NANOBIOTECHNOLOGY

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Contents

UNESCO – EOLSS
SAMPLE CHAPTERS

1. Microtechnology and Nanotechnology

Since the invention of the transistor in 1947, a miniaturization trend in electronic systems started and will surely continue. This miniaturization of electronic systems, aiming to include increasingly complex functions in limited space and with minimum weight, has originated an increase in information density- a key point in our “Information Society” in which information and communication technologies are integrated with the aim to store information in smaller and smaller spaces and transmit it faster and faster. Moreover, miniaturization of components results in a decrease of the material which is necessary, and therefore in a decrease in production costs.

These technologies have been investigated since the late 1950s. At the same time, many manufacturing processes and technologies originating from miniaturization in electronics have been used also for other components, such as mechanical, optical, chemical systems. Today, technology in the micron range, that is in the range of a millionth of a meter, is part of our everyday life, and research and development in this area has been expanding since the 1980s.

The term microtechnology, relating to such technology in the micron range, has been used for several decades.

Microtechnology relates to manufacturing products which are visible under the optical microscope- the most common type of microscope used in laboratory, in which visible light passes through a series of lens. This microscope, which is the most important device in a scientific laboratory, has gone through developments in the last four centuries and has now reached 0.2 micron resolution. This limitation cannot be overcome, since it is inherent in the method used as it derives from the wavelength of the light and its diffraction. An example of what can be seen by an optical microscope is the cell, whose typical size is about a few microns. The diameter of a human hair is about one hundred microns. Most bacteria- unicellular organisms, which are present in the environment and in the human body- have sizes ranging from 0.2 microns to 20 microns. Viruses- acellular organisms which have to replicate inside host cells- range in size from 0.02 microns to 0.25 microns, about one tenth of the size of bacteria. The diameter of the helix of DNA is about 0.002 microns. The typical diameter of an atom is about 0.0003 microns. This suggests that when considering increasingly small elements we reach the range of atoms and molecules. At this point a discontinuity is introduced. Atoms and molecules are a totally different kind of elements. When this range is reached, we are beyond what can be explained simply in terms of “reducing size” of matter- or of components. Working on smaller matter is completely different than working on an atom or on a molecule. Joining together two small parts of matter, no matter how small, is not like joining together atoms and molecules. The former case is mechanical, the latter is chemical. Whereas microtechnology relates to fabrication and manipulation at mechanical level, moving to fabrication and manipulation of structures within the molecular and atomic dimension means tackling fabrication and manipulation at the chemical level.

UNESCO – EOLSS SAMPLE CHAPTERS

Microtechnology is now extending into nanotechnology, which relates to the nanometer range, that is in the range of a billionths of a meter. This range is a thousand times smaller than the micron range, and is the range of the typical size of several biological substances. Aminoacids, that is organic compounds which combine together in chains and form the proteins, have sizes around 0.5 nanometers. Nucleotides, which are the structural units of RNA and DNA and play important roles in cell functions, have sizes ranging from 0.81 and 0.95 nanometers. Proteins, which are fundamental components of living cells and are present in foods such as milk, meat, eggs and legumes, have sizes ranging from a few nanometers to two hundred nanometers. Viruses have various sizes from a few tenths to a few hundreds nanometers. Cell membranes have sizes ranging from a few nanometers to about ten nanometers.

2. The Dawning of Nanotechnology

The word nanotechnology is relatively new, however functional structures and devices of nanometer dimensions have been present since the beginning of life, both as nanostructured components of biological structures and as nanoparticles present in materials fabricated by man. An example of the former is the construction of seashells, in which calcium carbonate is organized into strong nanostructured bricks held together by a carbohydrate protein-mix which works as a glu, resulting into a very strong structure. An example of the latter is the fabrication of glass containing nanosized metals, by which it is possible to obtain beautiful colours . It is known that glasses containing nanosized metals were fabricated by Roman glass-makers several centuries B.C. Nanosized materials technology was used in photography in the 1800s. Michael Faraday and Gustav Mie studied the way in which metal particles affect the colour of glass.

Richard Feynman, who was awarded the Nobel price in Physics in 1965, had a wide range of interests apart form the specific topic from which he was awarded the Nobel price (that is quantum electrodynamics). On 29 December 1959 Richard Feynman gave a lecture at a meeting of the American Physical Society, whose title was “There’s plenty of room at the bottom”. This lecture addressed the problem of manipulation and controlling things on a small scale and focused on the potential of nanosized materials. Richard Feynman gave a vision of the possibilities of such materials, and many aspects of his speculations have become accomplishments of present day nanotechnology. For example, he considered the possibility of etching lines a few atoms wide using beams of electrons. This technique, that is electron –beam lithography, is used nowadays for the production of silicon chips. He also considered the possibility of making new small structures manipulating individual atoms. This has now been achieved by the Scanning Tunnelling Microscope (STM), which emerged since 1990s as a powerful tool for manipulating surfaces at the atomic and nanometer scale, and by the Atomic Force Microscopy (STM and AFM will be described in the following section). Moreover, he considered the possibility of building nanometer size circuits that could become elements of computers, enhancing their power. Other examples are the fabrication of nanometer size structures on surfaces by local deposition and selective oxidation of surfaces and nanometer scale lithography, that is fabricating patterns with at least one lateral dimension within 100 nanometers. Nanolithography is used for the fabrication of semiconductor integrated circuits or Nanoelectromechanical Systems (NEMS). Feynman remarked that the principles of physics do not prevent to manipulate things atom by atom, but that this could be done in principle, however did not take place so far because we are too big. Feynman was the first scientist to envision the advantages that direct manipulation of atoms and molecules in order to build materials could achieve. He suggested a gradual approach based on the construction of machines that would be able to build another generation of machines that could operate on an order of magnitude ten times lower for each generational step. Most interestingly, Feynman also foresaw that with decreasing dimensions gravity would have a less and less important role if compared to the role of superficial tension and of Van der Waals forces. Scientists at that time did not give much attention to his thinking, and the reaction to

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this lecture was described by the title of his book “Surely you are joking Mr Feynman”. Nowadays this lecture has become legendary among researchers in nanotechnology, but this only happened when the technology caught up with his vision.

At that time the world nanotechnology did not exist, and the nanometer had not been proposed as a unit of measure at international level.

Actually, some experimental activities on small metal particles had taken place around that time, but it was not called nanotechnology. For example, some work on the properties of porous silicon had been carried out, which was given growing interest several decades later, when room temperature fluorescence was noticed in this material. A further example is the vaporization of sodium and potassium and subsequent condensation of cooler materials, which allowed to obtain substrates. Moreover, work on nanosized magnetic particles dispersed in liquids was also carried out and several properties and applications were discovered.

The world nanotechnology was first introduced by Nomo Taniguchi in 1974 in relation to the production of objects by mechanical precision devices. He argued that if industrial fabrications had increased its precision at the same pace, by 2 000 high precision machines would be able to obtain precision in the range of a few nanometers.

The first paper on a scientific journal in which the world nanotechnology was used was “Protein design as a pathway to molecular manufacturing” by K. Erik Drexler. The paper was published on the Proceedings of the National Academy of Sciences, USA, and Erik Drexler became a promoter and champion of this new discipline. Erik Drexler would have preferred to use the term “molecular manifacturing” which was more precise, and in principle more appropriate, however he realized the impact of the world “nanotechnology “, specially at the time in which the term “biotechnology” was becoming established.

It may be noticed that the paper by Drexler was published in the Chemistry section of the Proceedings of the National Academy of Sciences USA. This points out a natural progression in some sectors of chemistry (which had since the very beginning been regarded as the discipline which deals with atoms and molecules and their reactions) towards nanotechnology. The very keywords of that paper, that is molecular machines, protein design, synthesis chemistry, and computation, provide further cues to place the new discipline in the right place. Later on, in 1986, Drexler wrote the book “Engines of creation: the coming era of nanotechnology”, in which possible risks of the spreading of nanotechnologies are also considered (the further part of the book is titled “Danger and hopes”).

From a historical point of view it could be observed that nanotechnology is a convergence area among chemistry, from its very beginning dealing with interactions among atoms and molecules, physics, which deals with the structure of materials, biology, which provides examples of engineering molecules by proteins and their formation within cells, and information technology in a broad sense (both from a point of view of fabrication technology and from the point of view of computer aided design methods). Certainly the role of physicists and engineers not only as designers and

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builders of new materials, but also as designers of the machines that are able to observe and manipulate atoms, has been a key role. Actually, physicists and engineers have singled out two many approaches for the production of nanodevices.

1. The Top-down approach (from the top towards the bottom) is based on the use of micro- and nano-lithography and etching. Small features are made starting with larger materials (e.g. semi-conductors) and patterning and "carving down" to make nanoscale structures in precise patterns.

2. The Bottom-up approach (from the bottom towards the up) "applies to building organic and inorganic structures atom-by-atom, or molecule-by-molecule" and is similar to the ones which is adopted to use bricks. In nanotechnology the bricks represents atoms.

3. Nanoscale Structures: Technology and Applications

Materials whose structures reach dimensions of a few nanometers have mechanical or electrical or magnetic features which are very often higher than the ones of the same materials with higher structural dimension. There are two main reasons for this. One is that at very small dimensions quantum mechanical effects are relevant and bring about changes in physics and chemistry. The other is that at the nanoscale the surface to volume ratio of structures increases to a great extent, therefore every atom is quite near to a surface or interface, so the behaviour of atoms at these sizes has a remarkable influence on material properties. At the nanoscale material properties depend on size as well as on structure and composition. As a striking example, if aluminium particles with a few tens nanometer sizes are obtained (such as for example deriving from a common can used as a container for beer) they spontaneously explode in air. The reason is that the ratio between surface area and volume has changed to such an extent that aluminium becomes a high energy content material, which can be used for fuel. More generally, today some of the most important results from the point of view of industrial exploitation and investment return are nanoscale powders which are used for example in cosmetic industry, in paint fabrication and in the manufacturing of special clothing.

Some of the nanotechnology results which are particularly high potential for industrial applications, are fullerenes and nanotubes, which can be obtained by techniques which are close to typical microelectronics techniques. In the 1980s Robert Curl, Harold Kroto and Richard Smalley (who were awarded in Nobel Prize in 1996) discovered a structure. Unlike the better known kinds of carbon structures, that is diamond and graphite, they discovered a new carbon structure named Buckminsterfullerene. In the smallest stable Fullerene molecule 60 carbon atoms fit together forming a cage. The structure of this molecule can be obtained starting from a football shaped element in which each vertex of the seems is replaced by a carbon atom. The name derives from Richard Buckminster Fuller, an American architect, designer, poet and inventor who designed the Geodesic Dome, whose construction is based on a network of struts on circles lying approximately on the surface of a sphere. Structures built in this way are very lightweight and very stable. Fullerenes were obtained by vaporization of graphite using a laser. Since then, fullerene research has originated many applications, some of which are based on the substitution of metal atoms for one or more carbon atoms in the

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molecule to produce compounds. Fullerene research is being carried out towards a large set of metallic fullerene molecules, leading to new materials, lubricants, electro-optical devices, coatings, and biomedical applications. Carbon nanotubes and their biomedical applications will be described to a greater extent in section 8. Another example of nanoscale structures is the assembly of organized macromolecules and nanoparticles by methods used for the assembly of ultra thin films. Organized films that contain different polymers, proteins, dyes and nanoparticles can be obtained which are similar to the ones obtained with very sophisticated and expensive technology used for metals and semiconductors. These methods lead to the construction of ordered organic/inorganic nanocomposites which can be used for a variety of biomedical applications. Ultra thin films and their applications will be described to a greater extent in section 7.

Another possible application envisaged by the first supporters of nanotechnology is the one of nanorobots. An example is nanoscale machines able to navigate in the blood flow searching for cancer cells to be destroyed.

Nanoscale structures can be found, today, for example in cosmetics, in solar panels, in colour displays, in DVDs, in antireflections and self cleaning glass, and in spot repellent test styles.

4. A Key Instrument For Nanotechnology: The Scanning Tunnelling Microscope

According to some, the beginning of the nanotechnology era is in 1982 when the Scanning Tunnelling Microscope (STM) was invented. STM can image surfaces with such a level of magnification that individual atoms become visible. This made it possible to study and manipulate the structure of materials at the atomic level. This instrument is the basis of enormous developments within Physics, Chemistry and Biology. STM only images surfaces of materials that conduct electrical currents, but with modest technological changes it is possible to image also materials that are non conductive, such as for example biological materials, such as DNA and proteins. In 1986 the inventors of STM, Gerd Binning and Heinrich Rohrer from IBM were awarded the Nobel Prize in Physics.

STM uses a wire with a very fine point, which is positively charged and works as a probe when its distance from the surface under study is about one nm. Today, STM is widely used for semiconductor and microelectronic devices, to study chemical reactions on surfaces, and to examine biological molecules. Electrons at individual atoms of the surface are attracted by the probe and jump up (tunnel) to it. When the tip touches the surface of the specimen, which is being observed, the voltage results in a current, and when the tip is away from the surface the current is zero. The voltage applied is between a few millivolts and few Volts and the tunnelling current is always very low, usually between a few pico-Amperes and a few nano-Amperes. The tunnelling current gives a highly sensitive measure of the distance between the tip and the sample. The probe wire is scanned across the surface in a raster pattern, and a feedback loop maintains a constant probe high above the sample surface. The up/down probe’s variations are recorded. The Scanning probe provides a mapping of the distribution of the atoms on the surface sample. The principle of the STM can be compared to the one of an old fashion recorder which, when playing a record, uses a sharp needle (tip) to interrogate

UNESCO – EOLSS SAMPLE CHAPTERS

the surface.

A voltage is applied between the tip and the sample. Scanning microscopy is based on obtaining images of the surface of a specimen by scanning the surface with an electron beam in a raster pattern. This method is similar to the way in which an electron beam scans the screen in television sets. It is also possible to obtain surface information by a scanning probe in which the regions of particular interest on the surface are hit by an electron beam. The Scanning Transmission Electron Microscopy (SEM, TEM) is based on this principle. A further possibility is to carry out the scanning by a probe that monitors electrons that tunnel between the surface and the tip of the probe. This is the principle on which the STM is based. Another method, on which the Atomic Force Microscopy (AFM) is based, uses a probe that monitors the force between the tip and the surface (Figure 1).

SEM and TEM microscopes are both based on an electron defection system in which the deflection of the electron beam takes place magnetically through magnetic fields generated by electric currents through coils, as in most television sets. The magnetic field produced by a coil is proportional to the voltage applied to it, and the magnetic field produced by the coils deflects the electron beam. The electron beam scans repeatly across the sample in a raster pattern that covers the whole area of interest on the sample.

Another scanning probe microscope, which is in wide use for nanostructure surface studies, is the AFM, which was developed soon after the STM. The main difference between the STM and the AFM is that the STM monitors the electric tunnelling current between the surface and the tip of the probe, while the AFM monitors the force which is observed between the surface and the tip of the probe. Unlike in the STM, in the AFM the tip is not kept at a short distance from the surface, but it gently touches the surface. The AFM tip is attached to a leaf spring which has low spring constant, the cantilever. The banding of this cantilever is detected, often using a laser beam which is reflected from the cantilever. The AFM measures contours of constant attractive or repulsive force. The forces that can be detected are as small as a few pico Newton. Such forces are usually low enough to avoid damage to the surface or the tip. AFM does not rely on the presence of a tunnelling current, therefore it can be used to image a non conductive surface.

AFM technology has originated three most commonly used modes: the contact mode, the non contact mode and the tapping mode. The contact mode is the most commonly used one. The tip scans the sample in close contact with the surface. The force on the tip is set by pushing the cantilever against the sample surface with a piezoelectric positioning element. Contact mode imaging can be influenced by frictional and adhesive forces. The non contact mode is used when tip contact may alter the sample, but non contact imaging generally provides low resolution results. The tapping mode is a most relevant advance, which has allowed to obtain high resolution images of sample surfaces that are easily damaged or difficult to analyse. Tapping mode imaging takes place by oscillating the cantilever assembly using a piezoelectric crystal by which the cantilever oscillates with a high amplitude when it is not in contact with the surface. The oscillating tip is moved toward a surface until it lightly touches it. This vertically oscillating tip acts by contacting the surface and lifting off. The cantilever oscillation

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amplitude is kept constant by feedback. The tip is prevented from sticking to the surface, which may cause damage during scanning. With this technique soft and fragile samples, such biological ones, can be imaged. The tip can also be functionalized by attachment of biomolecules or other biological elements and used by a biosensor. Tapping mode has brought about many advances in nanobiotechnology.

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