K.B. dedicates this book to his mother (Rajni P. Balani), brother (Lohit P. Balani), newly joined daughter (Tripti Balani), and wife (Vandana K. Balani).
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The interdisciplinary nature of the biomaterials field requires a synergistic interaction of materials science, biomedical engineering and surgical medicine that brings together the requisite physical, chemical and biological paradigms of an implant surface. Since the biomaterials surface is the site of interaction with the host, the interactions are governed by tailoring the specific surface properties to the desired application. The ability to engineer successful implants will depend intimately on a thorough understanding of biosurfaces.

*Biosurfaces* details the types and classes of biomaterials and how they are used for specific applications (such as use of metals as structural materials, say as bone implants, use of ceramic, such as hydroxyapatite coating for rendering requisite bioactivity and polymer for degradable drug delivery systems).

This book describes in detail the interactions between biomaterials and tissues, the immune response to biomaterials and several other topics that are the basic building blocks of any biomaterial. The multi-length scale complexity that occurs in natural materials (such as bone, nacre, lotus leaf, gecko feet, spider web, etc.) is presented and described in excellent detail. The discussions of the role of superhydrophobicity in altering protein adsorption or cellular behavior, along with the discussions of designing gradient hydrophilic–hydrophobic surfaces for achieving tunable cellular response, are commendable.

This book also provides excellent sections on altering surfaces with coatings, micro/nano-fabrication of biomaterials via laser prototyping and other topics. The authors have done an excellent job in describing specific mechanical and tribological characterization methods for real-life biocomposites. The text has many excellent examples of the actual applications of bioengineered surfaces developed for specific enhancements in the quality of life and for restoration of function in the patient. Importantly, the generally ignored safety, societal effects and ethical aspects of using nano-biомaterials are well covered in this book for which the authors are to be commended.
Biosurfaces simplifies the concepts associated with biosurfaces and brings this understanding within reach of material scientists and biomedical engineers alike. Introduction of biomaterials, processing of biosurfaces, implementation as implants (or drug delivery conduits), evaluating the performance of materials and emphasizing the societal, safety and ethical issues are all covered.

I highly recommend this book as a textbook for students (both post-graduate and senior level undergraduate) and academicians, as a handbook or guide for industrial researchers/engineers/developers and as a refresher for scientists working in the emerging field of biosurfaces.

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Surfaces are highly critical in dictating the response of a biomaterial, hence the book, *Biosurfaces: A Materials Science and Engineering Perspective* is targeted for materials scientists, biomedical engineers, biologists, and design engineers to be able to comprehend the importance of biosurfaces and initiate a dialog between them. More importantly, this book provides a perspective of materials scientists and engineers that will allow parallel communication of materials scientists with biotechnologists, practitioners (dentists, surgeons, etc.) and biomedical professionals alike.

The contribution of understanding the material, being able to design the bulk components, has saturated in recent past, but the idea of engineering the surfaces and using them as potential sites for targeted interaction *in vivo* has triggered the research and funding in the area of biomaterials and bioengineering. Since primary interaction rests with the surface, appropriate selection (chemistry), design (surface topography and patterning), and performance (both biological and mechanical) are critical in imparting significant upliftment to the current technological applications. This book encompasses the fundamentals of materials, the interaction of biomaterials at molecular and cellular levels, surface and biological characterization followed with engineering aspects for practical dental/bone implants and as engineered devices. This book has been conceived in order to motivate the students (especially senior undergraduate and post-graduate) and young researchers alike. In addition, this book will serve as a handbook for experts for easy referral both in academia and in industry.

In this perspective, the present book provides a background and introduces the importance of biomaterials to a reader, who does not have a background on biosurfaces. Furthermore, the book develops the concepts of biomaterials, and provides an insight to the mechanisms and fundamentals of designing biosurfaces from an engineering perspective. The book has been structured into various chapters as described in the following sections.

In Chapter 1 on *Introduction to Biomaterials*, starting with the evolving definition of biomaterial, the content covers the classification of biomaterials. Although a complex interconnection of bioinertness to bioactivity is covered in later chapters, this chapter focuses on the class of polymeric, metallic, and ceramic materials. This chapter outlines the associated challenges and utility in terms of selection of materials for specific applications.

Chapter 2 focuses on the interaction between biomaterials and the tissue. The role of protein adsorption on inducing cell migration and controlled cell deposition is presented
in this chapter. The role of extracellular matrix in supporting the cellular growth, proliferation, and adhesion is portrayed. Later, biologically controlled biomineralization, and its utility in supporting the skeletal system, is depicted in detail in this chapter.

Response to implanted materials initially via activation of the immune system (recognizing antigen as foreign body) followed by humoral and cell-mediated immunity is described in Chapter 3. Activation of lymphocytes (B-cells) and bone marrow (T-cells) cells differentiating into helper and cytotoxic cells is introduced. In addition, release of cytolytic granules by natural killer cells, which lead to target cell lysis, monocytes and macrophages performing phagocytosis apart from releasing other immune substances such as cytokines, is also described in this chapter. Furthermore, the role of granulocytes, mast cells, dendritic cells and follicular dendritic cells in causing allergic reaction and phagocytosis, generating proteins, activation of T-cells and selective maturation of B cells is also presented. Moreover, in vitro agar diffusion test, direct contact method, elution/extract dilution and MTT assay are presented for quantification of cellular response. Designing an in vivo response and the test strategy and performing the sensitization and irritation tests are also detailed in this chapter.

Surface properties of biomaterials are described in Chapter 4. The phenomena of protein adsorption and cell adhesion in resulting biocompatibility is elicited. Following biomimetics, biodegradation is defined. Methods of surface modification (such as immobilization of molecules, organic films, self-assembly, etc.) are described in order to achieve engineered biosurface.

Chapter 5 provides an insight to Multi-Length Scale Hierarchy in Natural Materials, wherein biomimicking aspects in natural materials are discussed. This chapter includes fascinating aspects of (i) high toughness of human bone, turtle shell and nacre, (ii) high compression strength of wood, (iii) tensile strength of spider silk, (iv) sticking and de-sticking of gecko feet and (v) superhydrophobicity of lotus leaf. Furthermore, a few engineering aspects of making the gecko feet structures and mimicking the lotus leaf superhydrophobic structure are discussed.

Chapter 6 starts with the natural surfaces rendering superhydrophobicity, following with the learning from nature and being able to mimic such surfaces. The role of surface chemistry and roughness at multi-length scale makes mimicking of natural structures highly challenging. A new dimension of mechanical aspects of surface is also covered in describing the nature of wetting. A few fabrication techniques are listed that can be used in fabricating artificial superhydrophobic surfaces. In the end, engineering of controlled wettability surface is discussed that might open doors for applications in space, biomedical, automotive and other sectors.

Chapter 7 allows the reader to learn the need for altering the surface and applying a surface coating. Various classes of biosurfaces, namely inert, porous, bioactive and resorbable surfaces, are defined and related to surface activity and cellular response. Furthermore, key requirements for depositing a coating are listed, and extensively used substrate materials are also described for the reader. Surface preparation is of high importance in order to deposit the coatings successfully, and use of appropriate technique for depositing coatings (especially orthopedic, knee, dental, cardiac, and drug delivery devices) is also provided in the chapter. Various surface characterization techniques are also introduced to facilitate the reader.
Chapter 8 provides the engineering of micro- and nano-fabrication of biomaterials via laser prototyping. Use of laser technology in fabricating neural, ophthalmic and cardiovascular devices is described. Furthermore, making micro-needles via laser technology can be highly useful in providing controlled transdermal delivery of pharmacologic agents and vaccines.

Processing of carbon nanotubes (CNTs)-reinforced hydroxyapatite (HA) via electrophoretic deposition, aerosol deposition, laser processing and plasma spraying is presented in Chapter 9. In order to develop a free-standing HA–CNT composite via sintering, hot pressing and spark plasma sintering are also described. More importantly, the mechanical and tribological characterization (both at macro- and micro-length scale) is elicited. In order to physically perceive the adhesion strength, nano-scratch is used to quantify the adhesion force of bone cells. Furthermore, novel TiO$_2$- and boron-nitride-nanotubes-reinforced HA are also discussed in the chapter.

Chapter 10 deals with the implantable devices (such as bone and dental implants, stents, surgical devices and scaffolds, prosthesis, etc.) that allow the actual usage of bioengineered surfaces in enhancing the quality of life. The role of drug delivery in using the functionalization of specific molecules and using nanoparticles capsules is also presented herewith.

The last section of the book, in Chapter 11, covers the safety, societal and ethical aspects of using nanobiomaterials. Governmental Environment and Health Safety Organization Protocols and related safety hazards are discussed, and an approach toward developing safety protocols for the laboratory environment is listed. Current scenarios in the capability of capturing nanoparticles, and being able to evolve safety measures are presented. In addition, recommendations are provided in order to maintain safety while ethically using biomaterials for enhancing the quality of life.

The construction of these chapters will allow an easy understanding for students, academicians and industrial researchers working in the area of biosurfaces. In particular, this book has been sectioned in following major sections: (i) overview, fundamentals and class of biomaterials, (ii) biosurfaces and their role in initiating first response, (iii) processing and deposition of coatings as biosurfaces, (iv) engineering of biosurfaces (and performance evaluation) for biological applications, and (v) nanosafety and nanoethics.

Hence, this book can: (i) serve as a text book for teaching/academic purposes, (ii) provide research ideas in broader range of topics, while eliciting variety of materials (ceramics, polymers and metals), and biological response (both molecular and cellular), (iii) help adopting commercial technology for processing of biocoatings, (iv) guide in evaluating the performance of coatings, and (v) help implementing safety protocols, and listing ethical aspects of biomaterials.

It is important to mention that this book is an outcome of several years of teaching undergraduate and postgraduate level courses in the area of materials science and engineering, biomaterials processing and characterization, and surface phenomena related to materials. These have laid the foundation for understanding surfaces and controlling chemistry in order to engineer surface properties.

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INTRODUCTION TO BIOMATERIALS

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1.1 INTRODUCTION

“Any substance (other than drugs) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body” is known as a biomaterial [1]. In a broad sense, biomaterials are inert materials, synthetic or natural, designed to replace a particular part of a system or a specific body function.

The nineteenth century brought an advent of biomaterials in the field of medicine and health care. The applications of biomaterials encompass the perspectives of biology, medicine, and materials science and engineering, as shown in Fig. 1.1. From selection and processing of biomaterials, to their selective characterization and inferences from their interaction with the living system, all require a synergistic blend of biomaterials science and engineering. The interdisciplinary nature of biomaterials science and engineering (Fig. 1.1) demands the convergence of science and technology, exploring the existence of well-designed structure and function of products, which have found important applications in biomedical areas. The never-ending innovative motivation of researchers in mimicking the nature and the day-to-day needs and desires of common
INTRODUCTION TO BIOMATERIALS

Applications of biomaterials

Figure 1.1. Applications of biomaterials.

people has contributed immensely to the development of most advanced level biomaterials. These include biomaterials being used in replacing body parts, facilitating healing, correcting functional anomalies/deviations, and designing of devices used in the diagnosis and treatment of diseases.

Table 1.1 summarizes the role of biomaterials at the organ and system level. These evidences of newer technology biomaterials clearly state their relevance and usefulness in serving mankind. With such a pronounced breakthrough in the field of biomaterials and engineering, there would be an epoch introducing the development of almost all of the body parts made up of biomaterials that can replace an entire human body.

A diagrammatic representation of cell–material interaction in vitro, as shown in Fig. 1.2, presents the receptor ligand binding between the cell and biomaterial. A material can be declared an implant biomaterial depending on certain material properties, as illustrated in Fig. 1.3. Some of the highlighted properties include physical, mechanical, chemical, and biological, which add up together to form a suitable material for implant use.

One of the most important properties of a biomaterial to be used as an implant is its biocompatibility. Biocompatibility is the property of a biomaterial that does not elicit any adverse systemic (or host) response after implantation and does not lose its functional property at the same time. Thus, the normal functioning of the organ is not restricted in any manner. However, these requirements, along with non-toxicity and

Figure 1.2. Cell–material interaction.
TABLE 1.1. Role of Biomaterials at Organ and System Level [2–4]

<table>
<thead>
<tr>
<th>System</th>
<th>Organ/Site of action</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>Bones</td>
<td>Bone plate, intramedullary rods, bone cement, joint replacement, prostheses, artificial tendon and ligament, and dental implant for tooth fixation</td>
</tr>
<tr>
<td>Muscular</td>
<td>Muscles</td>
<td>Sutures and muscle stimulator</td>
</tr>
<tr>
<td>Circulatory</td>
<td>Heart</td>
<td>Artificial heart valve, artificial hip joint, blood vessels, blood vessel prosthesis, cardiac pacemaker, total artificial heart, and heart–lung machine</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Lungs</td>
<td>Oxygenator machine, heart–lung machine, tracheal implants, and tracheotomy tubes</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Skin</td>
<td>Sutures, burn dressings, artificial skin, and skin repair template</td>
</tr>
<tr>
<td>Urinary</td>
<td>Kidney and bladder</td>
<td>Kidney dialysis machine, catheter, stent, and artificial kidney (hemodialyzer)</td>
</tr>
<tr>
<td>Nervous and sensory</td>
<td>Brain and spinal cord</td>
<td>Hydrocephalus drain, cardiac pacemaker, nerve stimulator, cochlear replacement, intraocular lens, contact lens, and corneal bandage</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Endocrine glands</td>
<td>Microencapsulated pancreatic islet cells</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Reproductive organs</td>
<td>Augmentation mammoplasty and other cosmetic replacements</td>
</tr>
</tbody>
</table>

non-carcinogenicity, limit the selection of biomaterials to only a handful among countless engineering materials. Furthermore, temporal feedback from clinical trials, packaging, processing, transportation or cost, also play a major role in material selection. The flowchart (Fig. 1.4), shown with thick arrows, presents the track of a biomaterial, starting from its need for use and identification of the incorporable material, up to its successful implantation. The thin arrows represent the developer or the coordinator behind each activity. The circumferential envelop boxes describe the action in detail.

Biomaterials serve as a platform, which adds richness and grace to life at an accelerated pace in various aspects (classes), with a holistic approach toward evolution. Some of the examples (hip-screw, Herbert’s screw, dentures, orthodontic parts, and ceramic/metal crown) of the applications are labeled in Figs. 1.5–1.9. The X-ray images of some of the biomaterial implants (Hip screw, Ender nail, Screw and K-wire, external fixator, and Herbert’s screw) are shown in Figs. 1.10–1.14.

The first section of the chapter throws light on the various classes of biomaterials, as expanded in the following section.

1.2 CLASSIFICATION OF BIOMATERIALS

The versatility of biomaterials in the character of their applications can be highlighted in the form of their various classes, which could be in the form of a metal, polymer,
Figure 1.3. Schematic showing the major properties as indicated by the block arrows add up to give rise to the material with perfect properties to be called as an implant.

Figure 1.4. Schematic illustrating the track followed by a biomaterial (from its need and identification to its successful host implantation).
ceramic, and/or a mixture of these as composites. The bulk of this chapter focuses on the
documented classification of biomaterials, expanding basically on polymers, metals,
and ceramics. A schematic of classification of biomaterials is as shown in Fig. 1.15,
illustrating their four major classes.

We shall now move forward describing the class of biomaterials entitled as
copolymers.
Introduction to Biomaterials

Figure 1.8. Complete orthodontic appliance. (Courtesy: Dr. Siddharth Tripathi, Dental Clinic, Gorakhpur, India, for providing the images of dental implants.)

Figure 1.9. Ceramic and metal crown. (Courtesy: Dr. Siddharth Tripathi, Dental Clinic, Gorakhpur, India, for providing the images of dental implants.)

1.2.1 Polymers

Polymers are long chain molecules comprising several monomer units linked together by primary covalent bonding. They embody the largest class of biomaterials. The applications of polymers in the aspect of biomaterials include the domains of orthopedics, soft tissue reconstruction, dentistry, and cardiovascular device construction. Detailed aspects on physical, thermal, and mechanical properties of polymers are presented in Appendix A1. To have a complete understanding about polymers, we need to have a sound knowledge about their synthesis, classification, and properties, which shall be discussed in the further section of the chapter. To begin with, the synthesis of polymers is described in the following section.

1.2.1.1 Synthesis of Polymers. The two major methods of synthesizing a polymer are addition polymerization and condensation polymerization.