Series

What history tells us XVIII. When functional biologists propose mechanisms of evolution

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1. Introduction

The distinction between functional biology and evolutionary biology was firmly established by Ernst Mayr in 1961 in an article published in *Science* (Mayr 1961). Functional biologists – physiologists, biochemists, molecular and cell biologists – answer the questions "how" by describing mechanisms, whereas evolutionary biologists address the questions "why" by proposing evolutionary scenarios.

The gap between these two approaches was obvious during all the 20th century, but there is a present growing interest of functional biologists in evolution (Morange 2009). What will emerge from this recent encounter is still unknown.

The existence of this gap does not mean that functional biologists ignored the existence of evolutionary questions. But their attitude was ambiguous. In principle, they accepted the Modern Synthesis, and considered it to be the right basis on which to construct evolutionary explanations. But, in practice, they ignored the content of the evolutionary synthesis, and recurrently proposed mechanisms of evolution which were at odds with its most fundamental principles, such as the low amplitude of the variations screened by natural selection, the rejection of any distinction between different levels of evolution (micro and macro), and the corresponding variations proposed by Richard Goldschmidt (Goldschmidt 1940).

The attitude of molecular biologists was particularly representative of these ambiguities of functional biologists. The rises of evolutionary synthesis and molecular biology were simultaneous, and highly connected (Smocovitis 1992). One of the first results obtained by molecular biologists – on the spontaneous origin of mutations, through the Luria-Delbrück experiment – resulted in chasing the Lamarckian theory from its last realm – the domain of bacteria (Morange 1998). The two disciplines were narrowly associated in their fight against "old biology". When the eminent French zoologist Pierre-Paul Grassé criticized the highly influential book of Jacques Monod, *Chance and necessity* (Monod 1971), his attacks were not targeted at the molecular models the latter had proposed, but at the support that Monod brought to the Darwinian theory (Grassé 1978). In contrast, at the same time, the most serious challenges to the evolutionary synthesis originated from the results of molecular biologists, and the interpretation they gave to them. The neutralist theory of Motoo Kimura originated in the first comparison of protein sequences from different organisms (Kimura 1968), whereas the resurrection of Goldschmidt's ideas by Allan Wilson (King and Wilson 1975) and Stephen Jay Gould (Gould 1982) was based on the discovery of regulatory genes, and the potential dramatic effects of their variations on evolution.

The evolutionary models proposed by functional biologists, and in particular molecular biologists, deserve to be studied. Trying to discover characteristics common to these models has, as for as I am aware never been attempted. Such a study may cast some light on what should be expected from the present encounter between functional and evolutionary biology.

2. Evolutionary models proposed by early geneticists, biochemists and molecular biologists

What I will attempt to do is not a general presentation of these models, but a possible classification of them, based on a selection of examples.

The first mechanism of evolution that I will consider is gene duplication, and functional specialization of the two new genes. The model emerged from the work of geneticists

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on pseudoallelism, i.e. the existence of mutations occurring in narrowly-associated but distinct genes, having similar, but not identical effects. The hypothesis that pseudoallelism was the result of gene duplication and partial divergence, and that such a mechanism might be important in evolution was initially proposed by Calvin Bridges (Lewis 2003) and Hermann Muller, and amply developed later by Edward Lewis in his work on the bithorax complex. The same hypothesis was recruited to explain the characteristics of the pretended "*T*-complex" involved in early mouse development, which was the focus of many studies at the beginning of the 1970s (Bennett 1975; Morange 2000). The description of the first protein sequences confirmed the existence of gene duplication – the different chains of globin are the products of gene duplication – which led the Japanese biologist Susumu Ohno to make of this mechanism one of the principal mechanisms of evolution (Ohno 1970). The recent results of genome comparisons have amply confirmed these early observations: duplication can involve groups of genes, whole chromosomes and genomes.

A second mechanism, diametrically-opposed to the previous one, has also been recurrently proposed: evolution by loss of functions (Bateson 1914, in Bateson and Bateson 1928, p. 292: *see* Newman 2007). An important advocate of this idea was the French microbiologist André Lwoff in a book published in 1944 *L'évolution physiologique* (Lwoff 1944). Lwoff demonstrated that the evolution of organisms was parallel to a loss in metabolic capacities, through a loss or inactivation of the corresponding genes. It resulted in an increased dependence on the molecules provided by the environment: whereas some bacteria are able to grow in a medium containing only ammonium and glucose; such is not the case for humans! The loss of these basic functions allows organisms to acquire new, more complex functions. Despite numerous observations in its favour, this model raises a paradox – the first organisms were richer in metabolic functions that their successors! –, and does not explain how they first acquired these functions.

The obvious limits of such a model of "evolution by loss" did not prevent it to be recurrently proposed to explain diverse observations on evolution. The formation of modern human beings has been hypothesized to have resulted from a loss of the specialized functions present in our primate ancestors (Olson 1999). A good, albeit caricatural example of this way of thinking, was the hypothesis that loss of function of a myosin gene expressed in the jaws had been sufficient to "liberate" the growth of the head, and consequently of the brain, and to initiate the walk of these early ancestors of human beings towards higher cognitive abilities and language (Stedman *et al.* 2004). More recently, the same mechanism was proposed for the first steps of evolution from the Last Universal Common Ancestor (LUCA) (Forterre *et al.* 2005). The divergence between eubacteria, archaea and eukarya from LUCA would have been the result of the selective loss, in each lineage, of functions which were present in LUCA.

Another more "traditional" mechanism is that of evolution by addition and complexification. A recent example is that of the progressive formation of the 23S ribosomal RNA from simpler molecules (Bokov and Steinberg 2009). An earlier example concerns the formation of the metabolic cycles. The selective advantage provided by these cycles, and the way they originated from the association of different linear pathways that had pre-existed in micro-organisms were discussed by Hans Krebs himself (Baldwin and Krebs 1981).

A fourth mechanism does not consist in the global enrichment of genetic information, but in the recombination of fragments of genetic information to create new proteins and macromolecules, bearing complex functions. Exons, or groups of exons, can be recombined to generate new molecules. The structure of most extant proteins is probably the result of such a recombination process at an early step of their formation.

The last mechanism of evolution privileged by functional biologists is "evolution by change in gene regulation". The major evolutionary steps, at least for the evolution of complex organisms, would be the result of mutations in gene (or DNA sequences) controlling the expression of other genes. This hypothesis finds its origin in the rise of the regulatory gene concept (Morange 1998), even if it was not Monod and Jacob, but Roy Britten and Eric Davidson (Britten and Davidson 1971), as well as Allan Wilson, who exploited this hypothesis. This hypothesis supports the work of many contemporary specialists in Evo-Devo (Carroll 2008), who consider that the evolution of form, in contrast with functional adaptation, is the result of mutations altering gene expression.

Both this mechanism and the previous one see novelty as the result of new combinations of molecular components, or of their expression. The hypothesis of evolution by variation in gene expression is supported by the most recent work of Eric Davidson (Davidson and Erwin 2006; Erwin and Davidson 2009; Morange 2009), and has been applied to the evolution of modern humans. In the latter case, however, whereas the first data seemed "promising" (Enard *et al.* 2002), the most recent ones are inconclusive (Khaitovich *et al.* 2006).

3. Interpretation of the main characteristics of these functional evolutionary models

Two different antagonistic interpretations of these heterodox models, in comparison with the canonical models of evolutionary biology, can be proposed. The first is that most functional biologists are ignorant, and misunderstand the

Modern Synthesis. In particular, they are not conscious that big variations – leading directly to the formation of "hopeful monsters", such as human beings with small jaws – have a negligible probability to be selected for: selection acts in the present, not on the future developments that might emerge from the present variations.

In addition, functional biologists tend to see the action of natural selection as operating in a constant environment, and therefore naturally generating a "progress", whereas evolutionary biologists pay much more attention to the evolutionary processes triggered by irregular changes in the environment.

It is true that these criticisms can be addressed to the precise scenarios which have been proposed by functional biologists. But it is not the mechanisms themselves which are the targets of these criticisms, but their instantiation in simplistic cases. I consider that the five mechanisms previously described represent serious challenges to the canonical Modern Synthesis, and deserve to be considered with scrutiny, what I will do now. They probably represent the best way to anticipate what will emerge from the present intertwining of models from evolutionary and functional biology.

The first remark is that the contributions of functional biologists are not limited to what might have appeared as "natural" from their viewpoint, an emphasis on the functional and structural constraints which limit the action of natural selection. To better appreciate what these different contributions tell us, I will first develop a recent example concerning protein evolution. Some neurodegenerative diseases result from the formation of toxic protein aggregates within cells. The existence of characteristics common to all these aggregates had long suggested that there was probably a common biochemical mechanism at the origin of these aggregates. Recent data have led to the hypothesis that the initiation step in aggregation is the formation of tightly associated β-sheets (Nelson 2005). From the structural knowledge of the proteins involved in these diseases, it has been possible to deduce consensus sequences with a propensity to generate such structures, and to look for their occurrence in extant proteins. The result of such a study was evidence that the prevention of the formation of these aggregates has been a driving force of the evolution of proteins: such pro-aggregating sequences are under-represented in the genomes of extant organisms (Monsellier and Chiti 2007).

But the authors of this study did not limit their investigations to this result: they looked for the mechanisms by which the formation of these pro-aggregating sequences has been prevented – for instance, by the insertion of amino acids that disrupt the secondary structures, such as proline and glycine.

This emphasis on mechanisms is characteristic of the approach to evolution by functional biologists. The general statement that might be shared by all the authors of the studies that I have briefly described before is that there are mechanisms of variation specifically involved in one or another evolutionary process. The importance of natural selection is not contested, but emphasis is put on the mechanisms of variation, and the limits they present to the action of natural selection.

Consider, for instance, the most recent works of Eric Davidson. The central parts of the Gene Regulatory Network, what he calls the "kernels", have components so tightly interconnected that any variation is nearly impossible, and if it occurs, it leads to dramatic changes in the development of organisms (Davidson and Erwin 2006). Hence the hypothesis proposed by Davidson is that the formation of new phyla can be attributed to such variations in these kernel subsystems, whereas the formation of new species is due to the variation of more peripheral subcircuits of the Gene Regulatory Network (Erwin and Davidson 2009).

By mechanisms of variation, we mean two different aspects of variation: either the mechanism that generate diversity – such as gene duplication – or the nature of the genes or DNA sequences that are affected by the variations – such as regulatory sequences.

This emphasis on the mechanisms of genetic variation has a consequence: different forms of evolution correspond to different mechanisms. As we have seen, evolution of animal forms would be the result of variations in regulatory systems, whereas the early evolution of macromolecules would be the consequence of gene duplication, and recombination of parts of genes.

These different mechanisms did not play an identical role at every period of the evolution of organic forms: the nature of variations is historically constrained. For instance, evolution by recombination of gene fragments played a major role in the first steps of life, and, maybe, during prebiotic evolution, whereas evolution by loss of functions might have contributed at later periods, since it had to be complemented and preceded by periods during which other mechanisms of evolution were dominant.

Such hypotheses from molecular biologists lead to the abandonment of one principle which had been dominant since Darwin, and in which he was inspired by the British geologist Charles Lyell – the principle of uniformitarianism: the same mechanisms that operated in the past still operate today, with the same intensity. It remains to be seen whether such dramatic epistemological consequences will result from the present scientific developments at the boundary between functional and evolutionary biology.

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