3 Science and applications

3.1 Introduction

1 In this chapter we provide an overview of some key current developments in nanoscience and nanotechnologies, and highlight some possible future applications. The chapter is informed by evidence from scientists and engineers in academia and industry. It illustrates the wide-ranging interest in these areas and provides a background to the later chapters, which address health, environmental, social, ethical and regulatory implications of nanotechnologies. It does not consider in detail the developments in nanoscience and nanotechnologies in all scientific and engineering fields.

2 As nanoscience and nanotechnologies cover such a wide range of fields (from chemistry, physics and biology, to medicine, engineering and electronics), we have considered them in four broad categories: nanomaterials; nanometrology; electronics, optoelectronics and information and communication technology; and bio-nanotechnology and nanomedicine. This division helps to distinguish between developments in different fields, but there is naturally some overlap.

3 Where possible, we define the development of future applications as short term (under 5 years), medium term (5–15 years), and long term (over 20 years). It may be that some of the potential applications that we identify are never realised, whereas others that are currently unforeseen could have a major impact. We also identify potential in environmental, health and safety, ethical or societal implications or uncertainties that are discussed further in later chapters.

4 Current industrial applications of nanotechnologies are dealt with in Chapter 4, as are the factors that will influence their application in the future.

3.2 Nanomaterials

3.2.1 Introduction to nanomaterials

5 A key driver in the development of new and improved materials, from the steels of the 19th century to the advanced materials of today, has been the ability to control their structure at smaller and smaller scales. The overall properties of materials as diverse as paints and silicon chips are determined by their structure at the micro- and nanoscales. As our understanding of materials at the nanoscale and our ability to control their structure improves, there will be great potential to create a range of materials with novel characteristics, functions and applications.

6 Although a broad definition, we categorise nanomaterials as those which have structured components with at least one dimension less than 100 nm. Materials that have one dimension in the nanoscale (and are extended in the other two dimensions) are layers, such as a thin films or surface coatings. Some of the features on computer chips come in this category. Materials that are nanoscale in two dimensions (and extended in one dimension) include nanowires and nanotubes. Materials that are nanoscale in three dimensions are particles, for example precipitates, colloids and quantum dots (tiny particles of semiconductor materials). Nanocrystalline materials, made up of nanometre-sized grains, also fall into this category. Some of these materials have been available for some time; others are genuinely new. The aim of this chapter is to give an overview of the properties, and the significant foreseeable applications of some key nanomaterials.

7 Two principal factors cause the properties of nanomaterials to differ significantly from other materials: increased relative surface area, and quantum effects. These factors can change or enhance properties such as reactivity, strength and electrical characteristics. As a particle decreases in size, a greater proportion of atoms are found at the surface compared to those inside. For example, a particle of size 30 nm has 5% of its atoms on its surface, at 10 nm 20% of its atoms, and at 3 nm 50% of its atoms. Thus nanoparticles have a much greater surface area per unit mass compared with larger particles. As growth and catalytic chemical reactions occur at surfaces, this means that a given mass of material in nanoparticulate form will be much more reactive than the same mass of material made up of larger particles.

8 In tandem with surface-area effects, quantum effects can begin to dominate the properties of matter as size is reduced to the nanoscale. These can affect the optical, electrical and magnetic behaviour of materials, particularly as the structure or particle size approaches the smaller end of the nanoscale. Materials that exploit these effects include quantum dots, and quantum well lasers for optoelectronics.

9 For other materials such as crystalline solids, as the size of their structural components decreases, there is much greater interface area within the material; this can greatly affect both mechanical and electrical properties. For example, most metals are made up of small crystalline grains; the boundaries between the grain slow down or arrest the propagation of defects when the material is stressed, thus giving it strength. If these grains can be made very small, or even nanoscale in size, the interface area within the material greatly

increases, which enhances its strength. For example, nanocrystalline nickel is as strong as hardened steel. Understanding surfaces and interfaces is a key challenge for those working on nanomaterials, and one where new imaging and analysis instruments are vital.

10 Nanomaterials are not simply another step in the miniaturization of materials. They often require very different production approaches. As introduced in Chapter 2, and discussed further in Chapter 4, there are several processes to create nanomaterials, classified as 'top-down' and 'bottom-up'. Although many nanomaterials are currently at the laboratory stage of manufacture, a few of them are being commercialised.

3.2.2 Nanoscience in this area

11 Below we outline some examples of nanomaterials and the range of nanoscience that is aimed at understanding their properties. As will be seen, the behaviour of some nanomaterials is well understood, whereas others present greater challenges.

a) Nanoscale in one dimension

Thin films, layers and surfaces
12 One-dimensional nanomaterials, such as thin films and engineered surfaces, have been developed and used for decades in fields such as electronic device manufacture, chemistry and engineering. In the silicon integrated-circuit industry, for example, many devices rely on thin films for their operation, and control of film thicknesses approaching the atomic level is routine. Monolayers (layers that are one atom or molecule deep) are also routinely made and used in chemistry. The formation and properties of these layers are reasonably well understood from the atomic level upwards, even in quite complex layers (such as lubricants). Advances are being made in the control of the composition and smoothness of surfaces, and the growth of films.

13 Engineered surfaces with tailored properties such as large surface area or specific reactivity are used routinely in a range of applications such as in fuel cells and catalysts (see section 3.2.3b). The large surface area provided by nanoparticles, together with their ability to self assemble on a support surface, could be of use in all of these applications.

14 Although they represent incremental developments, surfaces with enhanced properties should find applications throughout the chemicals and energy sectors. The benefits could surpass the obvious economic and resource savings achieved by higher activity and greater selectivity in reactors and separation processes, to enabling small-scale distributed processing (making chemicals as close as possible to the point of use). There is already a move in the chemical industry towards this. Another use could be the small-scale, on-site production of high value chemicals such as pharmaceuticals.

b) Nanoscale in two dimensions

15 Two dimensional nanomaterials such as tubes and wires have generated considerable interest among the scientific community in recent years. In particular, their novel electrical and mechanical properties are the subject of intense research.

Carbon nanotubes
16 Carbon nanotubes (CNTs) were first observed by Sumio Iijima in 1991 (Iijima 1991). CNTs are extended tubes of rolled graphene sheets. There are two types of CNT: single-walled (one tube) or multi-walled (several concentric tubes) (Figure 3.1). Both of these are typically a few nanometres in diameter and several micrometres (10^{-6}m) to centimetres long. CNTs have assumed an important role in the context of nanomaterials, because of their novel chemical and physical properties. They are mechanically very strong (their Young's modulus is over 1 terapascal, making CNTs as stiff as diamond), flexible (about their axis), and can conduct electricity extremely well (the helicity of the graphene sheet determines whether the CNT is a semiconductor or metallic). All of these remarkable properties give CNTs a range of potential applications: for example, in reinforced composites, sensors, nanoelectronics and display devices.

Figure 3.1a Schematic of a single-walled carbon nanotube (SWNT)

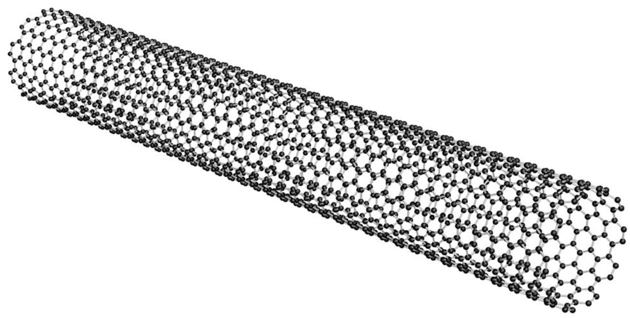
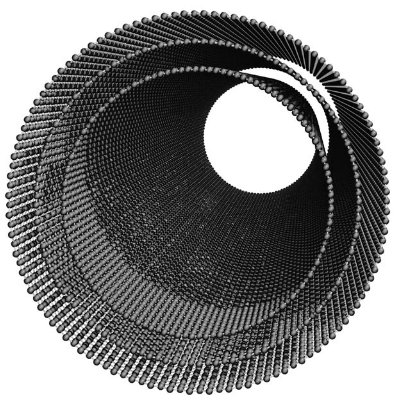


Figure 3.1b Schematic of a multi-walled carbon nanotube (MWNT)



17 CNTs are now available commercially in limited quantities. They can be grown by several techniques, which are discussed in section 4.3.1b. However, the selective and uniform production of CNTs with specific dimensions and physical properties is yet to be achieved. The potential similarity in size and shape between CNTs and asbestos fibres has led to concerns about their safety, which we address in detail in sections 5.3.1b and 5.3.2a.

Inorganic nanotubes
18 Inorganic nanotubes and inorganic fullerene-like materials based on layered compounds such as molybdenum disulphide were discovered shortly after CNTs. They have excellent tribological (lubricating) properties, resistance to shockwave impact, catalytic reactivity, and high capacity for hydrogen and lithium storage, which suggest a range of promising applications. Oxide-based nanotubes (such as titanium dioxide) are being explored for their applications in catalysis, photo-catalysis and energy storage.

Nanowires
19 Nanowires are ultrafine wires or linear arrays of dots, formed by self-assembly. They can be made from a wide range of materials. Semiconductor nanowires made of silicon, gallium nitride and indium phosphide have demonstrated remarkable optical, electronic and magnetic characteristics (for example, silica nanowires can bend light around very tight corners). Nanowires have potential applications in high-density data storage, either as magnetic read heads or as patterned storage media, and electronic and opto-electronic nanodevices, for metallic interconnects of quantum devices and nanodevices. The preparation of these nanowires relies on sophisticated growth techniques, which include self-assembly processes, where atoms arrange themselves naturally on stepped surfaces, chemical vapour deposition (CVD) onto patterned substrates, electroplating or molecular beam epitaxy (MBE). The 'molecular beams' are typically from thermally evaporated elemental sources.

Biopolymers
20 The variability and site recognition of biopolymers, such as DNA molecules, offer a wide range of opportunities for the self-organization of wire nanostructures into much more complex patterns. The DNA backbones may then, for example, be coated in metal. They also offer opportunities to link nano- and biotechnology in, for example, biocompatible sensors and small, simple motors. Such self-assembly of organic backbone nanostructures is often controlled by weak interactions, such as hydrogen bonds, hydrophobic, or van der Waals interactions (generally in aqueous environments) and hence requires quite different synthesis strategies to CNTs, for example. The combination of one-dimensional nanostructures consisting of biopolymers and inorganic compounds opens up a number of scientific and technological opportunities.

c) Nanoscale in three dimensions

Nanoparticles
21 Nanoparticles are often defined as particles of less than 100 nm in diameter. In line with our definitions of nanoscience and nanotechnologies (see Box 2.1), we classify nanoparticles to be particles less than 100 nm in diameter that exhibit new or enhanced size-dependent properties compared with larger particles of the same material. Nanoparticles exist widely in the natural world: for example as the products of photochemical and volcanic activity, and created by plants and algae. They have also been created for thousands of years as products of combustion and food cooking, and more recently from vehicle exhausts. Deliberately manufactured nanoparticles, such as metal oxides, are by comparison in the minority. In this report we will refer to these as natural, pollutant and manufactured nanoparticles, respectively.

22 As described in Chapter 2, nanoparticles are of interest because of the new properties (such as chemical reactivity and optical behaviour) that they exhibit compared with larger particles of the same materials. For example, titanium dioxide and zinc oxide become transparent at the nanoscale, however are able to absorb and reflect UV light, and have found application in sunscreens. Nanoparticles have a range of potential applications: in the short-term in new cosmetics, textiles and paints; in the longer term, in methods of targeted drug delivery where they could be to used deliver drugs to a specific site in the body. Nanoparticles can also be arranged into layers on surfaces, providing a large surface area and hence enhanced activity, relevant to a range of potential applications such as catalysts.

23 Manufactured nanoparticles are typically not products in their own right, but generally serve as raw materials, ingredients or additives in existing products. Although their production is currently low compared with other nanomaterials we have given them a considerable amount of attention in this report. This is because they are currently in a small number of consumer products such as cosmetics and their enhanced or novel properties may have implications for their toxicity. The evidence submitted during the course of our study indicates that for most applications, nanoparticles will be fixed (for example, attached to a surface or within in a composite) although in others they will be free or suspended in fluid. Whether they are fixed or free will have a significant affect on their potential health, safety and environmental impacts. We address these issues in detail in Chapter 5.

Fullerenes (carbon 60)
24 In the mid-1980s a new class of carbon material was discovered called carbon 60 (C_{60}) (Kroto et al 1985). A diagram of carbon 60 can be found in Figure 2.1. These are spherical molecules about 1 nm in diameter, comprising 60 carbon atoms arranged as 20 hexagons

and 12 pentagons: the configuration of a football. The C_{60} species was named 'Buckminsterfullerene' in recognition of the architect Buckminster Fuller, who was well-known for building geodesic domes, and the term fullerenes was then given to any closed carbon cage. In 1990, a technique to produce larger quantities of C_{60} was developed by resistively heating graphite rods in a helium atmosphere (Krätschmer et al 1990). Several applications are envisaged for fullerenes, such as miniature 'ball bearings' to lubricate surfaces, drug delivery vehicles and in electronic circuits.

Dendrimers
25 Dendrimers are spherical polymeric molecules, formed through a nanoscale hierarchical self-assembly process. There are many types of dendrimer; the smallest is several nanometres in size. Dendrimers are used in conventional applications such as coatings and inks, but they also have a range of interesting properties which could lead to useful applications. For example, dendrimers can act as nanoscale carrier molecules and as such could be used in drug delivery. Environmental clean-up could be assisted by dendrimers as they can trap metal ions, which could then be filtered out of water with ultra-filtration techniques.

Quantum dots
26 Nanoparticles of semiconductors (quantum dots) were theorized in the 1970s and initially created in the early 1980s. If semiconductor particles are made small enough, quantum effects come into play, which limit the energies at which electrons and holes (the absence of an electron) can exist in the particles. As energy is related to wavelength (or colour), this means that the optical properties of the particle can be finely tuned depending on its size. Thus, particles can be made to emit or absorb specific wavelengths (colours) of light, merely by controlling their size. Recently, quantum dots have found applications in composites, solar cells (Gratzel cells) and fluorescent biological labels (for example to trace a biological molecule) which use both the small particle size and tuneable energy levels. Recent advances in chemistry have resulted in the preparation of monolayer-protected, high-quality, monodispersed, crystalline quantum dots as small as 2 nm in diameter, which can be conveniently treated and processed as a typical chemical reagent.

3.2.3 Applications

27 Below we list some key current and potential short- and long-term applications of nanomaterials. Most current applications represent evolutionary developments of existing technologies: for example, the reduction in size of electronics devices.

a) Current

Sunscreens and cosmetics
28 Nanosized titanium dioxide and zinc oxide are currently used in some sunscreens, as they absorb and reflect ultraviolet (UV) rays and yet are transparent to visible light and so are more appealing to the consumer. Nanosized iron oxide is present in some lipsticks as a pigment but it is our understanding that it is not used by the European cosmetics sector. The use of nanoparticles in cosmetics has raised a number of concerns about consumer safety; we evaluate the evidence relating to these concerns in section 5.3.2b.

Composites
29 An important use of nanoparticles and nanotubes is in composites, materials that combine one or more separate components and which are designed to exhibit overall the best properties of each component. This multi-functionality applies not only to mechanical properties, but extends to optical, electrical and magnetic ones. Currently, carbon fibres and bundles of multi-walled CNTs are used in polymers to control or enhance conductivity, with applications such as anti-static packaging. The use of individual CNTs in composites is a potential long-term application (see section 3.2.3c). A particular type of nanocomposite is where nanoparticles act as fillers in a matrix; for example, carbon black used as a filler to reinforce car tyres. However, particles of carbon black can range from tens to hundreds of nanometres in size, so not all carbon black falls within our definition of nanoparticles.

Clays
30 Clays containing naturally occurring nanoparticles have long been important as construction materials and are undergoing continuous improvement. Clay particle based composites – containing plastics and nano-sized flakes of clay – are also finding applications such as use in car bumpers.

Coatings and surfaces
31 Coatings with thickness controlled at the nano- or atomic scale have been in routine production for some time, for example in MBE or metal oxide CVD for optoelectonic devices, or in catalytically active and chemically functionalized surfaces. Recently developed applications include the self-cleaning window, which is coated in highly activated titanium dioxide, engineered to be highly hydrophobic (water repellent) and anti-bacterial, and coatings based on nanoparticulate oxides that catalytically destroy chemical agents (Royal Society 2004a). Wear and scratch-resistant hard coatings are significantly improved by nanoscale intermediate layers (or multilayers) between the hard outer layer and the substrate material. The intermediate layers give good bonding and graded matching of elastic and thermal properties, thus improving adhesion. A range of enhanced textiles, such as breathable, waterproof and stain-resistant fabrics, have been enabled by the improved control of porosity at the nanoscale and surface roughness in a variety of polymers and inorganics.

Tougher and harder cutting tools
32 Cutting tools made of nanocrystalline materials, such as tungsten carbide, tantalum carbide and titanium carbide, are more wear and erosion-resistant, and last longer than their conventional (large-grained) counterparts. They are finding applications in the drills used to bore holes in circuit boards.

b) Short-term

Paints
33 Incorporating nanoparticles in paints could improve their performance, for example by making them lighter and giving them different properties. Thinner paint coatings ('lightweighting'), used for example on aircraft, would reduce their weight, which could be beneficial to the environment. However, the whole life cycle of the aircraft needs to be considered before overall benefits can be claimed (see section 4.5). It may also be possible to substantially reduce solvent content of paints, with resulting environmental benefits. New types of fouling-resistant marine paint could be developed and are urgently needed as alternatives to tributyl tin (TBT), now that the ecological impacts of TBT have been recognised. Anti-fouling surface treatment is also valuable in process applications such as heat exchange, where it could lead to energy savings. If they can be produced at sufficiently low cost, fouling-resistant coatings could be used in routine duties such as piping for domestic and industrial water systems. It remains speculation whether very effective anti-fouling coatings could reduce the use of biocides, including chlorine. Other novel, and more long-term, applications for nanoparticles might lie in paints that change colour in response to change in temperature or chemical environment, or paints that have reduced infra-red absorptivity and so reduce heat loss.

34 Concerns about the health and environmental impacts of nanoparticles (which we address in detail in Chapter 5) may require the need for the durability and abrasion behaviour of nano-engineered paints and coatings to be addressed, so that abrasion products take the form of coarse or microscopic agglomerates rather than individual nanoparticles.

Remediation
35 The potential of nanoparticles to react with pollutants in soil and groundwater and transform them into harmless compounds is being researched. In one pilot study the large surface area and high surface reactivity of iron nanoparticles were exploited to transform chlorinated hydrocarbons (some of which are believed to be carcinogens) into less harmful end products in groundwater (Zhang 2003). It is also hoped that they could be used to transform heavy metals such as lead and mercury from bioavailable forms into insoluble forms. Serious concerns have been raised over the uncontrolled release of nanoparticles into the environment; these are discussed in section 5.4.

Fuel Cells
36 Engineered surfaces are essential in fuel cells, where the external surface properties and the pore structure affect performance. The hydrogen used as the immediate fuel in fuel cells may be generated from hydrocarbons by catalytic reforming, usually in a reactor module associated directly with the fuel cell. The potential use of nano-engineered membranes to intensify catalytic processes could enable higher-efficiency, small-scale fuel cells. These could act as distributed sources of electrical power. It may eventually be possible to produce hydrogen locally from sources other than hydrocarbons, which are the feedstocks of current attention.

Displays
37 The huge market for large area, high brightness, flat-panel displays, as used in television screens and computer monitors, is driving the development of some nanomaterials. Nanocrystalline zinc selenide, zinc sulphide, cadmium sulphide and lead telluride synthesized by sol–gel techniques (a process for making ceramic and glass materials, involving the transition from a liquid 'sol' phase to a solid 'gel' phase) are candidates for the next generation of light-emitting phosphors. CNTs are being investigated for low voltage field-emission displays; their strength, sharpness, conductivity and inertness make them potentially very efficient and long-lasting emitters.

Batteries
38 With the growth in portable electronic equipment (mobile phones, navigation devices, laptop computers, remote sensors), there is great demand for lightweight, high-energy density batteries. Nanocrystalline materials synthesized by sol–gel techniques are candidates for separator plates in batteries because of their foam-like (aerogel) structure, which can hold considerably more energy than conventional ones. Nickel–metal hydride batteries made of nanocrystalline nickel and metal hydrides are envisioned to require less frequent recharging and to last longer because of their large grain boundary (surface) area.

Fuel additives
39 Research is underway into the addition of nanoparticulate ceria (cerium oxide) to diesel fuel to improve fuel economy by reducing the degradation of fuel consumption over time (Oxonica 2003).

Catalysts
40 In general, nanoparticles have a high surface area, and hence provide higher catalytic activity. Nanotechnologies are enabling changes in the degree of control in the production of nanoparticles, and the support structure on which they reside. It is possible to synthesise metal nanoparticles in solution in the presence of a surfactant to form highly ordered monodisperse films of the catalyst nanoparticles on a surface. This allows more uniformity in the size and chemical structure of the catalyst, which in turn leads to

greater catalytic activity and the production of fewer by-products. It may also be possible to engineer specific or selective activity. These more active and durable catalysts could find early application in cleaning up waste streams. This will be particularly beneficial if it reduces the demand for platinum-group metals, whose use in standard catalytic units is starting to emerge as a problem, given the limited availability of these metals.

c) Longer-term applications

Carbon nanotube composites

41 CNTs have exceptional mechanical properties, particularly high tensile strength and light weight. An obvious area of application would be in nanotube-reinforced composites, with performance beyond current carbon-fibre composites. One current limit to the introduction of CNTs in composites is the problem of structuring the tangle of nanotubes in a well-ordered manner so that use can be made of their strength. Another challenge is generating strong bonding between CNTs and the matrix, to give good overall composite performance and retention during wear or erosion of composites. The surfaces of CNTs are smooth and relatively unreactive, and so tend to slip through the matrix when it is stressed. One approach that is being explored to prevent this slippage is the attachment of chemical side-groups to CNTs, effectively to form 'anchors'. Another limiting factor is the cost of production of CNTs. However, the potential benefits of such light, high strength material in numerous applications for transportation are such that significant further research is likely.

Lubricants

42 Nanospheres of inorganic materials could be used as lubricants, in essence by acting as nanosized 'ball bearings'. The controlled shape is claimed to make them more durable than conventional solid lubricants and wear additives. Whether the increased financial and resource cost of producing them is offset by the longer service life of lubricants and parts remains to be investigated (along the lines of the methodology outlined in section 4.5). It is also claimed that these nanoparticles reduce friction between metal surfaces, particularly at high normal loads. If so, they should find their first applications in high-performance engines and drivers; this could include the energy sector as well as transport. There is a further claim that this type of lubricant is effective even if the metal surfaces are not highly smooth. Again, the benefits of reduced cost and resource input for machining must be compared against production of nanolubricants. In all these applications, the particles would be dispersed in a conventional liquid lubricant; design of the lubricant system must therefore include measures to contain and manage waste.

Magnetic materials

43 It has been shown that magnets made of nanocrystalline yttrium–samarium–cobalt grains possess unusual magnetic properties due to their extremely large grain interface area (high coercivity can be obtained because magnetization flips cannot easily propagate past the grain boundaries). This could lead to applications in motors, analytical instruments like magnetic resonance imaging (MRI), used widely in hospitals, and microsensors. Overall magnetisation, however, is currently limited by the ability to align the grains' direction of magnetisation.

44 Nanoscale-fabricated magnetic materials also have applications in data storage. Devices such as computer hard disks depend on the ability to magnetize small areas of a spinning disk to record information. If the area required to record one piece of information can be shrunk in the nanoscale (and can be written and read reliably), the storage capacity of the disk can be improved dramatically. In the future, the devices on computer chips which currently operate using flows of electrons could use the magnetic properties of these electrons, called spin, with numerous advantages. Recent advances in novel magnetic materials and their nanofabrication are encouraging in this respect.

Medical implants

45 Current medical implants, such as orthopaedic implants and heart valves, are made of titanium and stainless steel alloys, primarily because they are bio-compatible. Unfortunately, in some cases these metal alloys may wear out within the lifetime of the patient. Nanocrystalline zirconium oxide (zirconia) is hard, wear-resistant, bio-corrosion resistant and bio-compatible. It therefore presents an attractive alternative material for implants. It and other nanoceramics can also be made as strong, light aerogels by sol–gel techniques. Nanocrystalline silicon carbide is a candidate material for artificial heart valves primarily because of its low weight, high strength and inertness.

Machinable ceramics

46 Ceramics are hard, brittle and difficult to machine. However, with a reduction in grain size to the nanoscale, ceramic ductility can be increased. Zirconia, normally a hard, brittle ceramic, has even been rendered superplastic (for example, able to be deformed up to 300% of its original length). Nanocrystalline ceramics, such as silicon nitride and silicon carbide, have been used in such automotive applications as high-strength springs, ball bearings and valve lifters, because they can be easily formed and machined, as well as exhibiting excellent chemical and high-temperature properties. They are also used as components in high-temperature furnaces. Nanocrystalline ceramics can be pressed into complex net shapes and sintered at significantly lower temperatures than conventional ceramics.

Water purification

47 Nano-engineered membranes could potentially lead to more energy-efficient water purification processes, notably in desalination by reverse osmosis. Again, these

applications would represent incremental improvements in technologies that are already available. They would use fixed nanoparticles, and are therefore distinct from applications that propose to use free nanoparticles.

Military battle suits
48 Enhanced nanomaterials form the basis of a state-of-the-art 'battle suit' that is being developed by the Institute of Soldier Nanotechnologies at Massachusetts Institute of Technology, USA (MIT 2004). A short-term development is likely to be energy-absorbing materials that will withstand blast waves; longer-term are those that incorporate sensors to detect or respond to chemical and biological weapons (for example, responsive nanopores that 'close' upon detection of a biological agent). There is speculation that developments could include materials which monitor physiology while a soldier is still on the battlefield, and uniforms with potential medical applications, such as splints for broken bones. In section 6.7 we consider the possible social implications of the exploitation of nanotechnologies for military purposes.

3.3 Nanometrology

3.3.1 Introduction to nanometrology

49 The science of measurement at the nanoscale is called nanometrology. Its application underpins all of nanoscience and nanotechnologies. The ability to measure and characterise materials (determine their size, shape and physical properties) at the nanoscale is vital if nanomaterials and devices are to be produced to a high degree of accuracy and reliability and the applications of nanotechnologies are to be realised. Nanometrology includes length or size measurements (where dimensions are typically given in nanometres and the measurement uncertainty is often less than 1nm) as well as measurement of force, mass, electrical and other properties. As techniques for making these measurements advance, so too does the understanding of nanoscale behaviour and therefore the possibility of improving materials, industrial processes and reliability of manufacture. The instruments for making such measurements are many and varied; a description of some key instruments is given in Box 3.1. The characterisation of materials, particularly in the industrial context, is discussed further in Chapter 4.

50 As with all measurement, nanometrology is essentially an enabling technology. Nanotechnologies, however defined, cannot progress independently of progress in nanometrology. Apart from their direct influence on scientific research and its application, the solutions developed for nanometrology problems can often be exploited elsewhere. For example, the concept of the AFM, a key nanometrology tool, has had a direct influence on lithographic processes and techniques for molecular manipulation. Conversely, it is likely that continuing research into nanodevices will suggest new measurement methods.

51 Making measurements with nanoscale precision poses several major difficulties. Environmental fluctuations such as vibration or temperature change have a large effect at the nanoscale. For example, any external change to the large machines used in manufacturing microelectronics components will affect the creation of nanoscale features and their crucially important alignment to each other. The ability to measure these influences, and thereafter to minimise them, is therefore vital.

52 Currently, instruments are available that can make sufficiently precise measurements to support laboratory research. There are a number of sensor technologies and instruments with nanometre, or better, sensitivity for measuring length that repeat well if used carefully, including the scanning probe and electron microscopes and some optical devices (see Box 3.1). However, universal measurement standards have not yet been established. Data published recently from the Physikalisch-Technische Bundesanstalt in Germany (Breil et al 2002) shows that even apparently sophisticated users of atomic force microscopes can produce large variations in their measurements of the same artefacts. Without agreed standards, tools or machines cannot be calibrated at the nanometre scale. It is therefore not yet possible for laboratories and manufacturing plants to exchange or compare data or physical components. Also, health and safety standards cannot be set for legal requirements. Nanoparticle characterization for size, size distribution and shape is also lacking formal methods.

53 Evidence presented at our industry workshop highlighted that good comparative metrology is proving difficult to develop. There is no particular difficulty with working at the nanoscale within a single laboratory or organization in the sense artifacts (either universal or in-house 'gold standards' such as the spacing of the silicon lattice) can be used to calibrate instruments so that there is self-consistency across a set of measurements. In doing this there must naturally be levels of protection against vibration, thermal changes, etc that are becoming increasingly stringent. However, the determination of absolute measurements of length at the nanometer scale and below is very difficult and expensive.

3.3.2 Length measurement

54 Although there is not currently an international standard that can be applied to them, calibration artefacts are becoming available for AFMs for length measurement calibration in each of the three dimensions. Such artefacts can also be used for tip characterization, as the exact shape of the fine tip which scans across the surface can strongly influence length measurements, particularly when the tip

becomes blunt. The National Physical Laboratory (NPL) in the UK has a considerable reputation in formal metrology and has done much to develop measurement capability as well as to take responsibility for the UK's national standards. It also has excellent realisations of the metre, mainly through optical and x-ray interferometry, that can calibrate transfer standards with uncertainties of the order of nanometres when working with sufficiently large wave-fronts. However, comparative methods (akin to the interferometric measurement of optical lenses and mirrors) become ineffective when working with very small objects comparable to the wavelength of the photons being used. Hence, it is not yet possible to accurately determine dimensions or shape in all axes. Many surface characterization methods (especially for the electronics industries) directly exploit comparison via x-ray (occasionally optical) reflection or diffraction. It is likely that the practice of length metrology would be improved through better, more easily-used calibration systems and improved instrument design, relative to the current commercial versions. Undoubtedly, better education in best practice for nanometrology would also partly address this issue.

3.3.3 Force measurement

55 Along with length measurement, force measurement (measured in Newtons (N)) is likely to become an important area of nanometrology. The control of probe stiffness and geometry will need to improve if truly quantitative measurements of surface mechanical properties can be made, particularly when measuring biological and other soft materials. There is also likely to be an increasing need to accurately measure the elasticity of protein and nucleotide molecules, to determine bond strength and other properties of the molecules. Currently, there is a large capability gap in this field. There is a large, and growing, need for force characterisation in the pico- to micronewton (10^{-12}–10^{-6}N) range. Currently, no fully satisfactory techniques are available either for secondary standards or transfer artefacts, although a few research projects are in progress (NPL and the National Institute for Standards and Technology (NIST), USA, are both looking at methods based on electrostatic forces). Several groups, mainly within or sponsored by national laboratories (such as NPL and Warwick University in the UK, and NIST in the USA), are investigating systems that relate force to electrical properties and so to quantum standards. However, so far all of them remain experimental and a great deal more work is urgently needed into fundamental and transfer standards for forces much smaller than millinewtons. Unlike length measurement, there is also a lack of readily available and applicable force or mass instrumentation with sensitivity adequate for engineering on the nanometre scale. AFM cantilevers have nanonewton force sensitivity, but their calibration tends to be through indirect calculation from their dimensions, and batch-to-batch repeatability may be poor. Some nano-indentation instruments for hardness measurement use micro-electromechanical systems (MEMS), with broadly similar questions over traceability. Thus there is urgent need for research into basic laboratory and industrial nanoforce instrumentation alongside that for standards.

3.3.4 Measurement of single molecules

56 In the longer term, development in measurement at the scale of the single molecule is expected. Measurements of single organic molecules and of structures such as single-wall nanotubes are already made, providing the molecules can be anchored to a substrate. Electron microscope and AFM/STM determinations of shape are relatively routine in many research laboratories. Increasingly, there is interest in molecule stiffness, in effect producing a tensile test curve in which jumps indicate the breaking and by inference the location of various types of bond in folded proteins and nucleotides. AFM manufacturers are starting to offer options that can do this without the need for the skills of a large research team.

3.3.5 Applications

57 Metrology forms the basis of the semiconductor industry and as such is enormously advanced. The International Technology Roadmap for Semiconductors (ITRS) roadmap (see also section 3.4) highlights a series of challenges for nanometrology if it is to keep pace with the reduction in feature size of semiconductor devices. Shrinking feature sizes, tighter control of device electrical parameters and new interconnect materials will provide the main challenges for physical metrology methods. To achieve desired device scaling, metrology tools must be capable of measurement of properties at atomic distances. Compounding these is the uncertain nature of the development of device design, making it difficult to predict metrology needs in the long term and in particular the necessary metrology for manufacturing to ensure reliability. A major need is to integrate metrology data into the manufacturing process.

58 The developing capabilities of semiconductor processing, particularly the ever-reducing dimensions that can be defined using lithographic tools, are being combined with the techniques developed for MEMS device fabrication to enable the manufacture of electro-mechanical components with sub-100nm dimensions. The exploitation of these structures in nano-electromechanical systems (NEMS) devices has produced some interesting and exciting developments in the field of nanometrology. For example, Schwab et al (2000) have made a NEMS device that has enabled the measurement of the quantum of thermal conductance.

59 Another group has made ultra-thin silicon cantilevers with attonewton (10^{-18}N) sensitivity. These devices have potential applications in the

characterisation of single molecule properties and are examples of how the field of NEMS is increasing the capabilities of nanometrology.

60 The role of nanometrology and in particular the need for the standardisation of measurement at the nanometre scale is explored further in section 8.4.3. There is a need to develop agreed standards that can be used to calibrate equipment that will be used by both industry and regulators. We believe that this can best be addressed through existing programmes such as the Department of Trade and Industry (DTI) National Measurement System Programme and should be undertaken in collaboration with industry.

We recommend that the DTI supports the standardisation of measurement at the nanometre scale required by regulators and for quality control in industry through the adequate funding of initiatives under its National Measurement System Programme, and that it ensures that the UK is in the forefront of any international initiatives for the standardisation of measurement.

61 We are pleased to learn that initial steps in this area are being undertaken by the British Standards Institution, as part of the European Committee for Standardisation Technical Board working group on nanotechnology.

Box 3.1 Instruments used in nanometrology

a) Electron beam techniques

Transmission electron microscopy (TEM) is used to investigate the internal structure of micro- and nanostructures. It works by passing electrons through the sample and using magnetic lenses to focus the image of the structure, much like light is transmitted through materials in conventional light microscopes. Because the wavelength of the electrons is much shorter than that of light, much higher spatial resolution is attainable for TEM images than for a light microscope. TEM can reveal the finest details of internal structure, in some cases individual atoms. The samples used for TEM must be very thin (usually less than 100nm), so that many electrons can be transmitted across the specimen. However, some materials, such as nanotubes, nanocrystalline powders or small clusters, can be directly analysed by deposition on a TEM grid with a carbon support film. TEM and high-resolution transmission electron microscopy (HRTEM) are among the most important tools used to image the internal structure of a sample. Furthermore, if the HRTEM is adequately equipped, chemical analysis can be performed by exploiting the interactions of the electrons with the atoms in the sample.

The scanning electron microscope (SEM) uses many of the basic technology developed for the TEM to provide images of surface features associated with a sample. Here, a beam of electrons is focused to a diameter spot of approximately 1nm in diameter on the surface of the specimen and scanned back and forth across the surface. The surface topography of a specimen is revealed either by the reflected (backscattered) electrons generated or by electrons ejected from the specimen as the incident electrons decelerate secondary electrons. A visual image, corresponding to the signal produced by the interaction between the beam spot and the specimen at each point along each scan line, is simultaneously built up on the face of a cathode ray tube similar to the way that a television picture is generated. The best spatial resolution currently achieved is of the order of 1nm.

b) Scanning probe techniques

Scanning probe microscopy (SPM) uses the interaction between a sharp tip and a surface to obtain an image. The sharp tip is held very close to the surface to be examined and is scanned back-and-forth. The scanning tunnelling microscope (STM) was invented in 1981 by Gerd Binnig and Heinrich Rohrer, who went on to collect the Nobel Prize for Physics in 1986. Here, a sharp conducting tip is held sufficiently close to a surface (typically about 0.5nm) that electrons can 'tunnel' across the gap. The method provides surface structural and electronic information with atomic resolution. The invention of the STM led directly to the development of other 'scanning probe' microscopes, such as the atomic force microscope. The atomic force microscope (AFM) uses a sharp tip on the end of a flexible beam or cantilever. As the tip is scanned across the sample, the displacement of the end of the cantilever is measured, usually a laser beam. Unlike the STM, where the sample has to be conductive, an AFM can image insulating materials simply because the signal corresponds to the force between the tip and sample, which reflects the topography being scanned across.

There are several different modes for AFM. In contact mode, the tip touches the sample; this is simple to implement but can lead to sample damage from the dragging tip on soft materials. Tapping mode mitigates this difficulty: the tip is oscillated and only touches intermittently, so that dragging during scanning is minimized. Non-contact mode is where the tip senses only the attractive forces with the surface, and causes no damage. It is technically more difficult to implement since these forces are weak compared with contact forces. In non-contact mode at larger tip-surface separation, the imaging resolution is poor, and the technique not often used. However, at small separation, which requires specialized AFM apparatus to maintain, true atomic resolution can be achieved in non-contact mode AFM.

c) Optical tweezers (single beam gradient trap)

Optical tweezers use a single laser beam (focused by a high-quality microscope objective) to a spot on a specimen plane. The radiation pressure and gradient forces from the spot creates an 'optical trap' which is able to hold a particle at its centre. Small interatomic forces and displacements can then be measured. Samples that can analysed range from single atoms and micrometre-sized spheres to strands of DNA and living cells. Optical tweezers are now a standard method of manipulation and measurement. Numerous traps can be used simultaneously with other optical techniques, such as laser scalpels, which can cut the particle being studied.

3.4 Electronics, optoelectronics and information and communication technology (ICT)

3.4.1 Introduction to electronics, optoelectronics and ICT

62 The past 30 years has seen a revolution in information technology (IT) that has impacted the lives of many people around the world. At the heart of this revolution is the desire to share information, whether the printed word, images or sounds. This requires a technology that can absorb and process information on one side of the planet and deliver it almost instantaneously to the other in a form that is immediately accessible. Such a technology places enormous pressure on advances in processing and storing information, and on transmitting it and converting it from and to a human readable form. It also increasingly requires secure encryption of information so that access to information can ultimately be restricted to particular individuals.

63 The market size of the IT industry is currently around $1000 billion, the order of $150 for every human being on the planet, with an expectation that it will reach $3000 billion in 2020. In no other industry sector is the trend for miniaturisation so apparent. This is perhaps most obvious by charting the number of transistors, the building blocks of computer chips, over the past 30 years. In 1971 there were just 2300 transistors on Intel's 4004, their first computer chip, with a clock speed (a measure of how fast the chip could operate) of 0.8 million cycles per second. By 2003 the Intel Xeon processor had 108 million transistors operating at clock speeds in excess of 3,000 million cycles per second. Remarkably, the physical size of the computer chip has remained virtually unchanged over this time; it is the transistor and all the circuitry associated with it that has shrunk dramatically. The increase in the number of transistors on a chip coupled with increased speed have fuelled the economics of the IT industry; in 1971 the fabrication of a single transistor cost about 10 cents; it is currently less than one-thousandth of a cent. This evolutionary progression of technology is charted and anticipated in the ITRS roadmap, a worldwide consensus-based document that predicts the main trends in the semiconductor industry 15 years into the future (ITRS 2003) The roadmap which defines in detail all elements of technology that have to be realised for each step change improvement in manufacturing process. This roadmap is used by all industries that are directly or indirectly involved in the manufacture of silicon chips. It identifies material, architecture, metrology and process challenges as well as addressing environmental and heath issues in manufacturing.

3.4.2 Nanoscience in this area

64 Nanoscience research in ICT shares many of the same goals as for other applications of nanotechnologies: an improved understanding of nanoscale properties of materials and devices, advances in fabrication and process technology to satisfy increasingly stringent dimensional tolerances, and exploration of alternative technologies that may offer economic or performance benefit. There is no doubt that the ICT sector has effectively driven a large proportion of nanoscience. Indeed, the first use of the word nanotechnology was in relation to ultra thin layers of relevance to the then up-and-coming semiconductor industry. Since then, the research into all aspects of semiconductor device fabrication, from fundamental physics to process technology, has dominated the nanoscience landscape and will continue so to do. Decreasing device scales will add further impetus to the truly nanoscalar aspects of this global research activity. The ICT sector is, and for historical and economic reasons is likely to remain, heavily silicon-based for the foreseeable future. However, the end of the ITRS roadmap, currently set at 2018 (commonly referred to as the end of Moore's Law) has prompted intensive research into alternative or hybrid technologies for electronics such as conducting polymers, which are discussed further below.

3.4.3 Current applications

Computer chips

65 The dominant role of miniaturisation in the evolution of the computer chip is reflected in the fact that the ITRS roadmap defines a manufacturing process standard – a technology node – in terms of a length. The current 130 nm technology node that produces the Intel Xeon processor defines the size of the DRAM (dynamic random access memory) half-pitch (half the distance between two adjacent metal wires in a memory cell). This is turn places a requirement on the lithography, process technology and metrology required to manufacture a working device to this tolerance. As a comparison, the 1971 Intel 4004 chip used 10,000 nm technology; the chips of 2007 and 2013 will require 65 nm and 32 nm technology, respectively. In the broadest sense, computer chips in current manufacture are therefore already using nanotechnologies and have been so doing for over 20 years. Furthermore, it is not simply the DRAM half-pitch that is on the nanometre scale. All the technology that goes into the research, metrology and production of chips has been working, in some cases, at the sub-nanometre atomic level. The variety of tools that support the IT industry includes computer modelling of advanced devices and materials atom by atom, microscopies that can image single atoms, metrologies that can define the absolute position of a single atomic defect over a 30 cm diameter wafer (the substrate used for computer chips), thin-film growth processes that can produce layers of material with atomic precision, and lithographies that can 'write' features, such as the DRAM cell, with an accuracy of sub-10 nm.

Information storage

66. A technology that has necessarily developed in tandem with IT is that of memory for data storage. This

can be divided into two quite different types: solid-state memory such as DRAM that a processor chip would use or flash memory for storing images in a digital camera; and disk-based memory such as the magnetic hard drives as found in all computers. Solid-state memory essentially uses the same processes and technology as the computer chip, with very similar design rules and a similar emphasis on packing more memory into a given area to increase total memory per device. The development of the hard disk drive, however, has taken a quite different route in evolution as it is based on reading and writing information magnetically to a spinning disk. It is therefore primarily mechanical, or more strictly electro-mechanical, and presents quite different technical challenges. Once again, however, the importance of length scales is paramount as the ideal disk drive is one that has the minimal physical size with a massive ability to store data. This is reflected in the evolution of the disk drive over the past 50 years. The first magnetic hard drive was developed by IBM in 1956 and required fifty 24 inch disks to store five megabytes (million bytes) of data. In 1999 IBM introduced a 73 gigabyte (thousand million bytes) drive that could fit inside a personal computer; that is, over 14,000 times the available data storage in a device less than one-thousandth the size of the 1956 drive. Although the individual bits of magnetic information that are written onto the disk drive to give it the high-density storage are currently smaller than 100 nm, the constraints related to this nanotechnology on other aspects of the drive require fabrication of components with even greater precision. The importance of this nanotechnology in the related compact disk (CD) and digital versatile disk (DVD) drives that are now commonplace is equally ubiquitous.

Optoelectronics

67 The other crucial element of the IT revolution, optoelectronics, relates to devices that rely on converting electrical signals to and from light for data transmission, for displays for optical-based sensing and, in the future, for optical-based computing. Technology in this sector is strongly associated with those described above, and relies substantially on the tools developed there. Although some optoelectronic devices do not depend so critically on miniaturisation as computer chips do, there is nevertheless a similar trend towards miniaturisation, with some existing components, such as quantum-well lasers and liquid crystal displays, requiring nanometre precision in their fabrication.

3.4.4 Applications anticipated in the future

68 The future development of hardware for the IT industry can be conveniently separated into two paths: a path that is following the well-established ITRS roadmap (which projects out to 2018); and a path that explores alternative technologies and materials that may supersede the roadmap.

69 For the roadmap, miniaturisation remains a key driving force, so that a 22 nm technology node is envisaged for manufacture in 2016. Having set this technology target, it is possible to anticipate all the challenges associated with realising it. Such challenges are detailed extensively in the roadmap but include enhancing performance by introducing new materials such as low dielectrics and higher-conductivity interconnects (wiring), developing lithographies capable of fabricating structures in the sub-50 nm range, and integrating advanced metrology tools into the manufacturing process capable of detecting and sizing defects down to the nanometre size. As such, nanoscience and nanotechnologies will continue to have a pivotal role in developing new generations of chips. Related technology such as flash memory will evolve in a similar fashion, with the aim of maximising memory capacity in the smallest possible device.

70 Hard disk technologies, although not explicitly part of the ITRS roadmap, will continue to increase in memory density. However, there are prospects for some step changes in technology that may significantly change the data storage industry. One obvious potential trend is for solid-state memory to replace disk-based memory. This is already obvious in, for example, personal music players where, as solid-state memory increases in density, hard-disk-based storage is competing with the jog-proof solid-state players. It is likely that the hard disk, whether magnetic or optical, will still be the choice for large volume data storage for the foreseeable future, especially as the bit size shrinks even further. This is an active area of nanoscience research.

71 Optoelectronics, although not as dependent upon length-scale tolerances as computer chips and data storage, will nevertheless have challenges of its own. Integration of optical components into silicon devices has started and can be expected to evolve further. Some of the challenges where nanotechnologies will have an impact will be in the area of photonic band-gap materials, where the propagation of light through a device can be controlled with the aim of computing with light. Photonic crystals, fabricated either through a lithographic process or through a self-assembly technique, confine light into precisely controlled pathways in a device structure so that both transmission and functionality can be combined into a single structure. A typical photonic crystal would consist of an array of holes in a dielectric material, fabricated with sub-10 nm accuracy, so that the periodicity of the holes determines the ability of the material to transmit the light at any given wavelength. The development of photonic crystals could mean that optical integrated circuits are shrunk further, making a significant impact in areas such as communications and optical computing.

72 Quantum computing and quantum cryptography will also benefit from advances in optoelectronics. Both technologies rely on the fact that discrete energy

(quantum) levels increasingly dominate as electromagnetic energy is confined into smaller and smaller structures. Assuming that the considerable technological challenges of making nanostructures from complex materials can be solved, in some cases by designing at the level of the single atom, then on a 10 year time-scale quantum cryptography (a much more secure encryption technology) will replace current encryption methods. On a similar time-scale, quantum computing will start to provide solutions to complex problems that are difficult or impossible to solve by conventional computing.

73 Once controlling where, how and when light interacts is possible by the advances in technology alluded to above, there is the potential for developing new types of optical spectroscopy at the level of the single molecule, assembling nanostructures by arrays of optical tweezers placing objects into patterns on surfaces, new optical lithographic methods for fabricating computer chips, and optical devices that act as biosensors with detection of single molecules. The last type of sensor, able to detect the presence of a single molecule in, say, a drop of blood, represents one of the greatest challenges for nanotechnologies. Not only does it require precision in manufacture, but it also requires a unique mixture of electronics, optics, chemistry, biochemistry and medicine to make devices that can be used routinely, cheaply and reliably to monitor the state of human health. An example of this is in point-of-care health screening where a single drop of blood placed on a sensor chip would be almost instantaneously analysed to provide data to aid a diagnosis. This will require the processing power of a silicon chip with biochemical sensitivity to identify many blood components. This type of monitoring could also begin to be incorporated within the body to provide constant monitoring of health, such as in the control of diabetes or in critical care. There are many other potential applications of such devices in medicine, making this an area of increasing investment.

74 Alternative, ‘off-roadmap’ technology will have a similar reliance on nanoscience and nanotechnologies as that of the IT sector described above, but with far greater freedom to explore materials and architectures that may have little resemblance to existing technology. Plastic-based electronics is an example of an alternative technology. It does not directly compete with silicon-based devices but, because of its vastly cheaper fabrication, offers a far cheaper alternative. For inexpensive electronic and optoelectronic applications where speed and high memory density are less important, such as smart cards, plastic offers a new approach to building electronics. Plastic-based electronics is already moving into the commercial sector with potential for considerable growth. Similarly, the use of single molecules as functional elements in future circuits will continue to be an important element of nanoscience where the size of the molecule, typically less than 1 nm, offers the ultimate in miniaturisation. In fact, the goal of shrinking function down to single molecules and atoms, foreseen by Richard Feynman in 1959, is the only way to go beyond the currently foreseen evolutionary limit of the ITRS roadmap; conventional silicon transistors have a size limit of the order of tens of nanometres. Nanoscience is still pursuing the concept of storing and processing information at the atomic scale with the hope of, for example, quantum computing and atomic memory where each bit of data is stored on a single atom.

Sensors

75 Nanotechnologies play several important roles in developing sensor technology. First, the ideal sensor will be minimally invasive and therefore as small as possible. This includes the power supply, the sensing action, whereby the detected property is converted into an electrical signal, and the transmission of the sensing signal to a remote detector. Combining these actions into a device that is smaller than 1 mm^2 will certainly require nanofabrication techniques, similar to those employed by the IT industry. The second role for nanotechnologies will be in designing the sensing element to be as specific and accurate as possible; as the sensor dimension decreases the area of the sensor available to effect detection will also decrease, making increasing demands on sensitivity. In the limit of, say, chemical detection this may require detection at the single molecule level; close to the bottom end of the nanotechnology length scale and a significant technical challenge.

76 Nanotechnologies are therefore expected to enable the production of smaller, cheaper sensors with increasing selectivity, which can be used in a wide range of applications. These include monitoring the quality of drinking water, measuring mechanical stresses in buildings or vehicles to monitor for structural damage, detecting and tracking pollutants in the environment, checking food for edibility, or continuously monitoring health. Developments could also be used to achieve greater safety, security, and individualised healthcare, and could offer advantages to business (for example in tracking and other monitoring of materials and products). However, there are concerns that the same devices that are used to deliver these benefits might also be used in ways that limit privacy of groups or individuals; these are considered further in section 6.4. Other potential applications vary from monitoring the state and performance of products and materials to give early warning of the need for repair or replacement to enhancing human capabilities by extending physical performance.

3.5 Bio-nanotechnology and nanomedicine

3.5.1 Introduction to bio-nanotechnology and nanomedicine

77 Without doubt the most complex and highly functional nanoscale machines we know are the naturally occurring molecular assemblies that regulate and control biological systems. Proteins, for example,

are molecular structures that possess highly specific functions and participate in virtually all biological sensory, metabolic, information and molecular transport processes. The volume of a single molecule bio-nanodevice such as a protein is between one-millionth and one-billionth of the volume of an individual cell. In this respect the biological world contains many of the nanoscale devices and machines that nanotechnologists might wish to emulate.

78 Bio-nanotechnology is concerned with molecular-scale properties and applications of biological nanostructures and as such it sits at the interface between the chemical, biological and the physical sciences. It does not concern the large-scale production of biological material such as proteins or the specific genetic modification of plants, organisms or animals to give enhanced properties. By using nanofabrication techniques and processes of molecular self-assembly, bio-nanotechnology allows the production of materials and devices including tissue and cellular engineering scaffolds, molecular motors, and biomolecules for sensor, drug delivery and mechanical applications. Bio-nanotechnology can be used in medicine to provide a systematic, as well as a screening, approach to drug discovery, to enhance both diagnostic and therapeutic techniques and to image at the cellular and sub-cellular levels, at a much higher resolution than that of magnetic resonance imaging (MRI).

3.5.2 Nanoscience in this area

79 The primary aim of much current research is to obtain a detailed understanding of basic biochemical and biophysical mechanisms at the level of individual molecules. This knowledge will allow the design rules of naturally occurring molecular machines to be determined, which may lead to new technological applications. As we saw in section 3.3, several tools have developed in recent years, such as SPM, that allow the direct observation of the behaviour of single molecules within biological systems. Examples range from the relatively large (45 nm) rotary molecular motors that power bacterial flagella 'propellers' to the tiny enzymes such as ATP-synthase (9 nm) that catalyse energy conversion in biological processes. The intricate sequence of changes in molecular structure that forms the basis of such biomolecular machines can now be measured directly by using AFM and 'optical tweezers'. The recent development of high-speed AFM has enabled real-time molecular movement within a molecular motor to be observed directly. Future bio-nanotechnology and nanomedicine devices may exploit many classes of functional biological materials. One particular group of proteins that is attracting attention are the membrane proteins; these are another class of protein-based machine that regulate many physiological processes. They include ion channels that enable rapid yet selective flux of ions across the cell membrane, hormone receptors that behave as molecular triggers, and photoreceptors that switch between different conformational states by the absorption of a single photon of light, the process that is the basis of vision and photosynthesis. That approximately one-quarter of all genes code for membrane proteins provides evidence of their immense biological importance; it is estimated that they will be the target of up to 80% of all new drugs. Single molecule techniques for both observation and manipulation are now being used routinely to study the selectivity and gating mechanisms of ion channels, and their response to drugs.

3.5.3 Current and future applications

80 Bio-nanotechnology is regarded by many experts as a longer-term prospect: much fundamental science must first be investigated, and many applications, especially in the medical field, will by necessity have to undergo strict testing and validation procedures. The time-scale for such applications is 10 years and beyond. In the shorter term it may be possible to use proteins, DNA and other bio-polymers directly in nanoelectronics and biosensor applications, but factors such as biocompatibility and robustness may prove to be serious obstacles. Alternatively, bio-mimetic structures may be devised that are based on naturally occurring machines: examples include catenanes and rotaxanes, compounds that behave as rotary or linear molecular motors, respectively.

81 Applications in the field of medicine are especially promising. Areas such as disease diagnosis, drug delivery and molecular imaging are being intensively researched. Medical-related products containing nanoparticles are currently on the market in the USA. Examples that exploit the known antimicrobial properties of silver include wound dressings containing nanocrystalline silver, which release ionic silver over a sustained period of time to provide a claimed extensive antimicrobial spectrum of 150 different pathogens.

a) Array technologies

82 The enormously powerful array technologies, which use relatively large biological samples at the micrometre scale, are continuously being enhanced for sensitivity, size and data analysis. The original DNA chip approach, which carries an array of DNA molecules on an inert carrier, is now routinely used in gene and protein analysis. The push towards higher resolution and smaller sample volume makes this an emerging nanotechnology. Lab-on-a-chip technologies, which are used for sensing and supporting disease diagnosis, are also currently in the micrometre range, but progress in nanofluidic systems will potentially lead to integrated nanoscale systems becoming available. These could have a range of applications, for example in improved devices for detection of biological and chemical agents in the field (Royal Society 2004a).

b) Electronics and information and communication technology

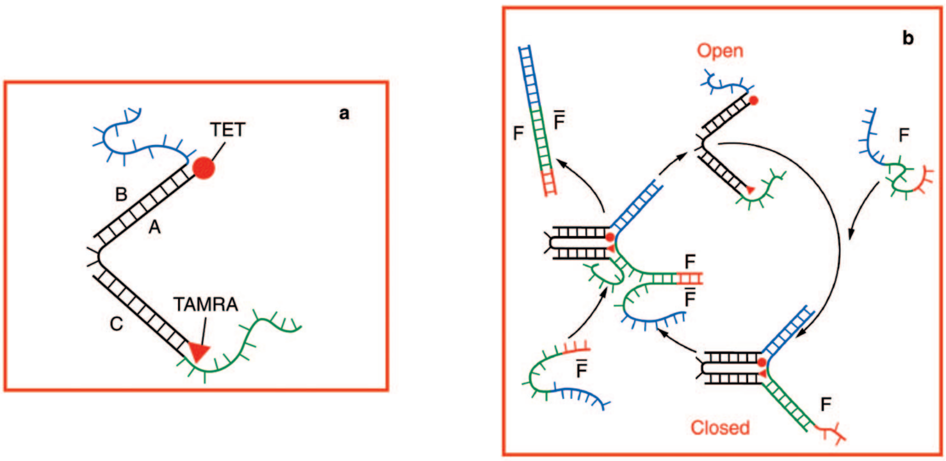
83 One of the objectives of bio-nanotechnology research is to use the highly specialised functionality of proteins in devices such as molecular sensors. One of the greatest challenges is to understand the fundamental electronic properties of such molecules and the mechanisms by which electronic charge is transferred between them and metals, semiconductors and novel nanoelectronic components such as CNTs. Progress in this area could allow these 'smart' molecules to be integrated into devices and networks for specific or indeed ICT applications: the realisation of a protein-based transistor is a major scientific challenge. DNA itself may turn out to be a useful electronic material, although the weight of experimental evidence indicates that it is not a good electrical conductor; however, used as a template, gold or silver 'coated' DNA nanowires can be produced, and integrated circuits using DNA interconnects have already been realised which use the information coded in the DNA.

84 Thin films and crystals of the membrane protein bacteriorhodopsin have already been demonstrated to have potential photonics applications such as optically addressable spatial light modulators, holographic memories and sensors. The photosynthetic reaction centre in this protein, which is only 5 nm in size, behaves as a nanometre diode and so it may be useful in single molecule optoelectronic devices. For example, its integration with electrically conducting CNTs and nanometre electrodes could lead to logic devices, transducers, photovoltaic cells, memories and sensors.

c) Self-assembly

85 The top-down approach to nanofabrication has the advantage that almost any pre-determined structure can be produced. However, much attention is now being focused on processes that involve some degree of molecular self-assembly, and in this respect biological materials have remarkable advantages over inorganic materials in the diversity of self-assembled structures that they can produce. Evolution in the natural world has produced an astonishing variety of biomolecular devices, and compared with conventional technologies, many natural molecular devices display enormous functionality. Among the most outstanding examples of synthetic structures now being fabricated are DNA-based geometrical structures (including artificial crystals) and functioning DNA-based nanomachines (and example of which can be seen in Figure 3.2).

Figure 3.2 DNA nanomachine (a) A simple device composed of three short single strands of DNA can be made to operate as a tweezer that opens and closes on the addition of another strand. The base sequences are chosen to make parts of A and B and parts of A and C complementary with each other so that double strands form; this produces the tweezer that is initially in the open state. (b) The addition of a strand F that is complementary to the unpaired sections of B and C causes the tweezer to close when pairing occurs. The tweezer opens again when a strand Fbar is added that is complementary to F: Fbar pairs with F to form a doubled stranded DNA by-product. The energy source for the machine is the hybridisation energy of the FFbar by-product. (Yurke et al 2000).



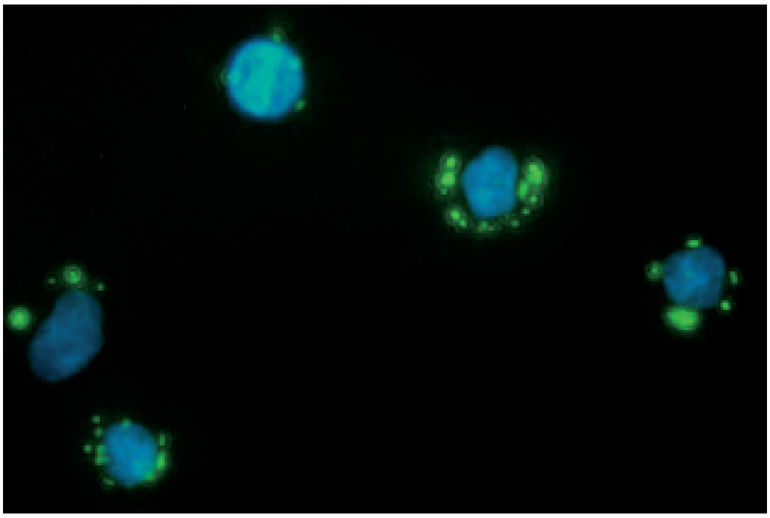
86 Hybrid nanomachines, composed of biological material with inorganic components, have been suggested as posing a threat if they are able to replicate. There are ongoing investigations into the application of biological machines that involve incorporation or transport of non-biological components or material, but these are basic molecular constructions compared with even a simple cell. Although they have the ability to move when chemical fuel is added, the working group found no convincing evidence that self-replication, a characteristic of a living organism, is possible.

d) Drug delivery

87 There is enormous potential for nanotechnology to be applied to gene and drug delivery. The vehicle might be a functionalised nanoparticle capable of targeting specific diseased cells, which contains both therapeutic agents that are released into the cell and an on-board sensor that regulates the release. Different stages of this approach have already been demonstrated, but the combined targeting and controlled release have yet to be accomplished. In this event the way will be opened up for initial trials, and the eventual approval of such techniques will be fully regulated as for any new pharmaceutical.

88 A related approach already in use is that of polymer-based drug therapies: they include polymeric drugs, polymer–drug conjugates, polymer–protein conjugates, polymeric micelles to which the drug is covalently bound, and multi-component complexes being developed as non-viral vectors for gene therapy. An illustration of how nanoparticles target cells for drug or gene delivery can be seen in Figure 3.3. Many of these materials are now undergoing clinical trials for a variety of disease states. Gene therapy, where the DNA has been packaged into a nanometre-scale particle, holds much promise for the treatment of genetic defects such as cystic fibrosis and immune deficiencies. Gene therapy using viral vectors has been successfully used to treat ten children with severe combined immunodeficiencies. These are life threatening diseases for which there is no alternative treatment. Unfortunately two of the children subsequently developed leukaemia leading to a temporary moratorium on all gene therapy trials in 2003. After intensive risk assessments most trials have now resumed. Alternative non-viral approaches bio-nanotechnology approaches are being actively researched although none has reached clinical trials. Advantages of these approaches include the versatility of synthetic chemistry, which allows tailoring of molecular weight, addition of biomimetic features to the man-made construct and even the possibility to include bio-responsive elements. The safety implications of nanoparticles in the body are discussed in section 5.3.

Fig 3.3 An illustration of how nanoparticles target cells for drug or gene delivery. Liver cells (stained blue) surrounded by 200nm semiconductor nanoparticles that have been coated with the outermost protein (E2) of the hepatitis C virus (HCV) which is believed to be the main binding protein. The nanoparticle is the same size as the virus and so it targets cells in the same way as the HCV. (Reproduced by permission James F Leary, University of Texas Medical Branch).



e) Drug discovery

89. Nanotechnology techniques offer the possibility of studying drug–receptor interactions at the single molecule level, for example by using optical tweezers and AFM, so that a more direct approach to drug discovery becomes feasible. This approach might also allow, for example, the discovery of disease at the single cell level, long before physical symptoms are manifested. This has been achieved by monitoring changes in atomic forces or ion conductance of a single receptor or ion channel when a drug molecule attaches. However, the industrial process will require the development of large arrays of such instruments working in parallel to create a high-throughput screening capability.

f) Medical Imaging

90 Non-invasive imaging techniques have had a major impact in medicine over the past 25 years or so. The current drive in developing techniques such as functional MRI is to enhance spatial resolution and contrast agents. Nanotechnologies already afford the possibility of intracellular imaging through attachment of quantum dots or synthetic chromophores to selected molecules, for example proteins, or by the incorporation of naturally occurring fluorescent proteins which, with optical techniques such as confocal microscopy and correlation imaging, allow intracellular biochemical processes to be investigated directly.

g) Nanotechnologies and cancer treatment

91 In the USA the National Nanotechnology Initiative has claimed that nanotechnology has potential in the treatment of cancer. It has been stated that 'It is conceivable that by 2015, our ability to detect and treat tumors in their first year of occurrence might totally eliminate suffering and death from cancer' (Roco 2004). We have, however, seen no evidence to support the notion that nanotechnologies will eliminate cancer in the short- to medium term, and feel that such a claim demonstrates an over-simplistic view of the detection and treatment of cancer. Although it is reasonable to hope that some measures based on nanotechnologies may make contributions to detection and treatment of some forms of cancer, other factors such as a greater understanding of environmental causes of cancer, public health measures, and advances in surgical, pharmacological and radiological management are important in the reduction of incidence of and death from cancer.

h) Implants and prosthetics

92 As discussed in section 3.2, some nanomaterials such as nanocrystalline ceramics have certain properties – such as hardness, wear resistance and biocompatibility – that may make them of use as implants in the long term. The development of nanoelectronic systems with high detector densities and data processing capability might allow the development of an artificial retina or cochlea. Important progress is already being made in this area, but many issues must be resolved before they can become viable treatments. Similarly, the introduction of nanoelectronics will allow biological neural processing to be investigated at much enhanced spatial resolution. Neurons of rodents have already been grown on nanofabricated surfaces to form elementary neural networks in which electrical signalling can be measured. By sending and receiving electrical impulses from the network, it might begin to be possible to understand how neurons create memory by their responses to different patterns of stimuli.

93 It is hoped that this research might help some visually impaired people regain their sight, or that muscle function might be restored to sufferers of Parkinson's disease. However, these developments raise potential ethical concerns about human enhancement and the convergence of technologies, in particular whether the availability of body alterations that enhance human performance might diminish the role of disabled people in society, and whether progress in information processing and data storage technologies combined with developments in neurophysiology could lead to the possibility of non-therapeutic enhancement of human performance. These concerns are explored in section 6.5.