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A new revolution?

The place of systems biology and synthetic biology in the history of biology

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Systems biology and synthetic biology have emerged at the dawn of the twenty-first century as two new research fields that hold much promise for both understanding living systems and novel practical applications. The two disciplines have much in common, not least that the scientists working within their respective frameworks share the conviction that organisms are made of partially independent functional modules that are organized in networks. However, whereas systems biology aims to describe this modular organization, synthetic biology is geared towards more practical developments.

My aim here is to localize these new disciplines in the changing landscape of biological disciplines using three successive strategies. First, I compare the rise of these new disciplines with the development of molecular biology during the 1950s and ask whether we are now observing a similar transformation of biology. Second, I question the epistemological novelty of these two disciplines and ask whether they introduce new ways to lead research projects in biology. Third, I consider the role that these disciplines play, or might play, in the encounter between functional biology and evolutionary biology, which is one of the major transformations that is currently affecting the life sciences.

Historians of molecular biology do not fully agree on the events that triggered its emergence. Some see its origin in the development of new technologies, such as ultracentrifugation or electrophoresis, for the study of macromolecules in the 1930s (Kay, 1993). Others put more emphasis on the inclusion of informational concepts in biology, which took place after the Second World War (de Chadarevian, 2002). In both cases, the rise of molecular biology was the result of interdisciplinary work that involved biologists, physicists and mathematicians.

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Similarly, the present transformations of biology, and the rise of systems and synthetic biology, are the result of combined efforts by biologists, physicists, computer scientists and engineers. Instead of focusing on the mere characterization of the components of organisms, their efforts are aimed at providing a global structural and functional description. This similarity raises the question of whether the important role of interdisciplinarity, which is common to the rise of molecular biology and the development of systems biology and synthetic biology, is sufficient to describe the development of the two latter disciplines as a revolution that is comparable with the advent of the former.

I do not think so, for at least two reasons. First, the state of knowledge in the 1930s was different from today. When molecular biology emerged, one part of the realm between the molecules that were studied by the organic chemist and the cellular substructures that were barely visible under the light microscope was totally ignored: this was supposed to be a new state of matter known as the colloid state. The disappearance of the colloid world and its progressive replacement by a precise description of macromolecules was a major breakthrough (Deichmann, 2007). Technological progress allowed the determination of ever-larger structures at an increasing rate. This structural knowledge retains a heuristic value by explaining functions and a practical value by forming the basis of drug development. The projects developed in systems and synthetic biology fully exploit this molecular knowledge, which has accumulated during the previous decades.

The second reason to doubt that the rise of systems and synthetic biology is an event of the same nature as the rise of molecular biology is the observation that nothing in the new discipline is comparable with the role that macromolecules play in the molecular paradigm. Ten years ago, in an influential article published in *Nature*, the Director of the Fred Hutchinson Cancer Research Center (Seattle, WA, USA), Leland Hartwell, and colleagues suggested that there was a transition from molecular to modular cell biology (Hartwell *et al*, 1999). However, I do not believe that modules are likely to play the same role in synthetic biology or systems biology that macromolecules have played in molecular biology. One reason is that macromolecules are still there. Another is that modules mean different things to different specialists: the module of the developmental biologist is not the same as the module of the molecular geneticist. Furthermore, it remains unclear whether modules really exist or whether they are

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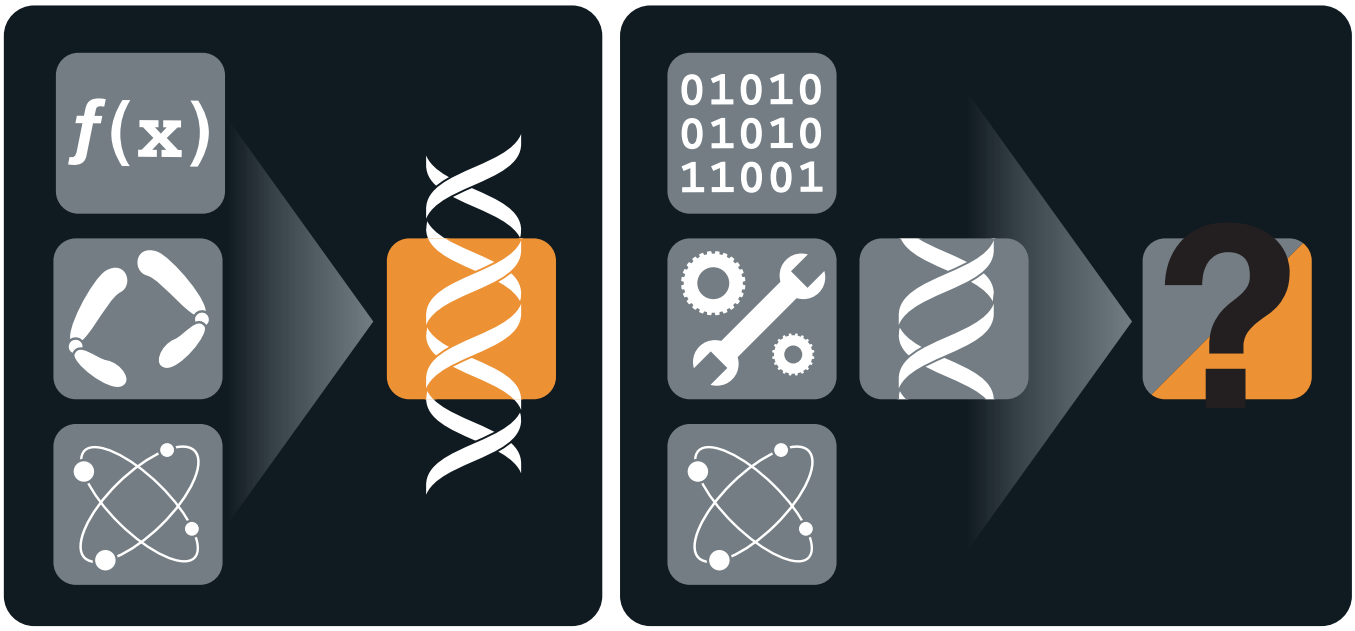

simply a construction used to disentangle complex biological networks (Mitchell, 2006). The fact that genes encode macromolecules or parts of macromolecules is another reason to give macromolecules—and not modules—a pre-eminent place in the descriptions of organisms.

By contrast, it is probably more appropriate to consider the rise of systems and synthetic biology as the last step in the project of early molecular biologists to 'naturalize' the organic world—that is, to provide natural explanations of biological phenomena and to weed out teleological explanations, the mere existence of which was considered to be a scandal by prominent molecular biologists such as the French biologist and Nobel laureate Jacques Monod (1910–1976; Morange, 2008). The development of synthetic biology, including some of its most ambitious projects, can be considered as the last step in this naturalization process. The best way to demonstrate that the 'mystery' has been definitively banished from the realm of organisms would be to synthesize a living organism 'from scratch'—from inorganic and organic components.

So, the rise of systems and synthetic biology cannot be compared to the development of molecular biology. Its significance lies elsewhere: in an important change in the way that biologists practice their science, and its potential role in reconciling functional biology and evolutionary biology.

To appreciate better how these two disciplines have changed the way in which biology is done, it is worth briefly recalling the experiments demonstrating that traditional molecular explanations were not sufficient to account for the phenomena occurring in organisms. The first challenge came from the study of intracellular-signalling networks. Initially described at the end of the 1960s as simple unidirectional pathways, they have been progressively developed into complex networks, with an ever-increasing number of components and interactions. The result is that understanding the functions of these complex networks is increasingly problematic. The results of gene-inactivation experiments have demonstrated that it is generally not possible to anticipate the consequences of modifications of these networks.

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This difficulty is not limited to complex systems. Even the behaviour of simpler systems can become unpredictable as soon as they contain, for instance, positive-feedback loops. Formal modelling is the only way in which to tackle these difficulties. Whatever the obstacles—be they huge numbers of different components, poor knowledge of their concentration or inhomogeneity of the intracellular medium—modelling is playing an increasing role in work on signalling and gene-regulation networks.

Even more significant than these models is the change in their position in publications and the part they play in organizing the work. Traditionally, a scientific article in molecular biology provided models at the end, as a summary of the progress that had been made in understanding the systems described in the article. Today, models have different and new functions. The first is as an obligatory step in the practical realization of the work, which is particularly obvious in synthetic biology. When an objective has been set—such as to introduce an oscillator into bacterial cells (Elowitz & Leibler, 2000)—it would not be reasonable to construct the system directly. Too little is known of the characteristics that the components must have for the system to be functional. Models are therefore used to select the different characteristics of the components before actually constructing the system.

Second, a model can also be used to check the present state of knowledge, to ascertain whether the components of a functional system and their relationships have been fully described. If this is the case, the model will mimic the *in vivo* functioning of the system. If the model does not generate a stable behaviour, or behaviours

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similar to those observed *in vivo*, it will lead to new research in order to characterize the missing components or connections.

Third and finally, a model can be used to test a simple hypothesis and to replace unnecessarily complex ones. A recent article raised the question of whether it was possible to account for the distribution of certain proteins in the membrane by a simple model combining diffusion, attraction and repulsion, or whether it was necessary to hypothesize the existence of membrane subdomains with different properties (Sieber *et al*, 2007). In this case, the model does not function as the final proof of a hypothesis, although it will direct the work of biologists. In all three cases—constructing a new system, checking the present state of knowledge and testing a hypothesis—the models hold the position that they traditionally held in physics, ecology and evolutionary biology: they assist, support and guide the work of the experimenters.

A last important epistemological change associated with the rise of synthetic biology is the need to combine an analytical and a synthetic approach in order to describe a system fully. This is the usual procedure in chemistry, in which a new molecule is considered to be described only when it is possible to synthesize it and demonstrate that the synthetic copy has the same properties as the natural molecule. This tradition has not been lost in biochemistry, in which reconstructing systems by putting together all of the components that have been isolated and characterized is still considered the last step in the full description of the system, although it was partially forgotten with the development of new molecular techniques.

The rise of synthetic biology is a return to the 'old' traditions: one can claim that a system has been fully described only when it has been possible to reconstruct it. The more 'artificial' the components used for the reconstruction, the better the demonstration. As seen earlier, the achievement of the distant goal of constructing an artificial living cell will be the ultimate proof that life has been fully explained.

There is a strong tendency today among biologists to try to reduce the gap that has grown between functional biology and evolutionary biology. There are many experimental and other reasons why this gap is no longer acceptable. The huge progress made in describing molecular mechanisms has paradoxically highlighted the limits of purely mechanical explanations, which fail to take into account the evolutionary history of systems. Comparing genomes and genome sequences to extract information from the rapidly increasing amount of data naturally raises questions about the evolution of molecular systems. Many young biologists and new researchers entering the field therefore see bridging the gap as both an intellectual challenge and a powerful argument against those who use the beauty of molecular structures to support intelligent design.

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The gap can be reduced from either side. 'Evo-devo'—the recent marriage between evolutionary biology and the knowledge about the genes that control development—is an attempt to give some flesh to the genetic events that are linked to the evolution of organisms. By contrast, evolutionary models and explanations can be introduced to explain 'pure' molecular mechanisms, such as genome imprinting.

What role do systems and synthetic biology play here? It is interesting that the *raison d'être* of specific architectures of biological systems—networks and modular organization—is immediately questioned. Is it possible to explain them by selective advantage—for instance, by the robustness that they would give the system—or by the rules that guided their construction during the evolution of complex systems? The rapidity with which preliminary data are over-interpreted does not diminish the value of this question or its importance for reducing the gap between the two branches of biology. The fact that these efforts are made by 'new biologists', who are not affected by the traditional opposition between functional biology and evolutionary biology, probably explains the place that evolutionary descriptions have in systems biology.

It has been a common belief among evolutionary biologists that only functions are selected, not structures. As a result, they have attached little value to work that seeks to characterize the structural variations associated with evolutionary processes; different structures would have been able to respond to the same pressures of selection and to provide the same adaptation. Systems biologists claim to be able to demonstrate that a specific class of structural organization can be selected because it is the only way in which a particular function that is required by the organism can be correctly fulfilled; a good example of this is the study of the pathways and networks that are involved in chemotaxis (Yi *et al*, 2000).

The role of synthetic biology is more problematic. The 'engineering spirit' of this new branch of biology seems to be at odds with the tinkering action of evolution (Jacob, 1977). The goal of researchers who add new functional modules to organisms is to make these new modules as insulated from, and as 'orthogonal' to, pre-existing modules as possible. Is this goal reasonable or will the 'blurring' action of evolution predominate and alter the structure of the newly introduced modules?

Biologists have an ambiguous vision of the action of natural selection. Although its blurring action is well demonstrated, it has also been advocated that natural selection might introduce rules and principles in the functioning of organisms. Monod proposed a model to explain the behaviour of regulatory enzymes and proteins based on a principle of structural symmetry (Monod *et al*, 1965). The emergence of this symmetry was the result of natural selection. Yet, observations of natural systems give ambiguous results both for and against the 'organizing action' of natural selection. Consider, for instance, the modular organization of proteins. There is good experimental evidence to indicate that modular organization was probably present from the beginning, although it is no longer visible in most proteins, which is the result of the blurring action of natural selection. However, some specific classes of protein—transcription factors and proteins of the extracellular matrix—have retained and exploited this modular organization. Therefore, the focus has been shifted: the aim now is to

look for the conditions in which the organizing action of natural selection predominates. The answer is of paramount importance for synthetic biologists.

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Synthetic biology can also make a notable contribution to evolutionary biology. When an evolutionary biologist observes that only certain structures and forms are present in organisms, it is always difficult for him or her to ascertain whether these are a 'frozen accident'—that is, whether some of the early organisms from which present-day organisms descended just adopted them, fixing them in their genetic lineage. A transition to a different structure or form has therefore become impossible. By contrast, the occurrence of these structures and forms might also be the result of the selective advantage that they afford. The question, therefore, is whether other structures or forms are possible. In principle, synthetic biology is, or will be, able to provide answers and therefore become a second experimental approach to evolution, in parallel and in association with the development of *in vitro* evolutionary systems. Synthetic biology can help evolutionary biologists to explore possibilities that have not been realized by existing organisms.

Although the development of systems biology and synthetic biology cannot be compared to the rise of molecular biology in the 1950s, the changes that these two new fields make to the way that biologists work and to what they consider as proof of value, as well as their possible contribution to reducing the gap between functional biology and evolutionary biology, are important for the discipline as a whole. Similarly, many historians of molecular biology consider that the changes physicists introduced to the relationship between theory and practice, and the quest for simple general principles that guide the functioning of organisms, are more important than their contribution to the determination of macromolecular structures (Morange, 1998). With its practical mind-set and spectacular results, synthetic biology is probably better placed than systems biology to trigger equally important transformations in the life sciences.

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