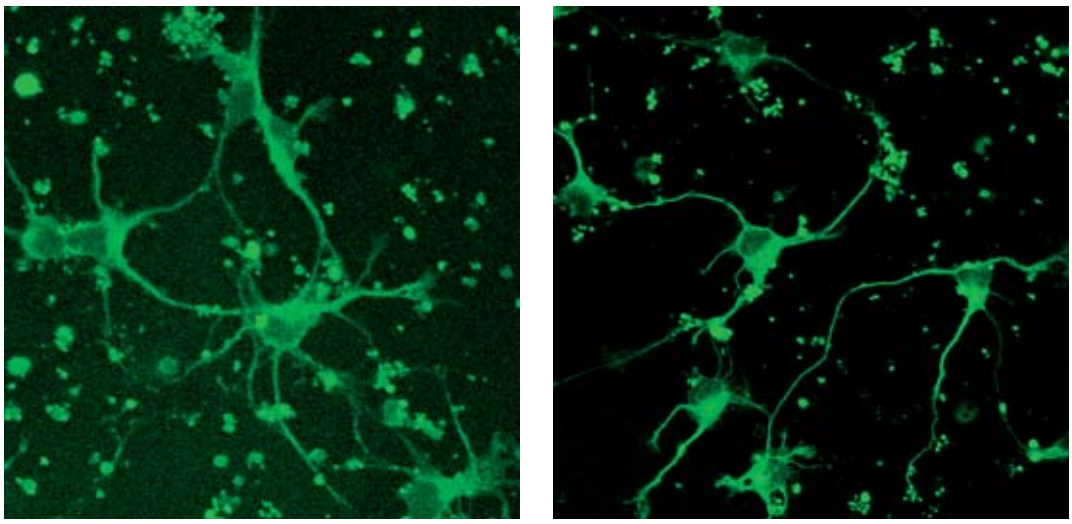
Giving nano-objects new properties by molecular grafting

The bottom-up approach to tomorrow's nanoelectronics involves the assembly a nd positioning of nanometric-sized objects to build functional superstructures. To achieve this, nanoelectronic engineers use molecular, biomolecular or inorganic nano-objects as elementary building blocks. These can be functionalized by molecular grafting to give them useful properties.



CEA/DSV/DSM

One of the routes for the functionalization of semiconductor nanocrystals lends them long-term photostability and a high specificity for binding to neurone cells. Left: fluorescence image of a primary culture of nerve cells tagged with biotinylated QDs (excitation at 458 nm). Right: control experiment with cells tagged with Alexa-488.

To construct devices that possess "classical" electronic functions such as **transistors**, **diodes**, optoelectronic transducers and molecular memory and switches, nanoelectronic engineers use electric current-carrying **molecules** and conjugated molecular wires, molecular structures incorporating metal complexes and/or bistable **redox** systems(1) for memory stores, **carbon nanotubes** and **nanowires** or **semiconductor** and/or conducting **nanoparticles** for interconnects, transistors, diodes and photo-emitters. The **functionalization** of these **nanometric** sized objects by molecular grafting gives them novel properties: bistability, photosensitivity, biological recognition, solubility, etc., and also allows their assembly into locally deposited structures. Here we review the advances made in the last four years in the "molecularization" of these elementary building blocks of the future for applications in molecular memories, and in particular in nanobiosensors.

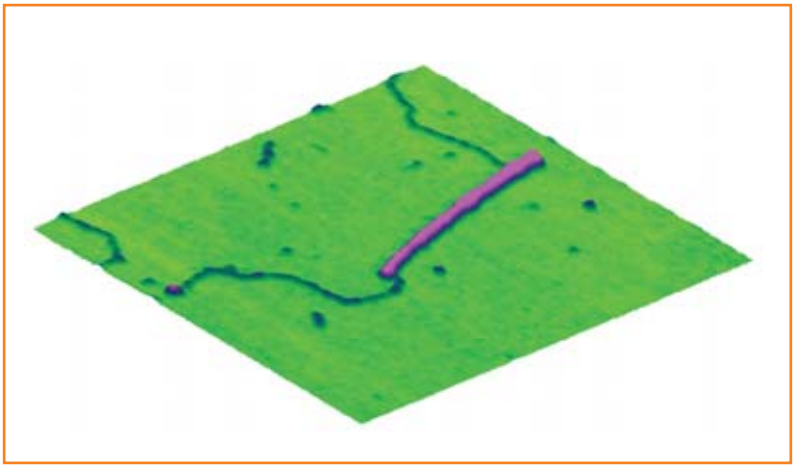
The "Lego®" approach to heterogeneous nanoelectronics using nano-objects

The use of molecules in the engineering of classical micro- and nanoelectronic devices has been basically limited to macromolecules (**polymers** and resins), which are passive materials used for overall fabrication and the coating of components. As its name suggests, molecular electronics (in the widest sense) means the incorporation into devices of molecules that play a functional role in the processing, conversion (photo-electronic) and storage (molecular memory) of information (see *Molecular electronics: a domain at the crossroads of chemistry, physics and engineering*). These molecules take the form of monolayers or **self-assembled** nanowires, interfacing with various surfaces and **nanostructures**, in a hybrid approach. Among these nanostructures, nano-objects such as carbon nanotubes, nanowires and conducting and semiconducting nanoparticles are the "Lego®" building blocks of nanoelectronics, an applied science that is still in its infancy.

Alongside these "artificial" structures, biological molecules, **DNA**, **proteins** and **viruses**, serve as templates (box) or scaffolding to build or assemble superstructures using "bio-inspired" processes (self-assembly is intrinsic to living matter).

The "Holy Grail" of tomorrow's heterogeneous nanoelectronics may be the all nano-object component, a sort of "bio-organo-mineral nanobrain", which will require making the different constituents compatible and achieving three-dimensional interconnections by

(1) Bistable system: a system that exists in two different states in the same external conditions of temperature, pressure, etc.



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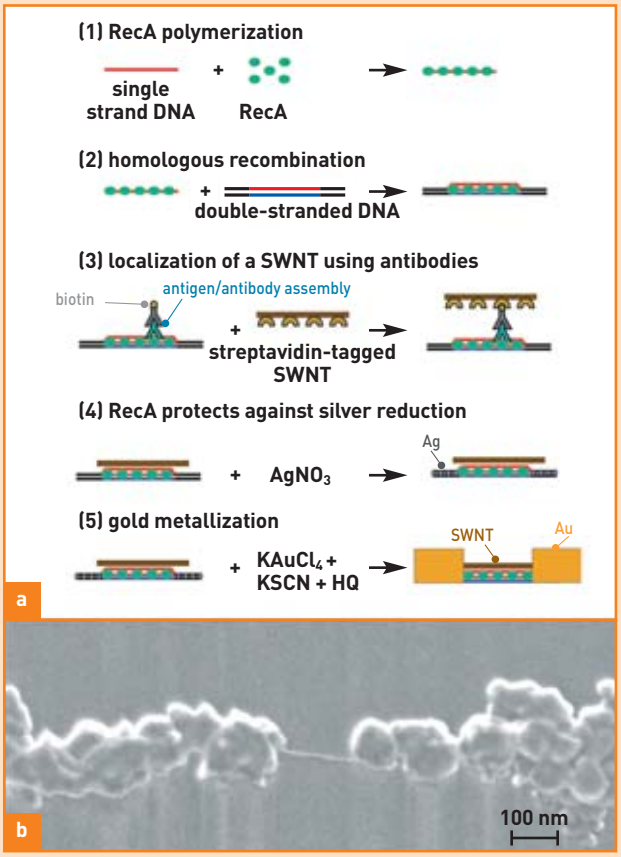
Atomic force microscope image of a carbon nanotube on DNA. These biological molecules can serve as templates or scaffolding elements to build or assemble devices by "bio-inspired" processes.

self-assembly processes. The literature reports octahedral assemblies and molecular engines based solely on DNA, and semiconductor materials nano-assembled by viruses.
However, industrialization may still be a long way ahead, and hybrid electronics remains an essential step in learning more about these nano-objects, and in making progress in the design of new highly defect-tolerant architectures that will enable the rapid development of industrial products. To accomplish this aim, scientists will make use of supramolecular chemistry, based on the use of weak interactions, which will make it possible to incorporate nano-objects into functional devices (Figure 1). At present, such integration in **CMOS** structures can be achieved through two approaches: *in situ growth*, where, for example, single-walled carbon nanotubes (SWNTs), synthesized by the **CVD** process, specifically bridge **source** and **drain** **electrodes** in **FET** transistors addressed by CMOS circuits, and the *ex situ* approach, where the positioning of nano-objects on a CMOS **wafer** is carried out after their synthesis. This last approach requires a much greater number of steps, but it allows prior purification of nano-objects according to sizes and properties, such as, for example, the separation of metallic and semiconductor SWNTs, which is currently at the stage of differential enrichment. Consequently, outside the synthesis step, the solubilization, positioning and sorting steps and the conferral of photophysical and (bio)recognition properties require the functionalization of these nano-objects.
The use of carbon nanotubes and semiconductor nanowires for transduction elements in many biosensors has been prompting growing interest, especially in the last four years. Miniaturization is not the main attraction, although the use of these nano-objects allows a **bottom-up** approach to the fabrication of nanobiosensors. Carbon nanotubes and semiconductor nanowires promise high detection sensitivities, because the depletion or accumulation of **charge carriers** caused by the attachment of charged biomolecules at their surface can affect the entire cross-section of the **conduction** path in these nanostructures. This is because the surface **atoms** predominate in nanowires (silicon Si, germanium Ge, etc.) or are the sole constituents in SWNTs. The electronic modifications induced by these molecules attached to surface atoms, for example by the modification of immobilized biological assemblies or by **redox reactions**, are turned directly into a change in the electrical properties of the nano-object. In addi-

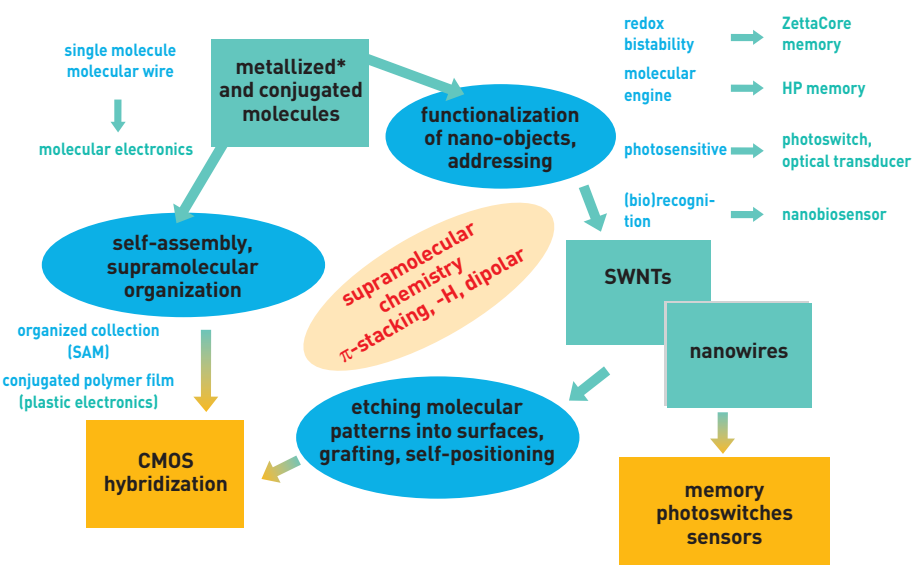
Naturally-occurring systems: a source of tools and inspiration

The structure of the human body is based on bio-assemblies constructed at different scales. At the **nanometric** level, these include the rigid double helix of **DNA** and its two paired strands, structures aggregated into nanotubules in the cytoskeleton(1), nanosheets of **proteins** and the films of cell membranes. The diversity of these assemblies is amazing, as shown by the biominerals derived from them (bone, teeth, pearl, shells, etc.). Just as a tailor makes a garment "to measure" using a pattern, so chemists have thought of using these biological **nanostructures** as templates to create and assemble metal or mineral structures. Thus protein nanotubules are used as templates. Their surface metallization makes it possible, after destruction of the organic template, to obtain metal nanotubules. The arrangement of **viruses** in liquid crystal structures, for example, provides hybrid materials made up of alternating organic sheets and **nanoparticles** of cadmium selenide CdS. In approaches inspired by biological systems, DNA plays a leading role. First, it acts as a template through its rigid structure (double helix) that can be decorated by metals. Second, it possesses a capacity for programmed assembly to organize nano-objects or build nanoscaffolding.
The example described opposite (from the work of Erez Braun *et al.* at the Technion-Israel Institute of Technology) combines these two properties, first by lining up a single-walled **carbon nanotube** (SWNT) on a double strand of DNA, and then by connecting it by "gold plating" the free ends of the DNA. The principle is as follows (Figure a): step (1), **polymerization** of a RecA protein from a single DNA strand followed by step (2), homologous recombination to insert this dual-function protein into the double strand DNA. This prevents the metallization of this inserted zone, and supplies a biotin *via* an antigen/antibody assembly. In step (3), a nanotube decorated with streptavidin, a protein, is positioned on this biotinylated part of the double-strand DNA. In the next two steps (4 and 5), only the free ends of the DNA are metallized. Figure b shows a scanning electron microscope image of a SWNT connected by gold nanowires at the end of the process.



"Bio-inspired" processes for the construction and positioning of nanostructures.

(1) Cytoskeleton: system of protein filaments in the cytoplasm of a eukaryote cell (one that possesses a distinct nucleus and cytoplasm), which gives the cell its shape and its directional mobility. The microtubules, long cylindrical structures composed of tubulin, make up one of the three main classes of filaments.



* A metallized molecule incorporates a metal complex-type part containing one or several complexed metallic ions.

Figure 1.
The concepts of supramolecular chemistry play a central role in the design of molecular entities, their incorporation by self-assembly in CMOS devices, and the functionalization and self-positioning of carbon nanotubes and nanowires.

tion, the chemical stability of these SWNTs, compared with **conjugated polymers** capable of a FET-type transduction, promise excellent reproducibility and lifespan.
Here we shall limit ourselves to a presentation of the functionalization of carbon nanotubes, nanowires and metallic and semiconductor nanoparticles (or **quantum dots** QDs), and recent advances with special reference to biosensor applications.

Functionalization of single-walled carbon nanotubes

A broad array of methods is now available for functionalizing the surface of carbon nanotubes (SWNTs) by chemical or biological species.

Two grafting approaches

Functionalization approaches can be non-**covalent** or covalent (Figure 2).
The *non-covalent approaches*, which are simple to implement, make use of **hydrophobic/hydrophilic** and electronic properties to achieve non-specific surface **adsorption** of proteins and **lipids** or **surfactants** and π-stacking(2) of poly**aromatic** compounds.
Covalent grafting can be of two types. The first involves covalent grafting onto surface functions created by means of an **oxidizing** pre-treatment (using a nitric/sulphuric acid mixture). This pre-treatment is aggressive and difficult to control. It is estimated that a nanotube loses its semiconductor properties after 5-10% of its aromatic (sp^2) carbons have been oxidized. Also, the new functions are not distributed evenly but cluster at the open ends of the SWNTs. For the ChemFET effect (see next paragraph) induced by biological or gaseous molecules at the surface of a SWNT to be significant and reproducible, grafting on the body of the SWNT must be favoured. Grafting on the metal-SWNT contact zone (**Schottky barrier**) is more difficult to control reproducibly. The second type concerns grafting *via* the addition of radicals; carbene, nitrene or ylide, generated by any of several routes; thermal, photochemical or electrochemical. These reactions favour direct electronic coupling between the immobilized species and the carbon structure, and make no distinction between the ends and the middle of the SWNT. However, they produce a high graft rate that has to be controlled. For example, the electrochemical **reduction** of aryldiazonium compounds is particularly attractive and should make it possible to overcome certain obstacles such as specific addressing, control of surface graft rate, and improvement of "electrical wiring" between the grafted entity and the SWNT.

(2) π-stacking: packing due to weak attraction forces between parallel π orbitals, such as between neighbouring sheets in **graphite**.

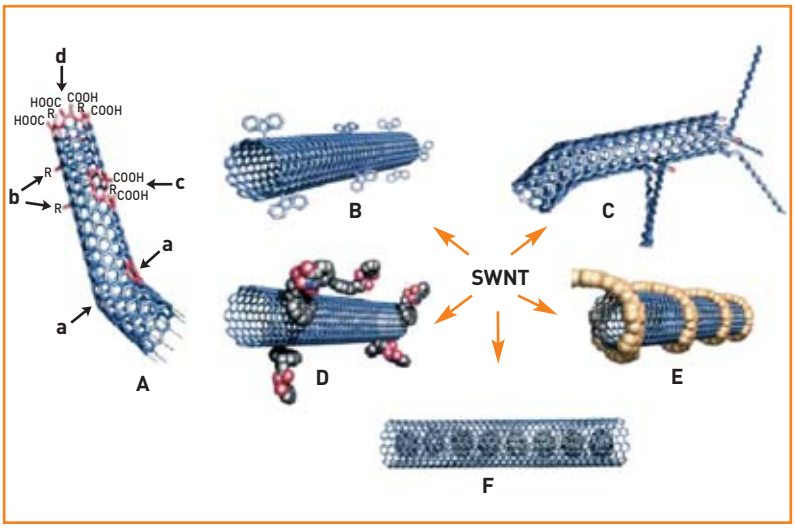


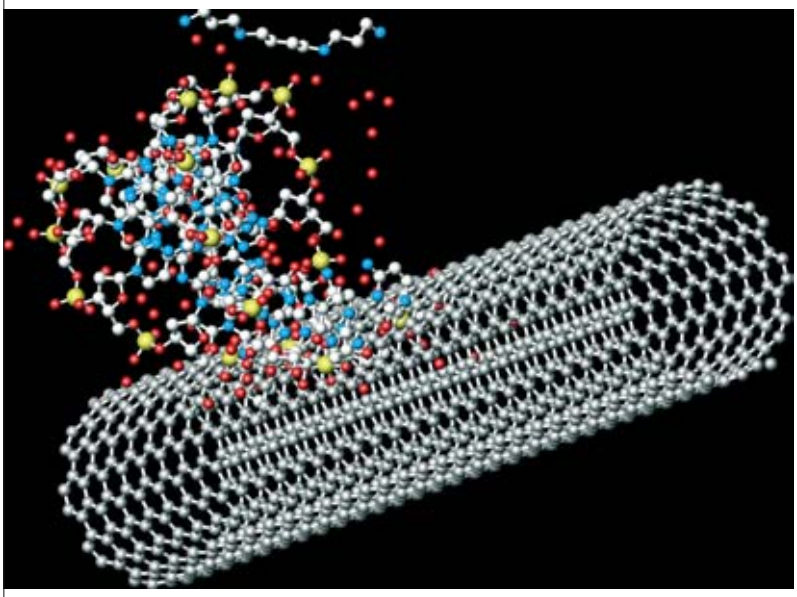
Figure 2.
SWNT functionalization routes. A, typical defects of nanotubes: rings with 5 or 7 atoms of carbon included in the carbon structure (a); defects in the aromaticity of a carbon with creation of a loose bond, *i.e.*, a sp^3 carbon in the sp^2 structure (b); defects that have produced, after oxidation, surface carboxylic groups (COOH) (c); open end with carboxylic groups (d). According to the treatment, $-NO_2$, –OH and =O groups are also possible. B, covalent grafts by the radical route. C, covalent grafts *via* the defect functions. D and E, non-covalent exohedral (external) functionalization by means of surfactants, polymers and π-stacking. F, endohedral (internal) functionalization by **fullerene** molecules (from A. Hirsch, "Functionalization of single-walled carbon nanotubes", *Angew. Chem. Int. Ed.*, 41, pp. 1853-1859, 2002).

Biosensors based on carbon nanotubes

Many biological species have been grafted onto SWNTs to build biosensors, either by coupling on surface carboxyl groups or *via* the grafting of a π-adsorbed pyrene that serves as an anchor point. Among the immobilized entities, we can cite **enzymes** such as glucose oxidase GOD (Figure 3), peroxidase MP-11, streptavidin, **peptides** and single-strand DNA probes.

Functional grafting of semiconductor nanowires

As emphasized above, one-dimensional nano-objects have a morphology and size that are particularly well adapted to applications in interconnective circuitry, field-effect transistors and diodes. However, there are notable limits to using SWNTs for integrated microelectronics or matrix devices, because metallic and semiconductor carbon nanotubes are currently produced simultaneously. On the other hand the physical and chemical characteristics of semiconductor nanowires, *i.e.*, composition, size, electronic and optical properties, can be rationally and predictably controlled during synthesis. The positioning of these nano-objects, when they are detached from the substrate used for growth is done in a fairly classical manner by combing under hydrodynamic flow. Their dispersion in solvents such as alcohol is easy, and there is no risk of bundling, as occurs with SWNTs. The functionalization of semiconductor nanowires especially concerns two applications; molecular memories and biosensors.



Yong Kong - Max Planck Institute for Metals Research/Stuttgart

Protein grafted onto a carbon nanotube. Many biological entities have been grafted onto SWNTs to make biosensors.

Molecular memories

The grafting of self-assembled monolayers (SAMs) of redox molecules on a **silicon** surface in a **capacitive** device affords molecular memories (Figure 4). The construction of such SAMs has been undertaken on hybrid devices with silicon microsurfaces (100 µm x 100 µm) by the team of David F. Bocian, who set up the ZettaCore company. The SAMs are prepared by the condensation of the benzyl alcohol group on the surfaces of hydrogenated silicon, with the formation of Si-O-(CH_2-phenylene)- bonds. Thus ferrocene and **porphyrin** redox systems were grafted to obtain multi**bit** molecular memories. Similarly, arylphosphonate groups have also been used as attachment points.
This approach can be adapted to silicon nanowires. The team of Charles M. Lieber at Harvard University (USA) integrated nanowires of ***p*-doped** silicon (*p*-Si), ***n*-doped** gallium nitride (*n*-GaN) and *n*-doped indium phosphide (*n*-InP) in FET assemblies. These last, covered with a layer of cobalt phthalocyanine, make it possible to construct a memory with a charge retention time of 20 min and an estimated on/off ratio of 10^4. Progress has recently been made by the group of Meyya Meyyappan at the Center for Nanotechnology (USA). A multilevel memory was obtained by grafting of Fe^{2+} terpyridine complexes on a nanowire of indium oxide (In_2O_3). Charge retention times of more than 600 h with estimated on/off ratios of 10^4 have been reported. The molecular structure, in particular the presence of the central metal atom that lends the molecule its redox properties, plays a determining role in the memory effect.

Nanobiosensors

Charles M. Lieber and his team were pioneers in validating the concept of a nanobiosensor based on the field effect applied to a semiconductor nanowire.

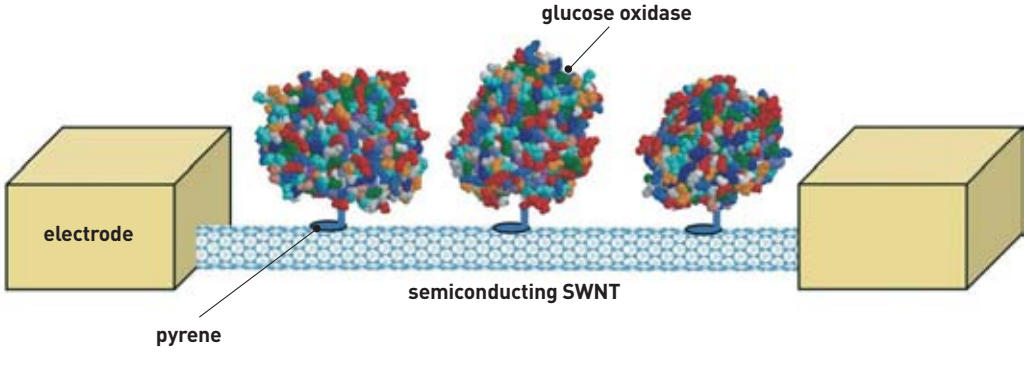


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Figure 3.
Configuration of a ChemFET nanobiosensor. Schematic representation of the two-electrode device connecting a semiconductor SWNT to a glucose oxidase enzyme immobilized *via* an adsorbed pyrene (blue "foot"). The variation in **conductance** responds in real time to the simple addition of an aqueous solution of glucose (from K. Besteman, J.-O. Lee, F. Wiertz, H. Heering and C. Dekker, "Enzyme-coated carbon nanotubes as single-molecule biosensors", *Nanoletters*, 3, pp. 727-730, 2003).

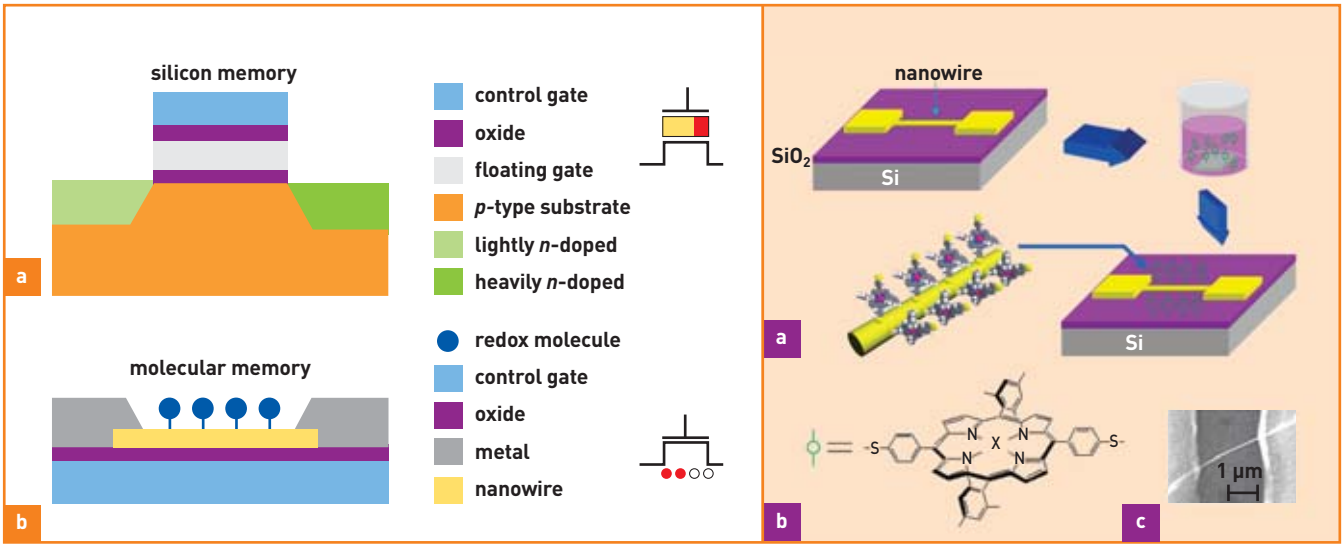


Figure 4.
Left: schematic comparison between a silicon flash memory (a) and a molecular memory for multilevel data storage (b). In a 2 bit silicon memory element, four non-identical charge quantities are placed in the floating gate *via* the electron injection channel. By contrast, the different levels of a molecular memory element are obtained by modifying the ratio of the population of molecules in the oxidized and reduced state, by applying gate potential pulses of ranging amplitudes (from C. Li, W. Fan, B. Lei, D. Zhang, S. Han, T. Tang, X. Liu, Z. Liu, S. Asano, M. Meyyappan, J. Han and C. Zhou, "Multilevel memory based on molecular devices", *Appl. Phys. Lett.*, 84, pp. 1949-1951, 2004).
Right: (a) example of a process for grafting on an In_2O_3 nanowire of diameter 10 nm and length 2 µm, by immersion in a solution of cobalt porphyrin (Co-ppr) containing thioacetate ligands for grafting and self-assembly, (b) structure of Co-ppr, and (c), scanning electron microscopy image of the In_2O_3 nanowire (from C. Li, J. Ly, B. Lei, W. Fan, D. Zhang, J. Han, M. Meyyappan, M. Thompson and C. Zhou, "Data storage studies on nanowire transistors with self-assembled porphyrin molecules", *J. Phys. Chem. B*, 108, pp. 9646-9649, 2004).

Simple **pH** nanodetectors have been constructed by grafting NH_2 groups by classical silanization (3-aminopropyltriethoxysilane) on surface-oxidized boron-doped Si wires. The first nanobiosensor based on Si nanowires biotinylated using the reaction of an activated ester of biotin (a constituent of the B vitamin group) on the surface OH groups on the nanowire, detects avidin (a protein) down to picomolar levels (10^{-12} **mole**/L). DNA detectors on nanowires make it possible to monitor **hybridization** reactions in real time, and thereby discriminate between samples with different mismatches. Sensitivities of 10 femtomoles (10^{-14} mole) were achieved by attaching PNA probes, an uncharged DNA substitute, on nanowires according to the assembly sequence Si/SiO_2-biotin/avidin/biotin-PNA. In this way the charges responsible for the ChemFET effect come mainly from the target DNA **sequences** supplied by the hybridization.
The team at Hewlett-Packard Laboratories (Palo Alto, USA) obviates handling of the nanowires by a **top-down** approach using **electron** beam **lithography** (Box E, ***Lithography, the key to miniaturization***) on a silicon-on-insulator (**SOI**) wafer of Si nanowires (50 nm x 60 nm x 20 µm). The surface of these wires is functionalized to receive single DNA strands using an approach different from that of Charles M. Lieber's group. The technique consists of a silanization by 3-mercaptopropyltrimethoxysilane followed by addition of DNA containing an acrylic phosphoramidite function. The variation in the conductivity of the wire makes it possible to detect a single mismatch. This somewhat surprising result can be explained by the fact that the DNA fragments used are short (12 **bases**). The detection limit is about 25 picomoles/L.
These label-free DNA detectors offer excellent reproducibility, opening the way to integrated nanosensor matrices. These advances in the biofunctionalization of nanowires are well illustrated by the recent extension of "nanobiochemFET" devices to more complex biological entities such as viruses. Thus, Charles M. Lieber and his team describe real-time detection on Si nanowires of influenza A virus, which is distinguished from other viruses such as paramyxovirus and adenovirus (Figure 5).

"Customized" nanoparticles

In the next decades, the ability to recognize, detect and "image" biological systems and living organisms using electrical, optical and magnetic effects will be revolutionized by developments in the physics and chemistry of nanomaterials. The possibility of controlling structural motifs in materials at the nanometer scale will lead to biosensors of a completely new type. These novel systems will be able to recognize and monitor in real time a single molecule inside a living cell. It will be possible to integrate them in parallel arrays for multiparameter detection, so that several experiments can be carried out simultaneously. Metal, magnetic and semiconductor nanoparticles are already being used in many detection methods. Below are a few examples concerning gold and semiconductor nanoparticles.

Gold nanoparticles

Gold metal nanoparticles are used as assembly platforms or building blocks for **catalysts**, sensors and nanostructured materials. They are commercially available(3) and include a wide range of functional features.
Using specific organic molecules or DNA, Chad A. Mirkin, founder of Nanosphere Inc., and his co-workers have shown that it is possible to organize gold nanoparticles into discrete **aggregates** by agglutination through bridging *via* a strand of complementary DNA (Figure 6). The optical transduction of the hybridization of the DNA strands is based on measurement of the coupling

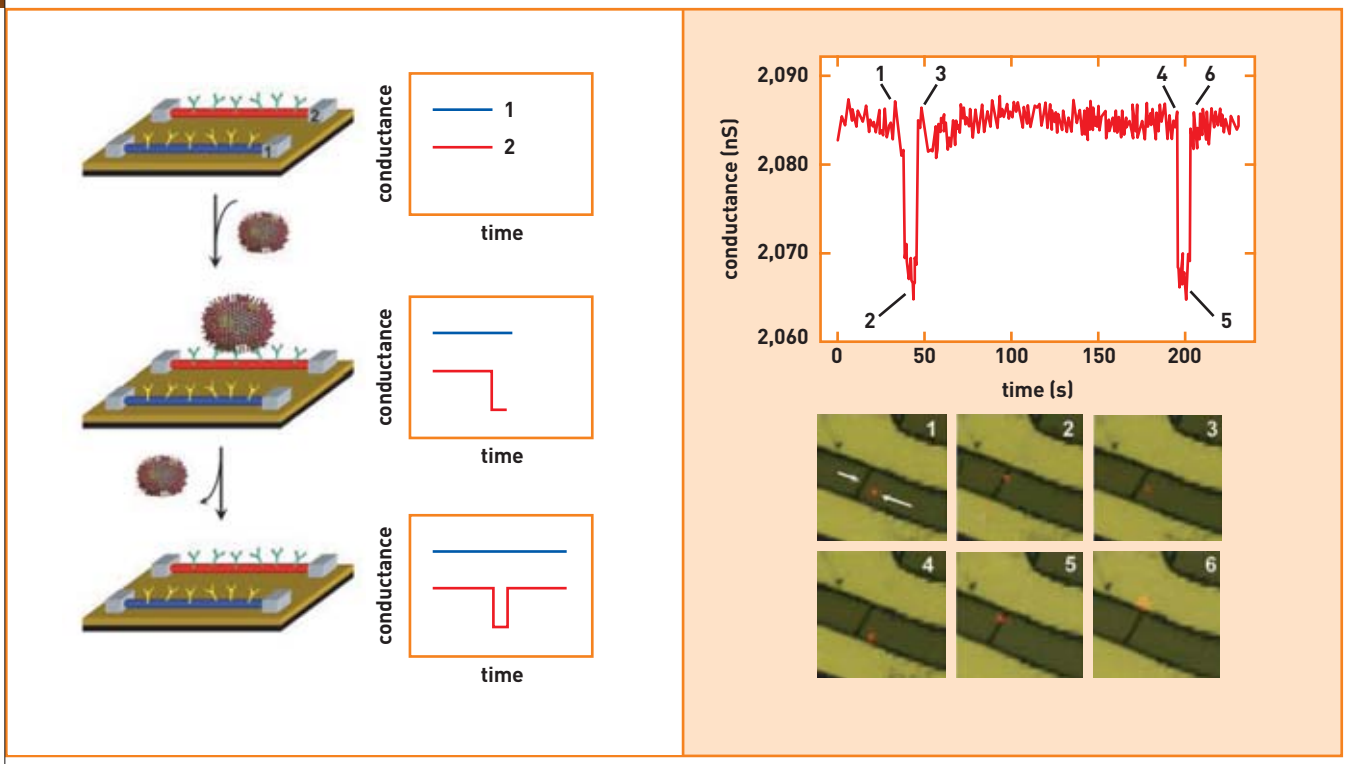


Figure 5.
Left: schematic representation of two devices each containing an Si nanowire of diameter approximately 20 nm and length 2 µm, modified by receptor antibodies of different types. The specific attachment of a single virus on nanowire 2 induces a change in conductance. After it is detached the conductance reverts to its initial value. Right: combining with confocal imaging makes it possible to monitor a series of 6 events each corresponding to different positions of the virus relative to the nanowire. The virus appears as a red spot. The white arrows in image 1 indicate the initial position of the virus and the nanowire. The images correspond to an 8 x 8 µm² field. The virus concentration was 100 particles per microlitre (from F. Patolsky, G. Zheng, O. Hayden, M. Lakadamyali, X. Zhuang and C. Lieber, "Electrical detection of single viruses", *Proceedings of the National Academy of Sciences*, 101, pp. 14017-14022, 2004 - www.pnas.org).

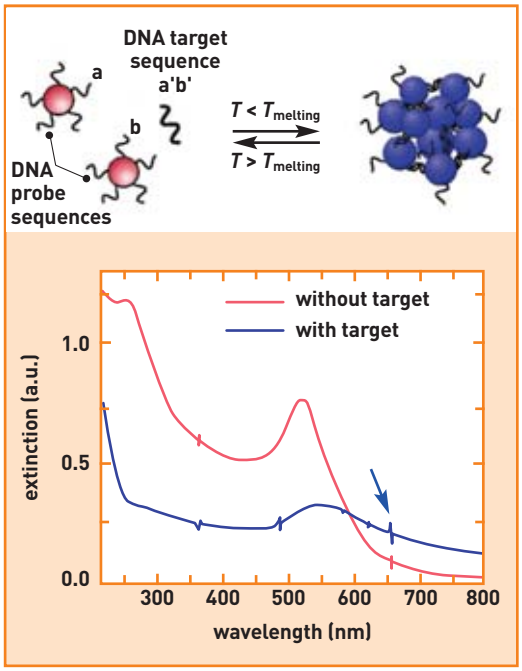


Figure 6.
Top, schematic representation of the principle. When a mixture of gold nanoparticles grafted with DNA probe sequences a and b is placed in contact with a target DNA sequence a'b' that recognizes a and b, this sequence acts like glue and aggregates the 13 nm diameter nanoparticles. The result is a shift towards the infrared in the absorption wavelength of the aggregate relative to the isolated nanoparticle, as shown in the bottom figure (from R. Jin, G. Wu, Z. Li, C. Mirkin and G. Schatz, "What controls the melting properties of DNA-linked gold nanoparticle assemblies?", *J. Am. Chem. Soc.*, 125, pp. 1643-1654, 2003).

of the incident light with the surface plasmon resonance of the nanoparticles (equivalent to an evanescent wave). Bringing together nanoparticles via hybridization allows electromagnetic coupling between nanoparticles, which induces a widening and a red-shift in the resonance frequency. Recently, this group described, in the *Proceedings of the National Academy of Sciences* (PNAS, 15 February 2005), the BCA process (Bar Code Amplification, Nanosphere Inc. licence) based on gold nanoparticles coded by DNA sequences that can detect a protein specific to Alzheimer's disease with a sensitivity a million times higher than the conventional ELISA method. This team is also responsible for developing DNA detection matrices based on the change in conduction of an interelectrode space filled with gold nanoparticles during hybridization (Figure 7). Detection limits of 50 nanomoles/L to 500 femtomoles/L are reported, while the detection limit of a confocal microscope[4] is about 5 picomoles/L.

(3) Gold metal nanoparticles are, for example, sold by Sigma-Aldrich and Ted Pella Inc.

Semiconductor nanocrystals

Semiconductor nanocrystals or quantum dots (QDs) have many applications in the field of nanostructured materials for **photovoltaic** or biological use. In contrast to technology based on gold nanoparticles or organic dyes, labelling with QDs is still in its early stages. For the last 3-4 years a vast array of QDs has become available[5]. These are mainly QDs of the CdSe(core) /ZnS(shell) type; see *Fluorescent semiconducting nanocrystals show their colours*. Various surface functions are proposed (**amines**, carboxylic acids, biotin, antibodies, etc.) together with a wide range of emission wavelengths (525, 565, 605, 655, 705, 800 nm) extendable to 2,500 nm, that are stable in aqueous media. Compared with organic labels, QDs offer two remarkable advantages. They *resist* ***photobleaching***, which makes it possible to monitor biological mechanisms ***in vivo*** over timescales ranging from days to weeks,

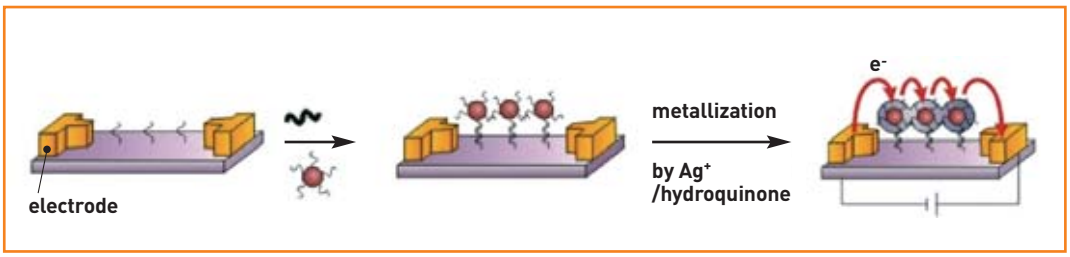


Figure 7.
Principle of detection. The segment of about 20 µm of Si/SiO_2 between the two gold electrodes is covered with DNA probe sequences by means of an attachment process identical to that developed by C. Lieber *et al*. Hybridization with a target sequence makes it possible, *via* a sandwich assembly, to immobilize 13-nm-diameter gold nanoparticles, which fill the interelectrode space. To increase the interelectrode conduction, a chemical deposit of silver can be used to coat the layer of gold particles continuously (from S.-J. Park, A. Taton and C. Mirkin, "Array-based electrical detection of DNA with nanoparticle probes", *Science*, 295, pp. 1503-1506, 2002).

instead of hours for organic dyes and GFPs (green fluorescent proteins). In addition, *their emission wavelength is adjustable according to their size*. These different emissions can be triggered simultaneously by excitation at a single wavelength, which allows multiple marking and even optical encoding.

Because biological processes take place in an aqueous environment, the surface of the QDs has to be rendered hydrophilic. QDs are classically hydrophobic, owing to the presence of the hydrophobic **coordinating** solvent (typically TOPO, trioctylphosphine) used during the synthesis. Out of the six biofunctionalization routes described in Figure 8, four main ones are used.

The first route involves *the replacement of the original* ***ligand*** *by bifunctional surfactants* bearing a hydrophilic function at one end and at the other a function that will bind to the ZnS shell. Thiols (-SH) are the most frequently used binding groups, and carboxylic groups (-COOH) are both hydrophilic and able to link up with the $-NH_2$ groups of proteins. Recently, at the CEA, Peter Reiss and his co-workers have used chelating ligands of the carbodithioic acid type, which exchange quantitatively and improve the resistance of QDs to **photo-oxidation**.

The second route, *silanization*, involves coating the QDs with a silane layer, which lends them high stability. The process comprises two steps. A first layer, obtained by the condensation of thio-trimethoxysilane, forms a *primer*, and a second layer of polysilane, which adheres to the first, provides thiol, phosphonate or ammonium groups to which biomolecules can be attached.

The third route involves *the inclusion of QDs in polymer microbeads for optical encoding* (Figure 9). The potential of such coding is enormous: 3 colours and 10 intensities generate 999 codes; 5-6 colours and 6 intensities provide 10,000 to 40,000 codes.

The fourth route involves *biotinylation of the QDs*. This is a highly versatile biofunctionalization that links the biotin conjugated nanoparticle to any biotin or avidin-conjugated biomolecule (often commercial) by biotin/avidin coupling. Long-term photostability and the high specificity of binding to neurone cells have been demonstrated on CdSe/ZnSe-type QDs (joint work by the Life Science and Materials Science Divisions of the CEA - DSV-DSM).

The *bioconjugation of QDs* was carried out with DNA sequences, peptides (immuno-sensors), proteins and neurotransmitters. Their utility is not restricted to replacing organic dyes but is supported by other effects such as optical coding (Figure 9) or interparticle energy transfer by FRET (fluorescence resonance energy transfer).

In the *in vivo* domain, the long-term monitoring of micro-organisms and living cells as a function of their environment, and of the presence of cytotoxic(6) compounds or drugs, is of great potential importance. However, studies have focused mainly on cytoplasmic(7) or membrane proteins. In addition to the stable **photoluminescence** yield, the chemical non-toxicity of the nanoparticle has to be ensured, because the photo-oxidation of cadmium-based QDs releases cytotoxic cadmium **ions**. Among the alternatives for *in vivo* imaging are nanoparticles of InN, which emit in the **infrared** range. Recent results show that thanks to their polysilane coating, CdSe/ZnS nanoparticles modified

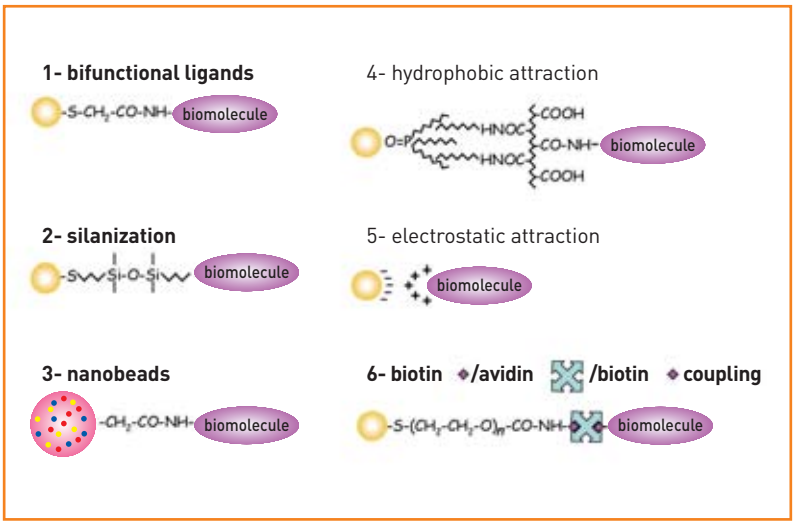


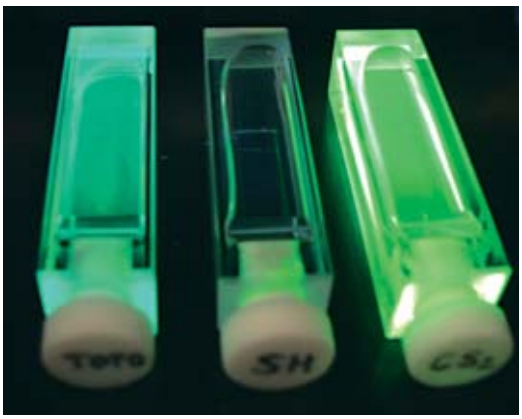
Figure 8.
Main routes for the biofunctionalization of semiconductor nanoparticles of the CdSe/ZnS type.

(4) Confocal microscopy: this elaborate system, made up of lasers, optical components, fast scanning devices and computers for digital image processing, can be used to analyze the inside of microscopic objects and visualize them in three dimensions.

(5) Quantum dots are, for example, sold by Evident Technologies, http://www.evidenttech.com and Quantum Dot Corporation, set up by Paul Alivisatos, http://www.qdots.com.

(6) Cytotoxic: toxic for cells.

(7) Cytoplasm: part of the cell bounded by a plasma membrane, and containing various microstructures, including the membrane organelles (Golgi body, mitochondria).



CEA

Nanocrystals of CdSe under continuous **ultraviolet** irradiation with: left, TOPO ligands; centre, thiol ligands; right, ligands of the carbodithioic acid type. The latter improve the resistance of the QDs to photo-oxidation.

with a viral peptide to cross the cell nucleus barrier (human HeLa cells) make no significant difference to the cell colony after 10 days growth. This opens the way to using QDs for the long-term visualization of biological events affecting the cell nucleus.

Surface functionalization: a key domain

From antireflective layers to water-repellent coatings on glass, *via* anticorrosion treatments for metals, bonding of materials and surface treatment(8) of textile fibres, surface functionalization is set to be a key domain. The control of interfaces is the control of the interactions between a material and the outside world. The functionalization of electron-conducting polymers developed by the Materials Science Division in the early 80s has become a classical approach to surface functionalization that has fuelled the development of wide-ranging applications in electrocatalysis, photovoltaic processes, biosensors, and more recently electronics and molecular photonics. The CEA has played the role of national and international leader in this field, making remarkable advances in ion recognition, and biosensors and **biochips** in particular. The functionalization of nano-objects, which is still in its infancy, will open up new exciting perspectives in the nanosciences. As part of the CEA's "chemistry for nanoelectronics" programme, joint work by the CEA's Technological Research and Materials Science Divisions (DRT-DSM) is in progress, including the development of silicon-based molecular memories and opto-electronic transducers based on carbon nanotubes. The continued development of this technology, which is present throughout the CEA program, is an important priority.

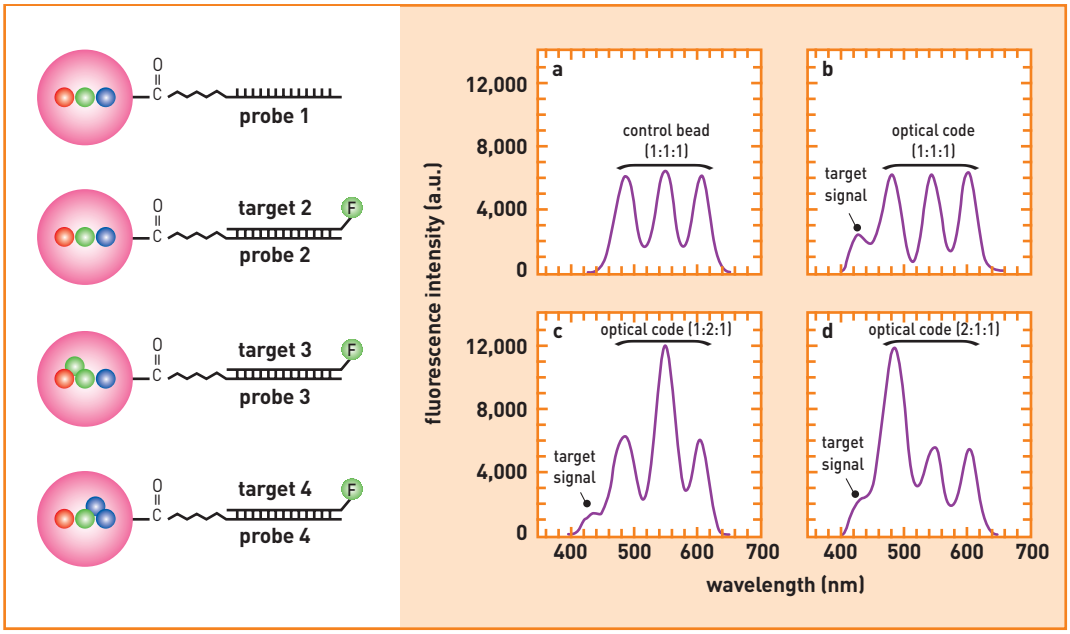


Figure 9.
Left: principle of optical coding by wavelength and intensity multiplexing of QDs. Polystyrene microbeads (0.1 to 10 µm) are swollen with a solvent to incorporate a mixture of QDs of different colours and in precisely set proportions. Right: fluorescence signal of a DNA probe (a) and fluorescence signals obtained after hybridization with the target sequence (b, c and d). The fluorescence signal of the target sequence (marked F) also appears, and can be readily distinguished from the QD code signal (from M. Han, X. Gao, J.Z. Su and S. Nie, "Quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules", *Nature Biotechnology*, 19, pp. 631-635, 2001).

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> **Gérard Bidan**
Materials Science Division
CEA Grenoble Centre

(8) Surface treatment of textile fibres: deposition of a binding agent to favour the cohesion of the yarn, reduce abrasion, facilitate subsequent operations (*e.g.*, weaving) and prevent the formation of **electrostatic** charges.

A From the macroscopic to the nanoworld, and vice versa...

In order to gain a better idea of the size of microscopic and nanoscopic* objects, it is useful to make comparisons, usually by aligning different scales, *i.e.* matching the natural world, from molecules to man, to engineered or fabricated objects (Figure). Hence, comparing the "artificial" with the "natural" shows that artificially-produced **nanoparticles** are in fact smaller than red blood cells.

Another advantage of juxtaposing the two is that it provides a good illustration of the two main ways of developing nanoscale systems or objects: ***top-down*** and ***bottom-up***. In fact, there are two ways into the nanoworld: molecular manufacturing, involving the control of single **atoms** and the building from the ground up, and extreme miniaturization, generating progressively smaller systems.

Top-down technology is based on the artificial, using macroscopic materials that we chip away using our hands and our tools: for decades now, electronics has been applied using **silicon** as a substrate and what are called "**wafers**" as workpieces. In fact, microelectronics is also where the "top-down" synthesis approach gets its name from. However, we have reached a stage where, over and above simply adapting the miniaturization of silicon, we also have to take on or use certain physical phenomena, particularly from **quantum** physics, that operate when working at the nanoscale.

The bottom-up approach can get around these physical limits and also cut manufacturing costs, which it does by using component **self-assembly**. This is the approach that follows nature by assembling molecules to create **proteins**, which are a series of amino acids that the super-molecules, *i.e.* **nucleic acids** (**DNA**, **RNA**), are able to produce within cells to form functional structures that can reproduce in more complex patterns. Bottom-up synthesis aims at structuring the material using "building blocks", including atoms themselves, as is the case with living objects in nature. Nanoelectronics seeks to follow this assembly approach to make functional structures at lower manufacturing cost.

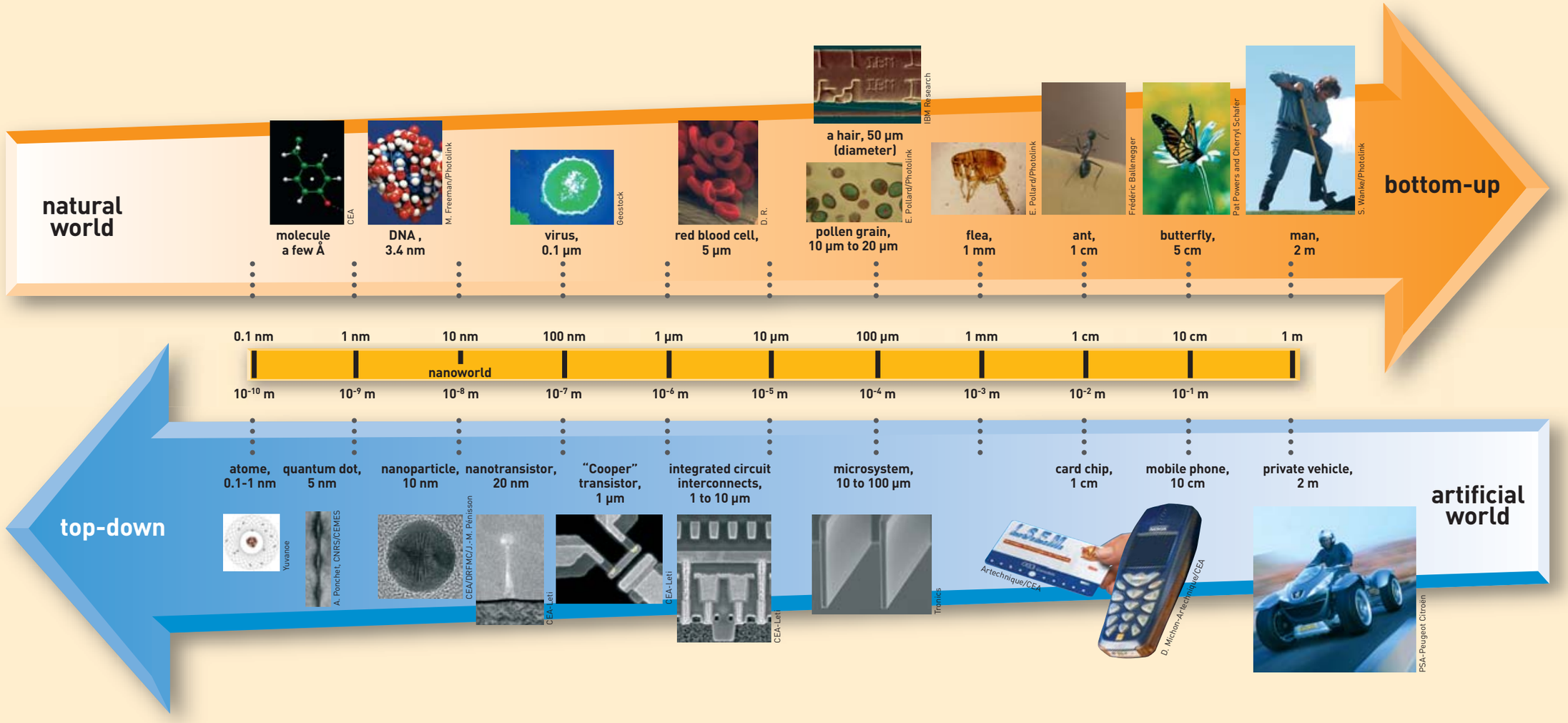
The **nanosciences** can be defined as the body of research into the physical, chemical or biological properties of nano-objects, how to manufacture them, and how they self-assemble by auto-organisazation.

Nanotechnologies cover all the methods that can be used to work at molecular scale to reorganize matter into objects and materials, even progressing to the macroscopic scale.

300-mm silicon wafer produced by the Crolles2 Alliance, an illustration of current capabilities using top-down microelectronics.

* From the Greek *nano meaning* "very small", which is also used as a prefix meaning a billionth (10^{-9}) of a unit. In fact, the **nanometre** (1 nm = 10^{-9} metres , or a billionth of a metre), is the master unit for nanosciences and nanotechnologies.

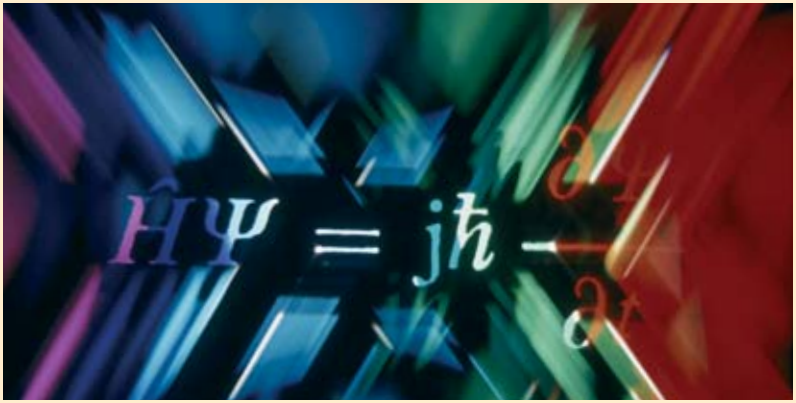
A (next)


natural world
bottom-up
molecule a few Å
CEA
DNA , 3.4 nm
M. Freeman/Photolink
virus, 0.1 µm
Geostock
red blood cell, 5 µm
D. R.
a hair, 50 µm (diameter)
IBM Research
pollen grain, 10 µm to 20 µm
E. Pollard/Photolink
flea, 1 mm
E. Pollard/Photolink
ant, 1 cm
Frédéric Ballenegger
butterfly, 5 cm
Pat Powers and Cheryl Schafer
man, 2 m
S. Wanke/Photolink
0.1 nm
1 nm
10 nm
100 nm
1 µm
10 µm
100 µm
1 mm
1 cm
10 cm
1 m
nanoworld
10-10 m
10-9 m
10-8 m
10-7 m
10-6 m
10-5 m
10-4 m
10-3 m
10-2 m
10-1 m
top-down
artificial world
atome, 0.1-1 nm
Yuvanoe
quantum dot, 5 nm
A. Ponchet, CNRS/CEMES
nanoparticle, 10 nm
CEA/DRFMC/J.-M. Pénisson
nanotransistor, 20 nm
CEA-Leti
"Cooper" transistor, 1 µm
CEA-Leti
integrated circuit interconnects, 1 to 10 µm
CEA-Leti
microsystem, 10 to 100 µm
Tronics
card chip, 1 cm
Artechnique/CEA
mobile phone, 10 cm
D. Michon-Artechnique/CEA
private vehicle, 2 m
PSA-Peugeot Citroën

B A guide to quantum physics

Quantum physics (historically known as quantum mechanics) covers a set of physical laws that apply at microscopic scale. While fundamentally different from the majority of laws that appear to apply at our own scale, the laws of quantum physics nevertheless underpin the general basis of physics at all scales. That said, on the macroscopic scale, quantum physics in action appears to behave particularly strangely, except for a certain number of phenomena that were already curious, such as **superconductivity** or superfluidity, which in fact can only explained by the laws of quantum physics. Furthermore, the transition from the validating the paradoxes of quantum physics to the laws of classical physics, which we find easier to comprehend, can be explained in a very general way, as will be mentioned later.

Quantum physics gets its name from the fundamental characteristics of quantum objects: characteristics such as the angular momentum (**spin**) of **discrete** or discontinuous particles called **quanta**, which can only take values multiplied by an elementary *quantum*. There is also a **quantum of action** (product of a unit of energy multiplied by time) called **Planck's constant** (symbolized as h) which has a value of 6.626 x 10^{-34} joule·second.



D. Sarraute/CEA

An "artist's impression" of the Schrödinger equation.

While classical physics separates *waves* from *particles*, quantum physics somehow covers both these concepts in a third group, which goes beyond the simple wave-particle duality that Louis de Broglie imagined. When we attempt to comprehend it, it sometimes seems closer to waves, and sometimes to particles. A quantum object cannot be separated from how it is observed, and has no fixed attributes. This applies equally to a particle - which in no way can be likened to a tiny little bead following some kind of trajectory - of light (**photon**) or matter (**electron**, **proton**, **neutron**, **atom**, etc.).

This is the underlying feature behind the **Heisenberg uncertainty principle**, which is another cornerstone of quantum physics. According to this principle (which is more *indeterminacy* than *uncertainty*), the position and the velocity of a particle cannot be measured *simultaneously* at a given point in time. Measurement remains possible, but can never be more accurate than *h*, Planck's constant. Given that these approximations have no intrinsically real value outside the observation process, this simultaneous determination of both position and velocity becomes simply impossible.

B (next)

At any moment in time, the quantum object presents the characteristic of *superposing* several states, in the same way that one wave can be the *sum* of several others. In quantum theory, the amplitude of a wave (like the peak, for example) is equal to a **probability amplitude** (or probability wave), a complex number-valued function associated with each of the possible sates of a system thus described as quantum. Mathematically speaking, a physical state in this kind of system is represented by a **state vector**, a function that can be added to others *via* superposition. In other words, the sum of two possible state vectors of a system is *also* a possible state vector of that system. Also, the product of two vector spaces is also the sum of the vector products, which indicates **entanglement**: as a state vector is generally spread through space, the notion of local objects no longer holds true. For a pair of entangled particles, *i.e.* particles created together or having already interacted, that is, described by the *product* and not the *sum* of the two individual state vectors, the fate of each particle is linked - entangled - with the other, regardless of the distance between the two. This characteristic, also called *quantum state entanglement*, has staggering consequences, even before considering the potential applications, such as quantum cryptography or - why not? - teleportation. From this point on, the ability to predict the behaviour of a quantum system is reduced to probabilistic or statistical predictability. It is as if the quantum object is some kind of "juxtaposition of possibilities". Until it has been measured, the measurable size that supposedly quantifies the physical property under study is not strictly defined. Yet as soon as this measurement process is launched, it destroys the **quantum superposition** through the "collapse of the wave-packet" described by Werner Heisenberg in 1927. All the properties of a quantum system can be deduced from the equation that Erwin Schrödinger put forward the previous year. Solving the **Schrödinger equation** made it possible to determine the energy of a system as well as the **wave function**, a notion that tends to be replaced by the probability amplitude.

According to another cornerstone principle of quantum physics, the **Pauli exclusion principle**, two identical half-spin ions (**fermions**, particularly electrons) cannot simultaneously share the same position, spin and velocity (within the limits imposed by the uncertainty principle), *i.e.* share the same *quantum state*. **Bosons** (especially photons) do not follow this principle, and can exist in the same quantum state.

The coexistence of **superposition states** is what lends **coherence** to a quantum system. This means that the theory of **quantum decoherence** is able to explain why macroscopic objects, atoms and other particles, present "classical" behaviour whereas microscopic objects show quantum behaviour. Far more influence is exerted by the "environment" (air, background radiation, etc.) than an advanced measurement device, as the environment radically removes all *superposition of states* at this scale. The larger the system considered, the more it is coupled to a large number of degrees of freedom in the environment, which means the less "chance" (to stick with a probabilistic logic) it has of maintaining any degree of quantum coherence.

TO FIND OUT MORE:

Étienne Klein, *Petit voyage dans le monde des quanta*, Champs, Flammarion, 2004.

C Molecular beam epitaxy

Quantum wells are grown using Molecular Beam Epitaxy (from the Greek *taxi*, meaning order, and *epi*, meaning over), or MBE. The principle of this physical deposition technique, which was first developed for growing III-V **semiconductor crystals**, is based on the evaporation of ultra-pure elements of the component to be grown, in a furnace under ultra-high vacuum (where the pressure can be as low as $5 \cdot 10^{-11}$ mbar) in order to create a pure, pollution-free surface. One or more thermal beams of **atoms** or **molecules** react on the surface of a single-crystal wafer placed on a substrate kept at high temperature (several hundred °C), which serves as a lattice for the formation of a film called epitaxial film. It thus becomes possible to stack ultra-thin layers that measure a millionth of a millimetre each, *i.e.* composed of only a few atom planes.

The elements are evaporated or sublimated from an ultra-pure source placed in an **effusion cell** (or Knudsen cell; an enclosure where a molecular flux moves from a region with a given pressure to another region of lower pressure) heated by the **Joule effect**. A range of structural and analytical probes can monitor film growth *in situ* in real time, particularly using surface quality analysis and grazing angle phase transitions by LEED (*Low energy electron diffraction*) or RHEED (*Reflection high-energy electron diffraction*). Various **spectroscopic** methods are also used, including Auger **electron** spectroscopy, secondary **ion** mass spectrometry (SIMS), **X-ray** photoelectron spectrometry (XPS) or **ultraviolet** photoelectron spectrometry (UPS).

As *ultra-high-vacuum* technology has progressed, molecular beam epitaxy has branched out to be applied beyond III-V semiconductors to embrace metals and insulators. In fact, the vacuum in the growth chamber, whose design changes depending on the properties of the matter intended to be deposited, has to be better than 10^{-11} mbar in order to grow an ultra-pure film of exceptional crystal quality at relatively low substrate temperatures. This value corresponds to the vacuum quality when the growth chamber is at rest. Arsenides, for example, grow at a residual vacuum of around 10^{-8} mbar as soon as the arsenic cell has reached its set growth temperature.

The pumping necessary to achieve these performance levels draws on several techniques using ion pumps, cryopumping, titanium sublimation pumping, diffusion pumps or turbomolecular pumps. The main impurities (H_2, H_2O, CO and CO_2) can present partial pressures of lower than 10^{-13} mbar.

D The transistor, fundamental component of integrated circuits

The first transistor was made in germanium by John Bardeen and Walter H. Brattain, in December 1947. The year after, along with William B. Shockley at **Bell Laboratories**, they developed the bipolar transistor and the associated theory. During the 1950s, transistors were made with **silicon** (Si), which to this day remains the most widely-used **semiconductor** due to the exceptional quality of the interface created by silicon and silicon oxide (SiO_2), which serves as an insulator. In 1958, Jack Kilby invented the **integrated circuit** by manufacturing 5 components on the same **substrate**. The 1970s saw the advent of the first microprocessor, produced by Intel and incorporating 2,250 transistors, and the first memory. The complexity of integrated circuits has grown exponentially (doubling every 2 to 3 years according to "Moore's law") as transistors continue to become increasingly miniaturized.

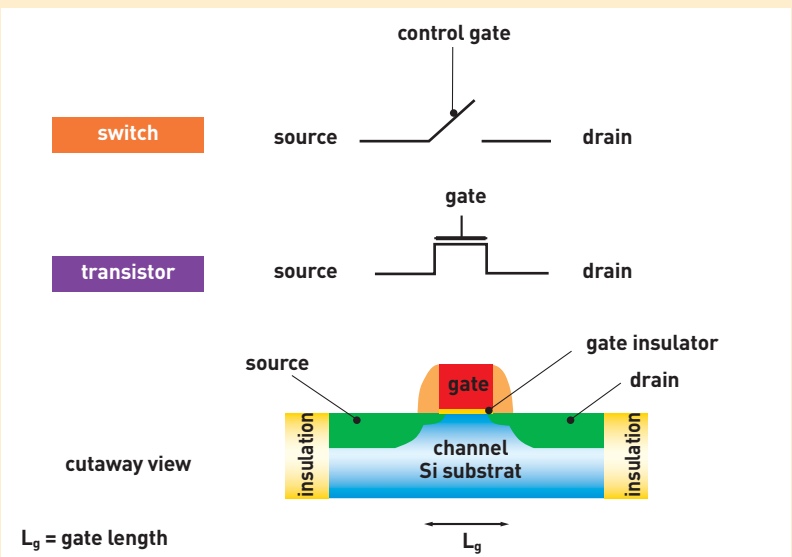


Figure.
A MOS transistor is a switching device for controlling the passage of an electric current from the source (S) to the drain (D) via a gate (G) that is electrically insulated from the conducting channel. The silicon substrate is marked B for Bulk.

The transistor, a name derived from *trans*fer and res*istor*, is a fundamental component of microelectronic integrated circuits, and is set to remain so with the necessary changes at the nanoelectronics scale: also well-suited to amplification, among other functions, it performs one essential basic function which is to open or close a current as required, like a switching device (Figure). Its basic working principle therefore applies directly to processing binary code (0, the current is blocked, 1 it goes through) in logic circuits (inverters, gates, adders, and memory cells).

The transistor, which is based on the transport of **electrons** in a solid and not in a vacuum, as in the electron tubes of the old **triodes**, comprises three **electrodes** (*anode, cathode* and *gate*), two of which serve as an electron *reservoir*: the **source**, which acts as the emitter filament of an electron tube, the **drain**, which acts as the collector plate, with the gate as "controller". These elements work differently in the two main types of transistor used today: *bipolar junction transistors*, which came first, and *field effect transistors* (**FET**).

Bipolar transistors use two types of **charge carriers**, electrons (negative charge) and **holes** (positive charge), and are comprised of identically **doped** (p or n) semiconductor substrate parts

D (next)

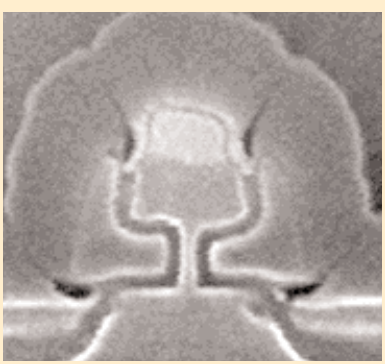
separated by a thin layer of inversely-doped semiconductor. By assembling two semiconductors of opposite types (a p-n junction), the current can be made to pass through in only one direction. Bipolar transistors, whether n-p-n type or p-n-p type, are all basically current amplifier controlled by a gate current[1]: thus, in an n-p-n transistor, the voltage applied to the p part controls the flow of current between the two n regions. Logic circuits that use bipolar transistors, which are called TTL (for transistor-transistor logic), consume more energy than field effect transistors which present a zero gate current in off-state and are voltage-controlled.

Field effect transistors, most commonly of **MOS** (metal oxide semiconductor) type, are used in the majority of today's **CMOS** (C for complementary) logic circuits[2]. Two n-type regions are created on a p-type silicon crystal by doping the surface. These two regions, also called drain and source, are thus separated by a very narrow p-type space called the **channel**. The effect of a positive current on the control electrode, naturally called the **gate**, positioned over the semiconductor forces the holes to the surface, where they attract the few mobile electrons of the semiconductor. This forms a conducting channel between source and drain (Figure). When a negative voltage is applied to the gate, which is electrically insulated by an oxide layer, the electrons are forced out of the channel. As the positive voltage increases, the channel resistance decreases, letting progressively more current through.

In an integrated circuit, transistors together with the other components (**diodes**, condensers, resistances) are initially incorporated into a "chip" with more or less complex functions. The circuit is built by "sandwiching" layer upon layer of conducting materials and insulators formed by **lithography** (Box E, ***Lithography, the key to miniaturization***). By far the most classic application of this is the microprocessor at the heart of our computers, which contains several hundred million transistors (whose size has been reduced 10,000-fold since the 1960s), soon a billion. This has led to industrial manufacturers splitting the core of the processors into several subunits working in parallel!

Lucent Technologies Inc./Bell Labs

The very first transistor.



STMicroelectronics

8 nanometre transistor developed by the Crolles2 Alliance bringing together STMicroelectronics, Philips and Freescale Semiconductor.

(1) This category includes **Schottky transistors** or **Schottky barrier transistors** which are field effect transistors with a metal/semiconductor control gate that, while more complex, gives improved charge-carrier mobility and response times.

(2) Giving **MOSFET** transistor (for Metal Oxide Semiconductor Field Effect Transistor).

E Lithography, the key to miniaturization

Optical lithography (photolithography) is a major application in the particle-matter interaction, and constitutes the classical process for fabricating integrated circuits. It is a key step in defining circuit patterns, and remains a barrier to any future development. Since resolution, at the outset, appears to be directly proportional to wavelength, feature-size first progressed by a step-wise shortening of the wavelength λ of the radiation used.

Artechnique

Photolithography section in ultra-clean facilities at the STMicroelectronics unit in Crolles (Isère).

The operation works via a reduction lens system, by the *exposure* of a photoresist film to energy particles, from the ultraviolet (UV) photons currently used through to X photons, ions, and finally electrons, all through a mask template carrying a pattern of the desired circuit. The aim of all this is to transfer this pattern onto a stack of insulating or conducting layers that make up the mask. These layers will have been deposited previously (the *layering* stage) on a wafer of semiconductor material, generally silicon. After this process, the resin dissolves under exposure to the air (*development*). The exposed parts of the initial layer can then be etched selectively, then the resin is lifted away chemically before deposition of the following layer. This lithography step can take place over twenty times during the fabrication of an integrated circuit (Figure).

In the 1980s, the microelectronics industry used mercury lamps delivering near-UV (g, h and i lines) through quartz optics, with an emission line of 436 nanometres (nm). This system was able to etch structures to a feature-size of 3 microns (μm). This system was used through to the mid-90s, when it was replaced by excimer lasers emitting **far-UV** light (KrF, krypton fluoride at 248 nm, then ArF, argon fluoride at 193 nm, with the photons thus created generating several electronvolts) that were able to reach a resolution of 110 nm, pushed to under 90 nm with new processes.

In the 1980s, the CEA's Electronics and Information Technology Laboratory (Leti) pioneered the application of lasers in lithography and the fabrication of integrated circuits using excimer lasers, and even the most advanced integrated circuit production still uses these sources.

The next step for high-volume production was expected to be the F_2 laser (λ = 157 nm), but this lithography technology has to all intents and purposes been abandoned due to complications involved in producing optics in CaF_2, which is transparent at this wavelength. While the shortening of wavelengths in exposure tools has been the driving factor behind the strong resolution gain already achieved, two other factors have nevertheless played key roles. The first was the development of polymer-lattice photoresists with low absorbance at the wavelengths used, implementing progressively more innovative input energy reflection/emission systems. The second was enhanced optics reducing diffraction interference (better surface quality, increase in numerical aperture).

Over the years, the increasing complexity of the optical systems has led to resolutions actually *below* the source wavelength. This development could not continue without a major technological breakthrough, a huge step forward in wavelength. For generations of integrated circuits with a lowest resolution of between 80 and 50 nm (the next "node" being at 65 nm), various different approaches are competing to offer particle projection at ever-shorter wavelengths. They use either "soft" X-rays at extreme ultraviolet wavelength (around 10 nm), "hard" X-rays at wavelengths below 1 nm, ions or electrons.

The step crossing below the 50 nm barrier will lead towards low-electron-energy (10 eV)-enabled nanolithography with technology solutions such as the scanning tunnelling microscope and molecular beam epitaxy (Box C) for producing "superlattices".

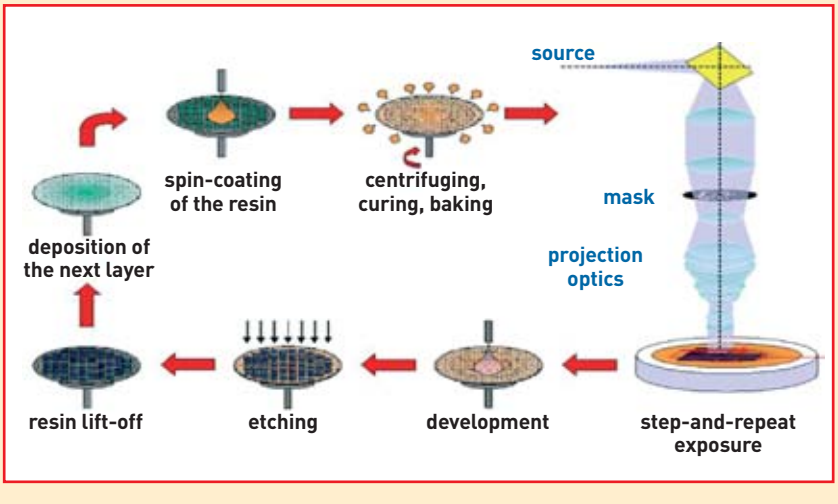


Figure. The various phases in the lithography process are designed to carve features out of the layers of conducting or insulating materials making up an integrated circuit. The sequences of the operation are laying of a photoresist, then projecting the pattern on a mask using a reduction optics system, which is followed by dissolution of the resin that is exposed to the light beam (development). The exposed parts of the initial layer can then be etched selectively, then the resin is lifted away before deposition of the following layer.

G The tunnel effect, a quantum phenomenon

Quantum physics predicts unexpected behaviour that defies ordinary intuition. The tunnel effect is an example. Take the case of a marble that rolls over a bump. Classical physics predicts that unless the marble has enough kinetic energy it will not reach the top of the bump, and will roll back towards its starting point. In quantum physics, a particle (proton, electron) can get past the bump even if its initial energy is insufficient, by "tunnelling" through. The tunnel effect makes it possible for two protons to overcome their mutual electrical repulsion at lower relative velocities than those predicted by classical calculations.

Tunnel effect microscopy is based on the fact that there is a finite probability that a particle with energy lower than the height of a potential barrier (the bump) can still jump over it. The particles are electrons travelling through the space between two electrodes. These electrodes are a fine metal tip terminating in a single atom, and the metal or semiconductor surface of the sample. In classical physics a solid surface is considered as a well-defined boundary with electrons confined inside the solid. By contrast, in quantum physics each electron has wave properties that make its location uncertain. It can be visualized as an electron cloud located close to the surface. The density of this cloud falls off exponentially with increasing distance from the solid surface. There is thus a certain probability that an electron will be located "outside" the solid at a given time. When the fine metal tip is brought near the surface at a distance of less than a nanometre, the wave function associated with the electron is non-null on the other side of the potential barrier and so electrons can travel from the surface to the tip, and *vice versa*, by the tunnel effect. The potential barrier crossed by the electron is called the tunnel barrier. When a low potential is applied between the tip and the surface, a tunnel current can be detected. The tip and the surface being studied together form a local tunnel junction. The tunnel effect is also at work in Josephson junctions where a direct current can flow through a narrow discontinuity between two superconductors.

In a transistor, an unwanted tunnel effect can appear when the insulator or grid is very thin (nanometre scale). Conversely, the effect is put to use in novel devices such as Schottky barrier tunnel transistors and carbon nanotube assemblies.