Introduction: The Essence of Life and the Labyrinth of the Genome

During this century, all scientific domains have been marked by important discoveries, often made by extraordinary researchers and by a dynamism which can truly be considered a permanent revolution. Since 1900, scientists and their ideas have brought changes so sweeping in their scope that they have modified our perceptions of the nature of the universe. The first of these changes was in physics, with biology hot on its heels. The revolution in physics started in the beginning of the 20th Century with the theories of quantum mechanics and relativity. It was concerned with the inside of the atom and the structure of space-time, continuing well into the 1930s and throughout the development of quantum mechanics. Most of what has happened in physics, at least until recently, has been the result of those three decades of work. With the Manhattan Project, physics was restructured at the deepest level. A new form of research called “Big Science” had been invented.

In biology, the modern revolution began in the mid-1930s. Its initial phase, molecular biology, reached a plateau of maturity in the 1970s. A coherent, if preliminary, sketch of the nature of life was set up during these decades, in which a mastery of the mechanisms of life was increasingly sought after, particularly for industrial use. There would be a second phase to the biological revolution, that of genetic engineering and genome research. The consequence of this contemporary revolution was the advent of a new form of research in biology. It is the harbinger of the eminent role that

biology will have in the evolution of society, and the effect this will have on our way of life and thinking.

Several decades after physics, biology has also become "Big Science" with the genome projects and is undergoing a revolution of a structural, methodological, technological and scientific nature. Less than half a century after the 1953 discovery of the structure of deoxyribonucleic acid (DNA) by James Watson and Francis Crick, the great dream of decoding the entire sequence of the genome of an organism became a reality. After viruses and other "simple" organisms, scientists were starting to work on the genomes of "complex" organisms.

In 1989, the United States initiated the Human Genome Project and several nations, including Japan, became involved in genome research, setting up large biotechnology and sequencing programs. At the same time, the biotechnology programs funded by the European Economic Community (the European Union) provided support for a consortium of European laboratories to sequence the genome of the yeast *Saccaromyces cerevisiae*.

Consequently in 1992, for the first time, an entire eucaryote chromosome, in the form of chromosome III of the aforementioned baker's yeast, was sequenced. In addition, the European consortium and its international collaborators managed in 1996 to break another record and obtain the entire sequence for the yeast genome, some 14 million base pairs. During this gene race, Europe managed to maintain its position as a leader in world genome research and provided the international scientific community with a tool whose usefulness, especially for our understanding of the human genome, becomes increasingly clear.

Scientific and industrial competition continues. The number of organisms for which the entire genome sequence has been read is increasing. Along with the yeast genome and smaller genomes that are nevertheless of biological or economic importance, we expect a forthcoming completion of the sequencing of the 100 million base pair genome of the nematode *Caenorhabditis elegans*. The first pilot programs for systematic sequencing of the human genome's three billion base pairs have been completed, making way for larger sequencing projects of whole human chromosomes.

A technological, scientific and economic revolution is under way, a revolution whose effects are already being felt and which will shake the fields of human and animal health, the pharmaceutical business, the agro-food industry, our environment and society as a whole. As announced by the scientists and publicized by the mass media, the prowess of the new biotechnology, the cloning of genes and even of entire animals (sheep and monkeys) as well as the prophecies of several great scientist pundits bring out fascination and concern within us. Science also produces perplexity.

Despite the importance of this new biology, of genome research and of the aura that surrounds them, it seems as if the general public is somewhat in the dark as to the real issues, progress, possibilities and risks. The history of these achievements is often misunderstood, even by some of the people involved in them. In view of the ongoing revolution and its consequences, whether scientific, political, economic, social or ethical, and the public's general misunderstanding of them, there was need for a book presenting the origins and the history of genome research, its current status and its future. This book hopes to fill that need.

At the source of this book there is a wonder, a passion, but also the chance meetings that led me to write it. The wonder is that of the philosophy of science and the window it provides on our world and its secrets, Man and his place in the universe. The passion is that of understanding science as it evolves, the challenges that human intelligence seeks and the risks linked to the discoveries and revelations of this increasingly powerful field of biotechnology. I first thought of writing this book during my post-doctoral period between 1993 and 1996 at the Université catholique de Louvain. It was during this time that I was fortunate enough to meet Professor André Goffeau who was then coordinating the European yeast genome sequencing project. During many conversations he opened up his archives and his laboratory to me, as well showing me the fascinating and multidisciplinary field of genome research, which lies at the frontier between fundamental and applied science, and where technology and biology, research and industry, economy, politics, law and science all meet.

Fascinated by the work under way and carried by my enthusiasm for the research despite the obstacles and difficulties involved in this endeavor, naturally I was taken by the idea of a book on the European and world effort to sequence the genome of *Saccharomyces cerevisiae*, but also on genome research as a whole, its origins and developments. I was immediately supported by Professor Goffeau who, prompted by some of his colleagues, was looking for someone to write the "little tale" of the European and world effort to sequence the yeast genome. As I browsed through the archives, I became more and more convinced that the origins, the size, and the consequences of the changes in biology and society in general, wrought by the initiators and managers of the genome project, had to be communicated to the world at large.

Academic work always uses a strict method of approach. This means an ordered process of disciplined progress. Like any study this work needed a perspective, an approach. But because it is a story, a rational approach would have been limiting and unsatisfactory, which accounts for the anecdotes included in this work. Ideas are often born of happy coincidences, during a conversation, while reading an article or meeting someone, or during a conference, and most often if not always in a propitious scientific, economic and sociological context. They generally begin as an attractive hypothesis. If the idea is stimulating enough, work begins in a new field or domain. It's often not a linear process. Various eddies influence the flow of scientific construction as it is taken away from the official paths and then often seems, to use a term from physics, chaotic and subject to sudden changes of direction. But that means surprise, and surprise is what researchers live for and from.

Besides contributing to an understanding of modern biology and biotechnology, this work also hopes to serve to explain scientific practice, its means, its rules, and its presence amongst us, in our individual and collective lives. In particular, it seeks to underline, through the history of biotechnology and the genesis and development of genome research, the deep relationship that links these domains, while stressing that they face not only the material world but society as a whole. Biotechnology and genome research goes beyond the purely operational perspective to embed itself resolutely in human history, in communication, negotiation and communal creation.

This work shows that the bases of biotechnology and the genome projects lie within historic projects in their own particular political, socio-cultural and economic context. It also demonstrates through its investigation of the history of this ongoing biological and particularly biotechnological and genome research revolution, the human aspect of science and the creativity which is inherent to it. It attempts to, through its philosophical and ethical reflections, clarify the manner in which they are products of society as well as an influence upon it.

To trace the story of biotechnology and the genome programs, in particular that of the yeast genome, one has to take into account the various groups affected, watch the development and change of their various scientifico-socio-economic aspects in reaction to conceptual and technical modifications and the rapprochement of previously quite separate disciplines. One single method would therefore not allow us to understand the highly multidisciplinary history and evolution of biotechnology and the genome programs. The multidisciplinary components involve:

– The scientific and technical bases
– The multisectoral applications
– The industrial and economic dimensions
– The national, European and international political levels
– The institutional and international organizations
– The legal dimensions
– The ethical dimensions
– The "public" dimensions

Each of these aspects must be taken into account.

Since it will be the record of some of the most modern developments in biology, in places this book will be unavoidably somewhat didactic. As for approach and methodology, it should be pointed out that for the purposes of this work, scientific creativity is not just seen in an abstract fashion, either conceptually or philosophically but mainly seen through the people at the root of it, through their social and intellectual biographies, the influences they have had, their motivations and the spirit in which they undertook their

studies. Great projects cannot be separated from the destinies of the people involved, nor can the intellectual process be separated from the many meetings and opportunities that happen in the course of a life. Scientific creation is, more so today than ever, incompatible with a closed society. Any rigid approach might lead to the pitfall of revisionism, and as Martin Heidegger wrote, "the inability to produce any point of view other than that of the author". It is necessary to point out to what extent apparently objective, upstanding arguments are personal and often empty, their rigorous formality masking the lightness of the ideas. For this reason, and in order to respect the story of modern biology and in particular its multidimensional nature, the historian-philosopher must go to meet those actually doing the science, dive into their culture, follow them in their paths and pilgrimages, understand the web of their community, their intellectual, cultural and social evolution and accept the humility needed to understand pure fact.

This book, on the development of biotechnology and the genome programs, owes a great deal of its substance to the author's interaction with the work and personality of Professor André Goffeau. It also depends on the author's observations as a listening, watching, external observer right inside the coordinating laboratory and community of the yeast genome project, much as an anthropologist would live with a far-flung tribe. Aside from these interviews, it also gained much from the archives of the yeast genome project and DG XII (Directorate General for Science, Research and Development of the European Commission in Brussels). Many documents, both biographical and scientific, were sent to the author by various laboratories and international institutions (DOE, NIH, HUGO, and the embassies) which helped to reconstitute the scientific, technical and economic environment to which the first genome projects were born.

This work is directed not only to the scientific community, but also to the lay reader. In its progression from the origins of biotechnology and its political and economic interpretation by the great nations, this book retraces the birth of the first national and international biotechnology projects. On reaching the end of the 1960s, it reveals the foundations of the modern biological revolution, in particular the techniques of genome sequencing and analysis and highlights the importance of Japan in this context on the

international research stage. This book also describes the completion of the first genetic and physical maps and the political and scientific genesis of the American Human Genome Project. It then follows with a detailed analysis of the establishment of European biotechnology strategy, the birth of the first European biotechnology programs and the yeast genome project.

After describing the main stages of technical, administrative, political and scientific successes leading to the yeast genome project and its major aspects in Europe and world-wide, this work mentions the other genome projects in order to provide the reader with a wide view of the importance and consequences of this science ongoing at the dawn of the 21st Century, as well as greater knowledge of current activities at the national and international level. In the last chapters, it considers the challenges to be overcome as well as the perspectives opened to us by systematic sequencing projects.

The conclusion, which is not meant to be a once-and-for-all answer, brings the reader clearer understanding of genome research at the biological, biotechnological, and current socio-economic level. It underlines their meanings, justifications and their perspectives. Through an epistemological analysis of the "dreams of the rational", it voices our confusion at the new definitions of life. It tries, with a critical eye, to find limits and lacunae, taking into account the ethical, social and political problems linked to the advent of this bio-society heralded since 1970 and which raises such hopes and fears.

This work is also a testimony to a new way of carrying out biological research. For some veterans who have survived from past generations of researchers, this change in the way science is being done, particularly in biology, is surprising and even shocking. The underlying determination to progress is still — but for how long? — that of curious scientists probing the mechanisms of nature. Of course, it is also the hope that some of the new knowledge will serve to better the human condition. But the main element, the main permanent and irresistible drive is most often the simple desire to discover. In fact, to work on hard biological problems, is for the biologist the greatest pleasure in the world, their reason for existence. However, when

you hear the description of the strategies, successes and risks of genome research, I fear that part of this pleasure is being taken away, in this current socio-economic context that restricts the opportunity to express and accomplish all that is possible to each of us.

It is true that some aspects of research have not changed, for example the long and feverish hours of waiting for an experiment's result, the surprises, the disappointments, the joys of attaining what was hoped for, of finding something, of contributing a snip of new understanding, of participating in the launch of an idea, of being part of that brotherhood sharing the same obsessions and speaking the same private language, the tedious task of writing articles and giving conferences... But other aspects have become very different than they were in the past. Competition has come knocking at the gates.

Of course, there has always been competition in research, especially when the expectations of the new information, are as high as they are today in the domain of genome research. But competition today sometimes looks more like a war at the national level and although cooperation continues and even develops science it does not bode well. Whereas before, science happened at the laboratory level, the new projects are at national level, involve colossal budgets and have fundamental economic consequences. In these projects individuals fade into the mass, strategies overlap with each other. The process looks like that previously seen in industry; from small firms to groups, chains and international holding companies.

At the local level, there is a real problem with jobs. There are more young researchers than before, in the early stages of their careers, who face a hierarchical pyramid with a limited number of university posts and stable positions in industry, a hierarchy often conservative and typified by a certain inflexibility. The breathtaking rate at which they work and publish is the consequence of this as well as the result of the new methods being used. These methods have allowed discovery in the field of life sciences to accelerate to an unprecedented pace, but they also have deep consequences in the organization and work patterns of laboratories, leading to ever larger teams of young researchers, mostly at the thesis or post-doctoral level, each

with a task linked to a minuscule element of the global picture, and each considering the success of that task as the hook from which their future career depends. The fight to survive is therefore more ferocious, positions increasingly rare and financial support ever more scarce. Worse, a large number of laboratory directors and professors neglect their students, being preoccupied with their own ambitions. In this context, as an independent and privileged witness, the author pays due homage to Professor Goffeau for his devotion to his laboratory, his researchers and to his students.

Another source of worry, money, has become a far more crucial problem. The story this book tells, shows that for some scientists, faith still can move mountains, that the pleasure of discovery can still drive scientific activity with the joy or even hope of a result, that setbacks, dead ends, unsuccessful experiments, can still be forgotten. But this pleasure has a cost and the cost can often be high. There are sacrifices made, long periods away from the family, career uncertainty (for many years), the dominance of science in a researcher's life often to the detriment of family life — has not more than one scientist's wife said "we are a *ménage à trois*, my husband, science and myself"? But most of all, there is the risk that this scientific activity be blunted by the increasingly tough competition currently reigning in scientific circles and which pervades far beyond the academic sphere. In the pages of this book it becomes apparent that there are new considerations on the scene, considerations of an economic nature, the large biotechnology companies running in the gene race are continually throwing more and more money at targeted research themes. The pressure exerted by the Member States on the European Union, during the negotiations for the Vth Framework Program, for a far more applied orientation to funded research, is symptomatic of this global movement in which research must be productive economically, and furthermore productive in the short term.

In less than 20 years since the end of the 1980s and with unprecedented acceleration, life science has migrated from being a pure science to being a hard science with endless applications and with fundamental industrial, economic and social expectations that will change our lives, with of course both the advantages and the dynamism it will bring but also the deep modifications in the way science is built and carried out, modifications that

will also have counterproductive effects. Not least of these will be the risk that communication of information within the scientific community, even through chatting, will be compromised.

If anything takes away the pleasure and dynamics from research, it will be the excess of confidentiality. The scientific networks described in this book, constituted of national and especially international cooperation, only work because the researchers and policy makers share what they know, at congresses and during private conversations... Telling other scientists what you have found is a fundamental part of the fun in being a scientist. Now that private firms are investing massively in genome research, it is easy to worry that events might end this privilege, a worry justified by the fact that life science information is more and more applicable to Man, with all the risks that that may mean for the future.

This book hopes to provide the public, often kept in the dark, the opportunity to keep current on the new progress in biology and the risks linked to the new direction science is taking. The only way to control them is to transcend both the approach of the geneticist and the industrials, and to remember that living beings are more than just vectors for the transfer of genetic information from one generation to the next, that human life, and life in general, is much more than the running of a computer program written in DNA. But maybe this is all an illusion? Might there still be a place for science with a conscience, when economic interest rules and profit is king? In any case, science in order to save itself must build stronger links with society and no longer remain in an elitist ivory tower. That is the only way it will be able to link up once more with a political and ethical conscience. What is a knowledge you cannot share, that remains esoteric, that can only be damaged by popularization or be used by industry in destructive processes, that influences the future of societies without control of itself and which condemns citizens to be the subjects of a rationality and technique that they no longer understand even as they are ignorant of the problems of their destiny? As Edgar Morin points out in "*Science avec Conscience*", "empirical science deprived of forethought, like purely speculative philosophy, is insufficient, conscience without science and science without conscience are

radically mutilated and mutilating." In genome research, a science without conscience risks to ruin Man, to paraphrase Rabelais. A new alliance has to be born. The author modestly hopes with this book to bring the reader the chance to understand what is going today in the field of genome research and therefore contribute to communication at the boundaries of three cultures: the scientific, the humanist and that of the citizen through the media. He hopes to have forged a link between scientific problems and problems of the citizen, who more than ever needs a vision of the world but also to debunk science from its fetish-religion position.

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to Virgilio and Nahui-Ollin
with love