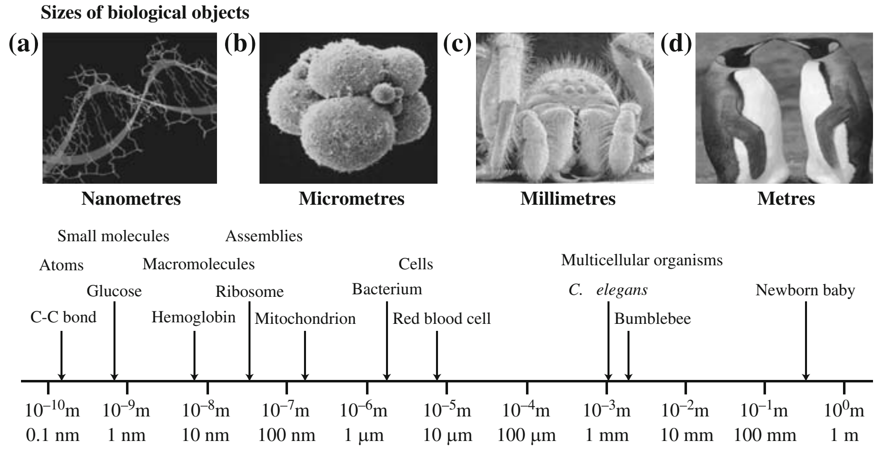
Preface to the French Edition

The Size of Biological Entities

From ancient times until the invention of the optical microscope by Van Leeuwenhoek in the seventeenth century, humankind could only study those biological objects that were visible to the naked eye, which means to say, bigger than one millimetre across. Optical microscopy took observation down to the micron, an improvement by a factor of a thousand. Then, in the last century, the invention of the electron microscope opened up the world on a scale of ten nanometers. Today, the nanometer and even the angstrom unit (0.1 nm) mark the limits of resolution in a whole range of modern molecular imaging techniques. Indeed, since the middle of the twentieth century, crystallographic studies of DNA and proteins have gradually revealed the structure of biological entities with a resolution slightly greater than 0.1 nm, which is the size of a hydrogen atom. Extremely complex protein molecules, built up from several smaller proteins, have now been successfully characterised and their three-dimensional coordinates can be obtained from data bases.

Molecular imaging has made considerable progress since the heroic work carried out by crystallographers at the Cavendish Laboratory in Cambridge. It is possible today to obtain the complete structure of a single molecule, whatever its size. The most difficult thing when working with a single molecule, if it is complex, is to be able to visualise its motion within a protein or, an even more delicate task, within a multiprotein structure. Electron microscopy and crystallographic techniqes can usually only be applied to preparations in which there is no molecular motion, although over the past twenty years or so, NMR techniques have become available to follow the internal motions of small proteins with a size of a few nanometers.

What is really new about the novel techniques described in the present book is that it is now possible to study the functioning of a living cell with nanometric resolution, i.e., on a scale a million times smaller than what can be observed with the naked eye. This is a genuine technological revolution, not restricted to observation of the living world, but which can be used to build



biological objects. One can now contemplate the reconstruction of a cell from its molecular components. Such a construction will exploit the self-assembly properties of biological constituents, using the fact that proteins recognise each other and can self-assemble. But it will also be possible to guide this assembly process using recently developed physical techniques.

The Convergence of Nanoscience and the Life Sciences

Physics and biology have long been in contact. The beginning of the twentieth century saw the fruitful collaboration between chemistry and biology, which made it possible to devise medicines, not from the plant extracts provided directly by nature, but by chemical synthesis from scratch, leading to a significant increase in the number of effective medicines available to treat an ever larger number of illnesses. From the middle of the twentieth century, the methods of physics were successfully applied to the living world, leading to the new field of molecular biology. One of the first conquests of this new field was the determination of the three-dimensional structure of nucleic acids and other macromolecules using the methods of X-ray diffraction, at which point crystallographic studies were effectively extended to biology.

Today one can speak of a new convergence, this time between the various branches of the nanosciences and the life sciences. One can already begin to imagine how this encounter will revolutionise our approach to the life sciences, just as microtechnology and nanotechnology have completely recast the fields of data processing and communications.

Everyday experience shows us that the capabilities of our personal computers double roughly every 18 months, while their cost remains approximately constant or even decreases. This has been made possible by the extreme miniaturisation of electronic devices and the reduction in size of the transistor. In

1950, a transistor would have measured several centimeters across (10^{-2} m), while today, it occupies a space of just a few tens of nanometers (10^{-8} m), a reduction by a factor of about a million in the linear dimensions. A genuine revolution has been occurring under our very eyes over the past 25 years. We can no longer fully appreciate the essential role played by electronic components in our everyday environment, from the portable telephone to the car.

This technology requires engineers to be able to observe and manipulate matter with a resolution varying between the micron (10^{-6} m or one millionth of a meter) and the nanometer (10^{-9} m or one billionth of a meter). Over the last few years, nanoscientists have also developed investigative methods appropriate to these new structures. The atomic force microscope (AFM) serves as an example, used to displace atoms one by one and place them according to specific arrangements.

For the purposes of comparison, the components of living organisms are also of micron or submicron dimensions. Our blood vessels and bronchial tubes are capillaries of diameter a few microns transporting fluids or gases. The cells, functional units of living beings, are tiny globules measuring a few microns across. Within the cells, chemical reactions occur within compartments of a few attoliters (10^{-18} L). Compounds such as medicines, chemical mediators, metabolites, and so on, enter the cells via pores measuring a few nanometers in aperture. Enemies of the cell such as bacteria or viruses are also micrometric or even nanometric entities. For example, the envelope of the influenza virus is built up from several protein macromolecules and has a diameter of a few hundred nanometers.

Operating on this kind of length scale, and often subject to the same laws, it was only natural that nanotechnology would eventually come into contact with the biological sciences to form the joint venture we now call nanobiotechnology.

There is no point trying to give an exhaustive definition of nanobiotechnology here. Indeed, there is still no definition that would obtain a general consensus. Some authors see this as an inevitable state of affairs in a newly born discipline, or one that is just coming into being. One may note in passing that some definitions are perhaps unnecessarily restrictive. For example, the National Nanotechnology Initiative, created under the auspices of the United States government, defines nanotechnology as anything involving structures with dimensions less than 100 nm. The problem with this kind of definition is that it runs the risk of leaving out devices that currently manipulate objects or fluids rather on the micrometric scale, not to mention truly macroscopic devices, but which merely make use of nanometric objects or structures.

In order to glimpse the way nanobiotechnology may develop in the future, it is tempting once again to draw a parallel with the rise of nanotechnology in the field of data processing and communications. Indeed, one can already discern two lines of attack, still quite distinct, which approach the question from completely opposite directions. The so-called top–down approach consists in miniaturising the investigative or analytic tools we possess in order to move from subjects of centimetric or millimetric dimensions to ones with the same function but much smaller. In a sense it is as though one were climbing down the length scale. The opposite approach aims to climb up this same scale by arranging nanoscopic elements likes atoms or clusters of atoms into novel structures, assembled in some appropriate way. It is clear that today most nanobiotechnological activity subscribes to the first approach, for while the second, bottom–up approach remains extremely attractive, it still faces many difficulties. One of these is that we are unable to predict the properties of elements conceived in this way, working solely from the knowledge of the individual properties of their components. In association with these two approaches, new imaging and measurement techniques are being developed to observe phenomena that have now become accessible to us.

There can be no doubt that within a few years these new tools will completely revolutionise our understanding of the most intimate mechanisms occurring within the cell, on a molecular scale and in real time, opening the way to novel and extraordinary therapeutic prospects.

The present book provides a cross-section of current understanding in several areas of nanobioscience. It is divided into three main parts:

- *Biological Nano-Objects.* This part describes the basic building blocks, i.e., DNA, typical biological structures, etc., used as example and support in nanobiotechnology.
- *Methods of Nanobiotechnology.* Chapters here present the physical, chemical and electrical tools and methods used to investigate biological nano-objects.
- *Applications of Nanobiotechnology.* The last part deals with the most common of current applications, pointing the way from nanobiotechnology to nanomedecine.

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