The Renaissance of Synthetic Biology

Juli Peretó
Institut Cavanilles de Biodiversitat i Biologia Evolutiva and Departament de Bioquímica i Biologia Molecular, Universitat de València
Spain
pereto@uv.es

Jesús Català
Instituto de Humanidades Ángel Ayala-CEU, Universidad Cardenal Herrera-CEU, Alfara del Patriarca, Spain

Recent years have witnessed a sort of collective enthusiasm around the emerging field of synthetic biology. This excitement pervades not only respected scientific journals but also political initiatives[1] and magazines addressed to the general public[2]. Many scientists, journalists, and administrators think that "synthetic biology" is a recently coined term. But the deep historical and epistemological roots of this new field are worth considering.

Over 90 years ago, the French biophysicist Stéphane Leduc (1912) used the term "synthetic biology" as the title of a work devoted entirely to the synthesis of life from inanimate materials. Interestingly enough, Leduc identified the synthesis of organic molecules as the very first step in his research program, recognizing that synthetic organic chemistry was already a well-respected scientific field. But emphatically, maybe sorrowfully, he asked: "In what way is the synthesis of a cell less admissible than the synthesis of a molecule?" (p. 14). For Leduc, the development of biology as a full-fledged science would require progress in the synthetic direction after a descriptive and analytical age. He found, however, an "inconceivable and absurd hostility" among his contemporary colleagues, the same attitude faced by other scientists in the early 20th century, like Alfonso L. Herrera in Mexico, who was convinced that a synthetic rather than an analytical approach would be the best way to answer the question of what life is (Keller 2002). Immersed in their anti-vitalistic struggle, they were perceived by other scientists as either excessively far ahead of their time or completely mistaken. Actually, looking at the impressive aspect of some of the synthetic life-like structures (see the beautiful pictures in Eastes and Darrigan 2006), we can understand why they elicited such notable fascination among the general public, as exemplified by Thomas Mann's passionate description of chemical gardens in *Doktor Faustus* (Keller 2002; Lazcano 2006).

The physiologist Jacques Loeb, discoverer of artificial parthenogenesis and one of the founders of modern biochemistry, pointed out in 1912 that "nothing indicates, however, at present that the artificial production of living matter is beyond the possibilities of science.. . . We must succeed in producing living matter artificially, or we must find the reasons why this is impossible" (pp. 5–6). In an earlier work, Loeb considered artificial synthesis of life (*artificial abiogenesis*) as the "goal of biology" and encouraged young scientists to bridge the gap between nonliving and living matter (Loeb 1906: 223). Now, a century after Loeb's reflections on that paradigm shift reserved only for the youngest minds of his time—a generation of scientists has already disappeared without succeeding in such a major endeavor—we could ask what *synthetic biology* really means for contemporary scientists. Apart from the political and media abuse of the term or classical computational artificial life, there are at least two main approaches to the synthesis of living systems (Benner and Sismour 2005): the top-down and the bottom-up strategies.

Top-Down Approach

A top-down strategy seeks the definition of the minimal requirements for life in terms of, for instance, minimalist genomes (Gil et al. 2004; Glass et al. 2006) or metabolic networks (Gabaldón et al. 2007). The aim is to build an artificial cell integrating modular and standardized parts previously isolated from real cells, in a chassis also derived from a living cell. We also include in this group the experimental expansions of the genetic alphabet or the code producing entirely new artificial genetic systems (Benner and Sismour 2005).

This approach represents a natural extension of genetic and metabolic engineering in the post-genomic era, the

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application of engineering thinking to biology through the computational modeling of rewired gene circuit dynamics, and the achievement of systems biology in practical terms through the assembly of designed organisms from standardized parts (Endy 2005). One example of this strategy is the International Genetic Engineered Machine Competition (iGEM) organized by the Massachusetts Institute of Technology, which reflects the confidence that only the youngest will be brave enough to achieve that Promethean ambition (http://parts.mit.edu/igem07/index.php/Main_Page), an echo of Loeb's dream.

The announcement of Craig Venter's intention to patent the list of the minimal gene set has stirred hot debate (Anonymous 2007; Kaiser 2007). Venter's group, led by Nobel laureate Hamilton O. Smith, has experimentally determined that a gene is essential by looking at the phenotypic effect of gene inactivation in *Mycoplasma genitalium*. The result is a list of 381 protein-coding genes (one less than the gene set published by Glass et al. 2006) that would represent the minimal genome for a free-living bacterium grown in a rich culture medium. They also have successfully assayed *genome transplantation* (Lartigue et al. 2007). The imminent debate on intellectual property and other social issues must include the ethical considerations in a wider agenda based on "informed, truly democratic debates within a secular framework, with sufficient transparency in the criteria for controlling such type of research by independent instances, and the proper guarantees that work in this area will not be driven solely by economic criteria" (Lazcano 2006).

Bottom-Up Approach

The bottom-up approach relies on the conviction that fundamental concepts about life (i.e., autopoiesis, autonomy, and self-replication) can be chemically implemented (Szostak et al. 2001). Clearly, there is continuity here with the ultimate aims of the research program of prebiotic chemistry as established in 1953 by Stanley L. Miller and Harold C. Urey under Aleksandr I. Oparin's theoretical umbrella (Lazcano and Bada 2003), since "the artificial building or synthesis of living things is a very remote, but not an unattainable goal along this road [leading to the ultimate knowledge of the nature of life]" (Oparin 1938: 252).

On comparing these two approaches to constructing life, we find that the first is like a pragmatist's effort to achieve useful goals (e.g., improvements in bioremediation or biomedicine or new energy resources), whereas the second seeks a more essential understanding of living phenomena and their potential connections with the historical steps leading to the chemical origins of life on Earth. In a more fundamental way, the first approach searches for the design of objects with well-defined and useful features in which mutation and evolution should be minimized. However, in the second strategy, at least for those of us who accept evolution as an essential attribute of life (Peretó et al. 2005), evolutionary processes must be implemented by the artificial construct, this becoming a compulsory step.

At any rate, it seems to us that the best result of any synthetic approach to living beings would be new theoretical findings. As has happened in other sciences, the disentanglement of some concepts is inaccessible to analysis and only becomes feasible through synthesis, i.e., exploring the landscape of the possible. The best example is the discovery of the constraints on the geometry of chemical reactions—the Woodward-Hoffmann rules—partially derived from the experimental work of the organic chemist Robert Woodward on B_{12} vitamin synthesis. The new insights into the reactivity of organic reactions accompanying the discovery of these rules enabled Albert Eschenmoser to redesign the complete corrin ring synthesis in a simpler and more elegant way, which was impossible to deduce from earlier chemical knowledge. Thus the experimental work inspired the theoretical progress and this conceptual achievement feed-forward stimulated a completely new experimental route for attacking the most intricate part of the B_{12} molecule (Ball 2005).

More than ever, we are now faced with the real possibility of producing an artificial cell under laboratory conditions. As predicted by John B. S. Haldane many years ago (1940: 27), this will occur before we fully understand the processes going on inside cells, though our hope is that such an extraordinary achievement will contribute to expanding our biological knowledge in a fundamental way—or at least agitate the theoretical debate (Anonymous 2007). We certainly agree with Szathmáry (2004) that "synthetic biology will no doubt deliver technological benefits. But its main intellectual 'deliverable' will be to show that we have understood some basic biology," in complete harmony with the "goal of biology" anticipated by Loeb a century ago.

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Notes

1. See, e.g. *Synthetic Biology–Applying Engineering to Biology*, NEST reports, European Commission, http://www.cordis.lu/nest/publications.htm

2. *The Economist*, September 2–8, 2006; *Newsweek International Edition*, June 4, 2007.

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