Act natural

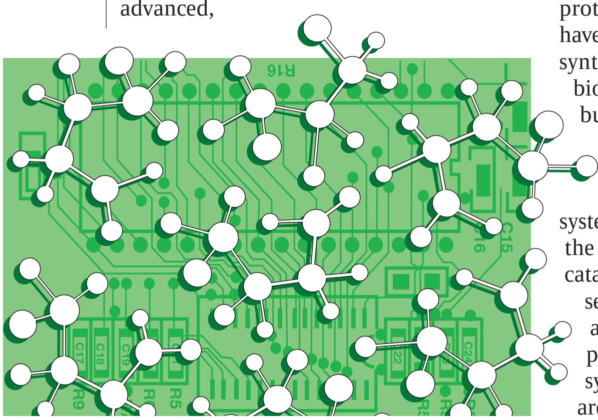
Steven A. Benner

Over the past two centuries, organic chemists developed their discipline by purifying natural products from biological systems and determining how they are assembled from their constituent atoms. As their deconstructive powers grew, chemists targeted larger biomolecules, first proteins and nucleic acids, and then supramolecular structures such as the nucleosome and the ribosome.

Sequencing the human genome represents a culmination, of sorts, of this type of chemical reductionism. After all, the human genome is nothing more (and nothing less) than a statement about how carbon, hydrogen, nitrogen, oxygen and phosphorus atoms are bonded together in the organic molecules that we inherit.

Traditionally, however, chemists complemented deconstruction with a second theme: synthesis. After determining the structure of a new natural product, organic chemists made some more of it. At first, chemists used synthesis simply to prove that the structure proposed for their natural product was correct. Over time, however, synthesis became a struggle that pits the wits of chemists against increasingly complex natural products. The struggle forced chemists to discover things about molecules. Perhaps best known are the observations made during the total synthesis of vitamin B12 that led to the Woodward–Hoffman rules of orbital symmetry, recognized by the Nobel Prize in 1981.

Chemists next attempted to synthesize molecular structures that were not identical to natural products, but reproduced some of the behaviours that natural biomolecules display. 'Biomimetic chemistry', as this endeavour came to be known, was more than the preparation of the plastics, pharmaceuticals and other synthetic materials of modern civilization. The goal became to reproduce advanced, dynamic behaviours of biological systems, including genetics, inheritance and evolution. These goals define synthetic biology as a field.



To a synthetic biologist, life is a special kind of chemistry, one that combines a frequently encountered property of organic molecules (the ability to undergo spontaneous transformation) with an uncommon property (the ability to direct the synthesis of self-copies), in a way that allows transformed molecular structures themselves to be copied. Any chemical system that combines these properties will be able to undergo darwinian selection, evolving in structure to replicate more efficiently. In a word, 'life' will have been created.

But what chemical structures combine these properties? Computer models that simulate replication and evolution *in silico* are relatively easy to come by. A computer program can suffer mutations and keep on ticking. But real molecules often change their behaviour dramatically upon even a slight change in structure. Chemists have in hand a modest number of chemical systems that can function as templates for their own synthesis. But those that can suffer mutation and still have 'children' are proving harder to find.

The pursuit of synthetic biology has already identified some structural features of natural self-replicating biomolecules that are crucial to their performance. For example, the repeating negative charges on DNA's phosphate backbone allow it to survive mutation while continuing to act as a template for copies. These charges are more important for evolution than the identity of the specific bases that carry the genetic information.

From such observations have come entirely new, artificial genetic systems. The first, created a decade ago, contains 12 bases rather than the four (A, T, G and C) found in natural DNA. The artificial genetic system can direct the synthesis of artificial RNA and proteins with extra amino acids. Chemists have appended functional groups onto synthetic genetic systems, creating a hybrid biomolecule that can be copied like DNA, but which also carries the functionality of proteins.

In parallel, molecular biologists have recruited tools from natural systems to generate synthetic evolution in the test tube. To identify new receptors and catalysts, libraries of random nucleic-acid sequences are generated and challenged in an artificial environment. Those that perform well are allowed to direct the synthesis of their copies. Those that fail are discarded. Chemists and molecular biologists are now set to merge the two, creating artificial evolution with artificial genetic systems from synthetic biology.

> **Synthetic biology**
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> *This burgeoning field aims to reproduce advanced, dynamic behaviours of biological systems, including genetics, inheritance and evolution.*

Synthetic biology is not merely demiurgy. In September, for example, the US Food and Drug Administration approved a diagnostic test that uses artificial genetics to measure the level of the HIV virus in infected individuals. The artificial genetic system allows high sensitivity and remarkable dynamic range, without interference from the natural DNA found in patient samples, and represents a remarkable step forward in the management of AIDS as a disease.

Synthetic biology should also help NASA to seek life in its probes of the Solar System. By asking what is possible in the chemistry that supports life, we are more likely to recognize weird life should we encounter it.

Perhaps most important, however, is the vista that synthetic biology offers at the frontier between chemistry and biology. Biology has been limited by "poke and measure the response" research strategies. Recombinant DNA technology allowed biologists to take the next step through synthesis of different sequences of natural molecules.

But synthetic biology with 'bottom-up' design may achieve much more. Building artificial genetic, regulatory and metabolic systems should offer a new way to learn more about genetic, regulatory and metabolic systems in general (and, dare we say it, universally). Thus, in this century, synthetic biology should aid the discovery of new, universal ideas about biology, ideas that might have remained undiscovered using simply reductionist analyses. Which is what synthesis did for chemistry in the twentieth century. ■

Steven A. Benner is in the Departments of Chemistry, and Anatomy and Cell Biology, University of Florida, Gainesville, Florida 32611, USA.

FURTHER READING

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