Vijay K. Varadan, Linfeng Chen, Jining Xie

Nanomedicine

Design and Applications of Magnetic Nanomaterials, Nanosensors and Nanosystems

WILEY

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DESIGN AND APPLICATIONS OF MAGNETIC NANOMATERIALS, NANOSENSORS AND NANOSYSTEMS

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NANOMEDICINE

Preface

Progress in nanoscience and nanotechnology has led to the development of a new field, nanomedicine, which is generally defined as the biomedical applications of nanoscience and nanotechnology. Nanomedicine stands at the boundaries between physical, chemical, biological and medical sciences, and the advances in nanomedicine have made it possible to analyze and treat biological systems at the cell and sub-cell levels, providing revolutionary approaches for the diagnosis, prevention and treatment of some fatal diseases. For example, the *US National Cancer Institute* expects that nanoscience and nanotechnology will be harnessed for the purposes of eliminating death and suffering from cancer. Many nanomedicine approaches are already quite close to fruition, and the *US Food and Drug Administration* has started to consider the complex issues related to the approval of nanomaterials, nanodevices and nanosystems, for human betterment.

Nanomagnetism is at the forefront of nanoscience and nanotechnology, and in the field of nanomedicine, magnetic nanomaterials are among the most promising nanomaterials for clinical diagnostic and therapeutic applications. The magnetic nanomaterials used for biomedical purposes generally include zero-dimensional nanospheres, one-dimensional nanowires and nanotubes, and two-dimensional thin films. Magnetic nanoparticles, mainly including nanospheres, nanowires and nanotubes, are widely used for labeling and manipulating biomolecules, targeting drugs and genes, magnetic resonance imaging, as well as hyperthermia treatment. Magnetic thin films are often used in the development of nanosensors and nanosystems for analyzing biomolecules and diagnosing diseases.

Due to the great market potential of nanomedicine, many universities, research institutions, hospitals, commercial companies and government organizations have spent a great deal of resources in the research of magnetic nanomaterials for biomedical applications, and amazing progress has been made in this field. Some magnetic nanoparticles and nanosensors are already commercially available. Some medical applications of magnetic nanoparticles and nanosensors are under clinical trials, and encouraging results have been reported.

Despite the rapid progress in nanomedicine, we are aware of the lack of good reference books in the field of magnetic nanomaterials and their biomedical applications. Though there are excellent reviews, book chapters, and books dealing with one or several topics in this field, a book containing a comprehensive coverage of up-to-date progress in this field is not available. The research in this field requires the collaboration between researchers from different disciplines, such as physics, chemistry, materials sciences, electrical engineering, biology and medicine. However, such cross-disciplinary cooperation is not easy. For example, the languages and the tools used by materials scientists are unfamiliar to many medical experts, and vice versa. Furthermore, the ways in which physicists and biologists, or chemists and cancer researchers, think about a biomedical problem may be totally different. Therefore a book, based on which the researchers with different backgrounds can communicate, is urgently needed.

Besides, due to the lack of a reference book that can provide a broad coverage and deep insight into this field, most research activities are based primarily on the information scattered throughout numerous reports and journals. Furthermore, because of the paucity of suitable textbooks, the training in this field is usually not systematic, and this is unfavorable for the further progress in this field.

This book aims to present a comprehensive treatment of this subject. It systematically discusses the synthesis techniques, the physical and chemical properties, and the working principles for biomedical applications of various types of magnetic nanomaterials. We aim to satisfy the need of a textbook for beginners and research students, and a reference book for professionals in this field. With such a book, beginners and research students can quickly obtain an overall picture of this field. Meanwhile, this book bridges the gaps between researchers from different disciplines, so that they can speak the same language, and get their ideas across to each other. The clinical doctors who are interested in this area will also find this book valuable.

The book mainly consists of three parts. The introductory part (Chapters 1 and 2) gives general information about magnetic nanomaterials and their biomedical applications, and provides the physical background for understanding and exploring the biomedical applications of magnetic nanomaterials. The second part (Chapters 3 to 7) deals with various types of magnetic nanoparticles and their biomedical applications. Chapters 3 and 4 discuss the synthesis, properties and biomedical applications of magnetic nanospheres. In Chapter 5, a special type of magnetic nanoparticle and magnetosomes that naturally exist in magnetotactic bacteria are discussed. Chapters 6 and 7 discuss the synthesis, properties and biomedical applications of nanowires and nanotubes, respectively.

The third part (Chapters 8 to 10) discusses the development of biosensors, biochips, and their biomedical applications, with emphases laid on the sensing effects of magnetic thin films. Chapter 8 discusses the development of magnetic biosensors widely used in biomedical tests, mainly including magnetoresistance-based sensors, Hall-effect sensors, sensors detecting magnetic relaxations, and sensors detecting susceptibilities of ferrofluids. Chapter 9 mainly discusses the development of magnetic biochips based on the magnetic biosensors discussed in Chapter 8. Chapter 10 discusses the typical biomedical applications of magnetic biosensor and biochip technologies. In these applications, magnetic biosensors and biochips are mainly used to detect the biomolecules labeled by magnetic nanoparticles. An outlook for the biomedical applications of magnetic biosensor and biochip technologies is made at the end of this chapter.

In this book, the interdisciplinary nature of nanomedicine is emphasized. We take bits and pieces from the contributing disciplines and integrate them in ways that produce a new conceptual framework. To make the book readable, the contents of the book are systematically and logically developed from the elementary level. Each chapter presents one of the major topics in the development of functional magnetic nanomaterials and their biomedical applications, and contains a brief introduction to the basic physical and chemical principles of the topic under discussion. Therefore, each chapter is a self-contained unit, from which readers can readily obtain comprehensive information on this topic. To provide an extensive treatment of each topic, we have condensed mountains of literature into a readable account within a reasonable size. Important references have been included for the benefit of the readers who wish to pursue further their interested topics in a greater depth.

In preparing the book, we have tried to emphasize the fundamental concepts. Though a considerable amount of the contents in this book is related to experimental details and results, we have tried to present the underlying sciences so that the readers can understand the process of applying fundamental concepts to design experiments and obtain useful results.

It should be indicated that, due to the rapid development of this field, and its interdisciplinary nature, a truly comprehensive coverage is difficult, and some important work in this field may have been missed. It is also difficult to always give proper credit to those who are the originators of new concepts and the inventors of new techniques. The summary and commentary we have written may not have grasped the essentials of the work under discussion. We hope this book does not have too many such errors, and we would appreciate it if readers could bring the errors they discover to our attention so that these can be corrected in future editions.

We would like to acknowledge the contributions made by the students and staff at the *Center of Excellence for Nano/Neuro Sensors and Systems (CENNESS)*, University of Arkansas, Fayetteville, including the contributions from Jose Abraham in Chapters 9 and 10.

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Vijay K. Varadan is currently the Twenty-First Century Endowed Chair in Nano-and Bio-Technology and Medicine, and Distinguished Professor of Electrical Engineering and Distinguished Professor of Biomedical Engineering (College of Engineering) and Neurosurgery (College of Medicine) at University of Arkansas. He is also a Professor of Neurosurgery at the Pennsylvania State University College of Medicine. He joined the University of Arkansas in January 2005 after serving on the faculty of Cornell University, Ohio State University and Pennsylvania State University for the past 32 years. He is also the Director of the Center of Excellence for Nano-, Micro- and Neuro-Electronics, Sensors and Systems and the Director of the High Density Electronics Center. He has concentrated on the design and development of various electronic, acoustic and structural composites, smart materials, structures, and devices including sensors, transducers, Microelectromechanical Systems (MEMS), synthesis and large-scale fabrication of carbon nanotubes, NanoElectroMechanical Systems (NEMS), microwave, acoustic and ultrasonic wave absorbers and filters. He has developed neurostimulator, wireless microsensors and systems for sensing and control of Parkinson's disease, epilepsy, glucose in the blood and Alzheimer's disease. He is also developing both silicon and organic based wireless sensor systems with RFID for human gait analysis and sleep disorders and various neurological disorders. He is a founder and the Editor-in-Chief of the Journal of Smart Materials and Structures. He is the Editor-in-Chief of the Journal of Nanomedical Science in Engineering and Medicine. He is an Associate Editor of the Journal of Microlithography, Microfabrication and Microsystems. He serves on the editorial board of International Journal of Computational Methods. He has published more than 500 journal papers and 13 books. He has 13 patents pertinent to conducting polymers, smart structures, smart antennas, phase shifters, carbon nanotubes, an implantable device for Parkinson's patients, MEMS accelerometers and gyroscopes. He is a fellow of SPIE, ASME, Institute of Physics and Acoustical Society of America. He has many visiting professorship appointments in leading schools overseas.

Linfeng Chen received his B.Sc. degree in modern applied physics (major) and his B.Eng. degree in machine design and manufacture (minor) from the Tsinghua University, Beijing, China, in 1991, and he received his Ph.D. degree in physics from the National University of Singapore in 2001. From 1991 to 1994, he was an Assistant Lecturer in the Department of Modern Applied Physics, Tsinghua University. From 1994 to 1997, he was a Research Scholar with the Department of Physics, National University of Singapore. In 1997, he joined the Singapore DSO National Laboratories, as a project engineer, and two years later, he became a Member of Technical Staff. From 2001 to 2005, he was a research scientist at the Temasek Laboratories, National University of Singapore. Since July 2005, he has been a member of the research faculty at the High Density Electronics Center, University of Arkansas, Fayetteville. He is senior member of IEEE. His research interests mainly include microwave electronics, electromagnetic functional materials and magnetic nanomedicine.

Jining Xie received his Bachelor of Engineering degree in Chemical Engineering from Tsinghua University, Beijing, China in 1997 and received his Ph.D. degree in Engineering Science from the Pennsylvania State University, University Park in 2003. He continued as a postdoctoral research fellow at the Center for the Engineering of Electronic and Acoustic Materials and Devices (CEEAMD), Pennsylvania State University. In 2005, he joined the department of Electrical Engineering, University of Arkansas, Fayetteville, as a Research Assistant Professor. His research interests include chemical synthesis, surface modifications and characterizations of micro-/nano-materials and their applications in the field of biosensors, electrodes, neuron science, etc. He is a member of MRS and IEEE. He has published over 40 technical papers in journals and conferences. He also serves as a paper reviewer for eight journals.

Contents

1

Introduction

1.1 What is Nanoscience and Nanotechnology?

In the lexicology of science and technology, the prefix 'nano' refers to one-billionth of a unit. For example, one nanometer (nm) is one billionth (10^{-9}) of a meter. The nanometer scale is the natural spatial context for molecules and their interactions. Nanoscience and nanotechnology deal with the objects at the nanometer scale (National Science and Technology Council 1999a). The properties and functions of objects at the nanometer scale are significantly different from those at a larger scale. Generally speaking, nanoscience investigates the properties of materials at atomic, molecular and macromolecular scales, while nanotechnologies deal with the design, production and application of devices and systems by controlling their shapes and sizes at the nanometer scale (Royal Society and Royal Academy of Engineering 2004).

Biology is one of the most active fundamental sciences, and it is also a science that is the most visible to the public. The need for improvement in medicine for the treatment of disease or, in a general sense, for the amelioration, correction and prevention of dysfunction in health, will never disappear (Whitesides and Wong 2006). The combination of biology and medicine, generally referred to as 'biomedicine', represents a most exciting blend of science and technology. The nanoscale provides a junction for biomedicine and materials science and technology. This book discusses the developments in nanoscience and nanotechnology and their applications in biomedicine.

1.1.1 Nanoscale: Where Physical and Biological Sciences Meet

As indicated in Figure 1.1, nanoscale is generally defined as the range from the size of atoms up to 100 nanometers, and a nanomaterial is usually defined as a material whose smallest dimension is less than 100 nanometers (Yih and Wei 2005). In a general sense, nanomaterials include all the structures, devices and systems at nanoscale. In some cases the size limit of a nanomaterial can be extended up to 1000 nm, and the essential point is that a nanomaterial exhibits unique properties that are quite different from those at a larger scale.

In Figure 1.1, a lot of biological entities are within the range of nanoscale, such as proteins, antibodies, viruses and bacteria, and they are usually called biological nanomaterials. The special functions and properties of biological nanomaterials provide much inspiration for the design of non-biological nanomaterials; meanwhile, due to their suitable sizes, non-biological nanomaterials can be used to access or manipulate biological nanomaterials (Yih and Wei 2005). Nanomaterials with sizes smaller than 50 nm can get

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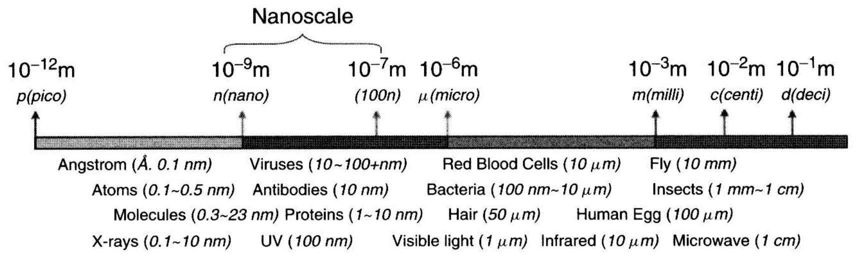

Figure 1.1 Nanoscale and typical materials whose dimension ranges are comparable to nanoscale. (Yih and Wei 2005)

inside most cells without difficulty. When nanomaterials with sizes smaller than 20 nm travel around the circulatory system of the body, they can move out of blood vessels. Therefore, after special treatments, nanomaterials are widely used as targeted drug delivery vehicles, which carry chemotherapeutic agents or therapeutic genes into the desired malignant cells while saving healthy cells. It should be noted that, in most of the technical literatures, nanomaterials are usually referred as non-biological nanomaterials, though biological entities and biological techniques have been widely used in the design and synthesis of non-biological nanomaterials.

The biological and physical sciences share a common interest in nanoscale, and the integration of biology and materials at the nanoscale has the potential to revolutionize many fields of science and technology. A vigorous trade across the borders of these areas exists in the development of new materials and tools, and the investigation of new phenomena. The advances in physical sciences offer materials useful in cell and molecular biology, and provide tools for characterizing cells and sub-cellular components; meanwhile the progress in biology provides a window for researchers to understand the most sophisticated functional nanostructures that have ever existed (Whitesides 2003).

1.1.2 Nanoscience

Nanoscience investigates those objects whose smallest dimensions range from several nanometers up to 100 nanometers (Royal Society and Royal Academy of Engineering 2004; Poole and Ownes 2003). As nanoscale may be the final engineering scale people have yet to master, nanoscience is regarded as a launch pad to a new technological era by many scientists and engineers (National Science and Technology Council 1999a).

Due mainly to the following two reasons, nanomaterials exhibit properties that are quite different from those of materials at large scales (Royal Society and Royal Academy of Engineering 2004; National Science and Technology Council 1999b). First, the surface areas of nanomaterials are much larger than those of the materials with the same mass but in a larger form. A larger surface area usually results in more reactive chemical properties, and also affects the mechanical or electrical properties of the materials. Second, nanomaterials are the natural home of quantum effects. At the nanoscale, quantum effects dominate the behaviors of a material, affecting its optical, electrical and magnetic properties.

1.1.2.1 Quantum Effect

To study the properties of the objects in the normal-sized realm, such as cars and houses, it is not usually necessary to use quantum mechanics, which is used by scientists to describe the properties of materials at the atom and electron levels. However, researchers