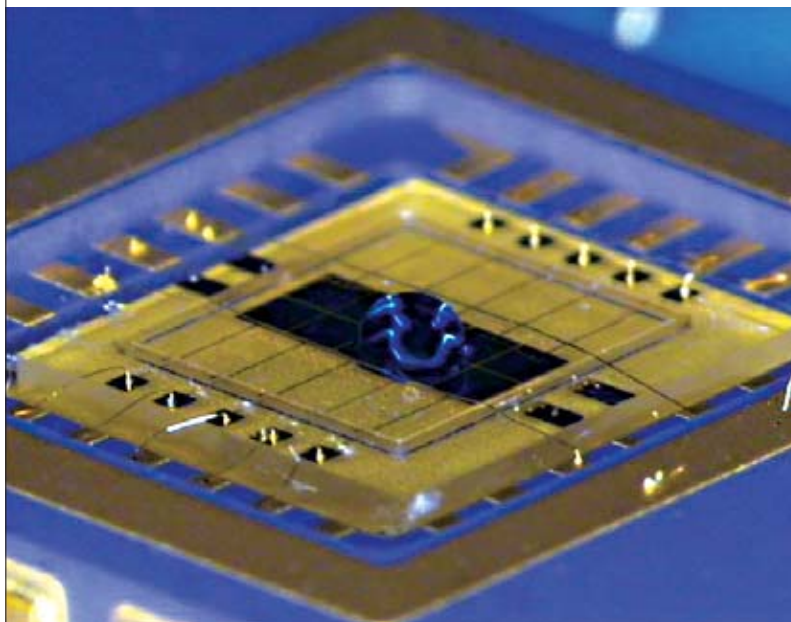# Micro- and nanotechnologies for the living world

An EWOD chip, a microsystem used to manipulate 100-nanolitre droplets by electrowetting. The sample droplet is moved by a current being sent through the electrodes one-by-one.

Our fundamental understanding of information management in the living world has progressed in leaps and bounds in recent decades, since the discovery of the double-helix structure of a DNA molecule, followed by DNA sequencing and functional gene analysis. In parallel, information science and technologies have achieved extraordinary feats. These two domains have cross-fertilized to generate new fields of research, providing applications to benefit individuals as well as society as a whole.

Towards analysis microsystems interfaced with the living world

Identifying a pathology, choosing the best therapeutic strategy and monitoring its effects, screening healthy individuals for genetic predisposition to certain diseases, performing biomedical analysis in veritable miniature laboratories using a single drop of blood, thereby cutting down sample volumes, reagent use, time and costs, or large-scale and custom analysis and manipulation of living cells... all these high-potential applications are currently under nanotechnological development.

Research engineers now have access to tools that go far beyond laboratory hardware and reagents. They use high-tech instruments and powerful software to reveal the underlying principles and behaviours governing the mechanisms behind how the living world functions at molecular, cellular, whole body and population-wide levels.

Technological progress will continue to strengthen diagnostic capabilities at all stages of patient management: identification of the disease, localization, choice of treatment strategy, and monitoring of the effects of the therapy on both disease and patient. The development of pharmacogenetics[1] has paved the way for the next major step forward: screening healthy subjects for **genetic** predisposition to certain cancers, cardio-vascular disease, or even other hereditary disorders. Similar tests will be put to work to identify patients whose genetic profile may lead to adverse events in response to certain drugs and drug classes. These new tests will require hospitals and medical analysis laboratories to equip themselves with instruments and information systems partly inspired by technologies currently developed for use in scientific research, such as **mass spectrometry** and **biochips**.

Biochips were developed in the 1990s for massively parallel high throughput analysis of data and correlates in new fields in biology, **genomics** and then **proteomics**. The first **DNA** chips were quickly marketed,

(1) Pharmacogenetics: study of the variability of pharmacological responses in relation to individual genetic profiles, performed by analyzing phenotype expression (apparent characteristics of a cell, or an organism, resulting from its gene expression, *via* protein synthesis), particularly differences in enzymatic equipment and the impact on metabolism.

scoring a resounding scientific and commercial success. These chips collected unprecedented masses of data in rapid turnabout times, revolutionizing research in biology. A new pathway was opened in high-speed analysis, and research teams threw themselves into R&D on analytical microsystems for application in biology. The panoply of miniaturized analysis tools currently under development covers molecular, structural and cellular biology, with applications ranging from medical diagnosis to environmental monitoring. Underlying these development are two approaches that meet the smaller, faster, cheaper credo: one is *microarrays*, made of thousands of **micrometre-scale** spots of biological **molecules** (DNA or **proteins**) organized in a matrix in a predetermined order on a glass or **silicon** slide, and the other is microfluidics, or the art of handling fluid samples and reagents in volumes below a microlitre (10^{-6} litre). In tomorrow's world, the lab-on-a-chip, which is at the crossover of these two disciplines, will have integrated all these steps, from sample processing to results feedback. Incorporating microelectronic, optical and software components along the way, it will be fabricated using techniques engineered for microelectronics.

Cells slip easily into this race towards miniaturization and integration, and many of today's developments aim to create analytical microsystems that are interfaced with the living world. *Cell-on-chips* will be able to perform phenotyping, electrical and optical analysis at large-scale as well as at the single-cell level. Integrating live cells is already an extremely tricky business, and protecting fragile microelectronic functions from biological pollution only complicates the task further. Biochips will necessarily follow the same route as their cousins the **microprocessors**, towards extreme minia-

turization. Nanosciences and nanotechnologies will be mobilized to fabricate **biomimetic** sensors, imitating the molecular recognition and signal transduction mechanisms encountered in living organisms. These "electronic noses" will offer sensitivity and selectivity capacities close to those found in the animal kingdom, a billion times more powerful than the best of today's technology.

The brute force of microarrays

Microarrays broke through in 1991 with a report, written by Stephen P.A. Fodor and published by the journal *Science*[2], on a method for fabricating oligonucleotide[3] chips by *in situ* **base** by base chemical synthesis using photolithography (Box E, *Lithography, the key to miniaturization*), one of the fundamental techniques in microelectronics. The US-based Affymetrix, world leader in biochips, developed a process for reaching a **probe** density of 1 million per cm^2. The first chips were marketed in 1995.

While Affymetrix chips were limited to small oligonucleotides with 25 or fewer bases, others implemented **PCR** (**Polymerase Chain Reaction**) products, plasmids[4], genomic DNA, or long oligonucleotides with 50 to 70 bases. The chips were developed by various methods, including simply printing probes onto microscope slides.

The most common use of microarrays is to measure the level of expression of hundreds to thousands of **genes**. The **messenger RNA** (**mRNA**) is extracted from single-type cells, converted into complementary DNA (cDNA), then amplified and tagged using a **fluorescent** substance. A cDNA molecule that is complementary to one of the chip probes will **hybridize** to the corresponding spot and can then be analyzed using a microarray scanner. The intensity of the emitted light varies as a complex function of the number of specific mRNA copies present, and therefore as a function of the activity or level of expression of the gene. In a sense, these microarrays give a representation, or profile, of active or inactive genes at a given time and in a particular cell type. The first results of microarray profiling were published in 1995 in *Science* and the first complete eukaryotic[5] genome (for the yeast[6] *Saccharomyces cerevisiae*) obtained on a microarray was published in 1997. A range of companies (Agilent, Affymetrix) are currently offering microarrays covering the full human genome sequence.

DNA chips can also detect genetic variations between individuals or between populations. The high probe densities that can be achieved make it possible to perform genetic testing of a panoply of potential genome modifications. These approaches have a bright future for use in many pathological settings. In infectious dis-

Thanks to the MeDICS system, floating, multi-directional motion, analysis and recovery of a single cell has become child's play.

P. Chagnon/BSIP-CEA

(2) *Science*, 251, pp. 767-773.

(3) Oligonucleotide: a short sequence of DNA comprising from two to a few tens of nucleotides. The nucleotides comprise a base (puric or pyrimidic), a sugar and a phosphate group.

(4) Plasmid: a circular DNA macromolecule present in bacteria, capable of autonomously replicating.

(5) Eukaryote: a living organism comprising one or more cells with a distinct nucleus and cytoplasm.

(6) Yeast: microscopic single-cell fungus undergoing mainly asexual reproduction.
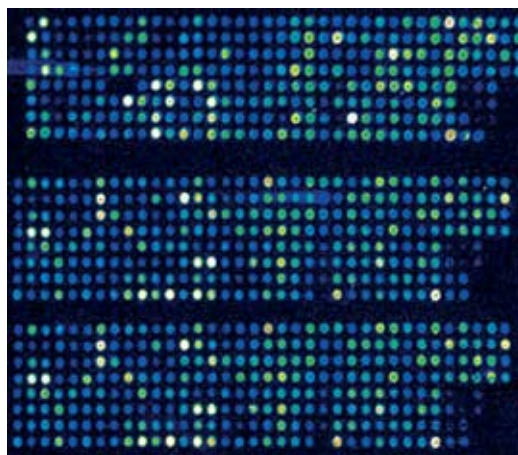
Image taken by fluorescence scanning of a DNA chip.

CEA

eases, for instance, they will provide the means to rapidly identify the causal agent, a **bacteria** or a **virus**, genotype it, and select the most efficient therapeutic treatment. In cancer, it will become possible to screen for genetic factors correlating with cancer predisposition. This would enable the patient to adapt their lifestyle and follow preventive therapy, and the disease would be detected at a very early stage, before the symptoms appear. The trend is moving towards chips "targeted" towards a particular disorder, symptom, or genetic trait. Priority will be given to industrial cost price, robustness, sensitivity and selectivity of low and mid-density chips designed for medical diagnostics.

But DNA isn't the same as proteins! The genome alone cannot describe the proteins it encodes[7], nor the mechanisms regulating protein concentration within cells. Moreover, active proteins often result from post-translational modifications[8] occurring in different cell **compartments**. In fact, there are an estimated 500,000 different proteins whereas the human genome contains only 30,000 genes. Here again, microarrays can contribute to identifying and quantifying the proteins in a cell sample by replacing the DNA strands of the chips described above with a protein matrix capable of binding specifically to other proteins. It would thus become possible to work back to the protein composition of a complex mixture. The first protein biochips have been marketed by California based Zyomyx Inc.

These protein analysis platforms can perform a huge number of analyses in record time, and they are branching out with recent developments in small protein chips, sugar chips, or **enzyme** chips. In the meantime, the field of applications has extended widely. In agri-business, for example, protein biochips provide a solution to issues such as meat traceability or the detection of GMOs (genetically-modified organisms).

Industrial development of microarrays now has to work in synergy with microfluidics to produce comprehensive platforms able to provide results from raw samples.

(7) Protein code: a sequence of DNA or a gene that enables the cell to synthesize a given protein.

(8) Post-translational modification: in the cell cycle, an enzymatic modification following the protein polypeptide synthesis phase.

(9) PATRICK TABELING, *Introduction à la microfluidique*, Collection Échelles, Belin, 2003.

Microfluidics: high-precision in the art of making coffee

For decades now, scientists and research engineers have been trying to cut down reaction volumes using ever smaller quantities of products, either because the initial sample is in limited supply or to cut down reagent costs, or else because the analyte, a cell for example, is so small that is has to be handled within a very small carrier volume. Hence, the high-throughput screening used in the pharmaceutical industry to identify candidate drugs from within databases containing thousands of chemical compounds has jumped from 96 to 384 and then 1,536 simultaneous experiments. At the same time, reaction volumes have dropped from 300 microlitres to less than 5.

MEMS (Micro-Electro-Mechanical Systems) are platforms between 1 and 300 **microns** in size that can detect or generate mechanical, electromechanical, thermal or acoustic energies. Originating in the early 1980s, they have led to major industrial and market breakthroughs, such as airbag impact sensors or inkjet print heads. There are currently an estimated 1.6 MEMS per head of the population in the US.

Since the early 1990s, MEMS systems have been developed in chemistry and biology for biomedical and chemical analysis applications. This involves moving, splitting, mixing or separating liquids at unprecedented dimensions. The drive to shrinking tube size and integrate components for controlling reagent transport has led to the creation of a new pluridisciplinary field drawing on physics, technology, chemistry and biology: microfluidics[9].

Interactions between liquid and wall surfaces play a major role in microsystems. In an ultra-small coffee cup measuring only a few nanolitres (10^{-9} litre), just mixing the milk by shaking becomes a task of Dantesque proportions. In fact, when constrained within a vessel of micrometre-scale dimensions, the coffee behaves like a highly viscous liquid, such as honey. Hence, it is harder to make it swirl. This phenomenon stems from

P. Stroppa/CEA

The Capucine project. The chip is comprised of a sequence of several hundred biological molecules, DNA, peptides, or proteins attached to the inside wall of a glass tube the size of a hair, with each element occupying a specific cylindrical section. This new configuration makes it possible to analyze a biological sample of only a few hundredths of a microlitre. A microfluidic connection links the capillary to a lab-on-a-chip, a capillary electrophoresis system, or a mass spectrometer.

surface forces that increase dramatically, making conventional approaches such as applying pressure or shaking mechanically almost obsolete in miniaturized systems. This has meant developing new microcomponents - valves, tubes, pumps, reactors - capable of manipulating fluids in these micron-sized apparatuses. This research has culminated in the development of a range of devices including **electrophoretic** separators, **electro-osmotic** pumps, micromixers, DNA amplification systems, microcytometers[10], and chemical reactors, to name but a few (see *Microfluidics, or the art of handling very small liquid samples*).

Moving off the well-beaten track of microfluidics, the EWOD (ElectroWetting-on-Dielectric, or digital microfluidics) method is able to handle droplets using an **electrode** array. Its operating principle is relatively simple. When an electrode is electrically activated, it exerts a stronger attraction for the liquid, and it is this that biochemists set out to exploit. A droplet on one of the neighbouring electrodes will jump naturally to the active electrode, which can be switched back into neutral state before proceeding to the following handling operation. Electrode by electrode, a droplet only a few tens of nanolitres in size is transported from one end of a square centimetre of the array to the other. At the Grenoble-based Electronics and Information Technology Laboratory (CEA-Leti: Laboratoire d'électronique et de technologie de l'information), researchers have managed to exploit this principle to generate droplets from a reservoir, separate them, sort them, and merge them, solely through a computer program. As with microplumbing, the aim is to integrate each of these sample preparation and analysis steps onto a single chip.

The lab-on-a-chip, functional integration

As progress is made and new, progressively more stunning developments are achieved in the field of biochips, the range of potential applications continues to broaden. MicroTAS (Micro Total Analysis Systems) have been set the target of seamlessly integrating all the elements required for analysis, *i.e.* link-up systems with the macroscopic world, microfluidics and detection components, onto a single device. Just like MEMS, MicroTAS will be controlled by computer software, and the signals detected will be converted into automatically-readable digital signals. "Electronic" biochips present all the virtues of MEMS: parallel fabrication, miniaturization potential, reduced volumes. The microelectronics industry was quick to catch on, and Motorola, Samsung and Intel have joined the race.

If **STMicroelectronics** lives up to its promise, it will become the first company to market a microlaboratory capable of performing complete genetic testing, from DNA extraction, amplification and gene-tagging by PCR, to hybridization on a microarray. Current technology enables PCR and microarray hybridization to be carried on a 2 cm^2 silicon chip loaded with the sample for analysis and inserted directly into a CD-player-like draw housed in the computer controller.

(10) Microcytometer: miniaturized system for cell analysis or sorting.
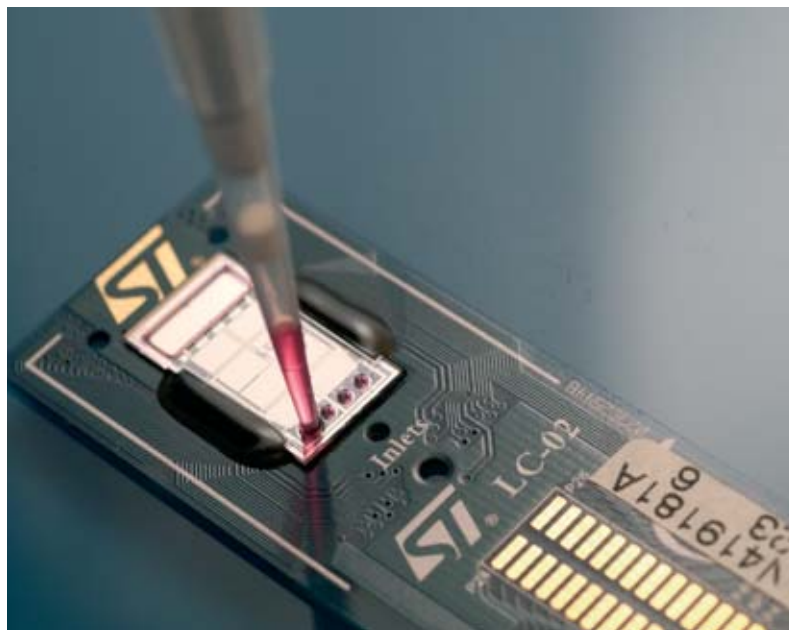
The chip is based on inkjet print head technology associating microchannels and microfabricated heating elements. The company intends to deploy these on-chip systems in medical practices.

Cell-on-chips: cells join the race

In the race towards integration, the cell has a leading role. Who better than a cell integrates the information of the genome, the regulation of the **transcriptome**, the activity of the proteome and the complexity of the **metabolome**? Interfacing microsystems with living organisms thus represents the most promising strategy for tapping these capabilities, dissecting unique events, identifying key elements, and thus potential markers or targets for medical diagnostics and therapeutics.

Progress in cell-on-chip research is booming. While some research teams are focussing on manipulating single cells using electrical, optical, or even holographic or acoustics energies, others, such as Peter Fromherz at the Max Planck Institute of Biochemistry in Munich, Germany, are interfacing neurones with electronic **transistors** to produce the first cellular-electronic interconnections. Other research teams are growing cells in micro-droplets in microarray configurations. Each micro-droplet is thus transformed into a virtual well and the substrate can be used for high-throughput screening of drugs, siRNA (RNA gene inhibitor) or new genes (the CEA's "Phénopuces" (Phenochip) project).

The main challenges faced include guaranteeing cell viability and minimizing the impact of the analysis and (or) handling method on function (the **Heisenberg uncertainty principle** already comes into play at the single-cell level). Conversely, the microelectronic system has to be protected against organic pollution from the living world.

Silicon BioSystems, a talented Italian start-up, and spin-off from the Microelectronics Department of Bologna University, has teamed up with the CEA (Biochips Laboratory) and the **Inserm** (Immunochemistry Laboratory, of the Cell Response and

Chip developed under the CEA/STMicroelectronics R&D agreement dedicated to genetic diagnostics. The device has embedded DNA sample preparation by enzymatic amplification (PCR) and sample analysis by hybridization on oligonucleotide probes.

P. Stroppa/CEA
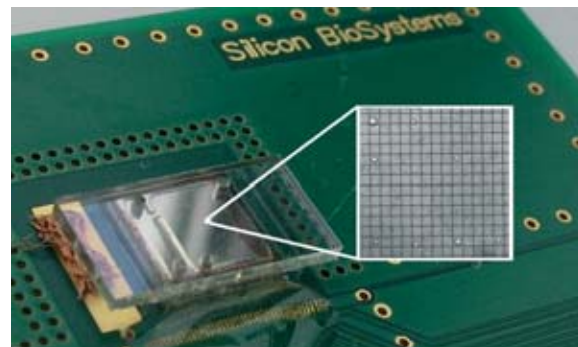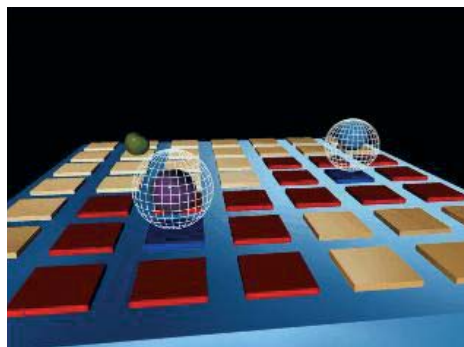
At left, a section of an electrode network (each electrode measures 20 µm) in which electric potential traps have been engineered to trap particles. At right, the MeDICS chip with cells organized in the trap (insert). By individually manipulating each cell, populations of rare cells can be sorted, for instance during analysis of biopsies or isolation of stem cells intended for therapeutic use.

Dynamics Department) to design a highly unconventional application of **CMOS** technology (standard technology in microprocessor and flat-screen manufacture). An array of over 100,000 multiplexed electrodes, *i.e.* all individually controllable, is used to individually manipulate each cell in a small population. The cells self-organize above the electrodes inside electric potential traps adjusted to contain only a single cell. On-chip optical or electronic sensors locate the cells, and the operator is then able to select one or more study cells that can be moved into a small chamber and recovered. Motion and the pathway taken by the cells occur without movement in the liquid, and are totally controlled by software that can be parameted to fit the required application. This revolutionary technology opens up previously unexplored paths, particularly in high-potential markets such as pre-natal non-invasive diagnostics, sorting of **stem cells**, and the manipulation of therapeutic cells.

An illustration of convergence between nanotechnology and biology

Biological receptors found at the cell surface display sensitivity and specificity for their **ligands** that go way beyond the performance levels of the best physical sensors known to date. A major challenge in biosensor R&D consists in finding a way to exploit these skills by mimicking these natural receptors in their environment. One solution is to bio-engineer specific ligand receptors for drugs, herbicides, insec-

ticides or heavy metals[11], and offer them a biomimetic environment in which their activity can be recorded and quantified. The Silipore project is a team effort driven by the Biochips Laboratory, the Leti, and the **CNRS**' Molecular and Cellular Biophysics (BMC) laboratory and Enzymes & Biological and Biomimetic Membranes (EMBB) laboratory, aiming to meet this challenge. Silipore is a sub-micron-sized silicon membrane with pores calibrated to host and stabilize both a **lipid** bilayer and these "bio-engineered" receptors. When a ligand binds to the receptor, the ion channel paired with this receptor opens to let through an **ion** current that can be measured through the electrical current it generates.
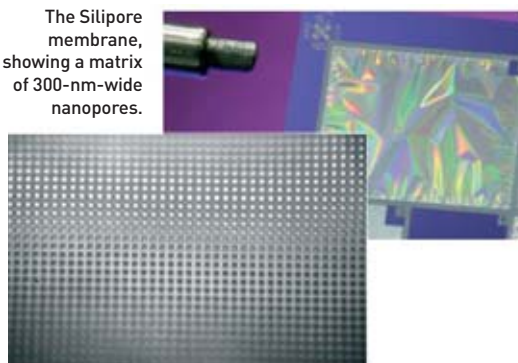
> **François Chatelain** and **Alexandra Fuchs**
Life Science Division
CEA Grenoble Centre

(11) Heavy metals: metal elements with a density above 4.5 g/cm^3. Includes zinc (7.14), cadmium (8.6), and lead (11.35), among others.

The Silipore membrane, showing a matrix of 300-nm-wide nanopores.

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

* 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.

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

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
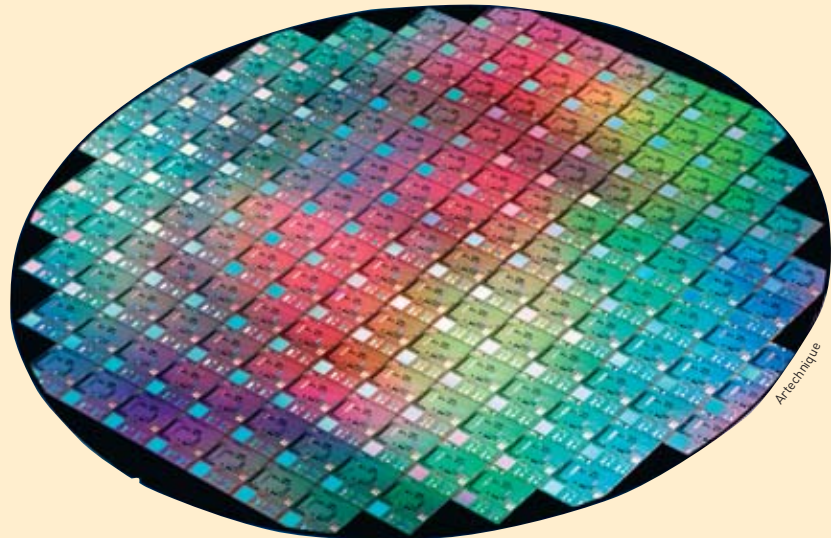
have to take on or use certain physical phenomena, particularly from **quantum** physics, that operate when working at the nanoscale.

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
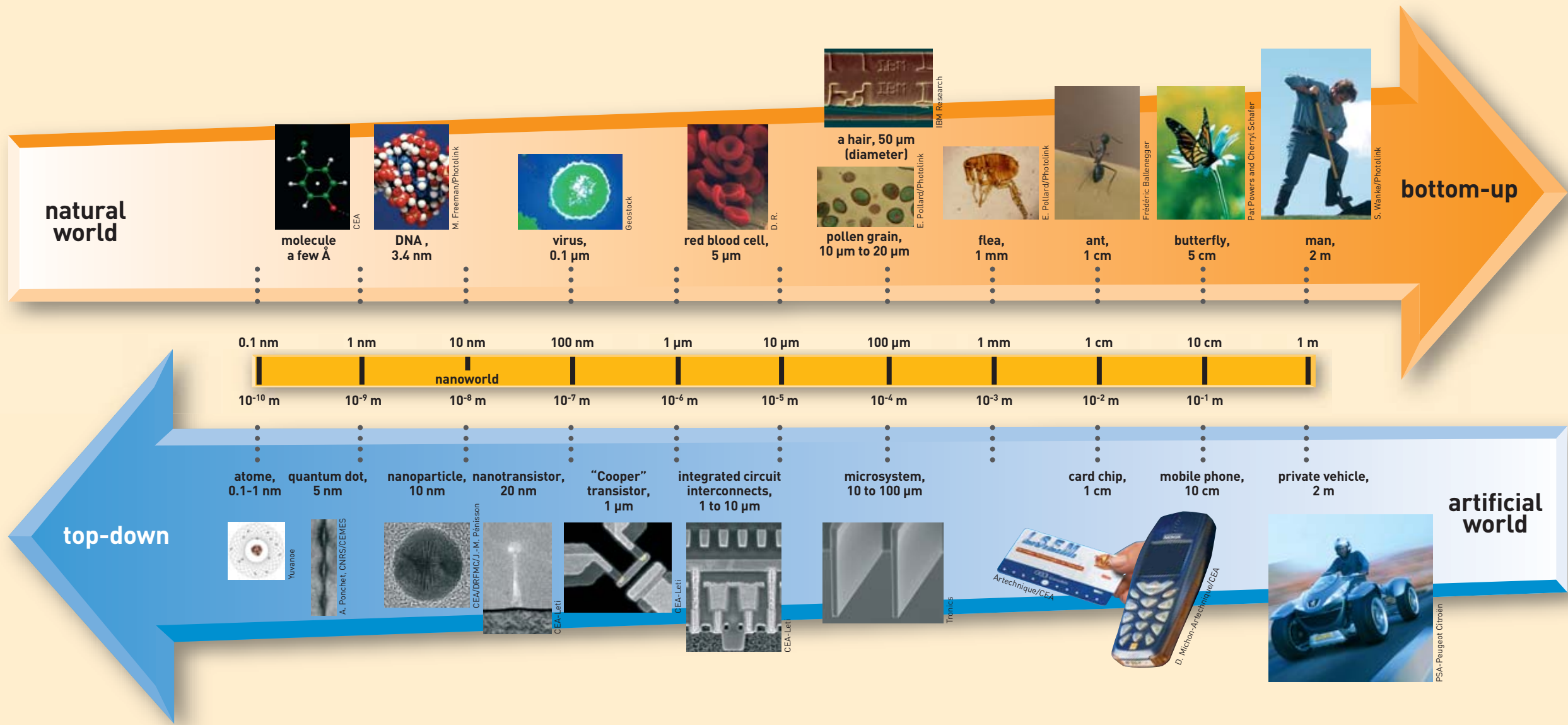
"building blocks", including atoms themselves, as is the case with living objects in nature. Nanoelectronics seeks to follow this assembly approach to make functional structures at lower manufacturing cost.

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.

A (next)

natural world

bottom-up

molecule
a few Å

DNA ,
3.4 nm

virus,
0.1 µm

red blood cell,
5 µm

a hair, 50 µm
(diameter)

pollen grain,
10 µm to 20 µm

flea,
1 mm

ant,
1 cm

butterfly,
5 cm

man,
2 m

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

atome,
0.1-1 nm

quantum dot,
5 nm

nanoparticle,
10 nm

nanotransistor,
20 nm

"Cooper"
transistor,
1 µm

integrated circuit
interconnects,
1 to 10 µm

microsystem,
10 to 100 µm

card chip,
1 cm

mobile phone,
10 cm

private vehicle,
2 m

top-down

artificial world

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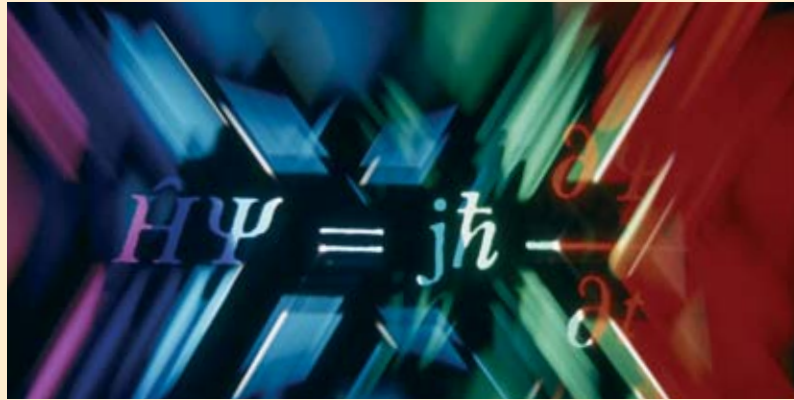
An "artist's impression" of the Schrödinger equation.

tant (symbolized as h) which has a value of 6.626×10^{-34} joule·second.

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 entan-glement*, 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.

The transistor, a name derived from *tran*sfer 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
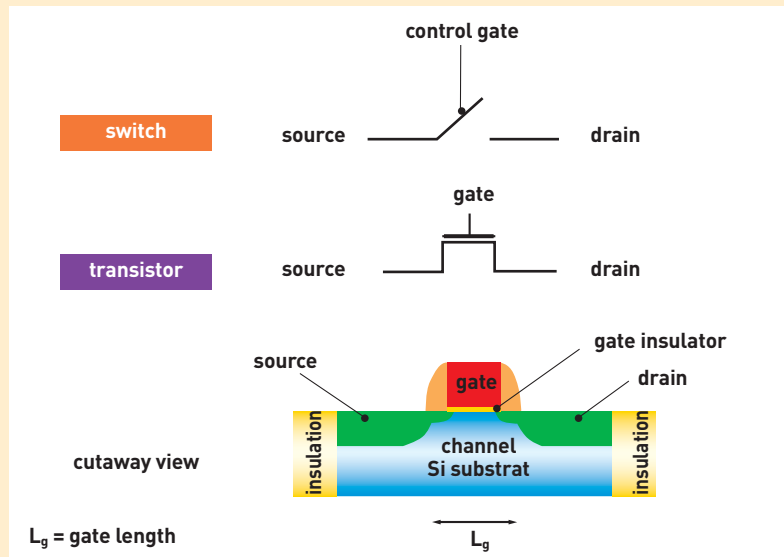

Figure.
A MOS transistor is a switching device for controlling the passage of an electric current from the source (S) to the drain (D) via a gate (G) that is electrically insulated from the conducting channel. The silicon substrate is marked B for Bulk.

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!

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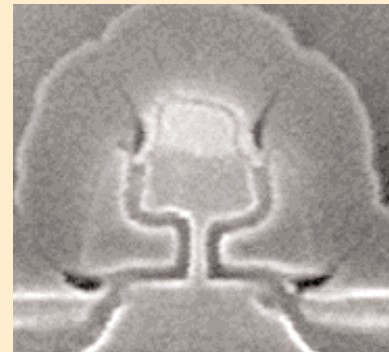
8 nanometre transistor developed by the Crolles2 Alliance bringing together STMicroelectronics, Philips and Freescale Semiconductor.

(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).

Lucent Technologies Inc./Bell Labs

STMicroelectronics

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.

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.

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

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".
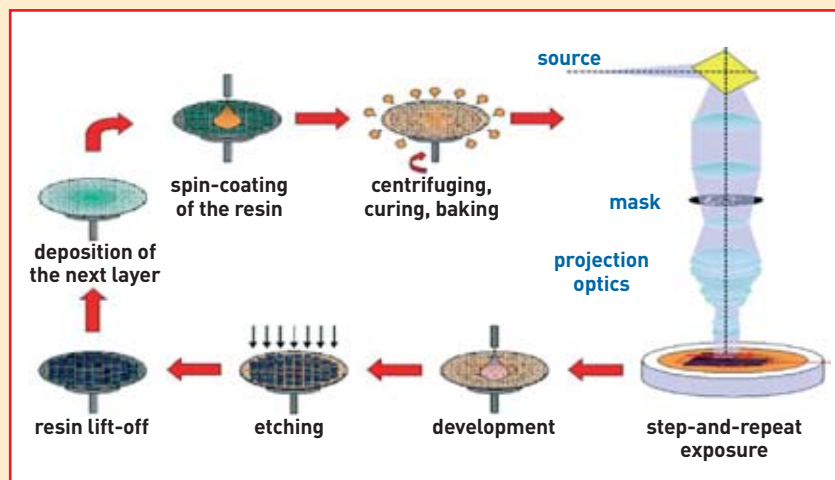

Figure. The various phases in the lithography process are designed to carve features out of the layers of conducting or insulating materials making up an integrated circuit. The sequences of the operation are laying of a photoresist, then projecting the pattern on a mask using a reduction optics system, 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.