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NEWS AND VIEWS

Engineering novel life

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A Scientist discovers that which exists. An Engineer creates that which never was.
Theodore von Karman

Biology will never be the same. The remarkable scientific success of biology in describing, explaining, and manipulating natural systems is so well recognized as to be a cliche—but the engineering application of that scientific knowledge is just beginning. In the same way that electrical engineering grew from physics to become a separate discipline in the early part of the last century, we see the growth of a new engineering discipline: one oriented to the intentional design, modeling, construction, debugging, and testing of artificial living systems. Currently published in *Molecular Systems Biology*, Chan *et al* (2005) describe the most compelling example of work in synthetic biology to date.

Bacteriophage T7 has been extensively studied for well over 50 years. Despite this intensive effort, many details of its functioning remain obscure. Attempts at detailed modeling of its infection process have met with limited success (Endy *et al*, 1997), and fail to predict the effect of many intentional modifications (Endy *et al*, 2000). Chan *et al* address this issue with the bold approach of challenging our understanding of the natural system by total synthesis and testing of a 'refactored' version. They define a notion of a 'part' in an engineering sense—a snippet of DNA with a defined biological function—and redesign the genome of T7 out of such defined parts. In a nod to the custom of version numbers for software releases, they denote the refactored genome as T7.1, and confidently discuss version T7.2.

The notion of a 'part' is essentially an engineering concept, reflecting important synthetic goals of modularity, standardized structural and functional composition, hierarchical assembly, isolation from other components, characterized behavior, and standardized interfaces. The 'parts' of the T7 genome are, from the standpoint of engineering practice, still poorly defined in many respects—we do not, for example, know the function of several of them. Nonetheless, the restructuring of the T7 genome by Chan *et al* represents an important step toward the intentional design and construction of artificial living systems.

The design, construction, cataloging, characterization, and documentation of biological parts is an important, ongoing effort of the synthetic biology community (Hayes 2001; Morton 2005), currently reflected in the database backed website for the Registry of Standard Biological Parts (http://parts.mit.edu). The primitive status of the efforts will be readily apparent, although we hope that the broad plan will prove effective as more characterization of parts and the systems composed of those parts is carried out.

The rapid advance of long-chain DNA synthesis technology (Carlson, 2003) makes possible the construction of novel small genomes such as phage T7.1. The recent total synthesis of the polio virus (Cello *et al*, 2002) and of bacteriophage phiX174 (Smith *et al*, 2003) are examples of applying this technology, but in both cases, the artificial sequences were only minor variants of the natural ones. T7.1 represents a redesign of over 30% of the T7 genome, removes complex gene overlaps, and rationalizes the sequence to ease future modification.

Over the next few years, we can anticipate the design, total synthesis, bootstrapping, and testing of small bacterial genomes. To do effective designs, we need a very much more detailed understanding of bacterial physiology than is currently available. Despite decades of scientific progress, we still are missing many—perhaps most—of the critical design principles and details necessary to engineer a cell. The attempt to do such designs rapidly exposes our collective ignorance in a way that is impossible to ignore, and may seed the most important scientific outcome of this work. The predictable but essential failures of early designs will teach us that there is still much to be learned from nature, and importantly, will provide the experience necessary to create the discipline of synthetic biology: an engineering technology based on living systems.

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