A Critical Perspective on Synthetic Biology

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Abstract: Synthetic biology emerged around 2000 as a new biological discipline. It shares with systems biology the same modular vision of organisms, but is more concerned with applications than with a better understanding of the functioning of organisms. A herald of this new discipline is Craig Venter who aims to create an artificial microorganism with the minimal genome compatible with life and to implement into it different 'functional modules' to generate new micro-organisms adapted to specific tasks. Synthetic biology is based on the possibilities raised by genetic engineering, but it aims to engineer organisms, and not simply to modify them, mimicking the practice of computer engineers. Three points will be discussed: In what regard does synthetic biology represent a new epistemology of the life sciences? What are the relations between synthetic biology and evolutionary biology? What is the *raison d'être* of synthetic biology as a discipline independent of nanotechnologies?

Keywords: *synthetic biology*, *engineering*, *modularity*, *evolution*, *modeling.*

1. Introduction: The Rise of Synthetic Biology

The use of the phrase 'synthetic biology' is recent. The first usage (with the modern meaning, see later) dates back to 2000, after which the expression has been increasingly used. In this paper I suggest that synthetic biology in its modern meaning was born in 1999-2000 from the conjunction of a widely quoted theoretical contribution (Hartwell *et al.* 1999) and some spectacular accomplishments published in 2000 demonstrating the possibilities opened up by the new approach. The two events are not independent, since the practical accomplishments were already briefly described in the theoretical contribution.

The theoretical contribution was published in a supplement of *Nature* at the end of 1999, authored by Leland Hartwell, John Hopfield, Stanislas Leibler, and Andrew Murray. This article was important because, in addition to the introduction of the expression itself, it described most of the characteristics of synthetic biology to be discussed later: the important role accorded to theoretical modeling, and the emphasis on the existence of functions and 'purpose' in organisms, which justify the significant contributions to biology expected from engineers and computer scientists. Modularity and evolvability are also discussed as central issues of the new discipline.

Nevertheless, that article still corresponds to a period of transition. Synthetic biology *per se* is only briefly mentioned at the end of the manuscript, and the distinction from systems biology is not clear. The significance of the rapid transformations of biology is interpreted in the traditional framework of the opposition between holism and reductionism characteristic of molecular biology.

The article already announced two iconic realizations of the new approach: the synthesis of an artificial device generating regular oscillations in bacteria (Elowitz & Leibler 2000) and the construction and introduction of a 'toggle switch', also in bacteria (Gardner *et al.* 2000): physical effects were generated by the introduction of artificial devices mimicking similar devices described in other organisms.

2. The Characteristics of Synthetic Biology

Synthetic biology consists of the design and construction of new biological devices and systems – or the redesign of existing natural biological systems – for useful practical purposes (De Vriend 2006). Therefore, three characteristics are central to any project of synthetic biology: (1) an engineering approach to organisms (Brent 2004, Endy 2005) – the expression 'engineering biology' is sometimes used instead of 'synthetic biology'; (2) the aim of creating new functional devices for practical use; and (3) the need to model the system before constructing these devices. The practical side of synthetic biology is such that this new approach is better illustrated by its iconic realizations than by any theoretical consideration. The generation of bacteria 'seeing light' (Levskaya *et al.* 20005) or of a multicellular system generating a pattern formation (Basu *et al.* 2005) were striking in their originality and elegance.

3. The Place of Synthetic Biology within the Biological Sciences

Synthetic biologists emphasize the importance of quantitative models and theorizing in biology. Synthetic biology is therefore a partial return to the tradition of theoretical biology, which occupied a significant place in the landscape of biological research in the first part of the twentieth century, but which had progressively disappeared with the rise of molecular biology.

But synthetic biology is also a legacy of molecular biology, of the work of Monod and Jacob on the regulation of gene expression, and in particular of the genetic engineering technologies elaborated in the 1970s. It is frequently considered that one of the present limits of synthetic biology is the difficulty of producing long DNA fragments – showing the dependency of the new discipline on molecular tools. Some projects aimed at generating bacterial and yeast cells, to synthesize compounds important for the pharmaceutical industry, are the extension of efforts that begun at the end of the 1970s. What distinguishes the new projects is their complexity, and the absolute requirement for the parallel elaboration of mathematical models to test the new devices before their construction. The rise of synthetic biology somehow constitutes the transition between the inefficient work of a tinkerer and the efficient work of an engineer. This engineering spirit is strong.

The modification of an organism is conceived exactly in the same way as the central unit of a computer can be implemented with different additional functions and different chips. The standardization of materials and procedures – with the elaboration of a stock of *biobricks* – is also considered as a significant characteristic of synthetic biology. Both synthetic biology and systems biology consider organisms as systems. Both consider that these systems are formed of subsystems or modules, at least partially structurally and functionally independent, *i.e.* insulated. It is obvious that the progressive characterization of preferred motifs in the organization of cell regulatory networks, and the search for the reasons why organisms favor these motifs – for instance to control 'noise' – prepared the ground for synthetic biology. The possibility of defining motifs with abstract functions such as 'coincidence detectors' or 'amplificators' was a crucial step in establishing links between the activity of computer scientists and engineers, on the one hand, and biologists, on the other. But synthetic biology can be distinguished from systems biology: whereas the description and characterization of these modules is the aim of systems biologists, the existence of insulated modules is simply a prerequisite for the work of synthetic biologists. Their objective is to create new subsystems, or even new systems in a more or less distant future. Their conviction is that 'nature is imperfect and should and can be revised and improved'.

4. A New Paradigm?

There were so many announcements in previous years of the formation of new disciplines in biology, with in particular the blossoming of many 'omics' (Kirkham 2003), that one can be reasonably skeptical about the real novelty of synthetic biology (as well as that of systems biology). However, there are some characteristics of synthetic biology that make this discipline a better candidate and deserving of more attention.

The first is its relative 'homogeneity'. There is a community of conceptual models, tools and techniques, and objectives which has no equivalent, for instance, in systems biology. Philosophers of science have already noticed that the latter brings together researchers favoring a bottom-up or conversely a top-down approach to biological phenomena. It is certainly possible to distinguish in synthetic biology different degrees of artificiality. For instance, construction of a module allowing the synthesis of a particular metabolite does not involve the same level of artificiality and/or the same level of abstraction as construction of a circuit mimicking a logical or mathematical operation. But the tools are identical in both cases.

The second characteristic is the close relation of synthetic biology to applications, or more often to practical realizations that could generate applications in the future. Bacteria that emit light at regular intervals or generate complex patterns (Basu *et al.* 2005) are spectacular results, which herald possibilities raised by the new approach, the 'icons' of the new discipline (Drubin *et al.* 2007). In contrast, the results of systems biology are far less accessible to non-specialists. It is difficult to imagine that this kind of spectacular realization will not be further substantiated in the near future to give synthetic biology an even higher profile.

Interesting also are the means by which synthetic biology has acquired its particular visibility. Traditional ways of demonstrating the formation of a discipline were used – construction of new departments in universities, organization of meetings –, but other, more original ways of raising the standing of this new approach were also imagined. A competition between students from different universities was organized: they were asked to imagine a synthetic biology project and then gathered at the Massachusetts Institute of Technology to realize this project in a limited period of time. This international Genetically Engineered Machine competition has been a great success since the summer of 2005. Even though there is a tradition of competition between students from different schools of engineering, its extension to biology was something really new. In addition to publicizing the new approach, it helped to attract young students, a good way to ensure a bright future for the new discipline.

5. Is Synthetic Biology Simply the Last Avatar of a Long Tradition?

While the ambition of most synthetic biologists is to modify preexisting organisms by implementing them with new functional modules, some leaders of the new discipline do not hesitate to announce more ambitious projects: the creation of a new, totally artificial, organism which could be used as a 'chassis' for the addition of these new functional modules.

To the initial work designated by the expression 'synthetic biology' was added a certain number of studies of a slightly different nature: research into the origin of life, and in particular work aiming by a bottom-up approach to create simple self-organizing systems mimicking what might have been the first steps towards life (Benner & Sismour 2005). It was difficult to exclude this work from synthetic biology – it does aim to synthesize simple life forms – although it clearly differs from the experiments that formed the basis of synthetic biology. Such work does not always share the same engineering spirit, with the attention paid to the creation of models and the standardization of procedures, nor the same modular vision of life. The same is true for attempts to modify the genetic code, to change and extend the nature of nucleotides or that of amino acids.

The extreme ambitions of some of the supporters of synthetic biology, as well as the heterogeneous cohort of studies that have been conducted around the original core work on synthetic biology, have progressively diluted its specificities. The result has been that it is clear for percipient observers of biology to notice that projects to create *de novo* organisms, new forms of life, are not new, and had already flourished at the beginning of the 20th century with scientists like Leduc (Keller 2002, Pereto & Catala 2007). Synthetic biology then seems to be a permanently recurring by-product of important advances in our understanding of living organisms. Present synthetic biology is the consequence of the huge transformations in the conception of organisms introduced by the development of molecular biology and genetic engineering.

The existence of permanent trends in biological thought cannot be denied. But this must not prevent the rapid rise of synthetic biology, with its peculiar characteristics, to be studied carefully, and not simply considered as some déjà-vu phenomenon.

6. The Epistemological Interest of Synthetic Biology

What is remarkable in synthetic biology is the close relation between the knowledge of a system and the ability to reproduce it artificially (Sprinzak & Elowitz 2005). This symmetry between the analytical and synthetic components of knowledge does exist in chemistry, particular in organic chemistry, but was virtually absent from the traditional epistemology of biologists. A system could be considered as perfectly understood even if its artificial reproduction was out of reach. The rise of synthetic biology somehow represents a shift in epistemology. This shift was probably made acceptable in biology by the revelation of the limits of the explanations provided so far by biologists. It is not within the scope of this article to describe these limits, nor the way they progressively became visible: let us simply recall the disappointment following the completion of the human genome sequencing program, as well as the surprises generated by gene inactivation experiments.

When applied to whole organisms, this close relation between an explanation and the ability to 'reproduce' the objects under study has the consequence that synthetic biology is a definition of life. The long-term ambition of synthetic biologists such as Craig Venter is not to reproduce functional modules of organisms, but organisms as a whole. By so doing, synthetic biologists will answer the question 'What is life?' and give an implicit definition of it.

7. The Challenges for Synthetic Biology

The success of synthetic biology projects is conditioned by the veracity of two statements which constitute its foundations: the existence of modules and the claim that the main action of natural selection is in the assortment and recombination of these different modules. Both statements are, in fact, tightly coupled.

The hypothesis that organisms are made of partially independent modules is a belief shared by systems biologists and synthetic biologists. Whereas for the former it is the result of their work, for the latter it is a *sine qua non* of the future success of their projects. In the writings of biologists one has to be very careful to distinguish modules as objects of wishful thinking and modules as structures whose existence has been demonstrated. Or, as discussed by Sandra Mitchell, modules can be ontological – the organisms are *really* formed of modules – or methodological – the simplest way to analyze a complex system is to imagine the existence of subsystems or modules within it (Mitchell 2006).

The existence of modules – components that operate in an integrated and relatively autonomous manner – in organisms is obvious. The question lies elsewhere: are organisms organized in modules, and is modularity a general principle of their construction? The answer is not obvious for various reasons. The first is that most examples of a modular organization originate from the description of intracellular and intercellular signaling pathways, which have been extensively studied in the last twenty years, in particular for their involvement in diseases such as cancer. The modular vision of life is therefore partially biased by the preeminent role that this field of research has assumed. The second problem is that even if a modular organization has been prevalent at one step in the history of life, it is not obvious that this modular organization has been conserved. A good example, but probably not the only one, is that of proteins. There are excellent arguments to suppose that many (most) proteins of extant organisms were the result of the assembly and recombination of smaller peptides and proteins. But with few exceptions, such as the proteins participating in the regulation of gene expression or proteins involved in cell-to-cell interactions, this modular organization has been progressively erased during evolution. Most proteins today cannot be said to be modular, since their different parts no longer have autonomous structures and functions.

Not only has the modular organization of proteins vanished, but also other principles of organization exist. Consider, for instance, the evidence that has accumulated during recent decades in favor of the existence of nanomachines within organisms. These nanomachines comprise proteins and have specific functions within organisms. One iconic example is the ATPase of the inner mitochondrial membrane which synthesizes ATP, the cellular currency of energy. These machines are insulated parts of the organisms, with precise structures and functions. They are not modules because these components are rigidly associated. In fact different models of organization coexist. To consider organisms as networks is not the same as to consider them as comprising modules.

The way evolution plays with modules is also a critical aspect of synthetic biology. It is generally admitted that the modular organization of organisms favors the action of natural selection (Kirschner & Gerhart 2005). The insulation of modules generates robustness, whereas the possibility of recombining independent modules underpins evolvability. But it is not obvious that evolution respects modules and uses them. We have seen that the modular organization of proteins was erased during evolution. In general, evolution can favor the formation of additional connections between components, and their recruitment for different tasks, both actions which oppose a clear modular organization. There are as many arguments in favor of a tinkering – disorganizing – action of evolution as there are arguments in favor of an engineering action. And, in contrast to what many developmental biologists say, there are no strong arguments in favor of a crucial role of modularity in the evolution of organisms. The illusion comes from the lax use of the notion of modules. Maybe natural evolvability is not identical to engineerability.

Two opposing visions of the action of natural selection are proposed in the writings of biologists. In the first, natural selection generates diversity, but no rules or order. In the second, natural selection can generate simple rules of organization. These two contrasting visions of the action of natural selection have coexisted in biology for decades. Synthetic biology favors the positive face of natural selection, its organizing power.

The place of modules in evolution is crucial for synthetic biologists. Let us imagine that they have succeeded in introducing a new functional module within organisms. If the action of natural selection is to erase the modular organization, one may fear that the artificial organism thus created will rapidly evolve towards something different: a nightmare for those pushing the practical use of these artificial organisms.

8. Synthetic Biology and Nanotechnology

It is quite remarkable how few references to nanotechnologies and nanobiotechnologies are made by those who support the rise of synthetic biology. There are obvious differences between the two: synthetic biology is biology, even if the devices that will be implemented are artificial in the sense that they did not previously exist in the organisms into which they will be plugged, or that they only mimic devices existing in organisms. But the principles of construction are those that have emerged from the studies of organisms.

This apparent ignorance by synthetic biologists may be a strategy to develop a new, independent niche instead of being lost in the vague and highly controversial field of nanotechnology. It can also come from the conviction that success will be more rapidly achieved by an approach based on what exists in organisms: 'biotechnology is the nanotechnology that works'. There are some synthetic biology projects that might easily belong to nanotechnology, such as the construction of ultrasensitive biosensors. But the way to construct them will be different in the two approaches. Synthetic biologists will initiate their projects by looking at what kind of similar devices exist in organisms, and how they are built. Synthetic biology does not abolish the boundary between organisms and other objects of the natural world: it abolishes the boundary between the creations by humans and those of the living world. The consequence is that the relation with machines is very different.

Nanotechnology can be seen as the reduction of organisms to mechanisms. In synthetic biology, the power to generate mechanistic devices is a property of organisms. And the work of synthetic biologists is only to use and extend this capacity of organisms; a vision which is not very different from the conception of the relations between organisms and machines elaborated by Georges Canguilhem (1994).

9. Conclusion

I consider that synthetic biology has characteristics – its engineering spirit and a new way of conceiving what is an explanation in biology – that legitimate its place in the present landscape of biological disciplines. Two risks exist for synthetic biology. The first is that by aggregating too many studies it loses its specificity. Around the core of synthetic biology has expanded a ring of poorly defined studies only distantly related to the central core. In particular, there is the temptation on the part of some synthetic biologists to incorporate into their discipline recent successful approaches, such as stem cell manipulation and protein design, which do not share the same vision of life. And the second risk is to assume a vague metaphysical discourse on the primacy of the whole which would mask its real epistemological originality.

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