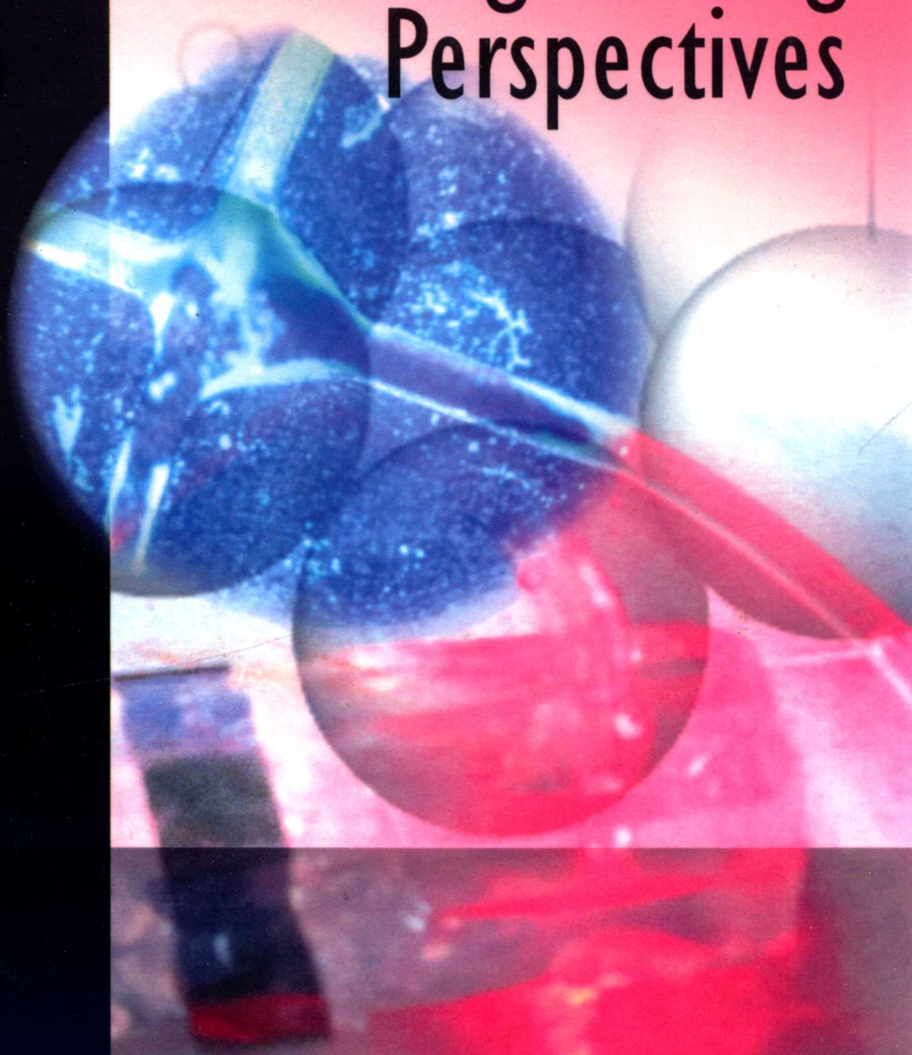
BioMEMS
Science and Engineering Perspectives



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SB: To Sabina and Iris, with love.

MP: To my wife, Indrani, son, Sudarsan, and parents, Kamatchi and Packirisamy, for their support and love.

Preface

We are proud to present this book as an attempt to bridge different areas that constitute the field of biomicroelectromechanical systems (BioMEMS), often called biomicrosystems. The field of BioMEMS has been growing rapidly since the early 1990s due to the advancements in microtechnologies that could cater to the vast application requirements of bio areas. The potential of BioMEMS suits this technology for many applications, including clinical and environmental diagnostics, drug delivery, agriculture, nutrition, pharmaceuticals, chemical synthesis, etc. It is foreseen that BioMEMS will have a deep impact on many aspects of the life science operations and functionalities in the near future.

Scientists and students that work in the field of BioMEMS will need to have knowledge and skills at the interface between engineering and biosciences. Development of a BioMEMS device usually involves many scientists and students from various disciplines, such as biosciences, medicine, biochemistry, engineering, physics, etc. One could anticipate many communication and understanding issues that would arise among these people with varied expertise and training. The methods, details, and languages of training are quite different for the students and researchers of engineering and biosciences. As a result, researchers and students involved with multidisciplinary projects like BioMEMS undergo an interesting and refreshing learning on multidisciplinary subjects along the project development. This book aims to support and expedite the multidisciplinary learning involved with the development of biomicrosystems, from both bioscience and engineering perspectives. Due to the variety and intensity of the subject matter that exists with an engineering and biological focus, there are many excellent books available dealing only with the engineering or biological aspect of biomicrosystems. But, this books attempts to cover the subjects that are important from both science and engineering perspectives. This effort of combining both perspectives in a single book presents a challenge of covering in detail the wide spectrum of areas and topics that are associated with those disciplines. The authors sincerely feel it is possible that some important works were unintentionally missed in this book due to the vastness of the subjects covered and other limitations. We suggest that readers refer to other advanced books and publications on the topics of interest that arise after reading this book.

The science perspectives of BioMEMS include an introduction to molecules of biological interest that are the building blocks of cells and viruses, and also to organic molecules that are involved in the formation of self-assembled monolayers (SAMs), linkers, hydrogels, etc., used for making different surfaces biocompatible through functionalization. The presented engineering perspectives include methods of manufacturing bioactive surfaces and devices, microfluidics modeling and experimentation, and also device level implementation of BioMEMS concepts for different applications. As the field of BioMEMS is application driven, the concepts of lab-on-a-chip (LOC) and micro total analysis system (μTAS) are also discussed, along with their pertinence to the emerging point-of-care (POC) and point-of-need (PON) applications.

This book tries to present both engineering and bioscience topics in a more balanced way. It has nine chapters, with four chapters assigned to science and four chapters assigned to engineering, while the first chapter introduces the readers to many aspects of biomicrosystems, including biological, engineering, application, and commercialization. Chapter 2 deals with different materials and platforms that are used for developing biomicrosystems. Biological entities, including pathogens, are introduced in Chapter 3, in the order of increasing complexities. The multidisciplinary aspects of engineering bioactive surfaces are provided in Chapter 4. Different types and methods of characterizing bioactive surfaces are outlined in Chapter 5, while the fundamentals of biosensing along with methods are given in Chapter 6. Chapter 7 presents the engineering aspects of fabricating

BioMEMS devices, and Chapter 8 introduces different aspects of microfluidics. Different life science applications along with case studies are presented in Chapter 9. With the present organization, it is expected that readers will enjoy not only the topics related to engineering, but also the topics related to the physicochemical understanding of biological processes that are involved in various BioMEMS devices.

The authors thank the graduate students of our Optical Bio Microsystems Laboratory at Concordia for their contribution toward this field. The authors are pleased to publish this book through Taylor and Francis Group.

The Authors

Dr. Simona Badilescu is a senior scientist with a background in physical chemistry and a rich experience in teaching and research. She received her PhD degree from the University of Bucharest (Romania) and specialized in molecular spectroscopy, surface science, and analytical applications of infrared spectroscopy. Dr. Badilescu has several years of experience in an industrial environment as director of the spectroscopy department of a petrochemical company in Romania. After three years of teaching in Algeria as associate professor at the University of Blida, she came with her family to Canada and was a research associate at the Universite de Montréal in the chemistry department. Her research interest focused on vibrational spectroscopy of molecules of biological interest. Since 1987, she has been part of an interdisciplinary group, at the University of Moncton in New Brunswick, working on ATR spectroscopy of thin-film systems. Afterward, she was a professor of chemistry at the University of Moncton in New Brunswick, and later a senior scientist in the physics department. Dr. Badilescu joined the electrical and computer engineering department in 2002, and since then, she has been a part of the Nanomaterials and Devices Laboratory and contributed to different projects related to biosensing. Presently, she is part of the Nanomaterials and Nanodevices Laboratory in the mechanical engineering department. Dr. Badilescu has published two books and several chapters, mainly on topics related to spectroscopy. She is author of more than two hundred articles and conference papers. She is a member of several professional societies and a reviewer for journals such as the *Journal of Physical Chemistry*, *Applied Physics Letters*, *Advanced Materials*, etc.

Muthukumaran Packirisamy is a professor and Concordia research chair on optical BioMEMS in the Department of Mechanical and Industrial Engineering, Concordia University, Canada. He is the recipient of the Fellow and I. W. Smith Award from the Canadian Society for Mechanical Engineers, the Concordia University Research Fellow, the Petro Canada Young Innovator Award, and the ENCS Young Research Achievement Award. His research interests include optical BioMEMS, integration of microsystems, and micro-nano integration.

He obtained his PhD from Concordia University, master's from the Indian Institute of Technology, Madras, India, and bachelor's from the University of Madras, India. He has also worked for many MEMS industries in Canada. He is presently involved with developing BioMEMS devices in collaboration with industries.

An author of more than 225 articles published in journals and conference proceedings, he has nine patents in the area of microsystems.

Contents

Preface...xv
The Authors xvii

Chapter 1 Introduction 1

1.1 Introduction to BioMEMS...1
1.2 Application Areas...2
1.3 Intersection of Science and Engineering...3
1.4 Evolution of Systems Based on Size..3
1.5 Commercialization, Potential, and Market 4
References 8

Chapter 2 Substrate Materials Used in BioMEMS Devices 9

2.1 Introduction 9
2.2 Metals 9
2.3 Glasses and Ceramics...10
2.4 Silicon and Silicon-Based Surfaces...13
2.5 Polymers 14
2.6 Biopolymers..19
2.7 Organic Molecules (Functional Groups) Involved in the Formation of Self-Assembled Monolayers 20
References 22
Review Questions...23

Chapter 3 Biomolecules and Complex Biological Entities: Structure and Properties 25

3.1 Amino Acids..25
3.2 Polypeptides and Proteins 31
3.3 Lipids...35
3.3.1 Fatty Acids and Their Esters...36
3.3.2 Phospholipids 37
3.3.3 Lipoproteins 40
3.4 Nucleotides and Nucleic Acids..42
3.4.1 Nucleotides..42
3.4.2 Nucleic Acids..42
3.4.3 DNA Sensing Strategies...46
3.5 Carbohydrates..47
3.5.1 Introduction 47
3.5.2 Monosaccharides..48
3.5.3 Oligosaccharides and Polysaccharides...48
3.5.4 Biosensing Applications..51
3.6 Enzymes 51
3.6.1 Definition and Nomenclature 51
3.6.2 Mechanism of the Enzymatic Catalysis...52
3.6.3 Catalysis by RNA...53

3.6.4 Applications of Enzymes in Biotechnology and Biosensing 53
3.7 Cells 55
3.7.1 Cellular Organization 55
3.7.2 Cell Movement 57
3.7.3 Whole Cell Biosensors: Applications 60
3.8 Bacteria and Viruses 61
3.8.1 Bacterial Cell Structure 62
3.8.2 Virus Structure 63
3.8.3 Biosensors and BioMEMS Sensor Systems for the Detection of Pathogenic Microorganisms and Bacterial Toxins 64
References 65
Review Questions 66

Chapter 4 Engineering of Bioactive Surfaces 69

4.1 Introduction 69
4.2 Plasma Treatment and Plasma-Mediated Surface Modification 72
4.3 Surface Modifications Mediated by Self-Assembled Monolayers (SAMs) 76
4.4 Langmuir-Blodgett and Layer-by-Layer Assembly 78
4.5 Biosmart Hydrogels 80
4.6 Immobilization and Detection of Biomolecules by Using Gold Nanoparticles: Case Studies 80
4.6.1 Gold Nanoparticles Functionalized by Dextran 80
4.6.2 Gold Nanoparticles in Hybridization Experiments 81
4.6.3 Enhanced Biomolecular Binding Sensitivity by Using Gold Nanoislands and Nanoparticles 81
4.6.4 Study of Antigen-Antibody Interactions by Gold Nanoparticle Localized Surface Plasmon Resonance Spectroscopy 82
4.6.5 Array of Gold Nanoparticles for Binding of Single Biomolecules 83
4.7 Biomimetic Surface Engineering 83
4.8 Attachment of Proteins to Surfaces 85
4.9 Surface Modification of Biomaterials for Tissue Engineering Applications 88
4.10 Temperature-Responsive Intelligent Interfaces 93
References 93
Review Questions 94

Chapter 5 Methods of Study and Characterization of Surface-Modified Substrates 95

5.1 Contact Angle 95
5.1.1 Introduction to Contact Angle and Surface Science Principles 95
5.1.2 Contact Angle Measurement 96
5.1.3 Evaluation of Hydrophobicity of the Modified Surfaces by Contact Angle Measurements: Case Studies 99
5.1.3.1 Sensitivity of Contact Angle to Surface Treatment 99
5.1.3.2 Contact Angle Measurements of Surfaces Functionalized with Polyethyleneglycol (PEG) 100
5.1.3.3 Study of Surface Wettability of Polypyrrole for Microfluidics Applications 100
5.1.3.4 Wetting Properties of an Open-Channel Microfluidic System 100
5.1.3.5 Contact Angle Analysis of the Interfacial Tension 101

5.2 Atomic Force Microscopy (AFM) ... 102
5.2.1 Basic Concepts of AFM and Instrumentation ... 102
5.2.2 AFM Imaging of Biological Sample Surfaces ... 103
5.2.2.1 *Ex Situ* and *In Situ* AFM Characterization of Phospholipid Layers Formed by Solution Spreading (Casting) on a Mica Substrate ... 106
5.2.2.2 Study of Bacterial Surfaces in Aqueous Solution ... 106
5.2.2.3 AFM Study of Native Polysomes of *Saccharomyces* in a Physiological Buffer Solution ... 106
5.2.2.4 Single DNA Molecule Stretching Experiments by Using Chemical Force Microscopy ... 107
5.2.2.5 AFM Measurements of Competitive Binding Interactions between an Enzyme and Two Ligands ... 107
5.2.2.6 Study of Antigen-Antibody Interactions by Molecular Recognition Force Microscopy (MRFM) ... 109
5.2.2.7 Study of Cancer Alterations of Single Living Cells by AFM ... 110
5.3 X-Ray Photoelectron Spectroscopy ... 110
5.3.1 Introduction ... 110
5.3.2 X-Ray Photoelectron Spectroscopy of Biologically Important Materials ... 112
5.3.2.1 Peptide Nucleic Acids on Gold Surfaces as DNA Affinity Biosensors ... 114
5.3.2.2 Application of XPS to Probing Enzyme-Polymer Interactions at Biosensor Interfaces ... 114
5.3.2.3 Detection of Adsorbed Protein Films at Interfaces ... 115
5.4 Confocal Fluorescence Microscopy ... 115
5.4.1 Introduction ... 115
5.4.2 Biological Confocal Microscopy: Case Studies ... 117
5.4.2.1 Bioconjugated Carbon Nanotubes for Biosensor Applications ... 117
5.5 Attenuated Total Reflection (Internal Reflection) Infrared Spectroscopy ... 117
5.5.1 Introduction: ATR-FTIR Basics ... 117
5.5.2 Applications of ATR-FTIR Spectroscopy to Biomolecules and Biomedical Samples: Case Studies ... 119
5.5.2.1 Hydration Studies of Surface Adsorbed Layers of Adenosine-5'-Phosphoric Acid and Cytidine-5'-Phosphoric Acid by Freeze-Drying ATR-FTIR Spectroscopy ... 119
5.5.2.2 Study of the Interaction of Local Anesthetics with Phospholipid Model Membranes ... 119
5.5.2.3 Assessment of Synthetic and Biologic Membrane Permeability by Using ATR-FTIR Spectroscopy ... 120
5.5.2.4 ATR Measurement of the Physiological Concentration of Glucose in Blood by Using a Laser Source ... 120
5.5.2.5 Application of ATR-FTIR Spectroscopic Imaging in Pharmaceutical Research ... 120
5.6 Mechanical Methods: Use of Micro- and Nanocantilevers for Characterization of Surfaces ... 121
References ... 122
Review Questions ... 123

Chapter 6 Biosensing Fundamentals 125
6.1 Biosensors 125
6.1.1 Introduction 125
6.1.2 Classification: Case Studies 129
6.1.2.1 Enzyme-Based Biosensors 130
6.1.2.2 Nucleic-Acid-Based Biosensors 138
6.1.2.3 Antibody-Based Biosensors 140
6.1.2.4 Microbial Biosensors 144
6.2 Immunoassays 145
6.2.1 Introduction 145
6.2.2 Enzyme-Linked Immunosorbent Assay (ELISA) 147
6.2.3 Microfluidic Immunoassay Devices 149
6.2.3.1 A Compact-Disk-Like Microfluidic Platform for Enzyme-Linked Immunosorbent Assay 150
6.2.3.2 Portable Low-Cost Immunoassay for Resource-Poor Settings 151
6.3 Comparison between Biosensors and ELISA Immunoassays 151
References 153
Review Questions 155

Chapter 7 Fabrication of BioMEMS Devices 157
7.1 Basic Microfabrication Processes 157
7.1.1 Introduction 157
7.1.2 Thin-Film Deposition 158
7.1.3 Photolithography 162
7.1.4 Etching 163
7.1.5 Substrate Bonding 164
7.2 Micromachining 166
7.2.1 Bulk Micromachining 166
7.2.2 Surface Micromachining 169
7.2.3 High-Aspect-Ratio Micromachining (LIGA Process) 170
7.3 Soft Micromachining 171
7.3.1 Introduction 171
7.3.2 Molding and Hot Embossing 172
7.3.3 Micro Contact Printing (μCP) 174
7.3.4 Micro Transfer Molding (μTM) 175
7.3.5 Micromolding in Capillaries 175
7.4 Microfabrication Techniques for Biodegradable Polymers 179
7.5 Nanofabrication Methods 182
7.5.1 Laser Processing, Ablation, and Deposition 182
7.5.2 High-Precision Milling 183
7.5.3 Inductively Coupled Plasma (ICP) Reactive Ion Etching 184
7.5.4 Electron Beam Lithography 185
7.5.5 Dip Pen Nanolithography 185
7.5.6 Nanosphere Lithography (Colloid Lithography) 187
7.5.7 Surface Patterning by Microlenses 188
7.5.8 Electrochemical Patterning 189
7.5.9 Electric-Field-Assisted Nanopatterning 190
7.5.10 Large-Area Nanoscale Patterning 190

7.5.11 Selective Molecular Assembly Patterning (SMAP) 192
7.5.12 Site-Selective Assemblies of Gold Nanoparticles on an AFM Tip-Defined Silicon Template 192
7.5.13 Highly Ordered Metal Oxide Nanopatterns Prepared by Template-Assisted Chemical Solution Deposition 193
7.5.14 Wetting-Driven Self-Assembly: A New Approach to Template-Guided Fabrication of Metal Nanopatterns 195
7.5.15 Patterned Gold Films via Site-Selective Deposition of Nanoparticles onto Polymer-Templated Surfaces 195
7.5.16 Nanopatterning by PDMS Relief Structures of Polymer Colloidal Crystals 197
References 199
Review Questions 200

Chapter 8 Introduction to Microfluidics 203

8.1 Introduction 203
8.2 Fluid Physics at the Microscale 204
8.3 Methods for Enhancing Diffusive Mixing between Two Laminar Flows 206
8.4 Controlling Flow and Transport in Microfluidic Channels 211
8.4.1 Physical Processes Underlying Electrokinetics in Electroosmosis Systems 214
8.4.2 Droplet Actuation Based on Marangoni Flows 217
8.4.3 Electrowetting 222
8.4.4 Thermocapillary Pumping 223
8.4.5 Surface Electrodeposition 223
8.5 Modeling Microchannel Flow 224
8.5.1 Introduction 224
8.5.2 The Finite Element Method 229
8.5.3 Simulation of Flow in Microfluidic Channels: Case Studies 229
8.5.3.1 Case 1: Silicon Microfluidic Platform for Fluorescence-Based Biosensing 229
8.5.3.2 Case 2: Numerical Simulation of Electroosmotic Flow in Hydrophobic Microchannels: Influence of Electrode's Position 229
8.5.3.3 Case 3: Prediction of Intermittent Flow Microreactor System 232
8.5.3.4 Case 4: Modeling of Electrowetting Flow 232
8.6 Experimental Methods 234
8.6.1 Flow Visualization at Microscale 234
8.6.2 Fluorescent Imaging Method 235
8.6.3 Particle Streak Velocimetry 237
8.6.4 Particle Tracking Velocimetry 237
8.6.5 Micro Particle Imaging Velocimetry (μPIV) 237
8.6.6 Micro-Laser-Induced Fluorescence (μLIF) Method for Shape Measurements 239
8.6.7 Caged and Bleached Fluorescence 241
References 241
Review Questions 243

Chapter 9 BioMEMS 245

Chapter Life Science Applications 245

9.1 Introduction to Microarrays 246
9.2 Microarrays Based on DNA 247
9.2.1 Introduction to DNA Chips 247
9.2.2 Principles of DNA Microarray: The Design, Manufacturing, and Data Handling 247
9.2.3 Applications of DNA Microarrays 250
9.3 Polymerase Chain Reaction (PCR) 251
9.3.1 Introduction 251
9.3.2 PCR Process 251
9.3.3 On-Chip Single-Copy Real-Time Reverse Transcription PCR in Isolated Picoliter Droplets: A Case Study 257
9.4 Protein Microarrays 258
9.4.1 Introduction 258
9.4.2 Fabrication of Protein Microarrays 262
9.4.3 Applications of Protein Arrays 267
9.5 Cell and Tissue-Based Assays on a Chip 267
9.6 Microreactors 272
9.6.1 Introduction 272
9.6.2 Microchannel Enzyme Reactors 273
9.6.3 Enzymatic Conversions: Case Studies 274
9.6.3.1 Glycosidase-Promoted Hydrolysis in Microchannels 274
9.6.3.2 Lactose Hydrolysis by Hyperthermophilic β-Glycoside Hydrolase with Immobilized Enzyme 277
9.6.3.3 Photopatterning Enzymes inside Microfluidic Channels 277
9.6.3.4 Integrated Microfabricated Device for an Automated Enzymatic Assay 280
9.6.3.5 Silicon Microstructured Enzyme Reactor with Porous Silicon as the Carrier Matrix 280
9.6.3.6 Enzymatic Reactions Using Droplet-Based Microfluidics 281
9.6.4 Synthesis of Nanoparticles and Biomaterials in Microfluidic Devices 283
9.6.5 Microfluidic Devices for Separation 283
9.6.5.1 Separation of Blood Cells 285
9.6.5.2 Cell or Particle Sorting 286
9.7 Micro Total Analysis Systems (μTAS) and Lab-on-a-Chip (LOC) 288
9.8 Lab-on-a-Chip: Conclusion and Outlook 295
9.9 Microcantilever BioMEMS 295
9.9.1 Introduction 295
9.9.2 Basic Principles of Sensing Biomechanical Interactions 296
9.9.3 Detection Modes of Biomechanical Interactions 301
9.9.3.1 Static Mode 301
9.9.3.2 Dynamic Mode 303
9.9.4 Location of Interaction in the Case of Mass-Dominant BioMEMS Devices 305
9.9.5 Location of Interaction for Stress-Dominant BioMEMS Devices 305
9.9.6 Fabrication and Functionalization of Microcantilevers 307

9.9.6.1 Case 1: Detection of Interaction between ssDNA and the Thiol Group Using Cantilevers in the Static Mode 308
9.9.6.2 Case 2: Specific Detection of Enzymatic Interactions in the Static Mode 308
9.9.6.3 Case 3: Detection of Enzymatic Interactions in the Dynamic Mode 311
References 312
Review Questions 315

Index 317

1 Introduction

1.1 INTRODUCTION TO BIOMEMS

The term *microelectromechanical systems* (MEMS) was coined in the 1980s to define devices that were fabricated using microfabrication techniques and whose primary function was not electronic but mainly mechanical. Within a short span of time, the field of MEMS exposed its immense potential to impact every aspect of human life.

A variety of areas, like aerospace, communication, medical, sensing, and actuation, started enjoying the advantages of miniaturization with MEMS technology or microsystem technology. As a result, the field of MEMS evolved into an enabling technology in the mid-1990s and gave rise to the creation of many subdisciplines, such as optical MEMS, radio frequency (RF) MEMS, power MEMS, etc., depending upon the focus of application. In this line, the field of BioMEMS was created with a focus on biological and chemical applications.

The concept of integrating biochemical analysis with microelectromechanical systems (MEMS) is involved in the new field of BioMEMS, which is undergoing tremendous growth in a multitude of applications. The applications spectrum covers from tissue engineering to proteomics. Some of the applications include cell culture, cell sorting, cell manipulation, stem cell growth, separation and mixing of biological and chemical fluids, enzymatic reactions and gene isolation and transformation, DNA purification, antigen-antibody interaction, protein level interaction, drug diagnosis and delivery, therapeutics, chemical and biosensing, etc. The important recent applications include point-of-care (POC) *in vitro* diagnostics, and synthesis of nanoparticles using BioMEMS.

The field of BioMEMS inherits all the advantages of miniaturization, such as small sample volume, scalability, integration of multiple functions and fields, low cost, low power consumption, etc. As a result, the microsystems facilitate the implementation of many laboratory works at the microchips that are millimeters to centimeters in size. Some of the standard laboratory tasks that can be implemented under a microenvironment include sample preparation, mixing, separation, diagnosis, sensing, manipulation, control, delivery, data acquisition, and analysis. When some of the laboratory functions out of a process are integrated at the microchip, the devices are called *lab-on-a-chip* (LOC). The concept of LOC was demonstrated by S. C. Terry et al. in 1979[1] with the development of a silicon-chip-based gas chromatographic analyzer. Manz et al.[2] introduced the concept of *micro total analysis system* (μTAS) in 1990, by developing a device that conducts all the steps of a process. μTAS is generally considered to incorporate all the operations needed in a process, involving sample preparation. Even though μTAS is a subset of LOC, it involves many functions and integrates many domains, such as micromechanical, microfluidic, microelectronics, microphotonics, etc. μTAS can also integrate moving elements, such as micropumps, microvalves, etc. LOC and μTAS will be used interchangeably in this book. Biomedical technologies contribute to the use of LOCs in healthcare of various specialties, ophthalmology, cardiology, anesthesiology, and immunology. For example, such LOCs combine a number of biological functions, such as enzymatic reactions, antigen-antibody conjugation, and DNA/gene probing, in addition to microfluidic function, such as sample dilution, pumping, mixing, metering, incubation, separation, and detection in micron-sized channels and reservoirs. Lab-on-a-chip devices aim to address a wide range of life science applications, including drug discovery and delivery as well as clinical and environmental diagnostics. The integration and automation capabilities of LOC can improve the reproducibility of results, reduce test time, and eliminate preparation errors that may occur in the intermediate stages of an analytical procedure.

BioMEMS devices are defined as the devices or microsystems that are fabricated with methods inspired from micro- and nanotechnologies and are used for many processes involving biological and chemical species.[3]

BioMEMS may involve in-parts or a combination of (1) microchannels, microchambers, etc., for handling a small volume of liquids in the range of microliters to nanoliters; (2) micromechanical elements, such as microvalves, micropumps, microcantilevers, microdiaphragms, etc.; (3) micro-electrical elements such as electrodes and heaters; and (4) microphotonic elements, such as wave-guides, gratings, interferometers, etc., to handle bio or chemical species with an elaborate integration feasibility. BioMEMS offers the following advantages: portability, scalability, reliability, reduced sample/reagent volume, low power consumption, high throughput, integrability, disposability, batch fabrication, low cost, high sensitivity, reduced test time, etc. BioMEMS devices combine a biological recognition system called a *bioreceptor* with a physical or chemical *transducer* to selectively and quantitatively detect the presence of specific compounds in a given external environment. A bioreceptor is a biological molecular species (e.g., antibody, enzyme, protein, or nucleic acid) or a living biological system (e.g., cells, tissue, or whole organisms) that undergoes a biochemical mechanism for recognition. The interaction of an analyte with a bioreceptor produces an effect to be measured by the transducer, which converts the information into a measurable effect, such as an electrical or optical signal.

Lab on a chip is characterized by some level of integration of different functions, and it can be used to perform a combination of analyses on a single miniaturized device, for biological and clinical assays. Most of the key application areas of this technology belong to the areas of life science research (genomics, pharmacogenomics, and proteomics), drug delivery, and point-of-care diagnostics, and they offer the advantages of integrating sample handling and preparation, mixing, separation, lysing of cells, and detection.

Biosensors and *biochips* can be classified by either their bioreceptor or their transducer type. Comprised of microarrays of genetic, protein, or cellular materials on microfluidic devices, these miniature platforms can perform parallel analysis of large data. Lab-on-a-chip can integrate many operations, including sample preparation, detection, and analysis on a single chip. It is also useful in drug discovery, target identification and validation, toxicology, and clinical drug safety.

1.2 APPLICATION AREAS

Research in BioMEMS covers a wide range, from diagnostics, DNA, and protein microarrays, to novel materials for BioMEMS, microfluidics, surface modification, etc. In addition, BioMEMS also finds many applications in the chemical, healthcare, biotechnological, and manufacturing industries.

The emerging applications for BioMEMS include agricultural and food engineering areas. DNA microarrays have become the most successful example of the integration among micro-electronics, biology, and chemistry. Similarly, protein and antibody arrays can identify disease-specific proteins with enormous medical, diagnostic, and commercial potential as disease markers or drug targets. With the recent thrust in genomics and proteomics technologies, many new gene products and proteins are being discovered almost daily, and it has become a difficult task to analyze experimental data. In such situations, array-based integrated BioMEMS chips and microfluidics hold great potential to analyze systematically the proteins and to determine protein-protein or protein-DNA interactions. In the case of protein chips, protein is arrayed into many spots using robots, and each spot is addressed by other affinity proteins. The binding between recognized proteins or antigen-antibody has traditionally been detected by fluorescence-based methods. But it can also be detected by changes in surface plasmon resonance (SPR) due to changes in surface refractive index, or in a mechanical way of detecting the changes in structural properties due to interaction. For example, enzyme-linked immunosorbent assay

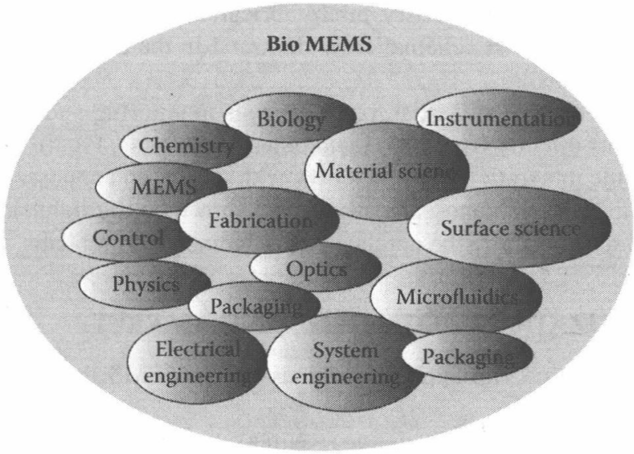

FIGURE 1.1 BioMEMS at the intersection of science and engineering.

(ELISA) type assays use selective bonding to antibodies immobilized on microfabricated surfaces and detect the bioaffinity binding using electrical or optical detectors. Several accomplishments in using BioMEMS with various modes of detection technologies have been reported. A current goal of BioMEMS research is identification and manipulation at the molecular/cellular level. Microfluidics based lab-on-a-chip devices has proved useful for realizing single molecule/cell detection also.

1.3 INTERSECTION OF SCIENCE AND ENGINEERING

The BioMEMS devices are made of silicon, glass, or polymer materials to produce highly functional miniaturized devices. A major driving force behind this is the rapidly emerging biochip market, wherein original MEMS techniques are integrated with advanced techniques from molecular biology, physics, chemistry, and data analysis, as shown in Figure 1.1.

Expansion of the biochip sector is predicted to be one of the key drivers for the growth of the microsystems market, and to have a profound impact on many aspects of life science industries. BioMEMS chips also promise to be among the most important pharmaceutical research and development tools in the postgenomic era.

Diagnostics applications form the largest part of BioMEMS applications. A very large and increasing number of BioMEMS devices for diagnostic applications have been developed and presented in the literature by many groups within the last decade. These devices are used to detect cells, microorganisms, viruses, proteins, DNA and related nucleic acids, and many small molecules of biochemical interest. BioMEMS devices for cell characterization will greatly contribute toward the development of new diagnostics and therapies. Cellular analysis will provide many benefits, including increased sensitivity for early detection of diseased conditions and lab-on-a-chip devices for faster analysis, lower cost, and efficient drug discovery.

1.4 EVOLUTION OF SYSTEMS BASED ON SIZE

One could consider the biological species like protein molecules, cells as tiny machines or mechanisms that produce low signals when they interact with the environment or other bio species. This necessitates the use of structures or devices of similar dimensional scale with the possibility of tuning their properties in order to increase the sensitivity and throughput while reducing the sample volume and cost. Hence, the use of BioMEMS becomes imminent for biological and chemical applications. As a result, BioMEMS devices could serve as a complete laboratory-on-a-chip,