Introduction to Biomaterials

This textbook gives students the perfect introduction to the world of biomaterials, linking the fundamental properties of metals, polymers, ceramics, and natural biomaterials to the unique advantages and limitations surrounding their biomedical applications.

- Clinical concerns such as sterilization, surface modification, cell–biomaterial interactions, drug delivery systems, and tissue engineering are discussed in detail, giving students practical insight into the real-world challenges associated with biomaterials engineering.
- Key definitions, equations and concepts are concisely summarized alongside the text, allowing students to quickly and easily identify the most important information.
- Bringing together elements from across the book, the final chapter discusses modern commercial implants, challenging students to consider future industrial possibilities.

Concise enough to be taught in a single semester, and requiring only a basic understanding of biology, this balanced and accessible textbook is the ideal introduction to biomaterials for students of engineering, materials science, and medicine.

C. Mauli Agrawal is the Vice President for Research at the University of Texas at San Antonio (UTSA), and the Peter Flawn Professor of Biomedical Engineering. Previously, he served as the Dean of the College of Engineering at UTSA. He specializes in orthopedic and cardiovascular biomaterials and implants and his inventions have been licensed to various companies. He is a member of the International College of Fellows of Biomaterials Science and Engineering, a Fellow of the American Institute for Medical and Biological Engineering, a former President of the Society for Biomaterials, and was awarded the 2010 Julio Palmaz Award for Innovation in Healthcare and the Biosciences.
Joo L. Ong is Chair of the Department of Biomedical Engineering and the USAA Foundation Distinguished Professor at the University of Texas at San Antonio. His research focuses on modification and characterization of biomaterials surfaces for dental and orthopedic applications, tissue engineering ceramic scaffolds, protein-biomaterial interactions, and bone–biomaterial interactions. He is a Fellow of the American Institute for Medical and Biological Engineering.

Mark R. Appleford is an Assistant Professor of Biomedical Engineering at the University of Texas at San Antonio, focusing on tissue–biomaterial interactions, cellular engineering, reconstructive tissue engineering, and biocompatibility.

Gopinath Mani is an Assistant Professor of Biomedical Engineering at the University of South Dakota, focusing on surface modification and characterization of biomaterials, nanomaterials and nanomedicine, biodegradable metals and drug delivery systems. He is the Program Chair for the Surface Characterization and Modification Special Interest Group of the Society for Biomaterials, and has developed and taught numerous graduate-level programs in biomaterials engineering.
CAMBRIDGE TEXTS IN BIOMEDICAL ENGINEERING

Series Editors
W. Mark Saltzman, Yale University
Shu Chien, University of California, San Diego

Series Advisors
Jerry Collins, Alabama A & M University
Robert Malkin, Duke University
Kathy Ferrara, University of California, Davis
Nicholas Peppas, University of Texas, Austin
Roger Kamm, Massachusetts Institute of Technology
Masaaki Sato, Tohoku University, Japan
Christine Schmidt, University of Florida, Gainesville
George Truskey, Duke University
Douglas Lauffenburger, Massachusetts Institute of Technology

Cambridge Texts in Biomedical Engineering provide a forum for high-quality textbooks targeted at undergraduate and graduate courses in biomedical engineering. It covers a broad range of biomedical engineering topics from introductory texts to advanced topics, including biomechanics, physiology, biomedical instrumentation, imaging, signals and systems, cell engineering, and bioinformatics, as well as other relevant subjects, with a blending of theory and practice. While aiming primarily at biomedical engineering students, this series is also suitable for courses in broader disciplines in engineering, the life sciences and medicine.
“This is a book that is destined to be a classic in biomaterials education. Written by leading bioengineers and scientists, it can serve not only as a textbook to support a semester-long undergraduate course, but also as an introduction to graduate-level classes. It is a well-written, comprehensive compendium of traditional and also modern knowledge on all aspects of biomaterials, and I am sure that both students and instructors will embrace it and use it widely.”

Kyriacos A. Athanasiou

University of California, Davis
Introduction to Biomaterials
Basic Theory with Engineering Applications

C. Mauli Agrawal
University of Texas at San Antonio

Joo L. Ong
University of Texas at San Antonio

Mark R. Appleford
University of Texas at San Antonio

Gopinath Mani
University of South Dakota
I dedicate this work to my parents who taught me to love excellence, and to my wife and children (Sue, Ethan and Serena), who have always supported my pursuit of it.

C. Mauli Agrawal

To my family, who have put up with me all these years.

Joo L. Ong

I express my deepest appreciation for my wife Lindsey, best friend, greatest love, supplier of green limes and good joss.

Mark R. Appleford

I dedicate this work to my wife Priya Devendran, my daughter Manushri Gopinath, and my parents Mani and Bagyam Mani.

Gopinath Mani
# Contents

<table>
<thead>
<tr>
<th>Preface</th>
<th>page xvii</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Introduction</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 Definitions</td>
<td>5</td>
</tr>
<tr>
<td>1.2 Changing focus</td>
<td>7</td>
</tr>
<tr>
<td>1.3 Types of bonds in materials</td>
<td>7</td>
</tr>
<tr>
<td>1.3.1 Ionic bonds</td>
<td>7</td>
</tr>
<tr>
<td>1.3.2 Metallic bonds</td>
<td>8</td>
</tr>
<tr>
<td>1.3.3 Covalent bonds</td>
<td>9</td>
</tr>
<tr>
<td>1.3.4 Secondary bonds</td>
<td>10</td>
</tr>
<tr>
<td>1.4 Types of materials</td>
<td>11</td>
</tr>
<tr>
<td>1.4.1 Ceramics</td>
<td>11</td>
</tr>
<tr>
<td>1.4.2 Metals</td>
<td>12</td>
</tr>
<tr>
<td>1.4.3 Polymers</td>
<td>14</td>
</tr>
<tr>
<td>1.4.4 Composites</td>
<td>14</td>
</tr>
<tr>
<td>1.5 Impact of biomaterials</td>
<td>15</td>
</tr>
<tr>
<td>1.6 Future of biomaterials</td>
<td>16</td>
</tr>
<tr>
<td>1.7 Summary</td>
<td>17</td>
</tr>
<tr>
<td>References</td>
<td>17</td>
</tr>
<tr>
<td>Problems</td>
<td>18</td>
</tr>
</tbody>
</table>

| 2 Basic properties of materials | 19 |
| 2.1 Mechanical properties | 20 |
| 2.1.1 Tensile testing | 21 |
| 2.1.2 Compressive testing | 26 |
| 2.1.3 Shear testing | 27 |
| 2.1.4 Bend or flexural tests | 27 |
| 2.1.5 Viscoelastic behavior | 28 |
| 2.1.6 Ductile and brittle fracture | 30 |
| 2.1.7 Stress concentration | 32 |
2.1.8 Fracture toughness 33
2.1.9 Fatigue 34
2.2 Electrochemical properties 35
  2.2.1 Corrosion 35
  2.2.2 Types of corrosion 37
2.3 Surface properties 43
  2.3.1 Contact angle 44
  2.3.2 Hardness 44
2.4 Summary 45
Suggested reading 45
Problems 46

3 Biological systems 48
  3.1 The biological environment 48
  3.2 Genetic regulation and control systems 51
  3.3 The plasma membrane 51
    3.3.1 Membranes are phospholipid layers 52
  3.4 Cytoskeleton and motility 53
  3.5 Cell to cell communication pathways 55
  3.6 Cell junctions 57
    3.6.1 Tight junctions 57
    3.6.2 Gap junctions 59
    3.6.3 Adherens and desmosomes 61
  3.7 Cell signaling pathways 62
    3.7.1 Receptors as signaling sensors 63
    3.7.2 Receptor classes 64
    3.7.3 Second messengers and their activation/deactivation 66
  3.8 Biological testing techniques 68
    3.8.1 Probe and labeling technologies 68
    3.8.2 Examination of gene expression 69
    3.8.3 The plasma membrane 69
    3.8.4 Cytoskeleton and motility 70
    3.8.5 Communication between cells 71
    3.8.6 Mapping intracellular signaling 72
  3.9 Summary 72
Suggested reading 73
Problems 73
4 Characterization of biomaterials 74

4.1 Contact angle 75

4.2 Infrared spectroscopy 80

4.2.1 Attenuated total reflection (ATR) 83

4.2.2 Specular reflectance 85

4.2.3 Infrared reflection absorption spectroscopy (IRRAS) 85

4.2.4 Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) 85

4.3 X-ray photoelectron spectroscopy 87

4.4 Secondary ion mass spectrometry 91

4.5 Atomic force microscopy 94

4.6 Scanning electron microscopy 98

4.7 Transmission electron microscopy 100

4.8 X-ray diffraction (XRD) 103

4.9 Chromatography 106

4.9.1 High performance liquid chromatography (HPLC) 106

4.9.2 Gel permeation chromatography (GPC) 108

4.10 Summary 110

Suggested reading 110

References 111

Problems 111

5 Metals: structure and properties 113

5.1 Titanium and its alloys 114

5.1.1 Classification of Ti and its alloys based on crystallographic forms 116

5.1.2 Surface properties 119

5.1.3 Applications 119

5.2 Stainless steel 119

5.2.1 Martensitic stainless steels 120

5.2.2 Ferritic stainless steels 120

5.2.3 Austenitic stainless steels 120

5.2.4 Duplex stainless steels 122

5.2.5 Recent developments in stainless steel alloys 122

5.3 Cobalt–chromium alloys 123

5.3.1 ASTM F75 123

5.3.2 ASTM F799 125

5.3.3 ASTM F90 125

5.3.4 ASTM F562 126

5.4 Nitinol 126

5.5 Tantalum 128
6 Polymers 134
6.1 Molecular structure of polymers 135
  6.1.1 Molecular weight 139
6.2 Types of polymerization 141
6.3 Physical states of polymers 142
  6.3.1 Amorphous phase 142
  6.3.2 Crystalline phase 144
6.4 Common polymeric biomaterials 146
  6.4.1 Polyethylene 146
  6.4.2 Polymethylmethacrylate (PMMA) 147
  6.4.3 Polylactic acid (PLA) and polyglycolic acid (PGA) 150
  6.4.4 Polycaprolactone (PCL) 152
  6.4.5 Other biodegradable polymers 153
  6.4.6 Polyurethanes 153
  6.4.7 Silicones 154
6.5 Hydrogels 155
  6.5.1 Synthesis of hydrogels 159
  6.5.2 Properties of hydrogels 160
  6.5.3 Applications 160
6.6 Nanopolymers 161
6.7 Summary 162
References 163
Suggested reading 163
Problems 163

7 Ceramics 165
7.1 General properties 166
7.2 Classifications 167
  7.2.1 Classification based on form 167
  7.2.2 Classification based on composition 168
  7.2.3 Classification based on reactivity 169
7.3 Bioceramics 169
  7.3.1 Silicate glass 170
  7.3.2 Alumina (Al₂O₃) 174
7.3.3 Zirconia (ZrO₂) 177
7.3.4 Carbon 179
7.3.5 Calcium phosphates (CaP) 180
7.3.6 Hydroxyapatite (HA) 183
7.3.7 Tricalcium phosphate (TCP) 186
7.3.8 Calcium sulfate (CaSO₄·H₂O) 187
7.3.9 Bioactive glass 188
7.4 Nanoceramics 189
7.5 Summary 195
References 196
Suggested reading 196
Problems 196

8 Natural biomaterials 198
8.1 Collagen 199
8.2 Elastin 204
8.3 Silk 207
8.4 Chitosan 210
8.5 Cellulose 213
8.6 Alginate 217
8.7 Hyaluronan 223
8.8 Chondroitin sulfate 226
8.9 Coral 228
8.10 Summary 231
References 231
Suggested reading 231
Problems 232

9 Surface modification 233
9.1 Abrasive blasting 234
9.2 Plasma glow discharge treatments 237
  9.2.1 Direct current glow discharge 239
  9.2.2 Alternating current glow discharge 240
  9.2.3 Capacitively coupled radiofrequency glow discharge 241
  9.2.4 Inductively coupled radiofrequency glow discharge 242
9.3 Thermal spraying 243
9.4 Physical vapor deposition (PVD) 251
  9.4.1 Evaporative deposition 252
  9.4.2 Pulsed laser deposition 253
  9.4.3 Sputter deposition 254
## Contents

9.5 Chemical vapor deposition (CVD) 261
9.6 Grafting 264
9.7 Self-assembled monolayer (SAM) 266
  9.7.1 Patterning of self-assembled monolayers 271
9.8 Layer-by-layer (LbL) assembly 274
  9.8.1 Different layer-by-layer (LbL) assembly techniques 277
9.9 Summary 279
References 279
Suggested reading 280
Problems 280

10 Sterilization of biomedical implants 282
10.1 Common terminology 282
10.2 Steam sterilization 283
10.3 Ethylene oxide sterilization 285
10.4 Gamma radiation sterilization 287
10.5 Other sterilization methods 289
  10.5.1 Dry heat sterilization 289
  10.5.2 Formaldehyde and glutaraldehyde treatments 290
  10.5.3 Phenolic and hypochloride solution treatments 290
  10.5.4 Ultraviolet (UV) radiation 290
  10.5.5 Electron beam sterilization 291
10.6 Recently developed methods 291
  10.6.1 Low temperature gas plasma treatment 291
  10.6.2 Gaseous chlorine dioxide treatment 292
10.7 Summary 292
References 293
Suggested reading 293
Problems 294

11 Cell–biomaterial interactions 295
11.1 The extracellular environment 297
11.2 Extracellular matrix mimics 309
11.3 Cell interactions with non-cellular substrates 309
11.4 Biocompatibility testing and techniques 314
  11.4.1 Immunostaining techniques for studying cell–ECM interactions 316
  11.4.2 Profiling a cell line for its ECM binding characteristics 317
  11.4.3 Immunoprecipitation and Western blotting 318
<table>
<thead>
<tr>
<th>11.5</th>
<th>Summary</th>
<th>319</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference</td>
<td>319</td>
</tr>
<tr>
<td></td>
<td>Suggested reading</td>
<td>319</td>
</tr>
<tr>
<td></td>
<td>Problems</td>
<td>320</td>
</tr>
<tr>
<td>12</td>
<td>Drug delivery systems</td>
<td>321</td>
</tr>
<tr>
<td>12.1</td>
<td>Diffusion controlled drug delivery systems</td>
<td>323</td>
</tr>
<tr>
<td>12.1.1</td>
<td>Membrane controlled reservoir systems</td>
<td>323</td>
</tr>
<tr>
<td>12.1.2</td>
<td>Monolithic matrix systems</td>
<td>324</td>
</tr>
<tr>
<td>12.2</td>
<td>Water penetration controlled drug delivery systems</td>
<td>325</td>
</tr>
<tr>
<td>12.2.1</td>
<td>Osmotic pressure controlled drug delivery systems</td>
<td>326</td>
</tr>
<tr>
<td>12.2.2</td>
<td>Swelling controlled drug delivery system</td>
<td>327</td>
</tr>
<tr>
<td>12.3</td>
<td>Chemically controlled drug delivery systems</td>
<td>328</td>
</tr>
<tr>
<td>12.3.1</td>
<td>Polymer–drug dispersion systems</td>
<td>328</td>
</tr>
<tr>
<td>12.3.2</td>
<td>Polymer–drug conjugate systems</td>
<td>329</td>
</tr>
<tr>
<td>12.4</td>
<td>Responsive drug delivery systems</td>
<td>331</td>
</tr>
<tr>
<td>12.4.1</td>
<td>Temperature-responsive drug delivery systems</td>
<td>331</td>
</tr>
<tr>
<td>12.4.2</td>
<td>pH-responsive drug delivery systems</td>
<td>332</td>
</tr>
<tr>
<td>12.4.3</td>
<td>Solvent-responsive drug delivery systems</td>
<td>333</td>
</tr>
<tr>
<td>12.4.4</td>
<td>Ultrasound-responsive drug delivery systems</td>
<td>333</td>
</tr>
<tr>
<td>12.4.5</td>
<td>Electrically responsive drug delivery systems</td>
<td>334</td>
</tr>
<tr>
<td>12.4.6</td>
<td>Magnetic-sensitive drug delivery systems</td>
<td>334</td>
</tr>
<tr>
<td>12.5</td>
<td>Particulate systems</td>
<td>335</td>
</tr>
<tr>
<td>12.5.1</td>
<td>Polymeric microparticles</td>
<td>335</td>
</tr>
<tr>
<td>12.5.2</td>
<td>Polymeric micelles</td>
<td>336</td>
</tr>
<tr>
<td>12.5.3</td>
<td>Liposomes</td>
<td>336</td>
</tr>
<tr>
<td>12.6</td>
<td>Summary</td>
<td>337</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>339</td>
</tr>
<tr>
<td></td>
<td>Suggested reading</td>
<td>339</td>
</tr>
<tr>
<td></td>
<td>Problems</td>
<td>340</td>
</tr>
<tr>
<td>13</td>
<td>Tissue engineering</td>
<td>341</td>
</tr>
<tr>
<td>13.1</td>
<td>Tissue engineering approaches</td>
<td>342</td>
</tr>
<tr>
<td>13.1.1</td>
<td>Assessment of medical need</td>
<td>342</td>
</tr>
<tr>
<td>13.1.2</td>
<td>Selecting a tissue engineering strategy</td>
<td>343</td>
</tr>
<tr>
<td>13.2</td>
<td>Cells</td>
<td>344</td>
</tr>
<tr>
<td>13.2.1</td>
<td>Stem cells</td>
<td>345</td>
</tr>
<tr>
<td>13.2.2</td>
<td>Biopreservation of cells</td>
<td>347</td>
</tr>
<tr>
<td>13.3</td>
<td>Scaffold properties</td>
<td>349</td>
</tr>
<tr>
<td>13.4</td>
<td>Fabrication techniques for polymeric scaffolds</td>
<td>350</td>
</tr>
</tbody>
</table>
13.4.1 Solvent casting and particulate leaching 350
13.4.2 Electrospinning 350
13.4.3 Solid free form fabrication (SFFF) 351
13.5 Fabrication of natural polymer scaffolds 354
13.6 Fabrication techniques for ceramic scaffolds 357
13.6.1 Template sponge coating 357
13.6.2 Non-sintering techniques 357
13.7 Assessment of scaffold architecture 358
13.8 Cell seeded scaffolds 361
13.8.1 Cell culture bioreactors 361
13.8.2 Cell seeding 363
13.8.3 Growth factors 364
13.8.4 Mechanical modulation 366
13.9 Assessment of cell and tissue properties 367
13.9.1 Cellular properties 367
13.9.2 Tissue properties 371
13.10 Challenges in tissue engineering 372
13.11 Summary 373
References 373
Suggested reading 373
Problems 374

14 Clinical applications 375
14.1 Cardiovascular assist devices 376
14.2 Cardiovascular stents 378
14.3 Dental restoration 381
14.4 Dental implants 384
14.5 Neural prostheses 386
14.6 Ophthalmology 387
14.7 Orthopedic implants 390
14.8 Renal 393
14.9 Skin applications 394
14.10 Summary 397
Additional reading 397
Problems 397

Index 399
Preface

Biomaterials have helped millions of people achieve a better quality of life in almost all corners of the world. Although the use of biomaterials has been common over many millennia, it was not until the twentieth century that the field of biomaterials finally gained recognition. With the advent of polymers, new processing and machining processes for metals and ceramics, and general advances in technology, there has been an exponential growth in biomaterials-related research and development activity over the past few decades. This activity has led to a plethora of biomaterials-based medical devices, which are now commercially available.

For students in the area of biomaterials, this is an especially exciting time. On the one hand, they have the opportunity to meet and learn from some of the stalwarts and pioneers of the field such as Sam Hulbert, one of the founders of the Society for Biomaterials (SFB). Other greats include Allan Hoffman and Buddy Ratner (biomaterials surfaces), Robert Langer (polymers and tissue engineering), Nicholas Peppas (hydrogels), Jack Lemons (orthopedic/dental implants), Joseph Salamone (contact lenses), and Julio Palmaz (intracoronary stents). Most of these individuals are still active in research and teaching. The authors of this book have been privileged to interact and learn from them in various forums, and students today have the same opportunities. On the other hand, with the current availability of sophisticated processing and characterization technologies, present day students also have the tools to take the field to unprecedented new levels of innovation.

This book has been written as an introduction to biomaterials for college students. It can be used either at the junior/senior levels of undergraduate education or at the graduate level for biomedical engineering students. It is best suited for students who have already taken an introductory course in biology. We have felt the need for a textbook that caters to all students interested in biomaterials and does not assume that every student intends to become a biomaterials scientist. This book is a balance between science and engineering, and presents both scientific principles and engineering applications. It does not assume that the student has a background in any particular field of study. Therefore, we first cover the basics of materials in Chapters 1 and 2 followed by basic biological principles in Chapter 3.
After presenting various techniques for the characterization of biomaterials in Chapter 4, we dedicate a chapter each to the discussion of metals, polymers, ceramics, and natural biomaterials (Chapters 5–8). Surface modification methods are presented in Chapter 9, followed by sterilization techniques in Chapter 10. The success of any biomaterial depends on the biological response to it and so protein chemistry, cell–biomaterial interactions, and the effect of biomaterials on tissue response are addressed in Chapter 11. The last three chapters (Chapters 12–14) cover the application of biomaterials in the clinical world; specifically drug delivery systems, tissue engineering, and clinical applications are presented and discussed.

This book has been designed to present enough material so that it can be comfortably covered during a regular length semester-long course. It should provide the student with a concise but comprehensive introduction to biomaterials and lays the foundation for more advanced courses.

The authors would like to thank the following individuals for assisting in a variety of ways in compiling this book: Jordan Kaufmann, Ethan Agrawal, Serena Agrawal, Tim Luukkonen, Amita Shah, Steve Lin, Angee Ong, Kevin Ong, Lisa Actis, Marcello Pilia, and Stefanie Shiels.