Part I Materials

1 Biocompatibility, sterilization, and materials selection for implant design

Inquiry

All medical implants must be sterilized to ensure no bacterial contamination to the patient. How would you sterilize a total hip replacement comprising a titanium stem, a cobalt-chromium alloy head, and an ultra-high molecular weight polyethylene acetabular shell? Could the same method be employed for all three materials? How do you ensure that there is no degradation to the material or its structural properties? What factors would you need to consider in the optimization of this problem?

The inquiry posed above represents a realistic challenge that one might face in the field of orthopedic biomaterials. At a minimum, one would want to know the **sterilization** methods available for medical implants and which materials they best serve. For example, steam or autoclaving work well for sterilization of metals and ceramics but are generally unsuitable for polymers due to the lower melting and distortion temperatures of medical plastics. Also, one needs to consider whether there are any changes in the mechanical properties or if any time-dependent changes are expected owing to the sterilization method employed; for example, gamma radiation is known to leave behind free radicals (unpaired electrons) and these free radicals are highly reactive with elements such as oxygen that may be present or may diffuse into the implant material. In certain polymer materials such as ultra-high molecular weight polyethylene, **gamma radiation** can result in oxidation-induced embrittlement (shelf aging) that can severely degrade its wear and fracture properties. The case study presented at the end of this chapter addresses this issue.

1.1 Historical perspective and overview

Designing medical implants is a complex process, and this textbook aims to provide insight into the material, mechanical, and clinical factors that affect implant design and performance. The goal of this book is to integrate all aspects of implant design including clinical issues, structural requirements, materials selection, and processing treatments.

Historically, medical implant designs were driven solely by the need to restore function to a patient. Early **medical devices** utilized the skill of the resident surgeon and materials available at that time; materials such as ivory, bone, and wood were the first materials

utilized to replace lost or damaged limbs. As time passed, implant designs utilized available metals such as gold, silver, or amalgams in facial reconstruction or dentistry; natural materials such as cat gut for sutures, porcine valves as heart valves; various steels in orthopedic implants; and polymers in soft tissue repair (Park and Bronzino, 2003; Ratner *et al*., 1996). It has only been in the last 50–60 years that engineering materials have been widely utilized for medical implants; the majority of material development used in medical devices has occurred in the last 50 years and has been accompanied by the growing research field of biomaterials science. Figure 1.1 shows the evolution of design-material combinations used for total hip repair in the last century.

1.2 Learning objectives

This introductory chapter provides a broad overview of biomaterials used in medical implants. The basic factors contributing to medical device design are presented. Issues of biocompatibility, sterility, and basic structure of biomaterials used in implants are addressed. The benefits and limitations of each material class are discussed. At the completion of this chapter, the student will be able to:

1. name the key factors that contribute to successful device performance
2. explain biocompatibility
3. define sterility and recommend sterilization schemes for various biomaterials
4. classify medical devices according to FDA regulatory requirements
5. identify mechanical properties used in describing structural requirements
6. describe the classification schemes for biomaterials
7. illustrate the materials selection process
8. discuss structure-property relationships associated with bonding mechanisms
9. list limitations and benefits of each class of synthetic material including composites used in medical devices
10. elucidate the role of the design process used in medical devices
11. describe a clinical case example involving sterilization and medical implants

1.3 Successful device performance and implant design

Successful medical device design brings together multifactorial challenges and synergistic solutions that build from diverse fields including engineering, manufacturing, biology, and clinical medicine. A schematic illustration of the variables that factor into the long-term success of a medical device is provided in Figure 1.2.

The *clinical issues* are paramount in the design process and in the long-term performance of the medical device. The primary requirement of any implantable device is that it is **biocompatible**; the implant must be able to restore function without adverse reaction or chronic inflammatory response. Combinations of materials selection (Chapters 2–5), loading (Chapters 6–11), and design (Chapters 13–16) can cause *in vivo* degradation.

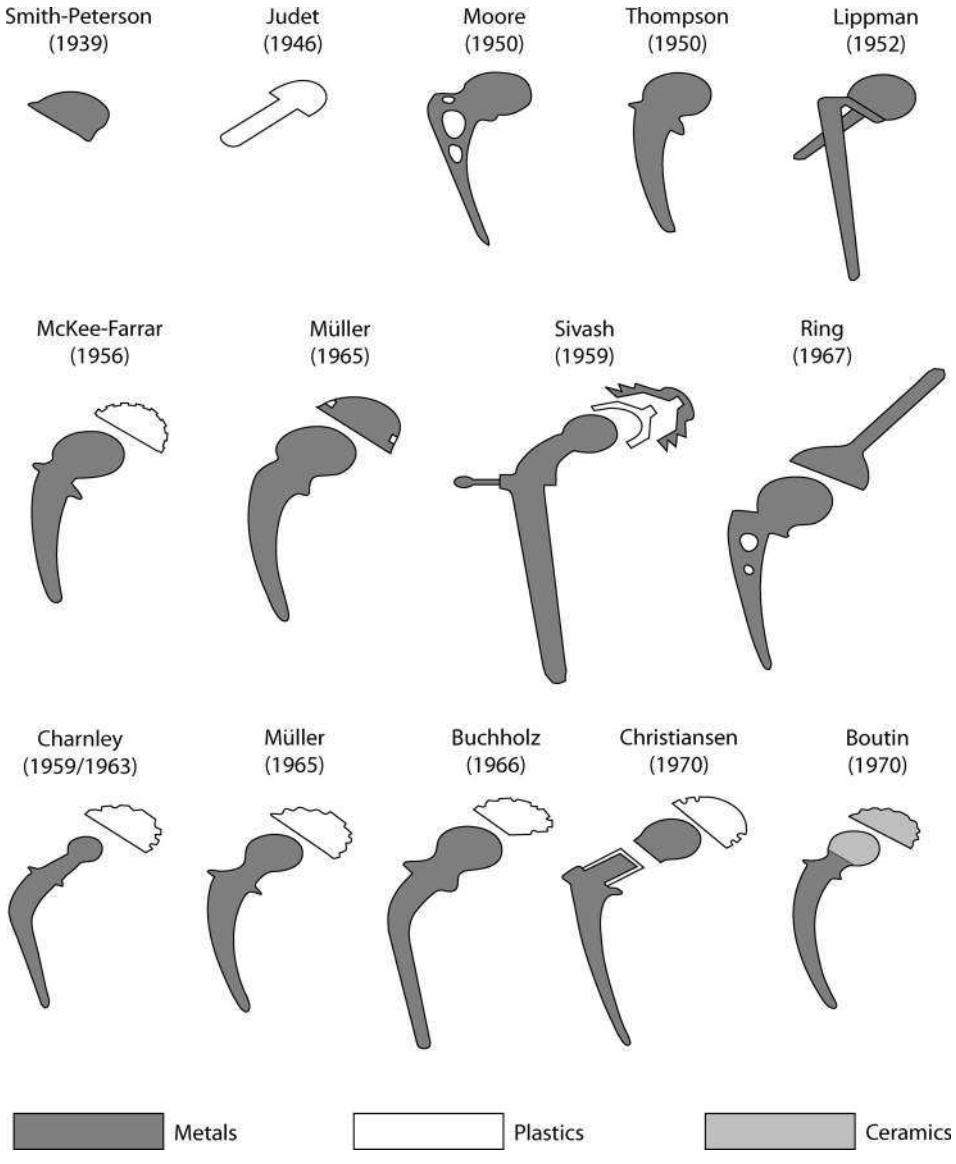

Figure 1.1

An example of material and design evolution in total hip replacements. (After Park and Bronzino, 2003.)

Moreover, the patient's specific immunological response and body environment also affect the long-term integrity and performance of the implant. The role of a good surgeon cannot be underestimated: a good surgeon provides appropriate assessment of the patient needs and assures optimized surgical placement of the implant. Patient factors also include health, anatomy, weight, and physical activity levels as these contribute directly to the structural requirements of the implant.

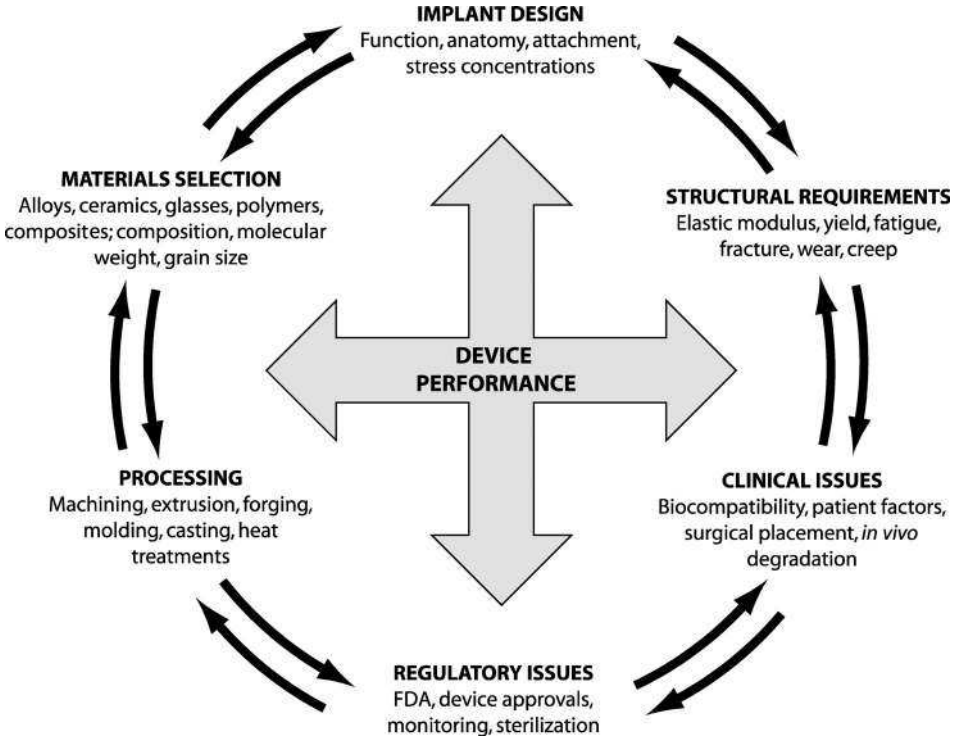

Figure 1.2

The multifactorial factors contributing to medical device performance.

The *structural requirements* of a medical device are typically found through an assessment of the expected **physiological stresses** on the implant. These stresses will vary depending upon the patient's anatomy, weight, and physical activity. For example, activities such as running can amplify the forces in a hip joint by nearly a factor of ten. Analysis of these stresses is key in making certain that the appropriate **elastic modulus** (Chapter 6), **yield strength** (Chapter 8), and other important material properties such as **creep** (Chapter 7), **fracture** (Chapter 9), **fatigue** (Chapter 10), and **wear** (Chapter 11) resistance are known. Simulator studies that mimic the physiological stresses are generally employed in the design process and help to assess the integrity of the implant in a laboratory environment. Such tests are often necessary in obtaining regulatory (FDA) approval of the medical implant.

Implant design involves the actual creation of the blueprints for the implant and calls out necessary materials to be utilized as well as geometric requirements such as component **tolerance**, **sphericity**, **surface finish**, and **notches**. The design of the implant directly incorporates the necessary geometry for anatomical constraints and desired function of the device.

The *materials selection* is first addressed by analyzing the structural requirements of the implant. The choice of a specific **alloy** (Chapter 2), **ceramic** (Chapter 3), **polymer** (Chapter 4), or **composite** is founded upon the knowledge of the structural requirements and function of the implant. Appropriate choice of material is necessary to make sure that appropriate material properties are provided. Within the materials selection process it is also important to understand the role of variations in microstructure, molecular weight, and composition as these directly contribute to the material properties and can be affected by the processing conditions of the implant.

Processing of the implant includes taking the raw material and bringing it into component form. Such processes include **machining**, **casting**, **molding**, **sintering**, **extrusion**, **forging**, and other manufacturing methods. Additionally the cleaning and sterilization protocols must be specified. Good manufacturing practice is necessary to ensure that the implant is void of defects and that specified tolerances and surface finish of the implant are achieved. Moreover, processing can directly alter the material properties and hence it is important to understand the critical interplay of such variables.

Regulatory issues include the FDA approval and monitoring of the implant (Chapter 12). The approval process often requires biocompatibility analysis of the material, simulated loading conditions in the implant, and clinical trials. This aspect of the design process is reliant upon all the other variables in this multifactorial challenge of medical device design.

1.4 Biocompatibility

Biocompatibility is the primary requirement of any material used in the body. Unless designed to degrade *in vivo*, the material must offer long-term resistance to biological attack. Biocompatibility is a multifaceted issue in that both the composition and size scale of the biomaterial can dictate the cellular or inflammatory response (Black, 1999; Bronzino and Yong, 2003). Materials that are considered biocompatible in bulk form can trigger an inflammatory response if the material becomes small enough to be ingested by an inflammatory cell such as a **macrophage** (Howie *et al*., 1993). The generation of debris associated with mechanical loading or corrosion of the implant can result in an acute **inflammatory response** and premature failure of the implant.

A standard definition of biocompatibility is "the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy" (Williams, 2008). Consequently, the total number of biocompatible materials that are suitable for use in medical devices is quite limited.

Assessment of biocompatibility is quite complex as variations in immune response, activity level, and overall health of individual patients can be considerable. *In vivo* degradation of implants is often nucleated by the coupled effect of mechanical loading

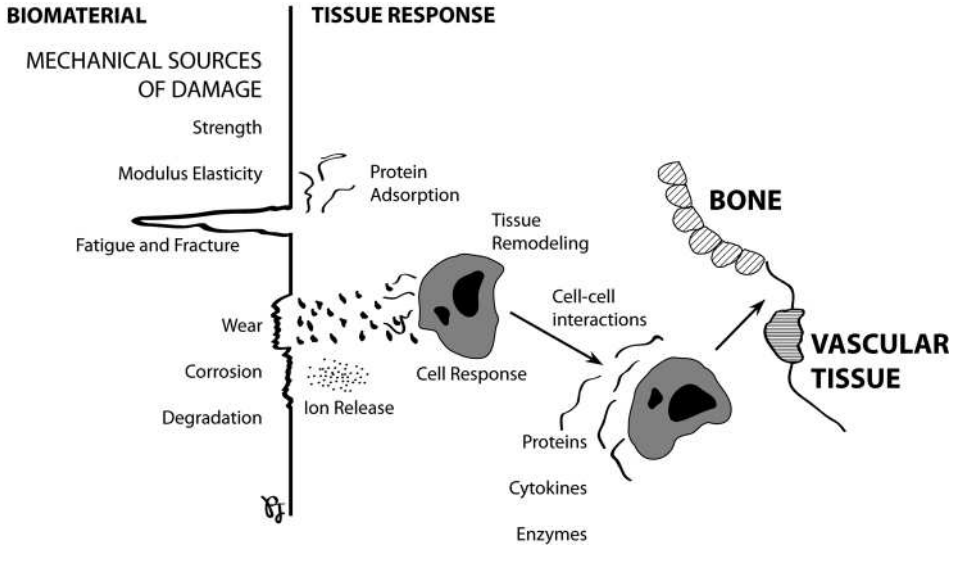

Figure 1.3

Illustration showing typical interactions at the interface between the biological system and a mechanically damaged synthetic biomaterial used in implants. (After Ratner *et al.*, 1996.)

and environment. Complications often arise because of corrosion, wear, fatigue, or fracture of the biomaterial (Figure 1.3). For this reason, the biocompatibility of a material often is not known until the material is used in its intended clinical environment. Accordingly, the historical and clinical performance of a material is crucial in assessing whether that material is suitable in a given device or application.

1.5 Sterility

Sterilization involves the elimination of bacterial contamination through a mechanism of **DNA** disablement. Sterility is defined as less than one in one million surviving bacterial spores in the medical device prior to implantation. There are several sterilization options available and these include autoclaving, irradiation, ethylene oxide gas, and gas plasma.

Autoclaving works by subjecting devices or materials to high-pressure steam at temperatures on the order of 121°C in order to destroy bacterial contamination. Autoclaving is highly accessible and is often available in hospitals and surgical units. These systems are commonly employed to sterilize surgical tools. Because of the temperature of the steam, autoclaving is generally not used with polymeric systems.

The gamma sterilization process uses high-energy photons that are emitted from a Cobalt 60 isotope source to produce ionization (electron disruptions) throughout the medical device (Bruck and Mueller, 1988). In living cells, electron disruptions result

in damage to the DNA and other cellular structures. These photon-induced changes at the molecular level cause the death of the organism or render the organism incapable of reproduction. The gamma process is deeply penetrating and has been employed in many devices and materials including the orthopedic-grade polyethylenes used in total joint replacements (Kurtz *et al*., 1999). However, **irradiation** can result in **crosslinking** or chain **scission** in polymers and leave behind free radicals that can lead to long-term **oxidation** (Premnath *et al*., 1996). Similarly, the **electron beam** method accelerates electrons to very high speeds in order to increase their energy and penetrate products to achieve sterility by damaging the DNA strands of the microorganisms (Bruck and Mueller, 1988). This method does not penetrate as deeply as gamma irradiation and is better suited for low-density, uniformly packaged materials.

Ethylene oxide (EtO) **gas** sterilization is a chemical process that utilizes a combination of gas concentration, humidity, temperature, and time to render the material sterile. Ethylene oxide is an alkylating agent that disrupts the DNA of microorganisms and prevents them from reproducing. Ethylene oxide sterilization is considered a low-temperature method and is commonly employed in a variety of materials including many polymers such as orthopedic-grade polyethylene (Ries *et al*., 1996). Materials sterilized with EtO are typically encased in final breathable packaging as an aeration process completes the sterilization cycle. **Gas plasma** is a low-temperature, sterilization method that relies upon ionized gas for deactivation of biological organisms on surfaces of devices or implants. Low-temperature hydrogen peroxide gas plasma is accomplished at temperatures lower than 50°C. This method is commonly employed in polymeric materials that are susceptible to irradiation damage (Goldman and Pruitt, 1998). The attributes and limitations of the primary sterilization methods are summarized in Table 1.1.

In general, materials that can withstand high temperatures, such as metals and ceramics, can employ any of these methods for sterilization. Polymers, because of their low melt temperatures, require low-temperature methods such as gas plasma, ethylene oxide gas, or irradiation. However, in using irradiation for polymeric materials it is extremely important to be aware of the radiation chemistry of the specific polymer system (Birkinshaw *et al*., 1988; Dole *et al*., 1958; Pruitt, 2003). Specifically, the irradiation process can result in a chain scission or crosslinking mechanism that can alter the physical structure, mechanical properties, and long-term stability of the polymeric implant. A case study examining the effect of gamma irradiation sterilization on medical grade ultra-high molecular weight polyethylene used in total joint replacements is presented at the end of this chapter.

1.6 Regulatory issues

Regulatory aspects of medical implants in the United States are governed by the **Food and Drug Administration** (FDA) and play an important role in the medical device development process (Figure 1.2). The FDA classifies implants based on risk to the patient in the event of a device failure. **Class I** implants are low-risk devices such as

Table 1.1 Summary of primary sterilization methods employed in biomaterials

Sterilization Type	Mechanism	Benefits	Drawbacks	Applications
Autoclaving	High-pressure steam (121°C) disables DNA	• Efficient • Easily accessible	• High temperature	• Metals • Ceramics
Gamma irradiation	Radiation disables DNA	• Efficient • Penetrating	• Radiation damage	• Metals • Ceramics • Polymers
E-beam irradiation	Accelerated electrons disable DNA	• Efficient • Surface treatment	• Radiation damage • Limited penetration	• Metals • Ceramics • Polymers
Ethylene oxide gas	Alkylating agent disables DNA	• No radiation damage • Surface treatment	• Requires extra time for outgassing • Requires special packaging	• Metals • Ceramics • Polymers
Gas plasma	Plasma chemistry disables DNA	• Low temperature • No radiation damage • Surface treatment	• Limited penetration • Requires special packaging	• Metals • Ceramics • Polymers

bandages; **Class II** implants are moderate-risk devices such as total joint replacements; and **Class III** implants are high-risk implants such as heart valves or pacemakers. Generally, devices that are life-supporting or life-sustaining must undergo the most rigorous FDA approval process before they can be marketed. When the implant or device is approved for marketing, it is still subject to further analysis. For example, clinical performance is a true marker of an implant's performance; clinical trials and retrieval studies provide invaluable insight into adverse reactions or complex problems that may not have been predicted in the laboratory. The FDA analyzes the performance of many devices annually to monitor safety and good manufacturing practice, and it also facilitates the actions of device recalls if necessary.

1.7 Structural requirements

The structural requirements of medical devices can vary widely. For example, some loads in the body are very high as is the case for many orthopedic and dental implants. These loads are then resolved into stresses in the medical device and vary depending on geometry and mode of loading of the implant. For example, in total knee reconstruction the two bearing surfaces of the **condyles** are highly non-conforming and the contact

stresses are high, while the ball-and-socket joint of the hip is highly conforming and the contact stresses are low. Variations in anatomical positioning and joint function result in a need for different material properties in the hip versus the knee. In the former, wear resistance is paramount because the surface area of contact is high, while in the latter fatigue resistance is critical owing to the high cyclic contact stresses. This difference makes it unlikely that one material choice would be suitable for both applications.

Most medical implants require very specific properties. For example, an arterial graft needs to offer flexibility, **anisotropic** behavior, and **compliance** that match that of adjacent tissue. A balloon **angioplasty** catheter needs to be tractable over a guide wire and must be stiff enough to prevent kinking yet flexible enough to navigate the vasculature. Sutures need to provide high tensile strength, and for the case of **resorbable** sutures this strength must decrease over time in a controlled manner. In a femoral stem of a hip replacement or other such applications, the biomaterial should offer compliance match to the adjacent bone in order to prevent stress shielding or loss of bone caused by lack of loading. For such reasons, the structural properties of the biomaterials are extremely important for the long-term success or performance of the implant. One such property that is extremely important in implant design is the elastic modulus of the material as this plays a key role in determining the geometric stiffness of the implant and load transfer to adjacent tissues.

A simple way to estimate the elastic modulus is through the assessment of interatomic force potential. The general form of the bond energy, $U(r)$, as a function of atomic separation, r, is shown in Figure 1.4. The equilibrium separation distance is denoted as r_o. If two atoms are displaced by an amount $r - r_o$, then the force, F, that resists this deformation is proportional to the separation distance for small displacements in both tension and compression.

This illustration given in Figure 1.4 also demonstrates that the force for the separation of atoms is given by the following relationship:

$$F = \frac{dU}{dr}. \tag{1.1}$$

Similarly, the stiffness of the bond is given as

$$S = \frac{dF}{dr} = \frac{d^2U}{dr^2}. \tag{1.2}$$

When the displacement between bonds is small, the bond stiffness behaves in a linear elastic fashion and is given as:

$$S_o = \left(\frac{d^2U}{dr^2}\right)_{r_o}. \tag{1.3}$$

The above relationship provides the physical foundation for elastic modulus. For small displacements (small strains), S_o is constant and represents the spring constant of the bond. One can envision that the material is held together by springs with a spring constant equal to S_o as shown in Figure 1.4. This assumes a very simple arrangement