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Post-genomics, between reduction and emergence

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Abstract It is frequently said that biology is emerging from a long phase of reductionism. It would be certainly more correct to say that biologists are abandoning a certain form of reductionism. We describe this past form, and the experiments which challenged the previous vision. To face the difficulties which were met, biologists use a series of concepts and metaphors - pleiotropy, tinkering, epigenetics - the ambiguity of which masks the difficulties, instead of solving them. In a similar way, the word "post-genomics" has different meanings, depending upon who uses it. Which of these meanings will become dominant in the future is an open question.

Keywords Post-genomics · Emergence · Reductionism · Holism · Epigenetics · Tinkering

In his introduction to *The Logic of Life*, François Jacob described the two main poles between which biological thought has swayed since the emergence of biology from natural history at the end of the eighteenth century: reductionism and holism (Jacob, 1973). Reductionism, under the label of molecular biology, seemed to have definitively won at the end of the twentieth century: the characteristics of organisms were considered to be explained by the structural properties and enzymatic capabilities of their macromolecules, which could be assessed using genome sequences.

This victory was only apparent and transient, and holistic models reemerged at the eve of the twenty-first century. A good indicator of the alternance between reductionism and holism is the importance given to the question "What is Life?". When the question is no longer asked, it means that life is considered as nothing more than the components present in organisms: this is the case when a reductionist vision is dominant. When the question is discussed by biologists, it means that they consider that there is something specific in organisms that cannot be directly deduced from the structure of their components and that the pendulum has shifted from a reductionist

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point of view to a more global one. The question was very actively discussed in the 1940s and then became taboo in the 1960s: a solution had been provided with the discovery of the genetic information and of the genetic code. However, the question recently reemerged (Morange, 2003): this is a clear sign that the reductionist approach of molecular biology is in difficulty.

I will first consider the reasons for the reemergence of the question "What is Life" and of holistic research programs. To illustrate more precisely the difficulties faced by biologists, I will consider successively three concepts that are widely used by biologists, the ambiguity of which precisely aims at masking these difficulties. In a similar way, I will show that the very fashionable post-genomic programs can have very different stakes, some reductionist and other holistic, depending upon who is supporting them. The current state of biological research is very contrasted, because biology is hesitating at a crossroads between reductionism and holism.

1 The fading of the reductionist approach

The reductionist approach of molecular biology was supported by a metaphor of gene action that emerged at the end of the nineteenth century, when biologists including Hugo de Vries and August Weismann designed a corpuscular materialistic mechanism of heredity (Allen, 2000). In this *preformationist* conception of gene action, the organism could be split into different structures and functions, each of which was somehow pre-contained in one or a limited number of genes. Strangely enough, this conception resisted the numerous changes concerning the nature and functions of genes that accompanied the development of genetics during the first half of the twentieth century. This model was still dominant in the 1970s, when biologists developed molecular tools for the study of higher organisms and started to decipher the role of genes in the formation of complex structures and functions. This preformationist vision of gene action was reductionist, because the complex structures and functions of organisms were considered to be fully explained by the limited group of genes involved in the control of their formation.

It is precisely this ambitious reductionist program that failed during the last two decades, because the data generated by genetic tools did not confirm this preformationist vision, but instead broke the simple model of correspondence between the genotype and the phenotype. To appreciate these changes fully it is necessary to dive into the complexity of data and observations accumulated during these years and which could not be explained by the previous model: it can be only adequately described by considering a lot of different results from very different fields of research. For this reason, the transformation did not attract a lot of attention from non biologists. A new model of gene action silently emerged, in which each complex structure and function results from the involvement of hundreds or thousands of genes, no one being more important than the others in its generation (Morange, 2000). The products of the genes—mostly proteins—are organized in pathways and networks. They participate in numerous functions—their action is *pleiotropic*. Many genes act in parallel—they are *redundant*. Genes and gene products have been conserved during evolution, but they frequently fulfill different functions in different organisms. The intra-cellular signaling networks, the intermingled structures of which have been characterized during the last two decades, constitute a major field of research at present: the complexity of feedback and crosstalk between the different pathways and the extremely high

number of components involved make these signaling networks, and the well documented role their dysregulation has in disease—in particular in cancer—emblematic of the goals and characteristics of post-genomic biology. The new model of gene action has sounded the end of the notion of *a gene for*. As complex processes are due to the action of hundreds of genes, the concept of *a gene for* is obviously absurd.

The results of the human genome sequencing program—the discovery that there are no more than 30,000 genes in the human genome, many of which are also present in simpler organisms—were not a real surprise for those who had been active in this silent transformation of biology during the two last decades. It was seen as the clear confirmation of the new model of gene action. The complexity of the human organism was found to lay not in the nature of the macromolecular components, but in the way these components associate and interact to generate complex structures and functions: the disentanglement of these complex networks is at the core of the post-genomic programs that we will describe later.

2 Some ambiguous concepts and metaphors

Some concepts and metaphors are fashionable among biologists, for the precise reason that they are at the border between reductionism and holism, and because their use prevents the need to choose between them. Such is the concept of pleiotropy. This concept is not new: geneticists from Morgan's school demonstrated the importance of pleiotropy in the 1930s (Morgan, 1978). However the limited influence of this concept at that time was nothing compared with the present "unbearable pleiotropy of macromolecular components"[1]. The meaning of this word is very ambiguous. A macromolecule—and its gene—can be said to be pleiotropic because it harbors different structural domains, each with precise functions and partners, or because the same structural component associates with different partners in different cells and situations to generate different structures and processes. In the second case, the function of this molecular component is said to be "context-dependent". This term is also very ambiguous, because the molecular function—the capacity to catalyze a precise reaction or to establish a specific interaction—remains the same in all cases. Only the global function in which this macromolecular component participates is different. A metaphor is frequently used to describe this pleiotropic action of genes and gene-encoded proteins: the notion of a role (Lawrence, 2001). Metaphors never solve conceptual difficulties; they only help to brush them under the carpet. Maybe the major conclusion that emerges from the wide use of this metaphor is the ambiguity of the term "gene function". Gene functions are as diverse as the role of actors in plays. Pleiotropy prevents us from having a simple, direct vision of the global functioning of systems based on knowledge of their isolated components.

A second metaphor, more scientific at a first glance, is that of tinkering—bricolage—proposed by Jacob (1977). Evolution has "tinkered" with the molecular components present in organisms, recycling them again and again to generate new structures and functions. Tinkering is a good way of explaining surprising evolutionary facts—the participation of the same molecular components in very different processes—and the absence of an apparent design. Unfortunately, one important facet of this concept has been forgotten in its current use: a tinkerer carefully chooses the

[1] To paraphrase the title of the novel of Milan Kundera: *The unbearable lightness of being: A novel.*

objects that he will use, even if he does not design *de novo* any part of the new device he intends to build. An excellent example of efficient tinkering was described in the movie *Operation Petticoat*, starring Cary Grant. To repair the belts of the engine that had broken, the mechanic used stockings provided by the nurses who had been taken aboard the submarine. This mechanic behaved in a rational manner: he converted the extraordinary mechanical properties of nylon to a new use. The tinkering action of evolution probably also exploits the chemical properties of molecules to generate new functions. Our current description of molecular tinkering lacks a clear understanding of these chemical properties and constraints. Using the term "bricolage" is a way of masking our ignorance of these rules.

In a similar way, epigenetics is an ambiguous way of facing up to the limits of the reductionist approach. Epigenetics is a polysemic word, the significance of which has constantly changed since its creation by Conrad Waddington in 1942 (Morange, 2002). It means "over genetics", but is more often used to mean "besides genetics": it has essentially been used to answer the questions that were considered as not properly explained by genetics. Today, the term epigenetics is used for mechanisms responsible for an inheritable change in gene activity that does not result from a modification in the DNA sequence: modification of gene expression by DNA methylation or by alteration of the chromatin state. The attention paid to these epigenetic mechanisms clearly illustrates the limits of the present reductionist explanation of gene control. The dominant model, according to which gene expression is controlled by a combination of proteins bound upstream of the gene, does not explain either the observed specificity of control or its stability and globality. The concept of epigenetics is a way of extending the scope of genetics without precisely discussing the origin of its limits: epigenetics is frequently used in a very vague sense, only to mask the present ignorance about the relationships between the genotype and the phenotype.

3 What is exactly post-genomics?

Post-genomic approaches developed after the completion of the human genome sequencing project. Some consider that these approaches are nothing more than a way for biologists to prolong the influx of money generated by the sequencing programs. However, at the conceptual level, post-genomic programs are more than this. The technologies gathered under this name aim at providing a global description of the organism: of gene activity, by studying the transcriptome with DNA microarrays; of the protein–protein interactions by systematic application of the two-hybrid technique; or of the different forms of proteins present within a cell or a tissue by proteomics—a possibility that has still not been fully completed.

What are the objectives beyond these global descriptions, whatever the precise technological approach chosen? The answer is not obvious and differs depending upon authors. It is possible to distinguish different degrees of ambition, corresponding to the increasing consideration given to the holistic approach. The first level is only to obtain new information by using efficient throughput devices: to do more rapidly what was previously done in a very fastidious way. However, the objective clearly remains the same as before: to explain the properties of the global system by precisely characterizing its molecular components. The second objective is more ambitious: to provide a precise and quantitative description rather than the present qualitative one. This quantitative description will make it possible to model what happens inside cells.

Beyond a certain degree of complexity, it is impossible to anticipate how a network functions by considering its architecture: in particular, it is impossible to predict the effect of disrupting one node of this network on the global functioning of the system or to predict how the network will adapt to this perturbation (Greenspan, 2001). In this vision, the properties of the global system are based on the properties of its components, but functions cannot be anticipated directly from the latter.

The third degree of ambition is to consider that a global look at the system will reveal unanticipated connections. They were unanticipated, because they link processes previously thought to be independent. Such a high degree of integration can only be elucidated by *data mining* without *a priori* limitations. This opens to a fourth degree of ambition, to reveal a new logic of life, totally foreign to the previous one: "Many of the new models that emerge will defy conventional wisdom" (Brown & Botstein, 1999). Such incompatibility between the present and past models is reminiscent of the incommensurability between successive paradigms described by Thomas Kuhn (Kuhn, 1970). This ambition is similar to that of early molecular biologists, such as Max Delbrück, who aimed at discovering new laws of reproduction specific for a given organisms (Fischer & Lipson, 1988). This new logic might be the logic of networks, because networks—of genes or of proteins — are at the core of the present description of organisms (Jasny & Ray, 2003). Interestingly, networks are present at all levels of the hierarchy, from the macromolecular level to the ecological one, through cells and organs. These new laws could therefore be applied with the same efficiency in all the disciplines that form biology.

4 Conclusion

We have focused our discussion on molecular biology, and the abandonment of a certain form of reductionism that had previously been dominant. The holistic vision has had a preeminent place in other fields of biology, including population genetics and above all ecology, for many decades. It would be very interesting—but beyond the scope of this contribution—to look at the influence these disciplines had on the transformation of molecular biology. The concept of emergence diffused into many different disciplines, including physics, during recent decades, and molecular biology was more the exception than the rule with its exclusively reductionist approach.

It is clearly too early to anticipate future developments in post-genomics and the form of holism that will emerge. All we can say for sure at the present time is that a specific form of reductionism is starting to disappear from biology, a form in which complex structures and functions could directly be explained by the properties of a limited number of gene products. Beyond this transformation, the future remains open. Two main schools of thought can be distinguished. The first remains reductionist, but with some hints of holism, centered around genes and gene products: the properties of organisms find their origin in the properties of gene products, even if they cannot yet be anticipated from what is actually known about these molecules. In the second, it is considered that the order of life is not in genes or gene products, but instead in the cytoplasm (Keller, 1995) or in certain forms of supramolecular organization, a good example of which are cell membranes (Moss, 2002). Clearly, the first point of view is dominant among biologists, whereas the second is strongly supported by philosophers of science. Will philosophers anticipate the next transformations within biology?

References

Allen, G. E. (1978). *Thomas H. Morgan, The man and his science* (p. 270). Princeton; NJ: Princeton University Press.

Allen, G. E. (2000). The reception of Mendelism in the United States, 1900–1930. *Comptes Rendus de l' Academic des Sciences*. *Paris, Sciences de la vie, 323*, 1081–1088.

Brown, P. O., & Botstein, D. (1999). Exploring the new world of the genome with DNA arrays. *Nature Genetics Supplement*, *21*, 33–37.

Fischer, E. P., & Lipson, C. (1988). *Thinking about science: Max Delbrück and the origins of molecular biology*. New York: W. W. Norton.

Greenspan, R. J. (2001). The flexible genome. *Nature Reviews/Genetics*, *2*, 383–387.

Jacob, F. (1973). *The logic of life*. Princeton, NJ: Princeton University Press.

Jacob, F. (1977). Evolution and tinkering. *Science*, *196*, 1161–1166.

Jasny, B. R., & Ray, L. B. (2003). Life and the art of networks. *Science*, *301*, 1863 *et s*.

Keller, E. F. (1995). *Refiguring life: Metaphors of twentieth century biology*. New York: Columbia University Press.

Kuhn, T. S. (1970). *The structure of scientific revolutions*. Chicago: University of Chicago Press.

Lawrence, P. A. (2001). Science or alchemy? *Nature Reviews/Genetics*, *2*, 139–141.

Morange, M. (2000). Gene action. *Comptes Rendus de l' Academic des Sciences. Paris, Sciences de la vie*, *323*, 1147–1153.

Morange, M. (2002). The relations between genetics and epigenetics: a historical point of view. In L. van Speybroeck, G. van de Vijver, & D. de Waele (Eds.), *From epigenesis to epigenetics Annals of the New York Acadamy of Sciences* (Vol. 981, pp. 50–60).

Morange, M. (2003). *La vie expliquée? 50 ans après la double hélice*. Paris: Odile Jacob.

Moss, L. (2002). *What genes can't do*. Cambridge, Mass.: MIT Press.

Waddington, C. (1942). L'épigénotype. *Endeavour*, *1*, 18–20.