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John X. J. Zhang
Kazunori Hoshino

MOLECULAR SENSORS AND NANODEVICES

Principles, Designs and Applications in Biomedical Engineering

Micro & Nano Technologies Series

Molecular Sensors and Nanodevices

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Molecular Sensors and Nanodevices

To Ting, Michael and Lauren

for the love, fun and bringing out the teacher in me

— **John X.J. Zhang**

About the Authors

John X.J. Zhang

Xiaojing (John) Zhang is an Associate Professor in the Department of Biomedical Engineering at the University of Texas of Austin (UT Austin). He received his Ph.D. from Stanford University, California, and was a Research Scientist at Massachusetts Institute of Technology (MIT) before joining the faculty at UT Austin.

Dr. Zhang's research focuses on integrating Micro-electro-mechanical Systems (MEMS), nano-materials, micro-imaging and biosensors to provide innovative solutions to critical healthcare issues. Dr. Zhang has actively engaged in teaching new concepts and methods in these emerging biomedical engineering frontiers and has demonstrated innovation and excellence in engineering education. The materials presented in this textbook are based on his lecture notes while teaching a popular course on molecular sensors and nanodevices at UT Austin for the past 8 years.

He has a track record for developing both core and emerging engineering curriculum along with developing well-funded research programs with fellow students. Among his numerous awards, Dr. Zhang received the Wallace H. Coulter Foundation Early Career Award in Biomedical Engineering, NSF CAREER award, DARPA Young Faculty Award among many others. To recognize his accomplishment in research and education, Dr. Zhang was selected to attend the prestigious US National Academy of Engineering, Frontiers of Engineering (NAE FOE) program in 2011, the NAE Frontiers of Engineering Education (NAE FOEE) program in 2012, and subsequently China-America Frontiers of Engineering Symposium (CAFOE) program in 2013.

As an active member in his professional community, Dr. Zhang has served on numerous international conference organizing committees and editorial boards. He is an editor for *ASME/IEEE Journal of Microelectromechanical Systems (JMEMS)* and an associate editor *Biomedical Microdevices*.

Kazunori Hoshino

Kazunori Hoshino received his PhD degree in mechanical engineering from the University of Tokyo, Tokyo, Japan, in 2000. He worked for the University of Tokyo from 2003 to

2006 as a lecturer in the Department of Mechano-Informatics, School of Information Science and Technology, where he conducted several government funded project as the principal investigator. In 2006, he joined the University of Texas at Austin, where he works as a Senior Research Associate in the Department of Biomedical Engineering.

His research interests are (1) NEMS/MEMS-based nanophotonic sensing and imaging systems and (2) microfluidic detection, imaging, and analysis of cancer cells. He has more than 100 peer reviewed publications in top international journals and conferences in the field of sensors, micro-electro-mechanical system (MEMS), and micro total analytical systems (μTAS). He is the inventor of 6 issued US patents and 12 issued Japanese patents. The courses he has taught at the University of Tokyo and the University of Texas at Austin include: molecular sensors and nanodevices, intelligent micro-electro-mechanical systems, digital control systems, and engineering mathematics.

Preface

Whether you are an undergraduate or graduate student, researchers, industrial professions or medical practitioners, you will find a body of enjoyable and useful information within the covers of this book. The comprehensive coverage of fundamental concepts, practical approach and use of case studies makes this book essential reading for a wide range of scientists and engineers using and evaluating molecular sensors and nanodevices across a variety of research settings and industry sectors. With detailed descriptions of principles and the end of chapter problems, it serves as an ideal textbook in engineering, biomedicine and interdisciplinary fields related to biomedical engineering.

In this book, we define the major categories of traditional and state of the art molecular sensors, and discuss details of the background, functions, structures and the sensing requirements towards the applications. The advent of the nanotechnologies has provided unlimited possibilities for molecular sensors design and applications, but the fast moving frontiers have also made it a daunting task for learners to capture the essential design principles and methods behind the implementations. This book aims to show a clear outline and detailed analysis on the technology of molecular sensors in the context of contemporary and future nanotechnology in biomedicine. The book is composed of the following seven chapters. **Chapter 1: Introduction to molecular sensors.** We will introduce fundamental concepts of the molecular sensor, the capture and recognition mechanism, and the sensor signal transduction. First, we define molecular sensors and describe their applications and performances. We will explain how recognition agents such as DNAs and antibodies work in a sensing system. We will also outline transduction technologies which will be detailed in chapter 4, 5 and 6. Finally, we will introduce the interesting use of animals as molecular sensors. There are many well-known sensing applications which utilize animals as detectors, processors, and outputs. Studies of animal-based sensors not only show us the sensing mechanism, but also provide vital insights into the future of man-made molecular sensors and their sensing requirements. **Chapter 2: Introduction to Nano/ Microfabrication.** The key technology that has enabled realization of modern intelligent devices is nano/microfabrication. Introduction of nano/microfabrication has expanded the possibilities for more versatile, miniaturized molecular sensors. We start the chapter from discussion on the benefits of system miniaturization by introducing the effect of size and shape in molecular sensing. We will then describe basic silicon microfabrication techniques including film deposition, photolithography, and wet and dry etching. We discuss design theories and fabrication techniques of a microelectrostatic actuator as a basic model element of microelectromehcanical systems (MEMS). We then introduce techniques of "soft lithography," where several novel materials including polymers, proteins, DNAs and other nanomaterial are implemented into molecular sensors. **Chapter 3: Microfluidics basics and total analytical systems.** Handling of carrier and analyte fluids is critical in many molecular sensing systems. Microfluidics enables control of small volumes in the range of nano- to microliters. The reduction of analyte volume can dramatically improve the reaction rate of conventional assays which are otherwise costly to automate and require extensive human intervention to complete. Smaller immunoassay platforms also use less power and allow sample preparation and analysis steps to be coupled together in an automatic streamlined process. We will start with fundamental theories of diffusion and fluid dynamics that govern the reaction processes in molecular sensors. It is followed by introduction of important applications of microfluidic bioassays, including immunoassay, cell separation, and DNA amplification and analysis. Emphasis is put on the authors' main areas of expertise, detection and analysis of cancer cells. **Chapter 4: Electrical transducers: electrochemical sensors and FET-based sensors.** We describe the fundamental principles and important applications of electrical transduction-based molecular sensors. The first part is a description of electrochemical measurements, followed by an introduction of important applications such as ion and gas sensors. The second part introduces the basics of semiconductors. We explain how semiconductor materials can be used as fundamental elements of integrated circuits, followed by an introduction of silicon field effect transistor (FET)-based molecular sensors. We also introduce FET molecular sensors based on novel nanomaterials such as organic thin films, polymers, carbon nanotubes, and graphene. **Chapter 5: Optical transducers: optical molecular sensors and optical spectroscopy.** We describe molecular sensors based on optical transduction. We explain the basics of electromagnetic waves which begin with Maxwell's equations. We then proceed to principles of optical guiding, which is the basis of many optical molecular sensors such as surface plasmon resonance (SPR) sensors and waveguide sensors. Another important part of the chapter is the introduction of optical spectroscopy. Optical microscopy and spectroscopy are cornerstones of modern life sciences. We describe theories and practices of optical absorption, scattering and fluorescence, along with details of important microscopy techniques. **Chapter 6: Mechanical transducers: cantilevers, acoustic wave sensors and thermal sensors.** We describe sensors that utilize mechanical structures for transduction. Binding events are detected using two general strategies: by detecting mechanical deflections induced by molecular binding or by detecting added mass as the change in resonant frequency. We start from sensors based on a mechanical cantilever, which is the fundamental building element of many mechanical structures. Structural analysis of a cantilever is included in the theoretical study. We then introduce acoustic sensors that rely on measurement of mechanical waves for detection of molecular binding.

Based on the piezoelectric effect, acoustic sensors transduce change in mechanical oscillations into measureable electrical signals. At the end of the chapter we introduce principles and applications of thermal sensors for biomedical applications. **Chapter 7: Implantable sensors.** We describe practical applications of miniaturized implantable sensors. The continual breakthroughs in device theory, design and fabrication methods have enabled engineers to implant smaller and smaller sensors into the human body. Sensing applications for human implanted biochips have been an increasingly popular field of research. First, we introduce the principles and the design of implantable pacemakers, which is one of the most important practical examples among existing implantable systems. Then we introduce recent studies that incorporate nano/ microfabrication in an attempt in create highly integrated multifunctional implantable systems. Such systems include microelectodes for electrochemical analysis, pressure sensors for blood monitoring, and techniques for energy harvesting. Finally, we discuss issues related to materials, designs, and use of implantable systems.

Throughout the book, some of the key features include:

- Reviews of state-of-the-art molecular sensors and nanotechnologies
- Explains principles of sensors and fundamental theories with homework problems at the end of each chapter to facilitate learning
- Demystifies the vertical integration from nanomaterials to devices design
- Covers practical applications the recent progress in state-of-the-art sensor technologies.
- Includes case studies of important commercial products
- Covers the critical issues of implantability, biocompatibility and the regulatory framework

On more personal notes, the inspiration for this book arose from many years of teaching experience of a popular course on molecular sensors and nanodevices at UT Austin. A rich set of lecture notes were developed, but the desire to have a textbook has grown stronger year by year. It can be clearly felt across the lecture room to enlighten and instill a greater appreciation of the fundamentals about a seemingly diverse subject and to inspire students to explore its fascinating, and almost infinite, applications. The mission of our writing is therefore to provide a comprehensive learning experience of the current and emerging technologies of molecular sensing, explaining the principles of molecular sensor design and assessing the sensor types currently available. We describe the role of nano/micro fabrication techniques in molecular sensors, including MEMS, BioMEMS, MicroTAS, and Lab on a Chip technologies. The miniaturization of versatile molecular sensors opens up a new design paradigm and a range of novel biotechnologies, which is illustrated through case studies of groundbreaking applications in the life sciences and elsewhere. The book is also aimed at a broader audience of engineering professionals, life scientists and students working in the multidisciplinary area of biomedical engineering. It explains essential principles of electrical, chemical, optical and mechanical engineering as well as biomedical science, intended for readers with a variety of scientific backgrounds. In addition, since each chapter contains discussions on practical applications and limitations of the sensors, it will be valuable for medical professionals and researchers. An online tutorial developed by the authors provides learning reinforcement for students and professionals alike.

Through these pages, we hope the readers will also appreciate just how profound the influence of these molecular sensors and small scale systems to our lives. The book also explores some of the most exciting frontiers at the interfaces of modern science, engineering and medicine, and the opportunities they present to young generation of students and engineers for future careers. New generation of functional microsystems can be designed to provide a variety of small scale sensing, imaging and manipulation techniques to the fundamental building blocks of materials. There is so much yet to be discovered and invented by the future leaders in science and technology, who choose to aim their minds and chisels towards exploring the almost infinite number of yet undiscovered land of molecular sensors and nanodevices.

Acknowledgement

This manuscript would not have come into shape without the great inspiration and help from many colleagues, who shared their experiences and insights with us throughout the writing of this book.

We would like a special note of appreciation to go to the students in the BME 354 Molecular Sensors and Nanodevices class at UT Austin, who have contributed though their active participation in our lectures over the years. They help expand the technical content through the interactive learning, timely presentations on recent publications and the identifications of emerging commercial systems based on molecular sensors and nanotechnologies. Cumulatively, the effort provided technical information that greatly strengthened the breadth and depth of our book.

The past and current members of the Zhang research group helped refining the content and providing detailed suggestions. Follow the sequence of the book chapters, Elaine Ng helped refine chapter 1, 2, 3 and 7, Kaarthik Rajendran helped refine chapter 1 and 3. Yu-Yen Huang and Gauri Bhave helped on the section of microfabrication in cleanroom facilities. Peng Chen provided summary of the methods on cancer cell separation. Dr. Dajing Chen and Nick Triesault reviewed the technical writing of chapter 4. Taewoo Ha and Youngkyu Lee provided the comments on the optics and surface plasmons in chapter 5. Dr. Tushar Sharma and Sahil Naik shared their knowledge on the theories and practices of implantable sensors in chapter 7. In addition, Dr. Ashwini Gopal and Dr. Eiji Iwase helped review the content of the book to further polish the content of our book. Our appreciation also goes to the colleagues whose names we may miss here. Together, we hope this book will reflect your contributions towards better serve the need of our community.

Our particular appreciation also goes to the editorial team at Elsevier. We enjoyed the productive collaborations, which brought a seemingly endless writing process to a successful end. In particular, we thank Wayne Yuhasz, Frank Hellwig and Matthew Deans for their expertise and experience in scientific publishing.

Finally, we see this book as the beginning of a journey for learning. While much of the materials are time-independent, we expect that frequent updates of certain areas such as applications will be desirable. Also, materials that could not be completely covered in the book because of space limitations, such as additional appendix, emerging concepts and methods, and end of chapter problems, should be of interest to some readers.

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