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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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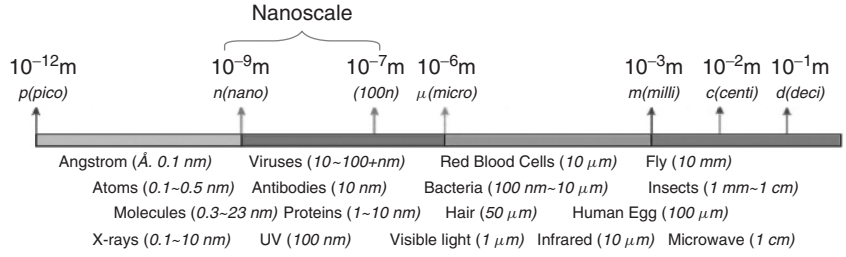

Figure 1.1 Nanoscale and typical materials whose dimension ranges are comparable to nanoscale. (Yih and Wei 2005)

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

in nanoscience are developing nanoscale building blocks, such as metallic and ceramic nanoparticles, and all-carbon nanotubes. These building blocks are hundreds of millions of times smaller than the bricks used for building houses and the tubes used for plumbing (National Science and Technology Council 1999a). Such nanoscale building blocks exhibit quantum effects.

Because the size of nanomaterials is close to the de Broglie wavelength of electrons and holes at room temperature, the states of free charge carriers in nanocrystals are quantized (Parak *et al*. 2003). For spherical nanocrystals, in which free electrons and holes are confined in all three directions, the movement of charge carriers is completely determined by quantum mechanics, and therefore the nanocrystals are often called quantum dots. Because of the similarity between the discrete energy levels of quantum dots and the discrete energy levels of atoms, quantum dots are often regarded as artificial atoms. Since the energy levels are determined by the size of the nanocrystal, they can be controlled by synthesizing nanocrystals of different diameters: the smaller a nanocrystal, the larger the spacing between its energy levels will be.

For semiconductor nanocrystals, their band gaps are size-dependent. If nanocrystals are excited optically, charge carriers are excited to upper energy levels. Fluorescent light will be emitted when the excited charge carriers fall back to the ground state. By controlled adjustment of the size during the synthesis of semiconductor nanocrystals basically all fluorescent colors in the visible region can be obtained, and there is no red-tail in the emission spectrum (Parak *et al*. 2003).

1.1.2.2 Surface Galore

For a given amount of material, the surface area compared to the volume increases when the particle size decreases, and thus the proportion of the constituent atoms at or near the surface increases. This feature is important because a lot of reactions occur at the surfaces of materials (National Science and Technology Council 1999a). For example, photosynthesis happens on the inside surfaces of cells, and catalysis happens on the surfaces of particles.

1.1.3 Nanotechnology

Nanotechnology usually refers to the capability of designing and controlling the structure of an object in the size range of nanometers. However, different researchers may have different opinions about what nanotechnology is, and it seems that the definitions of nanotechnology are as diverse as the applications of nanotechnology (Cao 2004; Malsch 2002; Taniguchi 1974). Some people consider the study of microstructures of materials using electron microscopy and the growth and characterization of thin films as nanotechnology. Other people consider a bottom-up approach in materials synthesis and fabrication, such as self-assembly or biomineralization to form hierarchical structures like abalone shell, to be nanotechnology. A drug-delivery system is a nanotechnology, and organizing molecules into functional complexes, for example a complex for delivering proteins to a certain position in the body, is also a nanotechnology. These definitions are true for certain specific research fields, but none of them covers the full spectrum of nanotechnology. The many diverse definitions of nanotechnology reflect the fact that nanotechnology covers a broad spectrum of research fields and requires true interdisciplinary and multidisciplinary efforts (Cao 2004). From the various definitions of nanotechnology listed above, we find that the only feature common to the diverse activities characterized as ‘nanotechnology’

is the tiny dimensions on which they operate (Royal Society and Royal Academy of Engineering 2004).

Generally speaking, nanotechnology can be understood as a technology of design, fabrication and applications of nanomaterials and nanostructures. Nanotechnology also includes a fundamental understanding of the physical properties and phenomena of nanomaterials and nanostructures. Study of fundamental relationships between physical properties and phenomena and material dimensions in the nanometer scale, is also referred to as nanoscience. To provide a more focused definition, nanotechnology deals with materials and systems whose structures and components possess novel and significantly improved physical, chemical and biological characteristics due to their nanoscale sizes (Cao 2004).

Though the word *nanotechnology* is new, the research on nanometer scale is not new. For example, the study of biological systems and the engineering of many materials such as colloidal dispersions, metallic quantum dots and catalysts have been in the nanometer regime for centuries. What is really new about nanotechnology is the combination of our capability of observing and manipulating materials at the nanoscale and our understanding of atomic scale interactions (Cao 2004). The invention and development of transmission electron microscopy (TEM), scanning tunneling microscopy (STM) and other scanning probe microscopy (SPM), such as atomic force microscopy (AFM), have opened up new possibilities for the characterization, measurement and manipulation of nanostructures and nanomaterials. Using these instruments, it is possible to study and manipulate the nanostructures and nanomaterials down to the atomic level.

After introducing the definition of nanotechnology by the US National Nanotechnology Initiative below, we discuss various nanotechnologies that often appears in the literature.

1.1.3.1 Definition by US National Nanotechnology Initiative

Though there are many different definitions for nanotechnology, most researchers follow the definition given by the US National Nanotechnology Initiative (NNI) (Alper 2005a). According to NNI, nanotechnology mainly involves three aspects: (i) research and technology development at the atomic, molecular or macromolecular levels; (ii) development and applications of structures, devices and systems with novel properties and functions due to their small and/or intermediate size; (iii) control and manipulation of materials at the atomic scale.

Encompassing science, engineering, and technology at the nanometer scale, nanotechnology involves imaging, characterizing, modeling and manipulating materials at the dimensions of roughly 1 to 100 nanometers. At this scale, the physical, chemical and biological properties of materials are fundamentally different from those of individual atoms, molecules and bulk materials (National Science and Technology Council 2004). By exploiting these novel properties, the main purpose of research and development in nanotechnology is to understand and create materials, devices and systems with improved characteristics and performances.

1.1.3.2 Natural Nanotechnology

Nanotechnology occurs in nature without intervention from human beings. The magic of natural nanotechnology encourages researchers in nanotechnology, including physicists, chemists, materials scientists, biologists, mechanical and electrical engineers and many other specialists, to learn from nature (National Science and Technology Council 1999a). In the following paragraphs, we discuss two examples of natural nanotechnology: chloroplast and F_1-ATPase complex.

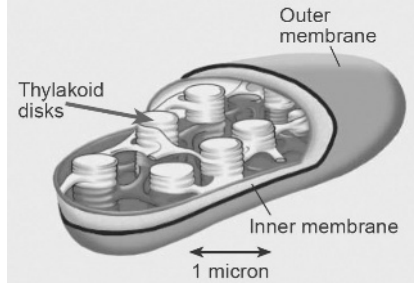

Figure 1.2 Basic structure of chloroplast. The nanoscale thylakoid disks arranged inside the stacked structures are the molecular machinery which convert light and carbon dioxide into biochemical energy. (National Science and Technology Council 1999a)

Photosynthesis is a biological way of capturing solar energy. Photosynthesis occurs in chloroplasts with nanometer and micrometer dimensions. Chloroplasts are a product of natural evolution. As shown in Figure 1.2, a chloroplast is a result of brilliantly engineered molecular ensembles, including light-harvesting molecules such as chlorophyll, arranged within the cell. These ensembles harvest the light energy by converting it into the biochemical energy stored in chemical bonds, which drives the biochemical machinery in plant cells (National Science and Technology Council 1999a).

F_1-ATPase complexes, approximately 10 nanometers across, are one of the greatest achievements of natural nanotechnology. They enable cells to produce the required biochemical fuel. As shown in Figure 1.3, F_1-ATPase complexes are molecular motors inside cells, and they continuously operate every time you move a muscle, or live another second. Each F_1-ATPase complex is a complex of proteins bound to the membranes of mitochondria, the bacteria-sized battery of a cell. F_1-ATPase complexes play a crucial role in synthesizing Adenosine triphosphate (ATP), which is the molecular fuel for cellular activity. Similar to fan motors, F_1-ATPase complexes can also make a rotary motion (National Science and Technology Council 1999a). The mechanism of rotary motion

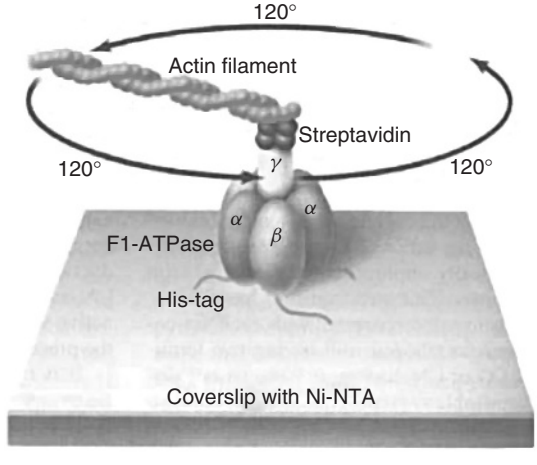

Figure 1.3 Basic structure of F_1-ATPase complex. (National Science and Technology Council 1999a)

seems to involve a sequential set of changes in conformation of the proteins driven by ions moving across the cell membrane. Though the rotary mechanism is yet to be further investigated, it certainly does not involve electrical current, magnetic fields or expansion of hot gasses in a cylinder (Whitesides 2003).

Natural nanotechnology provides much inspiration for researchers in nanotechnology. To learn from nature, it is necessary to have detailed knowledge about the basic biochemical and biophysical mechanisms at the level of the individual molecule, based on which the naturally occurring molecular machines operate. Knowledge about the working mechanisms of molecular machines is helpful for exploring new technological applications of the molecular machines and developing bio-mimic nanomaterials (Royal Society and Royal Academy of Engineering 2004).

1.1.3.3 Electronic Nanotechnology

Current nanotechnology is mainly driven by the continual shrinking of devices in the semiconductor industry and supported by the availability of characterization and manipulation techniques at the nanometer level (Cao 2004; Whitesides 2005). The continued decrease in device dimensions has followed the well-known Moore's law: the dimension of a device halves approximately every eighteen months. Electronic engineers have already shown how to extend existing methods for making microelectronic devices to new systems with wires and components whose dimensions are less than 100 nm. Scientists are currently working on molecular and nanoscaled electronics, which are constructed using single molecules or molecular monolayers. The continued size shrinkage of electronic circuits will sooner or later meet with the materials' fundamental limits imposed by thermodynamics and quantum mechanics.

1.1.3.4 Chemical Nanotechnology

For chemists, nanotechnology is not an entirely new field, as many existing chemical technologies employ nanoscale processes. Chemical catalysis is a typical example of chemical nanotechnology that has existed for more than a century. Catalysts accelerate numerous chemical transformations, such as the conversion of crude oil into gasoline and the conversion of small organic chemicals into drugs. Similarly, enzymes in cells are actually a kind of biological catalyst, and they organize and modulate the life chemistry of the body. It is expected that the nanoscale understanding of catalysis will lead to better and cleaner industrial processes.

1.1.3.5 Nanobiotechnology

Nanobiotechnology is a field that concerns the utilization of biological systems optimized through evolution, such as cells, cellular components, nucleic acids and proteins, to fabricate functional nanostructures and mesoscopic architectures comprised of organic and inorganic materials (Niemeyer and Mirkin 2004). Biological molecules can be harnessed for the creation of nanostructures, and can be used to assemble nanoscale building blocks based on the principle of molecular recognition (Parak *et al.* 2003). Many biological molecules, such as DNA, can bind to other molecules in a lock-and-key manner with very high selectivity and specificity. For example, the sequences of single-stranded oligonucleotides can be chosen so that they can bind to other partly complementary single-stranded oligonucleotides, causing the formation of complex patterns such as two-dimensional crystals or cubes.

The instruments originally developed for synthesizing and manipulating nanoscale materials have been refined and applied in the fundamental researches of biological activities (Niemeyer and Mirkin 2004). Nanotechnology has contributed important tools to investigate and manipulate biological nano-objects. One example is an atomic force microscope (AFM) based sensor, which detects biological molecules by binding them to a tiny cantilever, thereby tuning its resonance frequency. Another example is the miniaturization of a wide variety of laboratory apparatus to the size of a silicon chip. In this way the speed and throughput of classical biochemical methods, such as gel electrophoresis and polymerase chain reaction, can be increased (Parak *et al*. 2003).

1.1.3.6 Biomedical Nanotechnology

Nanomaterials and nanotechnology are widely applied in biomedicine, especially in the areas of biomedical diagnosis, drugs and prostheses and implants (Malsch 2002). The applications of biomedical nanotechnology generally fall into two categories: outside the body and inside the body. For applications outside the body, biosensors and biochips have been used to analyze blood and other biological samples. For applications inside the body, researchers are working on targeted drugs delivery, implantation of insulin pumps and gene therapy. In addition, great achievements have been made on the prostheses and implants that include nanostructured materials.

1.1.3.7 Cancer Nanotechnology

Cancer is one of the leading causes of death in developed countries. Conventional treatments, including surgery, radiation, chemotherapy and biological therapies (immunotherapy) are limited by the accessibility of the tumor, the risk of operating on a vital organ, the spread of cancer cells throughout the body and the lack of selectivity toward tumor cells (Arruebo *et al*. 2007). Nanotechnology can provide a better chance of survival. Cancer nanotechnology is actually a kind of biomedical nanotechnology. As more and more attention is paid to the diagnosis and therapy of cancers using nanotechnology, so cancer nanotechnology becomes a special branch in nanotechnology.

Cancer nanotechnology includes varieties of materials and techniques that are used for solving various problems. The research activities in cancer nanotechnology generally fall into seven categories. The first is the development of early imaging agents and diagnostic techniques for detecting cancers at their earliest, pre-symptomatic stage. Second is the development of techniques that can provide on-site assessments of the effects of the therapies. Third is the development of targeting devices that can bypass biological barriers and accurately deliver therapeutic agents to the tumor sites. Fourth, the development of agents that can be used to monitor predictive molecular changes and to prevent pre-cancerous cells from becoming malignant ones. Fifth is the development of surveillance systems for detecting the mutations that could trigger the cancer process and also for detecting genetic markers indicating a predisposition to cancers. Sixth is the development of methods for controlling cancer symptoms that badly affect quality of life. Seventh is the development of techniques helping researchers to rapidly identify new targets for clinical treatment and forecast possible side effects and drug resistance.

There are two major trends in cancer nanotechnology research (Alper 2005a). One trend is the development of multi-functional nanomaterials than can be used to simultaneously image a tumor and deliver drugs to the tumor. This may be the most radical improvement that nanotechnology can make for cancer treatment. The other trend in cancer nanotechnology is to dose a tumor with many drugs simultaneously, not just with one drug. In this way, the drug resistance problem, which is one of the most vexing

problems in cancer treatment, could be solved. Usually, the drug resistance of a cancer cell is due to its ability to pump out the anti-cancer drugs once they are delivered into the cell. However, by delivering an agent that can inhibit the pumping at the same time as the anti-cancer drugs are delivered to cancer cells, the problem of drug resistance may disappear.

1.1.4 Typical Approaches for Synthesis of Nanomaterials

The approaches for synthesis of nanomaterials are commonly categorized into top-down approach, bottom-up approach and hybrid approach.

1.1.4.1 Top-down Approach

Generally speaking, the top-down approach is an extension of lithography. This approach starts with a block of material, and reduces the starting material down to the desired shape in nanoscale by controlled etching, elimination and layering of the material (Cao 2004). Owing to the advancement of the semiconductor industry, the top-down approach for the fabrication of nanomaterials is a well developed method.

One problem with the top-down approach is the imperfection of the surface structure (Cao 2004). The conventional top-down techniques, such as lithography, may cause severe crystallographic damage to the processed patterns, and some uncontrollable defects may also be introduced even during the etching steps. For example, a nanowire fabricated by lithography usually contains impurities and structural defects on the surface. As the surface over volume ratio in nanomaterials is very large, such imperfections may significantly affect the physical properties and surface chemistry of the nanomaterials.

Regardless of the surface imperfections and other defects, the top-down approach is still important for synthesizing nanomaterials. However, it should be noted that, in the quest for miniaturization, top-down lithographic approaches for creating nanomaterials are approaching the fundamental limitations. Even cutting-edge electron beam lithography cannot create structures smaller than 10 nm (Darling and Bader 2005). Besides, lithographic techniques are usually expensive, and their productivities are usually low.

1.1.4.2 Bottom-up Approach

In a bottom-up approach, materials are fabricated by efficiently and effectively controlling the arrangement of atoms, molecules, macromolecules or supramolecules (Luo 2005). The bottom-up approach is driven mainly by the reduction of Gibbs free energy, so the nanomaterials thus produced are in a state closer to a thermodynamic equilibrium state. The synthesis of large polymer molecules is a typical example of the bottom-up approach, where individual building blocks, monomers, are assembled into a large molecule or polymerized into bulk material. Crystal growth is another example of the bottom-up approach, where growth species – either atoms, or ions or molecules – assemble in an orderly fashion into the desired crystal structure on the growth surface (Cao 2004).

The concept and practice of a bottom-up approach have existed for quite a while, and this approach plays a crucial role in the fabrication and processing of nanomaterials. The nanostructures fabricated in the bottom-up approach usually have fewer defects, a more homogeneous chemical composition and better short and long range ordering.

1.1.4.3 Hybrid Approach

Though both the top-down and bottom-up approaches play important roles in the synthesis of nanomaterials, some technical problems exist with these two approaches. For the top-down approach, the main challenge is how to accurately and efficiently create structures which are becoming smaller and smaller; while for the bottom-up approach, the main challenge is how to fabricate structures which are of sufficient size and amount to be used as materials in practical applications. The top-down and bottom-up approaches have evolved independently. It is found that, in many cases, combining top-down and bottom-up methods into a unified approach that transcends the limitations of both is the optimal solution (Royal Society and Royal Academy of Engineering 2004; Darling and Bader 2005). A thin film device, such as a magnetic sensor, is usually developed in a hybrid approach, since the thin film is grown in a bottom-up approach, whereas it is etched into the sensing circuit in a top-down approach.

1.1.5 Interdisciplinarity of Nanoscience and Nanotechnology

Nanoscience and nanotechnology are highly interdisciplinary, encompassing aspects of physics, chemistry, biology, materials science and engineering, and medicine (Hurst *et al.* 2006). Due to their interdisciplinarity, nanoscience and nanotechnology have brought about cooperation between scientists and engineers with different backgrounds to share their expertise, instruments and techniques (Royal Society and Royal Academy of Engineering 2004). The evolutionary developments within different areas in the investigation of materials that are becoming smaller and smaller have contributed to the rapid progress in nanoscience and nanotechnology, and meanwhile nanoscience and nanotechnology benefit not only the electronics industry, but also the chemical and space industries, as well as medicine and health care.

In the following subsections we concentrate on the roles of three disciplines in the research of nanoscience and nanotechnology: chemistry, physics and biology and medicine.

1.1.5.1 Chemistry

Chemistry plays a leading role in nanotechnology, and in a sense, chemistry is the ultimate nanotechnology. The opportunities for chemistry to make important contributions to nanoscience abound, and three promising areas include synthesis of nanomaterials, molecular mechanisms in nanobiology, and risk assessment and evaluation of safety (Whitesides 2005). Chemistry is unique in the sophistication of its ability to synthesize new forms of matter. In making new forms of matter by joining atoms and groups of atoms together with bonds, chemistry contributes to the invention and development of materials whose properties depend on nanoscale structure. Meanwhile, chemistry makes unique contributions to the study of the molecular mechanisms of functional nanostructures in biology, such as the light-harvesting apparatus of plants, ATPases, the ribosome and the structures that package DNA, ultimately the cell. Furthermore, analyzing the risks of nanomaterials to health and the environment requires cooperation across various disciplines, including chemistry, physiology, molecular medicine and epidemiology.

1.1.5.2 Physics

Compared with bulk materials, materials at the nanoscale exhibit quite different properties, and physics studies the underlying mechanisms of the changes of properties due to the

size changes. Physicists are investigating the special mechanical, thermal, electrical and optical properties of various types of nanomaterials, such as quantum dots and hybrid thin films, and most of the researches involves quantum mechanics.

Among various categories of nanomaterials, magnetic nanomaterials exhibit unique size dependence of magnetic properties in the nanoscale, and knowledge of these properties is essential for the design and modifications of magnetic nanomaterials and for the development their specific applications. The research on nanomagnetism, magnetism in nanomaterials, has been among the most challenging topic in nanoscience and nanotechnology (Himpsel *et al*. 1998).

1.1.5.3 Biology and Medicine

It is a main trend that biomedical and physical sciences share a common interest in nanomaterials, and the conventional borders of these areas are disappearing. The union of biologists and physicians with engineers and materials scientists is encouraging (Ritchie 2005). As few biologists and physicians know much about engineering and materials science, and even fewer engineers and materials scientists know much about medicine, the potential for such a union seems boundless.

Nanofabrication can provide analytical tools for investigating biomolecules as well as for exploring the interior structure and function of cells (National Science and Technology Council 1999b). In return, biology is clearly having an equally significant impact on nanoscience and nanotechnology. Methods in biology can be used to make nanomaterials that are difficult or impossible to be fabricated by synthetic means (Taton 2003). Due to the evolution of billions of years, organisms of all types are equipped with numerous nanomachines, such as DNA that can be used for information-storage and chloroplasts that capture the solar energy (Service 2002; National Research Council 1994).

Researchers in the field of nanoscience and nanotechnology are seeking practical help from biology. One of the most attractive features of biological systems is that an organism has the capability to produce extremely complex molecules, for example DNA and proteins, with atomic precision. The powerful biomachinery can further arrange different organisms into a complicated system. However, synthesized nanomaterials, for example carbon nanotubes and metal nanoparticles, do not have similarly efficient guiding mechanisms. Besides, it is very difficult to handle and manipulate nanomaterials using the traditional methods. Inspired by the discoveries in biology, researchers in the field of nanoscience and nanotechnology are trying to use the molecular toolbox in biology, for the synthesis of functional nanomaterials (Service 2002).

Researchers attempt to combine the capability of assembling complex structures in biology and the ability of developing functional devices in nanoscience and nanotechnology. Such a combination is helpful for the development of a variety of novel structures and devices (Service 2002). Williams *et al*. (2002) demonstrated the bioelectronic assembly, as shown in Figure 1.4. In this example, the assembly of the carbon nanotubes into molecular-scale electronic devices is based on the selective binding capabilities of peptide nucleic acid (PNA). Similar to DNA, PNA consists of a series of nucleotide bases (A's, T's, G's and C's) that selectively bind to one another. However, in a PNA, the backbone of sugar and phosphate groups in DNA is substituted with more stable links based on peptides. Due to this substitution PNAs can endure higher temperatures and stronger solvents, often used in chemical and biological processing, than DNAs.

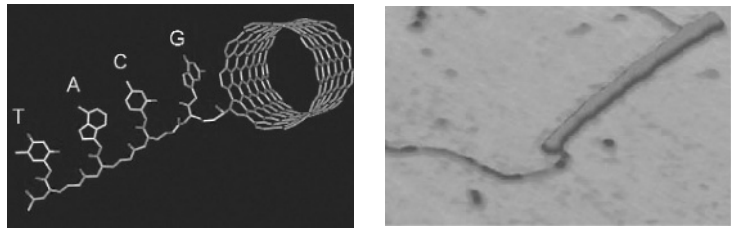

Figure 1.4 Bioelectronic assembly of a carbon nanotube. (a) Schematic drawing, and (b) micrograph. (Service 2002)

1.2 Magnets and Nanometers: Mutual Attraction

As physicists and materials scientists are becoming increasingly interested in the properties of magnetic materials on the nanometer scale, biology is benefiting from nanomagnets. Magnetic nanomaterials are quite different from other nanomaterials, because the fundamental properties of magnets are defined at nanometer length scales (Koltsov and Perry 2004). Nanomagnets can measure anything from just under a micron to a few nanometers in size, and have applications that range from medical imaging and drug delivery to sensors and computing. As will be discussed in later chapters, magnetic nanomaterials are widely used in biology and medicine.

Nanomagnetism is at the frontiers of nanoscience and nanotechnology, and magnetic nanomaterials are among the most promising nanomaterials for clinical diagnostic and therapeutic applications. Nanomagnetism basically involves studying how such ferromagnetic materials behave when they are geometrically restricted in at least one dimension. One of the central topics in nanomagnetism is the superparamagnetic properties of magnetic nanomaterials; in most cases, what makes ferromagnets useful in biomedical applications is their superparamagnetic properties. More discussions about nanomagnetism can be found in Chapter 2.

1.3 Typical Magnetic Nanomaterials

The magnetic nanomaterials used in biology and medicine generally fall into three categories: zero dimensional nanomaterials such as nanospheres; one-dimensional nanomaterials such as nanowires and nanotubes; and two-dimensional nanomaterials such as thin films. Usually, all the nanospheres, nanorods, nanowires and nanotubes are called nanoparticles, among which, nanorods, nanowires and nanotubes are high aspect-ratio nanoparticles.

In most of the biomedical applications, magnetic nanoparticles are suspended in appropriate carrier liquids, forming magnetic fluids, also called ferrofluids. The properties of ferrofluids are discussed in Chapter 2. In most of the biomedical applications, magnetic thin films are usually fabricated into magnetic biosensors or biochips, by etching them into certain patterns to perform specific functions. As discussed in detail in Chapter 8, most of the magnetic biosensors fabricated from magnetic thin films detect the stray magnetic fields from magnetic nanoparticles that are attached to biomolecules.

1.3.1 Nanospheres

Among the three types of magnetic nanoparticles, magnetic nanospheres are most widely used in biomedicine. To realize their biomedical applications, the magnetic nanospheres should be stably suspended in the carrier liquid, and they should also carry out certain biomedical functions. The magnetic material most often used is iron oxides, usually in the form of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), and the carrier liquids are usually water, kerosene or various oils.

Figure 1.5 shows the basic structures of magnetic nanospheres used for biomedical applications. Due to their small size, the magnetic nanoparticles in carrier liquids neither form sediment in the gravitational field or in moderate magnetic field gradients, nor do they agglomerate due to magnetic dipole interaction. However, a stable suspension can only be achieved if the particles are protected against agglomeration due to the van der Waals interaction. Usually this protection can be achieved by two approaches (Could 2004; Odenbach 2004). One is the electric charge stabilization. In this approach, a thin layer of gold is coated on the surface of the nanospheres. Meanwhile, the thin gold layer can also serve as an ideal base on which chemical or biological agents can be functionalized, as shown in Figure 1.5(a). These molecules generate a repulsive force, preventing the particles from coming into contact and thus suppressing the destabilizing effect of the van der Waals interaction. In practical applications, these two approaches are often used in combination for the majority of ferrofluids, since this allows the synthesis of suspensions which are stable over years (Could 2004). Usually, iron oxide nanoparticles used in biomedical applications are coated with gold or silica, and subsequently functionalized, for example, with antibodies, oligonucleotides or peptide ligands.

One major trend in the research of nanospheres is the development of multi-functional nanospheres, and one typical approach for realizing the multi-functionality is to functionalize a magnetic nanosphere with different functional groups. Figure 1.6 illustrates a multifunctional magnetic nanosphere. The targeting ligands and delivery peptides conjugated on the nanoparticle surface are used for targeting the nanosphere to the desired location and for delivering the drug respectively, and the sensor and reporter functional group is for checking the effects of drug delivery.

Another approach to performing multiple functions simultaneously is to use multicomponent nanomaterials, such as core–shell, alloyed and striped nanoparticles (Hurst *et al*. 2006). Researchers hope to design multicomponent nanostructures and exploit their

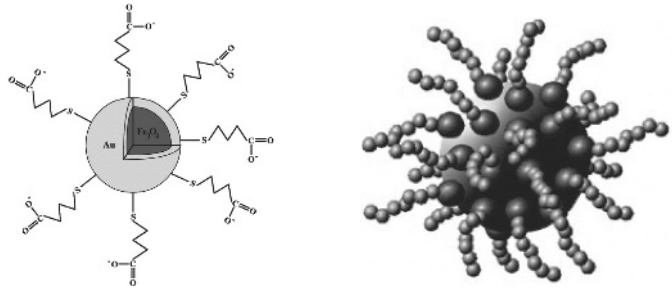

Figure 1.5 Two approaches for protection of nanospheres. (a) Electric charge stabilization (Could 2004); (b) organic molecule stabilization. (Odenbach 2004)

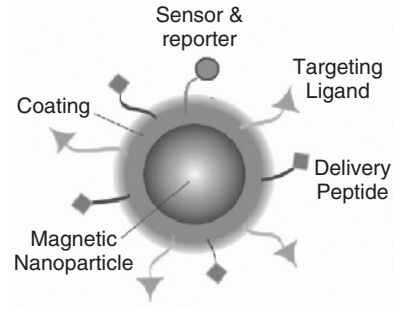

Figure 1.6 Illustration of a multifunctional magnetic nanosphere, modified from Could (2004)

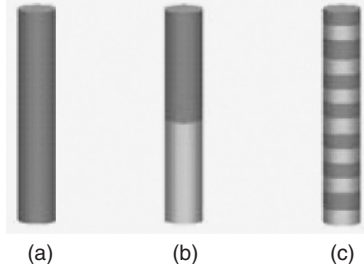

Figure 1.7 Configurations of three types of nanowires. (a) Single-segment nanowire; (b) two-segment nanowire; (c) multilayer nanowire. (Sun *et al*. 2005). Reprinted from IBM Sun, L., Hao, Y., Chien, C.L. and Searson, P.C. (2005) Tuning the properties of magnetic nanowires, *Journal of Research and Development*, **49**(1), 79–102, with permission from IBM

inherent multiple functionalities for use in many novel applications. For example, in a core–shell system, the favorable properties of the core are maintained, while the shell functions to provide additional stabilization, passivation or chemical functionality.

1.3.2 Nanorods and Nanowires

Nanorods and nanowires are straight solid one-dimensional high aspect ratio nanomaterials. Usually, a nanowire has a higher aspect ratio than a nanorod; however there is no strict standard by which we can differentiate a nanorod and a nanowire. A nanorod named by some researchers may be called a nanowire by other researchers, and vice versa. Therefore, in this book, we do not distinguish between nanorods and nanowires, calling them both nanowires.

As shown in Figure 1.7(a), in most cases nanowires are cylindrical in shape with a radius in the range from 5 to 500 nm, and length up to about 100 μm. The elongated structure of nanowires may result in inherent chemical, electrical, magnetic and optical anisotropy that can be exploited for interactions with cells and biomolecules in fundamentally new ways (Bauer *et al*. 2004). Although a majority of the magnetic carriers currently used for biomedical applications are magnetic nanospheres, nanowires are an alternative type of nanoparticles with considerable potential. Due mainly to the following attractive properties, many efforts are being made to explore the applications of nanowires in biomedicine (Hultgren *et al*. 2005).

1.3.2.1 Biocompatibility

Biocompatibility is one of the most important considerations in the development of biomedical applications of nanomaterials. Most of the magnetic nanowires are compatible with living cells. They can be functionalized with biologically active molecules, and they do not disrupt normal cell functions, such as cell proliferation and adhesion, and gene expression (Hultgren *et al*. 2005).

1.3.2.2 Magnetization

Magnetic nanoparticles can be used to apply forces to biological systems. Therefore, they can be used in the magnetic separation of biological entities, and the targeted delivery of drugs and genes, and they can also be used to study mechanotransduction at the cellular level (Hultgren *et al*. 2005). Usually, magnetic nanowires are made of solid metals, and thus they may possess large magnetic moments per volume of material. Therefore magnetic nanowires can be manipulated at weaker magnetic fields.

It should be noted that, due to its structural properties, the magnetization of a nanowire is quite different from that of a nanosphere (Sun *et al*. 2005). The magnetization of a sphere under an external magnetic field is independent of the direction of the applied magnetic field. However, it is easier to magnetize a nanowire along its axis than perpendicular to its axis. Furthermore, when a nanowire is placed between a north pole and a south pole, outside the nanowire, the magnetic field lines emanating from the north pole end at the south pole. While inside the nanowire, the magnetic field lines are in the direction from the north pole to the south pole, and thus in the opposite direction of the magnetization of the material. Therefore, the magnetic field inside the nanowire tends to demagnetize the nanowire, and this field is usually called the demagnetizing field.

1.3.2.3 Controllable Dimensions

As the geometry of nanoparticles may have biomedical effects, it is desirable to tune the size and shape of nanoparticles to study the mechanisms of their interactions with cells. Magnetic nanowires are often synthesized by the template method. In this method, the diameter and length of magnetic nanowires are independently controllable. The diameter of nanowires can be controlled in the range from nanometer to micrometer, by using templates with different pore diameters. Meanwhile, the length of magnetic nanowires can be controlled by using templates with different thicknesses.

1.3.2.4 Multi-segment Structure

As shown in Figures 1.7(b) and (c), different types of materials, for example, magnetic and non-magnetic, can be selectively electrodeposited along the nanowire axis, resulting in multi-segment nanowires. By precisely modulating the composition along the axis of a nanowire, the architecture and magnetic properties of the nanowire can be precisely controlled (Sun *et al*. 2005). Both single-segment and multiple-segment magnetic nanowires have been used in biomedicine. To optimize their biomedical applications, the magnetic properties of magnetic nanowire, for example, the Curie temperature, the easy magnetization axis, the saturation magnetic field, the saturate magnetization, remanent magnetization and coercivity, can be adjusted to meet special biomedical application requirements.

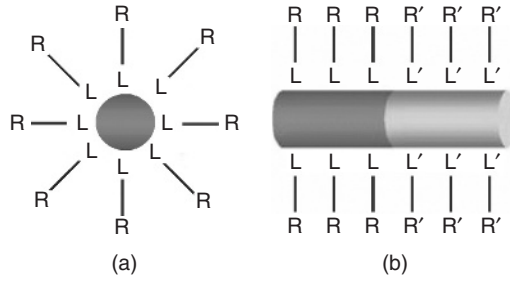

Figure 1.8 Functionalization of a nanosphere (a) and a two-segment nanowire (b). L and L′ represent two different types of ligands, and R and R′ represent two different types of functional groups. (Sun *et al*. 2005). Reprinted from IBM Sun, L., Hao, Y., Chien, C.L. and Searson, P.C. (2005) Tuning the properties of magnetic nanowires, *Journal of Research and Development*, **49**(1), 79–102, with permission from IBM

1.3.2.5 Multi-functionality

In biomedical applications, such as drug and gene delivery, magnetic nanowires are usually functionalized with biologically active molecules. As shown in Figure 1.8, compared to nanospheres, multi-functionality can be more easily realized on multi-segment nanowires (Sun *et al*. 2005, Reich *et al*. 2003).

Based on surface coordination chemistry, using ligands that bind selectively to different segments of a multi-component wire, spatially modulated multiple functionalization can be realized in the wire. Figure 1.8(b) shows a two-segment nanowire functionalized with ligands whose headgroups (L and L′) selectively bind to desired segments and whose tail groups (R and R′) will target two different biomolecules. The control of selective functionalization is crucial to the realization of the multi-functionality of nanowires. For example, for a Ni-Au nanowire, based on the differences in surface chemistry of the gold and nickel segments, different molecules can be bound to different segments of the nanowire, so different segments can be arranged to carry out different tasks.

1.3.3 Nanotubes

The magnetic nanotubes discussed in the literature can be classified into three types. The first type is non-magnetic nanotubes, such as carbon nanotubes, whose inner void is filled with magnetic nanomaterials. This type of magnetic nanotube can also be taken as a magnetic nanowire covered with a layer of non-magnetic material. The second type is non-magnetic nanotubes whose walls are deposited with magnetic nanomaterials. The third type is nanotubes whose whole structure is made of magnetic materials. In this book, we concentrate on the third type of magnetic nanotubes.

As shown in Figure 1.9(a), a magnetic nanotube is the hollow counterpart of a magnetic nanowire. Similar to magnetic nanowires, magnetic nanotubes have high aspect ratio, and usually have much stronger magnetization than magnetic nanospheres.

Due to their unique structural properties, nanotubes are ideal for the realization of multifunctionality. As shown in Figure 1.9(b), as a nanotube has distinctive inner and outer surfaces, the inner surface and the outer surface of a nanotube can be functionalized to perform different biomedical functions. Depending on the inner diameter of a nanowire, the inner empty space of the nanowire can be used to capture, concentrate and release biological entities ranging in size from small molecules to large proteins. The outer surface

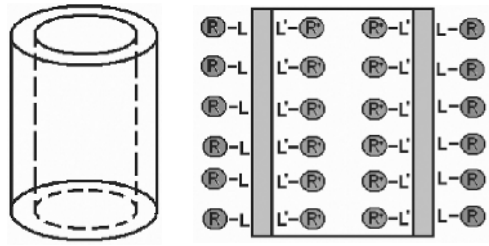

Figure 1.9 The basic structure of a magnetic nanotube (a), and its multi-functionalization (b)

of a nanotube is often functionalized with environment-friendly molecules or probing molecules to a specific target (Son *et al*. 2005).

Template method is often used in the synthesis of magnetic nanotubes. Using this method, the three major structural parameters can be independently controlled. The outer diameter of a nanotube is mainly determined by the pore diameter of the template, and the inner diameter of a nanotube can be controlled by the concentration of the solution and the filtration speed. The length of a nanotube is mainly determined by the thickness of the template.

1.3.4 Thin Films

Magnetic thin films are actually sheets of magnetic material with thicknesses usually less than one hundred nanometers. Magnetic thin films can have single-layer, or multilayer structures, and they can be single-crystal, polycrystalline or amorphous. One important property of a magnetic thin film is that its electrical resistance usually changes when an external magnetic field is applied, and the change of electrical resistance due to the application of external magnetic field is called magnetoresistance. For certain multilayer structures composed of alternating ferromagnetic and non-magnetic layers, the resistance of a multilayer thin film drops dramatically as a magnetic field is applied, and this phenomenon is called giant magnetoresistance (GMR) (Binasch *et al*. 1989; Baibich *et al*. 1988).

Figure 1.10 shows the change in room-temperature resistance ΔR *vs* in-plane magnetic field for two polycrystalline multilayers of Fe/Cr and Co/Cu, respectively (Parkin 1995). The resistance is measured with the current in the plane of the layers, and the magnetic field is applied orthogonal to the current also in the plane of the layers. The variation in resistance is related to a change in the relative orientation of neighboring ferromagnetic Fe or Co layers with applied magnetic field. The resistance is higher when adjacent magnetic layers are aligned anti-parallel to one another, as compared with parallel alignment, shown schematically in Figure 1.10.

Since the discovery of the GMR effect in magnetic multilayer systems, many biosensors employing this effect have been developed. As shown in Figure 1.11, GMR sensors could be employed for the detection of biomolecules that have been tagged with magnetic nanoparticles. GMR sensors are favored over competing optical detection schemes due to their higher sensitivity, lower background, compact size and easy integrability with existing semiconductor electronics (Li *et al*. 2004). GMR sensors with minimum dimensions below 100 nm have been fabricated using electron beam lithography (Wood 2005). Such technology has implications in many areas of biological and medical research, including disease detection, treatment and prevention.

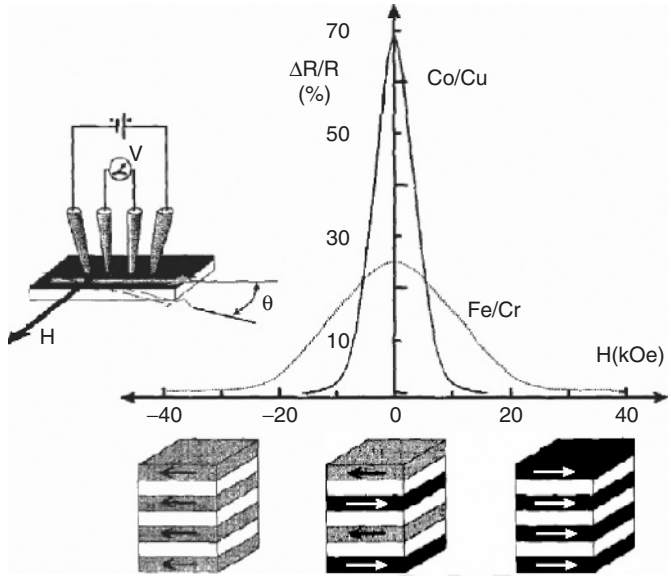

Figure 1.10 Room-temperature resistance *vs* in-plane magnetic field curves for polycrystalline Fe/Cr and Co/Cu multilayers. The measurement geometry is shown schematically in the top left corner. The magnetic state of the antiferromagnetically coupled multilayers is shown schematically in the lower portion of the figure for large negative, zero, and large positive magnetic fields (Parkin 1995)

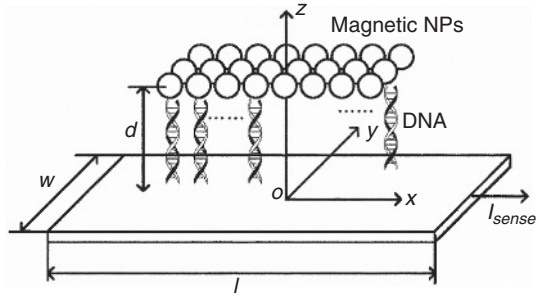

Figure 1.11 Schematic view of a magnetic nanoparticle array immobilized on a magnetoresistance sensor through DNA hybridization (modified from Li *et al*. 2004)

1.4 Nanomedicine and Magnetic Nanomedicine

The integration of biological and physical sciences at nanoscale has impacts in many areas of science and technology. One area that is particularly promising is the biomedical applications of magnetic nanomaterials.

1.4.1 Inspiration from Nature

It is well known that the most advanced nanoscale machines that have ever existed are cells regulating and controlling biological systems, and understanding cells is one of the

great unanswered questions in science (Royal Society and Royal Academy of Engineering 2004; Whitesides 2005). A cell is the smallest and most fundamental unit, from which the rest is built. It is a system of molecules and remarkable nanoscale 'machines' – functional molecular aggregates of great complexity. Understanding these molecular nanostructures in their full, mechanistic, molecular complexity is vital to understanding the cell. Proteins are one typical example of molecular nanostructures. They have numerous highly specific functions, and take part in almost all the biological activities, such as sensory, metabolic, information and molecular transport processes. However, compared to an individual cell, a single molecule bio-nanodevice, such as a protein, only occupies about one-millionth to one-billionth of the volume. Therefore, in the biological world, there are innumerable biological nanoscale structures, devices and machines, which the researchers in the field of nanoscience and nanotechnology may be interested to investigate and emulate. The methods emerging from this research will help us to move closer to understanding human life and health, and thus towards nanomedicine, which has attracted a lot of attention and has become a fast growing field.

It should be noted that current materials used in biomedicine have only a small fraction of the sophistication of the naturally occurring materials that they replace. In general, synthetic materials are poor or partial replacements for naturally occurring ones. However, synthetic materials are more satisfactory when they serve a function that does not exist in nature. For example, delivery of a drug by erosion of a polymeric matrix *in vivo*; and alteration of the relaxation time of protons in water to improve contrast in magnetic resonance imaging (Whitesides and Wong 2006).

1.4.2 What is Nanomedicine?

Nanomedicine stands at the boundaries between the physical, the chemical and the biological sciences. It originated from the imaginative idea that robots and other related machines at the nanometer scale could be designed, fabricated and introduced into the human body for repairing malignant cells at the molecular level. According to its original vision, nanomedicine is a process including the diagnosis, treatment and prevention of diseases and traumatic injuries, and the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body (Freitas 2005).

The progress in both nanoscience and nanotechnology makes nanomedicine practical. From a technical viewpoint, nanomedicine consists of the applications of particles and systems at the nanometer scale for the detection and treatment of diseases at the molecular level, and it plays an essential role in eliminating suffering and death from many fatal diseases, such as cancer (Yih and Wei 2005; National Institute of Health and National Cancer Institute 2004). Based on nanofabrication and molecular self-assembly, various biologically functional materials and devices, such as tissue and cellular engineering scaffolds, molecular motors and biomolecules, can be fabricated for sensor, drug delivery and mechanical applications (Royal Society and Royal Academy of Engineering 2004).

Nanomedicine has obvious advantages (Whitesides and Wong 2006). First, nanoparticles are potentially invaluable tools for investigating cells because of their small size. Second, as their size can be controlled, from that of large molecules to that of small cells, the ability of nanoparticles to escape the vasculature *in vivo* can also be controlled. Third, because of their small size, nanoparticles can circulate systemically in the bloodstream and thus serve in roles such as magnetic resonance enhancement, iron delivery

for the production of red blood cells and drug delivery to improve the availability of serum-insoluble drugs.

1.4.3 Status of Nanomedicine

Nanomedicine has developed in numerous directions, and it has been fully acknowledged that the capability of structuring materials at the molecular scale greatly benefits the research and practice of medicine. The investigation of fundamental problems regarding the biocompatibility of nanomaterials has been initiated both theoretically and experimentally. The complicated issues related to the future approval of nanomedical materials by the US Food and Drug Administration are extensively discussed. It seems that preparations are being made for our society to deploy nanomedicine for human betterment (Freitas 2005).

However, nanomedicine is a long-term expectation. Before nanomedicine can be used in clinics, fundamental mechanisms of nanomedicine should be fully investigated, and clinical trials and validation procedures should be strictly conducted. Though it is possible that some biological entities, such as proteins, DNA and other bio-polymers, could be directly used for biosensor applications, nevertheless some serious issues, such as biocompatibility and robustness, may hinder the progress of these efforts. Though in many areas, such as disease diagnosis, targeted drug delivery and molecular imaging, clinical trials of some nanomedicine products are being made, the clinical applications of these techniques, which require rigorous testing and validation procedures, may not be realized in the near future (Royal Society and Royal Academy of Engineering 2004).

At all events, it should be noted that although the applications of nanomaterials in biology and medicine are in an embryo stage, it is the great promise of nanomedicine that has inspired researchers to extensively investigate the interfaces between nanotechnology, biology and medicine (Satyanarayana 2005).

1.4.4 Magnetic Nanomedicine

Magnetic nanomedicine is growing rapidly, and there is already a broad range of applications including cell separation, biosensing, studies of cellular function, as well as a variety of potential medical and therapeutic uses. The magnetic nanomaterials used in magnetic nanomedicine can be generally classified into magnetic thin films and magnetic nanoparticles which include nanospheres, nanowires and nanotubes. Magnetic thin films are often used in the development of high sensitivity and high accuracy magnetic sensors and biochips, which are important for the detection of biological entities bound with magnetic nanoparticles. The magnetic nanoparticles used in magnetic nanomedicine usually consist of a single magnetic species and a suitable coating to allow functionalization with bioactive ligands. Magnetic nanoparticles have attractive advantages in biomedical applications as discussed below (Pankhurst *et al.* 2003).

1.4.4.1 Easy Detection

As almost all biological entities are non-magnetic, magnetic nanoparticles in biological systems can be easily detected and traced. One typical example is the enhancement of the signal from magnetic resonance imaging (MRI) using magnetic nanoparticles. In this technique, a subject is placed in a large, external magnetic field and then exposed to a pulse of radio waves. Changes to the spin of the protons in water molecules are measured

after the pulse is turned off. Tiny differences in the way that protons in different tissues behave can then be used to build up a 3D image of the subject (Koltsov and Perry 2004).

1.4.4.2 Magnetic Manipulation

Magnetic nanoparticles will rotate under an external uniform magnetic field, and will make translational movements under an external magnetic field gradient. Therefore, magnetic nanoparticles, or magnetically tagged molecules, can be manipulated by applying an external magnetic field. This is important for transporting magnetically tagged drug molecules to diseased sites. The magnetic manipulation of magnetic nanowires and nanotubes is important for applying forces to biological entities, and for nanowires or nanotubes to get into biological entities.

1.4.4.3 Energy Transfer

Magnetic nanoparticles can resonantly respond to a time-varying magnetic field, transferring energy from the exciting magnetic field to the nanoparticles and the tagged biological entities. This property has been used in hyperthermia treatment of cancer tumors (Pankhurst *et al*. 2003).

1.5 Typical Biomedical Applications of Functional Magnetic Nanomaterials

The advances in nanoscience and nanotechnology result in a variety of biomedical applications for magnetic nanomaterials. Most of the biomedical applications of magnetic nanomaterials are based on the specific characteristics of magnetic nanomaterials and the benevolent relationships between magnetic fields and biological systems. The strength of magnetic field required for manipulating magnetic nanoparticles does not have harmful effects on biological tissues, and the biotic environment does not interfere with the magnetism of magnetic particles (Could 2004). Though magnetic nanoparticles with different compositions, sizes and shapes have been developed for biomedical applications, the most frequently used magnetic materials are two types of iron oxide particles, maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4). In some applications of magnetic nanoparticles, magnetic beads of micrometer size, consisting of magnetic nanoparticles, are used.

As shown in Figure 1.12, the biomedical applications of magnetic nanoparticles can be generally classified into diagnosis and therapy (Pankhurst 2003; Arruebo *et al*. 2007). Magnetic thin films are often used in the development of biosensors and biochips, which play crucial roles in magnetic diagnosis. We briefly discuss below the diagnostic and therapeutic applications of magnetic nanoparticles, and the magnetic biosensors and biochips based on magnetic thin films. In the final part, the trends of magnetic nanomaterials in biomedicine are outlined.

1.5.1 Diagnostic Applications of Magnetic Nanoparticles

Magnetic nanomaterials have been widely used in the diagnosis of diseases. As diseases can be detected at the cell or molecular level, many diseases can be diagnosed at very early stages, much earlier than the disease symptoms appear. This is especially important for some fatal diseases, such as cancer. We discuss below several typical examples of diagnostic applications of magnetic nanoparticles.

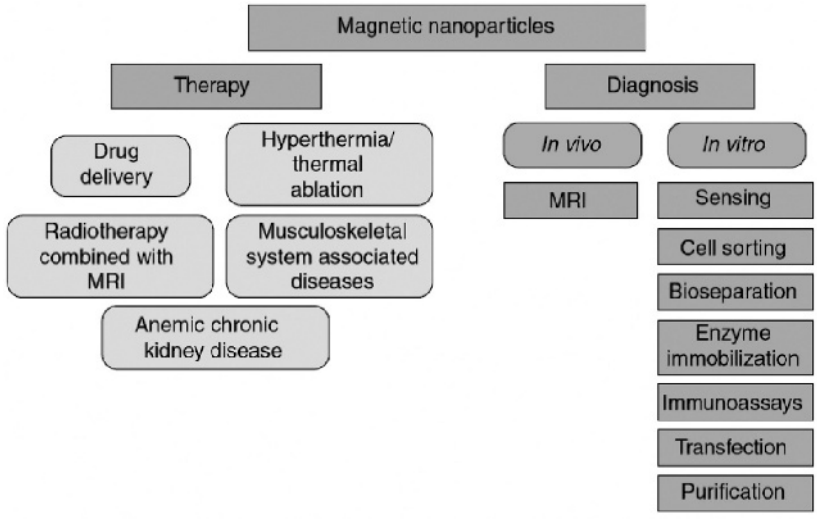

Figure 1.12 Biomedical applications of magnetic nanoparticles. (Arruebo *et al.* 2007)

1.5.1.1 Magnetic Separation

Separation of specific biological entities from their environments is very important in biochemical analysis and disease diagnosis. Magnetic nanoparticles usually exhibit superparamagnetic behaviors at room temperature. They have strong magnetization under an external magnetic field, but do not have remanent magnetism once the magnetic field is moved away. This magnetic on/off switching behavior is extremely helpful for magnetic separation (Could 2004; Pankhurst 2003).

Magnetic separation is a well-developed method and can be used as an alternative to the conventional centrifugal separation method. A typical magnetic separation procedure mainly consists of four steps, and iron oxide particles are often used in magnetic separation (Could 2004). In the first step, magnetic microbeads are made by encasing iron oxide nanoparticles in a biocompatible coating, and the surface of the microbeads is functionalized with a special biological or chemical agent that can selectively bind to the target cells or molecules to be separated. In the second step, the functionalized microbeads are added to the solution containing the target cells or molecules, and the target cells or molecules are subsequently bound to the magnetic microbeads. In the third step, a permanent magnet is placed at the side of the solution, inducing a magnetic moment on the magnetic microbeads and establishing a magnetic field gradient which drives the magnetized microbeads to move along the field lines. Finally, the magnetized microbeads cluster together near the magnet, and thus the target cells or molecules bound to the magnetic microbeads are separated.

1.5.1.2 Medical Imaging

One of the most attractive advantages of the magnetic resonance imaging (MRI) technique is that this technique is non-invasive. The MRI technique is extensively used in diagnosing diseases, making pre-surgical assessment and monitoring the therapy effects. A lot of efforts are being made to enhance its resolution and contrast. One way of boosting the MRI signal is to use contrast agents made of magnetic nanoparticles. Superparamagnetic

iron oxide particles coated with a suitable chemically neutral material to prevent them from reacting with body fluids are often used as contrast agents. These magnetic particles are usually injected into the bloodstream and travel to different organs depending on their size. Therefore, by selecting particles of particular sizes, researchers can study specific parts of the body (Koltsov and Perry 2004).

1.5.1.3 Targeted Detection

The targeted detection technique can be used for detecting extremely early signs of disease (Could 2004; Pray 2005). Usually, a tumor with a diameter of 10 mm has more than one hundred million tumor cells. Using the targeted detection technique, a cancer cluster with about 10–100 cancer cells could be detected, so cancers could be diagnosed at a very early stage of malignancy. It is expected that the targeted detection technique can be further improved to detect individual cancer cells before the formation of a cluster. This technique can also be used in AIDS research. To detect HIV viruses, ferromagnetic nanoparticles are usually coated with gold, and tagged with an HIV antibody via an Au-S covalent bond. Such nanoparticle probes could sensitively detect very small amounts of viral particles that could not be detected by the conventional AIDS diagnosing techniques.

It should be noted that before the targeted detection technique can be used in clinics, some practical problems should be addressed (Could 2004). For example, it should be investigated whether a small number of malignant cells can produce signals that are strong enough to be reliably detected by magnetic probes, whether the magnetic probes can reach the intended targets, and whether the signal is truly caused by the particulate clustering due to the probe–target binding.

1.5.2 Therapeutic Applications of Magnetic Nanoparticles

Using magnetic nanomaterials, therapeutic treatments could be performed at cell or molecular level, and therefore the therapy efficiency will be greatly improved, and the side effects will be greatly decreased. In the following subsections, we discuss five typical therapeutic applications of magnetic nanoparticles.

1.5.2.1 Hyperthermia Treatment

As some cancer cells are more susceptible to high temperatures than normal cells, such cancerous cells can be treated thermally. Therefore, by increasing the temperature of the tissue to above 42 °C, the cells could be selectively destroyed. To achieve this, a dose of magnetic nanoparticles could be injected into a region of malignant tissue, after which an alternating magnetic field could be applied to the magnetic nanoparticles. If the field is sufficiently strong and of optimum frequency, the magnetic nanoparticles will absorb energy and heat the surrounding tissue, affecting only the infected cells (Pankhurst *et al*. 2003).

However, this method still remains problematic for clinical use for several reasons (Koltsov and Perry 2004). In hyperthermia treatments, high magnetic fields are required for this technique to be effective. It is also difficult to localize enough magnetic particles in the cancerous region because the body's main defense system, the reticuloendothelial system, engulfs and removes any inert materials, so special coatings for the nanoparticles should be used to overcome this problem. Furthermore, to ensure the nanoparticles have a suitable Curie temperature, above which they no longer absorb energy, the size, shape and physical properties of the magnetic nanomaterials should be optimized.

1.5.2.2 Targeted Drug Delivery

As shown in Figure 1.13, the effectiveness of a drug is related to the drug dose over a certain dose range, and usually this relationship changes in the higher dose range. Often, toxicity sets in before the saturation limit is approached, and the therapeutic window with acceptable side effects is often narrow. The task of drug targeting is to push the systemic toxicity/side effect threshold to extremes such that the therapeutic window widens enough to cover the dose-response space up to the limit of local (target site) saturation (Plank *et al.* 2003b; Neuberger *et al.* 2005).

Magnetic nanoparticles can be used in targeted drug delivery. Functionalized magnetic nanoparticles used in drug delivery may contain drugs that are expected to be released into malignant cells and on-board sensors and actuators that control and regulate the drug release. As shown in Figure 1.14, in a drug delivery process, the drug molecules are bound to magnetic carriers. The process of drug localization is based on the competition between forces exerted on the carriers by blood compartment, and magnetic forces generated from the magnet. When the magnetic forces exceed the linear blood flow rates in arteries ($10\,\mathrm{cm\,s^{-1}}$) or capillaries ($0.05\,\mathrm{cm\,s^{-1}}$), the magnetic carriers are retained at the target site and maybe internalized by the endothelial cells of the target tissue. The use of nanoparticles favors the transport through the capillary systems of organs and tissues avoiding vessel embolism (Tartaj *et al.* 2003). Once the drugs/carriers are concentrated at

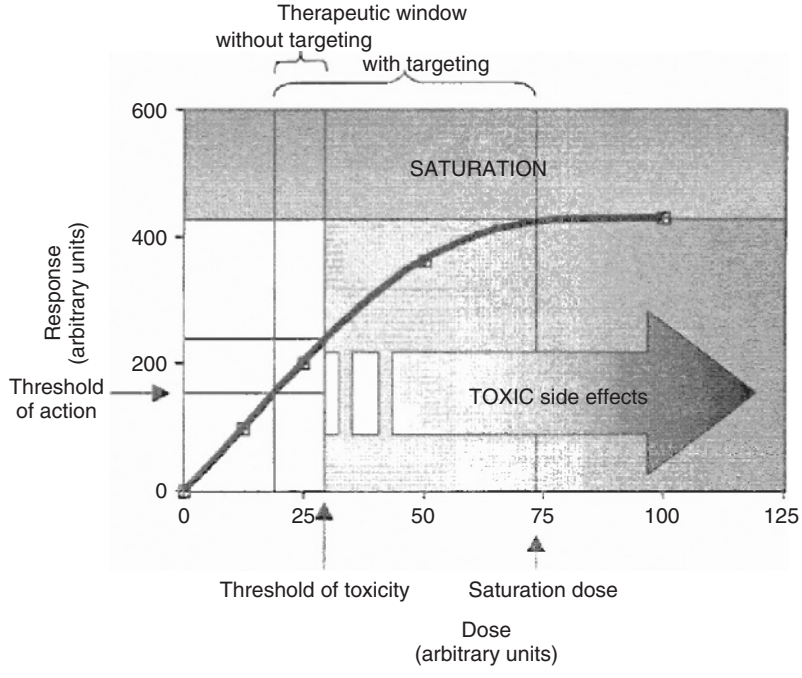

Figure 1.13 Toxic side effects often restrict the possibility of exploiting the full dose-response range of a drug up to (local) saturation levels. One objective of targeting is achieving target site saturation levels while pushing the non-target side toxicity threshold to higher doses. In this manner, the therapeutic window widens enough to achieve maximum local effect. Shown is a hypothetical dose-response relationship with arbitrary toxicity and saturation levels just to illustrate the potential of drug targeting. (Plank *et al.* 2003b)

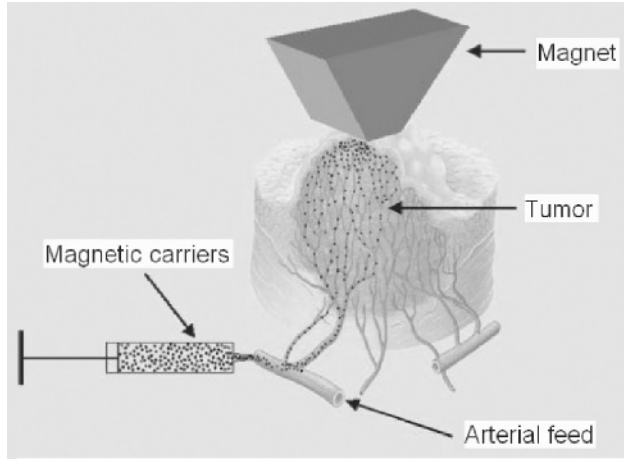

Figure 1.14 Schematic representation of the magnetically driven transport of drugs to a specific region. A catheter is inserted into an arterial feed to the tumor and a magnetic stand is positioned over the targeted site. (Alexiou *et al*. 2005)

the diseased site, the drugs are released from the carriers through modulation of magnetic field, enzymatic activity or changes in physiological conditions such as pH, osmolality or temperature. The released drugs then enter into the malignant cells. The treatment efficacy can be significantly improved by the magnetic 'tag-drag-release' process, and the required doses are simultaneously reduced.

The use of magnetic nanoparticles for drug delivery has significant advantages, such as the ability to target specific locations in the body, the reduction of the quantity of drug needed to attain a particular concentration in the vicinity of the target and the reduction of the concentration of the drug at non-target sites minimizing severe side effects (Arruebo *et al*. 2007). The advantages of targeted drug delivery make this method attractive for cancer treatment. Conventional chemotherapy has severe side effects as the agents used to kill cancerous tumors also kill healthy cells. In a targeted delivery approach, the chemotherapy agents are attached to magnetic nanoparticles, and the chemotherapy agents are then pulled towards malignant cells by a magnetic field focused on the target tumor. After the chemotherapy agents are aggregated around the tumor, the drug can be released by hitting the aggregate with an RF pulse, and therefore the drug concentration in the tumor is high, while the drug concentration at the rest of the body is relatively low (Could 2004).

To realize effective drug delivery, special attention should be paid to the choice of magnetic particles (Could 2004). Using a larger magnetic particle, a stronger magnetic force against blood flow can be exerted on the particle. Moreover, the particles should be small enough to avoid the risk of clogging small capillaries, whose diameter is about several micrometers. Magnetic nanoparticles for targeted drug delivery should also be completely biocompatible. It has been verified that iron oxide particles are non-toxic, and can be eventually used in the formation of blood hemoglobin. However, for gold-coated ferromagnetic particles, the situation is somewhat complicated. The small amount of gold may pass through the body eventually, and the iron will be metabolized. Cobalt is more stable than iron, and so it is easier for fabrication. However, cobalt is not suitable for *in vivo* applications due to its toxicity.

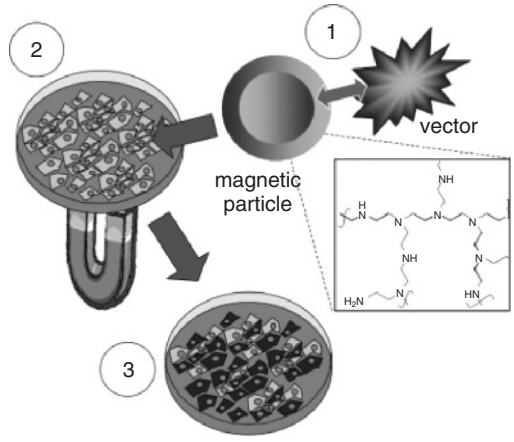

Figure 1.15 Procedure of magnetofection. Gene vectors are associated with magnetic particles coated with polyelectrolytes. Cells are cultured with the vector-magnetic particles under an external magnetic field. As the magnetic field attracts the vector-magnetic particles toward the cells, almost all the cells get in contact with vectors, and a high percentage of cells are rapidly transfected. (Plank 2003a)

1.5.2.3 Magnetofection

With advances in molecular biology and the sequencing of the human genome, gene therapy is playing a pivotal role in the treatment of genetic diseases. Gene therapy involves the introduction of healthy copies of mutated or absent genes into target cells so as to promote the expression of normal protein and to restore correct cellular function (Mehier-Humbert and Guy 2005). DNA drugs provide new hope in treating, preventing and controlling disease, almost certainly improving overall human health. Although non-viral DNA delivery systems have great therapeutic and prophylactic potential, their clinical utility has been limited by three major barriers (Luo 2005): inefficient uptake by the cell, insufficient release of DNA within the cell and ineffective nuclear targeting and transport. As the size of most cells is in the micrometer range, and the space inside a cell is extremely crowded, ideal DNA delivery systems must be in the nanometer range where they interact with or are delivered into a cell. Nanoscale science and nanotechnology provide more flexibility and precision to control the structure and composition of delivery systems, thus promising approaches for more effective and specific non-viral DNA delivery systems (Scherer *et al*. 2002; Plank *et al*. 2003a).

The magnetofection method is inspired by the method of targeted drug delivery using magnetic nanoparticles. Figure 1.15 illustrates the procedure of magnetofection. In this method, gene vectors are associated with superparamagnetic nanoparticles. Under the influence of magnetic gradient fields, the magnetic particles accumulate on the target cells. Due to the magnetic force exerted upon gene vectors, the entire vector dose is rapidly concentrated on the cells, and almost all the cells are in contact with a significant dose of gene vectors. The magnetic field may further push the magnetic particles associated with gene vectors across the plasma membrane and into the cell, and DNA is then released into the cytoplasm.

It should be noted that magnetofection is a method that enhances standard transfection procedures using viral or non-viral vectors. The magnetic field itself is ineffective unless the DNA vectors are complicated with magnetic particles. Magnetofection is applicable

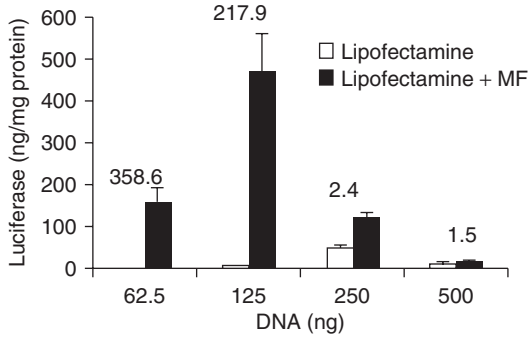

Figure 1.16 Luciferase expression in cultured HUVEC, using Lipofectamine with or without magnetofection (MF). Numbers above the bars represent the n-fold increase achieved by magnetofection compared to the conventional non-viral transfection technique. (Mehier-Humbert and Guy 2005)

to both viral and non-viral gene vectors, and it can be used in targeted gene delivery *in vitro* as well as *in vivo* (Plank 2003a). Magnetofection is a simple method. This method only requires a magnetic plate, and no expensive instruments are needed. However the magnetic plate should be specially designed so that the heterogeneous magnetic field generated by the plate can satisfy three requirements. First, the magnetic field should effectively magnetize the magnetic nanoparticles in solution. Second, the magnetic field should have a very strong gradient to attract the nanoparticles. Third, the magnetic field should cover the whole surface of the plate (Mehier-Humbert and Guy 2005).

As shown in Figure 1.16, magnetofection allows an increase in transfection efficiency by up to several hundred-fold (Mehier-Humbert and Guy 2005). In the experiment, the cell cultures subjected to magnetofection are placed on Nd-Fe-B magnetic plates for 15 minutes. Using a gene reporter encoding for Green Fluorescent Protein (GFP), transfection rates of about 40 % are achieved in human umbilical vein endothelial cells (HUVEC), which are well known as being difficult to transfect.

The magnetofection technique opens a novel perspective on gene delivery (Plank 2003a; Mehier-Humbert and Guy 2005; Scherer *et al*. 2002). Firstly, this technique can be used to rapidly and efficiently introduce nucleic acids into primary cells, and this will greatly improve the speed and efficiency of many gene-related tests, such as the examination of gene function, the identification of nucleic acids with therapeutic potential and the assessment of risks associated with the transfer of genetic material into cells. The high efficiency of magnetofection is mainly due to the quick sedimentation of the full vector dose on the target cells. In a magnetofection procedure, all the cells can be bound with vector particles in several minutes, while in a conventional transfection procedure, it takes several hours to achieve the same frequency of vector–target cell contact. Secondly, the magnetofection technique saves material. By using this technique, very low vector doses and extremely short incubation times are needed to achieve high transgene expression levels. In this way, the possible toxicity to the cells due to the transfection process can be avoided. Thirdly, it allows magnetic field-guided targeting. The force exerted on a magnetic particle in liquid suspension is related to the magnetic flux density, the magnetic field gradient and the particle volume. This provides flexibilities for optimizing these parameters to achieve the best effects. Fourthly, this method greatly profits from the fact that the individual modules of a system can be optimized independently and variants can be assembled in a combinatorial manner, thus facilitating optimization towards specific applications. The size and surface chemistry of magnetic particles can be tailored to meet

specific demands on physical and biological characteristics; also the linkage between vector and magnetic particle can be designed accordingly.

There are several perspectives to the future use of magnetofection (Scherer *et al*. 2002). For *in vitro* application, magnetofection is particularly useful in the transfection/transduction of difficult-to-transfect/transduce cells, and it is an ideal research tool when the available vector dose, the process time and the sustainable costs are limited. Magnetofection is also a very good choice for *in vivo* gene- and nucleic acid-based therapies which require local treatments. With a simple magnetofection set-up, gene delivery to surgically accessible sites such as gut, stomach and vasculature can be greatly improved and further local applications can be achieved.

1.5.2.4 Mechanical Forces on Cells

The mechanical forces on cells play a vital role in controlling the forms and functions of cells, and the processes of many diseases (Could 2004). Generally speaking, the forces applied on biological entities generally fall into two types: pulling (tensional) forces or twisting (torsional) forces. The tensional force often results from the magnetic separation process, where the functionalized magnetic particles pull their attached targets along the external magnetic field gradient. The torsional force often results from coated ferromagnetic beads, which are first magnetized by a strong and short magnetic pulse, and subsequently subjected to a weak but constant magnetic field whose direction is perpendicular to the direction of the pulsed field. The ferromagnetic beads try to realign along the direction of the constant magnetic field, and the movement of the beads results in a twisting force on the surfaces of cells associated to the beads. The information about the stiffness and viscoelasticity of the surrounding cells could be derived from the extent of the rotation. This procedure can be improved to study the effects of the mechanical force inside individual cells. Many efforts have been made to investigate how external mechanical forces are transferred across specific cell receptors and how this translates into the changes in intracellular biochemistry and gene expression.

1.5.2.5 Detoxification

Magnetic nanoparticles can be used in the treatment after a poison gas attack. The detoxification of contaminated personnel and environment is based on the magnetic 'tag and drag' mechanism, which is often used in the targeted drug delivery (Could 2004). As shown in Figure 1.17, in the detoxification process, the magnetic nanoparticles, which are specially functionalized for catching the toxin to be detoxified, are injected into the body of the patient, and then an external magnetic field is applied to concentrate the toxin-tagged particles and draw them out of the patient's body. To achieve efficient detoxification, the magnetic moment of the magnetic particles should be high enough, so that the magnetic particles attached with toxin molecules can be quickly concentrated and drawn out of the body by an externally applied magnetic field gradient.

1.5.3 Magnetic Biosensors and Biochips Based on Magnetic Thin Films

Nanotechnologies have been used in the development of high sensitivity, high accuracy and high spatial resolution sensors. A sensor usually consists of a power supply, a sensing action element which converts the detected property into an electrical signal and a reporting unit which transmits the sensing signal to a remote detector. Using nanotechnologies, sensors can be made as small as possible so that they are minimally invasive. Secondly,

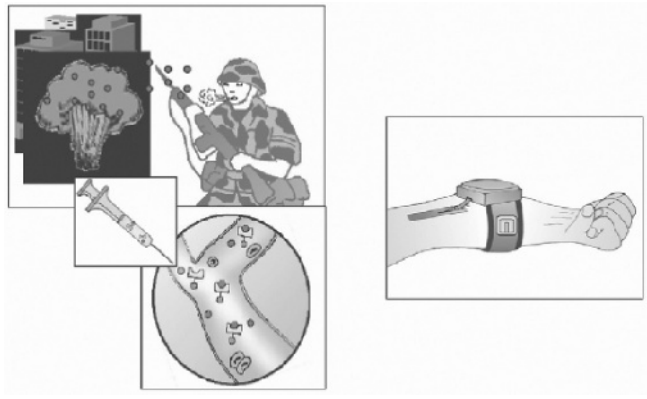

Figure 1.17 Mechanism of detoxification using magnetic nanoparticles. (Could 2004)

using nanotechnologies, the sensing element can be made to be very specific and accurate. Along with decrease of the sensor dimension, the sensing area also decreases, making increasing demands on sensitivity. This may require detection at the single molecule level, which is close to the limit of the length scale in nanotechnology. Therefore, nanoscience and nanotechnologies are expected to help the design and production of smaller, cheaper sensors with increasing selectivity (Royal Society and Royal Academy of Engineering 2004).

Nanosensors have been widely used in various areas, for example monitoring the quality of drinking water, detecting and tracking environmental pollution and checking food edibility. Nanosensors can also be used to achieve individualized healthcare with greater safety and security (Royal Society and Royal Academy of Engineering 2004).

Magnetic thin films have been used in the development of biosensors and biochips for biomedical applications. Most nanosensors developed from magnetic thin films are based on the magnetoresistance effect. The development of magnetoresistance nanosensors, along with other types of biosensors, is discussed in detail in Chapter 8. Here we briefly discuss biosensors and sensor arrays.

1.5.3.1 Biosensors

Biosensors usually detect the stray magnetic fields of magnetic nanoparticles which are attached to biological entities (Could 2004; Han 2006; Rife *et al.* 2003). In a magnetoresistive biosensor detection scheme, to perform genetic screening, iron oxide nanoparticles are functionalized, for example, with streptavidin, so that they can bind with targets containing biotinyl groups. Meanwhile, a surface is coated with biomolecular probes that can bind with complementary target species. As shown in Figure 1.18, the target hybridizes with the immobilized molecular probe, and links to the functionalized iron oxide magnetic label. The stray magnetic field of the captured magnetic nanoparticle is detected by the magnetic sensor beneath the functionalized surface.

1.5.3.2 Sensor Arrays

The efficiency of bio-analysis can be greatly improved by arraying biosensors. Generally speaking, there are two approaches to arraying biosensors. One approach is to array many sensors with the same functionality. Using such arrays, many bio-analyses of the same

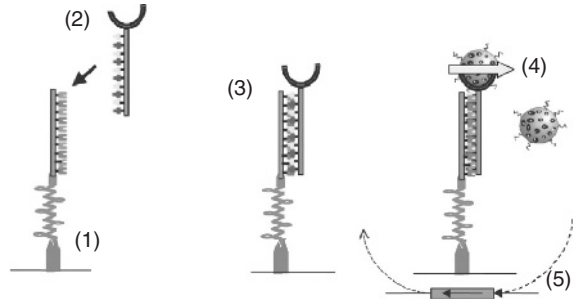

Figure 1.18 Detection scheme of a magnetoresistive (MR) sensor. (1) Immobilized probe DNA; (2) biotinilated target DNA; (3) biotinilated target DNA hybridizes with probe DNA; (4) magnetic label bound to biotinilated target; (5) MR sensor detects the fringe field from the magnetic label. (Could 2004)

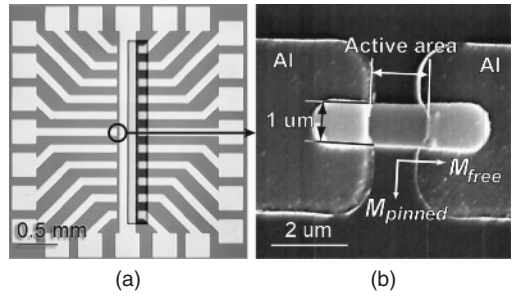

Figure 1.19 (a) Optical microscope image of a 1 μm wide spin valve sensor array and (b) scanning electron microscope image of a 1 μm wide sensor strip (center). The dark bar in the center of image (a) is the photoresist passivation layer. (Li *et al*. 2003)

type can be conducted concurrently. Figure 1.19 shows an array of 11 spin valve sensors (Li *et al*. 2003).

The other approach is to array different types of sensor together, resulting in multi-sensing chips, as shown in Figure 1.20. Using such an array, different bio-analysis on a sample could be simultaneously conducted using the different sensors on the array (Could 2004; Rife *et al*. 2003).

1.5.4 Trends of the Biomedical Applications of Magnetic Nanomaterials

Though great progress has been made in the applications of magnetic nanoparticles in biomedicine (Pankhurst 2003), many challenges remain. To realize the full potential of magnetic nanomaterials, researchers within different disciplines, such as physics, chemistry, materials science, electric and electronic engineering, biology and medicine, should work together. We discuss below two main trends in the biomedical applications of magnetic nanomaterials: multi-functional nanomaterials and lab-on-a-chip devices.

1.5.4.1 Multi-functional Nanomaterials

One of the main trends in the research of magnetic nanoparticles for biomedical applications is the development of magnetic nanoparticles that can perform more than one

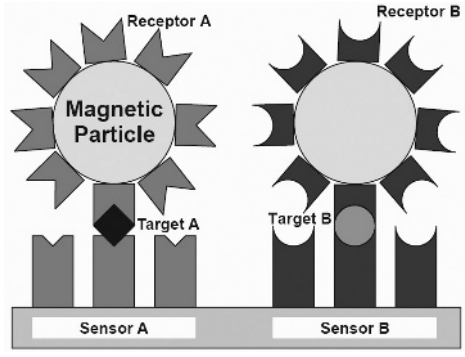

Figure 1.20 Detection of two different types of targets using an array with two types of sensors. (Rife *et al*. 2003). Reprinted from: Rife, J. C., Miller, M. M., Sheehan, P. E. Tamanaha, C. R. Tondra, M. Whitman, L. J. (2003). Design and performance of GMR sensors for the detection of magnetic microbeads in biosensors, *Sensors and Actuators A*, **107**, 209–218, with permission from Elsevier

function. A great deal of effort is being made to build a multi-functional nanoplatform that can be used to create desired multi-functional nanoparticles for diagnostic and/or therapeutic applications, as shown in Figure 1.21.

Figure 1.21(a) schematically shows a multi-functional nanoparticle for cancer therapy. The cancer cell targeting component ensures the nanoparticle reaches the cancer cells. The drug delivery indicator controls and reports the drug delivery. The cell death sensor reports whether the cancer cell has been killed, and the contrast agent checks the therapeutic effects. It should be noted that there is a long way to go to develop such a multi-functional nanoparticle, and at present it is still at an early stage (National Institute of Health and National Cancer Institute 2004). As shown in Figure 1.21(b), a multi-functional nanoplatform needs to be developed for the development of multi-functional nanoparticles. Such a multi-functional nanoplatform should include targeting unit, report unit, therapeutic unit, imaging unit and so on. Much effort needs to be made in developing such units, and constructing the nanoplatform using these units.

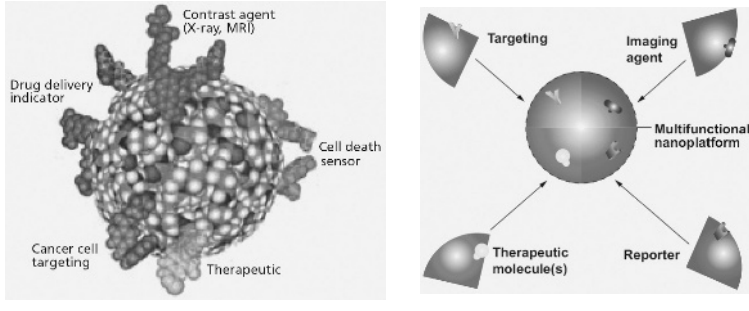

Figure 1.21 Development multi-functionality of particles for nanomedicine. (a) An example of multi-functional nanoparticle; (b) a multi-functional nanoplatform for the development of multi-functional nanoparticles. (National Institute of Health and National Cancer Institute 2004)

1.5.4.2 Microfluidics and Labs-on-chips

Many efforts have been made in the development of magnetoelectronic tools that can precisely detect and manipulate individual cells and biomolecules. The development of such magnetoelectronic tools is based on microfluidics, which deal with the knowledge and techniques for manipulating, investigating and utilizing tiny fluid volumes in a controlled way (Satyanarayana 2005). The microfluidic devices are usually built on microchips with channels conducting liquid under pressure or with an applied electrical current (Alper 2005b). This technology is expected to revolutionize many fields, especially chemistry, biology and medicine. In technical literatures, many words have been coined to describe such microfluidic devices: lab-on-a-chip device, micro total analysis system (μTAS), miniaturized analysis system, microfluidic system and nanofluidic system. In the following discussion, we use lab-on-a-chip and labs-on-chips.

A lab-on-a-chip device is a combination and integration of fluidic, sensor and detection elements to perform a complete sequence of chemical reactions or analyses, including sample preparation, mixing, reaction, separation and detection. In the example shown in Figure 1.22, microfluidic components with different functions are connected with each other to form an integrated system; therefore multiple functionalities can be realized on a single chip (Liu *et al*. 2004). In biomedical applications, the liquid in the channels may contain small particles, such as proteins, DNA or even single cells, so that changes during disease development can be monitored (Alper 2005b).

Lab-on-a-chip technology can be regarded as an interface between the nanoscale and the macro-world. It can be used for handling nanoparticles, cells or nanobarcodes, and for manipulating cellular machinery. However, it should be noted that the structures in a lab-on-a-chip device are not necessarily nanostructures, and they may be in the micrometer to even millimeter range. But, on the other hand, by integrating nanostructures, nanocoatings, nanoactuators and nano-detection and measurement tools such as nano-electrodes and nano-optics, more and more powerful microfluidic platforms are being developed.

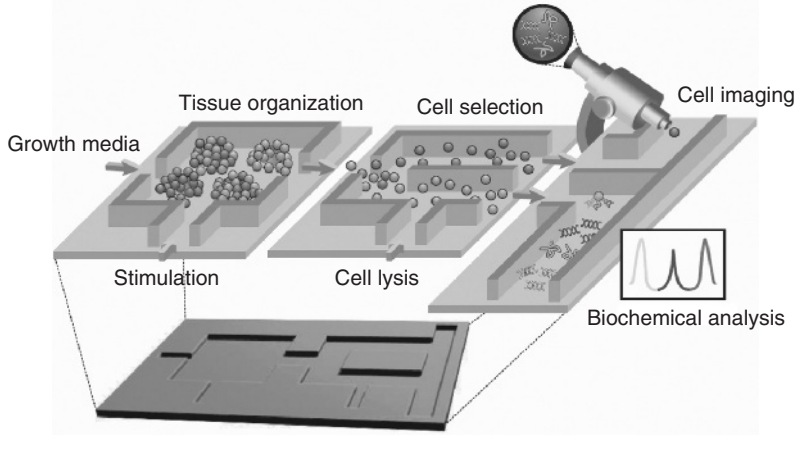

Figure 1.22 Tissue organization, culture and analysis in a lab-on-a chip device. (El-Ali *et al*. 2006)

Lab-on-a-chip technology exhibits both technical and economical advantages (Niemeyer and Mirkin 2004; Alper 2005b). First, as the surface to volume ratio of the fluids in lab-on-a-chip devices is extremely large, the surface effects dominate volume effects. This leads to well-defined flow characteristics: the flow is strictly laminar and turbulence only appears in very limited regions around sharp edges, the equilibrium conditions can be reached much faster and the capillary forces may advantageously be used for fluid transport. Meanwhile, the large surface implies a high reaction efficiency, as the surface areas which may be coated with catalysts or enzymes are large compared to the reaction volume. Second, the small sample volumes involved are of enormous advantage especially for highly parallel applications, like array devices used in genomics, proteomics and drug discovery. This fact is especially significant when analyzes are expensive or scarce. Furthermore, due to the small sample volumes needed, minimally invasive methods are sufficient for taking samples, for example blood or interstitial fluids. Third, lab-on-a-chip devices can be used to measure individual biomolecules, such as a single enzyme or a single piece of DNA. Because many biology effects are related to the behaviors of individual molecules, using this capability, we can investigate the topics that have been very difficult study, especially those related to rare biochemical and genetic events. Fourth, thousands of analyses can be performed concurrently by multiplexing individual microfluidic devices, or combining them in parallel. The integration and the mass-fabrication capabilities of micro-fabrication technology make the application of labs-on-chips economically attractive.

Lab-on-a-chip technologies show great application promise in cancer diagnosis (Satyanarayana 2005). As cancer is a very complicated fatal disease, it is necessary to identify quickly the mutations that may predispose one to cancer, and to study how the communications between cancer cells are made to cause the disease. The less invasive procedures and testing methods based on microfluidic technology can show early evidence of disease, and can be used to understand the circumstances that foster disease. This technique can provide genetic and proteomic information at the single-cell level which is valuable for the diagnosis and treatment of the disease. Furthermore, by using microfluidic devices, both the time and the amount of biological sample needed to conduct a large number of tests can be greatly reduced. As shown in Figure 1.23, in a lab-on-a-chip device which is slightly larger than a dime (with a diameter of 18 mm), thousands of experiments can be run concurrently, and this technique can be used to define the genetic bases of diseases, such as cancer (Balagadde *et al*. 2005).

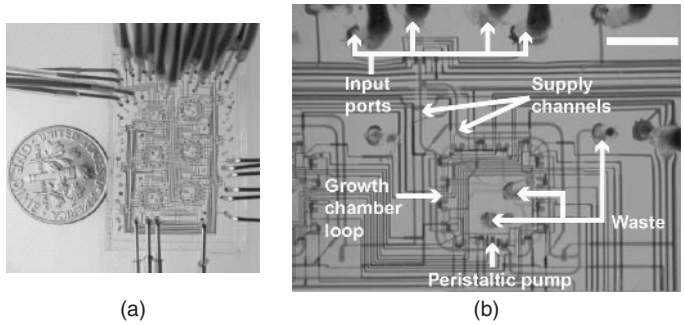

Figure 1.23 (a) Optical micrograph of six microchemostats that operate in parallel on a single chip; (b) optical micrograph of a single microchemostat and its main components. Scale bar, 2 mm. (Balagadde *et al*. 2005)

Though many problems for the design and fabrication of microfluidic devices have been solved, such as on-chip preparation of samples, functional complexity, integration level and fabrication cost (Liu *et al*. 2004), challenges still exist in the development of microfluidic devices. First, microfluidics is a new field of science and technology. When the dimensions of a system become smaller and smaller, the system behaviors may change greatly. More fundamental studies in fluid flows at the micro- and nanoscale are needed (Alper 2005b). Second, to satisfy the requirements of complex analysis, it is necessary to increase the integration density and the functionalities of lab-on-a-chip devices. Finally, before lab-on-a-chip devices can be widely used, they should be developed at lower cost, and in addition they should be portable and easy to operate.

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