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The Death of Molecular Biology?

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ABSTRACT - In recent decades the expression "molecular biology" has progressively disappeared from journals, and no longer designates new chairs or departments. This begs the question: does it mean that molecular biology is dead, and has been displaced by new emerging disciplines such as systems biology and synthetic biology? Maybe its reductionist approach to living phenomena has been substituted by one that is more holistic.

The situation, undoubtedly, is far less simple. To appreciate better what has happened it is necessary to acknowledge the following: the intial project of molecular biologists was not a reductionist one, but an attempt to naturalize the phenomena of life by using the epistemological principles of physics as a model; and, it is necessary to distinguish the early stages of molecular biology, and the later aggregating process which gave it its present characteristics. Only one of these characteristics, the importance of the informational vision, has been seriously challenged in recent years. But it is obvious that the ambition of most early molecular biologists to discover simple rules and principles explaining all of biological facts has vanished. The pendulum has now moved toward the study of the diversity generated by a long evolutionary history.

KEYWORDS – Reductionism; naturalizing life; molecular biology; mechanistic explanations; scientific discipline; information

The expression "molecular biology" is less and less used by biologists to designate their own research area. They present themselves as cell or developmental biologists, or as involved in the development of the new post-genomic technologies, in the description of the proteome or of the transcriptome. The same is true at the institutional level: "molecular biology" is no longer used to describe laboratories or label departments and chairs. The same also holds for journals. Certainly *The Journal of Molecular Biology* has lost its former prestige. New disciplines and sciences are emerging more in keeping with current research agendas: systems biology, synthetic biology, and the full set of "omics." Even research on what was previously considered the core of molecular biology, the study of gene expression, is no longer considered as belonging to this discipline. Biologists studying epigenetic

modifications of chromatin would probably prefer not to be named "molecular biologists."

These facts are concomitant with the criticisms directed at molecular biology. It is condemned as having represented a period of a too reductionist vision of organisms in contrast to emerging new disciplines that favor a more global approach. Some even consider the age of molecular biology as having been a period of extreme misorientation of biological research, an error that it is high time to repair.

In contrast with this negative view, a neutral observer will have little difficulty in noticing that methods and concepts of molecular biology have a preeminent place in publications of biologists. The mechanistic explanations of molecular biologists are omnipresent, as well as use of the techniques of genetic engineering. This also holds true for journal articles published in the emerging disciplines of systems and synthetic biology.

The difficulty in appreciating the true place of molecular biology is not new. Historians of science have long noticed that molecular biology did not fit the usual criteria retained for a discipline (Olby 1990). Molecular biology can no doubt be identified with a particular area of research or with a new vision of biological phenomena, more than with a discipline. What characterizes it is the description and explanation of biological facts at a specific level of organization, that of macromolecules. The expression "vision" is therefore well adapted: the outpouring of knowledge has been specifically focused on the macromolecular level.

The nature and future of molecular biology have not been completely solved by these early debates. However, the present rapid transformations in biology helps us to appreciate better the significance of the "molecular revolution," and to cast a new look on its future.

To do that, I consider it necessary, as a first step, to reexamine the roots of the new molecular vision and to distinguish them from its progressive construction in the decades following its emergence. I will then consider whether the molecular vision has been challenged in recent years and how we can position the episode described as "molecular biology" in the long history of the life sciences.

The Origin of the Molecular Vision

When one considers the general movement of biological descriptions since their resurgence in the sixteenth and seventeenth centuries, there was a progressive emphasis on lower levels of organization: the organisms first, tissues and organs at the end of the eighteenth century

and early nineteenth century, cells in the middle of the nineteenth century, and subcellular structures such as the chromosomes around 1900. This regular downward movement permitted by the invention of the optical microscope and in the twentieth century transformed by the development of the electron microscope, was made possible by constant progress in the construction of optical devices and the preparation of biological samples.

Different periodizations of molecular biology have been proposed by historians. Some consider that what characterizes molecular biology and distinguishes it from disciplines that predated it, such as biochemistry and genetics, is the informational vision with which it is pervaded. Such a model is supported by the abundance of informational expressions within molecular biology. In this historical account, molecular biology was a consequence of the Second World War, of the information theory and computer science which were developed to answer the needs of communication, and of computing generated by the war. I will adopt another periodization supported by Lily Kay in her pioneering book (Kay 1993) and by many other historians, positioning the birth of molecular biology earlier, in the 1930s. The rise of molecular biology found its initial impetus in the development of new technologies that allowed the study of a domain of the living world which had previously been partially absent from the descriptions. It stretched between the molecules studied by organic chemists and the cellular structures barely visible under the light microscope. This was the domain of macromolecules, so named when the colloid theory progressively vanished in the 1920s and the existence of macromolecules was clearly demonstrated.

But these technological developments were concomitant with an effort to "naturalize" the phenomena of life, to uncover the veil of mystery that had so far covered the intimate functioning of organisms. The sheer ignorance of what constituted "living" was considered as an intellectual scandal by many scientists, in particular physicists. This scandal became more obvious with the rapid progress made in physics in the three first decades of the twentieth century: matter and energy had been fully naturalized. The same had to occur for life.

Can these ambitions be in any way called "reductionist?" The fact that physics was considered as a model and the proclaimed intent was to naturalize organismic phenomena, are not sufficient reasons to answer in the affirmative. Even the development of technologies aiming at describing what happened at the level of macromolecules cannot be considered per se as a reductionist program. The objective was to obtain information on a domain which had been so far a "black box," and obscured by the models of colloidal chemistry. It did not mean that

this level would be the "explanatory" level. Its increasing place was not preformed in the early efforts to describe it. In fact, there was no agreement among the founders of molecular biology on the level and way in which living phenomena had to be naturalized. The reductionist approach of crystallographers, such as Max Perutz, was in sharp contrast to the ambitions of Max Delbrück, one of the founders of the phage group, who had set out to discover new laws that would explain global phenomena specific to life, such as reproduction (Fischer and Lipson 1988).

To acknowledge better this diversity of attitudes among the first molecular biologists, I examine the case of two French biologists who played a major role in the development of molecular biology and whose accomplishments reached international visibility, Boris Ephrussi and Jacques Monod. Ephrussi made decisive contributions, from his early work with George Beadle, which finally led to the "one gene – one enzyme" relationship (later established by Beadle and Edward Tatum), to the establishment of mitochondrial genetics, the development of cell fusion technique, and the early study of embryonic stem cells (derived from teratocarcinoma; Morange 2008a). He was an admirer of the epistemological principles of physics, of the ability to derive laws from simple general principles, and afforded to genetics a preeminent place in the development of biology during the twentieth century precisely for the reason that this discipline shared with physics the same characteristic of abstraction (Ephrussi 1979). Nevertheless, throughout his life Ephrussi remained an embryologist and at the end of his career he vehemently opposed the direct application of the genetic regulatory models derived from the study of microorganisms to the explanation of differentiation and development. There is no sign of a simplistic reductionist view in Ephrussi's work.

The same is true for Monod, co-author with François Jacob of the operon model. Monod was also convinced of the superior epistemological value of physics, and believed that principles preeminent in physical explanations, such as symmetry, had their place in biology. This conviction led him to propose the sophisticated allosteric model to account for the characteristics of regulatory enzymes. These proteins were formed of multiple identical subunits that might exist under two different conformations. The transition between these two different conformations was coordinated in order to maintain the symmetry of the macromolecule. Monod also considered that the place occupied by teleological arguments in biology – the justification for the existence of structures by the "functions" they fulfill in organisms – was a scandal, and for him the true motivation to turn toward biology was to overcome

it (Judson 1979). Reductionist approaches were simply one way to lift the veil of mystery surrounding organisms, a methodology that had been eminently successful in physical sciences.

Therefore, molecular biology was not the result of a reductionist program, but an attempt of *aggiornamento* of biology, by reducing the gap existing in its descriptions (between simple molecules and subcellular structures), and by employing the epistemology of physics as a model. Moreover, historical models that give one institution or one institute a major role in this story (the Rockefeller Foundation and Caltech for Kay) are obviously much too narrow in their perspectives (Kay 1993). Other institutions created similar research programs in countries other than the United States, all with the same objectives, and quite independently from the Rockefeller Foundation. One outstanding case was the Institute of Physico-Chemical Biology (IBPC) created in France by Jean Perrin and Baron Edmond de Rothschild, with the financial support of the latter's foundation, to bring together physicists, chemists, and biologists in efforts aimed at unravelling the fundamental mechanisms operating in organisms. The development of new technologies derived from physical knowledge constituted a part of the research program at the IBPC which, from its creation right up to the Second World War, was an active player in what in retrospect can be called "molecular biology" (Morange 2002).

The Progressive Construction of the Molecular Vision

What finally emerged as molecular biology in the 1960s was not written into these early motivations and initial attempts, but the result of a complex historical process. This is the reason why some institutes which had been successfully involved in the first hesitant steps in the development of molecular biology did not participate in the rise of molecular biology two decades later: such was the case of the IBPC. The difficulties faced by this institute during the Second World War, the disinterest of its researchers in bacteria and viruses, considered as in the domain of medicine and not biology, as well as its physicalist orientation that left a too limited place for biological explanations, prevented it from being active in the molecular revolution of the 1950s; this role was left to another French institute, the Pasteur Institute.

The new molecular vision that emerged in the 1960s was not preformed in the first steps of the 1930s. Essential evolutions had still to occur, as I shall briefly summarize in the following.

The first is the informational vision as described in the foregoing and

that progressively invaded molecular biology. Much has been already written on the development of this informational vision. These focus on its link with the technological and conceptual developments that occured during and immediately after the Second World War – namely the development of information theory, computer science, and cybernetics – but also its relative independence from the scientific core of these disciplines (Kay 2000). It was a more general cultural influence: while not driving the work of biologists, it created a sort of mold in which the different observations on genes and the relations between genes and proteins, adopted their final form. The influence of geneticists, the increasing role of genetic methodologies – for the study of bacteria and bacteriophages – and the informational vision contributed to give DNA the preeminent place it still has today in biological explanations.

But a parallel, quiet, and slightly later transformation, also took place: the conviction, progressively formed, that many phenomena occuring in organisms are explainable at the level of macromolecules, and that these explanations are mechanistic. The name "molecular biology" was not the most ideal choice; "macromolecular biology" would have been far more appropriate and significant.

It is generally admitted that such an evolution was a mere consequence of the efforts deployed by biologists to describe the structure of macromolecules. The fact that what happened at this level had an explanatory value naturally emerged from these efforts. I think that it is a mistake to consider that the importance presently attributed to the mechanistic explanations at the molecular level was preinscribed in the efforts made by biologists to describe these macromolecules.

The proof lies in the suspicion with which many biologists considered the first 3D-structures of proteins that were seen as unable to reveal the dynamic behavior of these macromolecules. Many thought that they were not precise enough and that the true explanation had to be sought out at the electronic level (Debru 1983). This overly cautious and even suspicious attitude of the past is in sharp contrast with the place 3D-structures obtained by X-ray diffraction studies have in the present-day descriptions of biologists: they are considered as an obligatory step to the understanding of the functions of proteins.

The characteristics of these mechanistic descriptions, which have not so far received the attention they deserve, are given elsewhere (Morange 2008b). Proteins and macromolecular protein complexes are machines; mechanisms within these machines are formed by the rigid parts of these proteins, elements of secondary structures organized to form motifs.

The mechanistic vision of protein functions (and macromolecule in general) constitutes a full part of present-day biology. It supports the

importance of mechanistic explanations in biology, as recently underlined by William Bechtel, Lindley Darden, and Carl Craver (Bechtel 2006; Darden 2006).

A third characteristic of present-day biology is the importance given to the subcellular organization, organelles, and compartments, and the protein and vesicular traffic between them. Organisms are not (only) informational devices permitting the synthesis of nanomachines; they have a precisely determined subcellular organization that allows these machines to be active at the right places in the cell.

The rise of cell biology occurred in the 1950s (Bechtel 2006). Its fusion with the molecular descriptions took place in the 1960s and 1970s. New technological developments such as immunolabeling and immunofluorescence played their roles, as well as the discovery of totally unpredicted phenomena: the existence of complex cell-signalling pathways formed of a large number of proteins, and relaying the "messages" brought by hormones and growth factors at the cell membrane to the nucleus; the existence of a complex traffic of vesicles between the different organelles, involved in secretion as well as in endocytosis, and in other cellular processes (Morange 1998).

The structural and functional descriptions of this intra-cellular traffic have a major place in biology. They are mechanisms formed of other mechanisms – the protein nanomachines: an additional example of the interlevel hierarchy of mechanisms existing in organisms (Darden 2006). As also already described, the existence of this hierarchy of mechanisms makes the description of molecular biology as a reductionist enterprise simplistic, unadapted to reveal the complex progression of explanations through different levels of organization.

A final observation which progressively emerged in the 1970s, in relation to the description of this complex intra-cellular organization, was the discovery that the molecular components involved in it are "conserved" in the sense that they have close structures, revealing a common ancestry. But the structural conservation does not mean a conservation of functions: the opposite is true. Similar structures can have very different functions: they have been "recruited" to fulfill these new functions by the tinkering action of evolution. The notion of tinkering was reinvented at the end of the 1970s and has been fully integrated into the vision of molecular biologists (Jacob 1977). At the beginning of the 1980s, a similar conservation was demonstrated for the genes and proteins controlling development, a complete surprise when one considers the apparent differences of the developmental processes involved in building a *Drosophila* and a mammal (Morange 1998). This conservation was at the origin of the reconciliation between

developmental biology (embryology) and evolutionary biology in the newly created discipline of Evo-Devo. The creation emphasized the necessity of comparing different organisms in order to disentangle the complex relation between present functions and their evolutionary construction. The possibility to sequence full genomes and to compare the genes they harbor and the way these genes are organized, arrived at the right time to support this new important trend in biological research.

Has the Molecular Vision been Challenged?

The description I have offered of the progressive construction of molecular biology with the serendipitous aggregation of different characteristics explains why the question posed in the heading to this section cannot receive a simple answer.

The informational vision has clearly been successfully challenged, as has been shown by Evelyn Fox Keller (Fox Keller 2000); neither the existence of the genetic code nor the importance of the information stored within the genome are of concern. What was challenged was the idea that a full knowledge of an organism, of its development and functions, will immediately emerge from the decipherment of the genetic information present within it; and the linked idea that there exists within the genome a "genetic program" similar to the program of a computer. The informational descriptions have lost most of their heuristic value and can be successfully replaced by a description of the molecular mechanisms involved. The expression "program" is still used by biologists, but it designates a succession of steps, not the equivalent of a computer program. Newly discovered phenomena such as epigenetic modifications have scrambled the initial and simple informational schemes. However, it does not mean that informational descriptions have lost all their heuristic value in specialized fields such as bioinformatics. Informational descriptions also remain useful, for the diffusion of the models of molecular and cell biology, and for their presentation to a broad audience.

When one considers the three other characteristics of the present molecular vision, the mechanistic description of molecular functions, the attention paid to the subcellular organization, and to the structural conservation of macromolecular components during evolution, none of these characteristics has been seriously challenged in recent years. The replacement of molecular biology by a modular cell biology remains a distant objective (Hartwell *et al.* 1999). The difficulty associated with

the fact that biologists have to give "modules" a clear significance makes this replacement problematic (Schlosser and Wagner 2004). For the moment, systems biology appears as a complement to the traditional approaches of molecular biology, a way to obtain in a unique experiment a wealth of information and to develop new hypotheses which can be tested only by the use of traditional methods. The projects of synthetic biology are totally dependent on the genetic engineering techniques of molecular biology – in particular on the possibility to synthesize long fragments of DNA. Synthetic biology is the last step in the naturalization process initiated by earlier biologists in the 1930s, by its ambition to create new artificial organisms with the knowledge resulting from the study of natural organisms. No global vision of organismic phenomena radically opposed to the previous molecular vision has yet emerged, and there is no sign of its future emergence. In fact, the opposite is true: the ambitions generated by the development of DNA chips aimed at discovering a new logic of life have been tempered (Brown and Botstein 1999). The study of macromolecular machines, intracellular protein and vesicular traffic, and sequence and genome comparisons, are flourishing fields of research. The research area called "molecular biology" is still alive.

Some Philosophical Conclusions

A simple transition from a reductionist to a holistic vision of biological phenomena does neither explain the present transformations of biology, nor the erasure of the expression "molecular biology." From its beginning, molecular biology was not a part of a reductionist program; its explanations are grounded at an intermediate level of organization, the level of macromolecules. In any case, the place occupied by mechanistic explanations prevents any form of simplistic reductionism from becoming dominant. The progressive replacement of the name "molecular biology" by new names such as "systems biology" is the result of a dual, antagonistic but finally convergent evolution, the pervasiveness of molecular techniques and explanations in all fields of biology, even those such as evolutionary biology that had strongly resisted the ambitions of molecular biologists to dominate biology; and also to the progressive integration of macromolecular mechanisms in cell and organismic mechanisms, a movement toward an interfield explanation made possible by the precise description of these macromolecular mechanisms.

Molecular biology is not dying, but evolving. The possibility of

limiting studies to some well-designed animal models, *Drosophila*, bacteria and bacteriophages, mice and nematodes, is no longer accepted (Davis 2003). Genome sequencing is a short-circuit that converts plenty of organisms into potential models of study for biologists. Comparison is gaining an increasing place in biology, at all levels of description, from the genes to behaviors. Comparison has always been a heuristic tool for biologists, since the first classifications made by Aristotle. For the French nineteenth-century philosopher Auguste Comte, all scientific disciplines shared a certain number of methodologies, but each had somehow privileged one of them: physics with experimentation and biology with the comparative approach. Comparison of sequences has an important place in present biological research: for this purpose, the tools derived from the theory of information can be used. But the latter are, and will remain, tools to acquire knowledge on molecular and cellular mechanisms: their use does not mean that the informational vision of molecular biology has conserved its dominant position.

The importance given to comparison parallels the abandonment of a crucial belief that supported the rise of molecular biology: the existence of simple universal rules which would explain what happens in the whole living world. These rules and principles were discovered but they are not sufficient to explain the diversity of the living world. In the permanent movement of balance between simplicity (and universality) and complexity (and diversity), the pendulum has now shifted toward complexity and diversity (Holton 1978). The belief that guided the first steps of molecular biology has been useful in establishing these rules, but the latter are no longer considered as sufficient to describe the living world. To account fully for the dominant place of diversity at all levels of organization, from the microRNAs whose complexity challenges the major role of proteins in cell functions, to the diversity of the developmental processes, the progressive historical construction of present organisms has to be integrated into the descriptions of functions and development. An increasing number of molecular biologists engage in serious efforts to integrate an evolutionary perspective into their molecular explanations.

Molecular biology was never a discipline and the apparent signs of death as a discipline – absence of new chairs and journals – is meaningless. It was created as a research area, which is still fully active. But it was also a philosophical view of life, with the ambition to naturalize organisms by the discovery of simple rules and principles. The process of naturalization has been successfully achieved: the rise of synthetic biology is the sign of this achievement. But diversity has not been replaced by simple

principles. The richness of the living world has still to be explained by the long evolutionary history of organisms, made of frozen accidents and Darwinian adaptation. This will be the goal of twenty-first-century biological research.

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