

## FROM MOLECULAR BIOLOGY TO BIOTICS: THE DEVELOPMENT OF BIO-, INFO- AND NANO-TECHNOLOGIES

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**Abstract** - Important scientific and technological developments have been achieved in biology during the last few years. Through the application of these developments, biotechnology will have a growing influence on the life sciences and their industrial use in the near future. This influence is evident in new drug design and in the development of diagnostic tests, bioelectronic equipment, and services. It has been observed that three fields of study are becoming increasingly interdependent: the molecular, the computational, and the mechanical. This convergence is achieved through the still closer relationships between biotechnologies, infotechnologies, nanotechnologies and microelectronics (2-8).

**Key words:** Biotechnologies, infotechnologies, nanotechnologies and microelectronics

### IMPACT OF SCIENTIFIC AND TECHNICAL ADVANCES ON RESEARCH IN BIOLOGY

The impact of scientific and technical advances on applied research in biology has been to accelerate significantly the pace of research and the development of new products. Combinatorial chemistry, which allows the parallel synthesis of numerous molecules, has provided traditional screening methods with numerous new ways to explore efficient and less costly treatments. The aid of the

computer in performing molecular graphics and in the simulation of complex processes has facilitated study of the molecular basis of enzymatic recognition and of the mechanisms underlying enzymatic catalysis. It is now possible not only to visualize complex molecules, but to test potential modifications, first on the computer and then in the laboratory. Advancements in polymers and "smart" materials has allowed the development of drug delivery systems with predetermined dosing schedules and localisation. Breakthroughs achieved in the fields of

genomics, bioinformatics and rational computer-assisted drug design have accelerated considerably the development of new therapeutic strategies. Finally, nanotechnologies that use powerful tools such as the scanning and tunnelling electron microscope (STEM), the atomic force microscope (AFM), and cutting-edge biochips, biotransistors and molecular electronics open new avenues for the development of diagnostic tests and therapies. Implanted chips, for example, might alter metabolic functions or correct disabilities. Some of these microstructures may be integrated into more complex micro-factories that include nano-scale laboratories or microelectromechanical systems (MEMS).

The advances in new drug development achieved from the decoding of the human genome rely on a still closer relationship between biology and informatics. The now strategic field of genomics appears in fact to be composed of numerous subspecialties. Genomics would be impossible without the development of bioinformatics. The different approaches of bioinformatics put into play genome data mining (searching for genes in DNA sequence databases), proteomics (application of genomic techniques to the study of proteins and of their functions), structural genomics (three-dimensional analysis of molecules encoded by the genome), and finally, automated analysis of high-resolution molecular structures (X-ray crystallography). The power of these tools leads directly to rational drug design by tailoring the properties of candidate molecules to the probable structure of the target receptor, and they benefit from computer simulations, which, by virtue of fast processors and large memories, facilitate the assessment of beneficial or detrimental effects caused by potential modifications to a test molecule. The large quantity of information resulting from genomic and proteomic studies requires the implementation of powerful analytical techniques. One example is the automated preparation and analysis of information from DNA microarrays, such as the Zeus system developed by the firm of Millennium Pharmaceuticals).

To illustrate in concrete terms the applications and opportunities offered by these new technologies in the fields of drug development or diagnostic testing, it seems advisable to present some examples.

### THE NEW GENE ENGINEERS

The evolution of the life sciences and their applicability to mankind can be envisioned as consisting of four major phases. The period of "descriptive" biology

(classification of species) transitioned to one of "explanatory" biology as the development of molecular biology provided underlying mechanisms. This has progressed into "transforming" biology as genetic engineering and biotechnologies provide the means to intervene in biological systems, and may now be entering a period of decidedly "interactive" biology, as advances in genomics enable mankind to become both the subject and the object of experimentation. New technologies, derived mainly from the fields of molecular biology, chemistry, and informatics, will pave the way to the drugs and diagnostic tests of the future and will have a deep impact on the industrial application of the life sciences.

The descriptive approach of biology was the only one used when, with the recognition of the diversity among living species, it was necessary to analyse, classify and consider inter-relationships. This approach had its own advantages: clarity, a guiding principle, and straightforward deductive reasoning. However, it often obscured the basic mechanisms of biological evolution, the province of explanatory biology. Molecular studies have provided an understanding of the basic processes of cellular function, first in bacteria and then later in more complex cells. The biology of transformation was born when we acquired the ability to reprogram life. Genetic engineering, using restriction enzymes, ligases and transfer vectors, has created a true language of molecular programming. Biology has become more and more a science of "biological information processing" assisted by powerful technical equipments. Thanks to biotechnology, the life sciences and their associated experimental techniques have acquired an industrial dimension. Just as with any nascent but competitive industry, the exploitation of biological knowledge on a global scale has led to products of interest to the pharmaceutical and agricultural industries, chemists, environmentalists, and the energy sector. With the advent of genomics, transgenic animals and bioinformatics, this evolution has reached a new stage, that of interactive biology. As we gain prowess as gene engineers, our enquiries into human biology cannot avoid influencing that biology. Mankind has become both the subject and object of the experiment. We transform the biosphere and this transformation is changing us in an irreversible manner.

Two examples will serve to illustrate this evolutionary progression: research into new molecules by the pharmaceutical industry and the development of new vaccines through the aid of biotechnology and bioinformatics.

Modern pharmaceutical research draws from several

important advances, not only in organic chemistry, but also in molecular biology, genetics, and bioinformatics. In addition to the expertise of investigators, it is necessary to have at hand technical procedures of the first rank. These protocols may be obtained through the sharing of materials and information among several laboratories. Moreover, this exchange of information is one of the keys to success. French laboratories are often hindered by their lack of communication, which reduces the synergistic effects required for developing new pharmaceutical products. For example, combinatorial chemistry and their application to studies of membrane receptors have required more time to gain credibility in the French pharmaceutical industry than in American or English laboratories. However, thanks to important efforts by public authorities and private companies in the field of biotechnology, France has increased its resources, not only to remain competitive, but also to foster innovation. Nevertheless, modern pharmaceutical investigations are particularly long and expensive. During the last 16 years, only 50 new products have resulted from European-based biotechnology efforts. 350 new drugs are currently being developed. The cost of development of a new molecule is roughly 3 billion French francs. The number of European biotechnology companies was 716 in 1996. Today there are 1100. The competition among firms is therefore intense, particularly within Great Britain, which hosts more companies in the biotechnology field than France.

With regard to the development of vaccines, the field has been equally transformed by advances in biotechnology and infotechnology. The former has provided mainly breakthroughs in genetic engineering, genomics, or immunotechnology, while the latter has offered bioinformatics, multimedia communication networks, and computerized databases. The vaccination process actually requires a complex approach to master the development and production of vaccines, the strategies for their deployment, vaccination follow-up, assessments of immunity, and storage in databases of the information needed by researchers, trainers, physicians, epidemiologists, sanitary authorities, or travellers.

The first phase in the evolution of modern vaccines was achieved by means of classical techniques in chemistry and biochemistry. These first steps included killed bacteria and attenuated virus, followed later by "split" vaccines, mixtures of viral subunits, reconstituted and associated with adjuvants. More recently, synthetic vaccines have been prepared from immunogenic peptides or from intact proteins obtained by genetic engineering. Bioinformatics, combined with various biotechnologies,

may be expected to play henceforth a major role in these innovative strategies. For example, comparisons of DNA sequences in genome libraries can reveal those genes best suited to the synthesis and expression of different antigens by a living vaccinal strain. These multivalent recombinant vaccines represent the wave of the future. An equally promising approach is the use of DNA vaccines. Antigenic structures coded by the corresponding DNA sequences provoke a specific immune response. Innovations in the vaccination process also include administration by non-invasive routes, such as absorption by the nasal mucosa or digestive tract. These research and development efforts require a multidisciplinary approach that includes molecular genetics, peptide and nucleic acid chemistry, immunology, cellular biology and, obviously, informatics.

The information generated through vaccine research and development, subsequent clinical trials, or epidemiological follow-ups, must rely, by necessity, on informatics to facilitate communication among investigators, as well as to provide access to scientific, technical, or clinical results. The Internet, search engine databases, and CD-ROMS offer a selection of tools essential to progress in the field of vaccines and its relations with the pharmaceutical industry. The development of the Internet and of multimedia has been achieved relatively quickly, requiring for their utilisation specialised training for researchers, students, physicians and hospital personnel. The quantity of available data requires the implementation of similarly specialized research methodologies linked to efficient modes of communication.

## SMART MATERIALS AND NANOTECHNOLOGIES

Self-regulating, responsive smart materials draw their inspiration from biological models. For many years, we have known the structure of membranes, the role of proteins, DNA, polysaccharides and lipids, and the composition of the molecular micromotors, all of which maintain the intimate functioning of living cells. It follows that researchers have many models from which they learn and copy. The organelles of the cell, such as microtubules, ribosomes and flagellae, can be considered as micromachines built from "intelligent" biomaterials. Indeed DNA, proteins, or polysaccharides are able to transfer energy, to react to environmental stimuli, to change their shape, to recognize other molecules, and to catalyse the building of additional supramolecular structures. DNA, in particular, can be considered as a true

molecular wire capable of conducting electrical current. Perhaps better known is its ability to process information. Progress in the development of smart materials will require the integration of biological intelligent materials and the synthetic materials with which they interface. This evolution could lead, for example, to biotic implantable chips capable of augmenting or replacing various defective organs (e.g., artificial retina, artificial hearing, insulin pump, cardiac stimulators, and defibrillators). Other possibilities include biochips intended for diagnostic purposes or molecular machines capable of executing numerous functions.

Moreover, new tools allow researchers to manufacture at the molecular level, indeed at the atomic level : the development of nanotechnologies based on the capability for the "bottom-up" self-assembly of supramolecular structures, from "smaller to larger". The traditional approach to miniaturisation has usually consisted of removing matter in successive layers, as illustrated by techniques such as the optical photolithography required for microprocessor production. Now, the knowledge of physical and chemical properties and the conditions necessary for self-assembly of complex structures, allow us to approach miniaturisation from the opposite direction. New materials will be synthesized by addition rather than elimination. It should thus become possible to produce thin layers with multiple applications. Such studies were initiated some years ago through the work of Langmuir (1881-1957, USA) and Blodgett (1898-1979, USA). These investigators were able to produce the thin layers that now bear their name (often abbreviated as LB layers) and represent the state-of-the-art in molecular electronics, one of the most promising arenas for smart materials of the future. Several laboratories are currently working on programmable nano-assemblers able to construct complex structures that range from a size invisible to the naked eye to a macroscopic scale. To manufacture these molecular nanoassemblies, one employs the scanning and tunneling electron microscope (STEM) or the atomic force microscope. Using these techniques, matter can be manipulated, atom by atom, allowing the production of materials impossible by other means. Other laboratories work on nanomachines and nanorobots able to take part in "molecular assembly lines" that will produce step-wise the complex materials of the future.

The field of biopolymers has provided some of the most spectacular breakthroughs in smart materials, with numerous applications in biotechnology and medicine. Natural biopolymers such as silk, collagen, cellulose, and

elastin have been known since antiquity. More recently, these natural materials have been replaced by synthetic biomaterials in the treatment and replacement of tissues, organs, or functions in the body. For example, capsules made up of biopolymers implanted in the body release molecules that are able to treat various afflictions. Other biomaterials can be used for prostheses, replacement cardiac valves, or permselective membranes. Several laboratories use collagen, cellulose, and even coral as a matrix on which living cells can reconstitute a damaged or missing part of an organ. For example, nose reconstruction has been achieved by growing skin cells on such biodegradable matrices.

Such "materials of intelligent support" will play an increasingly important role in the domain of tissue engineering. Because of their surface properties, modified biomaterials or synthetic polymers exert a direct influence on the cells covering them. Biological molecular signals imbedded in these materials confer surface characteristics mimicking natural recognition sites. Cells respond to such signals and behave as they do in the living organism. It should therefore be possible to direct cells so that they assemble or self-organize in a programmed manner. In fact, research teams have been able to encourage severed nerves to rejoin by making a temporary bridge with such smart materials.

### **INTELLIGENT PILLS, MEMS AND NANOLABORATORIES**

The advent of nanotechnology is opening a new universe of miniaturized devices able to serve in diagnostic systems or implantable instruments. Several examples of functional instruments have been described during the last few years, such as "intelligent pills" able to deliver drugs according to precise schedules after permanent implantation in the body and nanolaboratories able to analyze in parallel more than 500,000 new molecules per day. One can envision microfactories that contain MEMS (microelectromechanical systems) able to synthesize complex structures, to separate mixtures involving very small concentrations of molecules, or to catalyze various chemical processes. Such nanolaboratories are produced using microprocessor techniques (and often called a "lab on a chip") and can include minuscule channels through which fluids circulate, miniature pumps, microreactors, and separation systems. With their small size and parallel organization, they are able to perform hundreds of thousands of tests per hour.

The intelligent pills produced by Robert Langer take advantage of MEMS technology. In the laboratories of the Massachusetts Institute of Technology (MIT), professor Langer has developed a sub-cutaneous implant with miniature reservoirs filled with drugs and covered with a gold membrane which acts as an anode (10). Under the influence of a weak electric current, perhaps generated by a biosensor, the reservoirs open, releasing in situ the active product. For several years, numerous pharmaceutical laboratories have worked to perfect capsule- or vesicle-based systems for drug delivery that will slowly release their precious products over time. These programmed capsules are controlled remotely and consist of polymer gels which dissolve in water when stimulated with weak electrical currents. The trick has been to manufacture minuscule capsules in successive layers, much like the structure of an onion. Controlled doses of a drug (insulin, for example) are enclosed between each layer of the capsule. Upon passage of an electric current, a layer is eliminated, releasing the drug into the body. This process can be repeated as many times as necessary. The advantage: regular and controlled doses, as well as a high rate of drug delivery. The capsule is implanted under the skin and the electric current is programmed by a microprocessor. The applications are numerous, including delivery of insulin, other hormones or pain-killers. Professor Langer has used this principle to design a bioelectronic pill that is implantable in the body and capable of releasing product over periods of several months. This silicon-based pill contains thousands of small holes filled with powerful drugs. Each hole is in fact covered with a gel sensitive to an electric current and able to dissolve. As a consequence drugs are released at a specific location and at the desired concentration in response to signals received from a controlling biochip.

The American firm, Caliper Technology, has developed a lab on a chip with capillaries of eighty microns in diameter and volumes of a few picoliters. Professor Mauro Ferrari from Ohio State University has been able to manufacture an "intelligent implant" able to deliver insulin to diabetics via living cells lining the interior of a microreservoir featuring a porous membrane. Immunological reactions against the pancreatic islet cells can not come into play because antibodies are too large to pass through the pores of the membrane. It is only possible for glucose to enter and for insulin to exit. These implantable microcapsules may pave the way to true nanomedicine, that is, medicine at the molecular level.

## MOLECULAR MACHINES AND BIO-COMPUTERS

Smart materials will be used more and more as components of analytical equipment. Recently, teams at Berkeley have developed nanoparticles that can be utilized in a wide variety of biotests. At the heart of the tests are "quantum dots," which display vivid colours when they are excited by a light source. The colors vary among different sized particles. Attached to macromolecules such as proteins or DNA, quantum dots enable us to follow molecules during metabolic processes. The colors are perfectly visible with a simple optical microscope. Such techniques may prove to be more reliable than traditional tracers using radioactivity or fluorescence. The applications are numerous in basic and applied research, as well as in drug design, rapid diagnosis, and genetic analysis. Researchers at Berkeley and MIT have been able to manufacture quantum dot crystals from the semiconductor cadmium selenide using a very small number of atoms. The wavelengths of light produced by these crystals varies from the ultraviolet to the infrared, with a narrow bandwidth (and as a consequence, a high specificity). For example, a particle of 2 nanometers emits a very intense green color, whereas a particle of 5 nanometers will produce a vivid red color. A family of quantum dots can therefore generate a spectrum of colors ranging from violet, through blue, green, yellow and orange, and finally to red. Stuck to various molecules such as proteins or DNA with chemical "velcro," such nanoparticles facilitate the visualization of biological process inside cells. They can be developed into a battery of diagnostic tests that are specific, cheap, fast, and automated. It will be possible, for example, to detect in blood different types of virus, all at the same time. The cost of these reagents and ease of use will also be improved. With quantum dots, methods allowing the complete analysis of the 3 billion nucleotides of the human genome are under way.

Another particularly interesting approach to cheap biotests has been pursued by Professor Joseph Jacobson of the Massachusetts Institute of Technology. His team has been able to print functional integrated circuits on plastic rather than silicon. For this, Jacobson and his colleagues have used a modified ink jet printer charged with ink produced from semiconductors. In the near future, they will draw from the field of molecular electronics to make the new plastic circuits compatible with biological systems. Plastic microprocessors impregnated with biological materials may serve as biodetectors, allowing

the continuous monitoring of vital parameters, or even perhaps as transmitters able to transfer telemetry to remote sites. The fabrication techniques used for plastic microprocessors may pave the way to new types of conducting and semiconducting polymers, providing the basis for tomorrow's molecular electronics. Indeed, molecular electronic components may prove to be potential successors to traditional semiconductors. Synthetic components offer several advantages: three-dimensional assembly, made-to-measure customization, miniaturization approaching the scale of biological structures, and the possibility of a direct interface with living systems (9,12,14).

The goal of numerous investigators in molecular electronics is the manufacture of electronic components from biomaterials. These could include bio-computers based on DNA and mass data storage that utilize photosensitive proteins. The idea of DNA-based computation was put forward for the first time in 1994 by Leonard Adleman of the University of California. In a paper that quickly became famous (1), he explained how a biological method could be used to solve a classical mathematical problem, that of the traveling salesman. In its common form, this problem assumes a cluster of seven towns interconnected by roads. The goal is to construct an itinerary for the salesman that minimizes the distance traveled, yet visits each town only once. Several laboratories in the world have been able to reproduce the bioinformatic technique of Adelman, using classical molecular biology and enzymatic methods. DNA strands with nucleotide sequences representing each of the towns in the problem are allowed to recombine in test-tubes. In essence, this strategy takes advantage of many nanolaboratories functioning in parallel. The extraction, sorting, and sequencing of the resulting DNA molecules provide a solution to the question, but only after long and tedious operations. This is why numerous laboratories in the world are working towards automation of the enzymatic processes that would allow analysis of the molecules. Such a DNA biocomputer would analyze problems of high complexity in record time, and would presumably complement the computational powers of semi-conductors or molecular electronics. The advances achieved in the last two years bode well for the future processing of information at the molecular level.

The development of such information processing capability must go in parallel with the development of information storage on a molecular scale. Natural proteins could serve as mass memories for the biocomputers of the future. Photoreceptive proteins, such as bacteriorhodopsin

(BR), are able to convert light directly into a signal. With illumination, the conformation of BR is altered, shifting a positive charge across the cell membrane from the inside to the outside of the cell. The resulting electrical dipole represents an energy storage mechanism. This principle can be exploited to store information and data. Techniques of genetic engineering can be used to stabilize both natural states of the BR molecule. Light of different colors could be used to stimulate a shift from one state to the other. By representing the binary values, 0 and 1, as the two states of the protein, a collection of BR molecules can be used as a mass memory. Moreover, it may be possible to superpose several thin layers of BR, creating three-dimensional memories. Their very small sizes would allow the creation of enormous storage capacities per unit volume.

### BIOTRANSISTORS AND NEUROCHIPS

Other laboratories are trying to manufacture hybrid chips composed of both silicon and living cells. If successful, the potential applications as biosensors or diagnostic tools should be numerous. Early attempts at hybrids have been made by researchers from the University of Berkeley directed by Boris Rubinsky and Yong Huang. They have made a "biotransistor" which has at its heart a chamber in which living cells are grown in a nutrient medium (13). This miniature electronic circuit, smaller than a human hair, is controllable by an external computer. The biotransistor has been produced by techniques analogous to those used in manufacturing microprocessors. Two layers of translucent polysilicon comprise the electrodes, whereas a third layer creates a membrane which serves as a reactive compartment. The different layers are interconnected through a small hole in which human prostate cancer cells are grown. In response to an electric current generated by the controlling external computer and relayed by the surrounding silicon, the cells undergo electroporation, the opening of many small holes in the cell membranes that allow different types of molecules to penetrate. Electroporation has often been exploited to introduce DNA into cells during genetic engineering experiments. In response to the applied current in the biotransistor, the cells emit a weak electric current, indicating in real time that the pores of the cellular membrane are open. The hybrid circuit therefore acts like a diode, inserting for the first time a living component into an electronic circuit. Not surprisingly, these studies have suggested numerous industrial applications and prompted many patent applications. Patients suffering from metabolic deficiencies may be treated specifically in real

time. For example, it may become possible to deliver selectively anticancer drugs to a tumor without injuring neighbouring healthy cells. Hybrids like the biotransistor may foreshadow direct communication between the computer and the biological world and provoke the development of new generations of bioelectronic interfaces between man and machine.

One can imagine in the future how we might combine molecular computation systems with advanced polymers to create intelligent textiles, so called "smart cloth." The use of biosensors and intelligent textiles has already led to the development of clothes which allow physicians to monitor remotely a patient's metabolism. Coaches and trainers can measure metabolic indicators of endurance in athletes. Direct communication between the body and machines creates new possibilities for real time monitoring of major physiological functions. It has become possible to interface with surrounding networks by wearing on oneself computers or other communication devices. We are progressing logically from the portable computer or the portable telephone to the "wearable" computer and the "wearable" telephone. Indeed, why stuff into increasingly smaller boxes the powerful electronic and computer circuits used in telephones or pocket computers when we could weave them into the clothes we wear? Communication tools will gradually be worn closer and closer to the body and eventually create a direct interface.

A further step has been achieved in the development of bioelectronic systems by creating an interface directly between the nervous system and electronic machines or robots. The team of Professor John K. Chapin from the Philadelphia School of Medicine was able to harness a signal coming from the brain of a rat, which then operated by remote control an automated arm. More recently, scientists at Duke University under the direction of Miguel Nicolelis were able to transmit through the Internet across a distance of 1000 km a nervous impulse coming from the brain of a monkey that controlled an articulated arm (11). These contributions are the first steps towards neuroprostheses which could play a major role in the treatment of motor handicaps. Other laboratories have been able to create "neurochips" by growing neurons on silicon wafers. It has even been possible to force the axons from these neurones to follow a predetermined path, suggesting the eventual ability to build molecular circuits from living cells. These neurochips were able to process information and to pass it along to more traditional electronic computers.

Thanks to the emerging discipline which we have called as early as 1981 "biotics," the merging of biology and informatics in smart materials, mankind will enter a

symbiotic state with external information networks (2). These networks will eventually form the nervous system of a superorganism, and human beings will represent individual neurons within that system. As both the subject and the object of the biological revolution, man holds in his hands the future of the human species. Symbiotic man can live in harmony with the planetary organism he has created, or he can be subjected to the power of a Big Brother on a global scale. Mankind stands at the junction between a "microworld" -which defines in part our individuality- and a "macroworld" on which we act and which, in turn, defines our existence. Our lives depend on the molecular and microscopic, proteins, genes, cells..., but those lives also depend collectively on our actions within society and the ecosystem in which our development and future will evolve. The recently acquired knowledge of the microworld and the consequences of our actions on the macroworld change drastically our relations with nature and ourselves. Today we can intervene directly in our biological evolution through genetic engineering, genomics or transgenics. We are acquiring the power to modify adversely our societal and ecological environment by increases of economical disparity, pollution, or the modification of natural cycles. However, if we make wise decisions, we can satisfy the needs and desires of humanity.

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