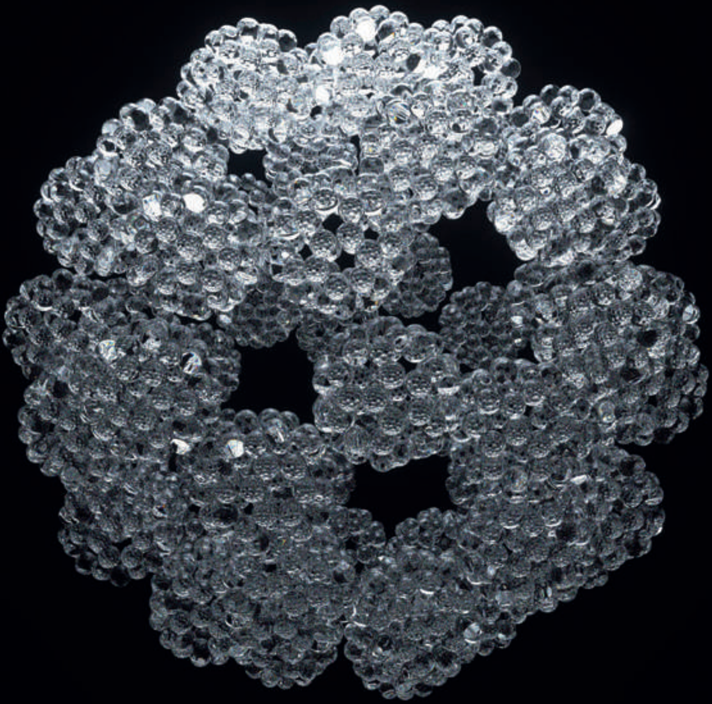
ATLANTIS ADVANCES IN NANOTECHNOLOGY,
MATERIAL SCIENCE AND ENERGY TECHNOLOGIES



Joseph B. Natowitz and Christian Ngô

# Our Nanotechnology Future

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# ATLANTIS ADVANCES IN NANOTECHNOLOGY, MATERIAL SCIENCE AND ENERGY TECHNOLOGIES

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The aim of "Atlantis Advances in Nanotechnology, Material Science and Energy Technologies" is to publish high quality manuscripts giving an up-to-date and clear view on topical scientific contents in nanotechnology, material sciences and energy technologies.

These three fields evolve rapidly and their understanding is essential with regard to contemporary science and as well as in the context of everyday life. Nanotechnology is a fast growing science and a technological field with applications in numerous areas such as materials, health, electronics, information processing, defence and security, catalysis, sensors, food, cosmetics and many more. The results of material sciences are the basis for any object around us, they are omnipresent in human life. Mastering materials and processes is therefore crucial. In particular, research on microscopic understanding is essential to develop models predicting the properties of new materials and structures. The final goal is to be able to predict macroscopic properties of materials from their microscopic properties. Finally, energy technologies enfold a complex area where each technological advance has to be weighed against economical, environmental, political and sociological constraints. Energy is closely linked to economic development and, more generally speaking, to everyday life.

As nanotechnology, materials science and energy technologies are closely interconnected, this series offers the reader both, highly specialized monographs as well as easy-to-grab overviews. Each publication focuses on one of the fields. At the same time, it is highly relevant to explore their interconnections and to include interdisciplinary approaches.

All book proposals submitted to this series are being reviewed by key experts before publication and each book focuses on a certain field putting it into perspective with its implications at the economic and societal level.

# Our Nanotechnology Future

*Christian Ngô and Joseph B.Natowitz*

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# Contents

# Introduction

Nanotechnology is pervasive in contemporary life. With applications in food, electronics, medicine, cosmetics, catalysis, construction, defense etc. Many of natural materials around us have a nanostructure that determines their behavior. Nanoscience and nanotechnology generally deal with objects that have one or more dimensions in the range of 1-100 nm. This range is arbitrarily fixed by convention and sometimes must be expanded. Modern nanoscience and nanotechnology really started about three decades ago when it was demonstrated that it is possible to observe and manipulate nano-objects. Before that, most manufactured nanomaterials were films or coatings with thicknesses in the range of 1-100 nm.

Nano-objects can be built from elementary components (atoms or molecules), or by breaking down or carving bulk materials using different methods. The first approach is usually called "bottom-up" while the second one is termed as "top-down". Nanocharacterization techniques play a major role in these processes because they can be used to monitor the properties of these objects in a size range spanning the region between the microscopic world that encompass atoms, small molecules and nuclei- where the physics is governed by quantum phenomena - and the macroscopic world that can be described by classical theories such as classical mechanics. A good understanding of phenomena at the nanoscale, affords us the ability to boost the properties of manmade materials by tailoring nanomaterials for specific purposes. The properties manifested at the nanoscale level can be harnessed to provide remarkable new materials and capabilities.

Although the rate of development of nanotechnology today is smaller than was foreseen a decade ago, it increases regularly in an irreversible way. This short book is intended to give the reader a flavor of this expanding domain and its applications The book is divided in two parts. Part 1 presents the fundamental tenets of nanoscience and nanotechnology. Part 2 discusses current and future applications that have, or will have, a major influence on our lives.

Because a sharp rise in the use of nanotechnology in commercial products is expected in the future, the question of the possible risk that nanoparticles pose to human health is an important issue. Although humans have always been faced with the presence of natural nanoparticles, the manufacturing and use of engineered nanoparticles should be carefully investigated as far as the risk to living species is concerned. The risk must be carefully balanced against the advantages that can be obtained through nanoparticle usage.

# Part 1 Nanotechnology basics

# I. Nanoscience and nanotechnology

## The size domain of nanoscience and nanotechnology

Nanoscience is the study of the performance of ultra-small autonomous structures. The nanoscience domain is typically viewed as having dimensions ranging between 1 nm and 100 nm. One nanometer (1 nm) is one billionth of a meter and one millionth of a millimeter. It is a very small distance. in fact, it is a length comparable to the size of individual atoms. One gold atom has a diameter of ≈ 0.144 nm. Seven gold atoms placed in a line and touching would extend for about 1 nm. For comparison, the cross sectional diameter of a strand of a human DNA molecule is about 2.5 nm, the diameter of a blood cell is about 7,000 nm and the diameter of a human hair is in the range of 80,000 to 100,000 nm.

If we could shrink all distances of our macroscopic world by one billion, one meter would become 1 nm. In this case the distance between the earth and the moon (≈ 360,000 km) would become 36 cm and the distance between the earth and the sun (≈ 150,000,000 km) would become 150 m.

In figure 1 we list some common units of length ranging from one meter to one femtometer, $10^{-15}$ meter. The nuclei of atoms have diameters in the range of 1 to 20 femtometers.

The conventional delineation of 1 nm to 100 nm for the nanoscience domain is useful, but should not be considered as a rigorous definition. Structures with larger dimensions can, in some cases, manifest phenomena belonging to this domain. It is important to investigate the different phenomena taking place on this size scale because they are often size dependent and different from those observed in our macroscopic world. Understanding and learning to model, simulate and manipulate nanoscale matter is a necessary step toward providing a firm underpinning for nanotechnology. *Nanotechnology* deals with the practical techniques of design, manufacturing and applications of nanostructured materials and devices. Nanotechnology has applications in many fields, including health, food, materials science, manufacturing, energy and chemical processes, among others. Nanotechnology is rapidly becoming more and more important in improving the materials and objects we routinely use in our daily lives.

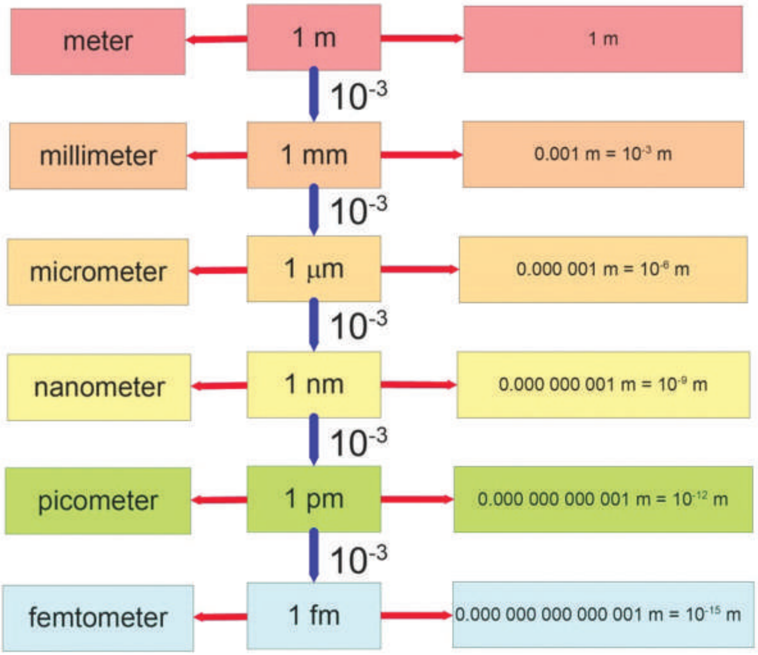

Figure 1. Length units descending from 1 meter to 1 femtometer. Each unit represented is separated from the adjacent units by a factor 1,000.

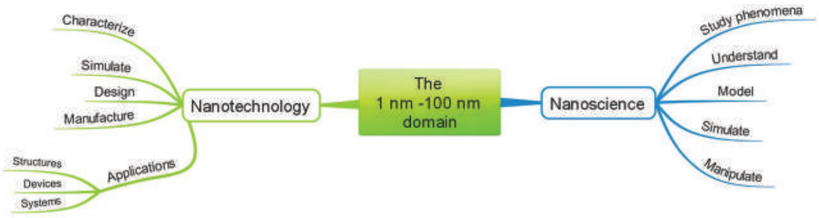

Figure 2. Some keywords of nanoscience ad nanotechnology.

Figure 2 provides a schematic view of the components constituting nanoscience and nanotechnology.

Nanomaterials need not be man-made. A number of natural nanostructured material exist. These occur in animals, in plants and in minerals. Examples include structures on the eye of a moth which increase the moth's ability to see in the dark, surface structures on the leaves of a lotus plant which make them water repellent and nano-structured clays which are often employed as additives to modify material properties.

Figure 3. The Lycurgus cup exhibited at the British museum. It was manufactured by the Romans around the 4th century AD. The color varies. This dichroic property comes from the presence of nanoparticles, which were produced during the manufacturing of the glass.

## Nanotechnology in the past

The first human created nanostructures were not understood to be such. For example the "Lycurgus cup", presently in the British Museum in London, is a glass cup manufactured in Rome around the fourth century A.D., representing a scene from mythology, it was made from dichroic glass, glass which undergoes color changes in different lighting conditions. Illuminated from the outside, the cup looks green. Illuminated from the inside the cup appears ruby red except for the figure of the king which takes on a purplish hue (figure 3).

The dichroism of the glass is due to nanosized particles (up to 100 nm) embedded in the glass. These nanoparticles are of silver and gold. There is also a small amount of copper nanoparticles. The absorption and the scattering of light by these nanoparticles determines the color which is observed. When this cup was made, nothing was known about nanotechnology, but the manufacturer succeeded in creating this unique object.

Nanoparticles are also present in other objects produced in the Middle Ages. In the 1850s the British physicist and chemist Michael Faraday proposed that the observed color variations in stained glass windows could be attributed to variations in size of the clusters of metal atoms embedded in them. Some Chinese porcelains produced in the same time period contain 20-60 nm nanosized gold particles.

## Intellectual foundations of nanotechnology

On December 1959, Richard Feynmann (Nobel Prize in Physics, 1965) gave a visionary lecture entitled "There's plenty of room at the bottom". In that lecture he stated his belief that it should be possible to manipulate atoms on an atomic scale and arrange them in desired patterns using nanoscale machines. At the end of his talk, he challenged his listeners to accomplish two tasks. The first was to build an electric motor smaller than 0.4 mm on a side. The second was to scale letters small enough to be able to write the entire Encyclopedia Britannica on the head of a pin. This requires being able to write a standard printed page on a surface 25,000 times smaller than that page. To do so each letter must have a size of about 9 nm. He offered $1,000 prizes to the first people able to solve either of these challenges.

The first task was achieved in November 1960 by William McLellan, who manufactured a motor weighing 2500 μg and having 13 parts which could function at 2000 rpm. Feynman was a bit disappointed because it was constructed with conventional tools and did not employ any new technology. The second challenge was met in 1985 by Tom Newman, a Stanford graduate student, who used an electron beam to inscribe the first page of Charles Dickens' *"A Tale of Two Cities"* on the head of the pin. Because most of the area of the head of the pin remained empty, he later actually had a hard time finding the written text on the pin.

Today Feynman's lecture is generally considered as the starting point of the nanotechnology story. The word "nanotechnology" itself was first introduced in 1979 by Norio Taniguchi, a Japanese scientist, to describe the control of semiconductor processes on the nanometer scale.

## Can we see atoms?

Around 450 BC, Leucippus and Democritus, two Greek philosophers, suggested that matter was made of very small particles, invisible to a naked eye. A convincing verification of this concept came in 1805, thanks to the work of English chemist John Dalton. The macroscopic matter we see around us is indeed composed of individual units we call atoms. Atoms are the smallest units of a chemical element which retain the characteristics of that element. While we have known for over two centuries that matter is made up of atoms, our understanding of the nature and structure of atoms has evolved greatly during that period.

"Seeing is believing." is a credo firmly ingrained in the human psyche. However there are many objects which the unaided human eye is not capable of seeing. Atoms are in this realm. We must rely on instruments much more sensitive than our eyes to detect or see individual atoms. In figure 4, we show examples of objects of different sizes and indicate the different length scales, each separated by a factor 1,000, associated with these objects. For example, we can easily see people with our eyes. Small insects may have a size of a few millimeters or centimeters and a magnifying glass may be needed to observe them better. Red blood cells with a size on the order of 7-8 µm can be observed with an optical microscope. Silicon wires of an integrated circuit, such as shown at the far right in figure 4, have widths of several nanometers and can be observed with electron microscopes or scanning tunneling microscopes.

Electron microscopes are instruments that employ accelerated electrons to observe small objects. The physical laws governing the propagation of these electrons lead to size resolutions ~ 100,000 times better than those achievable with visible light. With this higher the electron microscope can "see" extremely small objects. Figure 5 illustrates the kinds of images obtainable using different electron microscopy techniques.

The spatial resolution of a scanning electron microscope can be about 1 nm to 20 nm depending on the instrument. The transmission electron microscope has a better spatial resolution and can reach 0.05 nm.

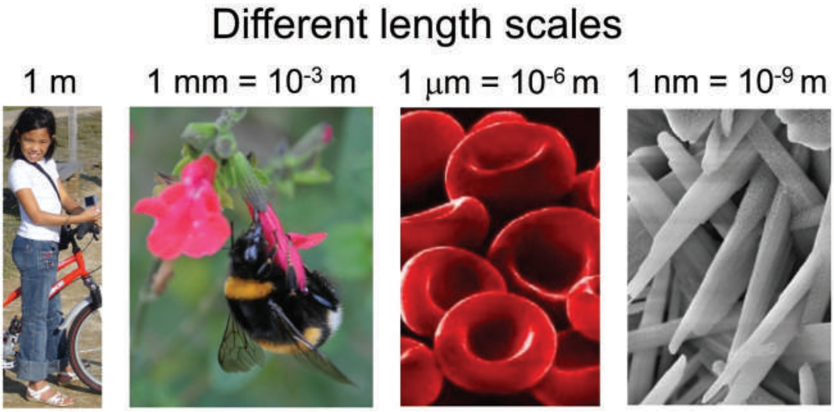

Figure 4. Examples of objects of different sizes.

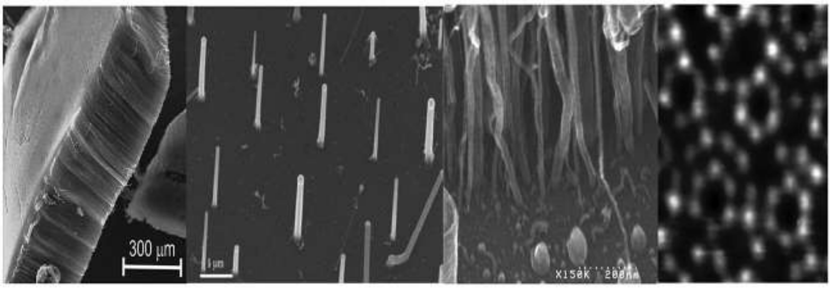

Figure 5. Images showing objects of various sizes taken using different microscopic techniques. From left to right – a carbon nanotube monolayer forest as seen by a standard electron microscope, a scanning electron microscope image showing silicon nanowires synthesized by vapor-liquid-solid techniques with diameters in the range 30-100 nm, a scanning electron microscope image of carbon nanotubes grown on a silicon substrate in a reactor at the CEA, an STM image of a silicon crystal with the surface oriented along the (111) plane. In the latter case, the bright dots correspond to individual Si-atoms at the surface. All these images are courtesy of CEA/LETI (France).

## The scanning tunneling microscope

An important breakthrough in the observation of the constituents of matter was made in 1981 when Gerd Binnig and Heinrich Rohrer, researchers at IBM-Zurich in Switzerland, invented the *Scanning Tunneling Microscope* (STM). With this device, it became possible to see (after computer processing) individual atoms on an electron microscope screen and, furthermore, to manipulate and arrange these individual atoms. In 1986 these two scientists received the Nobel Prize in Physics for this achievement.

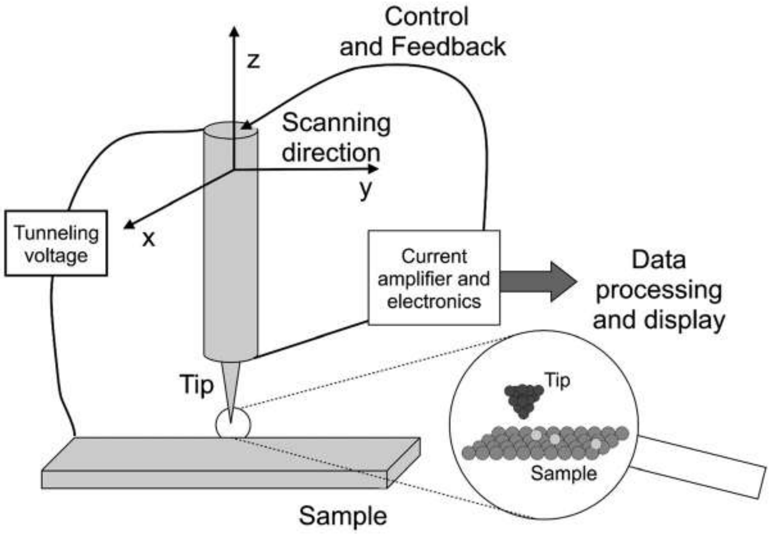

Figure 6. Schematic diagram of a scanning tunneling microscope.

The principle of the STM is shown in figure 6. A conducting tip is brought to a very small distance (a distance below 1 nm) from the surface of the sample being scanned. Materials used for the tip can be tungsten, a platinum-iridium alloy and even gold. The sample can be a conductor or a semi-conductor. The important interaction is between the outermost atom on the tip and an atom on the surface of the sample. When the tip and the surface are very close to each other, electrons can *tunnel* from the sample to the tip or vice versa depending upon the sign of the voltage difference between the tip and the sample. This exchange of electrons is not a classical phenomenon, but a quantum mechanical phenomenon. Quantum phenomena are discussed further in Chapter 2. The tunneling current which is measured depends on the tip position, on the applied voltage, and on the local density of electronic states of the sample. The tunneling current varies exponentially with the distance separating the tip from the surface. A 10 % decrease in this distance (≈ 1 nm) typically increases the current by an order of magnitude and vice versa. The range of distance separating the tip from the surface of the sample typically varies from 0.4-0.7 nm. A lateral resolution of about 0.1 nm and a depth resolution of 0.01 nm can be obtained with the STM.

A STM can operate in a wide range of temperatures from near zero Kelvin (≈-273°C) up to a few hundred degrees Celsius. The position of the tip with respect to the surface has to be perfectly controlled mechanically. This is done using piezoelectric mechanisms.

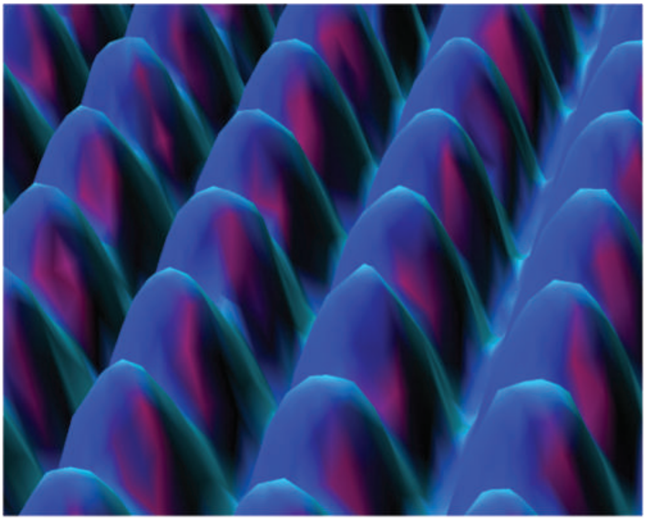

Figure 7. STM image of the surface of a nickel crystal. Image originally created by IBM Corporation.

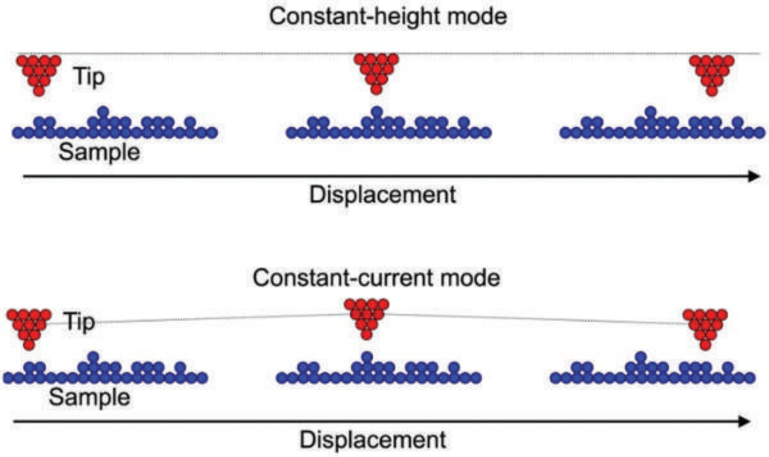

Figure 8. Schematic illustration of the two operating modes of the STM.

The measurement of the local density of the electron quantum states allows the imaging of the spatially-resolved electron density of the sample. Computer processing of that information produces an image of surface atoms on a screen. An example of such an image is that in figure 7 showing the regular arrangement of the nickel atoms on the surface of a nickel crystal.

As shown in figure 8, a STM can be operated in two different modes,: the constant-height mode and the constant-current mode. In the constant-height mode, the tip remains at a fixed height and scans the sample while remaining in a horizontal plane. This mode can quickly scan the sample, but requires a smooth sample surface. In the constant-current mode a feedback loop is used to adjust the distance between the tip and the surface of the sample in order to keep the tunneling current constant. This mode is slower than the preceding one, but is able to scan irregular surfaces.

## The atomic force microscope

One of the shortcomings of the STM is that it can only study conductive or semi-conductive surfaces. In 1986, Gerd Binnig, Christoph Gerber and Calvin Quate invented the *Atomic Force Microscope* (AFM) which can be used on insulating surfaces also. The principle, shown in figure 9, is to use a tip attached to a cantilever (flexible arm). When this tip is moved over the surface of the sample the atomic forces attract or repel the tip as the tip moves along. The motion of the tip induces a motion of the cantilever. A laser beam directed at the cantilever is reflected and the angle of reflection of this beam is measured (see figure 9). From this information, it is possible to build an image of the surface as the tip moves.

There are some basic differences between an AFM and a STM. With an AFM the tip makes a gentle direct contact with the scanned surface while the tip of a STM does not make direct contact and just measures the tunnel current existing between the tip and the surface. The AFM resolution turns out to be better than the STM resolution.

An AFM is well suited for nanotechnology studies because it gives better surface measurements than a STM and can be operated in a wider variety of environments. It can be used with conductors, semiconductors and insulators.

An AFM can be operated in several modes. In the *dynamic mode*, the cantilever vibrates around a given frequency and the tip oscillates with an amplitude of a few nanometers close to the surface of the sample. The long range forces, such as Van der Waals forces, affect the frequency of oscillation and a feedback loop is used to keep the frequency of oscillation constant by changing the distance separating the tip from the surface of the sample. In this way a topological mapping of the surface can be made. In the *intermittent* or *tapping mode*, the oscillations of the cantilever are much larger and there is an intermittent contact between the tip and the surface. This technique is particularly suitable when a thin layer of liquid

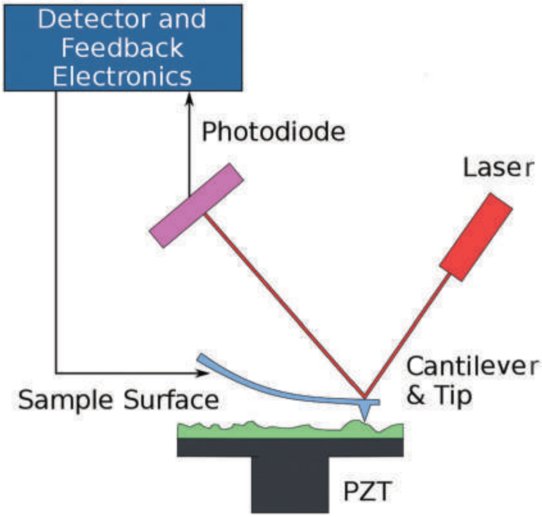

Figure 9. Schematic of an atomic force microscope with optical detection of the deflection of the microcantilever. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Grzegorz Wielgoszewski.

has developed on the surface of the sample because of the environmental conditions. It is the method most often employed in AFM measurements. In the *contact mode*, the tip touches the surface. The electrons of the atoms repel it and the cantilever is deflected.

## Manipulating atoms

Using a STM it is possible not only to see atoms but also to move individual atoms from one point on the surface to another. In 1989, Don Eigler, an IBM researcher, using a STM, picked up and moved an individual atom for the first time. He moved a xenon atom back and forth 3 times in order to check reproducibility. *In his lab notebook Eigler wrote "Did it," "Did it" and "Did it again! 3 in a row".* After this crucial breakthrough, in November 1989, Eigler succeeded in arranging 35 atoms of xenon on the surface of a nickel crystal to write the word "IBM" (figure 10). Eigler claimed that once the atom-moving process was under control, the biggest challenge was "remembering how to spell IBM".

Atoms moved and positioned on the surface of a crystal are often called *adatoms*[1]. The move can be done manually or with the aid of a computer. An autonomous atom assembler has been recently developed by researchers from the US Center for Nanoscale Science and Technology. It provides

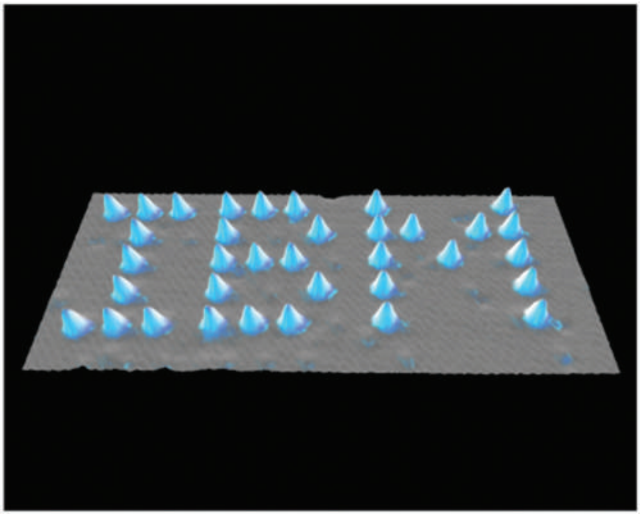

Figure 10. Atoms of xenon arranged on a nickel crystal surface to spell IBM. Courtesy of IBM company (www.almaden.ibm.com).

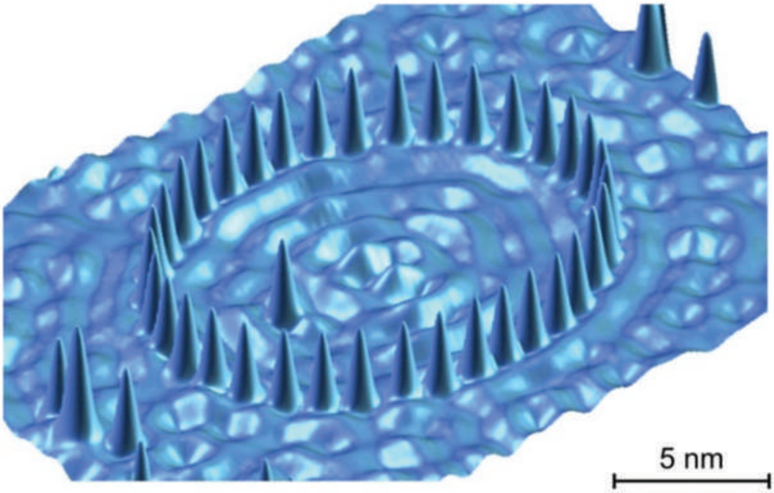

Figure 11. Image of an elliptical quantum corral built using the autonomous atom assembler; Co atoms were deposited at sub-monolayer coverage on a Cu(111) at 7K in ultra high vacuum and subsequent STM measurements were performed at a 4.3 K sample temperature. J.A. Stroscio, R.J. Celotta, S.R. Blankenship and F.M. Hess, http://www.nist.gov/cnst/epg/atom_manipulation_stm.cfm. Image from Wikimedia Commons (http://commons.wikimedia.org).

the ability to assemble a desired nanostructure from atoms initially randomly distributed on the surface of a crystal. The autonomous atom assembler is a dedicated instrument based upon an STM with upgraded hardware and software components. Figure 11 shows the result of the manipulation of cobalt adatoms on a copper surface to form a closed quantum structure (quantum corral) in which electrons can be trapped. The geometry of this structure defines new energy levels in this region of the surface. Such a structure, made to measure, may have important applications in the future.

## Summary

It is now possible to routinely see and move atoms. This represents an important technological breakthrough and opens a wide number of science and technological applications. The main issue is to be able to work at the nanoscale at a pace suffiency large to quickly obtain objects useful in the macroscopic word and a competitive cost.

The ability to see details in the nanosized range is necessary and essential for all developments of nanotechnology because it allows to control nanotechnology research developments and manufacturing processes. The possibility to see details, at the scale of the nanometer or better, allows a rational development of nanomaterials by giving the possibility to understand the mechanisms involved rather than developing materials using trial and error methods as it was done in the past.

An adatom is an additional atom lying on the surface of a crystal. This word comes from the contraction of the expression “adsorbed atom”. An adatom can be viewed as the opposite of a surface vacancy in which an atom has disappeared.

# II. The Quantum world

The motion of macroscopic objects such as soccer balls, vehicles and planets can be well described using classical mechanics. However, classical mechanics is inadequate to describe the movements or the structure of microscopic objects such as atoms, molecules or nuclei. To properly describe the properties of microscopic objects, the theory of quantum mechanics was developed. While quantum mechanics can be applied to macroscopic objects, it turns out that for objects of large dimensions the quantum mechanical laws evolve naturally into classical mechanics. In general, solving a problem in quantum mechanics is far more difficult than solving it in classical mechanics. Therefore, the laws of classical mechanics are employed when they can be applied safely.

As we descend to the nanoscale, the applicability of classical mechanics gradually diminishes. This does not occur at the same time for all of the variables describing the system, but below a certain size, quantum effects will become important. In this chapter, we briefly review some basic features of quantum mechanics. In the next chapter some of the consequences for nanotechnology of the appearance of quantum effects are discussed.

## Classical versus quantum mechanics

The dynamics of motion of a classical object is characterized by the mass of the object, its position, its velocity (i. e., the speed and direction) or its momentum which is the product of the mass of the object times its velocity. The mass is fixed. The position and velocity or the momentum are continuous variables. For example, the speed of a car can vary continuously from zero to its maximum value. These variables characterizing the object can be measured as accurately as the tools used to make the measurement allow. The evolution of the position and velocity defines the *trajectory* of the car.

To describe transfers of energy not accompanied by transfers of matter, such as occurs when sound and light (or other electromagnetic radiations) move through space, classical physics employs a picture of wave propagation. The theoretical description is based on solving differential equations with boundary conditions depending upon the specific situation under consideration. For example, vibrations which are confined in space generate waves with definite frequencies. Thus, sound waves generated by vibration of a guitar string are periodic and depend on the nature of the string and its length. The string does not generate all sound frequencies (white noise) but just those satisfying the boundary conditions. If the vibration is not confined, as it is the case for waves propagating in free space, all frequencies are possible.

## Wave-particle duality

At the macroscopic level, where classical physics applies, a particle always behaves as a particle and a wave always as a wave. In the microscopic quantum world particles and waves are not as easily separable. Depending upon the conditions, a particle can behave as a wave and a wave as a particle. For example, while, at the classical level light is described by wave equations, in the "photoelectric" and "Compton" effects, light behaves as a particle, the photon. This "wave-particle duality" has many practical implications. The photoelectric effect, ejection of electrons by collisions with photons, is exploited in photovoltaic cells, to transform sunlight into electricity. The Compton effect, scattering of photons by electrons, is used in imaging detectors for medical applications. Electrons or neutrons, which behave in many cases as particles, exhibit wave behavior evidenced by diffraction patterns analogous to those observed in the scattering of light and other electromagnetic radiations. Electron and neutron scattering are used to view small details of small objects and to determine the underlying structures of materials. These are just a few examples of the harnessing of quantum effects in devices that we use routinely. This behavior is schematically depicted in figures 12 and 13.

The experimental observation of wave-particle duality led naturally to a description of microscopic matter in which it was postulated that each particle had associated with it a wave which governed its motion. The corresponding wavelength of this wave is known as the *de Broglie wavelength*.

## Determinism versus a probabilistic approach

As indicated by the discussion so far, classical mechanics is a *deterministic* theory. If we know the initial conditions of the object (mass, position and speed) and the forces acting upon it (force field), it is possible to calculate

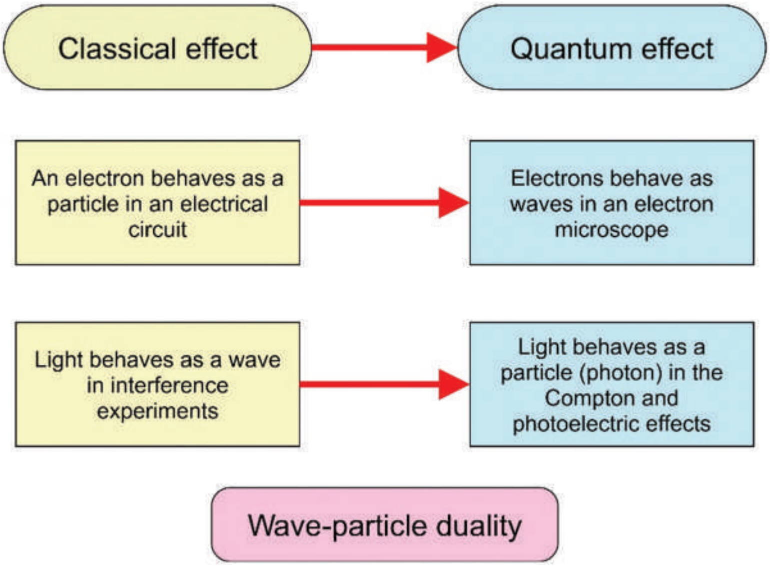

Figure 12. Quantum mechanics accounts for the fact that a particle can behave as a wave or a wave as a particle according to the boundary conditions placed upon a system. This is illustrated for an electron and light (photons) in this figure.

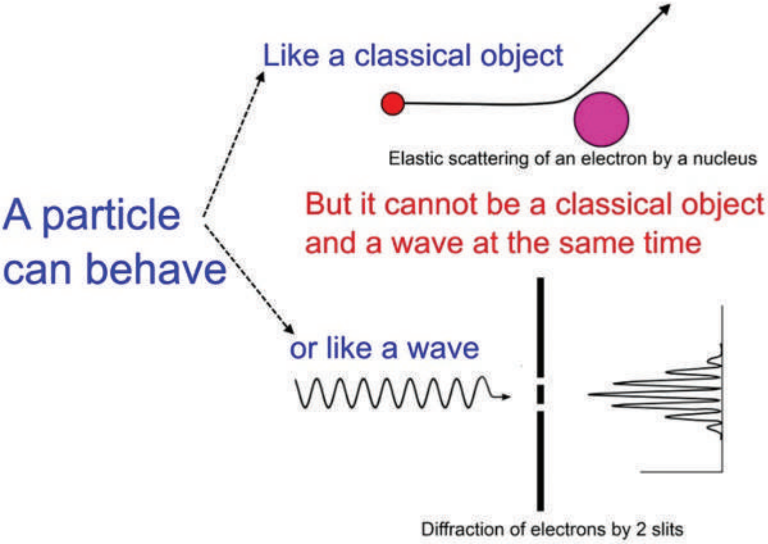

Figure 13. An electron can behave like a classical object or like a wave depending on the conditions, but it can never be both of them at the same time. This illustrates the wave-particle duality.

the position and the velocity at any later time. The object follows a well-defined trajectory. It has been amply demonstrated experimentally that classical mechanics does not provide an appropriate description of microscopic entities such as atoms, molecules, electrons and nuclei. Instead, these particles manifest wave-particle duality which incorporates features of both particle and wave behaviors. Thus, classical mechanics is not adequate to treat microscopic entities. For these, *Quantum Mechanics* is the proper theory to apply.

In quantum mechanics the notion of trajectory does not exist anymore. The behavior of the quantum object cannot be characterized completely by its position and momentum, but rather requires a knowledge of its associated *wave function*. All of the information accessible for the system is contained within this wave function. The wave function is a solution to a wave equation, a differential operator equation which controls the motion of the particle. An operator equation is one in which some specified mathematical operation, e. g., multiplication, division, differentiation…., is performed on a given mathematical function. For each physical quantity that we can measure, there is an associated operator. The theory requires that such operators be "Hermitian"[2]. Figure 14 gives a schematic comparison of some aspects of classical and quantum mechanics.

## Measurement

If we measure the speed of a car with radar waves, we can determine that speed with an error depending on the accuracy of the measuring device used. There is, in principle, no limit to the accuracy, except that of the device we employ. Quantum mechanics differs from classical mechanics in that a measurement is not always deterministic but probabilistic. In quantum mechanics, the result of a measurement can only be a value allowed by the wave function of the operator associated to the observable that we measure. Such an allowed value is called an "eigenvalue"[3]. If the system is initially in an "eigenstate", a state allowed by this operator, then the results will be deterministic: Our measurement will produce that particular eigenvalue. A second measurement of the same variable performed on the system will again give the same result.

If the system is initially not in an eigenstate corresponding to one particular eigenvalue of the observable, each of the possible eigenvalues corresponding to allowed states of the system can be, in principle, measured with a certain probability. The same measurement performed on a set of

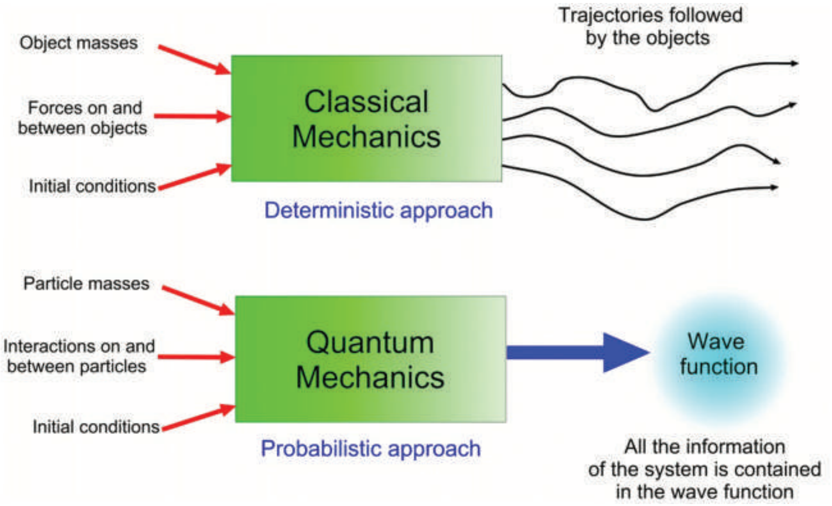

Figure 14. Comparison between classical and quantum mechanics.

such systems will give different results. Figure 15 summarizes this situation schematically.

## Quantization

At the macroscopic level the position and the momentum of a particle are both continuous variables. The kinetic energy of a particle is also a continuous variable. The situation for particles exhibiting wave behavior is different. We have already recognized that confined waves, such as those produced by plucking a guitar string, generate one frequency and its harmonics, and not a white noise associated with continuous frequencies. This means that only certain discrete energy states of the system are allowed. This discretization of the possible energies comes from the boundary conditions which confine the string of the guitar on two sides. More generally stated, *spatial boundary conditions lead to energy quantization*.

As a result, particles confined (by external forces) to small regions of space cannot have continuous distributions in energy but can only have certain discrete energies. Further, it is interesting to note that, unlike the classical case, the lowest energy state of a quantum system cannot be at zero energy. Even in the lowest energy "ground" state, the position of the particle fluctuates. The non-zero value of the energy is called the "*zero point energy*".

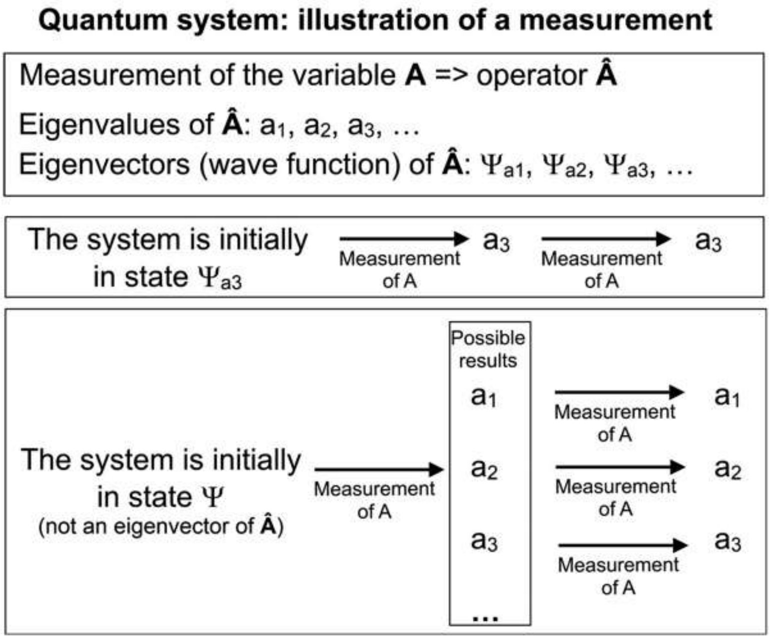

Figure 15. Illustration of results of a measurement on a quantum system. The variable (observable A) is measured and Â is the associated operator. If the wave function is in an eigenstate of Â, for example $\psi_{a3}$, one measures a value $a_3$. A second measurement will give the same result. If the system is not in an eigenstate of Â, all the eigenvalues are possible, but with different probabilities.

The simple schematic picture in Figure 16 illustrates these concepts. The external forces confining the particle are represented by a parabola (harmonic oscillator potential). In the classical case shown on the left, the particle can be at any distance above the bottom of this parabola and have any energy up to the maximum energy *E* indicated by the dashed lines. On the right, in the quantum case, only certain discrete energy levels of the system are allowed. These are indicated by horizontal solid lines. In this illustration, only the lower three states are allowed to the system. The energy spacing between the states will increase if the region in which the particle is confined decreases.

## Heisenberg uncertainty principle

In principle, it is always possible to make a measurement on a classical system without notably perturbing it. Measuring the speed of a car with radar waves does not materially modify the trajectory of the car. Thus, it is possible to measure the position and the momentum (or velocity)

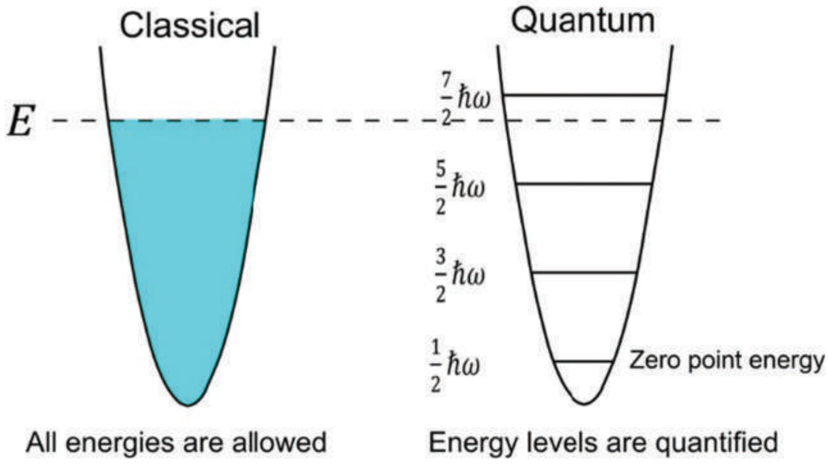

Figure 16. Particle confined by external forces. For the classical case on the left, all the energies from the bottom up to E are allowed (colored in the figure). For a quantum system only discrete energy values are allowed. Note that in the quantum case the lowest energy is greater than zero.

simultaneously. The accuracy of the measurement depends on the accuracy of the measuring instrument.

At the microscopic level the situation is different. In quantum mechanics, an operator is associated with each variable which can be measured and the result of a measurement is necessarily an “eigenvalue” of the operator. In contrast to the classical case, an accurate simultaneous measurement of two variables (having two different operators) is not possible unless the system is in an “eigenstate” common for both operators. This is related to the “commutivity” or “non-commutivity” of the two operators[4].

If the two operators do not commute[5], it is impossible to measure them simultaneously with all the accuracy we wish. This is true of position and momentum which are non-commuting variables. If, for a particle, $\Delta X$ and $\Delta P_x$ are, respectively, the uncertainties in the position and momentum along the x axis, then the“Heisenberg uncertainty principle” may be stated as:

$$\Delta X \times \Delta P_x \geqslant \hbar$$

Where $\hbar$ is the Planck constant divided by $2\pi$ ($\hbar = h/2\pi$). It is possible to measure either the position or the momentum as accurately as we want *but not both simultaneously*. The accuracies achievable are determined by the equation above. A small uncertainty in one of these variables leads to a large uncertainty in the other.

Figure 17 illustrates this correlation of uncertainties in the x and $p_x$ determinations, reflecting the Heisenberg uncertainty principle. The colored rectangles indicate the accuracy limits resulting from the non-commutivity. This same limitation also explains the zero point energy indicated in figure 16. Since the system is confined in a limited portion of space there will be an associated uncertainty in the momentum, and, as a consequence, on the energy. Neither the momentum or the energy can be zero. Associated with this zero-point energy is a zero-point motion. The particle cannot be at rest.

## Quantum numbers

A system is completely defined by the knowledge of its wave function. In the case where the energy levels are discrete, the wave function often depends on indices which characterize a particular energy state of the system. We can designate the wave function of the system, $\psi_n$. Here $n$ is an integer number which can be 0 (the lowest energy or "ground" state) or a positive integer. If $n = 1$, the system is in the first excited state, $n = 2$, the second excited state, etc. Then, each state can be identified by the appropriate integer, which is known as a *quantum number*. The energy of the state will depend upon this quantum number. For a system with $N$ degrees of freedom there will be $N$ quantum numbers. (The number of degrees of freedom is the number of parameters of a system which can vary independently.) A classical system with $N$ degrees of freedom requires $N$ position coordinates. For a point particle having no internal degrees of freedom this number is equal to 3 (the three coordinates locating the position). Similarly, a quantum system with $N$ degrees of freedom has $N$ quantum numbers to describe it completely. For example, a point particle inside a cubic box has 3 degrees of freedom and the energy levels depend on 3 quantum numbers.

## Spin – an intrinsic property

A particle can also have intrinsic degrees of freedom which do not depend on spatial position. One such intrinsic degree of freedom for particles such as electrons, protons, neutrons, nuclei *etc.* is known as angular momentum or spin. Sometimes the spin of a particle is represented as a rotation of the particle around an axis passing through its center. The spin is then a vector. This classical view helps to imagine what a spin can be. Spin is also quantized in quantum systems. Usually quantum angular momenta are measured in

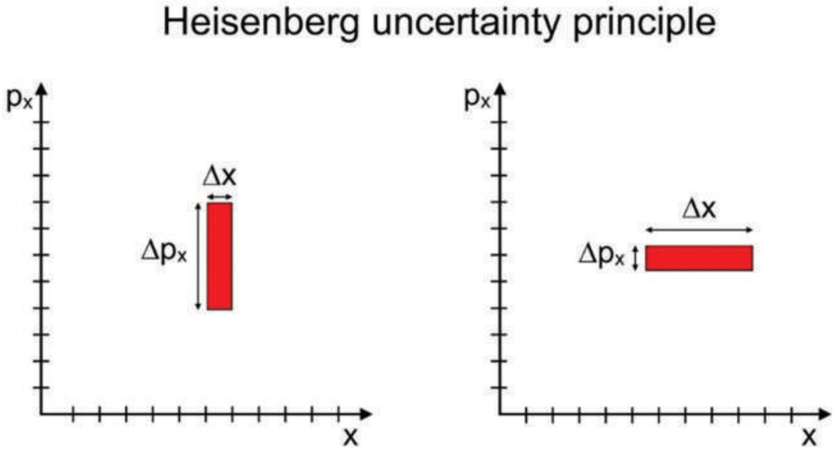

Figure 17. Illustration of the Heisenberg uncertainty principle for the position (x) and the momentum (px) of a particle. These two quantities cannot be measured simultaneously. The better one of these variables is known, the greater is the uncertainty on the other.

ħ units. Electrons or protons, for example, have a spin $S = ½\,\hbar$ and we say that the spin of an electron or a proton is $s = ½$. Quantum mechanics also says that the projection of this ½ ħ vector on a given axis can take only two values: +½ ħ and -½ ħ, often referred to as *up* or *down*. For larger spins, whether half-integer or integer, more projections (actually $2s + 1$ values) are possible.

All of the quantum particles found in nature have a spin. This spin can be either an integral spin (0, 1, 2...), or a half-integral spin (1/2, 3/2, 5/2...). Particles with integral spins are called *bosons* and particles with half-integral spins are called *fermions*.

## Fermions and bosons

At the microscopic level, identical particles are indistinguishable. There is no way to differentiate between two electrons, for example. This is in severe contrast to our experience with macroscopic objects such as billiard balls which are, or can be made to be, discernible, *e. g.*, by painting them different colors.

Symmetry plays a major role in nature and in quantum mechanics. The application of quantum mechanics to a set of identical particles requires that the total wave function is either totally symmetric with respect to the exchange of any two identical particles, *i. e.*, the sign of the wave function does not change when the particles are exchanged, or totally antisymmetric with respect to the exchange of two identical particles, *i. e.*, the sign of the wave function changes when the particles are exchanged. This symmetry requirement is intimately connected to the intrinsic spin of the particles. For bosons, the wave function is symmetric while for fermions it is antisymmetric. Bosons are said to obey *Bose-Einstein statistics* and fermions to obey *Fermi-Dirac statistics*.

One of the consequences of this is that, while it is possible to put as many identical bosons as we want into a given quantum state as in the right part of figure 18, completely identical fermions cannot occupy the same quantum state (a quantum state is one identified by *all* of the pertinent quantum numbers). In the left part in figure 18 we see that 2 fermions of identical spin ½ can be placed in a single energy level. This comes from the fact that there are two possibilities for the spin projection, $s_z = \pm 1/2$. The two particles with these different spin projections are not completely identical. However, given the limitation of two spin projections, a third particle of spin ½ cannot be placed in the same energy level. In the absence of an external magnetic field the spin of a particle is randomly oriented and the energies for different spin orientations are the same. The application of an external magnetic field results in a splitting of the energy levels as the spins will be oriented only in certain allowed directions relative to the magnetic field.

## Quantum tunneling

Classical energy waves, *e. g.* electromagnetic waves or sound waves, can tunnel through a potential barrier and an attenuated wave can reach the other side (consider for example the attenuation of a sound wave passing through an acoustic tile). This situation is illustrated in the top of figure 19. There, a classical wave incident from the left impinges on the barrier. In the forbidden region an *evanescent wave* is formed with a decaying intensity and a wave of diminished amplitude emerges from the other side of the barrier.

In contrast, if a classical particle is incident on such a barrier and its kinetic energy is below the maximum energy of the barrier, it cannot pass through the barrier. To do so requires an energy at least equal to the barrier energy. A tennis ball does not tunnel through a concrete wall because it behaves as a classical object. Classical wave and particle behaviors are different.

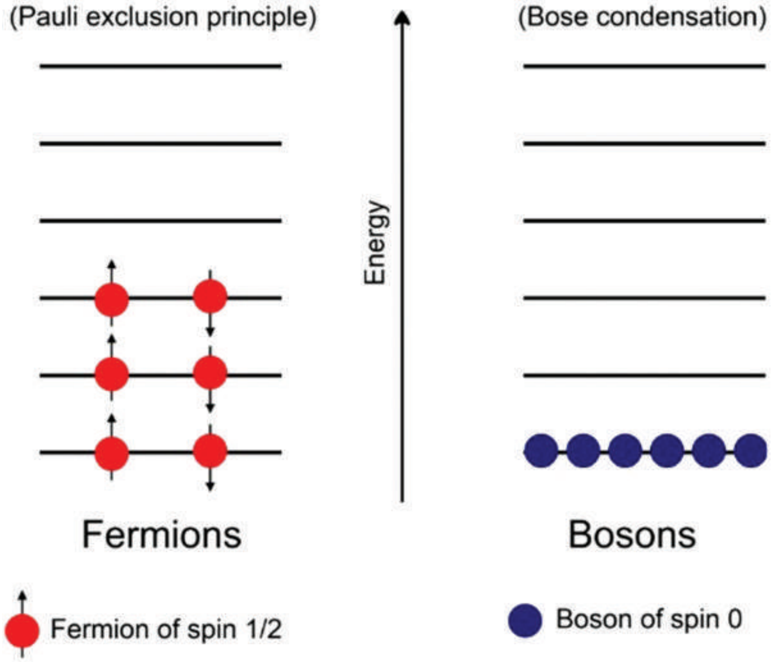

Figure 18. There are two families of particles at the quantum level: fermions and bosons. Completely identical fermions cannot be in the same quantum state. In the case of s = 1/2 particles illustrated here, two different projections of the spin are allowed so two otherwise identical fermions can occupy a single energy level. In contrast, the number of identical bosons in the same quantum state is not restricted.

In a quantum mechanical treatment, wave-particle duality means that in certain conditions a particle can behave as a wave and exhibit a similar tunneling behavior. That is, there is a certain probability that the particle will pass through the barrier and be found on the other side. This is illustrated in the bottom part in figure 19. This behavior is indeed observed for particles such as electrons, protons, neutrons, nuclei, etc. This is precisely the phenomenon used in the scanning tunneling microscope to see and move atoms on a surface.

As it is schematically illustrated in figure 20, the probability that a particle is able to tunnel through the barrier depends on the relationship between the particle energy and the height of the barrier. It is easier to tunnel with energies close to the top of the barrier than with smaller kinetic energies. The width of the barrier is also important. The larger the width, the smaller will be the tunneling probability.

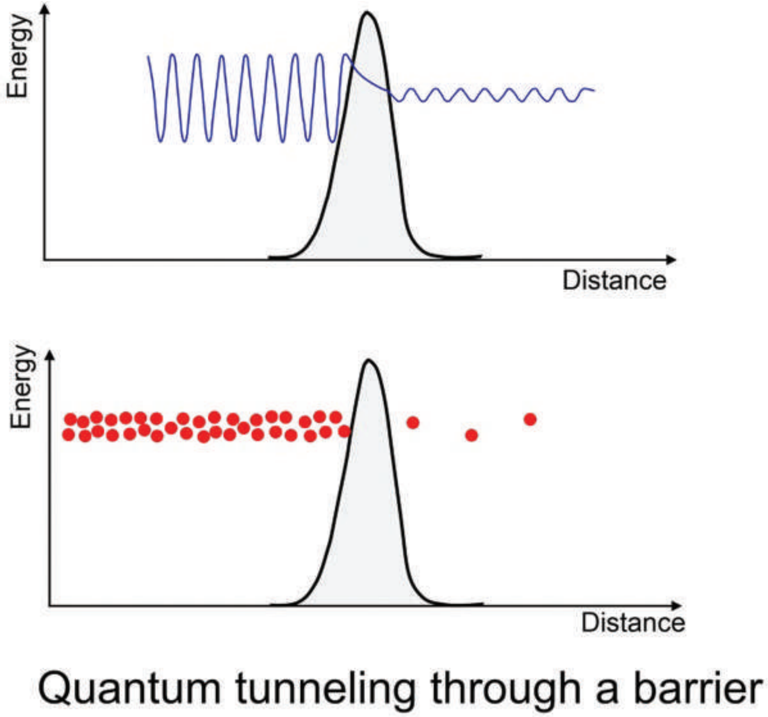

Figure 19. Schematic illustration of quantum tunneling. Top: the wave function decays exponentially inside the barrier and has a lower amplitude after passing through the potential barrier. Bottom: a small fraction of particles striking the barrier tunnel through the barrier.

## Summary

A given system has a behavior which is governed by the laws of physics. By looking at different observables of a system, we can characterize the system. Observables are measureable variables that describe the properties of the system. Observables might be energies, positions, angular momenta, *etc*. Classical physics (mechanics, hydrodynamics, optics...) describes our macroscopic world well. Classical physics allows us to precisely calculate the trajectories of planets, rockets, vehicles, *etc*. The microscopic world is very different from the classical world. To adequately describe this microscopic world requires that we apply the concepts of quantum mechanics. This is not because the underlying scientific laws are different. It is rather because the boundary conditions have changed and the relative importance of certain exigencies of the scientific laws can become more or less important with respect to each other depending on the size of the piece of matter we are dealing with. Some effects, which are negligible at the

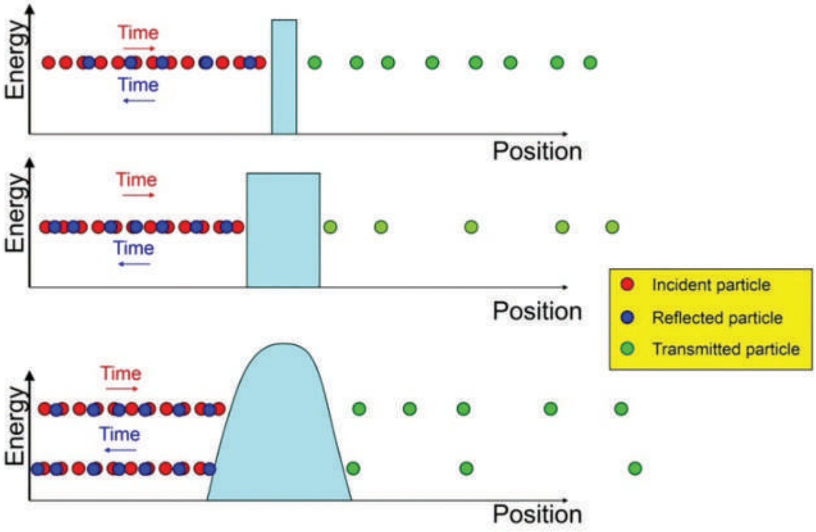

Figure 20. This figure illustrates, in a very simplified and schematic way, the fact that the probability to tunnel through a potential barrier decreases as the difference between the particle energy and the energy at the top of the barrier or the width of the barrier increase. In the figure red particles represent the incident flux on the barrier. Part of this incident flux tunnels through the barrier (green particles) while the remaining part bounces back (blue particles).

macroscale level, can become dominant at the microscale level. Although quantum mechanics is known to provide the foundation for accurately describing microscopic systems and predicting their behavior, a number of the concepts introduced in this chapter can be disconcerting when first encountered.

# III. The mesoscopic world

## The forces of nature

Nature is governed by four fundamental interactions:

- The *gravitational interaction* which operates between objects having mass
- The *electromagnetic interaction* which operates between objects with electrical charge
- The *strong interaction* which holds nuclei together
- The *weak interaction* which governs beta radioactivity and other weak decays

These interactions operate over different ranges and differ greatly in strength. The main properties of these interactions are recalled in figure 21.

The gravitational interaction and electromagnetic interactions have an infinite range while the nuclear and weak interactions are of short or ultra-short range, respectively. In modern theories, the interactions between particles are considered to take place through an exchange of virtual particles (the mediators of the interaction) called *gauge bosons*. The mediator of the electromagnetic interaction is the photon. The strong interaction needs 8 mediators, known as gluons. In the theory, the elementary particles, the quarks, interact through gluon exchange in the same way as electric charges interact by virtual photon exchange. Three gauge bosons, the $W^+$, $W^-$ and $Z^o$ are the mediators of the weak interaction. For gravitation the search for the mediator, called the graviton, is still underway. In February of 2016, scientists working at the The Laser Interferometer Gravitational-Wave Observatory (*LIGO*) with detectors located in Hanford and in Livingston, Lousiana reported the first experimental observation of gravitational waves. This is a first step towards a possible isolation of the graviton.

## The role of size

Nanoscience and nanotechnology deal with objects intermediate in size between the macroscopic world and the microscopic world. Because of the small dimensions involved, the behaviors of nanoscale objects having dimensions in the range of 1-100 nm can be very different from the behaviors

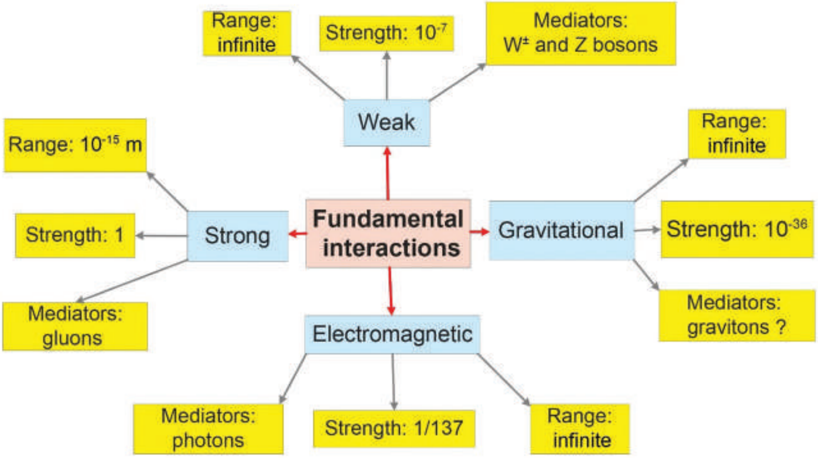

Figure 21. Main properties of the four fundamental interactions. Strengths are on a relative scale.

we have become accustomed to in the macroscopic world. Such objects can exhibit quantum behaviors.

As the size of a system decreases, the relative importance of various forces will change. Also, as the system reaches the nanoscale domain, there can be a transition from classical behavior to quantum behavior. This transition regime is typically referred to as the mesoscopic world. The transition is usually smooth and takes place over some range of sizes. This range can be wide or narrow, depending on the observable under consideration. We will call this region the *quantum wall* since it separates a region of sizes where classical mechanics is applicable from a region where quantum mechanics governs the physics of the observable. This is illustrated schematically in figure 22.

In this chapter we consider the role of diminishing size on various features of particular importance to nanoscale objects.

## Surface versus volume

A collection of objects of small size generally has a higher surface-to-volume ratio than macroscopic objects containing the same amount of matter. If we consider, for example, a cube with a side of 1 cm, the volume of the cube is 1 $cm^3$ and the surface area is 6 $cm^2$. If we cut it into nanocubes according to the scheme in figure 23, each nanocube has a volume of 1 $nm^3$ and a surface of 6 $nm^2$ or $6{\times}10^{-24}$ $cm^2$. Since there are a lot of nanocubes, *i. e.* $10^{21}$, the total

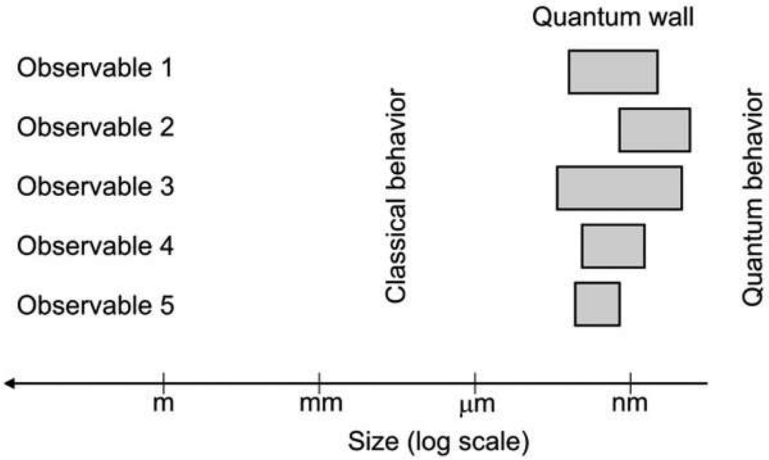

Figure 22. As the size of a system shrinks, the behavior of an observable (a variable that we can measure) can change from classical to quantum. The transition region where this happens is the quantum wall.

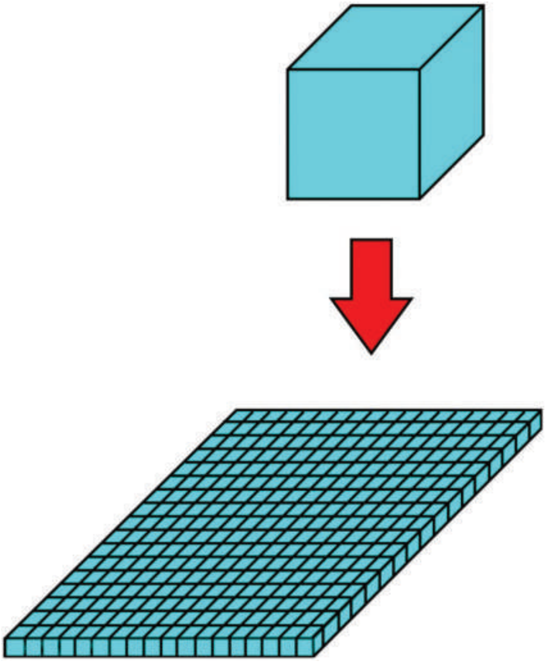

Figure 23. Dividing a cube into tiny little cubes increases substantially the surface area. See text.

area of this set of nanocubes is 6,000m$^2$. However the total volume of the system is the same (1cm$^3$). The ratio of surface to volume has increased by a factor of 10$^{11}$.

An increase of surface with respect to volume increases the reactivity of a material because the interface with the external environment or with other materials is larger. For example, while iron reacts with oxygen and rusts, it is difficult to burn a lump of iron. However, if this lump is ground into a small powder, or stretched into a fine thread, it burns easily. The key point to remember is that, at the nanoscale, *surface effects can become dominant over volume effects*.

## Surface tension

For liquids, increases of surface to volume ratios can result in greatly increasing the importance of the surface tension. Surface tension finds its origin in short range intermolecular forces. Such forces are discussed in more detail in section 8, below. For a given liquid, molecules on the surface typically have stronger attractions to molecules in the bulk of the liquid than to external molecules. In response to this difference, the liquid will tend to form drops in order to minimize the surface energy. Surface tension explains the stability of soap bubbles, the coalescence of two touching drops into a single one and why dew does not spread on flower petals.

For large volumes of liquid, surface tension is not as important as other forces which are operating. This explains why the water contained in a glass assumes the shape of the glass. Nevertheless, the surface tension exists. This explains why needles can float and small insects can easily walk on that surface. It is easy to understand that, due to surface tension, nanosized objects will have difficulties penetrating into a liquid.

## Nanofluids

Unless quantum effects appear, the laws of fluid dynamics are the same, whatever the size of an object moving in a fluid. However, the fluid reacts differently depending on the size of the object. The nature of fluid flow is characterized by a parameter known as the Reynolds number. The Reynolds number is a dimensionless quantity which is the ratio of the inertial forces to the viscous forces. In the case of a body entering a fluid, the

Reynolds number is proportional to the characteristic speed of the body and to its size and inversely proportional to the viscosity coefficient of the fluid. Two fluids with the same Reynolds number exhibit the same flow pattern. In the case of low Reynolds numbers, the flow is laminar, *i. e.*, the liquid flows in parallel layers whereas for large Reynolds numbers it is turbulent. Viscous forces become increasingly important on the nanoscale. At the macroscopic scale, we know that turbulence provides a way to mix two different fluids together. At the nanoscale, turbulence is reduced because of the viscous forces and it is very difficult to mix two liquids using this phenomenon.

## Heat transfer

Another issue at small sizes is the transfer of heat energy. Three main phenomena govern heat transfer at the macroscopic scale: *conduction*, *convection* and *radiation*. For nanostructures of very small size, heat transfer mechanisms are different. The classical Fourier law of heat conduction states that the rate of heat transfer through a material is proportional to the gradient in the temperature and to the area, at right angles to that gradient, through which the heat flows. On the nanoscale, this law breaks down because the mean free path of the particles becomes larger than the size of the nanostructure. The mechanism is closer to radiation than to conduction. Furthermore, at the nanoscale, because of the wave-particle duality, wave effects become important. In the mesoscopic world, where sizes intermediate between the microscopic and the macroscopic world are involved, heat transfer becomes a complicated process depending on several parameters such as the mean free path of the particles, their thermal wave length, their phase coherence, etc.

## Chemical bonding

Most materials are composed of atoms of different elements bound to each other to form chemical compounds. The bonds between atoms in these compounds find their origin in the electromagnetic interaction. They vary in strength depending on their nature. In chemical compounds, the bonds between atoms range between covalent bonds, in which electron pairs are shared between two atoms, to ionic bonds, in which oppositely charged ionized atoms attract each other. The bonds are strong and not easy to break. Carbon-hydrogen covalent bonds have an energy of the order of 400 kJ/mole of molecules. Ionic bonds are of comparable strengths to covalent bonds. In ionic crystals, ions located the lattice sites are bound to each other by electrostatic forces. Each ion feels the long range force from all the other ions. The net bonding is significantly larger than that between a single ion pair.

## Intermolecular forces

There are also attractive interactions between atoms and molecules which are much weaker than covalent or ionic bonds, but play a major role on the properties of materials. These are generally classified as *Van der Waals* interactions or *Van der Waals* forces. As indicated in section 4, the Van der Waals forces are responsible for such phenomena as the coalescence of drops and formation of bubbles.

### Van der Waals forces

The Van der Waals forces occur between atoms or molecules. They can also be present between a molecules and crystalline surfaces. They are of three types:

1. The *Keesom force* coming from the interaction between polar entities having permanent electric dipole moments[5].
2. The *Debye force* occurring between entities with permanent dipole moments and those with induced dipole moments.
3. The *London force* coming from the interaction between entities both of which have induced dipole moments.

These 3 forces are attractive and the strengths of these forces depend on the relative distance $r$ between the two entities. The change is proportional to $1/r^7$. The potential energy varies like $1/r^6$. For comparison the electrostatic interaction between two charged particles varies like $1/r^2$.

The Keesom force is a dipole-dipole interaction exerted between two polar molecules. The force tends to align the dipoles to increase the attraction between the species and minimize the potential energy.

The Debye force is an interaction between the permanent dipole of a polar molecule and an dipole induced in an initially non-polar molecule.

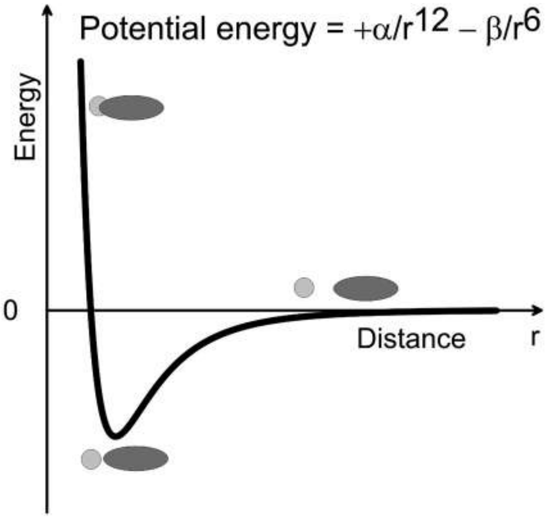

Figure 24. Schematic illustration of the potential energy curve between atomic and molecular interactions via Van der Waals forces. The repulsive core reflects the Pauli energy coming from the Pauli exclusion principle. The two parameters α and β in the expression of the potential energy are determined theoretically or chosen to match experimental data.

The London forces exist between all molecules. It is the only Van de Waals interaction observed with non-polar molecules and is due to internal charge fluctuations in these molecules. In a molecule, moving electrons create an instantaneous but fluctuating dipole moment. The order of magnitude of the London forces is ≈ 2 kJ/mole. London forces keep the atoms of noble gases close together when they are liquefied and are responsible for the fact that benzene is a liquid at room temperature.

At very short distances the interaction between atoms and molecules turns from attractive to repulsive reflecting the fact that two identical electrons cannot be in the same quantum state ,*i. e.*, the total wave function should be antisymmetric (the Pauli exclusion principle). This constraint on the total wave function gives rise to a short range repulsive force varying like $1/r^{13}$ (the potential energy empirically varies like $1/r^{12}$). This repulsive force is called the Pauli or Born force.

Figure 24 shows a schematic view of the potential energy of an atom and a molecule as a function of the distance *r*. This kind of potential is called a Lennard-Jones potential. As the molecules come close together the potential energy decreases because of Van der Waals interactions and then increases strongly due to the repulsive Pauli or Born interaction.

At the nanoscale, the Van der Waals forces are much more important than gravitational forces.

### Hydrogen bonds

Because of its unusual strength compared to that of other attractive Van der Waals forces, the *hydrogen bond* can be of particular importance. The *hydrogen bond* is an attractive electromagnetic interaction between a hydrogen atom already bonded to another atom in a polar molecule and a lone pair of electrons on a strongly electronegative element such as fluorine, oxygen or nitrogen. The strongest hydrogen bonds involve hydrogen-fluorine interactions. Hydrogen bonds can occur between atoms belonging to different molecules or between two atoms belonging to the same molecule.

The energy of a typical hydrogen bond is ≈ 20 kJ/mole, about an order of magnitude smaller than a strong covalent bond. The length of the bond is also about twice that of a covalent bond. Though significantly weaker than covalent bonds, hydrogen bonds can be extremely important. They are responsible for the high boiling point of water compared to other non -metallic hydrides[6] and thus the fact that most of the water on the earth's surface is liquid at typical ambient temperatures. Hydrogen bonding is also the interaction which holds the double helix structure of DNA together.

## Semi-classical approaches

Describing the microscopic world (atoms, molecules, nuclei…) requires us to use quantum mechanics. Quantum systems are characterized by quantum numbers which vary from small values to very large values. The quantum numbers of a system requiring a full quantum mechanical treatment are usually small because they are not too far from the ground state. In contrast, classical systems correspond to situations where the values of the quantum numbers are extremely large. As we noted above, nanotechnology covers a domain where some observables behave as classical and others behave quantum mechanically. This depends upon the nature and size of the system as well as on the external conditions. Fortunately, in many areas of nanotechnology, it is possible to meld the ideas of the classical and quantum approaches into *semi-classical* approaches which employ a large part of the classical thinking and invoke, ad hoc, a few quantization rules. These semi-classical approaches can then be employed to characterize nanoscale

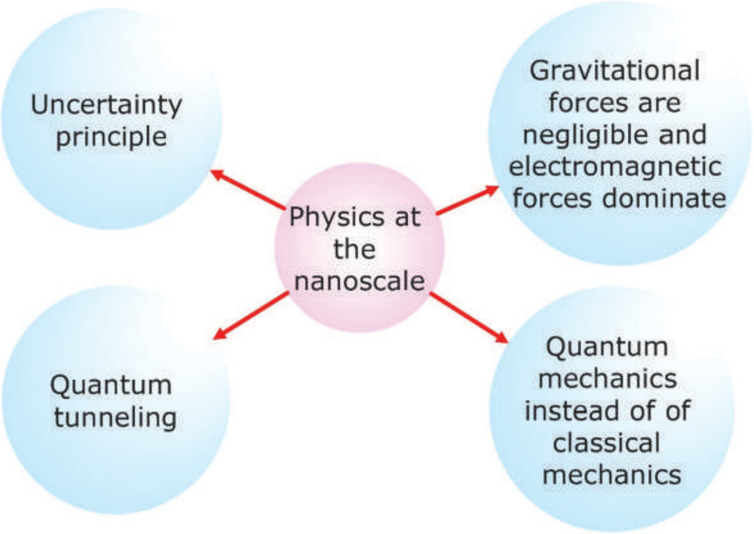

Figure 25. Important concepts manifested at the nanoscale.

phenomena.[7] To the extent that a semi-classical approach captures the principal features of the phenomenon, it is useful because its application is easier than solving the full quantum problem exactly. Furthermore, because the concepts are more aligned with those of our macroscopic world, it facilitates grasping and communicating the essential features of the phenomenon.

## Summary

As the dimensions of a system decrease and reach the nanometer range, new phenomena can be observed. Some of these can be understood as reflecting the natural size evolution of macroscopic behavior tempered by the relative change in importance of the forces operating on the system. In particular this is the case for surface effects which become more important than bulk effects. But there are also quantum phenomena which appear because the classical description is no longer adequate at these dimensions. In figure 25, we emphasize some concepts which play an important role in the physical and chemical behaviors of nanoscale objects.

# IV. Nanomaterials and nanostructures

A large part of the progress of human society is based on the development of materials. In the past metals have played a tremendous role in this respect. Progress in manufacturing techniques and the creation of new alloys have fostered advances in agriculture, transportation, warfare, cooking, etc. Various periods of rapid development in human history are identified by these advances: the age of copper, which occurred after the stone age, the bronze age, the age of iron. Today we are entering a new period corresponding to the age of nanomaterials. Creating new nanomaterials and understanding their properties will have far-reaching effects, Eiji Kobayashi, from Panasonic, says: "*those who control materials control technology*". This statement is certainly true for nanomaterials and their growing sociological and economic importance should not be underestimated.

## Classifying nanomaterials

According to The International Organization for Standardization a "nanomaterial" is a material with any external dimensions in the nanoscale range or having internal structure or surface structure in the nanoscale range. This size range is typically considered to be from approximately 1 nm to 100 nm. Nanomaterials are of particular interest because the unique properties, electrical, magnetic, optical *etc*., which can emerge on this size scale have wide application in a variety of fields.

It is possible to classify nanomaterials differently depending on which properties one focuses on, i. e., external or internal.

If attention is focused towards the external characteristics of a material, it is possible to classify it according to the external dimensions of the object. If only one dimension is smaller than 100 nm, it is considered as a one-dimensional (1D) nanomaterial. Ultra-thin films are an example of 1D nanomaterials. If 2 dimensions of the system are in the nanometer range, it is a two-dimensional nanomaterial (2D). Finally, if 3 of the dimensions of the system are smaller than 100 nm the material is a 3D nano-object. Nanoparticles or quantum dots belong to this category. Figure 26 summarizes some types of nanomaterials which can be produced and tailored to be utilized in applications such as those discussed in the remainder of this book.

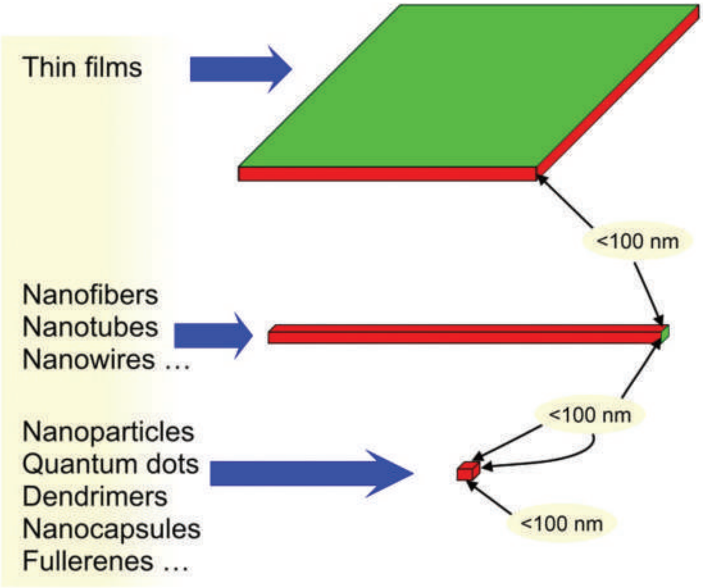

Figure 26. Some nanomaterials of interest.

In this classification, nanomaterials include:

- Materials such as thin films or surface coatings that are nanoscale in one dimension and are extended in the other two dimensions.
- Materials such as nanofibers, nanowires and nanotubes that are nanoscale in two dimensions and extended in the third dimension.
- Materials such as particles or molecules that are nanoscale in all three dimensions.
- Larger nano-crystalline materials composed of nanometer-sized pieces.

Man-made nanomaterials existed before people talked about nanotechnology. One of the examples developed over several decades, is ultra-thin films. The advantage of coating a surface with nanoparticles is that less material is needed to make the film and a better contact is realized. This is illustrated in figure 27 showing a monolayer of particles. Small particles provide a better surface coverage with less material than larger particles.

To show the importance of using ultra thin films in terms of material savings, suppose that we want to deposit a liquid film of one nanometer thickness on the surface Paris city. The question is: how much volume of liquid do we need? The area of Paris city is 105.4 $km^2 \approx 10^{26}$ $nm^2$. A volume of liquid of $10^{26}$ $nm^3$ = 0.1 $m^3$ = 100 liters is enough to do that. This simple

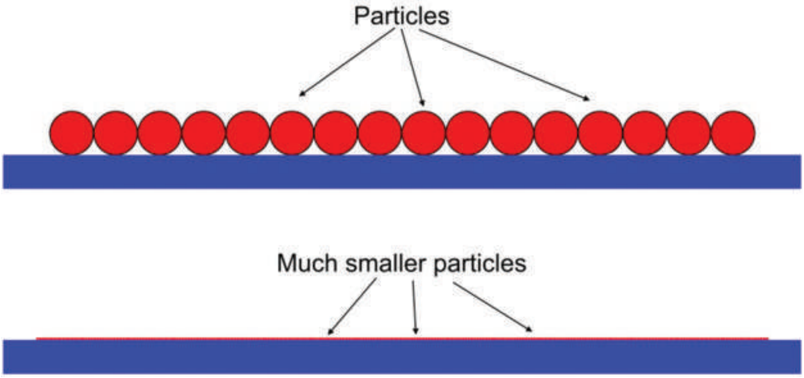

Figure 27. Difference between a monolayer made of particles (full circles) of different sizes coated on a surface.

example shows that the amount of material needed to cover Paris city is pretty small. Using nanosized films instead of microsized films, with the same properties, saves a lot of material and is a good for sustainable development.

Another way to classify nanomaterials is to focus attention on the internal structure of a macroscopic material and especially on the size of the nanostructures which are embedded within it (figure 28). In this classification, a structure has a non-zero dimension if one of its dimension at least is larger than 100 nm. For example, a nanoparticle is a nanostructure with all three dimensions smaller than 100 nm. Therefore, it is considered as a 0D (zero dimension) object. A nanowire or a nanofiber has just one dimension larger than 100 nm, consequently it is a 1D object. An ultra-thin film has two dimensions larger than 100 nm and is considered as a 2D nanomaterial. It is also the case of a stack 2D layers embedded in the bulk material. A 3D material will be just a bulk containing microstructures instead of nanostructures.

## Nanostructuration

Nanostructuring a material is interesting if improved properties are obtained. This can be done either by including specific nanostructures, or by an appropriate process generating nanostructures. Introducing nanostructures enhances the effects that are displayed in figure 29. It creates a large number of interfaces between the nanostructures and the bulk material, generating globally high surfaces in contact. These nanostructures, which are trapped in the bulk, show a size confinement into tiny parts of the bulk.

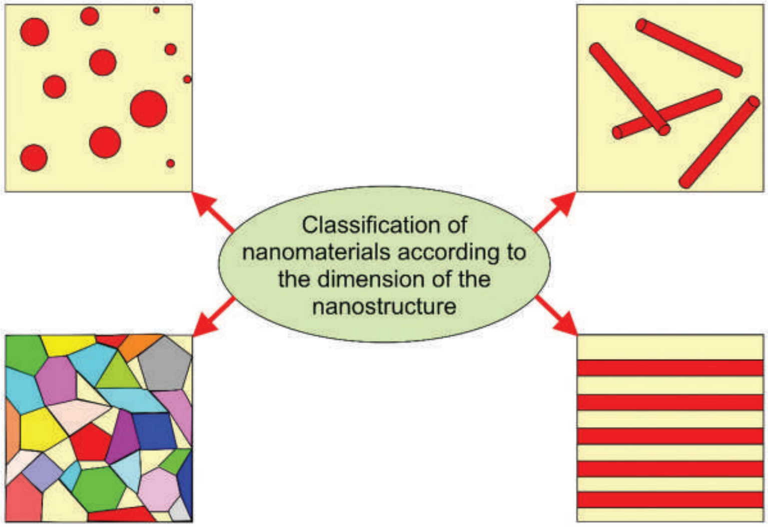

Figure 28. Classification of materials according to the dimensionality of the nanostructures. Illustration is made for 0D, 1D, 2D and 3D nanomaterials according to this classification.

Figure 29. Properties of nanostructures bringing new features in nanostructured materials.

The size and the nature of the nanostructures which are included in a bulk material can induce major changes in the properties of the original material and improve some of the characteristics which are required for a particular application. The nanostructures can introduce specific optical or magnetic properties, for example. The nature of the nanostructure and the distribution of the nanostructures in the bulk material will play a key role in determining the new properties. For example, the crystallographic orientation, the chemical composition or the possibility of having out-of-equilibrium nanometer crystallites of gold or sodium chloride can lead to interesting properties of the nanostructured material. Three keypoints need to be investigated in the development of nanomaterials. They are indicated in figure 30.

Dramatic changes can be obtained. For instance, nanoparticles of black carbon included in tires improve several properties such as the ride quality and wear resistance. Adding silica smoke containing nanoparticles in concrete make it less porous and less permeable to water. This new feature is worth for concrete staying in contact with sea water.

Nanoparticles possessing specific properties can also be introduced in the bulk material. There is a great variety of characteristics which are worth to provide to the bulk material such as optical, magnetic, catalytic… properties.

Nanostructures are the building blocks of nanostructured materials. The simplest nanostructures which can be used are nanoparticles but it can be more complicated structures such as fullerene, nanocrystallites, nanotubes…

For example, by dispersing ferromagnetic grains of a size of 5 and 10 nm inside a high-resistivity amorphous film, a nanostructured film of FeHf(NO) is obtained with a high permeability and resistivity. This nanostructured material is interesting because this material can be integrated close to inductive components and minimizes parasitic capacities at high operating frequencies (up to more than 2 GHz).

A crystallite is a small region of solid which is a single crystal. Figure 31 schematically shows an arrangement of several crystallites forming a polycrystalline material. Crystallites with a size in the nanometer range are called nanocrystallites. Materials used can be metals or metal oxides. For very small dimensions quantum effects can appear. Metal nanocrystalline materials are often used in heterogeneous catalysis.

An illustration of the structure of a nanocrystalline material is displayed in figure 32. Nanocrystals are embedded into an amorphous matrix.

In this chapter we shall focus our attention on some types of nanomaterials only, and postpone to next chapter the presentation of carbon-based nanostructured materials.

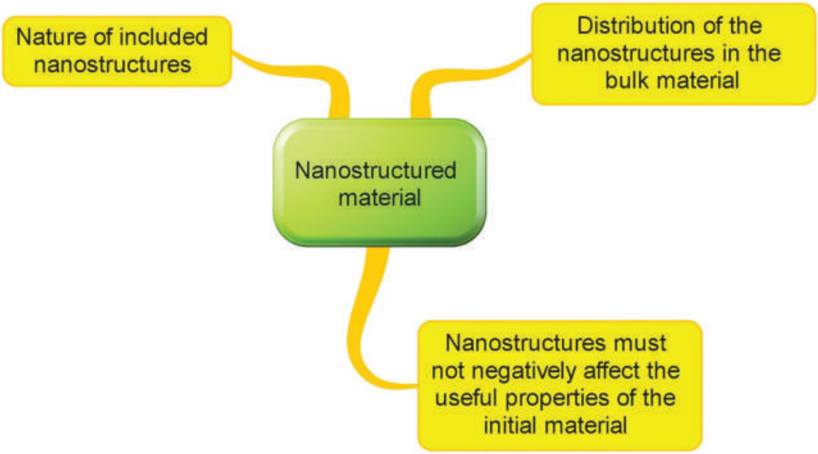

Figure 30. Three keypoints of nanostructured materials. Nanostructures included in materials can give to the nanostructured material new properties that depend on the nature of the nanostructures as well as on their geometrical distribution inside the material. Care should be taken not to negatively affect the initial properties of the material which are useful to the designed application.

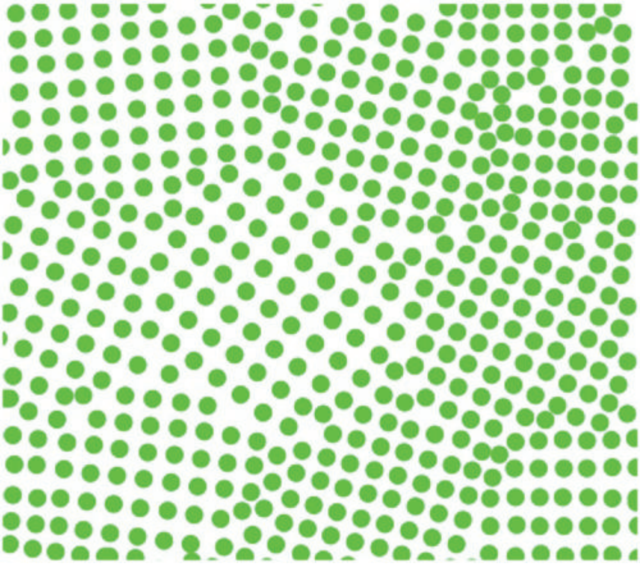

Figure 31. Schematic representation of polycrystalline material consisting of crystallites. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Edward Pleshakov.

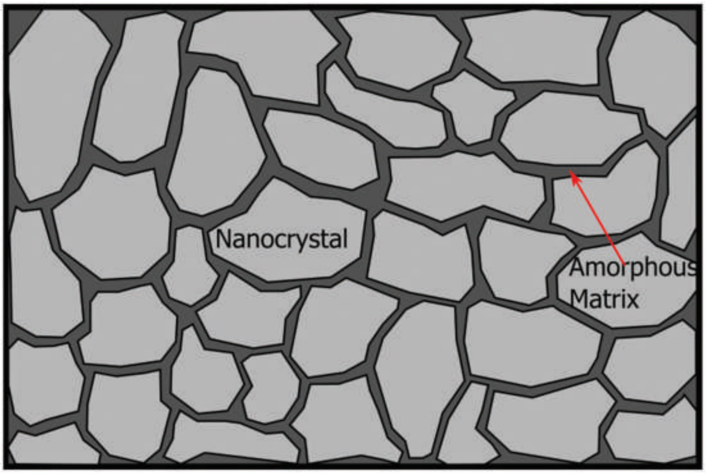

Figure 32. Schematic structure of a nanocomposite material with a nanocrystalline component embedded within an amorphous matrix. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Freundchen.

## Dendrimers

A dendrimer is a macromolecule made up of monomers which are assembled in a tree structure around a central core. It is a highly branched 3D structure with the ability to encapsulate nanoparticles. Figure 33 shows schematically the construction of a 2D dendrimer by the commonly used divergent method. The dendrimer grows outward from a core molecule containing several reactive sites. The principle illustrated in figure 33 is the following. In the first step, the core molecule reacts with monomers containing one reactive group and two dormant groups. This generates a first-generation dendrimer. The dormant groups are activated and react with monomer molecules to give the second-step dendrimer. The synthesis is repeated until the proper size of the dendrimer is obtained.

The other way to synthesize dendrimers is the convergent method. The end groups are the starting point and the synthesis is inward. A comparison between the two ways of synthesizing dendrimer is shown in figure 34.

Dendrimer chemistry was introduced in 1978 by F.Vögte and collaborators and the first family of dendrimers was synthesized in 1985 by D.A.Tomalia. Today it is possible to synthesize complex dendrimer structures and control the size, the shape, the surface and interior chemical functionalization. An example of dendrimer is shown in figure 35. This molecule has 54 ferrocenes attached at the surface.

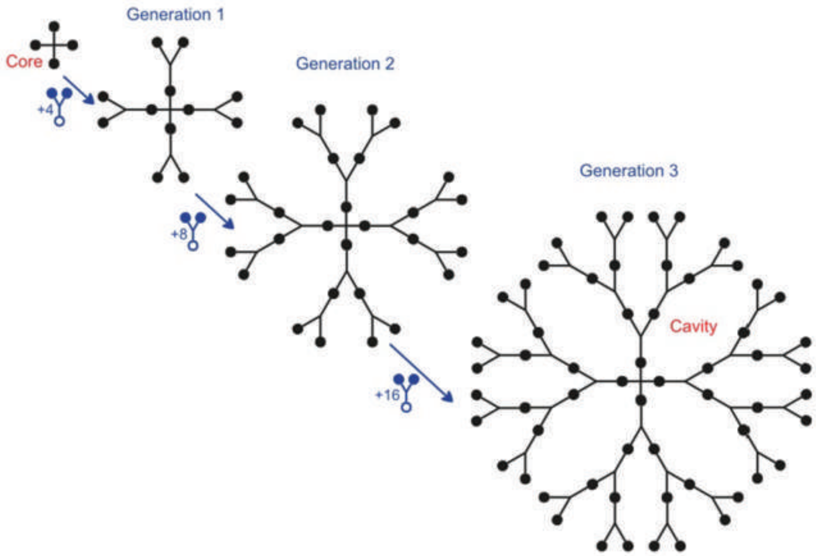

Figure 33. Schematic synthesis of a dendrimer by the divergent method.

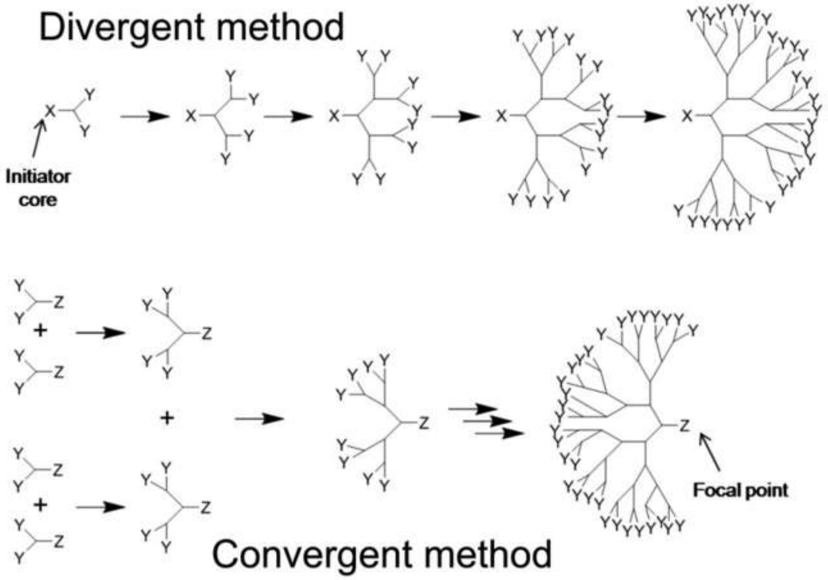

Figure 34. Principle of divergent and convergent method of synthesizing dendrimers. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Chem538w10grp10.

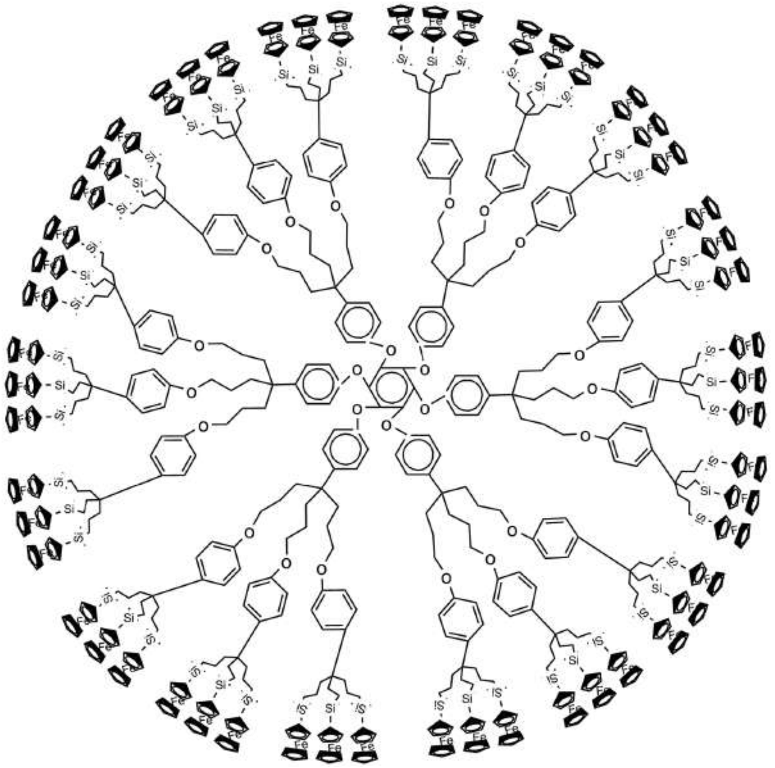

Figure 35. Dendrimer with 54 ferrocenes attached. . Image from Wikimedia Commons (http://commons.wikimedia.org). Author Skydivermonkey.

Dendrimers can be used to carry drugs for applications such as drug delivery, diagnostics or tumor therapy. Investigations are also carried out to use dendrimers as blood substitutes.

## Hybrid organic-inorganic nanomaterials

Hybrid organic-inorganic nanomaterials are interesting because they have on one side the good physical properties of ceramics and, on the other side, the convenience of organic molecules in terms of reactivity and functionalization.

Among these hybrid materials, the silsesquioxanes have interesting properties. Their stoichiometric formula reads $RSiO_{3/2}$, where R is an organic radical. Their name derives from the 3/2 oxygen. Sometimes they are also called T-resins (T for tri-substitued) because silicon is bonded to 3 oxygens substituants. Their most common geometrical structure is either a ladder or a cube. The cubic structure is commonly called the $T_8$-cube. It has the peculiarity that the O-Si-O angle is not 90°C although it is often drawn like that. Figure 36 shows an example of a $T_8$ cubic structure of silsesquioxane.

The cage structure shown in figure 36 gives the ability to put small molecules inside. Silsesquioxanes can be functionalized and used as antimicrobial coatings. Using for example quaternary ammonium salts, it is possible to make molecules which can kill bacteria and fungi while being harmless to humans and animals. Silsesquioxanes are also important for heterogeneous silica-supported transition metal catalysts.

## Nanocomposites

Nanocomposite materials cover a wide domain with many applications. A nanocomposite material is a material composed of several phases where at least one of the phase has a dimension in the nanometer range. Nanoparticles included into a matrix are an example of a nanocomposite material. It is also the case of multilayers structures, which are a stack of utra-thin films of different materials. Magnetic multilayers are for example used for storage media.

Inclusion of nanoparticles in a bulk material change its physical properties. It can become stronger, lighter, more ductile… The final properties of a nanocomposite depend on many factors such as the process of manufacturing, the nature of the nanostructure and the arrangement of the nanostructure within the bulk material.

A common example of nanocomposite is a tire. In this object, carbon black nanoparticles have been added in the initial rubber. Their presence improves the strength, tensile properties, the tear and abrasion resistance… However, a too high concentration of nanoparticles in the material lowers these properties.

The concentration of nanoparticles in the initial material plays a key role in the final properties. For example, a few ppm (parts-per-million) of nanoimpureties in aluminum alloys increases substantially the strength and the corrosion resistance of aluminum.

Polymer-clay nanocomposite can improve substantially the properties of a low-cost polymer. For example they are less flammable while keeping their good mechanical properties. Such nanocomposites can be synthesized using sol-gel techniques which are realized in mild conditions. Figure 37 shows the principles of a general synthesis procedure for a nanocomposite hydrogel.
Hydrogels are 3-dimensional polymer networks containing a large amount of water. They are usually fragile materials. Nanocomposite hydrogels

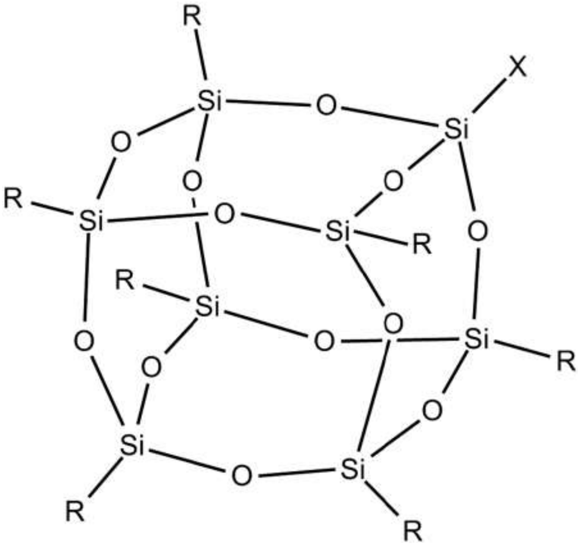

Figure 36. Example of a T8 cubic structure of Silsesquioxane. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Sephirothazule.

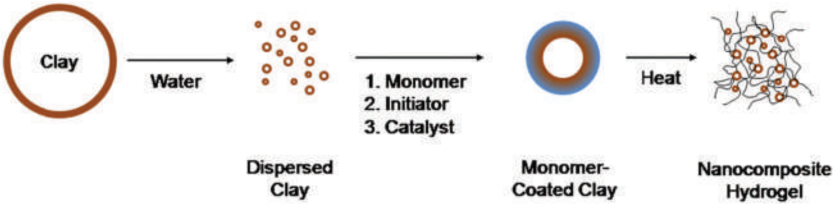

Figure 37. General synthesis procedure for a nanocomposite hydrogel. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Chem538w10grp6.

synthesized with mild chemistry has made a breaktrough in this field. It is now possible to manufacture nanocomposite hydrogels with various shapes and surfaces, with high toughness, with excellent optical properties and with the ability to respond to external stimuli.

## Smart materials

Smart materials are materials which can appropriately respond to stimuli provided by their environment. These materials are usually composite materials containing perception, response and control capabilities of various kinds (figure 38). External stimuli can be of various kinds: light, heat, electricity, radio waves, strain, etc. The materials are able to detect and

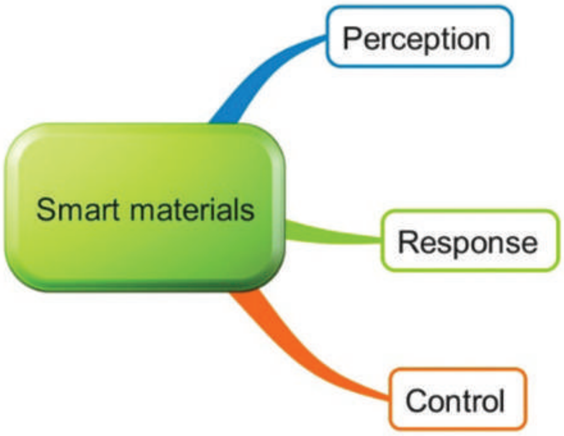

Figure 38. Main properties that a smart material should possess.

identify these stimuli above certain threshold levels and respond to them by choosing among a number of solutions decided by the designer. They should provide these responses within an appropriate time span and at the right level. The process should be reversible. After fulfilling its function, the smart material can be returned to its initial state. Some examples of smart materials are thermoelectric materials capable of converting temperature differences into electricital signals, shape-memory alloys or polymers which can return to their original shapes, and piezoelectric materials sensitive to external pressure changes. Nanotechnology provides new opportunities to fabricate *smart materials*.

## Summary

Nanomaterials will play increasingly important roles in the future, offering new or improved properties compared to materials which are not nanostructured. Nanotechnology will be applied to build new materials incorporating a number of desired capabilities. Nanotechnology also offers the opportunity to employ less material to accomplish the same goal. This is particularly important for sustainable development because the world may soon be short of some essential raw materials if we continue to use them as we do now. A full exploitation of the potential of nanomaterials demands a dependable understanding of their properties and mechanisms on all dimensional scales. The development of multiscale models, able to predict the properties of a material on all size scales is an important goal in this field.

# V. Natural nanomaterials

Materials are made of atoms. They are called *natural materials* if they belong to the mineral or living world and if no human modification or processing of their structure has been made. Natural materials have properties at the macroscopic level which are often due to their nano or microstructures.

## Nanomaterials in nature

A *natural nanomaterial* (figure 39) is a material exhibiting properties which reflect its structure at the nanoscale.

There are plenty of examples of natural nanomaterials; some of them are displayed in figure 40 and discussed in the following sections.

## Self-cleaning surfaces

Lotus flower leaves or taro leaves have a self-cleaning property (figures 41 and 42). Water droplets do not wet the surface. This phenomenon comes from superhydrophobicity, i. e, a very high water repellence. The surface of the lotus leaf is rough on the nanometer scale and covered with a waxy material. This material is hydrophobic and the rough surface reduces the area in contact with the leaf. The combination of both effects makes the droplets of water roll right off, taking out dirt that is on the surface. As a consequence, the surface is self-cleaning.

Nanomaterials which mimic this lotus effect have been developed to create surfaces which remain clean and dry, e. g. self cleaning windows or waterproof clothes.

Contrasting materials, surfaces that capture water also exist in nature. The Namib desert beetle uses special nanostructures to capture moisture from fog. A possible application of this phenomenon could be to manufacture surfaces trapping moisture to use as a water source.

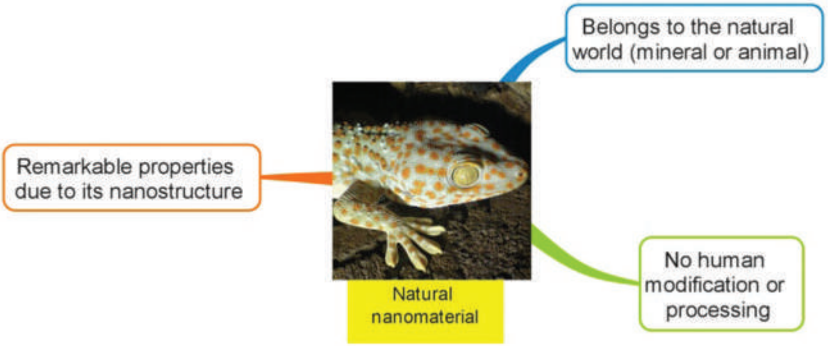

Figure 39. Definition of a natural nanometerial. The image of the Gekko comes from Wikimedia Commons (http://commons.wikimedia.org), author Robert Michniewicz.

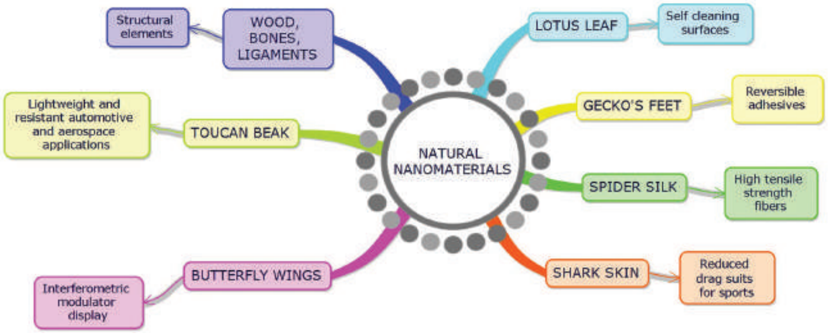

Figure 40. Examples of natural nanomaterials and some biomimetic applications.

## Reversible adhesives

The gecko is a lizard which can cling to any surface at any orientation. It can for example cling and walk on the ceiling with its feet over its head. It can cling on smooth as well as on rough, wet or dirty surfaces. While flies, for example, have similar abilities the gecko is the heaviest animal which can do this.

The weight of an adult Gecko is of the order of 140 g and, on a vertical wall, it can tolerate about 4 kg of additional weight without sliding. This astonishing reversible adhesive property is due to millions of setae (tiny bristles and hairs which are typically 100 μm long and 5μm in diameter) located on the soles of the gecko's feet. A Gecko foot is shown in figure 43. Each sata ends with hundreds of tiny pads (spatulae, with dimensions of the order of 200 nm in width and length) helping to cling to a surface (figure 44). Adhesion between the feet and the surface is due to Van der

Figure 41. Lotus leaves on pond in rain, showing the so called lotus effect; picture taken in the Chinese Garden at the "Gärten der Welt" (gardens of the world) in Erholungspark Marzahn, Berlin / Germany. Picture from ArchiKat, Wikimedia Commons (http://commons.wikimedia.org).

Waals forces discussed in chapter 3. Since there are a lot of hairs, the total interaction is large and this explains why the adhesion is so strong. The strong adhesive force between the hairs and the surface can be easily relaxed. In other words we have a reversible adhesive. The presence of hairs makes the feet of the Gecko self-cleaning. If dirt-clogged hairs are put on a surface, the dirt particle is left on the surface because there is a smaller contact area between the dirt particle and the satae than between the dirt particle and the surface.

If all the setae on a gecko's feet were active, the gecko could support the weight of two-medium sized persons (a shear force of 1,300 newtons is generated by the ~ 6.5 million satae). Actually, the number of active satae

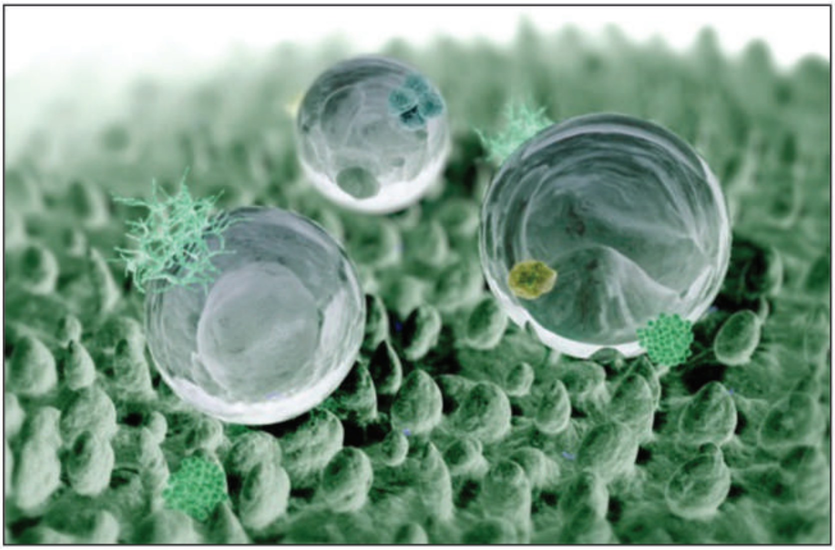

Figure 42. Computer graphics of lotus effect., Picture from Wikimedia Commons (http://commons.wikimedia.org) William Thielicke.

of a gecko is very small, of the order of 3 % but this still creates a very strong force (about 20 newtons).

Several attempts have been made to mimic the Gecko and develop reversible adhesives based on nanoproperties. One goal is surgical band aids that can remain for a long time and which can be removed without pain. The basic idea is to use contact splitting on the nanoscale.This technology was first developed in the US where scientists have used machines usually employed to etch patterns on microchips to create a rubber structure analogous to the gecko's foot. As in the gecko's foot, each hair was covered with thousands of protrusions which are responsible for strong adhesive power. On this nanostructured texture, scientists have added a biodegradable glue giving the ability to the bandage to remain glued when wet. First experiments were made on pigs and rats intestines in 2008 with success. It was found to work better than stitches. For human applications, such band aids can also be impregnated with drugs.

## Lightweight materials

In the aerospace or automotive industries it is important to have strong but light materials. Such materials exist in nature. The beak of a Toucan

Figure 43. Close-up of the underside of a gecko's foot as it walks on a glass wall. Van der Waals force interactions between the finely divided setae (hairs on the toes) and the glass enables the gecko to stay in place and walk on the seemingly smooth glass. Image from Bjørn Christian Tørrissen, Wikimedia Commons (http://commons.wikimedia.org), and http://bjornfree.com/galleries.html.

(figure 45) is a very strong and light biocomposite. It has hard nanotiles of a protein (keratin which also makes up fingernails, hair and horn) outside and nanosize fibers of bone inside acting as a lightweight supporting foam.

The structure of the toucan beak is interesting because of its high strength to weight ratio and because it is an excellent absorber for high energy impacts. Developing analogous materials for motorist protection in crashes can have many economic and safety implications.

## Manipulating light at the nanoscale

Butterflies (figure 46) manipulate light at the nanoscale thanks to nanometer size structures on their wings. Ridges with dimensions smaller than 1μm have nanostructures allowing for multiple reflection of light leading to beautiful iridescent colors. Similarly constructed artificial structures could be used to develop new fabrics, anti-counterfeit technologies for currency or dye-free paints.

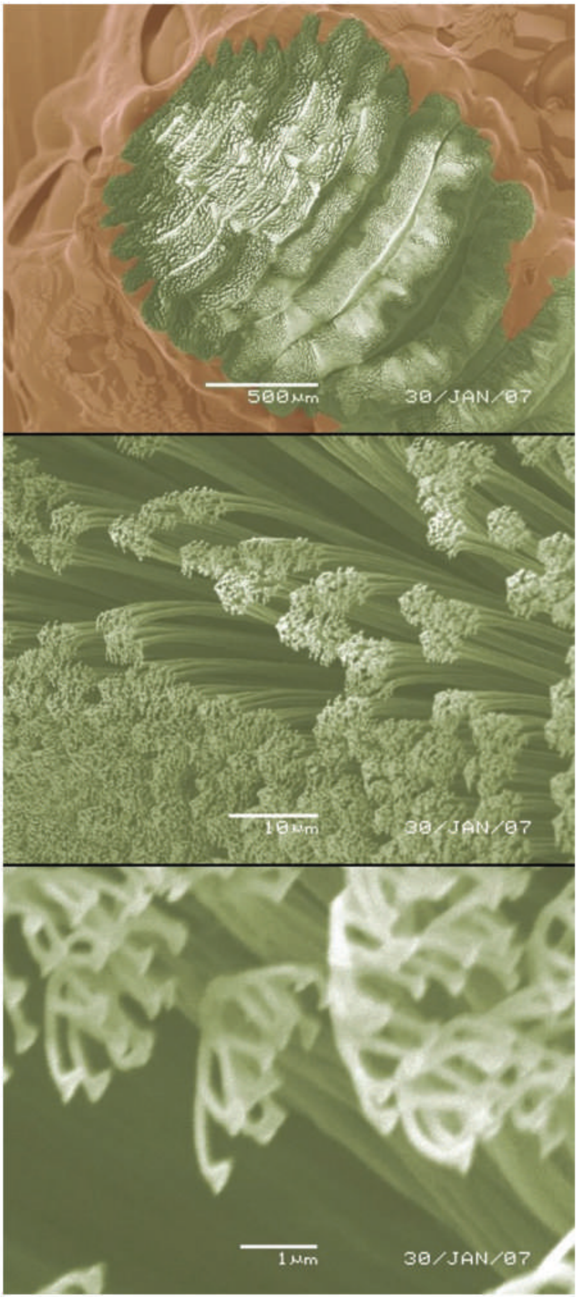

Figure 44. Foot of a Gecko viewed by a scanning electron microscope with increasing magnifications. As magnification increases, we see more and more clearly the tiny hairs. Image from Oskar Gellerbrant, Wikimedia Commons (http://commons.wikimedia.org).

Figure 45. Toucan.

Interferometric modulator displays (IMOD) employ a bio-inspired non -emissive technology where colors are created by controlling how light interferes with itself. The manipulation of light is done with micro-electromechanical systems. One of the advantages is the extremely low energy consumption of displays based on this technology.

## Fibers stronger than steel

The spider web (figure 47) is a very strong natural material. For the same weight, the silk of spider web has a strength about 5 times greater than that of steel. Furthermore, it is elastic and can be stretch up to 10 times its initial length. Spider silk consists of protein molecules produced by

Figure 46. Wings of butterflies have a nanostructure responsible for special optical properties.

Figure 47. Spider and cobweb. Spider silk is stronger than steel, for the same weight.

silk glands. The liquid which is produced hardens as it is squeezed outside the body to form silk fibers with outstanding properties. Nanomaterials mirroring the nature of spider silk would have many applications in sport equipment, aeronautics, automobile or household goods as well as in the defense domain, flak vests for example.

## Low-friction materials

The skin of a shark exhibits very low adhesion and large drag reduction for fluid flow. The shark skin is covered with placoid scales (dermal denticles) arranged in a special geometry that reduces friction and turbulent flow during swimming. As a result a shark can reach speeds greater than 70 km/h.

Several applications have been developed mimicking the shark skin structure. Swimwear has been manufactured to minimize the water resistance. Paints based on nanoparticles have been developed to cover the external surface of boats. The paints are applied using a pattern imitating the structure of the shark skin.These paints also resist UV radiation, temperature and mechanical changes.

Shark skin has also antimicrobial properties and a new material using a a pattern alone derived from shark skin has been recently developed.

## Multiscale structures

Many biological systems are made of self-assembled hierarchical structures over several size scales. This give them outstanding physical properties. This is the case, for example, for bones, wood, skin, teeth and the spider silk we discussed above. At the nanometer scale, there is always a structure which is involved to get excellent mechanical properties. In bones there are multiscale structures but also multiscale responses to deformation. Applying a multiscale philosophy to the development of advanced materials can lead to increased strength and desirable deformation characteristics.

## Summary

Nature is a pool containing very beautiful examples of nanomaterials and nanostructures that lead to unique properties and capabilities. Thoroughly investigating these and understanding the underlying structures and the operational mechanisms which are responsible can spur important advances in the development of man-made nanomaterials providing analogous benefits.

# VI. Nanofabrication

Nanofabrication techniques provide the ability to manufacture objects with details on the 1-100 nm lengthscale. Developing low cost manufacturing techniques with high throughputs and high yields is essential to facilitate wide-scale applications of nanotechnology.

## Top-down and bottom-up approaches

There are two approaches to building nanostructures or nanomaterials. The "top-down *approach"* and *"the bottom-up approach*" (figure 48). In the top-down approach the starting point is a bulk material and nanostructures are built by removing part of that material or adding extra material to get the desired structure. In microelectronics, for example, the top-down approach is currently used to manufacture integrated circuits or memories. The starting bulk material is often a silicon wafer. This wafer can be patterned using lithographic techniques. As the required accuracy increases and the dimensions of the circuit decrease, these lithographic techniques become more and more complicated and expensive.

Top-down approaches are a natural evolution of manufacturing processes used at the macroscopic scale. Small systems, with a size at the cm or mm lengthscale, can be manufactured by skilled mechanics with lathes, saws and sanders. The difficulty with top-down approaches at the micron or nanometer scale is to get perfect surfaces and edges. It is essential to master processes giving a perfect control of the size of the details to be manufactured. Because some parts of the initial macroscopic structure are removed, top-down approaches require more raw materials and generate more waste than the bottom-up approach.

In the bottom-up approach, Instead of removing material from a bulk structure, one selectively organizes atoms or molecules to build the nanostructure. This is actually the way nature builds complex microscopic or macroscopic structures. The bottom-up approach has several advantages compared to the top-down approach. It requires less material than the top-down approach because there is no waste material lost, for example due to etching. It is easy to make thin films and it allows the creation of detailed structures smaller than those produced with photolithography.

Figure 48. The two approaches to nanofabrication: the top-down and the bottom-up approaches.

The problem is that the number of atoms or molecules required to build a nano-object is very large and normally each atom or molecule cannot be handled individually. For example, suppose that we want to make a monolayer film (a film containing just one layer of molecules). If we use molecules with diameters of 0.2 nm and want to build a 1 $cm^2$ monolayer film, we need to arrange $2.5\times10^{15}$ molecules. Placing each molecule one by one at a rate of 1 per second would require almost 80 years of work. This is clearly an important issue. In the bottom-up approach, it is necessary to have a method to build nanostructures where the molecules *self-organize*. Other challenges for the bottom-up approach are to be sure that the nanostructure which is built by self-assembly is assembled in the correct way and that that there is no contamination during the self-assembly process.

The most efficient way to manufacture complex nanosystems is to combine the top-down and bottom-up approaches. The use of templates, catalysts or applied force fields can allow directed self-assembly.

## Lithography

Lithography is the corner stone of microelectronic fabrication and is the technique used to make microprocessors and memories. It is a technique in which a pattern is tranferred to a photosensitive material called *photoresist* or *resist*. A photoresist produces, under irradiation by light (UV or X-rays) or ions (electrons or ions) a negative or a positive image depending upon the nature of the resist (see figure 49). After exposure, there are physico-chemical changes in the exposed areas and the resist is developed, for example by immersion into a liquid. The principle of positive and negative resists is shown in figure 49. Positive and negative resists act in the same way as slides and negatives in the field of photography. A positive or negative image of the pattern on the resist is then transferred to another layer by etching or lift-off processes.

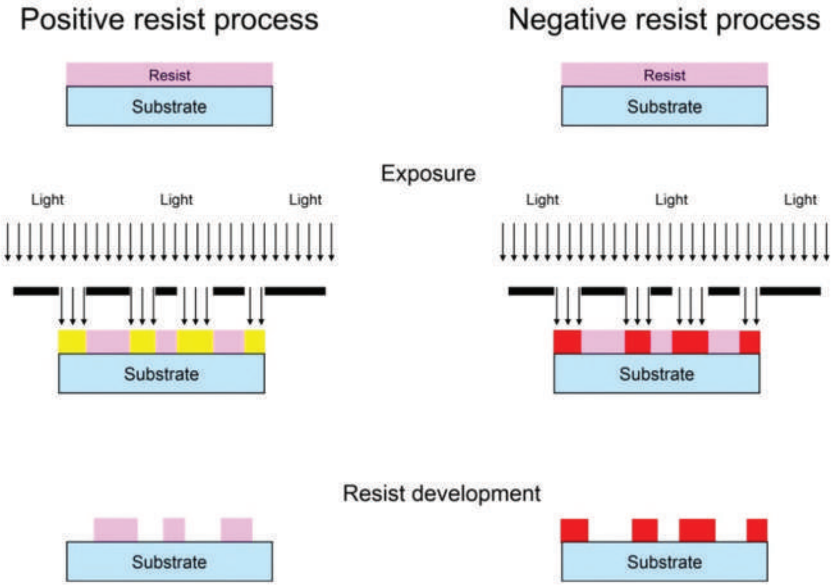

Figure 49. Principle of lithography using a positive and negative photoresist.

The semiconductor material most commonly used in microelectronics is silicon. Other materials such as SiC, GaAs or GaN are also used for specific applications.The silicon is usually in the form of wafers, circular thin slices of material obtained from an ingot of a high purity (99.9999999 %) single crystal of silicon. The available size of silicon wafers has increased with time. It was 4" diameter (100 mm) around 1975 and 300 mm (11.8") in 2001. The 300 mm technology is still used and technologists are bringing the 450 mm (18") technology to the industrial stage. A larger size for the wafer allows the manufacture of more integrated circuits at the same time which decreases the cost of each piece.

Several steps, called *mask levels*, are necessary to manufacture an integrated circuit. The different operations in each stage are schematically illustrated in figure 50. The starting point of the lithography process is to deposit a thin layer of resist by spin coating. In order to do that the wafer rotates at high speed and the dissolved resist is poured onto the wafer. This allows deposition of a thin homogeneous layer of photoresist. In a second step, curing and baking of the layer gets it prepared for use. In the third step, the pattern of the mask of the integrated circuit is projected using a reduction optics system and this is repeated until the whole wafer is illuminated (step and repeat exposure). After exposure, the resist is developed

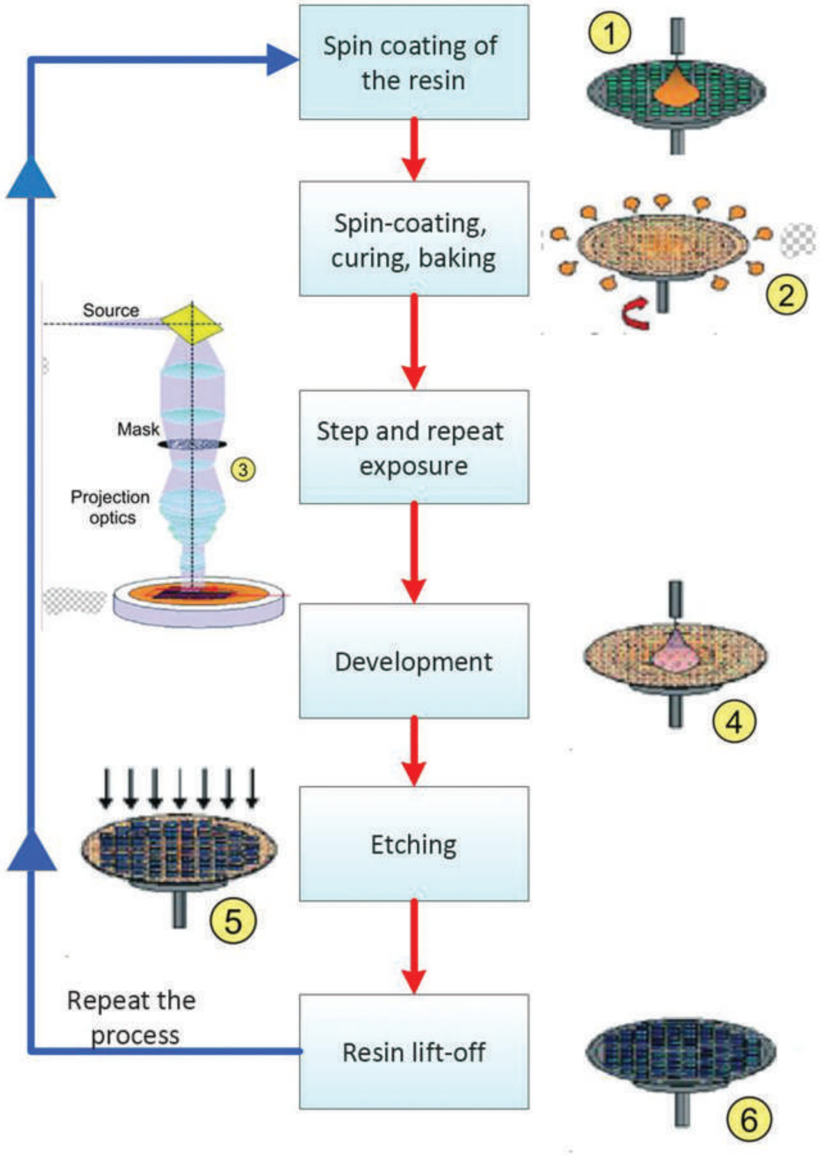

Figure 50. Different stages in a lithography process during one masking level. In the manufacturing of a microprocessor several masking levels are needed. Diagram built from a figure in Clef CEA n°52, courtesy of CEA/LETI.

and the parts of the resin which have been removed are etched. After this operation, the part of the resin that is left over is lifted-off before deposition of a next layer to start a new stage of lithography. Accurately positioning each mask level with respect to the previous ones is a critical issue.

As the dimension of the details of the circuit decreases, the lithography techniques become more and more complicated and expensive.

All lithography operations have to be done in rooms with exceptionally clean environments. In these rooms, the number of dust particles in the air must be severely restricted. If dust deposits onto the wafer surface during manufacturing, the circuit will either malfunction or not function at all. Sources of light with short wavelengths have to be used (excimer lasers for example) and new techniques have to be developed to further increase the resolution achievable. As a consequence, the cost of lithography machines exponentially increases as the required accuracy in dimension decreases.

## Nanolithography

Lithography, in the microelectronics domain, is progressing swiftly step by step. Each step is called a *generation* or *technology node*. For example, a 30 nm technology node, refers to the size of the details that one can design on a wafer, such as the size of the gate of a transistor or half the distance between two identical features (half-pitch) in the case of memories. In 1971, the technology node was at 10 μm while in 2011 the technology node was 22 nm, that is in the nanometer lengthscale. By the end of 2014, the 14 nm technology node has been used by Intel. Actually the 32 nm technology node was introduced 2010. In 2001, the technology node was 130 nm and in 2004 it was 90 nm. It is around that period that microelectronics moved in the nanorange.

Light sources used in lithography have a given wavelength.The smallest wavelengths used are obtained from excimer lasers (KrF at 248 nm and ArF at 193 nm). To go down to smaller dimensions, extreme UV lithography has been developed using a very short wavelength (13.5 nm). However, at these dimensions, conventional optics does not work anymore and special techniques need to be used.

*X*-ray lithography is difficult and expensive to use because conventional lenses do not work and it is necessary to use mirrors to guide the beam. The mask is also an issue and usually a 1:1 image is made. Conventional *X*-ray sources can be used as well as synchrotron radiation.

Extrapolating microelectronics technology to smaller dimensions (below 100 nm) also raises new problems if conventional materials are used. For example, despite the fact that a transistor consumes less energy and generates less heat when its dimensions are reduced, the number of transistors placed per unit area may increase dramatically. Therefore more and more heat must be dissipated per unit area and the question of heat dissipation becomes an important issue.

In order to be able to etch details smaller than the wave length of the light source, special tricks have been developed such as high numerical aperture optics, immersion lenses, phase shifting masks, optical proximity correction and double patterning approaches. This is fine for microelectronics applications below the 100 nm range which are able to make huge investments. However, non-microelectronics applications cannot afford such high costs because they do not have a high volume production.

For non-microelectronics applications, it is necessary to use low-cost and flexible lithography techniques. Three of them are available: electron beam, ion and nanoimprint lithography.

### e-beam lithography

Electron beam (*e*-beam) lithography uses an electron beam to pattern directly the resist deposited on the substrate. As far as the process is concerned, it works the same way as light lithography that we just discussed. However no mask is required and the exposure is done by direct irradiation. A resolution of a few nanometers can be routinely obtained. *e*-beam lithography is used to design masks and templates used in light lithography. The main drawback of *e*-beam lithography is that it takes a long time to expose the substrate because the irradiation is done point by point, in raster mode, similar to that employed to direct the electron beam in a cathode ray tube. This technique can only be used in the laboratory, or for low-volume production of nanosystems.

In *e*-beam lithography, PMMA (poly-methyl-methacrylate) is a resist often used as a positive tone. Exposed areas to the electron beam become more soluble in the developer. An example of a negative resist is HSQ (hydrogen silsesquioxane) which undergoes crosslinking under exposure and becomes less soluble.

### Helium-ion lithography

Lithography with ion beams is also possible. Scanning helium ion beam lithography (SHIBL) with subnanometer beams is an attractive technique for nanostructure manufacturing. This technique has been made possible by the development of the helium ion ($He^+$) microscope for imaging. A resolution of about 0.35 nm can be obtained filling the gap between scanning electron and transmission electron microscopy. This capability can also be applied for manufacturing. The technique can be used not only for lithography but also in ion milling of nanosystems. Features with dimensions below 10 nm can be obtained. One advantage of an ion beam compared to an electron beam is the negligible back scattering of ions compared to that for electrons.

## Nanoimprint lithography

Nanoimprint lithography is a low-cost technique with a high throughput. The resolution is moderate (for example 25 nm) but it can be applied to large areas. The principle of thermal nanoimprint is shown in figure 51.

To begin with, a mold (stamp) containing the negative image of the nanostructures we want to print is pressed into a thin film of resist cast on a substrate. The process is facilitated by operating just above the glass transition temperature of the resist, which is the temperature above which the resist becomes thermoplastic. The image of the mold is impressed onto the resist. This image can be made more precise using an anisotropic etching to remove the residual resist in the compressed areas.

Another nanoimprint technique consists in imprinting a liquid photocurable resist material at room temperature and low pressure. An external UV source is used to crosslink the resist. This technique, called ultraviolet assisted nanoimprint lithography, requires either a UV-transparent mold, or a UV-transparent substrate.

Three-dimensional nanostructures are interesting for biosensors, nanofluidic devices, photonic devices, *etc*. *e*-beam or *X*-ray lithography can be used but these methods are complex and expensive. Methods based on sophisticated nanoimprint are currently under development combining for example nanoimprint and *X*-ray lithography, or imprinting inorganic sol-gel materials. Nanoimprint lithography is an interesting alternative to conventional lithography to fabricate nanostructures. This technique is already in use to produce commercial microlenses. One promising application is 3-dimensional nanopatterning.

## Dip-pen nanolithography

Dip-pen nanolithography uses the tip of an atomic force microscope (AFM) coated with a chemical or biological compound to pattern the surface of the substrate. The tip of the cantilever of the AFM plays the role of the pen, the chemical or biological product that of the ink, and the substrate the role of the paper.

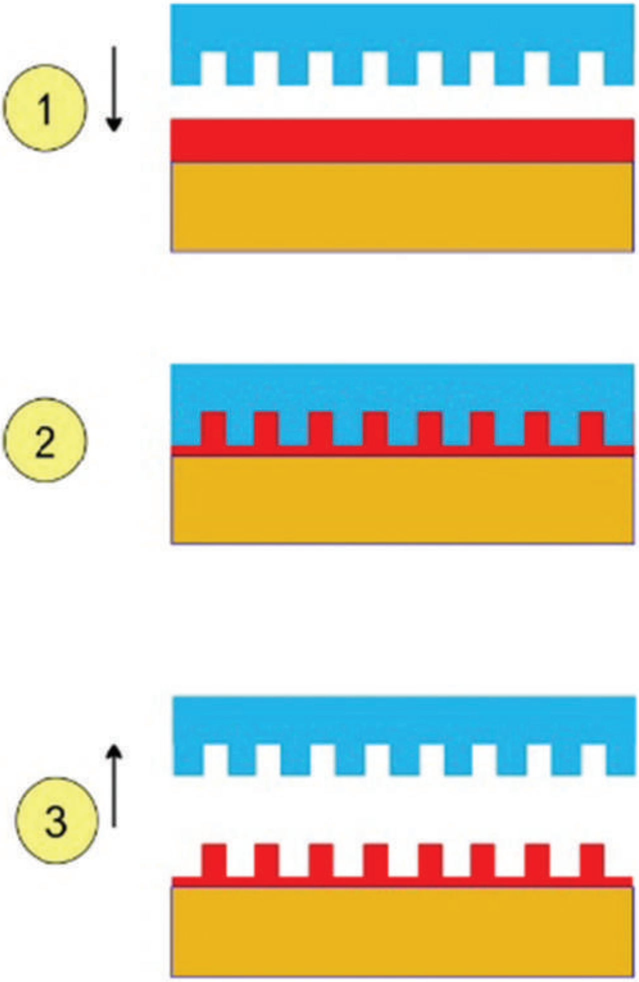

Figure 51. Principle of thermal nanoimprint lithography.

One-dimensional and two dimensional arrays of cantilever allow to have parallel processing which increases the throughput. Dip-pen arrays with more than a million tips have been made. Pen lithography can be improved with different method and other techniques exist such as polymer pen lithography or beam-pen lithography.

## Deposition at the nanoscale

Several methods exist to fabricate thin films with nanoscale thicknesses.

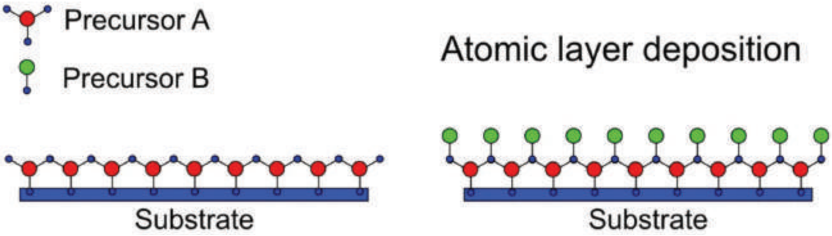

Figure 52. Principle of atomic layer deposition (see text).

### Atomic layer deposition

Atomic layer deposition (ALD) is a a chemical deposition technique to fabricate pinhole free and conformal (the thickness is the same everywhere on the surface of the substrate) nanometer thick films on a substrate. The substrate is not necessarily a flat surface. It can have a complex geometry. ALD requires two reactant gases (precursors) which are sequentially introduced into the reaction chamber containing the sample. The precursors react with each other to form an atomic layer.

The principle of ALD is schematically shown in figure 52 for a single cycle corresponding to the fabrication of a one atomic layer film. A cycle consists of four different steps where the two precursors, A and B are successively involved:

1 The first precursor (A) mixed with a carrier gas (nitrogen or argon, for example) is introduced into the reaction chamber containing the sample. It is chemically absorbed on the surface of the substrate until the surface is saturated.
2 The excess of precursor A is removed by sweeping the volume of the chamber with the carrier gas.
3 Precursor B is pulsed into the reaction chamber and reacts with the absorbed molecules. The quantity is large enough for the surface to be saturated.
4 The excess of precursor B is swept away by the carrier gas and by pumping.

This cycle can be repeated several times to get a film of desired thickness.

### Self-assembled monolayers

The self-assembled monolayer (SAM) technique can be used to create thin films on a surface of a metal or semiconductor, or on the surface of

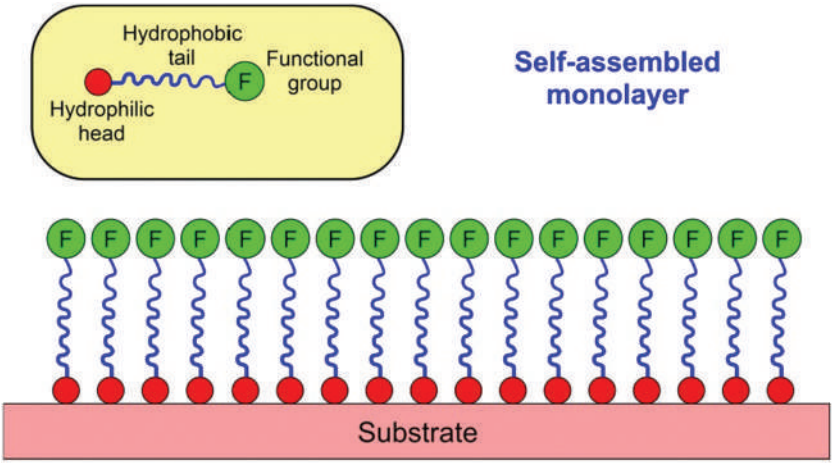

Figure 53. Illustration of a self-assembled monolayer.

nanoparticles using molecules with a hydrophilic head and a hydrophobic tail (amphiphilic molecules). A self-assembly process occurs because of the chemisorption of the hydrophilic head of the molecules on the surface of the substrate. After a time ranging from minutes to hours, a crystalline or semicrystaline structure can be formed on the surface of the substrate.

A schematic display of a SAM is shown in figure 53. As we can see in this schematic drawing, the molecules can even be functionalized.

Use of catalysts or applied stresses may allow for anisotropic or directed self-assembly. Of course the most efficient way to manufacture complex nanosystems is to combine the top-down and bottom-up approaches.

## Covalent bonds

There is a great practical interest in developing covalent bonds between a molecule and a surface because covalent bonds provide a strong anchorage to the surface. If a layer of polymer is simply deposited onto a surface and is attached by weak forces such as Van der Waals or hydrogen forces, it is easy to remove part of the layer during use. On the other hand, if it is anchored to the layer by covalent bonds, it is more resistant to external physical or chemical conditions because a much larger amount of energy is required to break the covalent bonds. Covalent bonds can be used to functionalize a surface

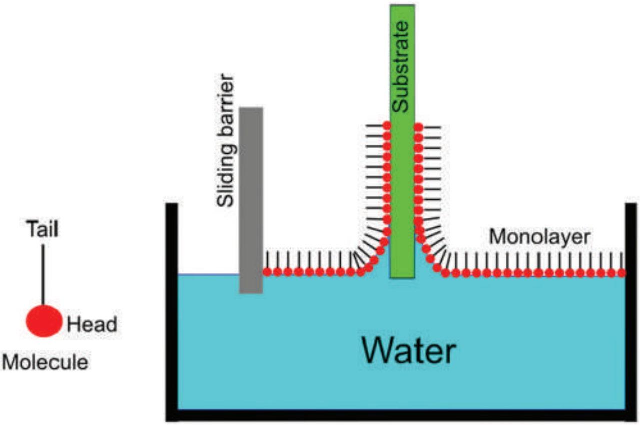

Figure 54. Principle of the preparation of a Langmuir-Blodgett film.

or protect it. Several methods have been developed to create covalent bonds on a layer. They are often based on stimulating the surface to facilitate a chemical reaction between the surface and the molecules to be anchored. This stimulation can be exposure to light, heat, electrical potentials, *etc*. Metals, silicon and carbon are examples of useful substrate materials.

Covalent bonds can also be formed with an already deposited layer (Langmuir-Blodgett films, SAMs, *etc.*). One of the advantages of anchoring covalent bonds on a nanothickness layer made by self-assembly is that the geometrical ordering of the first layer is used to build the second one.

## Langmuir-Blodgett films

Langmuir-Blodgett films consist of one or more monolayers of an organic material. The organic molecules which are used usually have a hydrophilic head (polar group) and a hydrophobic tail. The principle of fabrication is shown in figure 54. Organic molecules are put onto the water surface at a concentration such that they are not closely packed. A sliding barrier is used to closely packed them onto the surface. A substrate, immersed in water, is moved up slowly and a monolayer deposits onto its surface. The process can be repeated to form multilayers either with the same molecules or with different molecules.

The Langmuir-Blodgett technique is a typical example of bottom-up approach by self organization. Multilayers from two to hundreds of monolayers can be fabricated by this method.

## Polishing, etching, patterning

### Chemical mechanical polish

Clean polished surfaces are usually required for thin film deposition. The aim is to get a flat, smooth surface without defects. Historically, a number of polishing techniques have been used to obtain such surfaces. Polishing materials have been used for centuries to manufacture copper and bronze mirrors and more generally glass optics. More recently, water polishing has been used in wafers used in integrated circuit fabrication.

Chemical-mechanical polishing (CMP), sometimes called planarization, combines both mechanical and chemical polishing. It was developed first by IBM in the 1980s for microelectronics. A wafer is pressed against a rotating pad with a polishing slurry. Polishing slurries contain mechanically active abrasives and chemically active components. Abrasives are generally hard oxide particles suspended in the slurry. Depending on the polishing work to be done, abrasive particles have a diameter ranging between 10 nm and 10 μm. Active chemical components, dissolved in water, are substances that soften and oxidize the surface which is polished. After polishing, cleaning of the surface is necessary to eliminate residual chemicals and particles.

As an illustration of CMP, we shall consider the damascene process applied to copper. For a long time the electrical interconnections in integrated circuits have been made with aluminum. The interconnects were produced by substractive etching of a film of aluminum using a photoresist pattern. To improve the performances of microprocessors, it has been necessary to replace aluminum by copper. Copper has a lower resistivity than aluminum allowing better performance and a lower joule heating, thus higher current densities. It also leads to better overall reliability. The main issue with copper is the difficulty in patterning the interconnections with conventional etching techniques. Furthermore, copper quickly diffuses into oxides and silicon, and quicky oxidizes in air. In the 1990s, IBM introduced the Damascene process to form copper inetrconnections in integrated circuits. The principle of the Damascene process is shown in figure 55.

In the Damascene process, a dielectric is first deposited on the wafer and then etched according a photoresist pattern. A barrier is then deposited to prevent a mixing of materials above and below the barrier. This gives the substrate shown on top of figure 55. Copper is then deposited, by electroplating for instance. Finally the surface is planarized by CMP which removes the unneeded copper.

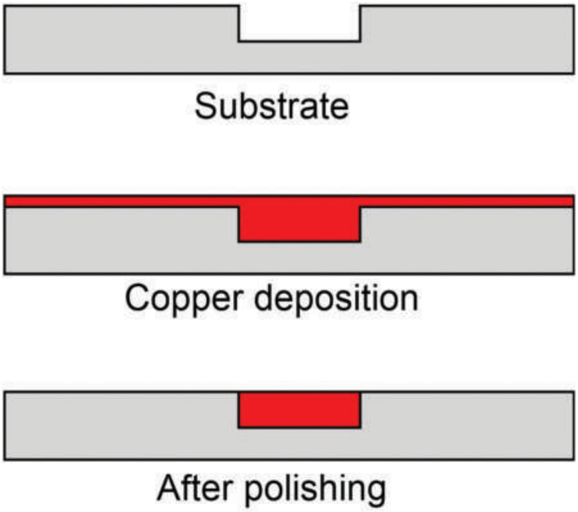

Figure 55. Principle of the damascene process.

## Summary

Developing and mastering different technologies to manufacture nanomaterials and nanosystems is essential in the development of nanotechnology. A large number of methods adopted from different fields are available and used in this area. Manufacturing can proceed in a "*top-down*" approach in which a nanosized system is obtained from a larger system, or in a "*bottom-up*" approach where it is built from elementary pieces. The two approaches can be combined for greater efficiency. The main concern is to develop economical high throughput techniques for large scale production of systems containing nanostructured parts.

# VII. King carbon

Organic chemistry is the chemistry of carbon compounds (other than simple salts such as carbonates, oxides, and carbides). It is a domain in its own right because of the huge importance of organic compounds in the living world. Until 1985, only three forms (allotropes) of pure carbon were known. These were graphite, diamond and lonsdaleite (which is a diamond with a hexagonal lattice instead of a cubic lattice). Other allotropic forms exist but are less known. In 1985, the discovery of new allotropes of carbon opened a vast field in nanotechnology because of outstanding properties of these new forms of carbon.

## Fullerenes

In 1985, R.Curl, H.Kroto and R.Smalley, inspired by the reported observation by Canadian radio astronomers of long linear chain molecules of carbon in interstellar space, carried out an experiment designed to simulate the conditions under which carbon nucleates in the atmosphere of red giant stars. By vaporizing graphite and condensing the vapor in an atmosphere containing an inert gas they discovered a new form of carbon. Several different clusters were identified. The simplest one contained 60 atoms of carbon arranged as a truncated icosahedron as shown in figure 56. The structure of this hollow molecule is similar to that of a soccer ball with 20 hexagons and 12 pentagons. Each carbon atom is bound to 3 neighboring carbons atoms by covalent bonds. It should be noted that two pentagons have no common edge. The discoverers named the molecule *buckerminsterfullerene* because of the similarity of its structure to that of the geodesic domes designed by the architect Buckminster Fuller for the 1967 Montreal world exhibition. Other designations such as *buckyball* or simply $C_{60}$ are used to identify this spherical molecule which has a diameter of about 0.7 nm.

The $C_{60}$ molecule is highly symmetric and remains invariant under 120 symmetry operations. The π-electrons are delocalized over the whole surface making this molecule particularly stable (breaking a $C_{60}$ molecule requires temperatures over 1,000°C). The delocalization of π-electrons over the surface of the sphere is somehow an extension of the delocalization of π-electrons over a hexagonal benzene molecule. Solid $C_{60}$, a yellow powder, turns pink when dissolved in toluene.

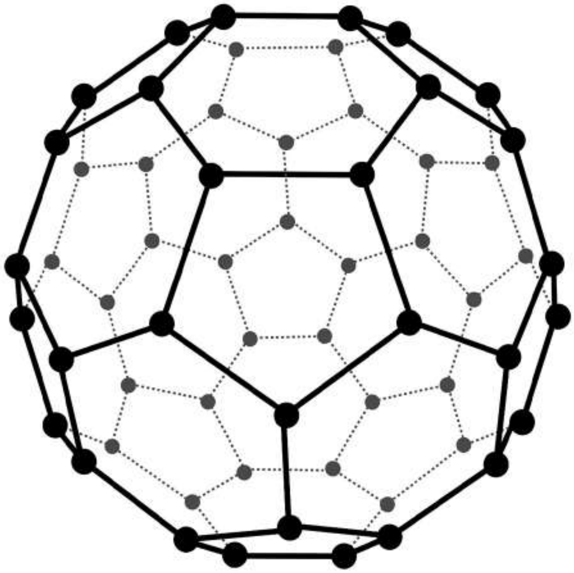

Figure 56. Schematic picture of a C60 molecule., also called a "Buckyball".

Other carbon clusters were also found In the condensed mixture, but the buckyball was the smallest stable molecule. The clusters belong to a larger family of molecules called *fullerenes* made only of carbon atoms and having a hollow shape (sphere, ellipsoid, tube). They have an even number of carbon atoms: $C_{60}$, $C_{70}$, $C_{76}$, $C_{78}$, $C_{82}$, $C_{84}$.... The discoverers of fullerenes were awarded the 1996 Nobel Prize in chemistry for this work.

Actually, fullerenes structures had already been predicted by E.Osawa in 1970, well before their discovery in 1985. But their importance was not appreciated. Fullerenes are exceptionally interesting molecules with many potential applications. The existence of a hollow shape provides the capability to encase an atom or another molecule. Figure 57 illustrates this schematically showing a noble-gas atom caged inside the $C_{60}$. The interest of putting another entity inside the $C_{60}$ structure is that it is protected against external interactions. In health care applications,for example, this could allow delivery of a drug to the right place in the body before it is released.

Another possibility illustrated in figure 58 is to functionalize the surface by adding specific chemical groups. It is possible to graft a molecule on the surface to make compound molecules that are more hydrophilic (water-loving) or lipophilic (fat-loving) than the initial fullerene. It is also possible to tailor the electronic or optical properties. Figure 58 represents such a fullerene. This molecule has potential applications in the catalyst domain or in non-linear optics.

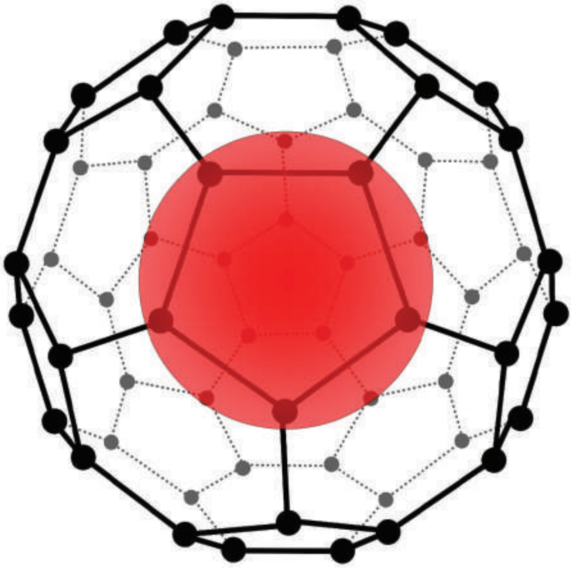

Figure 57. Schematic picture showing an atom of a noble gas caged within a C60 molecule.

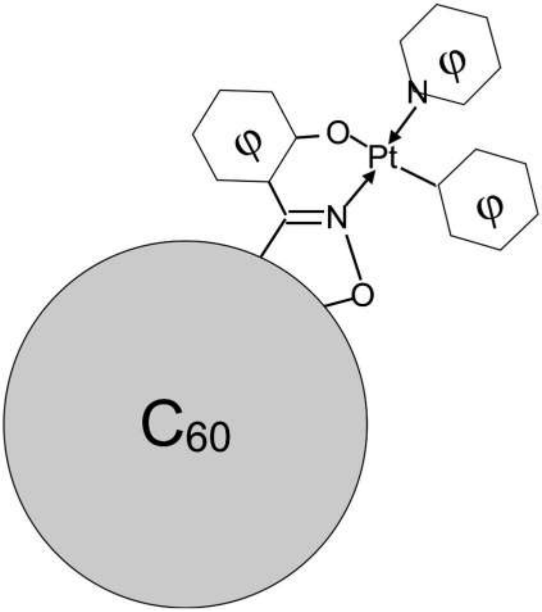

Figure 58. Isoxazoline fullerene chelating agent.

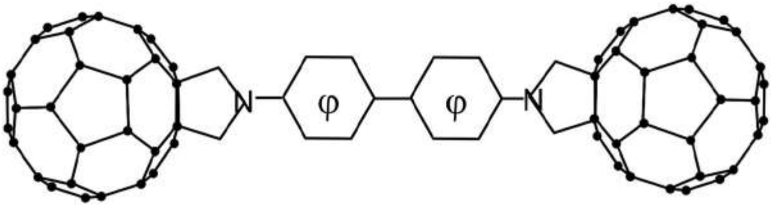

Figure 59. Schematic drawing of a dumbbell fullerene.

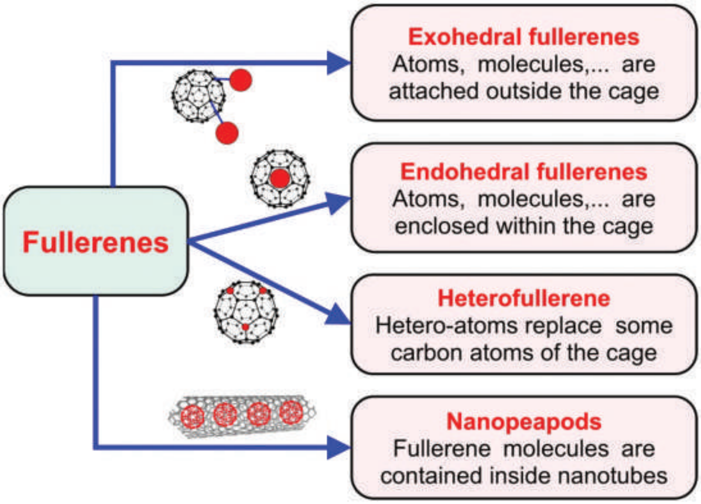

Figure 60. Different types of engineered fullerene molecules.

Many possibilities are open and complex structures with specific properties can be synthesized. For example, figure 59 shows two $C_{60}$ molecules connected by a molecule with delocalized electrons.

Many types of modified fullerenes can be synthesized for potential applications (see figure 60).

Exohedral fullerenes, such as that in Figure 60, are synthesized in a chemical reaction between a fullerene and another molecule or atom which can be grafted to the outside of the fullerene. This is the most important family. As fullerenes are insoluble in water, adding a proper chemical group can make the resulting exohedral fullerene soluble.

It also is possible to enclose an atom in the hollow of fullerene (endohedreal fullerene). When the atom trapped inside is a metal, the molecules are called metallofullerenes. The size of the atom enclosed must be small enough to fit in the hollow. Most of the endohedral molecules synthesized are made out of large size fullerenes: $C_{82}$, $C_{84}$... Atoms such as scandium, lanthanum, yttrium and light rare gases have been caged inside fullerenes.

In the litterature, they are usually denoted by a hybrid formula such as La@$C_{82}$, for example, which means that an atom of La is caged inside $C_{82}$.

In heterofullerenes, one or more carbon atoms of the cage are replaced by hetero-atoms such as nitrogen, for example.

Nanopeapods are single-walled carbon nanotubes with buckyballs inside. They are potentially interesting for molecular electronic devices.

Fullerene derivatives have many potential applications. Fullerenes are inert and are not absorbed when administered orally in a water-soluble form. Water-soluble fullerenes have a very low acute toxicity and are excreted by the kidney. They have many potential applications in biology and medicinal chemistry. For example, endohedral metallofullerenes can be used as magnetic resonance or *X*-ray imaging contrast agents. Some modified fullerene molecules are utilized as radiopharmaceuticals. They can be used as tracers or to kill cancerous tumors. Another application is the use of the cytotoxicity of $C_{60}$ water-soluble derivatives (carboxylic derivatives) when exposed to light. The cytotoxicity results from the ability of the product exposed to light to cleave DNA. This also can be utilized in cancer treatment.

Thanks to the delocalized π-electrons on the surface, fullerene molecules have the ability to strongly interact with free radicals (chemical entities with unpaired electrons). It has been shown the $C_{60}$ is able to interact with 34 methyl radicals, $CH_3^{\cdot}$ Fullerene can thus play the role of an anti-oxidant and free radical scavenger, useful in the medical domain.

## Graphene

Graphene is a monolayer of carbon atoms packed in a honeycomb lattice (figure 61). It is a two-dimensional structure formed of hexagons in which all the vertices are occupied by carbon atoms. The distance between two neighboring carbon atoms is 0.142 nm. This is a bit larger than in benzene (0.139 nm). It was isolated for the first time in 2004 by A.Geim and collaborators at Manchester University. In 2010, A.Geim and K.Novoselov won the Nobel price in physics for their work on graphene.

Interestingly, in the 1930s, graphene had been predicted by famous theoretical physicists to be thermodynamically unstable at finite temperature. In fact, graphene is stable and can be produced with several methods. The stability is due to 3D-ondulations (ripples) of the 2D lattice.

Graphene has outstanding physical properties. Although just an atomic layer thick it is extremely strong (about 200 times stronger than steel of the

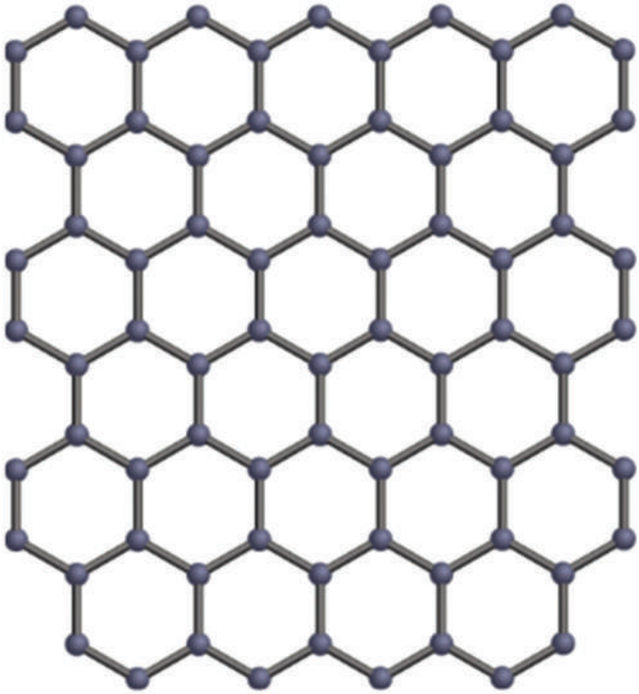

Figure 61. Schematic drawing of graphene. Image from Wikimedia Commons (http://commons.wikimedia.org) originally from Openclipart.

same dimensions, but 6 times lighter). It is an excellent conductor of electricity and heat. Compared to silicon, extensively used in microelectronics, its electrical conductivity is much higher, it is much less brittle and highly flexible.

Novoselov and collaborators first manufactured graphene by peeling a graphite crystal with an adhesive tape (scotch-tape method) and transferring it onto a colored and oxidized silicon wafer of thickness smaller than 300 nm. This peeling method is adequate for laboratory studies but cannot be generalized to mass-production.

In top-down approaches, graphene sheets can be produced by separation, peeling, cleaving or exfoliation (mechanical or electrochemical) of graphite and derivatives. These methods usually have low yields and require great investments. Bottom-up approaches are more appealing for mass-production. CVD (chemical vapor deposition) and epitaxial growth on various substrates which allow preparation of large quantities of graphene sheets (mono or multilayers) is preferred. Other bottom-up approaches such as arc discharge, chemical conversion, carbon nanotube unzipping, self organization of surfactants, etc. are also used.

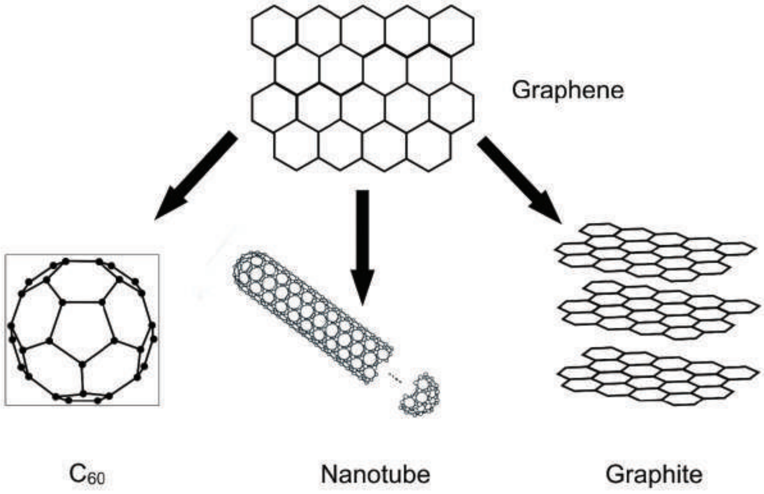

Figure 62. Carbon species that can be derived from graphene. Nanotube image courtesy of CEA/LETI (France).

Graphene belongs to the family of two-dimensional (2D) materials which have been extensively investigated because of their unusual physical properties compared to 3D materials. Some of them, such as layered metal dichalcogenides or copper oxides, exhibit high-temperature superconductivity. 2D materials can be used to make sandwich structures constructed from several different layers of such materials. These 2D-heterostructures can be tailored with atomic precision and the whole structure can be tailored to fulfill several applications.

## Carbon nanotubes

The honeycomb lattice of carbon atoms in graphene can be formally considered as the basic structure from which other carbon species are derived (figure 62). Graphite[8] is a stack of graphene layers, carbon nanotubes are rolled-up cylinders of graphene and $C_{60}$ needs the introduces pentagons into the hexagonal lattice of wrapped graphene.

In 1991, S.Iijima discovered nanotubes of carbon in the soot produced in a machine dedicated to $C_{60}$ production. They had been observed previously but not pursued. For example, in 1952, carbon nanofilaments with an inner cavity have been identified with a transmission electron microscope.

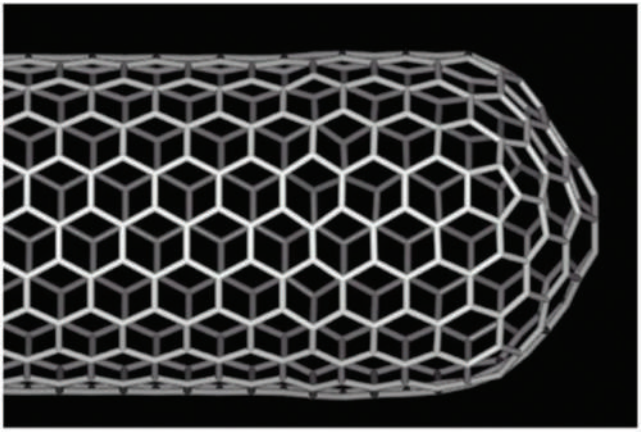

Figure 63. Schematic picture of a closed single-walled carbon nanotube. Image courtesy of CEA/LETI (France).

Carbon nanotubes are cylindrical tubes built from one or more sheets of graphene which are a few nanometers wide with lengths ranging from below a micrometer to several millimeters. Two families can be distinguished: single-walled carbon nanotubes and multi-walled carbon nanotubes.

- A single-walled carbon nanotube is a part of a graphene sheet wound on itself in a cylindrical manner. It can be eventually closed at the end by a fullerene-like the hemisphere (figure 63). Single-walled carbon nanotubes are often produced in tight bundles.
- A multi-walled carbon nanotube is made of several concentric single-walled carbon nanotubes. The distance between two sheets of graphene is of the order of 0.34-0.36 nm. This is about the distance separating two layers of carbon in graphite. The diameters of multi-walled nanotubes are between a few nanometers and tens of micrometers.

The ends of nanotubes can be open or closed (figure 63). Since empty space is present inside the nanotube, atoms or molecules can be trapped inside (the nanopeapods in figure 60 are an example).

According to the classification presented in Chapter 4, carbon nanotubes are 1D-nanomaterials with a diameter in the nanometer range and a length reaching several micrometers. They have outstanding mechanical properties. They are as stiff as diamond and their high strength is used to make fibers. The mechanical elastic modulus is for instance 5 times that of steel. Furthermore, their thermal conductivity is eight times that of copper, similar to that of diamond. Carbon nanotubes are currently incorporated into commercial products such as sporting goods, automotive parts, rechargeable batteries, *etc*. For example, the winning Tour de France bicycle in 2005 was made of a carbon nanotubes composite.

Several methods have been developed to produce carbon nanotubes in bulk quantities. They can be produced at high temperature with a graphite rod placed in an inert atmosphere. High temperatures are produced using an electric arc, laser ablation or a solar beam. They can also be produced at medium temperatures with catalytic chemical vapor deposition. More than 100 companies around the world manufacture and sell carbon nanotubes and this number increases regularly. Hundreds of tons of carbon nanotubes are produced each year and this amount is also constantly increasing. The production capacity by 2015 is expected to be over 9,000 tons. The largest installed capacity is found in the Asia-Pacific region.

Single-walled nanotubes with a purity greater than 95 %. are commonly produced using an arc discharge process The nanotubes have a diameter between 0.7 and 2 nm and form a bundle of about 8 nm. They have an excellent mechanical strength and very good thermal and electric conductivity. They are used in several applications: chemical sensors, nanobiomaterials, conductive heating films, conductive nano-ink, display, *etc.*

Multi-walled carbon nanotubes are produced with thermal chemical vapor deposition and a purity greater than 95 % is reached. Their diameters range from 10 to 30 nm. They are employed in a large number of applications such as: chemical sensors, conducting paints, polymer and metal composites, *etc*.

There are actually several ways to build a nanotube from a sheet of graphene. It can be made, in a “gedanken” experiment, in the same way as we curl a sheet of paper with a hexagonal lattice drawn on the paper.There are an infinite number of ways to fold a graphene sheet into a nanotube structure and the result is characterized by different helicities. This leads to three different families of nanotubes called: *zigzag*, *armchair* and *chiral* nanotubes (figure 64).

If the sheet is rolled along one of its the symmetry axis one can obtain either a zigzag or an armchair nanotube (figure 65). In all the other cases we get a chiral nanotube (asymmetric in such a way that the structure and its mirror image are not superimposable).

To characterize the nature of a nanotube built from a graphene sheet, it is convenient to define an origin and two unit vectors **a** and **b** (in brown in figure 64). A vertex on the lattice can be located by two numbers $m$ and $n$. The vector $m\mathbf{a} + n\mathbf{b}$ goes from the origin to the vertex. A carbon nanotube referred as $(n,m)$ means that the sheet of graphene has been rolled up in

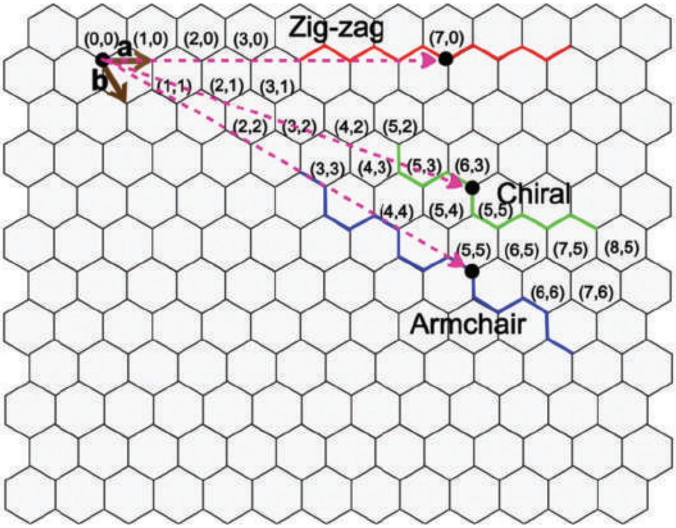

Figure 64. Graphene sheet from which a single-walled nanotube is made by rolling up the sheet (see text).

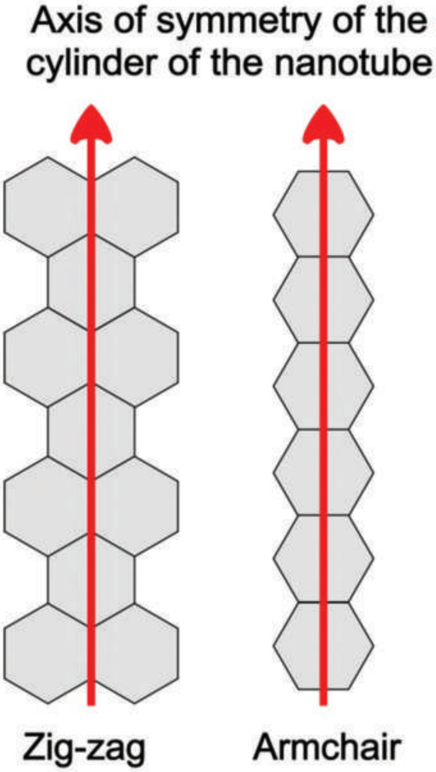

Figure 65. Difference between a zigzag and an armchair nanotube. The sheet of graphene is rolled up around the indicated symmetry axis.

such a way that the atom located in $(0, 0)$ is superimposed on the atom located in $(n,m)$. If $n = m$, we have an armchair nanotube. The physical properties strongly depend upon the way the graphene sheet is rolled. For example, armchair nanotubes behave as metals.

A carbon nanotube has a metallic behavior if $2n + m$ is a multiple of 3. This is the case of armchair carbon nanotubes because $n = m$. Zigzag carbon nanotubes can behave either as a metal if the previous relationship is satisfied (for example, for $(n,m) = (12,0)$, or as a semiconductor. Metallic nanotubes are, in principle, 1,000 times better conductors than copper but this property can be reduced by impurities or defects.

Multi-walled carbon nanotubes are good electrical conductors. They can be used in STM, AFM and in other probe instruments such as the electrostatic force microscope. With carbon nanotube tips, better quality images are obtained compared to those made from etched Si or metal.

Carbon nanotubes can also be used in chemical or biological sensors. Indeed the electrical resistivity changes on exposure to ambient air containing $NO_2$, $NH_3$ or biomolecules.

Aligned nanotubes can be produced by various methods with or without catalysts. Figure 66 shows an example of a carbon nanotube forest obtained in a CEA laboratory. They can have several applications such as membranes for water filtration, high-performance electric wires, *etc*.

Carbon nanotubes can contain atoms or molecules inside their cylinders. They can also be functionalized with other molecules giving them new properties. For example functionalized carbon nanotubes have been developed in the USA to detect and destroy an aggressive form of breast cancer (HER2-positive breast cancer) which does not respond well to chemotherapy or hormone treatment. Attaching an anti-HER2 antibody to short carbon nanotubes provides the ability to detect and destroy malignant cells using a near infrared laser at two wave lengths (one for detection, one for destruction of the cancer cell to which the carbon nanotube is attached).

## Summary

The discovery of fullerenes, carbon nanotubes and graphene has opened a new field of investigations with many real and potential applications. Fullerenes and carbon nanotubes turn out to have outstanding and useful properties in many fields. They can also be used as a basic component, grafting on their surfaces chemical groups with specific physical, biological

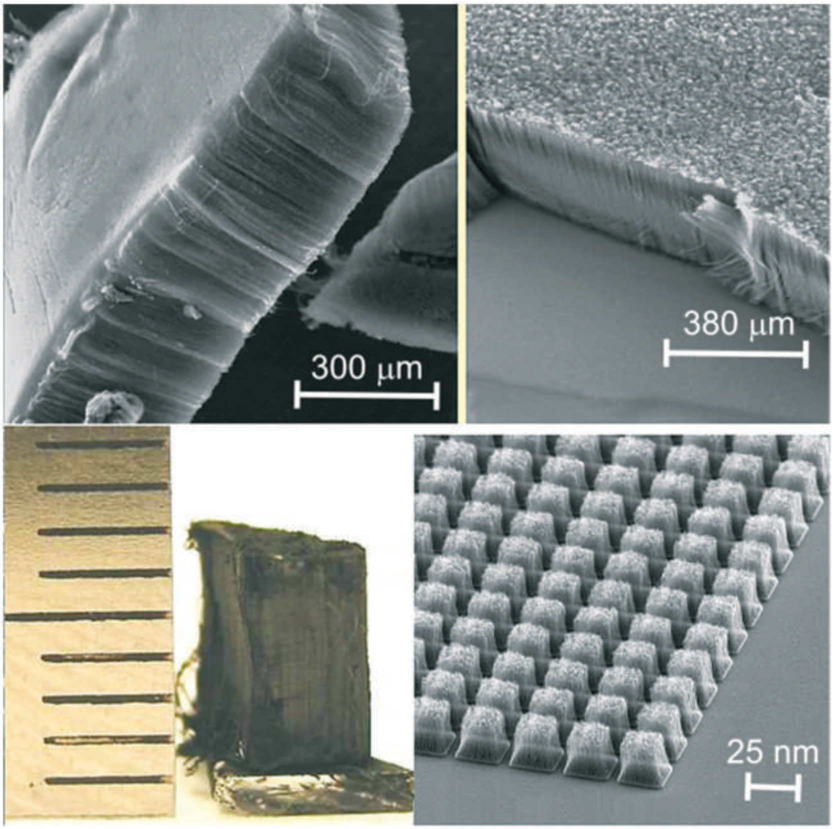

Figure 66. Manufacturing of carbon nanotube forests. In the top left part, a monolayer forest is shown. The top right part displays a multilayer forest. The bottom left part shows a forest of ultra long (> 5mm) nanotubes and finally the bottom right hand part of the figure displays a forest featuring controlled localized growth. Image courtesy of CEA/LETI (France).

or chemical properties. Furthermore, they can be to used protect active molecules during their travel to a target. Applications encompass fields as different as the medical sector, the catalysis domain and composite materials, for example. The ability to produce nanotubes with specific properties: diameter, number of walls, defects, chirality, inclusions *etc*. allows tailoring of these tubes to the desired application. Graphene is also a promising material for micro and nanoelectronics.

# Part 2 Applications of nanotechnology

# VIII. Health Diagnostics

Improvements in life style and progress in medicine have been responsible for a large increase of life expectancy during the last two centuries. Today, in developed countries, people live much longer than they did in previous eras. In France, for example, the life expectancy before the French revolution (1789) was less than 30 years. It reached 50 years in 1900 and has consistently improved since that period. Today it is above 80 years. In underdeveloped countries, the life expectancy is lower and can be of the order of 40 years in the poorest countries or in those where large segments of the populations are faced with a diseases such as AIDS or alcoholism, for example. As populations become older deaths due to chronic diseases increase. About 80 % of seniors have at least one chronic disease and 50 % have at least two. In the United-States 70 % of all deaths are due to chronic diseases. Technological advances such as those offered by nanotechnology can have far reaching consequences in healthcare.

The main issue in the health domain is to provide an affordable and efficient medicine that all can access. For our discussion we can classify health care can be classified into three main areas: diagnostics, therapeutics and restoration or regenerative medicine (figure 67).

Proper medical diagnoses usually require some combination of analysis and imaging. The current trend is to employ non-invasive or minimally invasive techniques to look inside the human body or to make specific analyses on samples of material taken from the patient. Diagnostics techniques should be as painless as possible so that they can be performed routinely and used to identify threats of serious disease. In the case where a sample is needed to perform an analysis, it is also desirable that the volume of the sample be as small as possible.

Once a disease or health disorder is identified, it is necessary to treat the patient in the most efficient way. In the therapeutics stage it is important to deliver the right quantity of drugs to the right place and at the right time in order to minimize side effects and increase treatment efficiency. Monitoring the efficiency of the treatment using minimally invasive diagnostic methods is also required.

Accidents or diseases can damage or destroy parts of the human body. Further, as people live longer and their bodies age, repair or replacement of components such as organs, bones or teeth may become necessary. The third domain of medicine, restorative and regenerative medicine, addresses such needs.

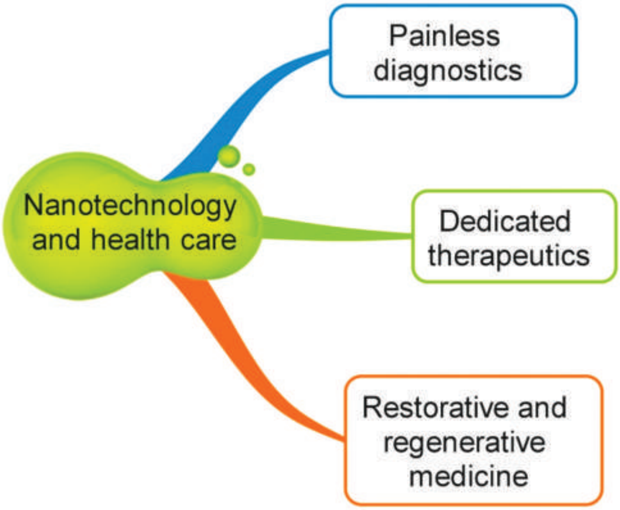

Figure 67. Nanotechnology can have impact in the three domains of medicine shown.

Nanotechnology can play a role in each of the health domains specified by providing improved diagnostics enabling early detection of or prevention of diseases and making more efficient techniques for treatment and follow-up monitoring available.

## Major diseases

While there are many health risks and all must be addressed, it is possible to categorize the major diseases that affect very large proportions of the human population. All have a large social and economic impact. These are shown in figure 68.

The leading cause of death in developed regions of the earth such as the United States and The European Union is cardiovascular disease. Cancer ranks as the second leading cause of death. Neurodegenerative diseases such as Alzheimer's or Parkinson's are a serious problem. Due to dietary and lifestyle factors Type II diabetes is an increasing health problem. Inflammatory and degenerative joint diseases as well as musculoskeletal disorders lower the quality of life of many people. These diseases demand a long-term medication. Bacterial infections require new strategies to complement antibiotics because some bacteria are becoming resistant to them. For economic reasons, little research is now devoted to antibiotics. Fighting against viral infections also requires novel treatments. Both bacterial and viral infections require quick detection.

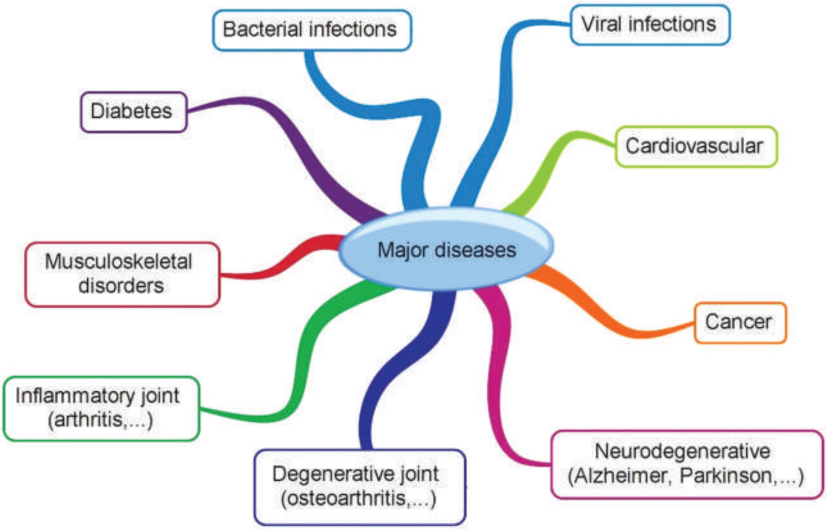

Figure 68. Major diseases touching a large part of the population.

## Diagnosis

Diagnosis is the first step in identifying a disease or a health disorder. Diagnostic techniques should be specific, reliable, fast and accurate. The risks of "false positives" or "false negatives" at the borderline of the detection threshold should be minimized as much as possible.

Diagnostics include both *in vitro* techniques and *in vivo* techniques. Medical imaging is an example of an *in vivo* technique because it is performed directly on the patient. A blood analysis is an example of an *in vitro* technique since it is done on a sample taken from the patient. An important issue is to have non-invasive or minimally invasive techniques for both types of techniques.

## Imaging

Imaging techniques which allow the investigation of a patient anatomy and, in some cases metabolic processes, are exceptionally powerful diagnostic tools (Figure 69). Functional imaging provides the ability to watch an organ function in real time. It allows the study the kinetics of biochemical and physiological phenomena. More recently molecular imaging allows visualizing the cellular function, genes and proteins directly or indirectly. They provide an unparalleled ability to identify dysfunctions of parts of the

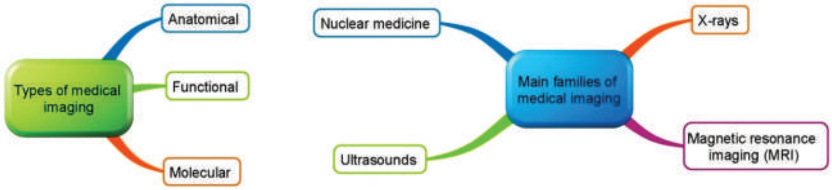

Figure 69. Types of applications of medical imaging (left hand side) and main families of medical imaging techniques (right hand part).

body and to anticipate appearance of disease. Modern Imaging techniques are highly accurate thanks to improvements in detection methods and computerized image treatment. The latter also allows most images to be digitized, leading to better storage and access to the data. While attempts are made to be as non-invasive as possible, these techniques sometimes require tracers to be injected into the patient.

The families of medical imaging which are mostly used are also indicated in figure 69.

The use of X-rays is an old technique, but has improved greatly in our era. The aim is to decrease as much as possible the irradiation dose administrated to the patient and get the best spatial resolution.

Magnetic resonance imaging is a field in strong development with the advantage of being painless to the patient. Ultrasound techniques are increasingly being in many pathologies or to follow pregnant women. Nuclear medicine imaging techniques encompasses techniques based on radioisotope decay. The most common are scintigraphy, requiring injection or ingestion of a radioisotope, SPECT (Single-photon emission computed tomography) or PET (positron emission tomography).

It is often necessary to use several imaging techniques to make a diagnosis because they reveal different or complementary aspects of the health disorder.

The introduction of nanotechnology into imaging techniques through the development of new microprocessors, detectors and electronics is a natural evolution of imaging techniques. However, at the same time nanotechnology is playing a key role in providing new methods to enhance diagnostic imaging. The use of nanoparticles (which have large surface areas relative to their volumes) to deliver imaging agents to the desired site in the body, provides the ability to achieve a great density of interaction sites for interaction with molecular agents or particles. This can result in stronger imaging signals that can be detected outside the body of the patient. Dedicated nanoparticle structures with attached proteins or other molecules can detect indicators of disease at an early stage. It is also possible to create multifunctional products which can be used in different imaging techniques. Functionalized nanoparticles can have both a diagnostic and therapeutic potential. This property is often referred as *theranostic*.

A few examples of the use of nanoparticles in imaging:

- Gold nanoparticles are used in research to detect colorectal cancer, especially those which are difficult to see on colonoscopy. The detection is based on Raman spectroscopy. They are particularly useful because their surfaces resist oxidation and can be functionalized with different molecules.
- Iron oxide nanoparticles coated with dextran, a complex polysaccharide made of many glucose molecules, are used to target lymph nodes in diagnostic magnetic resonance imaging (MRI) and to detect cancer spread. These nanoparticles are taken up in the lymph nodes by normal cells but not by cancer cells. A MRI of the patient is performed before injection of nanoparticles and a second one is done 24 hours later. Lymph nodes that accept the nanoparticles become black while cancer cells stay bright.
- A new tumor detection technique, photo-acoustic imaging employs carbon nanotubes or gold nanoparticles which have been modified to emit sounds when appropriately stimulated by laser light. This light is used to heat the particles which produce an ultrasound signal that can be detected outside the body of the patient. The temperature reached is kept moderate in order not to hurt the tissue.

Structures in which gold nanoparticles are deposited electrostatically onto the surface of a PLA (polylactic acid[9]) microcapsule allow ultrasound contrast imaging. This structure has the potential to operate as a theranostic agent as well because it is also a photo hyperthermia agent allowing photothermal therapy in cancer treatment.

## In-Vitro Diagostics

Presently diagnostic work typically has to be done in specialized laboratories and obtaining results can require hours or days. Required sample sizes can be large. Nanotechnology has an important role to play in the whole diagnostic process. The use of miniaturized laboratories, such as lab-on-chip systems which are in development and based on microelectronic techniques, can quickly provide a result using a very small amount of sample. Using smaller samples of body fluids or tissues makes the analysis

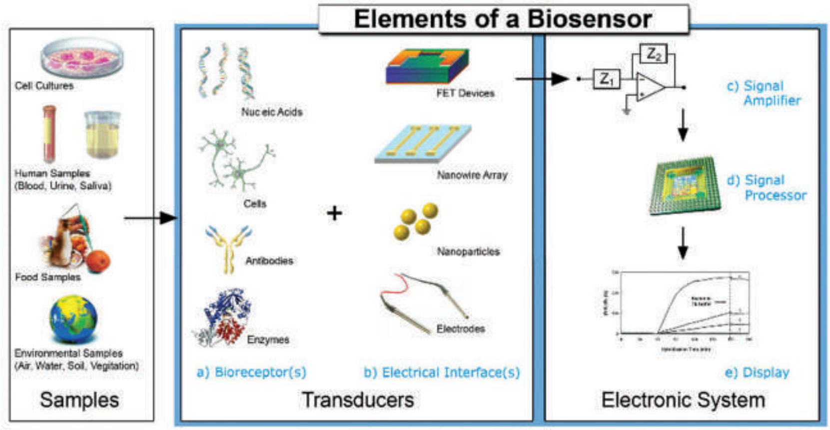

Figure 70. Biosensor system and components. Image from Wikimedia Commons (http://commons.wikimedia.org). Author Dorothee Grieshaber.

less invasive for the patient. The analysis can be done in a serial manner as it is done today, but also in parallel manner using arrays of miniaturized detectors when possible. Miniaturized analysis systems, including nanoscale components, will provide faster, cheaper results while producing less waste. Such low cost high speed analysis systems will soon become routinely available. The final goal is to make these capabilities directly available at the doctor's office.

## Biosensors

Sensors are analytical devices which are able to recognize a specific chemical or biological species present in a sample, for example in a small quantity of blood from a patient. When the sensing is based on biomolecular recognition, the sensor is called a *biosensor*. There are several different types of biosensors based on different techniques of recognition such as antibody/antigen, enzyme based, hybridization with a strand of DNA, *etc*. The main elements of a biosensor are displayed in figure 70. The *transducer* transforms the signal resulting from the interaction between the analyte and the biological element into a signal which can be easily measured. This signal is amplified, processed and visualized by an electronic system.

A simple example of biosensor based on a cantilever is shown in figure 71. The free molecules are supposed to bind specifically to the molecules attached on

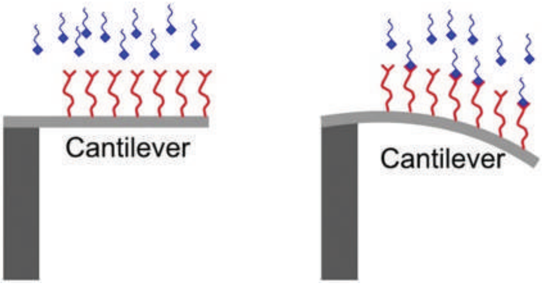

Figure 71. Principle of cantilever detection. The free molecules are supposed to bind to the molecules attached on the cantilever. When this happens the weight on the cantilever increases and it bends. The bending can be measured, by an optical method for example.

the cantilever. When this happens, the cantilever bends and information can be obtained from the measurement of the bending of the cantilever.

Nanoparticles of various types; gold or silica nanoparticles, quantum dots, fullerenes, *etc*. can be used in biosensors. Biological molecular species acting as sensors are attached to the surface of the nanoparticles. By the usual biological lock-and-key mechanism, they are able to detect the molecules of interest. The signal generated by the recognition mechanism can vary: a change of color, a change of mass, a change of emission properties *etc*.

Carbon nanotubes and nanowires can also be used in biosensors to detect a wide range of biological and chemical species. Viruses or proteins can be detected using these sensors which are often based on a change of electrical conductivity and employ semiconducting materials.

Although most of the biosensors developed from nanoscale materials are still in the laboratory, it is expected that they will enter operation at the patient scale during the next decade.

Microarrays of biosensors can be manufactured using the techniques of microelectronics. They can be used as diagnostic devices for DNA analysis, protein detection, virus detection, etc. Microarrays can consist of hundreds of biosensors acting independently and allowing specific detection of different bio-analytes within a mixture. Such microarrays can be used as screening tools, a function especially useful in new drug development.

Figure 72 introduces three families of microsystems containing nanocomponents which are under development.

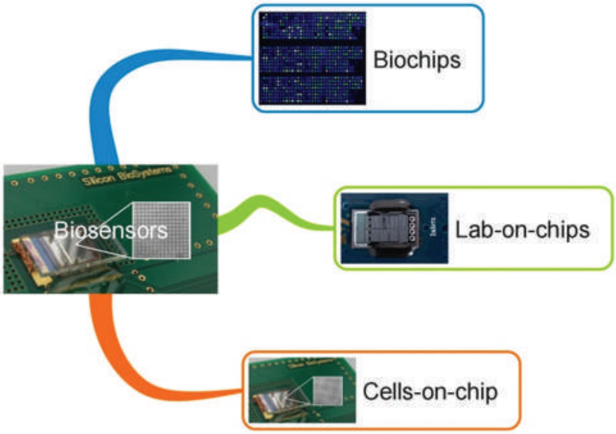

Figure 72. Different families of microsystems based on micro and nanoelectronics techniques and dedicated to diagnostics. The small images shown are courtesy of CEA/LETI (France).

## Biochips

Genetic biochips (DNA-chips) are microarrays of sensors with the ability to perform a large number of analyses at the same time. Each sensor consists of a short strand of DNA. DNA-chips are able to quickly decode genes. When they are put into a solution to be analyzed, the analytes hybridize with the strands of DNA fixed on the microarray. A DNA-chip consists of thousands different nucleotide sequences arranged in a two-dimensional matrix. Biochips have been used to identify the genes of human DNA or of other living species. They can be used to detect the genes expressed by a cell or a tissue giving the ability to detect breast or prostate cancers, for example. They can also be used to detect proteins and in toxicological studies.

In some cases, the concentration of DNA in a sample is not always large enough to be detected safely or perhaps to be detected at all. There does exist a powerful technique, the Polymerase Chain Reaction technique, PCR, which can actually multiply the initial pieces of DNA to be detected: A single strand or a few strands of DNA can be multiplied by several orders of magnitude using PCR. In this *in vitro* technique thousands to millions of copies of a DNA sequence can be obtained. This amplification makes the DNA visible to the analysis system.

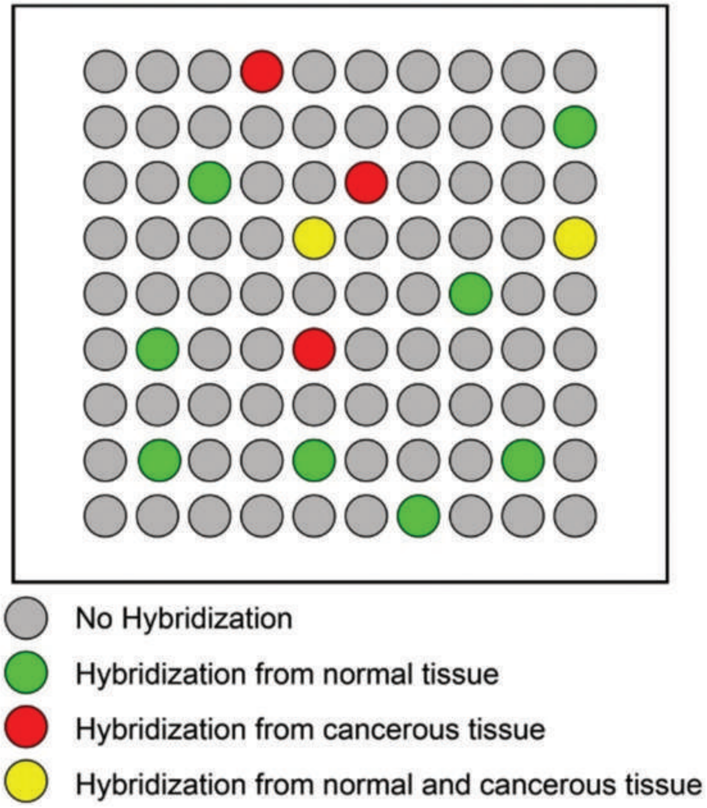

Figure 73. Schematic illustration of a DNA-chip.

PCR is performed in a vessel containing the DNA target to be amplified, a large concentration of olinucleotides (called primers) specific to the sequence investigated, the DNA polymerase and a mixture of the 4 bases which are the DNA building blocks. The PCR proceeds through a sequence of cycles, each of them comprises 3 steps lasting a few minutes: The cycle is repeated about 40 times, each time doubling the amount of DNA. About 100 billion copies can be obtained after 40 cycles. This process can be completely automated. Unlike some previous techniques it does not require the presence of bacteria.

Biochips such as these are used to detect oral cancers, for example. An oral cancer is usually discovered by dentists and oral surgeons and requires a biopsy of the cheek. The sample is sent to a laboratory and the result is received several days later. A nano-biochip recently developed in the US permits a painless test and the result is readily obtained in a quarter of an hour. Early detection of malignant or premalignant lesions is important because early treatment leads to a larger probability of survival. Early detection accords a 5-year survival of 90 %. This figure drops down to 60 % if the lesions are detected later.

Figure 73 explains schematically the way a DNA-chip is used in a small array. There are different spots indicating the probes hybridized on the array. Colored spots indicate that the probes have been hybridized. In this illustration it is supposed that red and green correspond to genes of the cancerous and normal tissue, respectively. Yellow spots correspond to a hybridization of both cancerous and normal tissue. This is because there are many probes located at a node of the array and not a single strand of DNA.

## Labs-on-chips

Labs-on-chips, also called micro-total-analysis systems, integrate several chemical and biological analytical functions on the same chip. These devices are made of micro and nanocomponents manufactured with micro-electronic techniques. Labs-on-chip manipulate tiny volumes of biological fluids to perform analyses similar to those made in conventional laboratories. Miniaturized sensing systems and fluid control are essential to these devices.

Labs-on-chips are not simply miniaturized versions of conventional macroscopic laboratory techniques. They actually exploit the possibilities of new physical phenomena which appear at small length scales. Since the volumes are very small, for example in the nanoliter or femtoliter range, liquids behavior is different from that exhibited on the macroscopic scale as discussed in chapter 3. For example, since fluid dynamics is dominated by laminar flow, it is possible to create concentration gradients in nanoscale devices which are not achievable at the macroscopic scale. A good understanding of microfluidics and nanofluidics is essential to the development of devices performing similar analyses to those made in conventional laboratories, but much faster and at a substantially lower cost. Small samples and less reagent volume are required to perform the analysis. This produces less waste and, in the case where the sample is taken from a patient, is less intrusive. Since the volume analyzed is small and compact, the analysis is fast because the diffusion distances are much smaller than in macroscopic samples. As with biochips, it is possible to parallelize the measurements and build an array of labs-on-chips to get a high output rate. A mass production of labs-on-chips is possible using micro-electronic techniques. This lowers the cost substantially and could provide disposable chips.

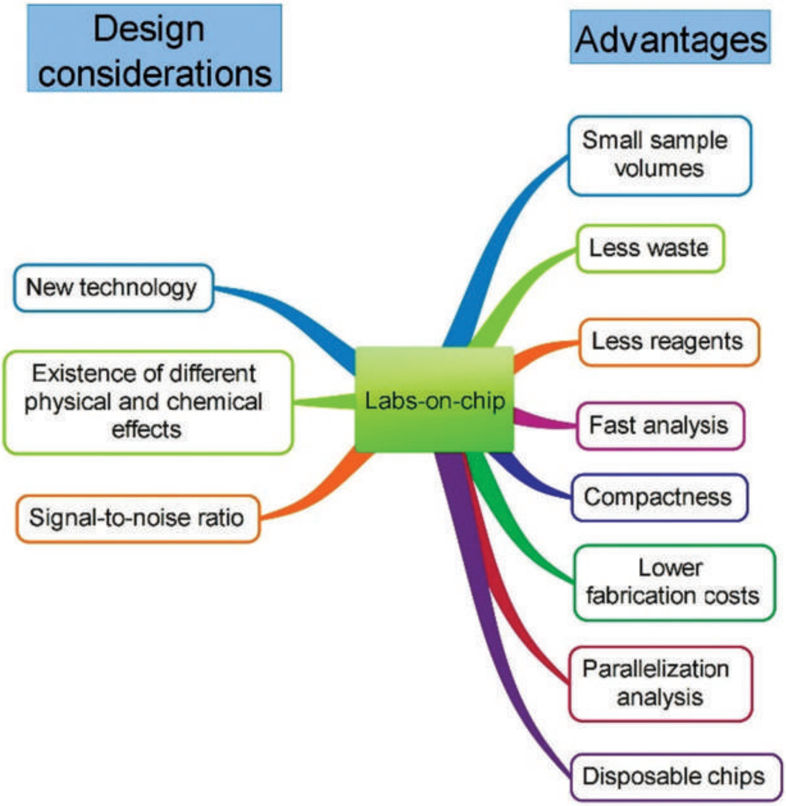

Figure 74. Design considerations and advantages of labs-on-chips compared to conventional technologies.

The first lab-on-chip system was a gas chromatographic microsystem developed in 1975. Developments in this field greatly accelerated about two decades ago. The main commercial applications up to now are in the medical and biological fields. However, applications in several other fields, environment, defense, chemical synthesis etc. are envisaged. ...
There are a lot of advantages to be realized with the development of labs-on-chip devices. Some of them are indicated in figure 74. Also indicated are some of the considerations to be addressed in such research. This is a new technology still in the state of infancy. The appearance of new physical and chemical processes at the nanoscale (see chapter 3) necessitates different designs then those existing in conventional laboratories. Furthermore, scaling down detection systems can reduce the signal-to-noise ratio requiring additional development to retain adequate sensitivity.

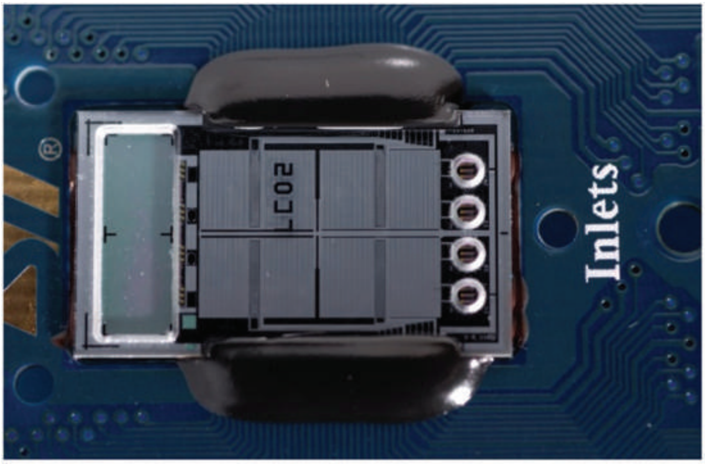

Figure 75. Lab-on-chip dedicated to genetic diagnosis developed by CEA and ST-Microelectronics. Image courtesy of CEA/LETI (France).

An example of lab-on-chip developed by the CEA and ST-Microelectronics is shown in figure 75. This device is dedicated to genetic analysis. On a single chip it integrates sample preparation using the PCR technique and analysis using hybridization of oligonucleotide probes.

## Cells-on-chips

Cells-on-chips couple living organisms such as cells with semi-conductor technology. Due to receptors on their surfaces cells are able to respond to changes in their environment with high selectivity and sensitivity. In cells-on-chips, a change in the cell metabolism or morphology is transduced and analyzed using micro- and nanoelectronics. The cells are the sensing elements and can be used for pathogen detection and toxicology screening, as well as in research to better understand how cells function. Cells-on-chips are organized in arrays, allowing parallel analyses and high speed screening. The key point in cell-on-chip development is to interface living material with inert material. It is for example possible to connect neurons with electronic transistors or to grow cells in microdroplets to create an array of living sensors. These are usually 2D arrays.

Drug development is an important issue in the health domain. Drugs have to be effective against targeted health disorders but must have minimal negative side effects. Normally a first screening of drug candidates is done to find the best candidates. This is done in *in vitro* experiments. Conventional *in vitro* platforms try to identify the different signal molecules which are involved in the interaction between a drug and cells but rarely can mimic the cell-to-cell interactions in the body or the extracellular environment. There is now an effort to develop new research platforms based on more complex sets of cells to mimic the 3D scaffolding of cells to form tissues or organs. Organs-on-chips systems are being developed to mimic the function of livers, hearts, blood vessels, lungs, kidneys, muscles, *etc*. The liver is particularly interesting for studies of drug metabolism and toxicity. One of the advantages of these developments is to reduce the necessity for animal experimentation.

## Summary

Treating a health problem begins with timely and accurate diagnosis. The less invasive the diagnosis technique, the more palatable it will be for the patient. Therefore, non-invasive imaging and small volume sampling are techniques which have many advantages. Presently in-vitro diagnostic work typically has to be done in specialized laboratories and obtaining results can require hours or days. Required sample sizes can be large. Nanotechnology has an important role to play in the whole diagnostic process. Micro- and nanotechnology allow a natural evolution of conventional diagnosis techniques and can provide rapid and reliable results economically. They also provide exciting new capabilities for research and development of new treatment modalities. Using miniaturized laboratories, such as lab-on-chip systems which are in development and based on microelectronics techniques, can quickly provide a result using a very small amount of sample. Using smaller samples of body fluids or tissues makes the analysis less invasive for the patient. The analysis can be done in a serial manner as it is done today, but also in parallel manner using arrays of miniaturized detectors when possible. Miniaturized analysis systems, including nanoscale components, will provide faster, cheaper results while producing less waste. The final goal is to make them available at the doctor's office. Such low cost high speed analysis systems will soon become routinely available.

# IX. Therapeutics

Our increasing knowledge of the mechanisms of cell interactions opens the medical field to new treatments which place nanotechnology at the forefront of personalized medicine. Nanotechnology supports the development of more efficient targeted delivery of drugs and offers the possibility of decreasing the drug quantities used while obtaining the same or better results. Sometimes more elaborate therapeutic actions such as surgery and radiation exposure are needed. Nanotechnology can support minimally invasive surgical procedures and can also provide miniaturized implantable devices for long term monitoring and treatment of a patient.

## Drug delivery

Medication constitutes the major portion of medical treatment. Modern pharmaceutics is evolving toward targeted drug delivery, a smart release of drug at the right place, at the right time, and in the right concentration. This can decrease the amount of drug delivered to a patient and provide a greater effectiveness of the treatment. A key point in targeted drug delivery is to minimize drug degradation and loss before it reaches the disease site. In current conventional methods of drug delivery, oral delivery for example, an excess amount of drug is given to the patient in order to get the right dose at the disease site. This excess can have negative side-effect on the patient. This is especially true in cancer chemotherapy where severe side-effects are often observed and need to be counteracted by other medications.

The perfect drug delivery system needs to have the following properties:

- It should protect the drug, allowing it to retain its biological and chemical effectiveness during its transit through the body to the target
- It should release the drug at the proper time and proper rate when the target is reached.
- It should minimize the toxicity and side-effects to healthy parts of the body as it performs its function.

One way to fulfill these conditions is to encapsulate the drug to protect it on its journey and to equip the vehicle carrying the drug with homing characteristics that carry it to the right place and a release mechanism allowing

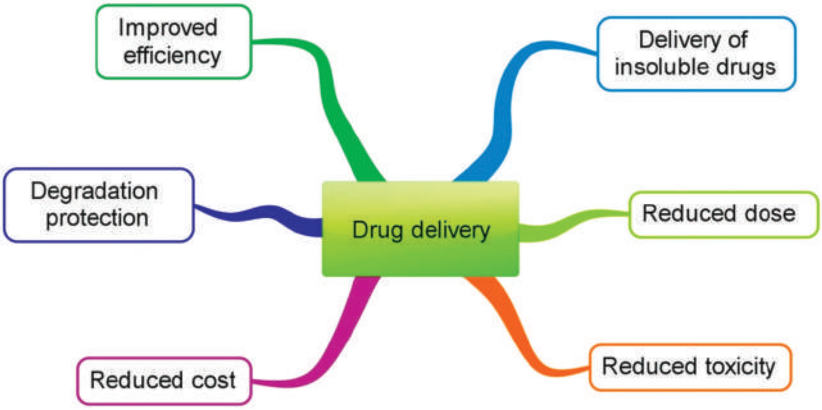

Figure 76. Advantages of nanotechnology in delivery of drugs.

optimal release of the drug on demand. Tailored nanoparticles have the ability to do that and represent a new way to control therapeutic treatments.

The expected benefits of introducing nanotechnology in drug delivery are summarized in figure 76. Note that encapsulation offers the possibility of delivering insoluble drugs to the appropriate site, an important issue in some cancer chemotherapy treatments.

Nanotechnology also allows detailed control over the rate at which drugs are delivered. The delivery can be passive or active, continuous or pulsed. A passive delivery corresponds to the case where there is a self-degradation of the encapsulating material. In an active delivery the drug is released thanks to an external stimulus. Continuous delivery can be achieved by diffusion of the drug out of a biodegradable polymer, for example. Using an external stimulus such as light, pH, temperature, electric field, etc. to trigger release of the drug allows a pulsed delivery.

## Delivery routes

There are several routes for administration of medication. These are indicated in figure 77. The selection of the delivery method will ordinarily be based on efficiency and effectiveness for the particular disease to be treated.

The most common technique to deliver drugs is oral delivery. Oral medication is convenient in administration, well accepted by the patient and

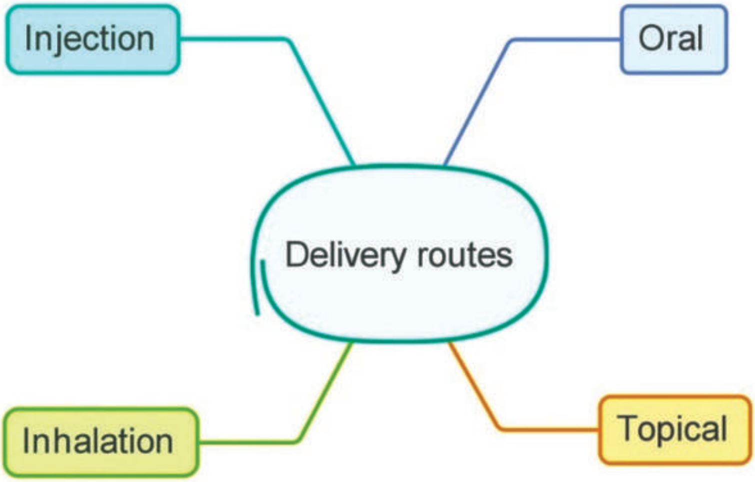

Figure 77. Different routes of administration of medication.

the manufacture of oral medicines is cost-effective. However, part of the drug may not reach the target leading to possible adverse side-effects.

Intravenous, intramuscular or subcutaneous injections are efficient ways to deliver drugs, but administration may be painful and require aseptic conditions for the patient.

Topical delivery consists in delivering the drug on or near the site to be cured, skin or mucous membranes for example.

Inhaled drugs are absorbed quickly and act locally. An inhaler device can be employed to deliver the right dose. Inhalation allows rapid drug delivery to the brain.

## Drug carriers

Drug carriers, typically soluble entities or particulate matter of size less than one micrometer, offer the ability to deliver a drug to its intended target and to release it at that location. Many delivery strategies employ colloidal carriers. Colloidal systems encompass structures such as micelles, liposomes nanoparticles, *etc.* Micelles are formed with molecules having a hydrophilic (water attracting) head and a hydrophobic (water repelling) tail. Liposomes are vesicles formed with a lipid bilayer (figure 78). The hydrophilic head is directed toward the surrounding solvent (water) and the hydrophobic tail is directed inwards. A micelle can be formed with a variety

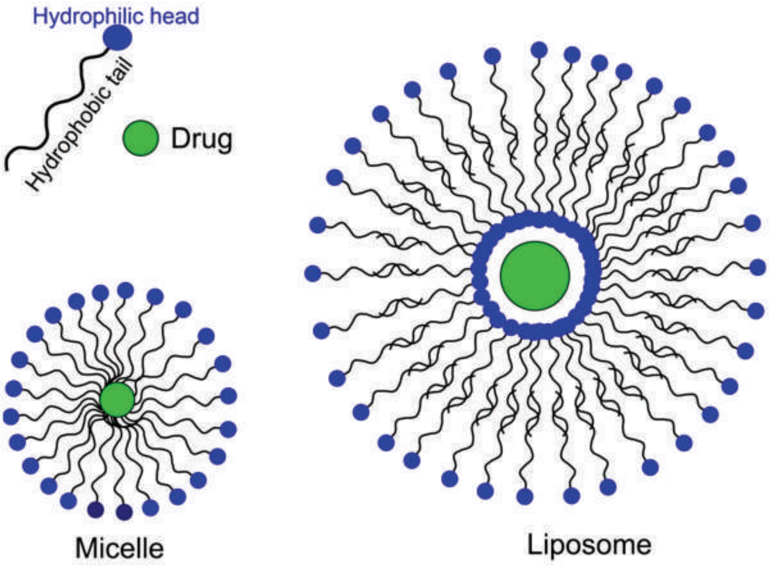

Figure 78. Schematic representation of a micelle and a liposome.

of molecules such as fatty acids (soap), phospholipids, detergents, *etc*. In a micelle, the molecules form a hydrophilic shell and it is possible to put a molecule (drug) inside that shell. Especially interesting is the case in which the drug molecule itself is insoluble in water. The carrier makes it feasible to administer a larger concentration to the patient than is possible in the case of administering the free drug molecule. Furthermore, the shell protects the drug molecule until it is delivered to the right place.

The high selectivity of biological molecules, such as hormones or neurotransmitters, with respect to other molecules, is due to a "key-and-lock" mechanism (figure 79) in which a molecule can bind perfectly to another one. For example, a hormone (the key) binds to a receptor molecule. When this take place at the surface of a target cell, the properties of the cell are modified. Several drugs behave similarly to hormones and produce the same responses when they bind to the receptors. They are called *agonists*. Examples of agonists are morphine and nicotine. Other drugs (*antagonists*) behave in exactly the opposite way. When they bind to the receptor they do not produce the same response. Rather they inhibit responses. Examples of antagonists are caffeine, atropine and endocrine disruptors.

A molecular imprinted polymer has properties similar to those of active biological molecules. It behaves as a key to a receptor site molecule. This is schematically illustrated in figure 80. Because of their similarities

Figure 79. The key-and-lock scheme.

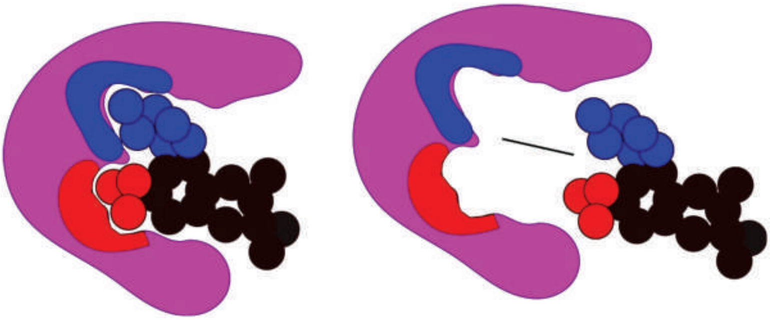

Figure 80. Interaction of an imprinted polymer with a receptor.

to biological molecules, imprinted polymers have great potential in the field of drug delivery.

## Nanoparticles and drug delivery

Nanoparticles provide several advantages for drug delivery compared to conventional methods. They are stable and can be designed to be highly specific. They can also carry a high dosage of drug while protecting it from outside interactions.

It is possible to graft specific molecules at the nanoparticle surface. These molecules can have different functions. Some molecules can make

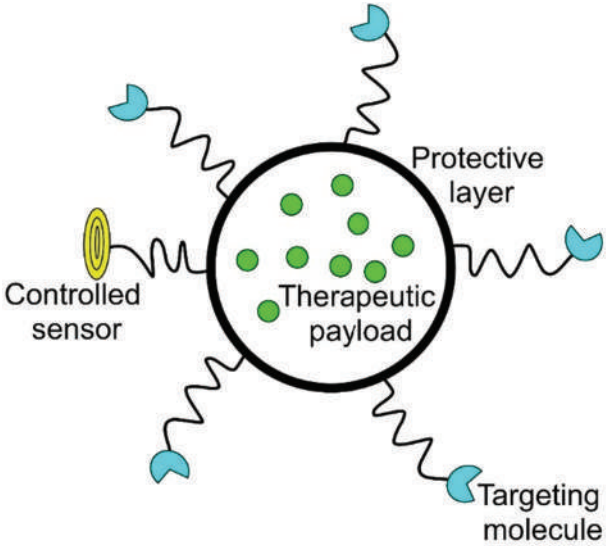

Figure 81. Illustration of a drug delivery nanoparticle. The nanoparticle, which can be a biodegradable polymer for example, encapsulates the drug (green circles) which constitutes the therapeutic payload. The nanoparticle can also contain an imaging contrast agent. The surface of the nanoparticle plays also the role of shield to make the nanoparticle invisible to the immune system. Targeting molecules grafted to the nanoparticle surface guide it and attach it to the cells of interest.

the nanoparticle invisible to the immune system so that they can travel through to the target without being attacked by the immune system. A typical illustration of this concept is shown in figure 81. Since the drug is protected until it reaches the target region, the side effects of the drug are minimized. Other molecules, with the ability to target specific cells, cancer cells, for example, can be attached. After reaching the target, the drug can be released using either passive or active techniques (see above). A schematic illustration of a functionalized nanoparticle is shown in figure 81.

There are several families of nanoparticles that can be used to improve therapeutic treatments. This is a fast developing area and here we quote a few examples which illustrate the possibilities.

Drugs are often insoluble into water. Higher quantities than necessary are administrated to the patient to be sure that the right dose reaches the target region. This can lead to side effects because part of the drug is lost during the journey in the body of the patient. Encapsulating the drug into nanoparticles soluble in water can overcome this drawback. They are several such nanoparticle based techniques. A colloidal dispersion of nanoparticles is used for intravenous delivery of insoluble molecules. This allows more efficient delivery of the drug payload.

Colloidal gold has been known since ancient times. Gold nanoparticles are easily manufactured and functionalized and have good biocompatibility. They are used in the treatment of rheumatoid arthritis and sclerosis. Small size gold nanoparticles, typically with diameters smaller than 50nm, have the ability to cross the brain-blood barrier. This is an interesting property which allows transfer of drugs from the blood to the brain.

Protein nanoparticles are often used for drug delivery. Albumin nanoparticles are used to deliver paclitaxel, a cancer drug, isolated from the bark of the Pacific yew tree. Paclitaxel is a highly toxic hydrophobic product. It is used in chemotherapy to treat lung, breast and ovarian cancers. Paclitaxel has many possible side effects such as a decrease in white blood cells, red cells and platelets; hair loss, inflammation of the mucous membranes, damage of the nerves, water retention, skin reactions, nail alteration…The cancer drug Abraxane is a solvent-free formulation of the paclitaxel. Binding Paclitaxel to albumin nanoparticles that will, in turn, bind to the tumor tissue reduces the toxic side effects and 50 % more drug can be delivered at the right place.

Chitosan is a polysaccharide obtained from crustaceans such as shrimps. It has several applications but an interesting one is that it has the ability to clot blood. Nanoparticles of chitosan can be included in bandage and hemostatic agents. Chitosan has also antibacterial properties.

Another helpful application of nanoparticles is thermotherapy. By time-resolved infrared imaging it is possible to know the exact location of a tumor in the body by locating nanoparticles, attached to cancer cells. After this is done, it is possible to heat this specific region by laser irradiation and kill the cancer cells. Another advantage of time-resolved infrared imaging is that it can find metastasis cells located far from the initial tumor allowing the ability of an early treatment.

As a last example, consider carbon nanotubes. Either open or closed at one end (nanohorns). they can be used to encapsulate molecules, proteins and nucleotides. Their surfaces can also be functionalized. Carbon nanotubes have the ability to penetrate into cells without harming them, thanks to their very small size. Carbon nanotubes are particularly useful to deliver insoluble and toxic drugs because they are encapsulated and protected.

## Summary

Drug delivery is an essential tool in health treatment. The goal is to deliver the right quantity at the right place and at the right time in order to maximize efficiency and minimize any side-effects. Nanoparticles have many advantages for drug delivery compared to conventional techniques. Drugs can be attached to nanoparticles that are eventually functionalized to go at the right place in the patient's body. Drug molecules can be also encapsulated within a functionalized nanoparticle that guides and releases them at the right place while protecting them during the travel in the body of the patient. With these new techniques, the trend towards dedicated treatments and personalized medicine is greatly accelerated.