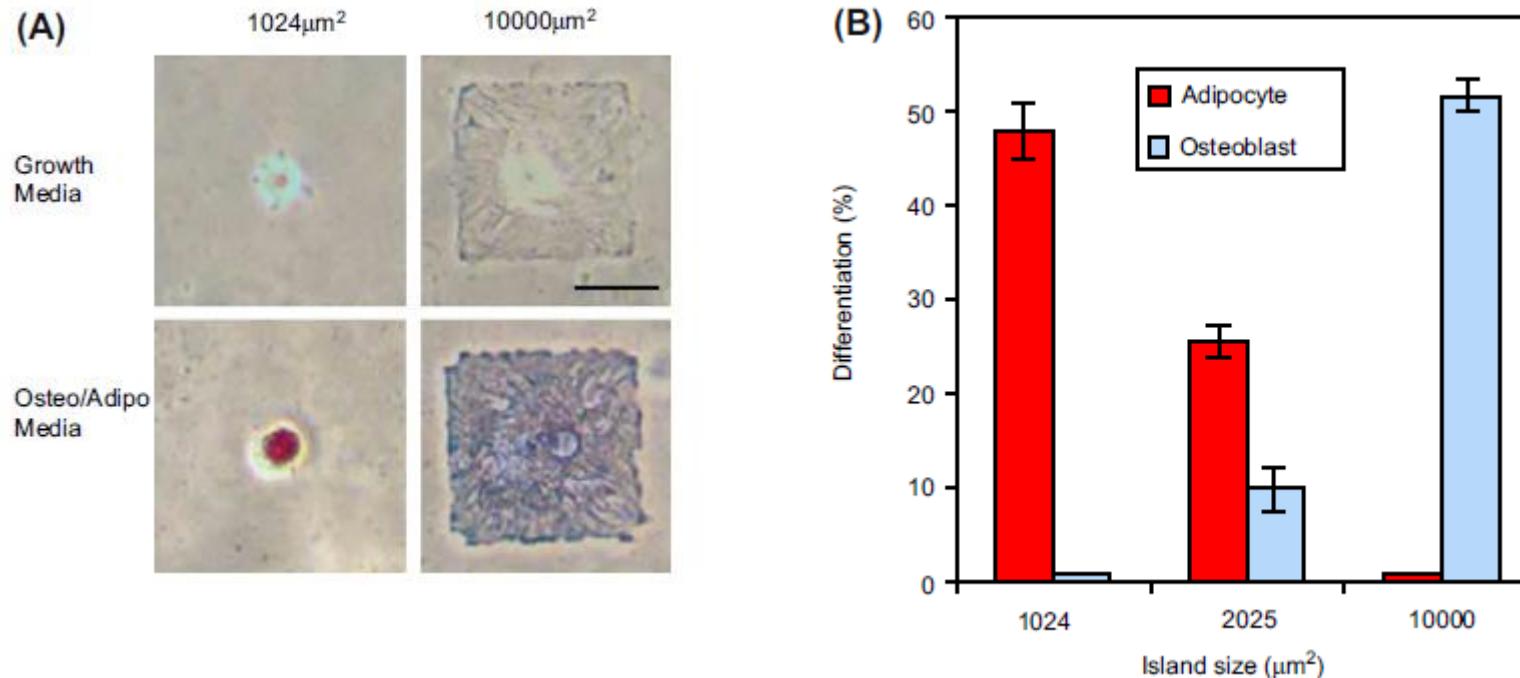
Peptide Sequence	Derived from ECM Protein	Conjugate Receptor	References
RGD	Fibronectin, laminin $\alpha$ -chain, collagen, vitronectin	Multiple integrins	(Ruoslahti and Pierschbacher, 1987; Massia and Hubbell, 1990a,b; Massia and Hubbell, 1991a,b; Ruoslahti, 1996)
YIGSR	Laminin $\beta 1$ -chain	$\beta_1$ integrins	(Boateng et al., 2005; Weber et al., 2007; Weber and Anseth, 2008)
IKVAV	Laminin $\alpha$ -chain	LBP110	(Tashiro et al., 1989; Weber et al., 2007; Weber and Anseth, 2008)
REDV	Fibronectin	$\alpha_4\beta_1$ integrin	(Hubbell et al., 1991)
DGEA	Collagen type I	$\alpha_2\beta_1$ integrin	(Staatz et al., 1991; Weber et al., 2007; Weber and Anseth, 2008)
KQAGDV	Fibronectin $\gamma$ -chain	$\beta_3$ integrins	(Mann and West, 2002; Gobin and West, 2003)
VAPG	Elastin	Elastase receptor, $\alpha_5\beta_3$ integrin	(Mann and West, 2002; Gobin and West, 2003)

## CELL RESPONSE TO SUBSTRATE CHEMISTRY

- At the macroscale, a variety of strategies can be employed to modify culture surface chemistry. **Most coating strategies aim to increase cell adhesion or to preferentially select for certain cell types.**
- Substrates have been coated in these ways with a **variety of organic and inorganic compounds**, such as collagen, fibronectin, gelatin, and poly-L-lysine.
- Culture surfaces have also been broadly **coated with specific adhesion-related peptides**. The peptide sequence arginine–glycine–aspartate (RGD) has been immobilized on a number of materials as a means of enhancing two-dimensional cell attachment.

## ➤ Micrometer-Scale Chemical Patterns

- Using micropatterned fibronectin islands, Chen et al. reported that the area available for cell adhesion and the resultant cell shape governed whether individual cells grow or die



**FIGURE II.1.3.2 Cell shape modulates hMSC differentiation:** (A) Brightfield images of hMSCs plated onto small ( $1024 \mu\text{m}^2$ ) or large ( $10,000 \mu\text{m}^2$ ) fibronectin spots after 1 week. Fibronectin spots were patterned on a mixed SAM substrate by micro-contact printing. Large fibronectin spots supported osteogenesis (blue) while small fibronectin spots supported adipogenesis (red). Scale bar 50  $\mu\text{m}$ . (B) Differentiation of hMSCs on  $1024$ ,  $2025$ , or  $10,000 \mu\text{m}^2$  islands after 1 week of culture. Small fibronectin spots resulted in adipogenesis, medium fibronectin spots supported both adipogenesis and osteogenesis, and large fibronectin spots resulted in osteogenesis. (Reprinted from McBeath et al. (2004). Cell shape, cytoskeletal tension, and RhoA regulate stem cell lineage commitment, *Developmental Cell*, **6**(4), 483–495. Copyright (2004), with permission from Elsevier.)

## ➤ Nanometer-Scale Chemical Patterning

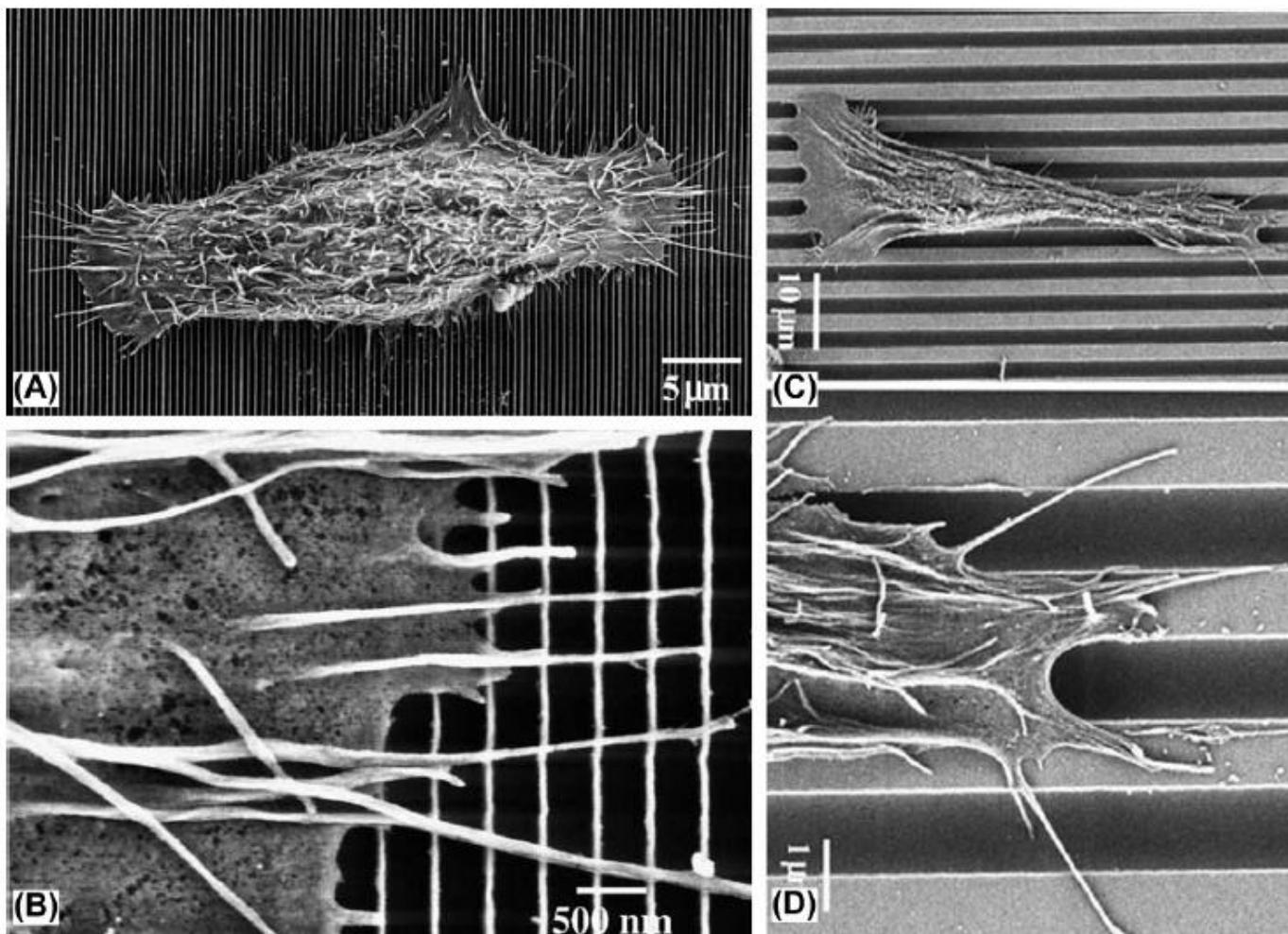
- Nanosized chemical patterns generally do not direct cell shape or orientation as a result of their extremely small size relative to the cell.
- However, surfaces with chemical features on the nanoscale do modulate cell functions such as adhesion, proliferation, migration, differentiation, and gene expression.

## CELL RESPONSE TO SUBSTRATE TOPOGRAPHY

- surface topography defines the specific morphological characteristics of a surface. Surface topography may be generally described as isotropic (uniformity in all directions) or anisotropic (uniformity in one direction).
- In terms of cell activity, surface topography has been reported to affect proliferation, gene expression, cell adhesion, motility , alignment , differentiation , and matrix production .
- In sensing and interacting with the topographical environment, evidence suggests that cells extend fine processes termed *filopodia*.
- While the specific mechanisms are poorly understood, changes in cell activity resulting from interaction with surface features have been linked to changes in cytoskeletal arrangement including actin filaments, nuclear shape, and ion channels.

## ➤ Micrometer-Scale Topography

- With microscale-sized features, cell alignment generally increases with increasing groove depth and decreasing groove spacing ; however, cell response to topography is highly dependent upon cell type



**FIGURE II.1.3.4** Effect of micro and nano patterns on corneal epithelial cell alignment. (A) Cells were aligned perpendicularly to ridges that were 70 nm wide and 330 nm apart. (B) Expanded view of (A) showing filopodia also aligned perpendicularly to the patterns. (C) With increasing width and spacing (1900 nm ridge width, 2100 nm spacing), cells were aligned with the ridges; and (D) filopodia were guided by the topographic pattern. (Reprinted from Teixeira et al. (2006). The effect of environmental factors on the response of human corneal epithelial cells to nanoscale substrate topography. *Biomaterials*, **27**(21), 3945–3954. Copyright (2006), with permission from Elsevier.)

## Nanometer-Scale Topography

- cells can sense and respond to features as small as 10–30 nm
- Compared to the microscale, repetition of similar features at the nanoscale has the greatest effect and provides the most predictable results regarding cell behavior.
- Proteomic-based studies have shown that cells respond to nm-sized pits and pores in irregular patterns, leading to **increased differentiation and matrix production by human osteoprogenitor cells**.
- Likewise, studies with surfaces fabricated by the arrangement of titanium nanotubes have demonstrated that the **nanotube diameter affects both hMSC differentiation and adhesion** (Oh et al., 2009).
  - **Smaller diameter nanotubes (30 nm) increased adhesion, while larger diameters (100 nm) increased differentiation.**
- **Topography at the nanoscale can also be used to effectively reduce cell adhesion.**
  - Kunzler et al. generated a constant gradient of nano-features (65 nm diameter and height) with the spacing as the only changing parameter along the gradient (Kunzler et al., 2007).
  - This study demonstrated that the **spacing or density of non-adhesive nanoscale features can disrupt cell adhesion, likely by restricting receptor–ligand interaction.**

## CELL RESPONSE TO SUBSTRATE ELASTICITY

- Cells respond to the physical or mechanical properties (stiffness) of the substrate.
- **Stiffness** can be described as the resistance of a solid material to deformation, and is commonly defined by elastic modulus ( $E$ )
- **Hydrogels are well-suited to the study of cell substrate interactions** since their stiffness can be varied by controlling the water content of the gel, which is controlled by modifying the polymer concentration or the relative extent of cross-linking.
- Hydrogels can also be made from a very diverse variety of natural and synthetic materials, such as hyaluronic acid (HA), fibrin, alginate, agarose, chitosan, polyacrylamide, and PEG.

- The stiffness of the substrate affects cell adhesion, spreading, and migration, especially the last two.
- In two-dimensional cultures, cells preferentially migrate towards surfaces of greater stiffness, a phenomenon referred to as mechanotaxis.
  - In two-dimensional systems endothelial and fibroblast cells cultured on collagen-coated substrates that were classified as compliant ( $\sim 5 \times 10^3$  Pa) or stiff ( $\sim 70 \times 10^3$  Pa) demonstrated remarkably different behaviors.
  - **Cells cultured on compliant substrates** had reduced spreading, increased lamellipodia activity, and greater migration.
  - **Cells cultured on stiffer substrates** generally increased in proliferation; however, the specific effect seen is cell-type dependent .
  - There is substantial evidence that substrate stiffness also affects cell proliferation in two-dimensional as well as three-dimensional culture systems

## CELL RESPONSE TO MECHANICAL DEFORMATION (STRAIN)

- Forces can be applied directly to adherent cells *in vitro* by either elongation or compression of their substrate (two-dimensional) or matrix (three-dimensional).
- With respect to cyclic tensile loads, in both two-dimensional and three-dimensional cultures, **cells predominantly align in the direction of the applied load and assume an elongated morphology.**
- Because of the loadbearing function and **well-known adaptation to load of the musculoskeletal system**, cells of this system have been evaluated on surfaces under conditions of tensile and compressive strain.
  - Toyoda et al. cultured **cells harvested from the anterior cruciate ligament (ACL) and synovium**. Cells were subjected to cyclic tensile load for 24 hours on culture plates with flexible rubber bases.
  - **For both cell types, tensile load increased cell alignment and elongation; however, tensile load only increased the production of collagen type I in cells derived from the ACL.**

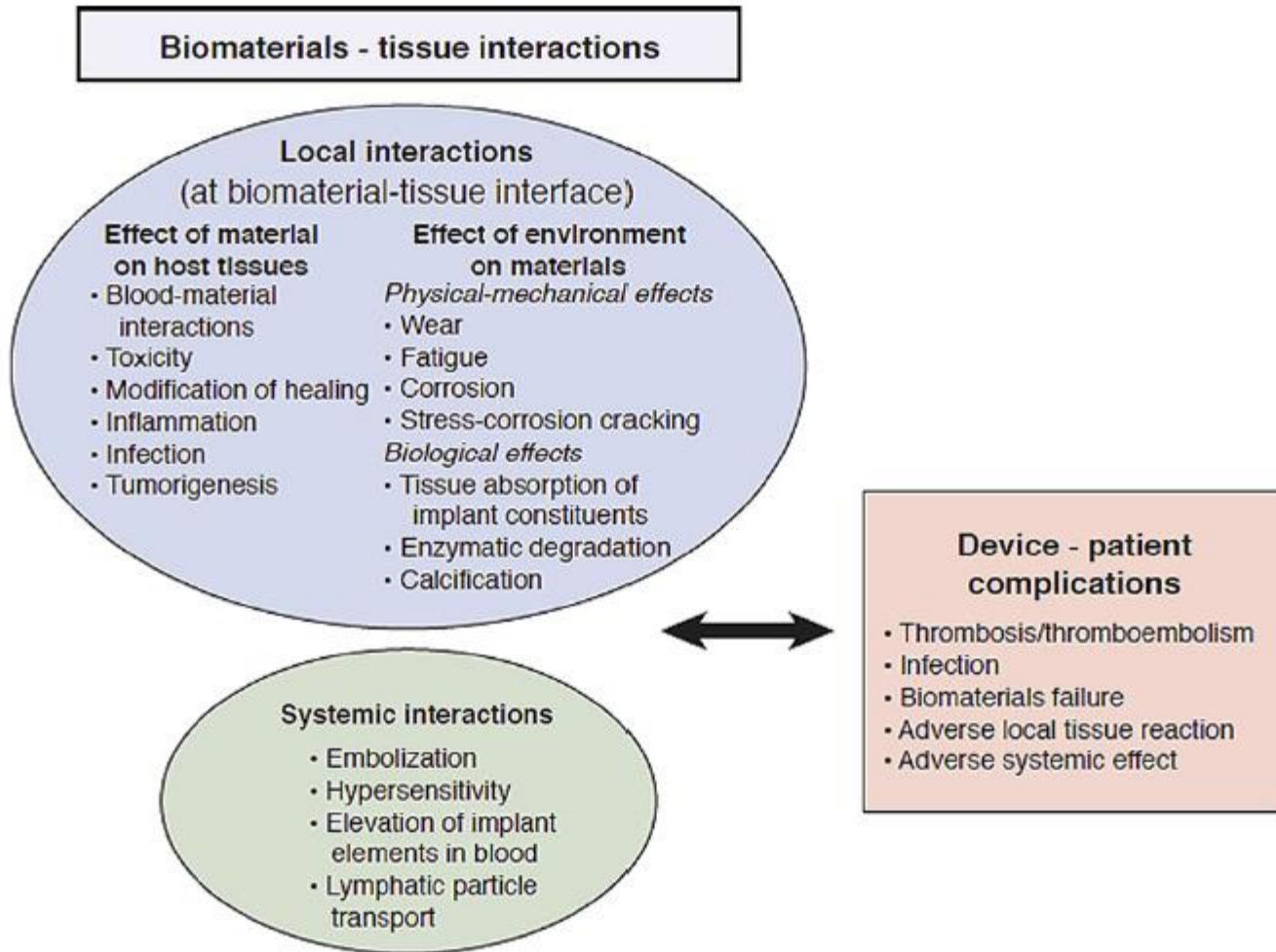
- **fibroblasts subjected to cyclic tensile strain increased the formation of organized ECM**, increased collagen production, and increased metabolic activity compared to unloaded controls.
- **Bone** is another well-known loadbearing tissue, and the extent of mineralization and **bone mineral density is load dependent** .
  - *In vitro*, cyclic strain in both tensile and compressive loading enhances osteoblast mineralization. **Thus, strain appears to be an important stimulus for the generation of mineralized and tendon-like tissues *in vitro*.**
- These findings have led to the **fabrication of bioreactors** that can apply physiologic loads to developing tissue to enhance the production and alignment of ECM in a number of tissues including cardiac , bone , cartilage , and tendon .

# Host Reaction to Biomaterials

- **Biomaterials are commonly used**

- as implants and other tissue-contacting medical devices over a wide range of applications such as
  - *prostheses* in cardiovascular, orthopedic, dental, ophthalmological, and reconstructive surgery
- in minimally invasive interventions such as
  - stent placement in the biliary tree or in the blood vessels
- in extracorporeal devices such as
  - hemodialysis membranes, in surgical sutures or bioadhesives
- in controlled drug-release devices.

- Most implants serve their recipients well for extended periods by alleviating the conditions for which they were implanted.
- However, **some implants and extracorporeal devices ultimately develop complications** – adverse interactions of the patient with the device or *vice versa* – which constitute device failure, and thereby may cause harm to or death of the patient.
- **Effects of both the implant on the host tissues and the host on the implant are important in mediating complications and device failure**



**FIGURE II.2.1.1** Biomaterials–tissue interactions. (Reproduced from Schoen, F. J. (2002). Prosthetic-materials: Past, present and future. In: *Advances in Cardiovascular Medicine* (Harvey 1602–2002 Symposium, on the 4th Centenary of William Harvey's Graduation at the University of Padua), Thiene, G., & Pessina, A. C. (Eds.), Universita degli Studi di Padova, pp. 289–307 and Schoen, F. J. & Padera, R. (2012). Cardiovascular Pathology. In: *Cardiac Surgery in the Adult*, 4th edn., Cohn, L. H. & Edmunds, L. H. (Eds.). McGraw–Hill, pp. 95–148.)

## INFLAMMATION, WOUND HEALING, AND THE FOREIGN-BODY RESPONSE

- Inflammation, wound healing, and foreign-body reaction are generally considered as parts of the tissue or cellular host responses to injury.

**TABLE II.2.2.1**

**Sequence/Continuum of Host Reactions Following Implantation of Medical Devices**

**Injury**

Blood–material interactions

Provisional matrix formation

Acute inflammation

Chronic inflammation

Granulation tissue

Foreign-body reaction

Fibrosis/fibrous capsule development

- Overlap and simultaneous occurrence of these events should be considered.
  - the foreign-body reaction at the implant interface may be initiated with the onset of acute and chronic inflammation.

- From a biomaterials perspective, placing a biomaterial in the *in vivo* environment requires
  - **Injection**
  - **Insertion**
  - **Surgical implantation**
- all of which injure the tissues or organs involved.
- The placement procedure **initiates a response** to injury by the tissue, organ or body, and mechanisms are activated **to maintain homeostasis**.
- The degrees to which the homeostatic mechanisms are perturbed, and the extent to which pathophysiologic conditions are created and undergo resolution, are a measure of the host reactions to the biomaterial and may ultimately determine its biocompatibility.

## OVERVIEW

- **Inflammation is generally defined as the reaction of vascularized living tissue to local injury. It sets a series of events that may heal and reconstitute the implant site through replacement of the injured tissue by regeneration of**
  - native parenchymal cells
  - formation of fibroblastic scar tissue

or

a combination of these two processes.
- **Immediately following injury, there are changes in vascular flow, caliber, and permeability.** Fluid, proteins, and blood cells escape from the vascular system into the injured tissue in a process called **exudation**.
  - Following changes in the vascular system, which also **include changes induced in blood and its components, cellular events occur.**
  - **Regardless of the tissue or organ into which a biomaterial is implanted, the initial inflammatory response is activated by injury to vascularized connective tissue**

**TABLE II.2.2.2 Cells and Components of Vascularized Connective Tissue**

**Intravascular (Blood) Cells**

- Erythrocytes (RBC)
- Neutrophils (PMNs, polymorphonuclear leukocytes)
- Monocytes
- Eosinophils
- Lymphocytes
- Plasma cells
- Basophils
- Platelets

**Connective Tissue Cells**

- Mast cells
- Fibroblasts
- Macrophages
- Lymphocytes

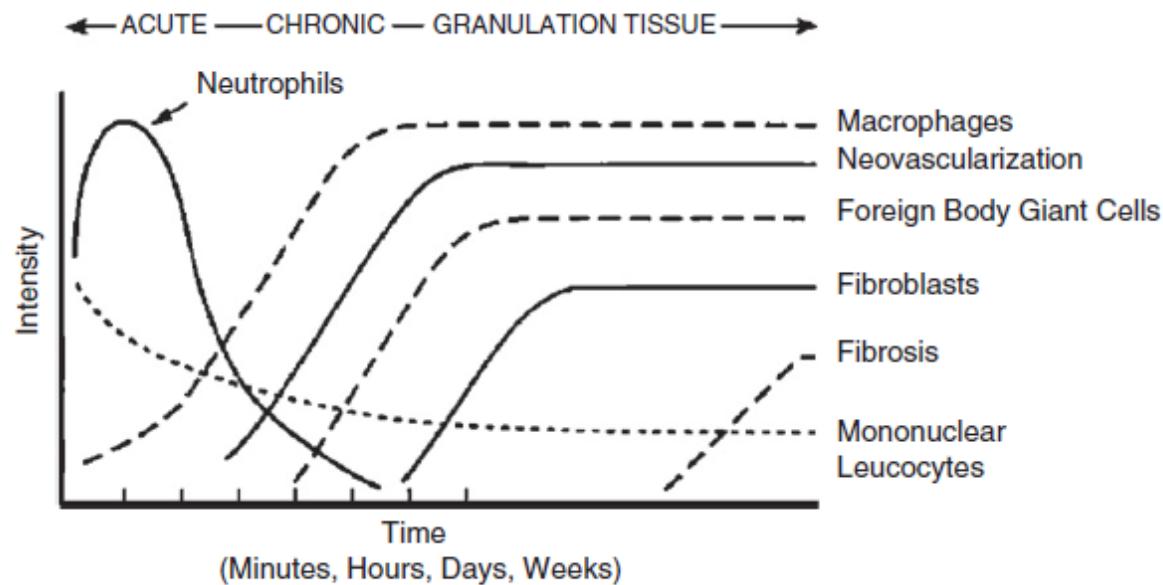
**Extracellular Matrix Components**

- Collagens
- Elastin
- Proteoglycans
- Fibronectin
- Laminin

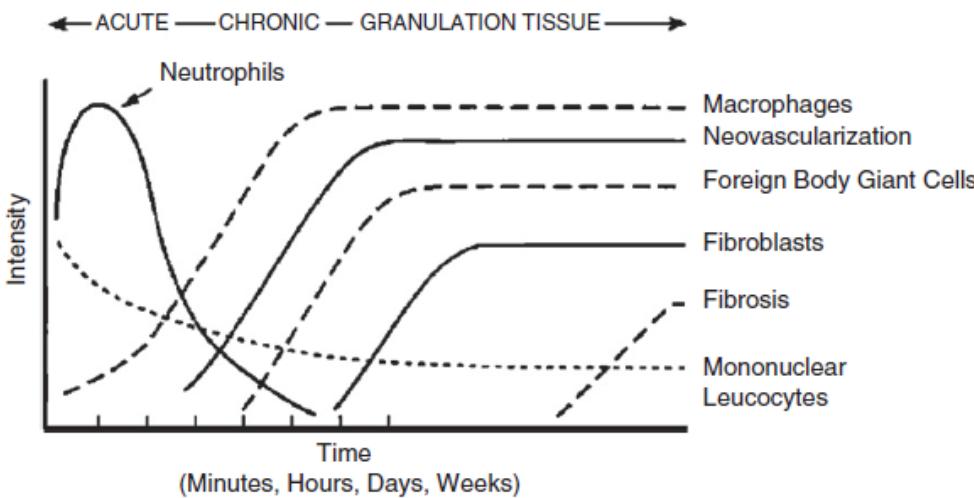
- Thrombus or blood clot formation on the surface of a biomaterial is related to the well-known Vroman effect in which a hierarchical and dynamic series of collision, absorption, and exchange processes, determined by protein mobility and concentration, regulate early time-dependent changes in blood protein adsorption.
- Injury to vascularized tissue in the implantation procedure leads to immediate development of the provisional matrix at the implant site within minutes to hours following implantation of a medical device.
- This provisional matrix consists of
  - fibrin produced by activation of the coagulation and thrombosis systems
  - inflammatory products released by the complement system, activated platelets, inflammatory cells, and endothelial cells

- The provisional matrix may be viewed as a naturally derived, biodegradable, sustained release system in which mitogens, chemoattractants, cytokines, and growth factors are released to control subsequent wound-healing processes.
- Components within or released from the provisional matrix, i.e., fibrin network (thrombosis or clot), initiate
  - the resolution
  - Reorganization
  - repair processes such as inflammatory cell and fibroblast recruitment.
- The complex three-dimensional structure of the fibrin network with attached adhesive proteins provides a substrate for cell adhesion and migration.

- The predominant cell type present in the inflammatory response varies with the age of the inflammatory injury



**FIGURE II.2.2.1** The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign-body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.



**FIGURE II.2.2.1** The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign-body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

- **neutrophils predominate during the first several days following injury and then are replaced by monocytes as the predominant cell type.**
- Following emigration from the vasculature, **monocytes differentiate into macrophages and these cells are very long-lived (up to months).**
- **Monocyte emigration may continue for days to weeks, depending on the injury and implanted biomaterial, and chemotactic factors for monocytes are activated over longer periods of time.**

- The size, shape, and chemical and physical properties of the biomaterial may be responsible for variations in the intensity and duration of the inflammatory or wound-healing process. Thus, **intensity and/or time duration of the inflammatory reaction may characterize the biocompatibility of a biomaterial.**
- While injury initiates the inflammatory response, the chemicals released from plasma, cells or injured tissue mediate the inflammatory response. Important classes of chemical mediators of inflammation are:**

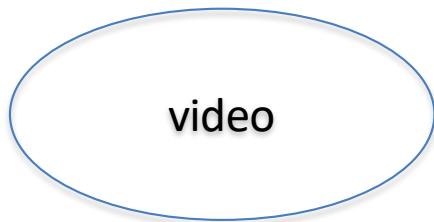
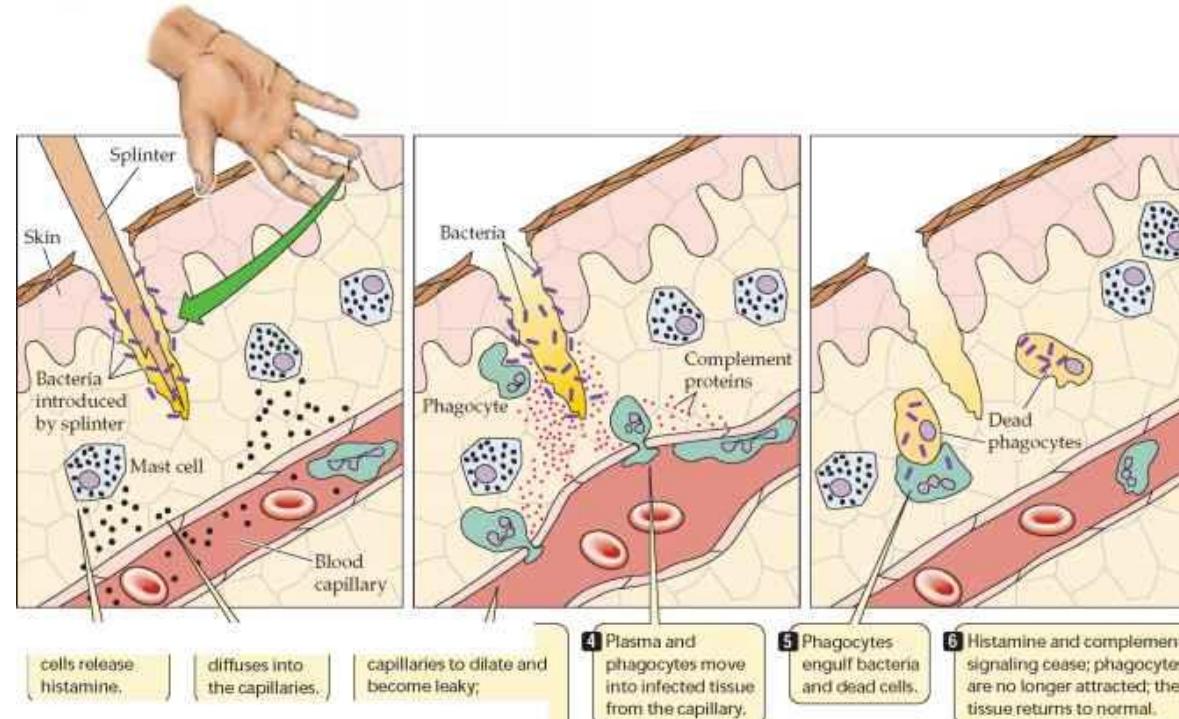


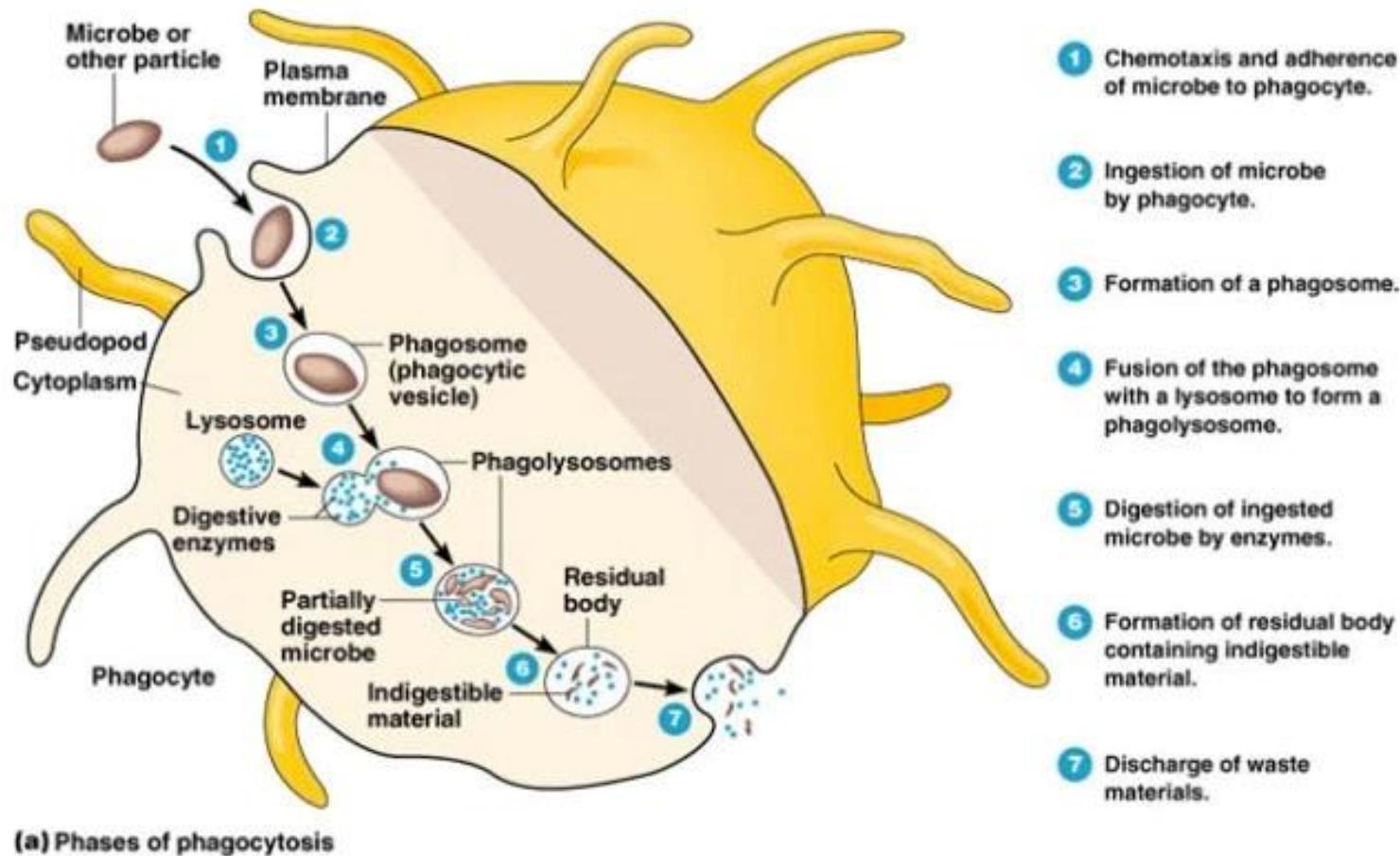
TABLE II.2.2.3 <b>Important Chemical Mediators of Inflammation Derived from Plasma, Cells or Injured Tissue</b>	
Mediators	Examples
Vasoactive Agents	Histamines, serotonin, adenosine, endothelial-derived relaxing factor (EDRF), prostacyclin, endothelin, thromboxane $\alpha_2$
Plasma Proteases	
Kinin system	Bradykinin, kallikrein
Complement system	C3a, C5a, C3b, C5b–C9
Coagulation/fibrinolytic system	Fibrin degradation products, activated Hageman factor (FXIIA), tissue plasminogen activator (tPA)
Leukotrienes	Leukotriene B <sub>4</sub> (LTB <sub>4</sub> ), hydroxyeicosatetraenoic acid (HETE)
Lysosomal proteases	Collagenase, elastase
Oxygen-derived free radicals	H <sub>2</sub> O <sub>2</sub> , superoxide anion
Platelet activating factors	Cell membrane lipids
Cytokines	Interleukin 1 (IL-1), tumor necrosis factor (TNF)
Growth factors	Platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor TGF- $\alpha$ or (TGF- $\beta$ ), epithelial growth factor (EGF)

## ACUTE INFLAMMATION

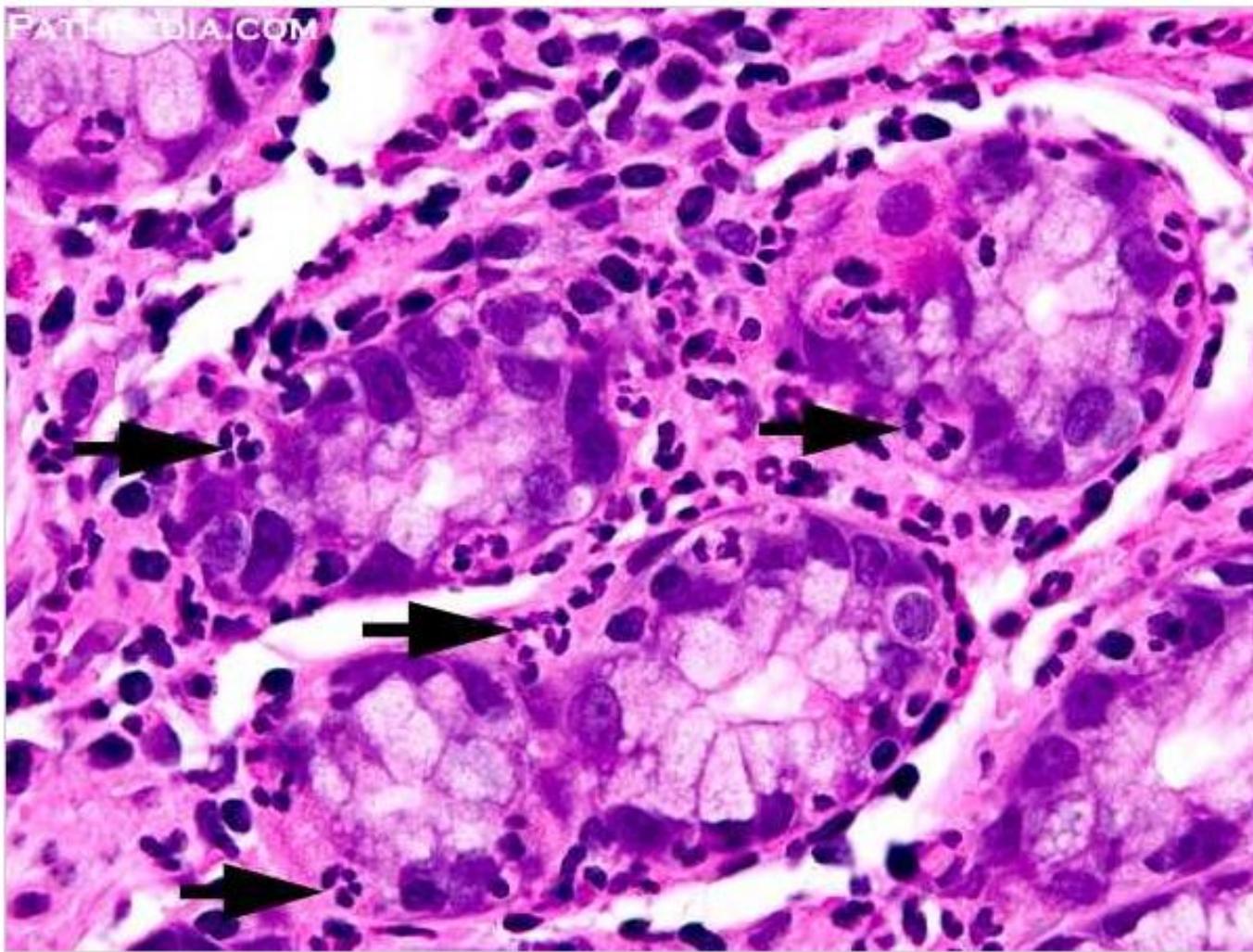
- Acute inflammation is of relatively short duration, lasting for minutes to hours to days, depending on the extent of injury.
- Its main characteristics are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes (predominantly neutrophils).
- **Neutrophils (polymorphonuclear leukocytes, PMNs) and other motile white cells emigrate or move from the blood vessels to the perivascular tissues and the injury (implant) site.**
  - Leukocyte emigration is assisted by “adhesion molecules” present on leukocyte and endothelial surfaces. Specific receptors for chemotactic agents on the cell membranes of leukocytes are important in the emigration or movement of leukocytes.



- Following localization of leukocytes at the injury (implant) site, phagocytosis and the release of enzymes occur following activation of neutrophils and macrophages.
- The major role of the neutrophil in acute inflammation is to phagocytose microorganisms and foreign materials.
- Phagocytosis is seen as a three-step process in which the injurious agent undergoes recognition and neutrophil attachment, engulfment, and killing or degradation

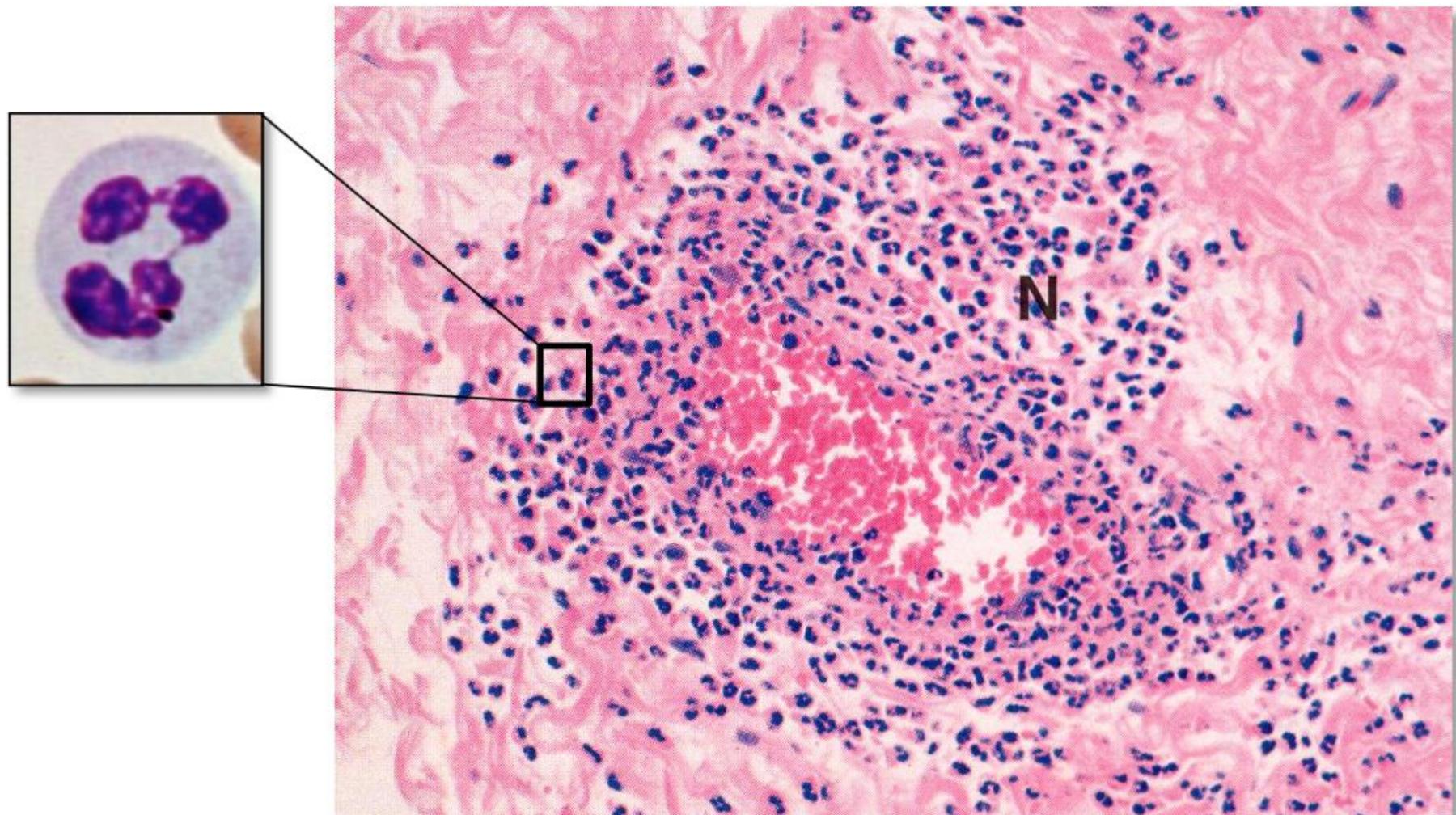


- **biomaterials are not generally phagocytosed by neutrophils or macrophages but certain events in phagocytosis may occur.**
  - The process of recognition and attachment is expedited when the injurious agent is coated by naturally occurring serum factors called “opsonins”.
  - The two major opsonins are immunoglobulin G (IgG) and the complement-activated fragment, C3b.
  - Both of these plasma-derived proteins are known to adsorb to biomaterials, and neutrophils and macrophages have corresponding cell-membrane receptors for these opsonization proteins.
  - Other blood proteins such as fibrinogen, fibronectin, and vitronectin may also facilitate cell adhesion to biomaterial surfaces.
  - This process does not involve engulfment of the biomaterial, but does cause the extracellular release of leukocyte products in an attempt to degrade the biomaterial.
- **Acute inflammation normally resolves quickly, usually less than 1 week, depending on the extent of injury at the implant site.**
  - the presence of acute inflammation at the tissue/implant interface at time periods beyond 1 week (i.e., weeks, months, or years) suggests the presence of an infection



[ACUTE INFLAMMATION]. Acute inflammation is a quick natural response of the host to tissue injuries and certain foreign injurious agents. The response is mediated by neutrophils and certain plasma proteins and other chemicals. The response is aimed at containing the injurious insult and repairing the damage. Neutrophils are recruited from blood to the site of injury in a series of steps beginning with the release of certain substances at the site of injury that help guide the neutrophils exodus. Acute inflammation may last for hours to several days. This photomicrograph shows acute gastritis with many neutrophils in and around the gastric glands.

Histologically, acute inflammation presents as an abundance of **neutrophils** accumulated around **venules** within **connective tissue**

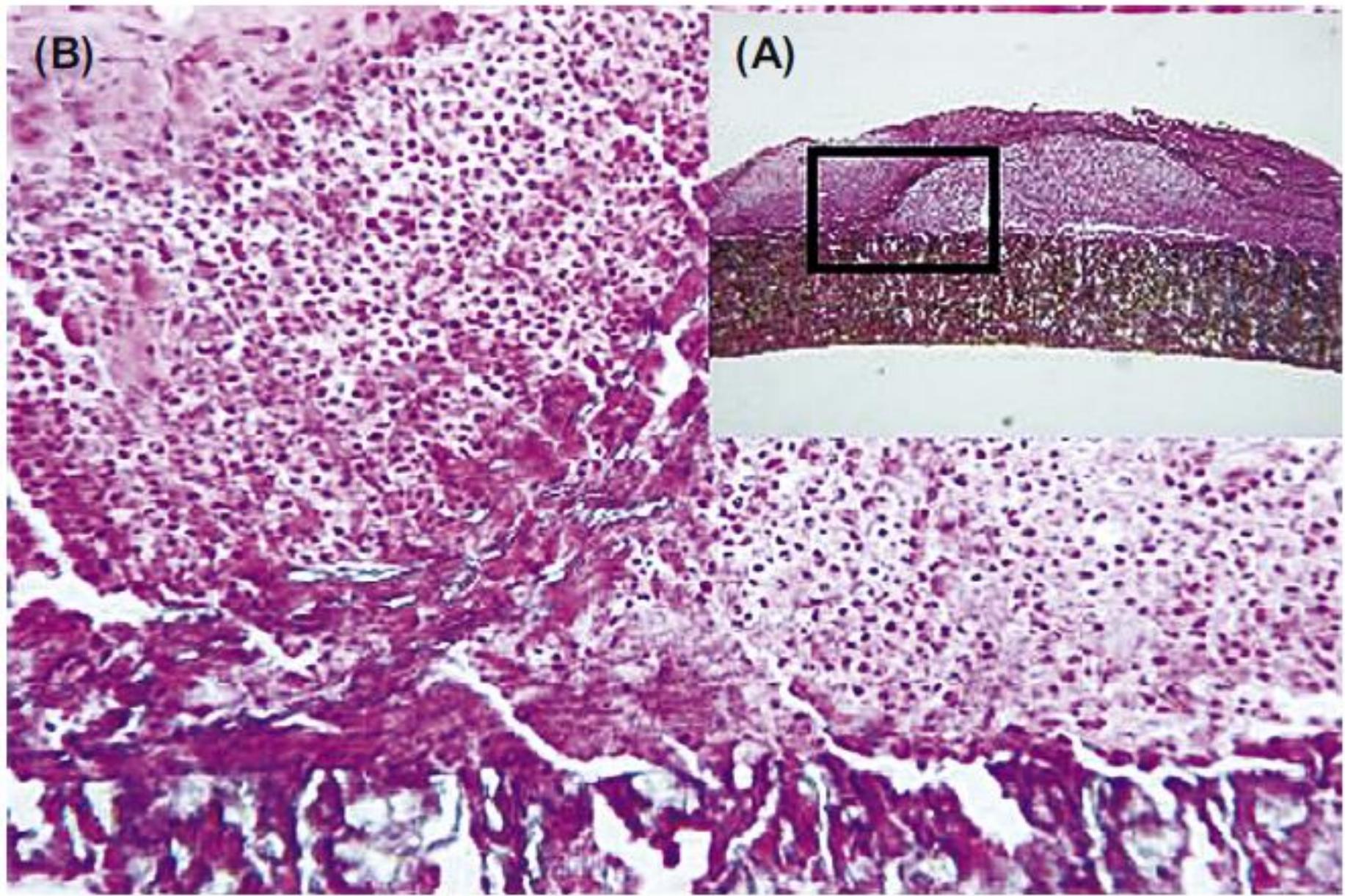


## CHRONIC INFLAMMATION

- Chronic inflammation is characterized by the presence of macrophages, monocytes, and lymphocytes, with the proliferation of blood vessels and connective tissue.
  - **chemical and physical properties of the biomaterial**
  - **motion in the implant site by the biomaterial**
  - **Infection**

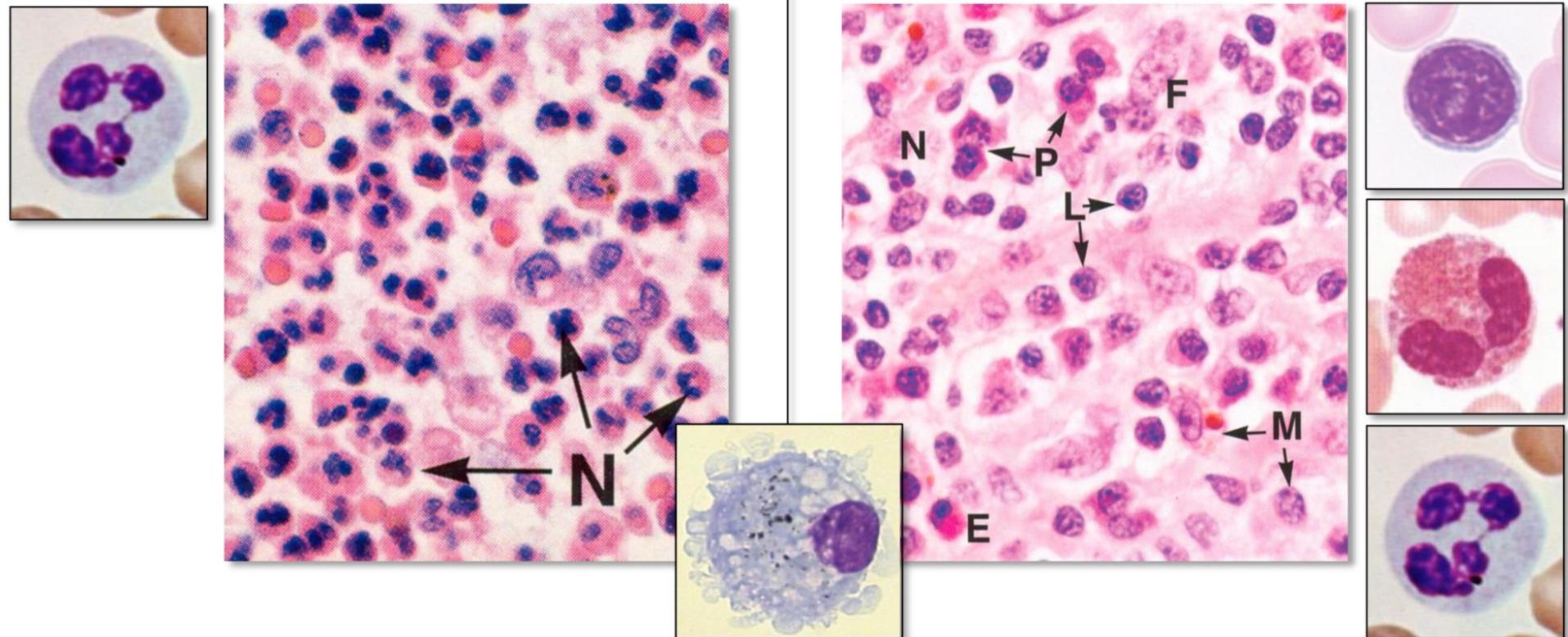
**may lead to chronic inflammation.**

- The presence of mononuclear cells, including lymphocytes and plasma cells, is considered chronic inflammation
- Chronic inflammation with the presence of collections of lymphocytes and monocytes at extended implant times (weeks, months, years) may also suggest the presence of a long-standing infection



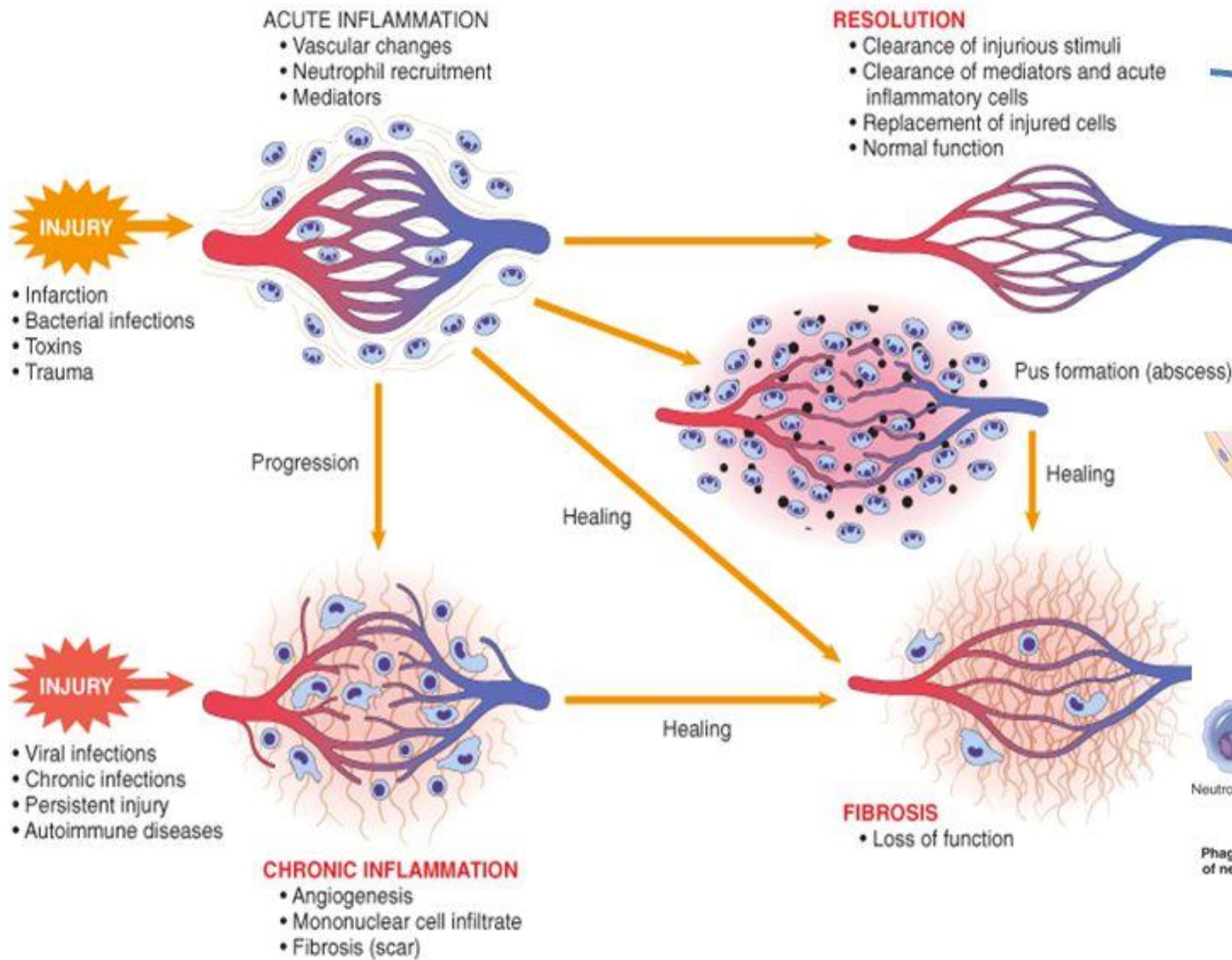
**FIGURE II.2.2.3** Chronic inflammation, secondary to infection, of an ePTFE arteriovenous shunt for renal dialysis. (A) Low-magnification view of a focal zone of chronic inflammation. (B) High-magnification view of the outer surface with the presence of monocytes and lymphocytes at an area where the outer PTFE wrap had peeled away from the vascular graft. Hematoxylin and eosin stain. Original magnification (A) 4  $\times$ , (B) 20  $\times$ .

Acute inflammatory exudate



Chronic inflammatory exudate

# Outcomes of acute inflammation: Resolution, healing by fibrosis, or chronic inflammation



- The macrophage is probably the most important cell in chronic inflammation, because of the great number of biologically active products it can produce.
- Growth factors such as
  - platelet-derived growth factor (PDGF)
  - fibroblast growth factor (FGF)
  - transforming growth factor- $\beta$  (TGF- $\beta$ )
  - TGF- $\alpha$ /epidermal growth factor (EGF)
  - interleukin-1 (IL-1) or tumor necrosis factor (TNF- $\alpha$ )

are important to the growth of fibroblasts and blood vessels, and the regeneration of epithelial cells.

- Growth factors released by activated cells can stimulate production of a wide variety of cells; initiate cell migration, differentiation, and tissue remodeling; and may be involved in various stages of wound healing.

	<b>ACUTE</b>	<b>CHRONIC</b>
<b>ONSET</b>	IMMEDIATE	DELAYED
<b>DURATION</b>	FEW DAYS	UPTO MONTHS, YEARS
<b>CAUSATIVE AGENTS</b>	BACTERIA INJURED TISSUES	PERSISTENT ACUTE , FOREIGN BODY , VIRAL AUTOIMMUNE
<b>MAJOR CELLS</b>	NEUTROPHILS ,BASOPHILS MONOCYTESMACROPHAGES	MONONUCLEAR CELLS MONO,LYMPHOCYTES PLASMA CELLS FIBROBLASTS
<b>PRIMARY MEDIATORS</b>	VASOACTIVE AMINES	EICOSANOIDS
<b>OUTCOMES</b>	RESOLUTION ABSCESS FORMATION CHRONIC INFLAMMATION	TISSUE DESTRUCTION FIBROSIS NECROSIS

## GRANULATION TISSUE

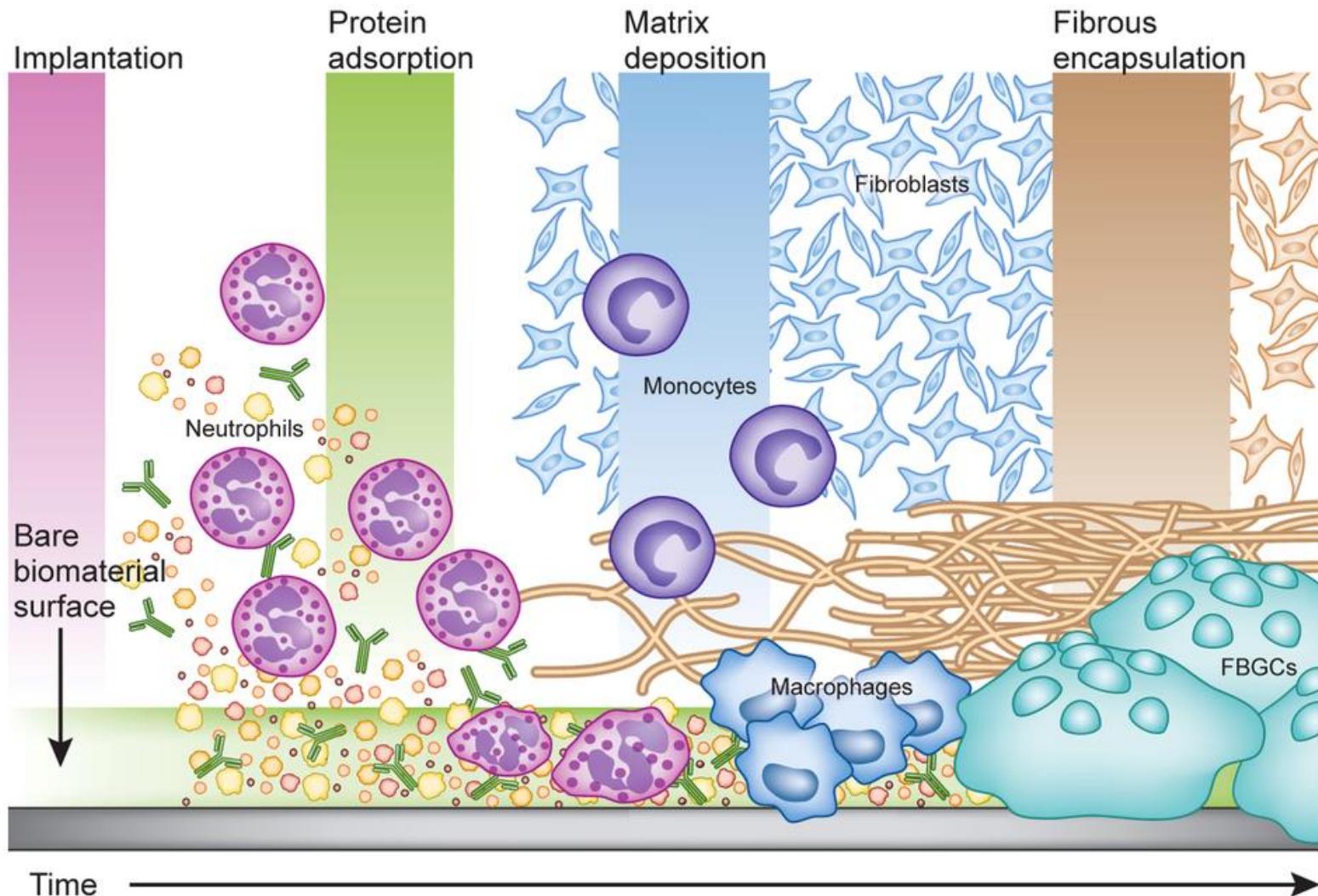
- Within one day following implantation of a biomaterial (i.e., injury), the healing response is initiated by the action of monocytes and macrophages.
- Fibroblasts and vascular endothelial cells in the implant site proliferate and begin to form granulation tissue, which is the specialized type of tissue
- The new small blood vessels are formed in a process known as neovascularization or angiogenesis.
- Fibroblasts also proliferate in developing granulation tissue, and are active in synthesizing collagen and proteoglycans.
- In the early stages of granulation tissue development, proteoglycans predominate but later collagen, especially type III collagen, predominates and forms the fibrous capsule.
- Macrophages are almost always present in granulation tissue. Other cells may also be present if chemotactic stimuli are generated



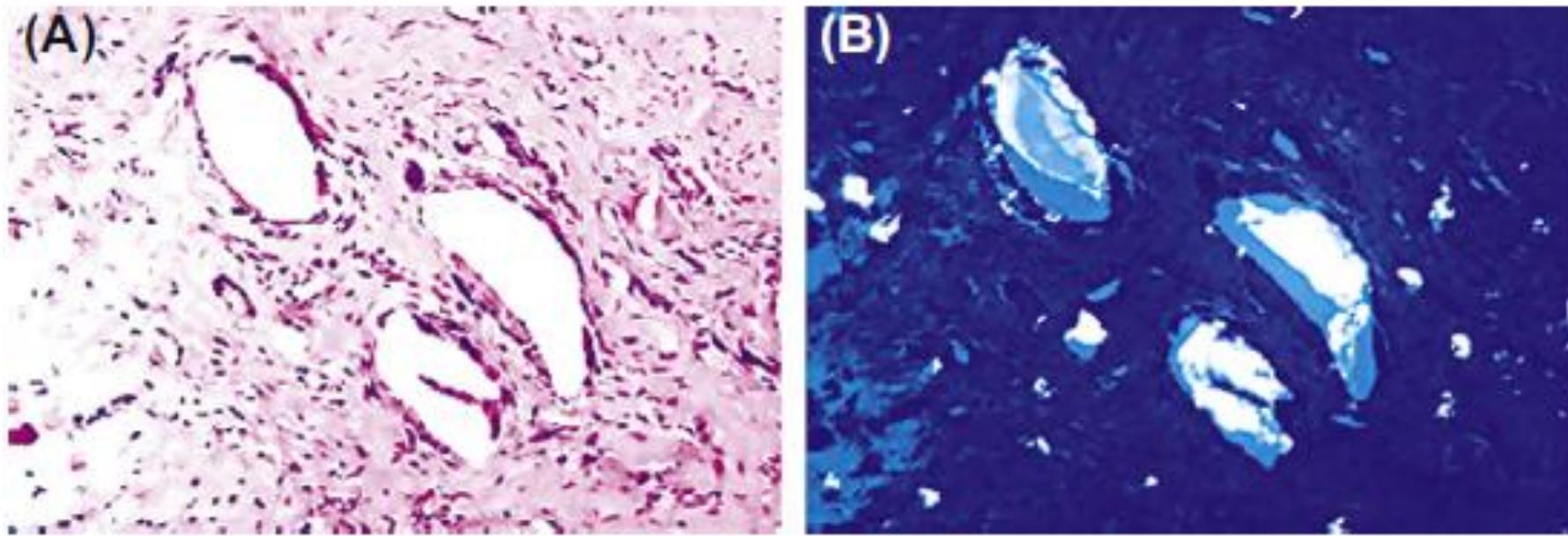
- The wound-healing response is generally dependent on the extent or degree of injury or defect created by the implantation procedure.
  - **Wound healing by primary union** or first intention is the healing of clean, surgical incisions in which the wound edges have been approximated by surgical sutures. Healing under these conditions occurs without significant bacterial contamination, and with a minimal loss of tissue.
  - **Wound healing by secondary union** or second intention occurs when there is a large tissue defect that must be filled or there is extensive loss of cells and tissue.
    - Regeneration of parenchymal cells cannot completely reconstitute the original architecture, and much larger amounts of granulation tissue are formed that result in larger areas of fibrosis or scar formation.

## FOREIGN-BODY REACTION

- The foreign-body reaction to biomaterials is composed of foreign-body giant cells.
- **Foreign body giant cells are formed by the fusion of monocytes and macrophages to phagocytose the material**

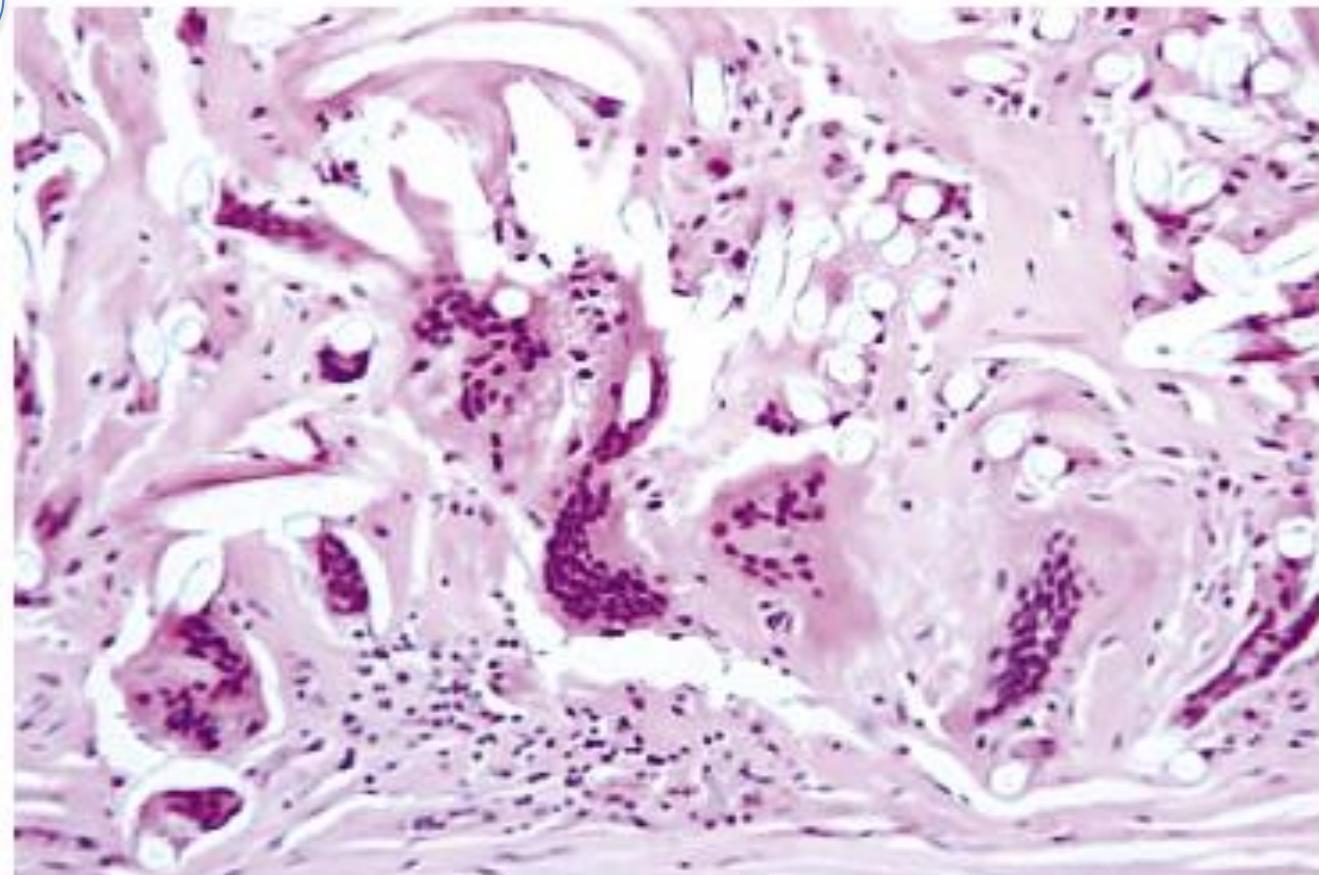


- The foreign-body reaction depending upon the form and topography of the implanted material
  - Relatively flat and smooth surfaces such as those found on breast prostheses have a foreign-body reaction that is composed of a layer of macrophages one-to-two cells in thickness.
  - Relatively rough surfaces such as those found on the outer surfaces of expanded polytetrafluoroethylene (ePTFE) or Dacron vascular prostheses have a foreign-body reaction composed of macrophages and foreign-body giant cells at the surface.



**FIGURE II.2.2.6** (A) Focal foreign-body reaction to polyethylene wear particulate from a total knee prosthesis. Macrophages and foreign-body giant cells are identified within the tissue and lining the apparent void spaces indicative of polyethylene particulate. Hematoxylin and eosin stain. Original magnification 20  $\times$ . (B) Partial polarized light view. Polyethylene particulate is identified within the void spaces commonly seen under normal light microscopy. Hematoxylin and eosin stain. Original magnification 20  $\times$ .

video



**FIGURE II.2.2.7** Foreign-body reaction with multinucleated foreign body giant cells and macrophages at the periadventitial (outer) surface of a Dacron vascular graft. Fibers from the Dacron vascular graft are identified as clear oval voids. Hematoxylin and eosin stain. Original magnification 20 x.

## FIBROSIS/FIBROUS ENCAPSULATION

- The end-stage healing response to biomaterials is generally fibrosis or fibrous encapsulation
- Repair of implant sites can involve two distinct processes:
  - **regeneration**, which is the replacement of injured tissue by parenchymal cells of the same type
  - **replacement by connective tissue** that constitutes the fibrous capsule.
- The regenerative capacity of cells allows them to be classified into three groups:
  - labile : continue to proliferate throughout life ( e.g. **epithelial cells, lymphoid and hematopoietic cells**)
  - stable (or expanding) : retain this capacity but do not normally replicate **parenchymal cells of the liver, kidney, and pancreas**; **mesenchymal cells (e.g., fibroblasts, smooth muscle cells, osteoblasts, and chondroblasts)**
  - permanent (or static) : cannot reproduce themselves after birth ( nerve cells and cardiac muscle cells)

- Perfect repair with restitution of normal structure can theoretically occur only in tissues consisting of stable and labile cells, whereas all injuries to tissues composed of permanent cells may give rise to fibrosis and fibrous capsule formation with very little restitution of the normal tissue or organ structure.