

## Contents

**Preface** xv

|          |   |          |
|----------|---|----------|
| <b>1</b> | <b>Fundamentals of Acoustic Wave Generation and Propagation</b>       | <b>1</b> |
|          | <i>Mehmet A. Sahin, Mushtaq Ali, Jinsoo Park, and Ghulam Destgeer</i> |          |
| 1.1      | Introduction  | 1        |
| 1.1.1    | Acoustic or Sound Waves   | 1        |
| 1.1.2    | Dominos Effect  | 1        |
| 1.1.3    | Elastic vs Inelastic Waves  | 2        |
| 1.1.4    | Scope of Acoustics  | 4        |
| 1.2      | Brief History of Acoustic Waves                                       | 4        |
| 1.2.1    | Early History   | 4        |
| 1.2.2    | History of Acoustic Streaming   | 4        |
| 1.2.3    | History of Acoustic Radiation Force                                   | 5        |
| 1.3      | What Is an Acoustic Wave?   | 6        |
| 1.3.1    | Acoustic Parameters   | 6        |
| 1.3.2    | Displacement, Velocity, and Pressure Fields                           | 6        |
| 1.3.3    | Wave Propagation  | 7        |
| 1.3.4    | Wave Dissipation  | 7        |
| 1.3.5    | Wave Dispersion   | 8        |
| 1.4      | Modes of Acoustic Waves   | 8        |
| 1.4.1    | Categorization Based on Frequency Range                               | 9        |
| 1.4.2    | Categorization Based on Propagation Mode                              | 9        |
| 1.4.2.1  | Longitudinal Waves  | 9        |
| 1.4.2.2  | Shear Waves   | 10       |
| 1.4.2.3  | Rayleigh Waves  | 11       |
| 1.4.2.4  | Love Waves  | 12       |
| 1.4.2.5  | Lamb Waves  | 12       |
| 1.4.3    | Categorization Based on Wave Configuration                            | 12       |
| 1.4.3.1  | Traveling Waves   | 12       |
| 1.4.3.2  | Standing Waves  | 13       |
| 1.5      | Acoustic Wave Propagation and Interaction                             | 13       |
| 1.5.1    | Transmission and Reflection of Acoustic Waves                         | 13       |

|         |  |    |
|---------|--|----|
| 1.5.2   | Acoustic Scattering  | 14 |
| 1.5.3   | Acoustic Radiation   | 16 |
| 1.6     | Acoustic Wave Attenuation  | 18 |
| 1.6.1   | Viscoelastic Attenuation   | 18 |
| 1.6.2   | Acousto-Thermal Heating  | 19 |
| 1.6.3   | Acoustic Streaming Flow  | 19 |
| 1.6.3.1 | Eckart Streaming   | 20 |
| 1.6.3.2 | Rayleigh Streaming   | 20 |
| 1.6.3.3 | Bubble-Driven Microstreaming   | 21 |
| 1.6.3.4 | Applications of Acoustic Streaming Flow                                | 21 |
| 1.7     | Generation and Propagation of Acoustic Waves                           | 22 |
| 1.7.1   | Acoustic Waves Generation in Nature                                    | 22 |
| 1.7.2   | Generation of Acoustic Waves in Lab                                    | 22 |
| 1.7.2.1 | Lower-Frequency Acoustic Waves   | 22 |
| 1.7.2.2 | Piezoelectricity and High-Frequency Wave Generation                    | 23 |
| 1.8     | Acoustic Waves Effects in Fluidic Media                                | 24 |
| 1.8.1   | Vibrating Membranes and Sharp-Edge Structures                          | 25 |
| 1.8.2   | Oscillating Bubbles  | 25 |
| 1.8.2.1 | Cavitation   | 26 |
| 1.8.3   | Optoacoustic Imaging   | 27 |
| 1.8.4   | Manifestations of Acoustic Radiation Force and Acoustic Streaming Flow | 28 |
|         | List of Abbreviations and Symbols                                      | 28 |
|         | References   | 29 |

## **2 Basic Theories and Physics of Acoustic Technologies** 37

*Khemraj G. Kshetri and Nitesh Nama*

|         |  |    |
|---------|--|----|
| 2.1     | Introduction   | 37 |
| 2.2     | Acoustic Waves in Solids   | 38 |
| 2.2.1   | Governing Equation   | 39 |
| 2.2.2   | Acoustic Waves in Non-piezoelectric Solids                                   | 39 |
| 2.2.3   | Acoustic Waves in Piezoelectric Solids                                       | 40 |
| 2.3     | Acoustic Waves in Fluids   | 40 |
| 2.3.1   | Governing Equations  | 40 |
| 2.3.2   | Acoustic Streaming   | 41 |
| 2.3.2.1 | Modeling Approach for Slow Streaming   | 44 |
| 2.3.2.2 | Modeling Approach for Fast Streaming   | 45 |
| 2.3.3   | Distinction Between Lagrangian and Eulerian Fluid Velocity and Stokes' Drift | 46 |
| 2.3.4   | Acoustic Streaming Near Solid Particles                                      | 47 |
| 2.3.5   | Acoustic Streaming Near Fluid–Fluid Interfaces                               | 47 |
| 2.4     | Forces in Acoustofluidic Systems   | 49 |
| 2.4.1   | Primary Acoustic Radiation Force   | 49 |
| 2.4.2   | Secondary Acoustic Radiation Force   | 52 |
| 2.4.2.1 | Forces Between Two Rigid Spheres   | 53 |

|          |  |           |
|----------|--|-----------|
| 2.4.2.2  | Forces Between Two Bubbles                                   | 53        |
| 2.4.2.3  | Forces Between a Solid Particle and a Bubble                 | 54        |
| 2.4.2.4  | Forces Between a Liquid Drop and a Bubble                    | 55        |
| 2.4.3    | Hydrodynamic Drag Force                                      | 55        |
| 2.5      | Conclusions and Perspectives                                 | 57        |
|          | References   | 58        |
| <b>3</b> | <b>Materials for Acoustic Wave Generation and Modulation</b> | <b>67</b> |
|          | <i>Noé Jiménez</i>   |           |
| 3.1      | Introduction   | 67        |
| 3.1.1    | Generation and Detection of Ultrasound                       | 67        |
| 3.1.2    | Technologies for Ultrasound Transducers                      | 68        |
| 3.2      | Piezoelectricity   | 68        |
| 3.2.1    | Model Equations  | 68        |
| 3.2.1.1  | Stress-Charge Formulation                                    | 69        |
| 3.2.1.2  | Strain-Charge Formulation                                    | 70        |
| 3.2.1.3  | Stress-Field Formulation                                     | 70        |
| 3.2.1.4  | Strain-Field Formulation                                     | 70        |
| 3.2.2    | The Piezoelectric Constants                                  | 70        |
| 3.2.3    | Longitudinal Motion in a Piezoelectric Material              | 71        |
| 3.2.3.1  | A Simple Piezoelectric Model                                 | 71        |
| 3.2.3.2  | Waves in the Piezoelectric Material                          | 72        |
| 3.3      | Piezoelectric Materials                                      | 73        |
| 3.3.1    | Piezoelectric Crystals                                       | 73        |
| 3.3.2    | Piezoelectric Ceramics                                       | 74        |
| 3.3.3    | Piezoelectric Polymers                                       | 74        |
| 3.3.4    | Piezoelectric Composites                                     | 74        |
| 3.4      | Ultrasound Transducers                                       | 75        |
| 3.4.1    | Elements of a Transducer                                     | 75        |
| 3.4.2    | The Piezoelectric Slab                                       | 75        |
| 3.4.3    | Matching Layers  | 76        |
| 3.4.3.1  | Classical Matching Layer Design                              | 76        |
| 3.4.3.2  | Multiple Matching Layer Design                               | 77        |
| 3.4.3.3  | Broadband Matching Layer Design                              | 77        |
| 3.4.4    | Backing Layer  | 77        |
| 3.4.5    | Electrical Impedance Matching Network                        | 78        |
| 3.5      | Ultrasound Beams   | 78        |
| 3.5.1    | Circular Aperture Transducers                                | 78        |
| 3.5.2    | Focused Transducers  | 80        |
| 3.5.3    | Phased-Array Transducers                                     | 83        |
| 3.6      | Acoustic Lenses  | 83        |
| 3.6.1    | Refraction by Bulky Lenses                                   | 84        |
| 3.6.1.1  | Spherical Lenses   | 84        |
| 3.6.1.2  | Ellipsoidal Lenses   | 85        |
| 3.6.1.3  | Axicon Lenses  | 85        |

|         |                                      |    |
|---------|--------------------------------------|----|
| 3.6.1.4 | Fresnel and Fraxicon Lenses          | 86 |
| 3.6.1.5 | Lenses for Vortex Generation         | 86 |
| 3.6.2   | Diffraction by Gratings              | 87 |
| 3.6.2.1 | Cartesian Diffraction Grating        | 87 |
| 3.6.2.2 | Asymmetric Diffraction Grating       | 87 |
| 3.6.2.3 | Fresnel Zone Plates                  | 88 |
| 3.6.2.4 | Archimedean Spiral Gratings          | 89 |
| 3.6.2.5 | Fresnel-Spiral Zone Plate            | 90 |
| 3.6.3   | Reflection by Curved Surfaces        | 90 |
| 3.6.3.1 | Parabolic Reflectors                 | 91 |
| 3.6.3.2 | Ellipsoidal Reflectors               | 91 |
| 3.6.4   | Holograms                            | 91 |
| 3.6.4.1 | Field Projections                    | 91 |
| 3.6.4.2 | Synthesis of Acoustic Images         | 93 |
| 3.6.4.3 | Biomedical Applications of Holograms | 94 |
|         | References                           | 95 |

#### **4      **Ultrasound and Ultrasonic Imaging in Medicine: Recent Advances**** 99

*Tuğba Ö. Onur*

|         |  |     |
|---------|--|-----|
| 4.1     | Introduction   | 99  |
| 4.2     | Ultrasound Waves   | 99  |
| 4.2.1   | Types of Ultrasonic Waves                                | 100 |
| 4.2.2   | Behavior of Ultrasound Waves at Interfaces               | 100 |
| 4.2.3   | Ultrasound Power and Intensity                           | 101 |
| 4.2.4   | Ultrasound Applications                                  | 102 |
| 4.3     | Ultrasonic Imaging                                       | 103 |
| 4.3.1   | Ultrasonic Imaging System                                | 106 |
| 4.3.1.1 | Transducer   | 106 |
| 4.3.1.2 | Probes   | 107 |
| 4.3.1.3 | Central Processing Unit                                  | 109 |
| 4.3.1.4 | Output Display   | 109 |
| 4.3.2   | Focus  | 109 |
| 4.3.3   | Resolution   | 109 |
| 4.3.4   | Beamforming  | 110 |
| 4.4     | Sound-Tissue Interactions in Ultrasonography             | 110 |
| 4.4.1   | Reflection   | 110 |
| 4.4.2   | Refraction   | 111 |
| 4.4.3   | Absorption   | 112 |
| 4.4.4   | Attenuation  | 112 |
| 4.4.4.1 | Attenuation by Reflection, Refraction, and Deflection    | 112 |
| 4.4.4.2 | Attenuation by Scattering                                | 113 |
| 4.4.4.3 | Attenuation by Absorption                                | 113 |
| 4.4.4.4 | Time Gain Reduction (TGR) and Depth Gain Reduction (DGR) | 114 |
| 4.5     | Ultrasonic Imaging Methods                               | 114 |

- 4.5.1 Real-Time Imaging 114
  - 4.5.1.1 A-Mode 115
  - 4.5.1.2 M-Mode 116
  - 4.5.1.3 B-Mode 117
- 4.5.2 Doppler Ultrasonography 118
  - 4.5.2.1 Continuous Wave Doppler 119
  - 4.5.2.2 Duplex Doppler 119
  - 4.5.2.3 Color Doppler 119
- 4.5.3 Real-Time Artifacts in Imaging 119
- 4.5.4 Factors Affecting Image Quality 120
- 4.6 Tissue Harmonic Imaging (THI) 121
  - 4.6.1 The Occurrence of Harmonic Signals 121
  - 4.6.2 The Separation of Harmonic Signals from the Main Signal 122
  - 4.6.3 The Advantages of Harmonic Signals 122
- 4.7 Recent Advances in Ultrasound Imaging for Medicine 122
  - References 123

## 5 Photoacoustic Imaging and Sensing for Biomedical Applications 127

*Amalina B. E. Attia, Ruochong Zhang, Mohesh Moothanchery, and Malini Olivo*

- 5.1 Introduction 127
- 5.2 Photoacoustic Imaging Applications 130
  - 5.2.1 PAI of Breast Cancer 130
    - 5.2.1.1 In Vivo Imaging 130
    - 5.2.1.2 Ex Vivo Imaging 132
  - 5.2.2 PAI for Skin Imaging 133
    - 5.2.2.1 PAI of Skin Cancer 135
    - 5.2.2.2 PAI of Inflammatory Skin Diseases 137
    - 5.2.2.3 PAI of Wounds 137
- 5.3 Photoacoustic Sensing for Biomedical Applications 139
  - 5.3.1 Noninvasive Temperature Monitoring in Deep Tissue 139
  - 5.3.2 Noninvasive Glucose Sensing 142
    - References 148

## 6 Therapeutic Ultrasound 159

*Bar Glickstein, Hila Shinar, and Tali Ilovitsh*

- 6.1 Introduction 159
- 6.2 Ultrasound-Induced Bioeffects 160
  - 6.2.1 Introduction 160
  - 6.2.2 Thermal Effects 160
  - 6.2.3 Mechanical Effects 161
    - 6.2.3.1 Cavitation 161
  - 6.2.4 Contrast-Enhanced Effects 161
    - 6.2.4.1 Microbubbles 161

|          |   |            |
|----------|---|------------|
| 6.2.4.2  | Nanobubbles   | 162        |
| 6.2.4.3  | Nanodroplets  | 162        |
| 6.2.5    | Safety and Regulations  | 163        |
| 6.3      | Therapeutic Ultrasound Applications   | 164        |
| 6.3.1    | High-Intensity Focused Ultrasound   | 164        |
| 6.3.2    | Histotripsy   | 166        |
| 6.3.3    | Shock Wave Lithotripsy  | 169        |
| 6.3.4    | Drug Delivery and Gene Therapy  | 170        |
| 6.3.5    | Blood–Brain Barrier Opening   | 171        |
| 6.3.6    | Low-Intensity Ultrasound for Neuromodulation                                      | 172        |
| 6.3.7    | Bone Healing  | 172        |
| 6.3.8    | Sonothrombolysis  | 172        |
| 6.3.9    | Other Applications  | 173        |
| 6.4      | Conclusions   | 173        |
|          | References  | 174        |
| <b>7</b> | <b>Application of Ultrasound-Responsive Reagents for Drug Delivery Systems</b>    | <b>181</b> |
|          | <i>Hiroshi Kida and Katsuro Tachibana</i>   |            |
| 7.1      | Historical Background of Research on Bubble Reagents for Medicine                 | 181        |
| 7.2      | Use of Bubble Reagents as Drug Delivery Systems                                   | 182        |
| 7.2.1    | Acoustic Cavitation   | 182        |
| 7.2.2    | Importance of Inertial and Non-inertial Cavitation in Improving Drug Permeability | 184        |
| 7.2.3    | Targeting and Focusing Using Acoustic Means                                       | 186        |
| 7.3      | Variation of Ultrasound-Responsive Reagents for DDS                               | 186        |
| 7.3.1    | Shell Composition   | 186        |
| 7.3.2    | Improved Stability by Polyethylene Glycol (PEG) Modification                      | 187        |
| 7.3.3    | Modification with Targeting Ligands   | 188        |
| 7.3.4    | Drug and Gene Loading   | 188        |
| 7.3.5    | Extended Adaptation of Ultrasound-Responsive Reagents                             | 190        |
| 7.4      | Research on Treatment of Diseases Using Ultrasonic Drug Delivery                  | 192        |
| 7.4.1    | Cancer  | 192        |
| 7.4.2    | Central Nervous System Diseases   | 195        |
| 7.5      | Conclusion  | 197        |
|          | References  | 198        |
| <b>8</b> | <b>Acoustic Levitation and Acoustic Holograms</b>                                 | <b>217</b> |
|          | <i>Tatsuki Fushimi and Yoichi Ochiai</i>  |            |
| 8.1      | Introduction  | 217        |
| 8.1.1    | History of Acoustic Levitation  | 217        |
| 8.1.1.1  | Classical Acoustic Levitator  | 218        |
| 8.1.1.2  | Phased Array Levitator (PAL)  | 221        |
| 8.2      | Acoustic Holograms  | 224        |

|          |   |            |
|----------|---|------------|
| 8.3      | Numerical Simulation of Acoustic Levitator  | 227        |
| 8.3.1    | Pressure Field Calculation  | 227        |
| 8.3.1.1  | Huygens' Approach   | 227        |
| 8.3.1.2  | Spherical Harmonics Expansion   | 228        |
| 8.3.1.3  | Angular Spectrum Method   | 229        |
| 8.3.2    | Acoustic Radiation Force  | 230        |
| 8.3.2.1  | Gor'kov   | 230        |
| 8.3.2.2  | Spherical Harmonic Approach   | 231        |
| 8.4      | Acoustic Hologram Optimization  | 231        |
| 8.4.1    | Optimization Example with Diff-PAT  | 233        |
| 8.5      | Applications in Biology and Medicine  | 234        |
| 8.5.1    | Specimen Holding  | 234        |
| 8.5.2    | Experiment Automation   | 234        |
| 8.5.3    | 3D Display  | 235        |
| 8.6      | Conclusion and Future Remarks   | 236        |
|          | Acknowledgments   | 237        |
|          | References  | 237        |
| <b>9</b> | <b>Application of Ultrasonic Waves in Bioparticle Manipulation and Separation</b> | <b>243</b> |
|          | <i>M. Bülent Özer and Barbaros Çetin</i>  |            |
| 9.1      | Introduction  | 243        |
| 9.2      | Bioparticle Manipulation  | 244        |
| 9.2.1    | Hydrodynamic Bioparticle Manipulation   | 244        |
| 9.2.2    | Immunological (Antigen–Antibody Reaction) Bioparticle Manipulation                | 245        |
| 9.2.3    | Electrokinetic Bioparticle Manipulation   | 245        |
| 9.2.4    | Magnetophoretic Bioparticle Manipulation  | 245        |
| 9.2.5    | Acoustophoretic Bioparticle Manipulation  | 246        |
| 9.2.6    | Unification of Field Manipulation Methods   | 246        |
| 9.2.7    | Comparison of Bioparticle Manipulation Methods                                    | 248        |
| 9.3      | General Architecture of Acoustofluidic Devices                                    | 249        |
| 9.3.1    | BAW Device Architecture   | 249        |
| 9.3.1.1  | Piezoelectric Actuator  | 249        |
| 9.3.1.2  | Chip Material   | 250        |
| 9.3.1.3  | Lid Material  | 251        |
| 9.3.1.4  | Device Assembly and Critical Dimensions   | 251        |
| 9.3.2    | SAW Device Architecture   | 252        |
| 9.3.2.1  | Piezoelectric Actuator  | 252        |
| 9.3.2.2  | Interdigital Electrodes (IDT)   | 253        |
| 9.3.2.3  | Microfluidic Chamber  | 254        |
| 9.3.2.4  | Device Assembly and Critical Dimensions   | 254        |
| 9.3.3    | Comparison of BAW and SAW Devices   | 254        |
| 9.4      | Governing Equations in Acoustic Bioparticle Manipulation                          | 255        |
| 9.4.1    | First-Order Acoustic Field Variables  | 255        |

|           |  |            |
|-----------|--|------------|
| 9.4.2     | Second-Order Acoustic Field Variables  | 257        |
| 9.4.3     | Acoustic Radiation Force on a Particle   | 258        |
| 9.4.4     | Acoustic Radiation Force on a Particle Considering the Effect of Chip Material                                 | 260        |
| 9.5       | Simulation of Acoustophoretic Bio-Particle Manipulation  | 264        |
| 9.5.1     | Simulation of Piezoelectric Actuators  | 264        |
| 9.5.2     | Numerical Simulations of the Elastic Material Surrounding the Channel  | 265        |
| 9.5.3     | Simulation of Fluid Flow   | 266        |
| 9.5.4     | Simulation of Particle Motion  | 267        |
| 9.6       | Acoustofluidic Devices in Biological and Medical Applications  | 269        |
| 9.6.1     | Applications Regarding Lipid Particles   | 269        |
| 9.6.2     | Applications Regarding Cell Wash   | 278        |
| 9.6.3     | Applications Regarding Separation of Blood Components  | 279        |
| 9.6.3.1   | Plasma Separation  | 279        |
| 9.6.3.2   | Platelet Separation  | 279        |
| 9.6.3.3   | Separation of WBCs   | 280        |
| 9.6.4     | Applications Regarding Cancer Cells  | 281        |
| 9.6.5     | Applications Regarding Miscellaneous Cells   | 282        |
| 9.6.6     | Application Regarding Bacteria   | 284        |
| 9.6.7     | Applications Regarding Nanoscale (Bio)Particles  | 287        |
| 9.6.8     | Miscellaneous Applications   | 289        |
| 9.7       | Commercial and Regulatory Considerations for Acoustofluidic Devices  | 290        |
| 9.7.1     | Cost   | 291        |
| 9.7.2     | High Volume Manufacturing  | 292        |
| 9.7.3     | Sterilization  | 292        |
| 9.7.4     | Biocompatibility   | 294        |
| 9.7.5     | Storage and Transportation Requirements  | 294        |
| 9.8       | Summary and Outlook  | 294        |
|           | References   | 296        |
| <b>10</b> | <b>Acoustic Biosensors</b>   | <b>305</b> |
|           | <i>Alper Şişman, Paddy French, Ayşe Ogan, Erdal Korkmaz, Abbas A. Hussein, Ali M. Yazdani, and Johan Meyer</i> |            |
| 10.1      | Introduction   | 305        |
| 10.1.1    | Bulk Acoustic Wave (BAW) Mode  | 305        |
| 10.1.2    | Surface Guided Acoustic Wave (SGAW) Modes  | 307        |
| 10.2      | Biochemical Fundamentals of Sensing  | 310        |
| 10.2.1    | Immobilization Strategies of Detection Element   | 311        |
| 10.2.1.1  | Noncovalent Immobilization   | 311        |
| 10.2.1.2  | Covalent Immobilization  | 312        |
| 10.2.1.3  | Bioaffinity Bindings   | 313        |
| 10.3      | Bulk Acoustic Wave Biosensors  | 314        |
| 10.3.1    | Quartz Microbalance (QMB) Crystal Biosensors   | 315        |



|           |   |            |
|-----------|---|------------|
| 10.3.2    | Film Bulk Acoustic Wave (FBAR) Biosensors             | 316        |
| 10.4      | Surface Transverse Wave Biosensors                    | 317        |
| 10.4.1    | SH-Wave and Love Wave Biosensors                      | 317        |
| 10.4.2    | Lamb Waves Biosensors                                 | 321        |
| 10.4.3    | Rayleigh Wave Biosensors                              | 324        |
| 10.4.4    | Crystal Cuts and Axis Orientation                     | 325        |
| 10.5      | Commercial Biosensors and Trends                      | 327        |
| 10.6      | Conclusion  | 331        |
|           | References  | 332        |
| <b>11</b> | <b>Acoustic Micro/Nanorobots in Medicine</b>          | <b>343</b> |
|           | <i>Murat Kaynak, Amit Dolev, and Mahmut S. Sakar</i>  |            |
| 11.1      | Introduction  | 343        |
| 11.2      | Theoretical Background                                | 345        |
| 11.2.1    | Introduction to Acoustics                             | 345        |
| 11.2.2    | Time-Averaged Acoustically Induced Forces             | 348        |
| 11.2.2.1  | Primary Radiation Forces                              | 348        |
| 11.2.2.2  | Secondary Radiation Forces                            | 351        |
| 11.2.2.3  | Drag and Thrust-Induced Acoustic Streaming            | 354        |
| 11.3      | Acoustic Micromanipulation Techniques                 | 355        |
| 11.3.1    | Introduction to Acoustic Tweezers                     | 356        |
| 11.3.2    | Acoustic Micromanipulation Using Bulk Acoustic Waves  | 357        |
| 11.4      | Micro/Nanorobotic Devices Actuated by Acoustic Fields | 361        |
| 11.4.1    | Mobile Acoustic Micromachines                         | 361        |
| 11.4.2    | Soft Robotic Microsystems                             | 363        |
| 11.5      | In Vivo Actuation of Micro/Nanorobotic Devices        | 365        |
| 11.6      | Discussion and Outlook                                | 367        |
|           | Acknowledgment  | 368        |
|           | References  | 368        |
|           | <b>Index</b>  | <b>375</b> |

