Top-down strategies towards the synthesis of minimal (living!) cells

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Abstract

The quest for the minimal cell can be posed as the search for the necessary and sufficient features of life. This question, with a long tradition in theoretical biology has become amenable to experimentation. Approaches to identify minimal components of life can be conceptually divided in two, namely the *bottom-up* and the *top-down* (Peretó and Català, 2007). The *bottom-up* approach aims at constructing artificial chemical systems capable of replication and evolution starting from simpler components (i.e., building up cells from scratch). By recreating some of the steps that pre-cellular systems may have followed from chemistry to biology under primitive Earth conditions, this research program is motivated by the possibility to better understand the origin of life on Earth. Although no such a system has being developed yet, extremely simple systems might eventually be constructed from this approach showing some fundamental biological behaviors. It is worth noting that those efforts are in context of the origin-of-life research program as originally formulated by Oparin (1924), i.e., to discover the articulation of chemical subsystems exhibiting life-like properties under plausible early Earth conditions.

On the other hand, the *top-down* approach starts from existing organisms with the objective of simplifying their genome, arriving at a minimal (or at least reduced) gene set. The rationale behind is common ground. Since the cell's hereditary information needed for structure and function is coded in its genes, cell simplification can be reduced to the task of engineering the genome. Essential genes are identified through deletion mutant experiments or by *in silico* comparative genome analysis. The difference between computational and experimental approaches is that the former identifies a set of essential genes that is shared among diverse taxa, whereas the latter searches for individual genes that are essential for growth in a single species and under the study conditions. Then, a theoretical minimal genome is proposed comprising the set of essential genes thus identified. Recent progress in synthetic genomics (including the total synthesis of genomes by chemical and biological techniques, plus the genome transplantation between different bacterial species) is also an effort towards the engineering of simpler biological systems starting from present day cells.

However, an evolutionary perspective of cells is a good framework for better understanding the properties of minimal living systems. In particular, attention must be given to the diversity of naturally evolved reduced genomes, both in free-living and intracellular endosymbiont microorganisms. In this context, engineering a cell with the minimum number of genes, functions or components required for living in a defined environment has become one of the promises of synthetic biology. Theoretical as well as experimental approaches have been undertaken in order to identify essential genes and functions for different model organisms. Thus recent technical and conceptual advances have opened the possibility of the construction of newly designed cells.

In summary, in synthetic biology we address both basic biological questions and the design and implementation of simpler biological systems relevant from a biotechnological point of view. We could consider the use of defined minimal cells with biomedical, bioremediation, or bioenergy applications, for instance, by taking advantage of existing naturally minimized cells. In principle, simplified versions of extant cells should be easier to understand and engineer towards a variety of tasks, like the production of biomolecules or the exploitation of some metabolic or physiological process. But importantly, the search for simpler cells through genome reduction will help to identify novel, species specific, essential genes under a set of defined conditions. This in turn will lead to improvements in our understanding of the basic machinery of cells, and ultimately will throw light into the necessary and sufficient features of life.

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